Cardiology Research and Practice

Heart Failure

Guest Editors: Gregory Giamouzis, Filippos Triposkiadis, Javed Butler, Dirk Westermann, and George Giannakoulas

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Editorial Board

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SAGE-Hindawi Access to Research
Cardiology Research and Practice
Volume 2011, Article ID 159608, 2 pages
doi:10.4061/2011/159608

Editorial

Heart Failure

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Received 12 April 2011; Accepted 12 April 2011

Heart failure is a growing epidemic. Over the last decade, the annual number of hospitalizations has increased from 800,000 to over a million for heart failure as a primary, and from 2.4 to 3.6 million for heart failure as a primary or secondary diagnosis. Approximately 50% of heart failure patients are rehospitalized within 6 months of discharge. With aging of the population, heart failure rates and the associated hospitalizations will continue to rise. The complex array of physiologic, psychological, social, and health care delivery issues makes it a challenging chronic disease to manage. Understanding the epidemiology and pathophysiology of the syndrome, identifying the predictors and their strength of association with outcomes, and using the available diagnostic modalities cost-effectively are essential in order to devise effective prevention interventions and implement novel therapeutic approaches to curb this epidemic. In this special issue on heart failure, we have invited a few papers that address such issues.

The first two papers provide insight into the epidemiology of two specific populations: women and children. The former is a systematic review of qualitative studies that examined the influence of sex and gender on heart failure self-care. It identifies that women with chronic heart failure represent a highly vulnerable population that needs more support for psychosocial well-being and self-care. The latter is a prospective study aiming to evaluate the long-term effects of therapy for childhood lymphoma on cardiac function using clinical parameters, electrocardiography, and echocardiography. The authors report that most parameters of cardiac function remain normal in survivors of childhood lymphoma after a mean follow up of almost 11 years. This is likely due to relatively low doses of anthracyclines in modern protocol modalities. However, they comment that frequent abnormalities in mitral valve flow and QTc prolongation necessitate long-term cardiac follow up in this population.

Shedding light into pathophysiology pathways the following 3 papers deal with 3 distinct and interesting fields: hyperthyroidism, right ventricular function, and inflammatory cardiomyopathy. The first is an original research paper that evaluates the effect of acute experimental hyperthyroidism on basal and volume-induced atrial natriuretic peptide secretion in healthy subjects. The second describes the development of right ventricular dysfunction and failure in patients with chronic pressure overload. The third review gives an overview about how inflammation triggers the functionality of mesenchymal stem cells, how it induces cardiac homing and, finally, discusses the potential of intravenous application of such cells.

Moving to noninvasive diagnostic modalities, we provide a thorough review of multimodality imaging of chronic ischemia using echocardiographic strain, magnetic resonance, and histology findings in a chronic ischemia model in preclinical study. This case illustrates the features of multimodality imaging in chronic obstructive coronary disease and gives us great insight in understanding the mechanism of ischemic cardiomyopathy. The next paper underscores the role of acoustic cardiography in the detection of left ventricular systolic dysfunction in patients with chronic atrial fibrillation. In the same section, the reader may find an interesting case report of isolated left ventricular noncompaction with a strange ECG-tracing strongly suggestive of Brugada syndrome.

The following section of this focused issue contains 3 papers devoted to novel therapeutic approaches in heart failure. The first is an original prospective study that evaluates the efficacy and safety of prolonged levosimendan infusion, an inotropic drug with unique pharmacological advantages, in patients admitted with acute heart failure. The second is a review paper that provides an evidence-based analysis of how heart failure patients—with and without systolic dysfunction—benefit from exercise training. The last paper evaluates the effect of exercise training on interleukin-6, tumour necrosis factor alpha, and functional capacity in heart failure patients.

Next session moves the reader to the fields of personalized medicine and myocardial regeneration therapy. First, we discuss the role of individual genetic background in the progression of left ventricular dysfunction and remodelling in heart failure patients under optimal medical therapy, in a prospective study that performed a genotype analysis for ACE I/D, β-1 adrenergic receptor (AR) Arg389Gly, β-2AR Arg16Gly, and β-2AR Gln27Glu polymorphisms. Then, we present a novel technique for the development of bioartificial myocardium using stem cells and nanobiotechnology templates.

The final part of this special issue is devoted to contemporary device therapies and contains 5 papers. An original study suggests that cardiac resynchronization therapy (CRT) improves hemodynamic condition and exercise capacity and reduces the ventilator response during effort. The second paper presents a prospective study that aims to predict the response to CRT implantation by comparing pre-CRT left ventricular dyssynchrony by tissue Doppler imaging and regional volumetric analysis by 3-dimensional transthoracic echocardiography. The following paper describes the use of epicardial electrogram as a simple guide to select optimal site of left ventricular pacing in CRT. The forth paper is a focused review on transthoracic echocardiographic assessment of patients with continuous axial left ventricular assist devices. We close this special issue with a thorough review on the role of device diagnostic algorithms in the assessment and management of patients with systolic heart failure.

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SAGE-Hindawi Access to Research
Cardiology Research and Practice
Volume 2011, Article ID 918973, 6 pages
doi:10.4061/2011/918973

Review Article

Women with Heart Failure Are at High Psychosocial Risk: A Systematic Review of How Sex and Gender Influence Heart Failure Self-Care

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Received 20 November 2010; Revised 10 January 2011; Accepted 14 January 2011

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To improve patient support, it is important to understand how people view and experience Heart Failure (HF) self-care. This systematic review of qualitative studies included all published studies that examine the influence of sex and gender on HF self-care. A systematic search was done for papers (1995–2010) indexed in Ovid MEDLINE, Ovid Medline, Ovid EMBASE, Ovid PsycINFO, CSA Sociological Abstracts, OVID AARP Ageline, EBSCO Academic Search Complete, EBSCO CINAHL, EBSCO SocINDEX, ISI Web of Science: Social Sciences Citation Index and Science Citation Index Expanded, and Scopus. After screening of 537 citations, six qualitative studies identified that differences existed in perceptions of symptoms with women having less family involvement and psychosocial support around self-care. Moreover, women had considerably more negative views of the future, themselves and their ability to fulfill social self-care roles. Women with HF represent a highly vulnerable population and need more support for psychosocial wellbeing and self-care.

1. Introduction

Due to ageing populations and increased survival rates from myocardial infarction, Heart Failure (HF) is now at epidemic levels in high-income countries [1, 2]. As a result, the costs of caring for people with HF are very high and rising. Over past decades, a primary strategy in reducing the personal and cost-related HF burden has been to promote the use of evidence-based medication prescribing [3–5]. However, over the last 5 years, there has been a growing recognition that to reduce the HF burden, it is vital to also address HF *self-care* [6–15]; that is, "the decisions and strategies undertaken by the individual in order to maintain life, healthy functioning and wellbeing" [16]. After being comparatively neglected for many years, *self-care* is now recognized as a "*cornerstone*" of effective HF management [9, 11].

Effective HF self-care improves the performance of the heart, reduces the demands of the body on the heart, and promotes general wellbeing. Evidence to support the importance of self-care in each of these areas has improved vastly over recent decades [15]. There is now strong evidence from large randomized trials and cohort studies that mortality, morbidity, and symptoms can be improved in key self-care domains through

(i) consumption of key medications [17, 18],

(ii) behavioural/lifestyle management (including smoking cessation, and salt, fluid and weight management) [1, 15, 19],

(iii) timely use of health services [1], regular physical activity and good social relationships [1, 15].

Self-care of HF is important because the vast majority of ongoing care is undertaken by the person with HF and their caregiver(s) *in the home*—outside of the direct presence, supervision, or support of the health professional in a healthcare setting [9, 11]. Recognition of the importance of self-care has been made in recent clinical guidelines [1, 15, 19–22]. Although recent research on self-care and its determinants has recognized a number of influential

factors (including age, knowledge, coping skills, confidence, cognition) [12], the influence of sex and gender on HF self-care is not well understood [23]. To increase our understanding of the influence of sex and gender on HF self-care, we reviewed existing qualitative studies of self-care in HF patients. These studies specifically contained data on the influence of sex and gender on self-care practices.

2. Materials and Methods

With the definition of HF self-care guiding the paper—and the perception of HF self-care as a complex process, qualitative research studies were selected for inclusion. Qualitative studies have been used extensively in health research to understand user approaches and behaviours [24]. Qualitative approaches do not presuppose the topics or factors that will be identified in a research study as influencing self-care. As such, qualitative methods are used to inform the understanding of complex phenomena prior to quantitative research. A qualitative systematic paper is used to synthesize findings from similar qualitative studies [25, 26]. It has been used previously to examine patients' reactions and experiences of HF [27].

Sex was defined in the review as "the classification of living things, generally as male or female according to their reproductive organs and functions assigned by the chromosomal complement" [28]. Gender was defined as the, *distinct* and *individual* properties of men and women that are "expressed through the values they hold, their psychosocial characteristics, and ultimately their behaviours" ([29] page 275]). Gender also has *interactive or contingent* dimensions of social identity; individual properties of masculinity or femininity are elicited from men and women in some social contexts, but not others [30, 31].

2.1. Inclusion Criteria. The search strategy involved general and specific terms in relation to HF. To be included in the review, studies had to include, adults over 18 years of age, be in English, men only, women only or mixed-sex studies that specifically explored the influence of gender or sex using qualitative or mixed (qualitative and quantitative) methods. The search included studies using different qualitative methodologies (including grounded theory, interpretive descriptive, and ethnography) and various techniques for data collection (including interviews and focus groups). Studies that contained data for people with coronary heart disease were excluded because these populations have different self-care needs compared to HF patients. Surveys were also excluded as these studies do not constitute qualitative research as conventionally defined.

A search was done for studies published from 1995 to 2010 that were indexed in Ovid MEDLINE, Ovid Medline, Ovid EMBASE, Ovid PsycINFO, CSA Sociological Abstracts, OVID AARP Ageline, EBSCO Academic Search Complete, EBSCO CINAHL, EBSCO SocINDEX, ISI Web of Science: Social Sciences Citation Index and Science Citation Index Expanded and Scopus. Over 110 keywords were used around heart failure and self-care (e.g., heart, self-manage*) and relevant research methods (e.g., semistructured, interview, narrative methods). Additional studies were identified from reference lists.

2.2. Literature Reviewing Process. Quality of the studies meeting the inclusion criteria was independently assessed using the Critical Appraisal Skills Programme (CASP) tool for qualitative research [32]—a valid tool for the assessment of quality in qualitative research [33]. Data extraction was undertaken by the primary author for each paper and checked by the second author. Data were extracted on the focus of the study, the population (i.e., patients, family/caregivers, health professionals), sample (i.e., men only, women only, mixed), type of sampling (i.e., convenience, purposive, theoretical, other), number and age of the sample, sample setting (i.e., country) and the method/approach of the study (i.e., grounded theory, interpretive, mixed methods, ethnography, critical theory phenomenology, etc.) and data collection methods (i.e., face to face/telephone interviews). Quality was assessed independently using the CASP tool with disagreements resolved by consensus. The metaethnographic approach [34] was used to synthesize findings from the studies. This involved the primary author reading each study to identify, based on the team's approach to self-care, the main self-care needs of patients/lay caregivers and links between different needs and age. Matrices were developed to record these first order interpretations [26, 35]. These represent the main findings of each study as presented by the participants in the studies [33, 36]. The details of each study in terms of setting and quality were also extracted and taken into account at this stage. *Stage two* (second-order coding) involved the researchers examining the relationships between concepts identified in the findings from the matrices [37]. Second-order interpretations of common or reoccurring concepts were sought and interpreted in the context of study quality and setting [36]. For the *third stage* (synthesis), the main concepts identified during the second stage (second order interpretations) were used to reinterpret each paper and reconsider the relationships between the papers. The results of this synthesis will be the findings of the review.

3. Results

After initial screening of 537 studies, 78 papers were retrieved, and reviewed in full. From these studies, six studies were identified that used qualitative methods containing or examined themes related to gender differences in HF patient's perceptions and experiences (Table 1). These studies recruited patients with a wide range of ages (35 to 95 years). Sample sizes ranged from 4 to 32 with a total of 61 women and 31 men. Only one study [38] had a sample of men only. Four studies recruited women-only samples [39–42]. Two studies from Sweden used a "phenomenographic" approach [38, 39], two studies from the United States of America (USA) used a "phenomenology" approach [40, 41], and two studies (USA and Australia) used "mixed methods" [42, 43].

All the included studies used semistructured interviews as a method of data collection, and recruited patients ≥18

Table 1: Summary of included studies.

Author, year, and country	Main aim	Data collection	Sampling criteria	Sample and gender
Mårtensson et al., (1997) (Sweden) [38]	From a nurses perspective, explore how male patients with CHF conceive their life situation.	One open and semi-structured interview. Time elapse between Dx and interview: *5 patients*: 2–6 months *3 patients:* 7–12 months *2 patients*: 13–18 months *2 patients*: 19–24 months.	Male patient's from medical clinic with CHF. Variables on the log list were, age, month/year of diagnosis, NYHA classification, aetiology, education, civil status, occupation.	$n = 12$ Male
Mårtensson et al., (1998) (Sweden) [39]	From a nurses perspective how female patients with CHF conceive their life situation.	One open, semi-structured interview Time elapse between Dx and interview: *2 patients*: 2–6 months; *4 patients*; 7–12 months; *3 patients*: 13–18 months; *3 patients:* 19–24 months.	Female patients from a medical clinic, between ages of 65 and 83 years. Variables on the log list were, age, month/year of diagnosis. NYHA classification, aetiology, education, civil status, and occupation.	$n = 12$ Female
Rhodes, and Bowles (2002) (USA) [40]	Examine and describe the experience of older women living with NYHA class II HF.	Four semi-structured interviews, <1 hour each.	Female patients between ages of 60–90 years who self-reported they had been Dx by their cardiologist with NYHA stage II HF or identified by health professionals and through presentations at retirement centre's, Caucasian, diagnosed with HF from 2 to 10 years.	$n = 5$ Female
Allen et al., (2009) (USA) [41]	Explore the lived experience of HF, in middle aged women with NYHA class III.	Audiotape recorded, semi structured telephone interview.	Convenience sample of 4 women screened by case manager at cardiology practice using criteria: female; dx with NYHA class III HF; ≥21 years of age; verbally articulate; willing to participate	$n = 4$ Female Consecutive women with class III HF were recruited until redundancy in description was obtained.
Gary, (2006) (USA) [42]	Examine the frequency of self-care practices in women with DHF and describe the demographic and clinical characteristics that affect self-care practices in women with DHF.	2 hr audio taped, semi structured interview guide by telephone or face to face interview.	Convenience sample of 32 women Dx diastolic HF, NYHA Class II-III >50 years of age at a large health science center recruited by a cardiologist from a study comparing combined walking and education program and an education program only. MMSE >25, on optimal pharmacologic HF therapy.	$n = 32$ Female
Riegel, et al., (2010) (Australia) [43]	Describe HF self-care in men and women and identify gender-specific barriers and facilitators influencing HF self-care.	Cross-sectional, comparative mixed methods study quantitative survey and qualitative semi structured narrative audio taped and transcribed interview, either face to face or telephone.	A 2008 cross-sectional, comparative mixed methods study was reviewed for in-depth interviews eliciting self-care behaviors and exploring barriers and facilitators of self-care. From this study a purposive sample of English speaking NYHA Class II/III HF of ≥6 months with a MMSE score of >24.	Mixed $n = 19$ (70% Male) $n = 8$ (30% Female)

NYHA: New York heart association; HF: heart failure; CHF: congestive heart failure; Dx: Diagnosis; SD: standard deviation; MMSE: mini mental status exam.

years of age with NYHA classifications of Class II or III. The six qualitative studies varied in methodological quality (2 high quality, 1 medium quality, and 2 low quality papers). The qualitative studies chosen were systematically evaluated to comprehend the influence of gender on HF patients' willingness and capacity for effective self-care. The stated foci of studies were illness experiences [38–41] or barriers and facilitators of HF self-care [42, 43]. However, each used gender as a means to interpret data that resulted in similar categories/themes. These similarities not only

identify relevant issues, they also support the value of each study and their findings.

The data from all these studies, having been organized into various themes/categories, gave adequate illustration of the different aspects of the self-care experience of men and women with HF. The qualitative research objectives covered several aspects about living with HF, including: (1) new self concept, (2) physical limitations, (3) negative emotions/losses, (4) support/deepening relationships, (5) rejuvenate/rest, (6) hope, (7) uniqueness of gender. Participants were recruited from outpatient clinics [38, 39]; professional referrals [40], unspecified healthcare settings [41], and from a previously hospitalized sample of HF patients [43].

3.1. Synthesis

3.1.1. Overwhelming Physical Limitations. The most overarching theme identified across the sexes in relation to HF was the overwhelming physical limitations experienced by men and women—their loss of energy, high fatigue and shortness of breath/breathlessness affected all aspects of life, including occupation, social, and recreational roles [38–43]. This occurred even when participants were not clear what was causing their symptoms, for example, some women reported difficulty in differentiating HF symptoms from their wider emotions [43].

Reductions in physical activity in the form of sitting or sleeping were used to prevent and/or alleviate symptoms in all the studies. Taking time to try and complete the activities of daily living, while accepting the fact they may not complete the task was common across sexes [38–43].

3.1.2. Changes to Social Roles and Identity. Life after a diagnosis of HF, compared to past functioning, and social roles, was seen in negative terms by both sexes. However, women viewed themselves in a range of more negative ways, including: being "handicapped", "sick", "burdensome" or "worthless" [39, 41, 42].

Fears of death, isolation, of being a burden, and struggles with depression and unhappiness over their physical limitations were common across the sexes [39–42]. However, again women experienced more negative feelings of anger and hate towards their HF [40, 41] and reported greater loss of hope [41, 43]. The women worried over a lack of money, not being able to care for others or of being dependent on others [39, 40, 42]. Some women increased coping by consciously refocusing "…their mental energy in ways more productive for dealing with their HF" [40] or placed great hope in maintaining their present level of functioning [39, 42].

Conversely, men reported a wider range of positive and negative emotions compared to women. Some reported being more "anxious" or "fearful" both about HF [43] and its effects on their family [38]. However, in relation to the future, other men were hopeful and determined [38]. Age appeared to moderate men's emotions—with younger men being more negative about HF and the negative effects on life [43].

3.1.3. Social Support and Relationships. While women saw supportive relationships as being based on having someone to talk to [39–43], women in all the studies frequently reported that they did not have another close person they could rely on to even help with activities of daily living [39, 40, 42, 43]. Conversely, men reported having more tangible support with family members being involved in supporting their HF self-care [38, 43]. With the assistance of family, men had more confidence in interpreting symptoms of HF and self-care [38, 43].

4. Discussion

This paper identified that though HF has severe effects on the physical and psychosocial wellbeing of both sexes, women frequently experience more negative emotions in relation to the HF, tend to have lower confidence, poorer social and family support, and see the future as more bleak. Age and culture did appear to influence the experiences and reactions to HF in conjunction with gender and sex. Further research into these interactive effects is needed.

These patterns in women are a cause for concern because achieving effective HF self-care is difficult for both sexes. This process is complex as it requires a range of activities, skills, confidence and sustained efforts. As HF is associated with older age, women comprise more than half of the already large population with HF [44, 45]. Achieving optimal conditions for effective self-care in the large female HF population is therefore of high clinical significance.

Though people with HF tend to be at risk for poor psychosocial health with 40% having depression or depressive symptoms [46], women are particularly vulnerable to adverse psychosocial health and support. This may be because women with HF tend to have more symptoms than men [47, 48]. However, it may also be related to the lower psychosocial and family support identified in the studies in this review or to a reluctance of men to voice being isolated or fearful. That said, there is wider evidence from observational studies that psychosocial factors are more adverse in women with HF and that these psychosocial factors not only affect wellbeing but also HF self-care [49–51].

The large size and distinctive self-care needs of the population of women with HF suggest that more gender-sensitive approaches are needed for care and disease management. While supporting self-care is now recognized to be a vital part of effective disease management [11], there is as yet little appreciation or acknowledgement in clinical guidelines that women have distinct or greater needs for psychosocial support than men with HF. This paper and other evidence [49–51] indicate that women need additional support around psychosocial factors and self-care that is sensitive to elements of gender and sex.

Health professionals providing care to people with HF during the self-care management phase should be aware of the vulnerability that women can experience around psychosocial health and support. Where possible, families, partners and other lay caregivers should be mobilized to provide effective support to the women with HF not only around

self-care but also in relation to more general psychosocial wellbeing. In addition to increasing psychosocial support, antidepressant medications should be considered for women who are suitable candidates [52].

As with most systematic reviews, this review was confined to studies that had been published. While there is a sizable body of qualitative research into HF, relatively few studies included or incorporated gender into analyses. The data in the studies contain only preliminary insights into *how* gender influences HF patients' willingness and capacity for effective self-care. Further research is needed into understanding the nature and influences on psychosocial factors in women with HF. The effects of contextual factors such as being married, widowed, ethnicity, living alone, years of HF experience, education, income and age on women need further exploration.

5. Conclusions

Patients of both sexes experience severe physical and psychosocial effects from HF. Yet, women with HF tend to have considerably more negative views of the future, themselves and their ability to fulfill social self-care roles. Women also report having less support for psychosocial wellbeing and self-care. As a highly vulnerable population, women need more and better support from health professionals, families and caregivers for psychosocial wellbeing and self-care.

Acknowledgments

Alexander M. Clark receives career awards from Alberta Innovates Health Care Solutions and the Canadian Institutes of Health Research.

References

[1] Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of European Society of Cardiology et al., "ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology," *European Journal of Heart Failure*, vol. 29, pp. 2388–2442, 2008.

[2] M. Jessup et al., "2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: a report of the American college of cardiology foundation/american heart association task force on practice guidelines: developed in collaboration with the international society for heart and lung transplantation," *Circulation*, vol. 119, no. 14, pp. 1977–2016, 2009.

[3] J. J. V. McMurray, "Failure to practice evidence-based medicine: why do physicians not treat patients with heart failure with angiotensin-converting enzyme inhibitors?" *European Heart Journal*, vol. 19, supplement, pp. L15–L21, 1998.

[4] J. G. F. Cleland, K. Swedberg, F. Follath et al., "The EuroHeart Failure survey programme—a survey on the quality of care among patients with heart failure in Europe—part 1: patient characteristics and diagnosis," *European Heart Journal*, vol. 24, no. 5, pp. 442–463, 2003.

[5] M. Komajda, F. Follath, K. Swedberg et al., "The EuroHeart Failure survey programme—a survey on the quality of care among patients with heart failure in Europe—part 2: treatment," *European Heart Journal*, vol. 24, no. 5, pp. 464–474, 2003.

[6] C. Jillings, "Patients with heart failure had inadequate information about the disease and lacked the tools for optimal self-care," *Evidence-Based Nursing*, vol. 7, no. 4, p. 127, 2007.

[7] V. V. Dickson, N. Tkacs, and B. Riegel, "Cognitive influences on self-care decision making in persons with heart failure," *American Heart Journal*, vol. 154, no. 3, pp. 424–431, 2007.

[8] S. B. Dunbar, P. C. Clark, C. Quinn, R. A. Gary, and N. J. Kaslow, "Family influences on heart failure self-care and outcomes," *Journal of Cardiovascular Nursing*, vol. 23, no. 3, pp. 258–265, 2008.

[9] L. S. Evangelista and M. A. Shinnick, "What do we know about adherence and self-care?" *Journal of Cardiovascular Nursing*, vol. 23, no. 3, pp. 250–257, 2008.

[10] D. K. Moser and J. F. Watkins, "Conceptualizing self-care in heart failure: a life course model of patient characteristics," *Journal of Cardiovascular Nursing*, vol. 23, no. 3, pp. 205–218, 2008.

[11] B. Riegel, "Foreword: self-care of heart failure: what is the state of the science?" *Journal of Cardiovascular Nursing*, vol. 23, no. 3, pp. 187–189, 2008.

[12] B. Riegel and V. V. Dickson, "A situation-specific theory of heart failure self-care," *Journal of Cardiovascular Nursing*, vol. 23, no. 3, pp. 190–196, 2008.

[13] A. M. Clark, C. N. Freydberg, F. A. McAlister, R. T. Tsuyuki, P. W. Armstrong, and L. A. Strain, "Patient and informal caregivers' knowledge of heart failure: necessary but insufficient for effective self-care," *European Journal of Heart Failure*, vol. 11, no. 6, pp. 617–621, 2009.

[14] T. Jaarsma, K. F. Årestedt, J. Mårtensson, K. Dracup, and A. Strömberg, "The European Heart Failure Self-care Behaviour scale revised into a nine-item scale (EHFScB-9): a reliable and valid international instrument," *European Journal of Heart Failure*, vol. 11, no. 1, pp. 99–105, 2009.

[15] B. Riegel, D. K. Moser, S. D. Anker et al., "State of the science: promoting self-care in persons with heart failure: a scientific statement from the american heart association," *Circulation*, vol. 120, no. 12, pp. 1141–1163, 2009.

[16] T. Jaarsma, A. Strömberg, J. Mårtensson, and K. Dracup, "Development and testing of the European Heart Failure Self-Care Behaviour Scale," *European Journal of Heart Failure*, vol. 5, no. 3, pp. 363–370, 2003.

[17] M. K. Davies, C. R. Gibbs, and G. Y. H. Lip, "Management: diuretics, ACE inhibitors, and nitrates," *British Medical Journal*, vol. 320, no. 7232, pp. 428–431, 2000.

[18] E. Lonn and R. McKelvie, "Drug treatment in heart failure," *British Medical Journal*, vol. 320, no. 7243, pp. 1188–1192, 2000.

[19] J. M. O. Arnold, P. Liu, C. Demers et al., "Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: diagnosis and management," *Canadian Journal of Cardiology*, vol. 22, no. 1, pp. 23–45, 2006.

[20] Heart Failure Society of America, *Self-Care: Following your Treatment Plan and Dealing with your Symptoms*, Heart Failure Society of America, St Paul, Minn, USA, 2006.

[21] Heart Failure Society of America, *HFSA 2006 Comprehensive Heart Failure Practice Guideline*, Heart Failure Society of America, St Paul, Minn, USA, 2006.

[22] J. M. O. Arnold, J. G. Howlett, A. Ducharme et al., "Canadian Cardiovascular Society Consensus conference guidelines on heart failure—2008 update: best practices for the transition of care of heart failure patients, and the recognition, investigation

and treatment of cardiomyopathies," *Canadian Journal of Cardiology*, vol. 24, no. 1, pp. 21–40, 2008.

[23] A. C. C. Ng, H. S. P. Wong, A. S. C. Yong, and A. P. Sindone, "Impact of gender on outcomes in chronic systolic heart failure," *International Journal of Cardiology*, vol. 117, no. 2, pp. 214–221, 2007.

[24] C. Pope and N. Mays, "Qualitative Research: reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research," *British Medical Journal*, vol. 311, no. 6996, pp. 42–45, 1995.

[25] M. Dixon-Woods and R. Fitzpatrick, "Qualitative research in systematic reviews," *British Medical Journal*, vol. 323, no. 7316, pp. 765–766, 2001.

[26] P. Pound, N. Britten, M. Morgan et al., "Resisting medicines: a synthesis of qualitative studies of medicine taking," *Social Science and Medicine*, vol. 61, no. 1, pp. 133–155, 2005.

[27] D. S. F. Yu, D. T. F. Lee, A. N. T. Kwong, D. R. Thompson, and J. Woo, "Living with chronic heart failure: a review of qualitative studies of older people," *Journal of Advanced Nursing*, vol. 61, no. 5, pp. 474–483, 2008.

[28] Institute of Medicine, *Exploring the Biological Contributions to Human Health: Does Sex Matter?* National Academy Press, Washington, DC, USA, 2001.

[29] K. M. King and H. M. Arthur, "Coronary heart disease prevention: views on women's gender-based perceptions and meanings," *The Journal of Cardiovascular Nursing*, vol. 18, no. 4, pp. 274–281, 2003.

[30] S. Fenstermaker and C. West, Eds., *Doing Gender, Doing Difference: Inequality, Power, and Institutional Change*, Routledge, New York, NY, USA, 2002.

[31] C. West and D. H. Zimmerman, "Doing gender," *Gender and Society*, vol. 2, no. 2, pp. 125–151, 1987.

[32] NHS Learning and Development, *Critical Appraisal Skills Programme (CASP) and Evidence-Based Practice: CASP Qualitative Appraisal Tool*, 2007.

[33] G. S. Feder, M. Hutson, J. Ramsay, and A. R. Taket, "Women exposed to intimate partner violence: expectations and experiences when they encounter health care professionals: a meta-analysis of qualitative studies," *Archives of Internal Medicine*, vol. 166, no. 1, pp. 22–37, 2006.

[34] G. Noblit and R. Hare, *Meta-Ethnography: Synthesizing Qualitative Data*, Sage, London, UK, 1988.

[35] N. Mays, C. Pope, and J. Popay, "Systematically reviewing qualitative and quantitative evidence to inform management and policy-making in the health field," *Journal of Health Services Research and Policy*, vol. 10, no. 1, pp. 6–20, 2005.

[36] N. Britten, R. Campbell, C. Pope, J. Donovan, M. Morgan, and R. Pill, "Using meta ethnography to synthesise qualitative research: a worked example," *Journal of Health Services Research and Policy*, vol. 7, no. 4, pp. 209–215, 2002.

[37] I. D. Graham, J. Logan, M. B. Harrison et al., "Lost in knowledge translation: time for a map?" *The Journal of Continuing Education in the Health Professions*, vol. 26, no. 1, pp. 13–24, 2006.

[38] J. Mårtensson, J. E. Karlsson, and B. Fridlund, "Male patients with congestive heart failure and their conception of the life situation," *Journal of Advanced Nursing*, vol. 25, no. 3, pp. 579–586, 1997.

[39] J. Mårtensson, J. E. Karlsson, and B. Fridlund, "Female patients with congestive heart failure: how they conceive their life situation," *Journal of Advanced Nursing*, vol. 28, no. 6, pp. 1216–1224, 1998.

[40] D. L. Rhodes and C. L. Bowles, "Heart failure and its impact on older women's lives," *Journal of Advanced Nursing*, vol. 39, no. 5, pp. 441–449, 2002.

[41] J. W. Allen, C. Arslanian-Engoren, and J. Lynch-Sauer, "The lived experience of middle-aged women with New York Heart Association class III heart failure: a pilot study," *Progress in Cardiovascular Nursing*, vol. 24, no. 3, pp. 96–101, 2009.

[42] R. Gary, "Self-care practices in women with diastolic heart failure," *Heart and Lung*, vol. 35, no. 1, pp. 9–19, 2006.

[43] B. Riegel, V. V. Dickson, L. Kuhn, K. Page, and L. Worrall-Carter, "Gender-specific barriers and facilitators to heart failure self-care: a mixed methods study," *International Journal of Nursing Studies*, vol. 47, no. 7, pp. 888–895, 2010.

[44] A. L. Pruitt, "Heart failure: it's not just for men," *Critical Care Nursing Clinics of North America*, vol. 20, no. 3, pp. 327–341, 2008.

[45] C. W. Yancy, G. C. Fonarow, N. M. Albert et al., "Influence of patient age and sex on deliveryof guideline-recommended heart failure care in the outpatient cardiology practice setting: findings from IMPROVE HF," *American Heart Journal*, vol. 157, no. 4, pp. 754–762, 2009.

[46] T. Rutledge, V. A. Reis, S. E. Linke, B. H. Greenberg, and P. J. Mills, "Depression in heart failure. A meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes," *Journal of the American College of Cardiology*, vol. 48, no. 8, pp. 1527–1537, 2006.

[47] I. Ekman and A. Ehrenberg, "Fatigue in chronic heart failure—does gender make a difference?" *European Journal of Cardiovascular Nursing*, vol. 1, no. 1, pp. 77–82, 2002.

[48] V. Vaccarino, Y. T. Chen, Y. Wang, M. J. Radford, and H. M. Krumholz, "Sex differences in the clinical care and outcomes of congestive heart failure in the elderly," *American Heart Journal*, vol. 138, no. 5 I, pp. 835–842, 1999.

[49] S. Heo, D. K. Moser, T. A. Lennie, B. Riegel, and M. L. Chung, "Gender differences in and factors related to self-care behaviors: a cross-sectional, correlational study of patients with heart failure," *International Journal of Nursing Studies*, vol. 45, no. 12, pp. 1807–1815, 2008.

[50] M. L. Chung, D. K. Moser, T. A. Lennie et al., "Gender differences in adherence to the sodium-restricted diet in patients with heart failure," *Journal of Cardiac Failure*, vol. 12, no. 8, pp. 628–634, 2006.

[51] B. González, J. Lupón, T. Parajón et al., "Nurse evaluation of patients in a new multidisciplinary Heart Failure Unit in Spain," *European Journal of Cardiovascular Nursing*, vol. 3, no. 1, pp. 61–69, 2004.

[52] C. M. O'Connor, W. Jiang, M. Kuchibhatla et al., "Antidepressant use, depression, and survival in patients with heart failure," *Archives of Internal Medicine*, vol. 168, no. 20, pp. 2232–2237, 2008.

SAGE-Hindawi Access to Research
Cardiology Research and Practice
Volume 2011, Article ID 316927, 8 pages
doi:10.4061/2011/316927

Research Article

Cardiac Function in Long-Term Survivors of Childhood Lymphoma

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Received 3 November 2010; Revised 4 January 2011; Accepted 4 January 2011

Academic Editor: Dirk Westermann

Objectives. We studied long-term effects of therapy for childhood lymphoma on cardiac function. *Design and patients*. We prospectively evaluated 45 survivors of childhood lymphoma, using clinical parameters, electrocardiography and echocardiography. Further comparisons were made between lymphoma subgroups and between males and females. *Results*. Mean age at diagnosis was 9.1 years. Mean followup duration was 10.9 years. The NYHA functional class was I in 43 patients and II in 2 patients. A prolonged QTc interval (>0.44 msec) was found in 8 patients. Left ventricular (LV) systolic function and compliance were normal (LV shortening fraction $40 \pm 5.6\%$; cardiac index 2.84 ± 1.13 L/min/m^2; E/A wave ratio 2.5 ± 1.3; mean ± S.D.), LV mass was normal (97 ± 40 grams/m^2, mean ± S.D.). Mitral regurgitation was observed in 7/45 patients (16%). Asymptomatic pericardial effusions were found in 3/45 (7%) patients. *Conclusions*. Long-term follow-up shows that most parameters of cardiac function are normal in survivors of childhood lymphoma. This is likely due to relatively low doses of anthracyclines in modern protocol modalities. Abnormalities in mitral valve flow, QTc prolongation and in a small proportion of survivors, and functional capacity necessitate long-term cardiac follow-up of these patients.

1. Introduction

Increased long-term survival following effective treatment of childhood lymphomas has placed greater emphasis on residual sequelae of therapy for lymphoma and the impact of these sequelae as the cause of further morbidity and mortality. Following treatment of childhood Hodgkin's disease, cardiac pathology is second only to neoplasm as the cause of death in initial survivors [1]. As the number of cancer survivors increases, so does the number of patients exposed to therapies toxic to the heart and lung, including radiation and chemotherapeutic modalities that employ anthracyclines [2]. The literature is replete regarding effects of anthracyclines and radiation on the heart; however, there is still debate regarding the detection of cardiac sequelae [3], their significance [4], and the relation between different treatment modalities and the development of cardiac sequelae. We hypothesized that protocols employing anthracyclines and radiation would adversely affect long-term cardiac function and that these effects would differ between survivors who received different treatment modalities. We therefore prospectively evaluated long–term cardiac function in 45 survivors of childhood lymphomas, using clinical parameters, electrocardiography,

Table 1: Demographic characteristics of survivors by lymphoma subtype.

	HD	BL	NHNB	Total/Average
Males (n)	14	7	5	26
Females (n)	12	5	2	19
Mean age at diagnosis (years)	10.8	7.4	5.5	9.1 (range: 2.1–16.4)
Treatment duration (years)	0.9	0.8	1.7	0.94
Age at follow-up (years)	23.1	19.1	16.7	21 (range: 2.1–16.4)
Followup duration (years)	11.3	10.9	9.5	10.9 (range: 2.1–16.4)

and echocardiography and compared these parameters between lymphoma subtypes.

2. Patients and Methods

The study included survivors of histology-diagnosed childhood lymphomas who had at least 5 years of followup from termination of therapy, and who were less than 18 years of age at treatment initiation. These criteria identified 45 survivors of 108 children treated for lymphoma at the Pediatric Hematology and Oncology department of a tertiary care center during a nineteen-year period. Fifteen additional survivors meeting these inclusion criteria declined complete participation in the protocol. All participants underwent evaluation which included an interview to assess functional class (New York Heart Association), physical examination, 12-lead electrocardiography (ECG), and echocardiography. Data were taken from a single assessment at the last available follow-up.

Informed consent was obtained from all participants or their legal guardians.

2.1. Statistics. Statistical analysis was performed using a commercially available package (Sigmastat 5.0 Jandel Scientific, San Rafael, California). Comparisons between the different lymphoma subgroups were made using one way ANOVA or the Tukey correction of this test where normality failed, and where relevant by the Student's T-test or the Mann-Whitney rank sum test where normality failed. Statistical significance was set at $P < .05$.

2.2. Study Population. Characteristics of the study population including treatment duration and mean follow-up duration are presented in Table 1.

2.3. Treatment Modalities. Tumor characteristics and therapeutic modalities are detailed in Table 2.

The BL subgroup was divided between those treated in earlier years with protocols (COMP) that did not include anthracyclines (7/12 patients), and those that were treated more recently (5/12 patients) with protocols (LMB, NCI) containing anthracyclines. These two subgroups did not differ significantly with regard to age at diagnoses (6.7 ± 3.7; 8.30 ± 5.1 years, resp., $P = .52$) or age at follow-up (21.2 ± 4.2; 16.1 ± 5.8 years, $P = .1$).

The mean dose of doxorubicin (adriamycin), for the group as a whole was 25 mg/m^2 per treatment, leading to a cumulative dose of 150 mg/m^2 or a total cumulative dose of 225–250 mg.

All participants underwent evaluation which included an interview to assess functional class (New York Heart Association (NYHA)), physical examination, 12-lead ECG, and echocardiography. Cardiovascular physical examination, ECG, and echocardiography were performed by 2 senior staff pediatric cardiologists (A. Lorber and Y. Braver). Analyses of ECG and echocardiography images were then undertaken in a blinded manner by different investigators (M. Friedberg and I. Solt). Stroke volume was calculated by multiplying the aortic valve area, measured from the 2-dimensional echocardiographic long axis view of the internal aortic diameter at valvular level, with the velocity time integral (VTI) of aortic flow. Cardiac index (CI) was then calculated by multiplying this value by heart rate, and dividing the product by body surface area. Left ventricular indices were measured by M-mode echocardiography. Left ventricular mass was calculated by the Devereux method [5]. Left ventricular diastolic function was assessed from mitral valve inflow Doppler. Mitral regurgitation was graded according to the routine clinical gradation used in the lab as none, trivial, mild, moderate or severe. Echocardiographic data were compared to well-established normal values [6]. Normal values were defined as being within 2 standard deviations of the mean normal value: for LV ejection fraction $66 \pm 4\%$, and LV fractional shortening $36 \pm 4\%$, LV mass index 70.4 gram/m^2 for males (10–95 percentile 48.5–103 gram/m^2) and 60.7 gram/m^2 for females (10–95 percentile 35.6–81 gram/m^2). Early diastolic mitral inflow velocity (E wave) to late diastolic mitral inflow velocity (A wave) ratio is 1.7 ± 0.4 to 2.5 ± 0.9. Cardiac dimensions were defined as being within 2 standard deviations of the normal mean for body surface area. A QTc > 0.44 seconds was defined as prolonged.

3. Results

3.1. Functional Capacity and History. All patients had normal cardiovascular function prior to initiation of therapy.

The NYHA functional class was class I in 43 patients (96%) and class II in 2 patients (4%). These 2 patients did not have other comorbidities or notable toxic effects on follow-up. No Raynaud's phenomenon was reported. No events of near-syncope, syncope, or sudden death were noted. Clinical features of the cohort as a whole and of the Hodgkin's disease subgroup are shown in Table 3.

Table 2: Lymphoma characteristics and treatment data of survivors by lymphoma subtype.

Patient	Staging	Histology	ChemoTx	Irradiation	Total dose (cGy)	Mantle dose (cGy)
HL						
1	3B	NONE	MOPP	MANTLE	1500	1500
2	2B	NS	MOPP	MANTLE	3000	3000
3	2B	NS	MOPP	MANTLE	4000	4000
4	1A	LP	MOPP	MANTLE	2000	2000
5	2B	LP	MOPP	MANTLE	4000	4000
6	3A	MC	MOPP/ABVD	TOT. NODAL	1650	1500
7	1A	NS	MOPP	MANTLE	2600	2800
8	2A	MC	MOPP/ABVD	MANTLE	2000	2000
9	2B	MC	MOPP/ABVD	MANTLE,INV.Y.SPLEEN	5800	4000
10	2A	NS	MOPP/ABVD	MANTLE	1800	1800
11	3B	NS	MOPP/ABVD	MANTLE,PARAAORTIC	8000	4000
12	2B	NS	MOPP/ABVD	MANTLE,INV.Y	4000	4000
13	2B	MC	MOPP/ABVD	MANTLE	3060	3060
14	3B	NS	MOPP	MANTLE,INV.Y,SPLEEN	5100	2500
15	2A	NONE	MOPP	MANTLE,INV.Y	8400	4400
16	2B-BULKY	MC	MOPP/ABVD	MANTLE	2600	2600
17	3A	NS	MOPP/ABVD	MANTLE	2600	2600
18	2A-BULKY	NS	MOPP/ABVD	MANTLE	4000	4000
19	1A	NS	MOPP/ABVD	MINIMANTLE	3600	3600
20	2A	NS	MOPP/ABVD	MANTLE	3000	3000
21	3B	LD	MOPP	MANTLE,INV.Y	8000	4000
22	2A	NS	MOPP	MANTLE	4000	4000
23	1A	LP	NONE	MANTLE	4000	4000
24	2A	NS	MOPP/ABVD	MANTLE	2600	2600
25	2A	NS	NONE	MANTLE,PARAO,SPLEEN	8000	4000
26	2B-BULKY	NS	MOPP/ABVD	MANTLE	3000	3000
Average					3935	3152
BL						
27	NP	6	COMP		0	0
28	ABD	6	NCI		0	0
29	ABD	6	LMB		0	0
30	ABD	6	COMP		0	0
31	ABD	6	COMP		0	0
32	ABD	6	COMP		0	0
33	ABD	6	COM		0	0
34	ABD	6	COMP	WHOLE ABDOMEN	1550	0
35	ABD	6	NCI		0	0
36	ABD	6	LMB		0	0
37	NP	6	ACOMP		0	0
38	ABD	6	NCI		4000	0
Average					462	0
NHNB						
39	0	7	LSAL2		0	0
40	0	7	LSAL2/COM	BRAIN,TOT.LUNG	3600	0
41	0	7	LSAL2	BRAIN,INV.Y	5600	0
42	0	7	COM		0	0
43	0	7	LSAL2	MEDIASTINUM	750	0
44	0	7	LSAL2	MEDIASTINUM	2000	0
45	0	7	COMP	BRAIN	2400	0
Average					2050	0

MOPP: nitrogen mustard, oncovin, prednisone, and procarbazine; COM/P: cyclophosphamide,oncovin, and methotrexate/prednisone; ABVD: adriamycin, bleomycin, vinblastine, and deticen; NCI: national cancer institute; ACOMP: like comp with adriamycine; LSA2L2: norma wollner protocol; LMB: no abbreviation; NS: nodular sclerosis; LP: lymphocyte predominance; MC: mixed cellularity; LD: lymphocyte depletion.

Table 3: Electrocardiographic and echocardiographic data of all survivors and the Hodgkins disease subtype.

	All	Hodgkins disease	
Electrocardiography			
Heart rate (bpm) (mean ± SD)	77 ± 11		
PR interval (seconds) (mean ± SD)	0.144 ± 0.024		
QTc interval (seconds) (mean ± SD)	0.411 ± 0.032	0.417 ± 0.034	N.S
Echocardiography			
LV Fractional shortening (%)	40 ± 5.6	39.5 ± 5.6	N.S
Cardiac Index (L/min/m^2)	2.84 ± 1.13	3.4 ± 1.03	N.S
LVED (cm)	4.43 ± 0.057		N.S
Septal thickness (cm)	0.65 ± 0.12	0.65 ± 0.13	N.S
Posterior wall thickness (cm)	0.66 ± 0.1	0.67 ± 0.1	N.S
LV mass (gm/m^2)	97 ± 40	96 ± 38	N.S
E/A wave ratio	2.5 ± 1.3	2.29 ± 1.09	N.S
Mitral regurgitation (*n*, %)	7/45 (16)	4/26 (15)	N.S

3.2. Electrocardiography. All patients demonstrated normal sinus rhythm with no bradycardias or tachycardias noted. The percentage of survivors with a prolonged QTc interval by lymphoma subgroup is shown in Figure 1(a). A prolonged QTc interval was not associated with sinoatrial or atrioventricular node dysfunction-conduction anomalies.

Incomplete right bundle branch block was recorded in 4 patients (9%, all diagnoses); complete right bundle branch block was recorded in 2 patients. No evidence of ischemia or "strain" was noted on nonstress ECG.

3.3. Echocardiography. Cardiac systolic and diastolic function was normal or low-normal for the group as a whole without significant differences between the subgroups (Table 3).

LV mass and shortening fraction did not correlate with mantle irradiation dose, QTc interval, or length of follow-up. Mean LV mass was within normal limits (97 ± 40 grams/m^2, mean ± S.D.). LV mass was significantly higher for males as compared to females (all subjects, 112 grams versus 76 grams, resp.; $P < .01$). There was no significant difference in shortening fraction between males and females. Left ventricular end diastolic internal dimensions did not increase following relatively smaller shortening fraction values. Cardiac index and mass by lymphoma subgroup are presented in Figures 1(b) and 1(c), respectively.

Mild mitral regurgitation was observed in 7 of the 45 patients (16%). The percentage of survivors with mitral regurgitation by subgroup is shown in Figure 1(d). Mitral valve prolapse was recorded in 1 HD survivor. Pulmonary valve insufficiency, more than the accepted physiological norm, was found in 1 survivor of NHNB.

Asymptomatic small pericardial effusions were found in 3 of the 45 patients (7%). No larger effusions or pericardial thickening was noted in any of the patients. A mitral inflow pattern consistent with constrictive or restrictive physiology (elevated E wave velocity, elevated E/A ratio, and short deceleration time) was not noted in any of the patients.

Selected electrocardiographic and echocardiographic parameters for the subset of BL survivors treated with anthracyclines versus those not treated with anthracyclines are presented in Table 4.

4. Discussion

Cardiac abnormalities described after treatment for childhood lymphomas can involve almost any aspect of cardiac function and include pericarditis, pericardial effusions, pericardial fibrosis, pancarditis, myocardial fibrosis with functional impairment, valvular disease, conduction defects, and coronary artery disease [1]. Although sequelae may develop at variable time intervals following treatment, emphasis is now placed on the long-term sequelae of lymphoma therapy [7, 8], which are caused mainly by anthracyclines and radiation [9].

In our study population, most parameters of cardiac status were within normal limits. This is most likely due to the relatively low dose of anthracyclines used. Previous study has shown that an average cumulative dose of 450 mg/m^2 of doxorubicin causes a 23% abnormality rate in echocardiographic findings during a 7-year follow-up period [10] and that sequelae are rare at doses under 300 mg/m^2 [10, 11]. Our study population received an average of 150 mg/m^2 of doxorubicin, leading to a total dose of 225–250 mg, which is less than the average toxic dose. This is achieved in modern protocols through regimens employing multidrug therapy. The average follow-up duration for our population was 10.9 years, which is longer than that of many other studies, with relatively few cardiac sequelae from anthracyclines. However, these patients still warrant long-term cardiac follow-up, as the risk for cardiomyopathy continues to increase over time [12, 13]. This vigilance is further justified by previous findings that patients may develop cardiac complications from anthracyclines, even when lower doses are used [13].

Studies performed 2 to 3 decades ago identified factors that augment the cardiotoxicity of anthracyclines. These include radiation of the mediastinum [14, 15], previous cardiac abnormalities, including involvement of the heart by the tumor [16, 17], uncontrolled hypertension [11, 12], and exposure to other chemotherapy modalities such as

Table 4: Comparison of selected electrocardiographic and echocardiographic characteristics between Burkitt lymphoma survivors who received or did not receive anthracyclines as part of their treatment regimen.

	B.L. patients who received anthracyclines	B.L. patients who did not receive anthracyclines	
LV shortening fraction (%)	41 ± 5	39 ± 3	N.S
QTc	0.416 ± 0.03	0.4 ± 0.02	N.S
LV mass	121 ± 36	85 ± 37	N.S

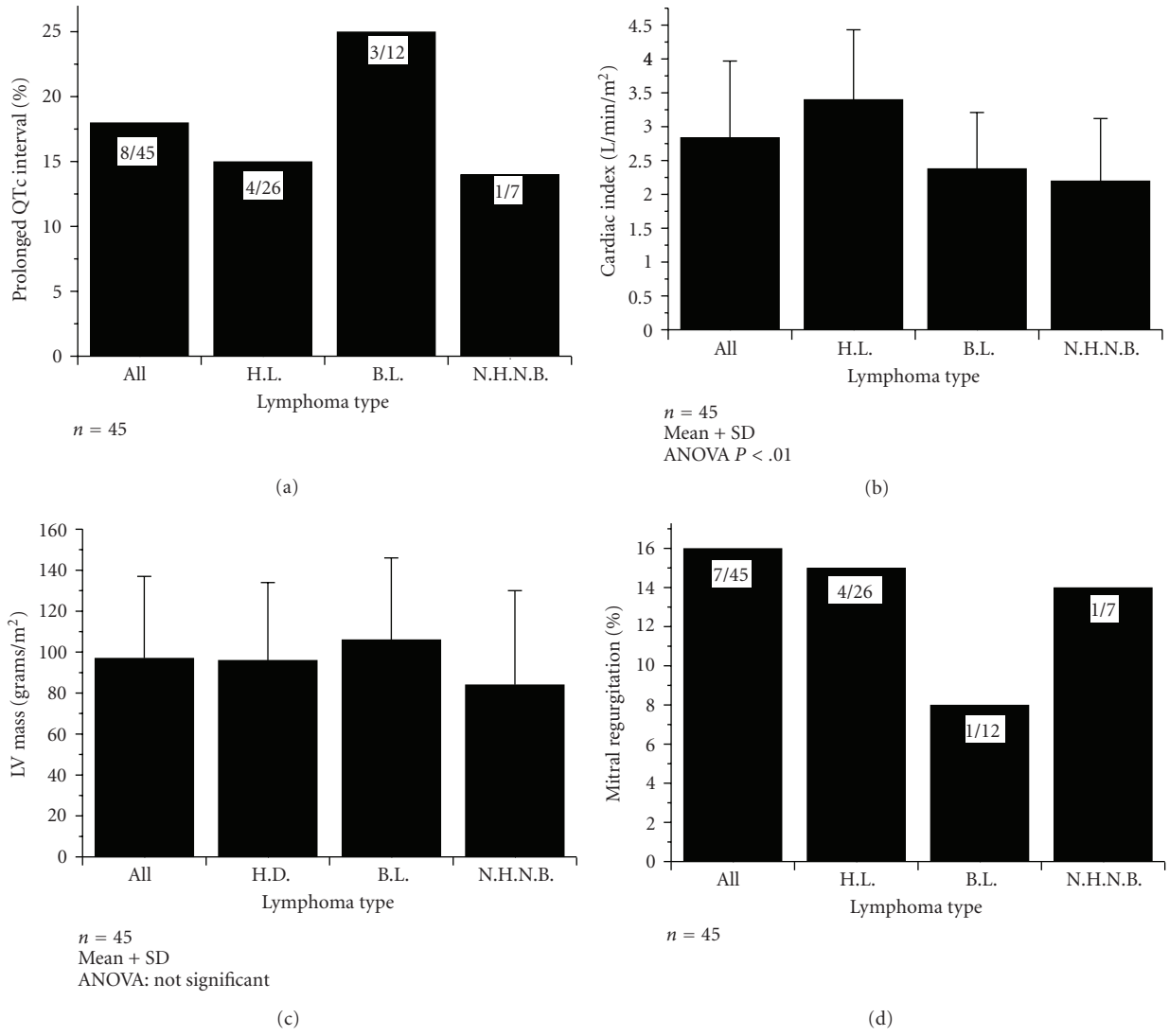

Figure 1: (a) Percentage of survivors with prolonged QTc interval (>0.44 s) among the lymphoma subgroups. (b) Cardiac index among the lymphoma subgroups. $N = 45$, Mean + SD, ANOVA $P < .01$. (c) Left ventricular mass among the lymphoma subgroups. $N = 45$, Mean + SD, ANOVA not significant. (d) Percentage of survivors with mitral regurgitation among the lymphoma subgroups. $N = 45$. H.D.: Hodgkin's Disease, B.L.: Burkitt's Lymphoma, N.H.N.B.: Non Hodgkin Non Burkitt lymphoma.

cyclophosphamide, dactinomycin, mitomycin, vincristine, bleomycin and methotrexate [13, 18, 19]. Demographic factors include young age, female sex, black race and also trisomy 21 [7]. Among these, our study population was exposed to radiation of up to 4400 cGy (but in most instances less than this) and to polychemotherapy, including vincristine and bleomycin, as dictated by the various treatment protocols. More recently a pathophysiological role for the tyrosine kinase receptor, ErbB2, has been implicated in cardiomyocyte susceptibility to anthracyclines [20].

Again, the total dose of doxorubicin was probably the most important factor in preventing significant cardio toxicity among our population. These findings are consistent with other studies that found that modern protocol therapies using MOPP/ABVD and radiation hold low risk for cardiac toxicity [21, 22].

Leandro et al. [9] suggested that cardiac status following anthracyclines is described by a pattern consistent with a thin-walled, compliant left ventricle with reduced muscle mass performing under above-normal levels of wall stress. Our results are consistent with this description and show left ventricular dimensions at the lower level of normal, with good compliance.

It is surprising that no statistical differences in systolic function and left ventricular mass and thickness were found between the lymphoma type subgroups, in the light of the substantial differences in therapy that these groups received. Although differences in left ventricular mass between BL patients who received anthracyclines and those who did not reach statistical significance, our data may correlate with the aforementioned findings that anthracyclines reduce ventricular mass and reduce left ventricular wall thickness. However, no differences were found between the various lymphoma subgroups, among whom HD patients were exposed both to anthracyclines as well as to radiation. Indeed, these patients exhibited increased cardiac output in comparison to the other lymphoma subgroups. We do not have a clear interpretation for this result. More importantly, cardiac index was at the low range of normal, or slightly below normal, for all groups. Differences between males and females were significant regarding LV mass, a factor that contributes to the greater susceptibility of females to anthracyclines [7], and the greater prevalence of prolonged QTc interval among females.

We found an increased prevalence of mitral valve regurgitation in our study population. An earlier study [23] found mitral valve regurgitation in 24% of patients. The significance of mitral valve regurgitation in these patients is not entirely clear. Minimal mitral insufficiency, in the absence of valve deformity, is usually of little clinical significance [24]. However, Allen et al. [25] detected an increase in the prevalence of mitral regurgitation among children who had received anthracyclines, 12% (4 of 34) of whom later developed left ventricular systolic dysfunction, concluding that mitral regurgitation might be an early marker of anthracycline-related cardiac dysfunction.

Seventeen percent of the patients we studied demonstrated a prolonged corrected QT interval. Cardiac dysrhythmias are prevalent in survivors of lymphoma treated with anthracyclines [26]. Our findings correlate with those of previous studies, where both QT and QT dispersion were prolonged following treatment with anthracyclines [27, 28]. A prolonged QT interval may result from myocardial cell damage but does not correlate with decreased contractile function [29, 30]. As dysrhythmias may occur years after termination of treatment and these are potentially life-threatening, patients should be evaluated at regular followup with a 12-lead ECG [8, 31]. Although no sudden death events were observed in our population, following our findings of a prolonged Q-T interval in a substantial percentage of the population, it may be suggested that a 24-hour holter-ECG recording be part of the routine follow-up of these patients.

Coronary artery disease has been reported after radiation therapy to the mediastinum, but not after anthracycline therapy [1, 32]. This pathology led to significantly increased mortality at 7-year follow-up. Our results did not show resting ECG changes, and there was no premature mortality among our study group on a longer follow-up period. In the light of findings from other studies, we would suggest periodic ergometry in the long-term follow-up of patients who have undergone radiation therapy [33].

Additional well-described sequelae of radiation therapy to the mediastinum are pericardial effusion and constrictive pericarditis [34, 35].We did not note these pathologies to any significant degree in our study population.

The use of possible cardioprotective agents such as dexrazoxane may provide additional protection against long-term cardiac sequelae of anthracyclines, especially in girls [36, 37]. These agents were not used in our study, and we cannot comment further on their effects.

Limitations. This study has certain limitations. This study was performed as a retrospective analysis of data with inherent limitations. The study group is relatively small and the number of patients in subgroups is small. We did not compare the study group with a control group, as our primary objective was definition of cardiac status among survivors. However, we used well-established norms that are commonly and widely used as the basis for this definition. Further comparisons between the different lymphoma subgroups, provided a comparative basis for the different treatment modalities, and specific comparison between Burkitt lymphoma survivors who had been exposed to anthracyclines and those who had not strengthened this comparison. Echocardiographic parameters such as ejection fraction and fractional shortening are limited by load dependency and constitute basic indicators of global ventricular function. Although other echocardiographic methods are available for assessment of cardiac function, each has its specific limitations and in daily clinical practice many oncologists are more familiar with the traditional parameters used in this study. Likewise assessment of left ventricular mass by echocardiography is limited. This study focused on long-term follow-up with data collected at the last available assessment, and we did not collect data on acute or subacute toxicity.

In summary, in this cohort, relatively few long-term cardiac complications were seen in most patients following low-dose anthracycline therapy used in modern treatment protocols for childhood lymphoma. However, anthracycline cardio toxicity has previously been well established and in the current study, abnormalities were found in mitral valve regurgitation abnormalities, QT prolongation, low-normal cardiac index, and in 2 survivors functional capacity reduction leading to a compromised quality of life. The greater frequency of abnormalities in females requires increased vigilance in this group. These findings necessitate comprehensive and long-term cardiac follow-up of these patients.

References

[1] S. L. Hancock, S. S. Donaldson, and R. T. Hoppe, "Cardiac disease following treatment of Hodgkin's disease in children and adolescents," *Journal of Clinical Oncology*, vol. 11, no. 7, pp. 1208–1215, 1993.

[2] M. A. Grenier and S. E. Lipshultz, "Epidemiology of anthracycline cardiotoxicity in children and adults," *Seminars in Oncology*, vol. 25, no. 4, pp. 72–85, 1998.

[3] T. J. Porea, Z. E. Dreyer, J. T. Bricker, and D. H. Mahoney, "Evaluation of left ventricular function in asymptomatic children about to undergo anthracycline-based chemotherapy for acute leukemia: an outcome study," *Journal of Pediatric Hematology/Oncology*, vol. 23, no. 7, pp. 420–423, 2001.

[4] M. T. Meinardi, W. T. A. Van Der Graaf, D. J. Van Veldhuisen, J. A. Gietema, E. G. E. De Vries, and D. TH. Sleijfer, "Detection of anthracycline-induced cardiotoxicity," *Cancer Treatment Reviews*, vol. 25, no. 4, pp. 237–247, 1999.

[5] R. B. Devereux and N. Reichek, "Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method," *Circulation*, vol. 55, no. 4, pp. 613–618, 1977.

[6] N. H. Silverman, *Pediatric Echocardiography*, Williams & Wilkins, Baltimore, Md, USA, 1st edition, 1993.

[7] J. P. Krischer, S. Epstein, D. D. Cuthbertson, A. M. Goorin, M. L. Epstein, and S. E. Lipshultz, "Clinical cardiotoxicity following anthracycline treatment for childhood cancer: the Pediatric Oncology Group experience," *Journal of Clinical Oncology*, vol. 15, no. 4, pp. 1544–1552, 1997.

[8] C. Putterman and A. Polliack, "Late cardiovascular and pulmonary complications of therapy in Hodgkin's disease: report of three unusual cases, with a review of relevant literature," *Leukemia and Lymphoma*, vol. 7, no. 1-2, pp. 109–115, 1992.

[9] J. Leandro, J. Dyck, D. Poppe et al., "Cardiac dysfunction late after cardiotoxic therapy for childhood cancer," *American Journal of Cardiology*, vol. 74, no. 11, pp. 1152–1156, 1994.

[10] K. Nysom, K. Holm, S. R. Lipsitz et al., "Relationship between cumulative anthracycline dose and late cardiotoxicity in childhood acute lymphoblastic leukemia," *Journal of Clinical Oncology*, vol. 16, no. 2, pp. 545–550, 1998.

[11] L. C. M. Kremer, E. C. Van Dalen, M. Offringa, J. Ottenkamp, and P. A. Voûte, "Anthracycline-induced clinical heart failure in a cohort of 607 children: long-term follow-up study," *Journal of Clinical Oncology*, vol. 19, no. 1, pp. 191–196, 2001.

[12] L. J. Steinherz, P. G. Steinherz, C. T. C. Tan, G. Heller, and M. L. Murphy, "Cardiac toxicity 4 to 20 years after completing anthracycline therapy," *Journal of the American Medical Association*, vol. 266, no. 12, pp. 1672–1677, 1991.

[13] P. K. Singal and N. Iliskovic, "Doxorubicin-induced cardiomyopathy," *New England Journal of Medicine*, vol. 339, no. 13, pp. 900–905, 1998.

[14] M. N. Prout, M. J. S. Richards, and K. Ja Chung, "Adriamycin cardiotoxicity in children. Case reports, literature review, and risk factors," *Cancer*, vol. 39, no. 1, pp. 62–65, 1977.

[15] A. C. Gilladoga, C. Manuel, C. T. Tan, N. Wollner, S. S. Sternberg, and M. L. Murphy, "The cardiotoxcicity of adriamycin and daunomycin in children," *Cancer*, vol. 37, no. 2, supplement, pp. 1070–1078, 1976.

[16] D. D. Von Hoff, M. W. Layard, and P. Basa, "Risk factors for doxorubicin-induced congestive heart failure," *Annals of Internal Medicine*, vol. 91, no. 5, pp. 710–717, 1979.

[17] R. A. Minow, R. S. Benjamin, and J. A. Gottlieb, "Adriamycin cardiomyopathy: an overview with determination of risk factors," *Cancer Chemotherapy Reports*, vol. 6, no. 2, pp. 195–201, 1975.

[18] J. R. Kushner, V. L. Hansen, S. P. Hammer, and R. N. Matthews, "Cardiomyopathy after widely seperated courses of adriamycin exacerbated by actinomycin D and mithramycin," *Cancer Treatment Reports*, vol. 36, pp. 1577–1584, 1975.

[19] P. J. Smith, H. Ekert, K. D. Waters, and R. N. Matthews, "High incidence of cardiomyopathy in children treated with adriamycin and DTIC in combination chemotherapy," *Cancer Treatment Reports*, vol. 61, no. 9, pp. 1736–1738, 1977.

[20] S. A. Crone, Y. Y. Zhao, L. Fan et al., "ErbB2 is essential in the prevention of dilated cardiomyopathy," *Nature Medicine*, vol. 8, no. 5, pp. 459–465, 2002.

[21] C. S. LaMonte, S. D. J. Yeh, and D. J. Straus, "Long-term follow-up of cardiac function in patients with Hodgkin's disease treated with mediastinal irradiation and combination chemotherapy including doxorubicin," *Cancer Treatment Reports*, vol. 70, no. 4, pp. 439–444, 1986.

[22] L. S. Constine, R. G. Schwartz, D. E. Savage, V. King, and A. Muhs, "Cardiac function, perfusion, and morbidity in irradiated long-term survivors of Hodgkin's disease," *International Journal of Radiation Oncology Biology Physics*, vol. 39, no. 4, pp. 897–906, 1997.

[23] M. B. Lund, H. Ihlen, B. M.R. Voss et al., "Increased risk of heart valve regurgitation after mediastinal radiation for Hodgkin's disease: an echocardiographic study," *Heart*, vol. 75, no. 6, pp. 591–595, 1996.

[24] J. D. R. Thomson, J. Allen, and J. L. Gibbs, "Left sided valvar regurgitation in normal children and adolescents," *Heart*, vol. 83, no. 2, pp. 185–187, 2000.

[25] J. Allen, J. D. R. Thomson, I. J. Lewis, and J. L. Gibbs, "Mitral regurgitation after anthracycline treatment for childhood malignancy," *Heart*, vol. 85, no. 4, pp. 430–432, 2001.

[26] L. J. Steinherz, P. G. Steinherz, and C. Tan, "Cardiac failure and dysrhythmias 6-19 years after anthracycline therapy: a series of 15 patients," *Medical and Pediatric Oncology*, vol. 24, no. 6, pp. 352–361, 1995.

[27] T. Nousiainen, E. Vanninen, A. Rantala, E. Jantunen, and J. Hartikainen, "QT dispersion and late potentials during doxorubicin therapy for non-hodgkin's lymphoma," *Journal of Internal Medicine*, vol. 245, no. 4, pp. 359–364, 1999.

[28] C. L. Schwartz, W. L. Hobbie, S. Truesdell, L. C. Constine, and E. B. Clark, "Corrected QT interval prolongation in anthracycline-treated survivors of childhood cancer," *Journal of Clinical Oncology*, vol. 11, no. 10, pp. 1906–1910, 1993.

[29] J. Leandro, J. Dyck, D. Poppe et al., "Cardiac dysfunction late after cardiotoxic therapy for childhood cancer," *American Journal of Cardiology*, vol. 74, no. 11, pp. 1152–1156, 1994.

[30] D. L. Keefe, "Anthracycline-induced cardiomyopathy," *Seminars in Oncology*, vol. 28, no. 4, pp. 2–7, 2001.

[31] R. L. Larsen, R. I. Jakacki, V. L. Vetter, A. T. Meadows, J. H. Silber, and G. Barber, "Electrocardiographic changes and arrhythmias after cancer therapy in children and young adults," *American Journal of Cardiology*, vol. 70, no. 1, pp. 73–77, 1992.

[32] J. F. Boivin, G. B. Hutchison, J. H. Lubin, and P. Mauch, "Coronary artery disease mortality in patients treated for Hodgkin's disease," *Cancer*, vol. 69, no. 5, pp. 1241–1247, 1992.

[33] K. M. Weesner, M. Bledsoe, A. Chauvenet, and M. Wofford, "Exercise echocardiography in the detection of anthracycline cardiotoxicity," *Cancer*, vol. 68, no. 2, pp. 435–438, 1991.

[34] R. G. Martin, J. C. Ruckdeschel, and P. Chang, "Radiation related pericarditis," *American Journal of Cardiology*, vol. 35, no. 2, pp. 216–220, 1975.

[35] D. I. Scott and R. D. Thomas, "Late onset constrictive pericarditis after thoracic radiotherapy," *British Medical Journal*, vol. 1, no. 6109, pp. 341–342, 1978.

[36] S. E. Lipshultz, R. E. Scully, S. R. Lipsitz et al., "Assessment of dexrazoxane as a cardioprotectant in doxorubicin-treated children with high-risk acute lymphoblastic leukaemia: long-term follow-up of a prospective, randomised, multicentre trial," *The Lancet Oncology*, vol. 11, no. 10, pp. 950–961, 2010.

[37] G. Chvetzoff, B. Bonnotte, and B. Chauffert, "Anticancer chemotherapy: prevention of toxicityChimiotherapie anticancereuse: prevention de la toxicite," *Presse Medicale*, vol. 27, no. 39, pp. 2106–2112, 1998.

SAGE-Hindawi Access to Research
Cardiology Research and Practice
Volume 2011, Article ID 381865, 6 pages
doi:10.4061/2011/381865

Clinical Study

Acute Experimental Hyperthyroidism Does Not Affect Basal and Volume-Induced Atrial Natriuretic Peptide Secretion in Healthy Subjects

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Received 30 September 2010; Accepted 27 October 2010

Academic Editor: Georgios Giannakoulas

Background. Excess circulating thyroid hormones are associated with increased cardiac atrial natriuretic peptide (ANP) secretion but the exact mechanisms involved have not been fully elucidated in vivo. *Methods*. To examine whether thyroid hormone regulation of ANP secretion is the result of a direct action on the myocardium and/or of an indirect action through alterations in the peripheral circulation, plasma ANP levels (baseline and volume expansion-induced) were evaluated in 14 healthy men, before and after triiodothyronine (T_3) administration. *Results*. T_3 administration was followed by a significant increase in serum T_3 levels and a significant decrease in serum TSH levels, without significantly affecting ANP levels. Systemic vascular resistance, plasma rennin activity (PRA), and aldosterone (ALDO) levels, as well as indices of left atrial function, were not significantly altered, despite a significant increase in cardiac output. Plasma volume expansion, induced by a 1500 ml normal saline (NSal) infusion, both before and after T_3 administration, was followed by a significant decrease in PRA and ALDO and a significant increase in plasma ANP levels, without significantly affecting the mean blood pressure (BP) and heart rate (HR) in each study period. The NSal-induced response, measured as the integrated area under the curve corrected for baseline values (-AUC), was not different after T_3 administration for ANP, ALDO, PRA, HR, and mean BP. *Conclusion*. In vivo thyroid hormone-induced myocardial ANP secretion is the result of an indirect action mainly through hemodynamic changes that increase atrial stretch.

1. Introduction

Excess thyroid hormone is associated with changes in cardiovascular system, including increase in heart rate, blood volume, cardiac contractility, and cardiac output [1, 2] and decrease in systemic vascular resistance, whereas thyroid hormone deficiency has been associated with the opposite effects [3]. It has been postulated that these changes are the result of both a direct regulation of cardiac-specific genes by triiodothyronine (T_3) [4, 5] and indirect changes in hemodynamic function [6].

Atrial natriuretic peptide (ANP) is a hormone synthesized by atrial cardiomyocytes [7, 8] and is involved in blood pressure and electrolyte homeostasis [9]. Human studies have shown that plasma ANP secretion is affected by thyroid hormones, being higher in hyperthyroid patients compared to euthyroid controls [10–12] and returning to normal levels after appropriate treatment [13]. There is a strong

Table 1: Clinical and laboratory characteristics of the study population before and after T_3 administration.

Parameter	Before T_3	After T_3	P value
Heart rate, beats/min	72 ± 7	75 ± 6	.061
Mean blood pressure, mmHg	117 ± 13	117 ± 10	.966
T_3, nmol/L	1.80 ± 0.6	4.3 ± 1.0	<.001
T_4, nmol/L	107 ± 18	97 ± 20	.018
TSH, μU/mL	1.04 ± 0.70	0.09 ± 0.04	<.001
ANP, pmol/L	10.4 ± 2.9	11.8 ± 4.9	.256
PRA, nmol/L/h	1.8 ± 1.23	2.2 ± 0.9	.099
ALDO, pmol/L	633 ± 472	665 ± 325	.836

ALDO: plasma aldosterone; ANP: plasma atrial natriuretic peptide; PRA, plasma renin activity.

positive relationship between circulating thyroid hormones and both atrial and ventricular ANP mRNA contents [14, 15], supporting the hypothesis that ANP synthesis and/or secretion from atrial cardiomyocytes remain under thyroid hormone control.

The exact mechanism(s) by which thyroid hormones regulate cardiac ANP secretion have not been fully elucidated. In vitro studies, in rat atrial myocytes, have shown a direct, dose-dependent stimulation of ANP synthesis and secretion by thyroid hormones [16], but in vivo studies are missing. On the other hand, atrial stretch and/or pressure within the atria is considered the primary mechanism that regulates ANP secretion from cardiomyocytes [17, 18]. Therefore, in chronic hyperthyroidism, the increased ANP secretion could be the result of both the direct action of thyroid hormones on the myocardium and/or the indirect action through the alterations in peripheral circulation that may drive the change in cardiac work [19–21]. It is not known which of the above mechanisms predominates in vivo.

The aim of this study was to examine whether in vivo thyroid hormone regulation of ANP secretion is the result of a direct action on the myocardium and/or of an indirect action through the alterations they pose in the peripheral circulation.

2. Materials and Methods

2.1. Design. We examined the cardiac ANP secretion (baseline and volume expansion induced) in healthy subjects before and after per os T_3 administration for 3 days to establish serum T_3 levels compatible with hyperthyroidism. Fourteen healthy male volunteers were recruited in the study (mean age 29 ± 4.3 years). None of them was using any medication known to interfere with thyroid hormones metabolism or cardiovascular system function. There was no dietary restriction. 50 μg T_3 was administered per os twice daily for three days. To exclude serum T_3 level variation (due to its $T_{1/2}$ of ~8 hours), before T_3 initiation and in the morning of the fourth day, the participants reported in the testing room between 8:00 AM and 8:30 AM after an overnight fasting.

A heparinized indwelling intravenous (IV) line was placed in a forearm vein, and the subject remained in the supine position until the end of the study. Blood samples for measurement of ANP, PRA, ALDO, T_4, T_3, TSH, serum creatinine, sodium, and potassium levels were obtained after 30 minutes of being in the supine position before (i.e., baseline) and after a 1500 mL normal saline (NSal) infusion (IV, rate 25 mL/min). New blood samples were thereafter obtained for ANP, PRA, and ALDO measurement at 30, 60, 75, 90, and 120 minutes from the completion of NSal-induced volume expansion (60 minutes from initiation of NSal). All blood samples were immediately centrifuged, and plasma or serum was separated and frozen at −70°C until assayed. For ANP determinations, venous blood was drawn directly into ice-chilled disposable glass tubes containing EDTA (1 mg/mL) and 500 IU/mL aprotinin. Plasma was immediately separated by centrifugation for 15 minutes at 4°C and stored frozen at −70°C until the assay. Plasma ANP levels were measured by RIA as previously described [13] using an antiserum to human ANP (1–28) (Nichols Institute Diagnostics LtD., UK). Assay results were corrected for recovery. PRA was measured using solid-phase RIA from DiaSorin (Saluggia, Italy). For the statistical analysis, all PRA levels below the sensitivity value (0,2 ng/mL/hr) were set at this level. Serum ALDO, T_3, T_4, and TSH concentrations were measured using commercial RIA kits. Serum and urine creatinine and electrolytes were measured by routine laboratory methods.

Additionally, two urine samples were collected for two- and- a- half-hour periods, at baseline and after NSal infusion for urine ALDO, electrolytes, and creatinine level measurement. Baseline and 60- and 120-minute blood pressure (BP) and heart rate (HR) were recorded. Mean arterial blood pressure (MAP) was calculated as follows:

$$\text{MAP} = \text{diastolic BP} + \left(\frac{1}{3}\text{pulse pressure}\right). \quad (1)$$

MAP was used for the determination of the systemic vascular resistance (SVR) according to the formula

$$\text{SVR} = \frac{\text{MAP}}{\text{cardiac output}}. \quad (2)$$

All participants underwent a comprehensive 2D and tissue Doppler imaging transthoracic echocardiography at baseline (i.e., before treatment with T_3) and after 3 days of treatment, performed by a single experienced echocardiographer with the ultrasound apparatus ATL-Ultramark 9 (Bothell, Seattle, USA) and a 2.5 MHz transducer. Complete M mode, two dimensional, and spectral and color Doppler recordings were made with subjects in the left lateral decubitus position using conventional parasternal and apical views, according to the standardization of the American Society of Echocardiography [22]. Three consecutive sinus beats were measured, and the averaged Doppler analysis of the transmitral early (E) and late (A) inflow velocity was performed in the apical 4-chamber view. Systolic function of the left ventricle was also evaluated. The study was conducted in accordance with the 1964 Declaration of Helsinki and was approved by the ethics

Table 2: Echocardiographic characteristics of the study population before and after T_3 administration.

Parameter	Before T_3	After T_3	P value
Left atrial diameter, cm	3.38 ± 0.25	3.31 ± 0.27	.660
LV end-systolic diameter, cm	3.32 ± 0.25	3.09 ± 0.26	.024
LV end-systolic volume, mL	45.5 ± 8.2	38.2 ± 7.5	.034
Shortening fraction, %	33.6 ± 0.9	39.6 ± 2.8	.002
Ejection fraction, %	62.1 ± 1.4	69.8 ± 3.4	.001
Mean V(cf) shortening, circ/sec	1.14 ± 0.07	1.43 ± 0.11	<.001
Stroke volume, mL	73.8 ± 10.7	87.1 ± 12.1	.010
Stroke index, mL/m^2	37.6 ± 6.7	46 ± 5.9	.049
LV ejection time, msec	284.7 ± 20.4	268 ± 14.4	.069
Cardiac output, L/min	4.97 ± 0.62	6.51 ± 0.98	.038
LV PET/ET ratio	0.27 ± 0.06	0.28 ± 0.03	.749
Peak E velocity, m/sec	0.73 ± 0.13	0.59 ± 0.12	.006
Peak A velocity, m/sec	0.44 ± 0.04	0.48 ± 0.05	.440
Acceleration velocity, m/sec^2	7.3 ± 1.6	5.2 ± 1.8	.018
SVR, mmHg·mL^{-1}·min^{-1}	24.5 ± 2.9	18.2 ± 2.7	.046

LV: left ventricular; PET/ET: pre-ejection/ejection time; SVR: systemic vascular resistance; V(cf): velocity of circumference fiber.

Table 3: Area under the curve differences in clinical and laboratory characteristics following normal saline-induced plasma volume expansion before and after T_3 administration in the study population.

Parameter	Δ-AUC		P value
	Before T_3	After T_3	
Heart rate, beats per minute ∗ hour	0.28 ± 19	5, 15 ± 14	.457
Mean BP, mmHg ∗ hour	−4.43 ± 45	2.58 ± 28.8	.668
ANP, pmol/L ∗ hour	18.7 ± 11.1	22.7 ± 12.6	.212
PRA, nmol/L/h ∗ hour	−1.67 ± 1.42	−0.72 ± 1.42	.122
ALDO, pmol/L ∗ hour	−3.08 ± 3.9	−3.08 ± 1.36	1.000

Δ-AUC: area under the curve differences; ALDO: plasma aldosterone; ANP: plasma atrial natriuretic peptide; PRA: plasma renin activity.

committee at the HAF and VA General Hospital of Athens. All participants provided an informed consent.

2.2. Statistical Methods. The hormone responses were calculated either as the peak minus baseline (or Δ response) or as the integrated area under the curve (AUC) values on the baseline (0 minute) corrected response, using the trapezoidal model. One-way ANOVA and paired t-test were used for statistical comparisons in each group. Nonpaired t-test and Mann Whitney, for non-parametric data, were used for comparisons between groups. Results are expressed as the mean ± standard deviation (SD). Differences were considered significant at the level of $P < .05$.

3. Results

T_3 administration resulted in a significant increase in serum T_3, a significant decrease in serum TSH, and a small but significant decrease in serum T_4 levels (Table 1). Mean BP and HR were not significantly affected by T_3 administration. Similarly, the induced hyperthyroid serum T_3 levels resulted in a nonsignificant increase in plasma ANP, ALDO, and PRA (Table 1). T_3 administration was followed by a significant increase in shortening fraction, velocity of circumferential fiber shortening, ejection fraction, stroke volume, stroke index, and cardiac output and a significant decrease in left ventricular (LV) end-systolic diameter, LV end-systolic volume, LV ejection time, peak E velocity, acceleration velocity, and systemic vascular resistance (Table 2). On the contrary, peak A velocity and left atrial diameter were not significantly affected (Table 2).

The NSal-induced plasma volume expansion was followed by a significant decrease in PRA and ALDO levels without significantly affecting MAP and heart rate over each study period (i.e., before and after T_3 administration; Table 3). On the contrary, plasma ANP levels increased significantly compared with baseline values in both study periods (Table 3, Figure 1). However, hormone responses to NSal-induced volume expansion, measured as the integrated area under the curve values corrected on the baseline (Δ AUC), were comparable before and after T_3 administration for ANP, PRA, and ALDO (Table 3, Figure 1).

Plasma volume expansion did not alter urine ALDO excretion but affected the urine electrolyte excretion. Urine sodium and potassium levels increased significantly after NSal-induced volume expansion compared to levels before NSal infusion (Table 4) and to comparable degree in both study periods that is, the NSal-induced significant changes (Δ responses) were comparable before and after T_3 administration.

4. Discussion

Atrial stretch is the primary factor that regulates ANP secretion. This has been shown in isolated cardiac preparations [23, 24] and in intact animals with volume expansion or direct atrial distention [24–26]. However, in vitro studies in rat atrial myocyte cultures have shown that ANP synthesis and secretion are also stimulated directly by thyroid hormones in a dose-dependent manner [16]. There are no data in vivo, indicating direct or indirect thyroid hormone stimulatory effect on myocardial ANP secretion.

Our study is the first to show that a short-term increase in T_3 levels, induced by an exogenous administration of

Table 4: Urinary electrolyte excretion before and after normal saline-induced plasma volume expansion at baseline and after T_3 administration.

Parameter	Before T_3			After T_3		
	Before NS	After NS	Δ Response	Before NS	After NS	Δ Response
Aldo/creatinine, pmol/gr	113 ± 45	115 ± 51	55 ± 192	168 ± 190	124 ± 96	9 ± 89
Na/creatinine, mEq/gr	111 ± 84	451 ± 278†	340 ± 288	113 ± 70	338 ± 231†	224 ± 186
K/creatinine, mEq/gr	29 ± 12	76 ± 21*	47 ± 18	34 ± 17	83 ± 40*	49 ± 34
Ca/creatinine, mg/gr	167 ± 56	285 ± 161	119 ± 190	224 ± 84	248 ± 152	23 ± 179
P/creatinine, mg/gr	611 ± 161	456 ± 222	−155 ± 120	597 ± 223	345 ± 191	−251 ± 276
Mg/creatinine, mg/gr	49 ± 24	109 ± 101	60 ± 112	83 ± 47	72 ± 42	−11 ± 23

*$P < .01$ compared to values before plasma volume expansion.
†$P < .05$ compared to values before plasma volume expansion.
NS: normal saline-induced plasma volume expansion.

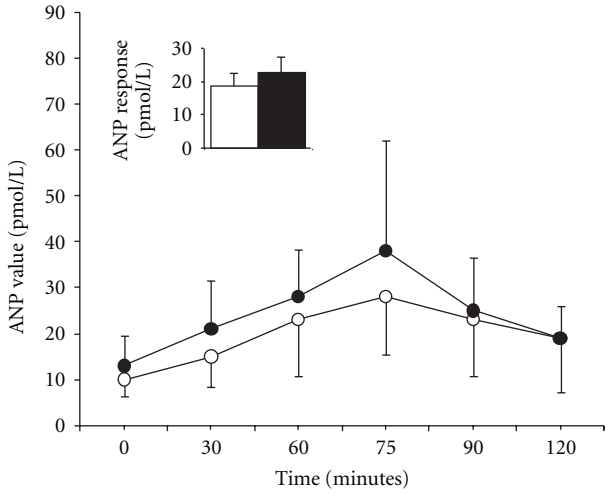

Figure 1: Mean (+SD) ANP values following administration of normal saline. The lines represent subjects before T_3 (open circles) and after T_3 administration (black circles). The mean integrated AUC values together with SEM are shown in the insets, with bars representing subjects before (white) and after T_3 administration (black) (ANP units pmol/L.h). There was no difference in the integrated AUC values when responses before and after T_3 administration were compared.

T_3, despite reaching T_3 values comparable to that seen in hyperthyroidism, did not have any significant impact on plasma ANP levels. We administered T_3 for 3 days, as the 72-hour length has been reported to be an adequate time frame for a T_3-induced ANP-mRNA synthesis and subsequent significant protein secretion. Argentin et al. [27] have demonstrated that treatment of neonatal rat cardiomyocytes (primary cultures) with T_3 results in a significant increase in pronatriodilantin (the precursor for ANP) mRNA, whereas Matsubara et al. [16] have shown a significant increase in secreted ANP levels following treatment with T_3 in primary cultures. The effect in the former study was already apparent at 12 hours and reached its maximal effect at 48 hours [27], whilst in the later became apparent at 48 hours [16]. The stimulatory effect of T_3 was near maximal at a concentration of 5×10^{-9} M [27], which correlates very well with the affinity of T_3 for its nuclear receptor [28].

Our study is in accordance with previous studies showing a significant increase in LV contractility following T_3 administration, resulting in a profound increase in stroke volume, cardiac output, and cardiac index [1, 2]. However, the non-significant influence of short-term hyperthyroidism in left atrial diameter and in peak *A* velocity, which reflect atrial contraction, indicate that the resulting alterations in cardiac preloading conditions were not sufficient enough to significantly affect atrial wall stretch. On the other hand, the significant decrease in peak *E* velocity, which represents an early active relaxation of the left ventricle, in conjunction with the unchanged peak *A* velocity and left atrial diameter, may indicate a more active relaxation of the left ventricle and rapid filling phase [29–31] without significant change in atrial function. Nevertheless, if the action of thyroid hormones were to be direct on cardiac myocytes, one should expect a significant increase in plasma ANP levels following T_3 administration. The above-mentioned alterations in cardiovascular system do not seem enough to increase atrial stretch and hence ANP secretion.

In healthy men, blood volume expansion has previously been shown to increase plasma ANP levels, and this increase closely correlates with the relative intravascular expansion [32]. Intravascular volume expansion following NSal infusion in our subjects is validated by the significant decrease of PRA and ALDO levels. The comparable NSal-induced decrease in PRA and serum ALDO levels before and after T_3 administration and the non-significant change in the MAP and heart rate indicate comparable plasma volume expansions, which have been proved to induce increased cardiac preload [33, 34], velocity of the diastolic rapid filling phase [29, 30], cardiac output and stroke volume [34–36]. In agreement this, a comparable amount of NSal-induced natriuresis was observed in our study participants before and after T_3 administration. Therefore, thyroid hormone action in our population was exerted predominantly through indirect modification of the peripheral cardiovascular system rather than a directed effect.

Our observation that the short-term hyperthyroid T_3 levels in normal men do not affect baseline plasma ANP levels is in contrast to what is seen in chronic hyperthyroid

patients, where ANP levels are significantly increased [10–13]. The possibility that this finding is attributed to different serum T_4 levels should be excluded taking into account that the stimulating effect of T_4 on cellular ANP content and ANP-mRNA levels in rat atria is entirely induced after its conversion to T_3 by type I 5′-deiodinase [37]. Based on our observations, we can speculate that the increased plasma ANP levels in long-lasting hyperthyroidism are mainly the result of hemodynamic changes on the heart and peripheral circulation that move the cardiovascular system to a new functional equilibrium accompanied by increased atrial stretch. This is supported by the fact that hyperthyroid patients with atrial fibrillation have significantly higher plasma ANP levels compared to patients without atrial fibrillation [38]. Additionally, artificial pacing in intact animals [39] as well as in humans [40] increases the secretion of ANP through the elevation of atrial pressure, despite the stable normal thyroid hormone levels. The nondifferent baseline and post NSal-infusion plasma ANP levels in our study may indicate that short-term hyperthyroid serum T_3 levels are not able to induce hemodynamic changes sufficient enough to increase atrial stretch.

In conclusion, our data indicate that thyroid hormone-induced myocardial ANP secretion in healthy subjects is not the result of a direct action on the myocardium, rather, it is mainly the result of an indirect modification in cardiovascular hemodynamics that lead to increased atrial stretch. More studies are needed to replicate these results and confirm this evidence.

References

[1] R. C. Smallridge, M. H. Goldman, K. Raines, S. Jones, and D. Van Nostrand, "Rest and exercise left ventricular ejection fraction before and after therapy in young adults with hyperthyroidism and hypothyroidism," *American Journal of Cardiology*, vol. 60, no. 10, pp. 929–931, 1987.

[2] I. Klein and K. Ojamaa, "Thyroid hormone and the cardiovascular system," *New England Journal of Medicine*, vol. 344, no. 7, pp. 501–509, 2001.

[3] M. J. M. Diekman, M. P. M. Harms, E. Endert, W. Wieling, and W. M. Wiersinga, "Endocrine factors related to changes in total peripheral vascular resistance after treatment of thyrotoxic and hypothyroid patients," *European Journal of Endocrinology*, vol. 144, no. 4, pp. 339–346, 2001.

[4] W. H. Dillmann, "Biochemical basis of thyroid hormone action in the heart," *American Journal of Medicine*, vol. 88, no. 6, pp. 626–630, 1990.

[5] G. A. Brent, "Mechanisms of disease: the molecular basis of thyroid hormone action," *New England Journal of Medicine*, vol. 331, no. 13, pp. 847–853, 1994.

[6] I. Klein, K. Ojamaa, A. M. Samarel, R. Welikson, and C. Hong, "Hemodynamic regulation of myosin heavy chain gene expression: studies in the transplanted rat heart," *Journal of Clinical Investigation*, vol. 89, no. 1, pp. 68–73, 1992.

[7] A. J. de Bold, H. B. Borenstein, A. T. Veress, and H. Sonnenberg, "A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats," *Life Sciences*, vol. 28, no. 1, pp. 89–94, 1981.

[8] M. G. Currie, D. M. Geller, B. R. Cole et al., "Bioactive cardiac substances: potent vasorelaxant activity in mammalian atria," *Science*, vol. 221, no. 4605, pp. 71–73, 1983.

[9] J. H. Laragh, "Atrial natriuretic hormone, the renin-aldosterone axis, and blood pressure-electrolyte homeostasis," *New England Journal of Medicine*, vol. 313, no. 21, pp. 1330–1340, 1985.

[10] E. Rolandi, B. Santaniello, M. Bagnasco et al., "Thyroid hormones and atrial natriuretic hormone secretion: study in hyper- and hypothyroid patients," *Acta Endocrinologica*, vol. 127, no. 1, pp. 23–26, 1992.

[11] K. Widecka, J. Gozdzik, T. Dutkiewicz, U. Majewska, and S. Czekalski, "Atrial natriuretic factor in untreated hyperthyroidism," *Annals of Clinical Biochemistry*, vol. 27, no. 4, pp. 313–317, 1990.

[12] C. Parlapiano, E. Campana, N. Alessandri et al., "Plasma atrial natriuretic hormone in hyperthyroidism," *Endocrine Research*, vol. 24, no. 1, pp. 105–112, 1998.

[13] G. Koukoulis, A. Polymeris, I. Tzavara, D. Pappas, and N. Thalassinos, "Normalization of thyroid hormone levels in patients with either hyper- or hypothyroidism results in a profound change of atrial natriuretic peptide (ANP) levels," *Hormones (Athens)*, vol. 1, no. 2, pp. 104–112, 2002.

[14] M. Kohno, K. Takaori, and T. Matsuura, "Atrial natriuretic polypeptide in atria and plasma in experimental hyperthyroidism and hypothyroidism," *Biochemical and Biophysical Research Communications*, vol. 134, no. 1, pp. 178–183, 1986.

[15] P. W. Ladenson, K. D. Bloch, and J. G. Seidman, "Modulation of atrial natriuretic factor by thyroid hormone: messenger ribonucleic acid and peptide levels in hypothyroid, euthyroid, and hyperthyroid rat atria and ventricles," *Endocrinology*, vol. 123, no. 1, pp. 652–657, 1988.

[16] H. Matsubara, Y. Hirata, and H. Yoshimi, "Effects of steroid and thyroid hormones on synthesis of atrial natriuretic peptide by cultured atrial myocytes of rat," *Biochemical and Biophysical Research Communications*, vol. 145, no. 1, pp. 336–343, 1987.

[17] B. S. Edwards, R. S. Zimmerman, T. R. Schwab, D. M. Heublein, and J. C. Burnett Jr., "Atrial stretch, not pressure, is the principal determinant controlling the acute release of atrial natriuretic factor," *Circulation Research*, vol. 62, no. 2, pp. 191–195, 1988.

[18] N. Katsube, D. Schwartz, and P. Needleman, "Release of atriopeptin in the rat by vasoconstrictors or water immersion correlates with changes in right atrial pressure," *Biochemical and Biophysical Research Communications*, vol. 133, no. 3, pp. 937–944, 1985.

[19] C. Cottier, L. Matter, P. Weidmann, S. Shaw, and M. P. Gnadinger, "Renal response to low-dose infusion of atrial natriuretic peptide in normal man," *Kidney International*, vol. 34, no. 25, pp. S72–S78, 1988.

[20] J. Anderson, A. Struthers, N. Christofides, and S. Bloom, "Atrial natriuretic peptide: an endogenous factor enhancing sodium excretion in man," *Clinical Science*, vol. 70, no. 4, pp. 327–331, 1986.

[21] P. Weidmann, B. Hellmueller, and D. E. Uehlinger, "Plasma levels and cardiovascular, endocrine, and excretory effects of atrial natriuretic peptide during different sodium intakes in man," *Journal of Clinical Endocrinology and Metabolism*, vol. 62, no. 5, pp. 1027–1036, 1986.

[22] D. J. Sahn, A. DeMaria, J. Kisslo, and A. Weyman, "Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements," *Circulation*, vol. 58, no. 6, pp. 1072–1083, 1978.

[23] J. R. Dietz, "Release of natriuretic factor from rat heart-lung preparation by atrial distension," *The American Journal of Physiology*, vol. 247, no. 6, pp. R1093–R1096, 1984.

[24] R. E. Lang, H. Tholken, D. Ganten, F. C. Luft, H. Ruskoaho, and T. Unger, "Atrial natriuretic factor—a circulating hormone stimulated by volume loading," *Nature*, vol. 314, no. 6008, pp. 264–266, 1985.

[25] J. R. Ledsome, N. Wilson, C. A. Courneya, and A. J. Rankin, "Release of atrial natriuretic peptide by atrial distension," *Canadian Journal of Physiology and Pharmacology*, vol. 63, no. 6, pp. 739–742, 1985.

[26] C. H. Metzler, M. E. Lee, T. N. Thrasher, and D. J. Ramsay, "Increased right or left atrial pressure stimulates release of atrial natriuretic peptides in conscious dogs," *Endocrinology*, vol. 119, no. 5, pp. 2396–2398, 1986.

[27] S. Argentin, J. Drouin, and M. Nemer, "Thyroid hormone stimulates rat pro-natriodilatin mRNA levels in primary cardiocyte cultures," *Biochemical and Biophysical Research Communications*, vol. 146, no. 3, pp. 1336–1341, 1987.

[28] J. H. Oppenheimer, "Thyroid hormone action at the cellular level," *Science*, vol. 203, no. 4384, pp. 971–979, 1979.

[29] F. Pèronnet, R. J. Ferguson, H. Perrault, and G. Ricci, "Echocardiographic dimensions determined in normally active college women and in female athletes," *Medicine and Science in Sports and Exercise*, vol. 14, no. 3, pp. 181–182, 1982.

[30] C. P. Cheng, Y. Igarashi, and W. C. Little, "Mechanism of augmented rate of left ventricular filling during exercise," *Circulation Research*, vol. 70, no. 1, pp. 9–19, 1992.

[31] M. R. Curtois, B. Barzilai, Z. Vered, N. Ricciotti, and P. A. Ludbrook, "Effects of preload reduction on atrioventricular pressure relations and Doppler flow velocity," *Circulation*, vol. 76, no. Sl, pp. IV–124, Abstract, 1987.

[32] P. V. Nguyen, D. L. Smith, and F. H. Leenen, "Acute volume loading, atrial natriuretic peptide release and cardiac function in healthy men. Effects of beta-blockade," *Life Sciences*, vol. 43, no. 10, pp. 821–830, 1988.

[33] S. K. Rerych, P. M. Scholz, D. C. Sabiston Jr., and R. H. Jones, "Effects of exercise training on left ventricular function in normal subjects: a longitudinal study by radionuclide angiography," *American Journal of Cardiology*, vol. 45, no. 2, pp. 244–252, 1980.

[34] E. F. Coyle, M. K. Hopper, and A. R. Coggan, "Maximal oxygen uptake relative to plasma volume expansion," *International Journal of Sports Medicine*, vol. 11, no. 2, pp. 116–119, 1990.

[35] M. K. Hopper, A. R. Coggan, and E. F. Coyle, "Exercise stroke volume relative to plasma-volume expansion," *Journal of Applied Physiology*, vol. 64, no. 1, pp. 404–408, 1988.

[36] I. L. Kanstrup and B. Ekblom, "Acute hypervolemia, cardiac performance, and aerobic power during exercise," *Journal of Applied Physiology Respiratory Environmental and Exercise Physiology*, vol. 52, no. 5, pp. 1186–1191, 1982.

[37] Y. Mori, M. Nishikawa, H. Matsubara et al., "Stimulation of rat atrial natriuretic peptide (rANP) synthesis by triiodothyronine and thyroxine (T_4): T_4 as a prohormone in synthesizing rANP," *Endocrinology*, vol. 126, no. 1, pp. 466–471, 1990.

[38] S. Czekalski, K. Widecka, J. Gozdzik et al., "Atrial natriuretic peptide and cyclic guanosine monophosphate plasma concentrations in patients with thyrotoxicosis and atrial fibrillation. Effect of short-term methimazole therapy," *Journal of Endocrinological Investigation*, vol. 17, no. 5, pp. 341–346, 1994.

[39] G. Christensen and E. Leistad, "Atrial systolic pressure, as well as stretch, is a principal stimulus for release of ANF," *American Journal of Physiology*, vol. 272, no. 2, pp. H820–H826, 1997.

[40] J. C. Burnett Jr., M. J. Osborn, S. C. Hammill, and D. M. Heublein, "The role of frequency of atrial contraction versus atrial pressure in atrial natriuretic peptide release," *Journal of Clinical Endocrinology and Metabolism*, vol. 69, no. 4, pp. 881–884, 1989.

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Cardiology Research and Practice
Volume 2011, Article ID 568095, 7 pages
doi:10.4061/2011/568095

Review Article

Right Ventricular Dysfunction and Failure in Chronic Pressure Overload

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Received 7 December 2010; Accepted 25 January 2011

Academic Editor: Georgios Giannakoulas

Right ventricular (RV) dysfunction is the main cause of death in pulmonary arterial hypertension (PAH). Our understanding of the pathophysiology of RV dysfunction is limited but improving. Methods to better diagnose RV dysfunction earlier and treatments specifically designed to minimize or reverse the remodeling process are likely to improve outcomes. We review the current understanding of RV dysfunction in chronic pressure overload and introduce some novel insights based on recent investigations into pathophysiology, diagnosis, and treatment.

1. Introduction

Dysfunction of the right ventricle (RV) can occur in a number of clinical scenarios including pressure overload, cardiomyopathies, ischemic, congenital, or valvular heart disease, arrhythmias, and sepsis. Pressure overload can occur in an acute or chronic setting. Diagnosis is made on the compilation of data from the history and physical examination, electrocardiogram, chest X-ray, echocardiogram, and invasive hemodynamics. RV failure is associated almost universally with poor prognosis. Early recognition is essential to improve outcomes. Although pressure overload can occur with pulmonary valvular stenosis, the most common cause of pressure overload is pulmonary arterial hypertension (PAH). Recent advances, particularly in PAH management, have highlighted the importance of RV function and stimulated renewed interest in better understanding its adaptation to pressure overload. This is particularly evident over the past year, in which RV function has been reviewed several times [1, 2], as has echocardiographic methods of imaging the RV [3], RV function in cardiac and thoracic surgery [4–6], the mechanisms underlying RV failure in PH [7], and the treatment of acute right heart failure [8].

2. Chronic RV Pressure Overload

PAH is defined as a mean pulmonary artery pressure >25 mm Hg with a pulmonary capillary wedge pressure, left atrial pressure, or left ventricular end-diastolic pressure ≤15 mm Hg [9]. Historically, long-term outcomes have been quite poor because of progressively increasing hypertension resulting in severe RV failure. But clinical outcomes have significantly improved with the recent advent of several pulmonary-specific vasodilators [10–13], such as prostanoids, endothelin receptor antagonists, and phosphodiesterase 5A (PDE5A) inhibitors. Median survival for patients with PAH without treatment is 2.8 years with 1-, 3-, and 5-year survival rates of 68%, 48%, and 34%, respectively [10]. With continuous prostanoid treatment, survival has improved 87-88%, 63–71%, and 56%, respectively [12, 14]. Similar results have been seen with the oral endothelin receptor antagonist bosentan (82–96% survival at 1 year; 67–89% 2-year survival) [15]. RV function is a critical determinant of patient outcomes in PAH and has recently been recognized as an important avenue for further research [16]. RV failure is the end result of PAH and the cause of at least 70% of all PAH deaths [10]. Unfortunately, identifying which patients will progress to RV

failure and at what time in the course of disease has been difficult.

3. Pathophysiology of RV Adaptation to Chronic Pressure Overload

One of the key features to RV adaptation to chronic pressure overload is hypertrophy. In general terms, this is felt to be due to increased wall stress due to increased pressure (Laplace's Law). Myocyte size increases via the synthesis of additional sarcomeres [7]. Extracellular matrix increases as well, with resultant increased fibrosis. At some point, adaptation is insufficient in the face of the pressure overload, resulting in dilation, decreased systolic and diastolic function, and frank RV failure. Unfortunately, this sequence of events is not understood well in the RV. There is a decrease in α-subtype myosin heavy chain relative to the β-subtype that is implicated in decreased systolic function [17, 18]. Actin expression is also altered in PAH, as might be the troponin complex [7]. Pressure overload causes alterations in β-adrenoreceptor and angiotensin type 1 receptor densities. As with LV failure, RV failure is associated with upregulation of the renin-angiotensin system. RV ischemia also has been documented in PAH indicating that oxygen supply-demand mismatch is likely implicated in the development of RV hypertrophy and failure [19] which may be due to decreased microvasculature recruitment or reduced vasodilatory capacity [7]. Upregulation of myocyte apoptosis in the pressure-overloaded RV also likely contributes to progressive RV dysfunction [7]. Mitochondrial nitric oxide synthase (mtNOS) is upregulated in the hypertrophied RV myocardium and is partially reversed by treatment with the PDE5A inhibitor, sildenafil [20]. These findings are in keeping with prior studies showing increases in PDE5 expression [21], the mitochondrial membrane potential [22], and glucose uptake [23] in RV tissue in patients with PAH and may represent a novel target for RV-specific therapeutic intervention [24].

Regional heterogeneity of RV remodeling and dysfunction has been observed in patients with PAH [25]. Hypertrophy is greatest in the RV outflow tract and worse in patients with decompensated RV function (Figure 1). Regional wall thickening, as a measure of regional function, is significantly decreased in the outflow tract (infundibulum) of patients regardless of RV functional status, with corresponding increased wall stress in this region. Initial reports from our group have suggested that alterations in regional RV structure and function, particularly in the outflow tract, precede overt hemodynamic RV decompensation, in that patients with less severe RV failure have selective outflow tract hypertrophy, whereas patients with severe RV failure have a generalized RV hypertrophy. These results need to be confirmed prospectively in patient cohorts in whom the progression of disease can be followed over time and treatments, but this asymmetrical hypertrophic response is consistent with an earlier study that found greater fiber shortening in the outflow tract compared with the RV sinus region and a sequential timing of contraction in the two regions [26]. Hypertrophy and dysfunction in the outflow tract may be an early sign of RV impending RV failure and suggests that a better understanding of RV remodeling on a regional level may greatly advance our knowledge of RV response to disease.

4. Identifying RV Dysfunction

Identifying RV dysfunction at less severe stages, which would allow for earlier intervention and potentially better long-term results, has been limited largely due to complex RV three-dimensional geometry that defies the assumption of a simple ellipsoid, complex LV/septum interactions, and lack of accepted approaches to assess regional and organ-level RV function. Current markers of RV failure that have been associated with poor outcomes only recognize end-stage disease. There have been several recent approaches to better identify RV dysfunction.

The clinically accepted gold standard for identifying RV dysfunction and understanding physiology in the pressure-overloaded state remains invasive hemodynamics [1]. Right atrial pressure, cardiac output, and mean pulmonary arterial pressure all have been prognostic of outcomes in PAH [10]. Measurement of hemodynamics with exercise can further identify PAH not apparent at rest, distinguish from LV diastolic dysfunction, and aid in prognosis (failure to increase cardiac output with exercise) [1]. Pressure-volume loops of RV function in chronic PAH can provide additional information beyond standard hemodynamics. For example, prostacyclin has been shown to improve ventricular-vascular coupling (ratio of contractility as defined by the end-systolic pressure-volume relationship, Ees, to afterload as defined by pulmonary arterial elastance, which itself is the ratio of end-systolic pressure to stroke volume; Figure 2) [27]. This methodology has been used to show enhanced contractility (end-systolic pressure-volume relationship, Ees) despite lower cardiac output and ventricular-vascular decoupling (lower ratio of Ees to pulmonary arterial elastance, Ea) in PAH [28]. Measures of hemodynamics that take into consideration the pulsatility of pulmonary blood flow further offer an opportunity to better understand the hydraulic load that the RV encounters. Increased vasculature stiffness results in increased fluid wave reflections and an increased RV pump workload. While pulmonary vascular resistance (transpulmonary gradient divided by cardiac output) is the clinical standard measurement of pulmonary vascular load, this only provides information on the static load. However, 1/3 − 1/2 of the pulmonary load (hydraulic power) is due to the pulsatile nature of blood flow [1]. Load in a pulsatile flow system is better characterized by input impedance. One recent study of pulmonary vascular input impedance in 49 pediatric patients with PAH predicted clinical outcomes at one year better than pulmonary vascular resistance [29]. Such measures of pulsatile load and ventricular-vascular coupling may help explain when and how the RV fails [30], leading to improved diagnosis and more individualized treatment [31].

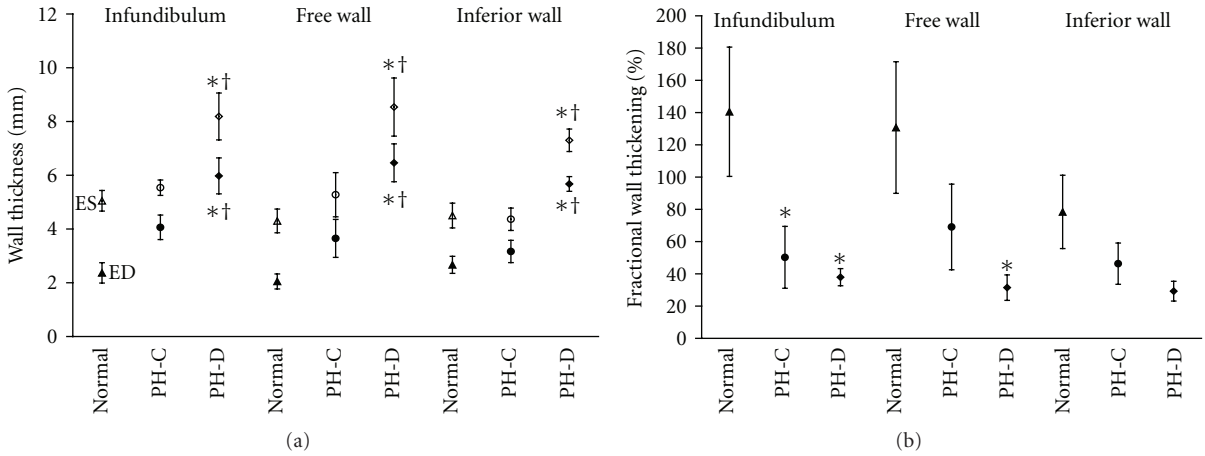

Figure 1: Regional heterogeneity of RV remodeling and dysfunction observed in patients with pulmonary hypertension. Patients were divided into one of three groups based upon hemodynamic parameters: Normal (normal pulmonary artery [PA] pressure, defined as mean PA pressure ≤25 mmHg), PH-C (PH with hemodynamically compensated RV function, defined as mean PA pressure >25 mmHg and right atrial [RA] pressure <10 mmHg), and PH-D (PH with hemodynamically decompensated RV function, defined as mean PA pressure ≥25 mmHg, and RA pressure ≥10 mmHg). (a) Regional RV wall thickness in end diastole (ED, filled symbols) and end systole (ES, open symbols). (b) Corresponding fractional wall thickening. $^{*}P < 0.05$ PH-C versus Normal or PH-D versus Normal; $^{\dagger}P < 0.05$ PH-D versus PH-C, from [25].

Echocardiography is a standard clinical method to assess the RV in PAH. It has, as its major advantage, its noninvasive nature allowing sequential studies over time and good visualization of the major RV structures and functions in a dynamic fashion. Although echocardiographic assessment of pulmonary artery pressure can be made from the tricuspid regurgitant jet, treatment decisions based on PAH hemodynamics need to be confirmed invasively. Additionally, the ability to estimate pulmonary artery pressure from the tricuspid regurgitant jet is quite useful, although for treatment decisions in PAH hemodynamics must be confirmed invasively. Fractional area change (FAC), as a surrogate of ejection fraction, is calculated by analyzing the difference in the cross-sectional area of the RV in systole and diastole and has prognostic value in small studies, as does RV enlargement, tricuspid regurgitations, pericardial effusion, and the Tei (myocardial performance) index [9]. Newer techniques include tissue Doppler imaging (TDI) and speckle tracking. Peak systolic strain of the RV free wall by TDI is reduced in PH patients, and this measure correlates with transpulmonary gradient, pulmonary vascular resistance, and cardiac index [32]. RV free wall peak systolic strain has been found to decrease with PH and decreases further with RV decompensation [33]. TDI of the RV has also demonstrated good correlation with cardiac magnetic resonance (CMR) derived RV ejection fraction [34]. Speckle tracking has also been used to quantify RV myocardial strain and may be a valuable method to detect preclinical disease because it detects minor changes not easily quantified by TDI. For example, speckle tracking RV myocardial strain patterns have identified abnormal RV contraction in systemic sclerosis patients with normal pulmonary pressures, even when other markers such as tricuspid annular plane systolic excursion were unchanged from normal [35–37]. A reliable method to identify pre-clinical RV dysfunction would be an important advance in RV imaging. Three-dimensional echocardiography has been validated as a method to assess RV volumes and has been used to evaluate RV function [38–40]. Limitations of echocardiography include limited acoustic windows for imaging the complex three-dimensional structure of the RV.

CMR has been useful for anatomical assessment of the RV and more recently functional assessment as well. Two recent reviews of CMR in PAH have recently been published [41, 42]. RV volume, mass, and stroke index measures by CMR predicted 1-year survival in 64 PAH patients [43]. Measures of PA stiffness by CMR (pulsatility, compliance, capacitance, distensibility, elastic modulus, and the pressure-independent stiffness index) have been reported to be a sensitive measure of early PAH [44]. Blood flow imaging by CMR has been used to detect vortices of blood flow in the main pulmonary artery of patients with PAH [45]. However, many, if not most, measures of RV function by CMR are not yet standardized.

Computed tomography (CT) also can be useful to assess RV structure and function due to its high spatial resolution, accessibility, and quick scan times, though it is limited by radiation and contrast exposure [46–48]. CT has been used to identify regionally heterogeneous RV remodeling and dysfunction in pulmonary hypertension [25]. This is consistent with findings of a study by CMR and echocardiography that found greater fiber shortening in the outflow tract compared with the RV sinus region [26].

5. Treatment of Pressure Overload-Induced RV Dysfunction

Clinical trials data are still quite limited on the effect of PAH-specific treatment on RV function as are data on any specific

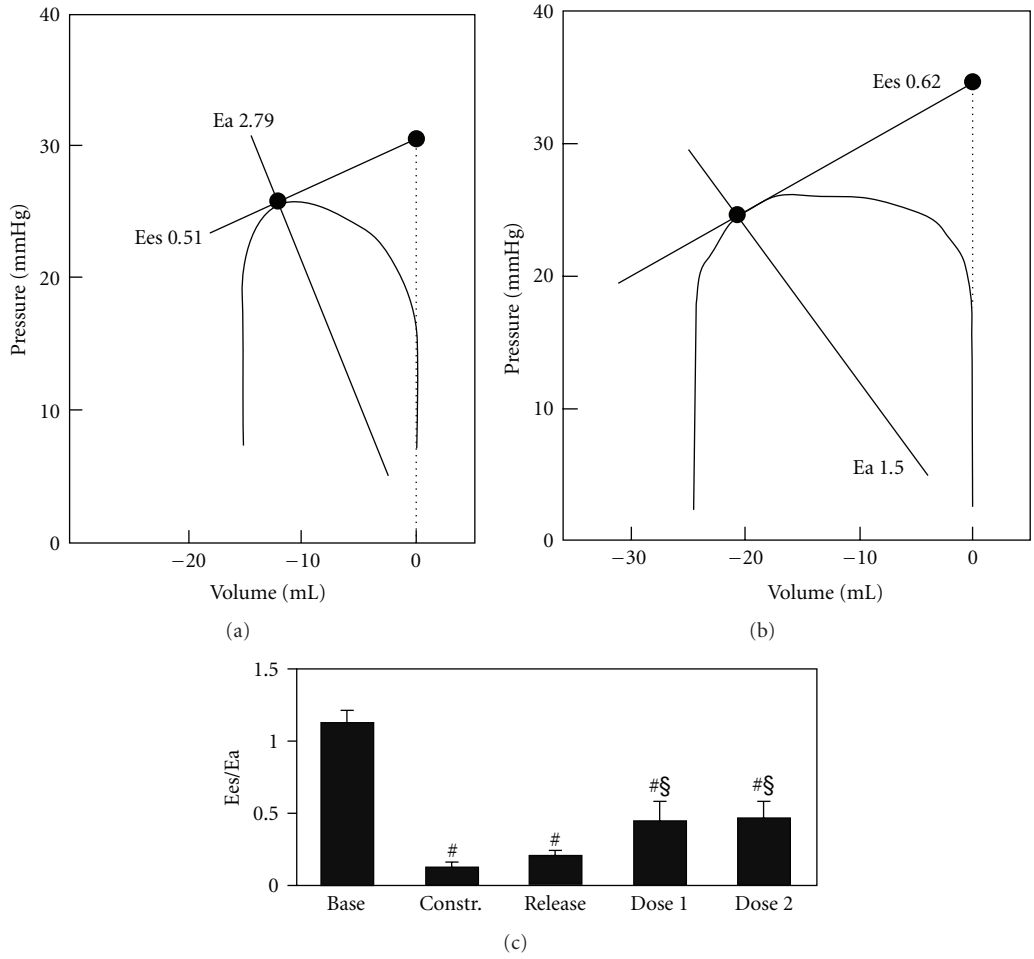

Figure 2: Example of ventricular-vascular coupling analysis. Systolic portions of the RV pressure-volume curves showing end-systolic elastance (Ees) and arterial elastance (Ea) lines. Ventricular-vascular coupling (Ees/Ea) is improved with prostacyclin due to a decrease in arterial elastance (Ea) in a dog with acute RV failure induced by transient pulmonary artery constriction. (a) Prior to prostacyclin infusion. (b) After prostacyclin infusion. (c) Ventricular-vascular coupling efficiency (Ees/Ea) at baseline, during pulmonary artery constriction (Constr.), after pulmonary artery release, and during prostacyclin infusion at 2 doses ($n = 7$; values are means + standard error). $^{\#}P < 0.05$ compared with baseline; $^{\S}P < 0.05$ compared with release, adapted from [27].

therapy for RV dysfunction. Regression of RV hypertrophy has been seen after 1 year of treatment with high-dose calcium channel blocker [49]. Prostacyclin treatment has been associated with modest RV reverse remodeling, specifically reversing some dilation and sphericity, as well as improved RV stroke volume [50, 51]. In a small retrospective study, the endothelin receptor antagonist bosentan resulted in improvements in invasive hemodynamics, functional status, and a trend in improvement in RV stroke volume, but no significant change in RV volume or ejection fraction [52]. The PDE5A inhibitor sildenafil increases RV contractility in isolated rat heart preparations and individual cardiomyocytes [21]. A least one ongoing multicenter PAH treatment study (with bosentan) is currently evaluating RV response to treatment with serial cardiac MRI with results hopefully to be reported within the next year [53].

There are some unique therapies in early-stage investigation that have been reported specifically to improve RV function in the pressure-overloaded state. A plant extract improved RV function in a rat model of PAH with severe RV failure [54]. A tissue-engineered skeletal myoblast sheet improved RV diastolic function, minimized fibrosis, and increased capillary density in a rat model of PAH [55]. There has been a suggested role for RV pacing as cardiac resynchronization therapy in PAH as RV dyssynchronous contraction has been observed to correlate with disease severity [56–58].

6. Conclusion

Although our knowledge of RV dysfunction in chronic pressure overload is progressing, there is still much that needs to be understood. Particular attention should be paid to the impact of PAH on ventricular-vascular interactions and how pathophysiologic derangements result in organ level dysfunction. Regional assessments of the RV may provide an avenue for better understanding mechanisms of RV

dysfunction and earlier diagnosis because nonhomogeneous RV adaptation appears to be an early marker of impending RV failure in PAH. Importantly, novel therapies to specifically improve RV remodeling and dysfunction in chronic pressure overload are greatly needed.

Disclosures

Dr. M. A. Simon reports receiving consulting fees or serving on paid advisory boards for Gilead and receiving lecture fees from United Therapeutics and Gilead. Dr. M. R. Pinsky has no conflict of interests.

Acknowlegments

NHLBI grants KL2 RR024154, HL073198, and HL67181. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH. Information on NCRR is available at http://www.ncrr.nih.gov/. Information on Re-engineering the Clinical Research Enterprise can be obtained from http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp.

References

[1] H. C. Champion, E. D. Michelakis, and P. M. Hassoun, "Comprehensive invasive and noninvasive approach to the right ventricle-pulmonary circulation unit state of the art and clinical and research implications," *Circulation*, vol. 120, no. 11, pp. 992–1007, 2009.

[2] M. A. McDonald and H. J. Ross, "Trying to succeed when the right ventricle fails," *Current Opinion in Cardiology*, vol. 24, no. 3, pp. 239–245, 2009.

[3] K. D. Horton, R. W. Meece, and J. C. Hill, "Assessment of the right ventricle by echocardiography: a primer for cardiac sonographers," *Journal of the American Society of Echocardiography*, vol. 22, no. 7, pp. 776–792, 2009.

[4] F. Haddad, P. Couture, C. Tousignant, and A. Y. Denault, "The right ventricle in cardiac surgery, a perioperative perspective—I. Anatomy, physiology, and assessment," *Anesthesia and Analgesia*, vol. 108, no. 2, pp. 407–421, 2009.

[5] R. W. C. Scherptong, H. W. Vliegen, M. M. Winter et al., "Tricuspid valve surgery in adults with a dysfunctional systemic right ventricle repair or replace?" *Circulation*, vol. 119, no. 11, pp. 1467–1472, 2009.

[6] A. Pedoto and D. Amar, "Right heart function in thoracic surgery: role of echocardiography," *Current Opinion in Anaesthesiology*, vol. 22, no. 1, pp. 44–49, 2009.

[7] H. J. Bogaard, K. Abe, A. Vonk-Noordegraaf, and N. F. Voelkel, "The right ventricle under pressure: cellular and molecular mechanisms of right-heart failure in pulmonary hypertension," *Chest*, vol. 135, pp. 794–804, 2009.

[8] T. Lahm, C. A. McCaslin, T. C. Wozniak et al., "Medical and surgical treatment of acute right ventricular failure," *Journal of the American College of Cardiology*, vol. 56, no. 18, pp. 1435–1446, 2010.

[9] V. V. McLaughlin, S. L. Archer, D. B. Badesch et al., "ACCF/AHA 2009 expert consensus document on pulmonary hypertension. A report of the American college of cardiology foundation task force on expert consensus documents and the American Heart Association developed in collaboration with the American college of chest physicians; American Thoracic Society, Inc.; and the pulmonary hypertension association," *Journal of the American College of Cardiology*, vol. 53, no. 17, pp. 1573–1619, 2009.

[10] G. E. D'Alonzo, R. J. Barst, S. M. Ayres et al., "Survival in patients with primary pulmonary hypertension: results from a national prospective registry," *Annals of Internal Medicine*, vol. 115, no. 5, pp. 343–349, 1991.

[11] V. V. McLaughlin, K. W. Presberg, R. L. Doyle et al., "Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines," *Chest*, vol. 126, no. 1, pp. 78S–92S, 2004.

[12] V. V. McLaughlin, A. Shillington, and S. Rich, "Survival in primary pulmonary hypertension: the impact of epoprostenol therapy," *Circulation*, vol. 106, no. 12, pp. 1477–1482, 2002.

[13] D. B. Badesch, S. H. Abman, G. Simonneau, L. J. Rubin, and V. V. McLaughlin, "Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines," *Chest*, vol. 131, no. 6, pp. 1917–1928, 2007.

[14] R. J. Barst, N. Galie, R. Naeije et al., "Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil," *European Respiratory Journal*, vol. 28, no. 6, pp. 1195–1203, 2006.

[15] V. V. McLaughlin, "Survival in patients with pulmonary arterial hypertension treated with first-line bosentan," *European Journal of Clinical Investigation*, vol. 36, no. 3, pp. 10–15, 2006.

[16] N. F. Voelkel, R. A. Quaife, L. A. Leinwand et al., "Right ventricular function and failure: Report of a National Heart, Lung, and Blood Institute working group on cellular and molecular mechanisms of right heart failure," *Circulation*, vol. 114, no. 17, pp. 1883–1891, 2006.

[17] B. D. Lowes, W. Minobe, W. T. Abraham et al., "Changes in gene expression in the intact human heart: downregulation of α-myosin heavy chain in hypertrophied, failing ventricular myocardium," *Journal of Clinical Investigation*, vol. 100, no. 9, pp. 2315–2324, 1997.

[18] T. J. Herron and K. S. McDonald, "Small amounts of α-myosin heavy chain isoform expression significantly increase power output of rat cardiac myocyte fragments," *Circulation Research*, vol. 90, no. 11, pp. 1150–1152, 2002.

[19] A. Gomez, D. Bialostozky, and A. Zajarias, "Right ventricular ischemia in patients with primary pulmonary hypertension," *Journal of the American College of Cardiology*, vol. 38, no. 4, pp. 1137–1142, 2001.

[20] T. Zaobornyj, L. B. Valdez, D. E. Iglesias, M. Gasco, G. F. Gonzales, and A. Boveris, "Mitochondrial nitric oxide metabolism during rat heart adaptation to high altitude: effect of sildenafil, L-NAME, and L-arginine treatments," *American Journal of Physiology*, vol. 296, no. 6, pp. H1741–H1747, 2009.

[21] J. Nagendran, S. L. Archer, D. Soliman et al., "Phosphodiesterase type 5 is highly expressed in the hypertrophied human right ventricle, and acute inhibition of phosphodiesterase type 5 improves contractility," *Circulation*, vol. 116, no. 3, pp. 238–248, 2007.

[22] J. Nagendran, V. Gurtu, D. Z. Fu et al., "A dynamic and chamber-specific mitochondrial remodeling in right ventricular hypertrophy can be therapeutically targeted," *Journal of Thoracic and Cardiovascular Surgery*, vol. 136, no. 1, pp. 168.e3–178.e3, 2008.

[23] M. Oikawa, Y. Kagaya, H. Otani et al., "Increased [18F]fluorodeoxyglucose accumulation in right ventricular free wall in patients with pulmonary hypertension and

the effect of epoprostenol," *Journal of the American College of Cardiology*, vol. 45, no. 11, pp. 1849–1855, 2005.

[24] J. Nagendran and E. D. Michelakis, "Mitochondrial NOS is upregulated in the hypoxic heart: implications for the function of the hypertrophied right ventricle," *American Journal of Physiology*, vol. 296, no. 6, pp. 1723–1726, 2009.

[25] M. A. Simon, C. Deible, M. A. Mathier et al., "Phenotyping the right ventricle in patients with pulmonary hypertension," *Clinical and Translational Science*, vol. 2, no. 4, pp. 294–299, 2009.

[26] T. Geva, A. J. Powell, E. C. Crawford, T. Chung, and S. D. Colan, "Evaluation of regional differences in right ventricular systolic function by acoustic quantification echocardiography and cine magnetic resonance imaging," *Circulation*, vol. 98, no. 4, pp. 339–345, 1998.

[27] F. Kerbaul, S. Brimioulle, B. Rondelet, C. Dewachter, I. Hubloue, and R. Naeije, "How prostacyclin improves cardiac output in right heart failure in conjunction with pulmonary hypertension," *American Journal of Respiratory and Critical Care Medicine*, vol. 175, no. 8, pp. 846–850, 2007.

[28] T. Kuehne, S. Yilmaz, P. Steendijk et al., "Magnetic resonance imaging analysis of right ventricular pressure-volume loops: in vivo validation and clinical application in patients with pulmonary hypertension," *Circulation*, vol. 110, no. 14, pp. 2010–2016, 2004.

[29] K. S. Hunter, P. F. Lee, C. J. Lanning et al., "Pulmonary vascular input impedance is a combined measure of pulmonary vascular resistance and stiffness and predicts clinical outcomes better than pulmonary vascular resistance alone in pediatric patients with pulmonary hypertension," *American Heart Journal*, vol. 155, no. 1, pp. 166–174, 2008.

[30] H. A. Ghofrani, R. J. Barst, R. L. Benza et al., "Future perspectives for the treatment of pulmonary arterial hypertension," *Journal of the American College of Cardiology*, vol. 54, no. 1, pp. S108–S117, 2009.

[31] D. B. Badesch, H. C. Champion, M. A. Gomez Sanchez et al., "Diagnosis and assessment of pulmonary arterial hypertension," *Journal of the American College of Cardiology*, vol. 54, no. 1, pp. S55–S66, 2009.

[32] N. Rajagopalan, M. A. Simon, M. A. Mathier, and A. Lopez-Candales, "Identifying right ventricular dysfunction with tissue Doppler imaging in pulmonary hypertension," *International Journal of Cardiology*, vol. 128, no. 3, pp. 359–363, 2008.

[33] M. A. Simon, N. Rajagopalan, M. A. Mathier, S. G. Shroff, M. R. Pinsky, and A. Lopez-Candales, "Tissue doppler imaging of right ventricular decompensation in pulmonary hypertension," *Congestive Heart Failure*, vol. 15, no. 6, pp. 271–276, 2009.

[34] L. E. Sade, Ö. Gülmez, U. Özyer et al., "Tissue doppler study of the right ventricle with a multisegmental approach: comparison with cardiac magnetic resonance imaging," *Journal of the American Society of Echocardiography*, vol. 22, no. 4, pp. 361–368, 2009.

[35] C. Matias, L. P. D. Isla, M. Vasconcelos et al., "Speckle-tracking-derived strain and strain-rate analysis: a technique for the evaluation of early alterations in right ventricle systolic function in patients with systemic sclerosis and normal pulmonary artery pressure," *Journal of Cardiovascular Medicine*, vol. 10, no. 2, pp. 129–134, 2009.

[36] S. R. Jategaonkar, W. Scholtz, T. Butz, N. Bogunovic, L. Faber, and D. Horstkotte, "Two-dimensional strain and strain rate imaging of the right ventricle in adult patients before and after percutaneous closure of atrial septal defects," *European Journal of Echocardiography*, vol. 10, no. 4, pp. 499–502, 2009.

[37] A. Meris, F. Faletra, C. Conca et al., "Timing and magnitude of regional right ventricular function: a speckle tracking-derived strain study of normal subjects and patients with right ventricular dysfunction," *Journal of the American Society of Echocardiography*, vol. 23, no. 8, pp. 823–831, 2010.

[38] S. T. Schindera, P. S. Mehwald, D. J. Sahn, and D. Kececioglu, "Accuracy of real-time three-dimensional echocardiography for quantifying right ventricular volume: static and pulsatile flow studies in an anatomic in vitro model," *Journal of Ultrasound in Medicine*, vol. 21, no. 10, pp. 1069–1075, 2002.

[39] M. Hubka, E. L. Bolson, J. A. McDonald, R. W. Martin, B. Munt, and F. H. Sheehan, "Three-dimensional echocardiographic measurement of left and right ventricular mass and volume: in vitro validation," *International Journal of Cardiovascular Imaging*, vol. 18, no. 2, pp. 111–118, 2002.

[40] T. Menzel, T. Kramm, A. Brückner, S. Mohr-Kahaly, E. Mayer, and J. Meyer, "Quantitative assessment of right ventricular volumes in severe chronic thromboembolic pulmonary hypertension using transthoracic three-dimensional echocardiography: changes due to pulmonary thromboendarterectomy," *European Journal of Echocardiography*, vol. 3, no. 1, pp. 67–72, 2002.

[41] R. Benza, R. Biederman, S. Murali, and H. Gupta, "Role of cardiac magnetic resonance imaging in the management of patients with pulmonary arterial hypertension," *Journal of the American College of Cardiology*, vol. 52, no. 21, pp. 1683–1692, 2008.

[42] L. E. R. McLure and A. J. Peacock, "Cardiac magnetic resonance imaging for the assessment of the heart and pulmonary circulation in pulmonary hypertension," *European Respiratory Journal*, vol. 33, no. 6, pp. 1454–1466, 2009.

[43] S. A. Van Wolferen, J. T. Marcus, A. Boonstra et al., "Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension," *European Heart Journal*, vol. 28, no. 10, pp. 1250–1257, 2007.

[44] J. Sanz, M. Kariisa, S. Dellegrottaglie et al., "Evaluation of pulmonary artery stiffness in pulmonary hypertension with cardiac magnetic resonance," *Cardiovascular Imaging*, vol. 2, no. 3, pp. 286–295, 2009.

[45] G. Reiter, U. Reiter, G. Kovacs et al., "Magnetic resonance-derived 3-dimensional blood flow patterns in the main pulmonary artery as a marker of pulmonary hypertension and a measure of elevated mean pulmonary arterial pressure," *Circulation*, vol. 1, no. 1, pp. 23–30, 2008.

[46] C. Plumhans, G. Mühlenbruch, A. Rapaee et al., "Assessment of global right ventricular function on 64-MDCT compared with MRI," *American Journal of Roentgenology*, vol. 190, no. 5, pp. 1358–1361, 2008.

[47] K. Koch, F. Oellig, K. Oberholzer et al., "Assessment of right ventricular function by 16-detector-row CT: comparison with magnetic resonance imaging," *European Radiology*, vol. 15, no. 2, pp. 312–318, 2005.

[48] S. V. Raman, M. Shah, B. McCarthy, A. Garcia, and A. K. Ferketich, "Multi-detector row cardiac computed tomography accurately quantifies right and left ventricular size and function compared with cardiac magnetic resonance," *American Heart Journal*, vol. 151, no. 3, pp. 736–744, 2006.

[49] S. Rich and B. H. Brundage, "High-dose calcium channel-blocking therapy for primary pulmonary hypertension: evidence for long-term reduction in pulmonary arterial pressure and regression of right ventricular hypertrophy," *Circulation*, vol. 76, no. 1, pp. 135–141, 1987.

[50] A. L. Hinderliter, P. W. Willis, R. J. Barst et al., "Effects of long-term infusion of prostacyclin (epoprostenol) on echocardiographic measures of right ventricular structure and function in primary pulmonary hypertension," *Circulation*, vol. 95, no. 6, pp. 1479–1486, 1997.

[51] R. J. Roeleveld, A. Vonk-Noordegraaf, J. T. Marcus et al., "Effects of epoprostenol on right ventricular hypertrophy and dilatation in pulmonary hypertension," *Chest*, vol. 125, no. 2, pp. 572–579, 2004.

[52] K. M. Chin, M. Kingman, J. A. de Lemos et al., "Changes in right ventricular structure and function assessed using cardiac magnetic resonance imaging in bosentan-treated patients with pulmonary arterial hypertension," *American Journal of Cardiology*, vol. 101, no. 11, pp. 1669–1672, 2008.

[53] 2010, http://clinicaltrials.gov/ct2/show/NCT00433329.

[54] H. J. Bogaard, R. Natarajan, S. C. Henderson et al., "Chronic pulmonary artery pressure elevation is insufficient to explain right heart failure," *Circulation*, vol. 120, no. 20, pp. 1951–1960, 2009.

[55] T. Hoashi, G. Matsumiya, S. Miyagawa et al., "Skeletal myoblast sheet transplantation improves the diastolic function of a pressure-overloaded right heart," *Journal of Thoracic and Cardiovascular Surgery*, vol. 138, no. 2, pp. 460–467, 2009.

[56] A. Lopez-Candales, K. Dohi, N. Rajagopalan et al., "Right ventricular dyssynchrony in patients with pulmonary hypertension is associated with disease severity and functional class," *Cardiovascular Ultrasound*, vol. 3, article 23, 2005.

[57] J. Lumens, T. Arts, B. Broers et al., "Right ventricular free wall pacing improves cardiac pump function in severe pulmonary arterial hypertension: a computer simulation analysis," *American Journal of Physiology*, vol. 297, no. 6, pp. H2196–H2205, 2009.

[58] M. L. Handoko, R. R. Lamberts, E. M. Redout et al., "Right ventricular pacing improves right heart function in experimental pulmonary arterial hypertension: a study in the isolated heart," *American Journal of Physiology*, vol. 297, no. 5, pp. H1752–H1759, 2009.

SAGE-Hindawi Access to Research
Cardiology Research and Practice
Volume 2011, Article ID 757154, 8 pages
doi:10.4061/2011/757154

Review Article

Mesenchymal Stem Cells and Inflammatory Cardiomyopathy: Cardiac Homing and Beyond

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Received 16 December 2010; Accepted 14 January 2011

Academic Editor: Gregory Giamouzis

Under conventional heart failure therapy, inflammatory cardiomyopathy usually has a progressive course, merging for alternative interventional strategies. There is accumulating support for the application of cellular transplantation as a strategy to improve myocardial function. Mesenchymal stem cells (MSCs) have the advantage over other stem cells that they possess immunomodulatory features, making them attractive candidates for the treatment of inflammatory cardiomyopathy. Studies in experimental models of inflammatory cardiomyopathy have consistently demonstrated the potential of MSCs to reduce cardiac injury and to improve cardiac function. This paper gives an overview about how inflammation triggers the functionality of MSCs and how it induces cardiac homing. Finally, the potential of intravenous application of MSCs by inflammatory cardiomyopathy is discussed.

1. Introduction

Myocarditis, described as an inflammatory infiltration of the myocardium with necrosis and/or degeneration of cardiomyocytes, is likely caused by a wide variety of infectious organisms, autoimmune disorders, and exogenous agents [1]. The major long-term consequence of myocarditis is inflammatory dilated cardiomyopathy (DCMi) with chronic heart failure. Persistent DCMi usually has a progressive course under standard heart failure therapy. At present, specific treatment options are not yet available or have not yet been proofed in major trials. In virus-negative patients, immunosuppression [2] is an option whereas in patients with cardiac virus persistence, the role of immunoglobulin or immunomodulation with interferon (IFN) [3] is under investigation. Finally, immunoabsorption [4] could be an option in favour of the idea that also autoantibodies may play a role in a subset of DCMi populations. However, the search for alternative therapies is still open.

There is accumulating experimental [5, 6] and clinical support [7–9] for the application of cellular transplantation as a strategy to improve myocardial function. Mesenchymal stem cells (MSCs) have antiapoptotic [10], antifibrotic [11], and proangiogenic [12] features. They have the advantage over other stem cells that they have immunomodulatory properties [13], which make them an attractive cell source for the treatment of inflammatory cardiomyopathy, given the importance of the inflammatory component in this disorder. Application of MSCs in experimental models of Coxsackievirus- (CVB-3) induced myocarditis [14] and autoimmune myocarditis [5, 15], attenuated myocardial injury and dysfunction. Both intramyocardial and intravenous administration of MSCs were successful. However, the MSC-mediated reduction in cardiac injury in the acute model of CVB3-induced myocarditis was not paralleled with a decrease in cardiac viral load, disabling a view of the final outcome on the long term. Therefore, as long as evidence in models of chronic virus-induced myocarditis are lacking,

the use of MSCs could be more important or restricted for the treatment of nonviral inflammatory cardiomyopathies.

Systemic delivery of MSCs requires efficient homing of MSCs to the place of injury. This review gives an overview about how inflammation triggers the functionality of MSCs and how it induces cardiac homing. The impact of inflammation/cytokine expression on the different aspects of homing, including chemokine-chemokine receptor interactions, adhesion on endothelial cells, transendothelial migration, and invasion through the extracellular matrix, is outlined. Finally, the potential of intravenous application of MSCs by inflammatory cardiomyopathy is discussed.

1.1. Mesenchymal Stem Cells. MSCs, which can be alternatively referred to as multipotent mesenchymal stromal cells or marrow stromal cells, are a heterogeneous population of cells which can proliferate *in vitro* as plastic-adherent cells, have fibroblast-like morphology, form colonies *in vitro*, and can differentiate into bone, cartilage, adipose, and stromal tissues [16, 17]. MSCs are positive for many characteristic markers including CD29, CD44, CD71, CD90, CD106, CD120a, CD124, SH2, SH3, and SH4, and negative for CD14, CD34, and CD45, which are specific markers of hematopoietic stem cells [18]. MSCs are rare in bone marrow, representing ~1 in 10,000 nucleated cells.

MSCs have the capacity to differentiate into cardiomyocytes, endothelial cells, and smooth muscle cells. Quevedo et al. [6] could demonstrate via using female swine and injecting male allogeneic MSCs 12 weeks after myocardial infarction that engrafted MSCs differentiated into cardiomyocytes as ascertained by colocalization with GATA-4, Nkx2.5, and α-sarcomeric actin. In addition, Y^{pos} MSCs exhibited vascular smooth muscle and endothelial cell differentiation, contributing to large and small vessel formation. Besides their trilineage differentiation capacity [6], it is believed that the cardioprotective effects of MSC are predominantly due to facilitating endogenous repair processes via their antifibrotic, immunomodulatory, antiapoptotic and proangiogenic features.

In brief, MSCs have the capacity to reduce cardiac fibroblast proliferation [19] and collagen I and III expression [20], and they are able to promote matrix metalloproteinase secretion by cardiac fibroblasts [11], leading to reduced cardiac ventricular fibrosis. These effects may at least partially be mediated via the release of antifibrotic factors such as hepatocyte growth factor [21].

An emerging body of evidence indicates that MSCs possess immunomodulatory properties, affecting T cells [13], dendritic cells [22], B cells [23], and natural killer cells [24]. Immunosuppression occurs hereby most effectively under conditions in which MSCs make physical contact with allogeneic tissue and release soluble factors, including interleukin- (IL-)10, transforming growth factor- (TGF-)β, Indoleamine 2,3-dioxygenase [25], and prostaglandin E2. Moreover, the inflammatory environment/condition plays an important role in the ability of MSCs to exert their immunosuppressive effects. In fact, in the absence of T cell activation or exogenous inflammatory cytokines, MSCs actually prolong the survival of lymphocytes [26], supporting the immunomodulatory nature of MSCs.

Studies in models of diabetic cardiomyopathy [10], myocardial infarction [27], and myocarditis [14] demonstrated that MSC application leads to less cardiac apoptosis, which might be in part due to improved angiogenesis [27]. We demonstrated *in vitro* via coculture of MSCs with CVB3-infected HL-1 cardiomyocytes that MSCs have intrinsic antiapoptotic features, and that these effects are nitric oxide- (NO-)dependent [14]. Furthermore, Nagaya et al. [5] showed that cultured MSCs secreted large amounts of the angiogenic, antiapoptotic, and mitogenic factors vascular endothelial growth factor, hepatocyte growth factor, adrenomedullin, and insulin-like growth factor-1. Finally, MSCs also have proangiogenic effects: they can differentiate into endothelial cells [28], increase *in vitro* tube formation [12], and secrete proangiogenic factors including vascular endothelial growth factor [29, 30]. Their proangiogenic features have been demonstrated in models of peripheral hindlimb ischemia [31] and myocardial infarction [27, 32].

1.2. Inflammatory Cytokines Induce Mesenchymal Stem Cell Activation. Various reports have demonstrated the importance of IFN-γ for the activation of MSCs [13, 14, 33]. Sheng et al. [33] showed that IFN-γ, a well-known proinflammatory cytokine produced by activated T cells, plays an important role in priming the immunosuppressive property of MSCs. Mechanistically, IFN-γ acts directly on MSCs and leads to upregulation of B7-H1, an inhibitory surface molecule in these stem cells. MSCs primed by activated T cells derived from IFN-$\gamma^{-/-}$ mouse exhibited dramatically reduced ability to suppress T cell proliferation, a defect that could be rescued by supplying exogenous IFN-γ. Moreover, siRNA-mediated knockdown of B7-H1 in MSCs abolished immunosuppression by these cells. In agreement Ren et al. [13] found that the immunosuppressive function of MSCs is elicited by IFN-γ and the concomitant presence of any of three other proinflammatory cytokines, tumor necrosis factor-α (TNF-α), IL-1α, or IL-1β. These cytokine combinations provoke the expression of high levels of several chemokines and inducible nitric oxide synthase (iNOS) by MSCs. Chemokines drive T cell migration into the proximity of MSCs, where T cell responsiveness is suppressed by NO. This cytokine-induced immunosuppression is absent in MSCs derived from iNOS$^{-/-}$ or IFN-γR1$^{-/-}$ mice. Administration of wild-type MSCs, but not of IFN-γR1$^{-/-}$ MSCs, prevented graft-versus-host disease in mice, an effect reversed by anti-IFN-γ or iNOS inhibitors. Therefore, proinflammatory cytokines are required to induce immunosuppression by MSCs through the concerted action of chemokines and NO. Moreover, Ren et al. [34] found that intracellular adhesion molecule- (ICAM-)1 and vascular cell adhesion molecule- (VCAM-)1 were critical for MSC-mediated immunosuppression. When MSCs were cocultured with T cells in the presence of T cell antigen receptor activation, they significantly upregulated the adhesive capability of T cells due to the increased expression of ICAM-1 and VCAM-1. The greater the expression of ICAM-1 and

VCAM-1 by MSCs was, the greater the immunosuppressive capacity that they exhibited. Furthermore, ICAM-1 and VCAM-1 were found to be inducible by the concomitant presence of IFN-γ and inflammatory cytokines (TNF-α, IL-1). Finally, MSC-mediated immunosuppression was significantly reversed *in vitro* and *in vivo* when the adhesion molecules were genetically deleted or functionally blocked, which corroborated the importance of cell-cell contact in immunosuppression by MSCs. These findings not only reveal a novel function of adhesion molecules in immunoregulation by MSCs, but also provide new insights for the clinical studies of antiadhesion therapies in various immune disorders.

Furthermore, we demonstrated that MSCs not only require IFN-γ to exert their immunomodulatory properties, but also to perform their antiapoptotic, antioxidative, and antiviral features [14]. Coculture of MSCs with Coxsackievirus B3-infected HL-1 cardiomyocytes reduced cardiomyocyte apoptosis, oxidative stress, and viral progeny release, an effect which was reduced in the presence of an IFN-γ antibody [14]. In line with Oh et al. [35], we could also demonstrate that MSCs request IFN-γ for the production of NO, which is known for its antiapoptotic [36] and antiviral properties [37]. Furthermore, Kemp et al. [38] demonstrated that the secretion of the antioxidative enzyme superoxide dismutase 3 by MSCs is regulated synergistically by TNF-α and IFN-γ, rather than through direct exposure to reactive oxygen species.

1.3. Cardiac Homing of Mesenchymal Stem Cells. Homing is a multistep process which involves chemokine-chemokine receptor interactions, adhesion to endothelial cells, transmigration through the endothelial vasculature, cytoskeleton rearrangement, and adhesive interactions with the extracellular matrix [39]. Numerous *in vivo* studies have shown that MSCs have the capability to migrate from the blood, across endothelial cells, into damaged tissues.

MSCs express a variety of chemokines [40–42], including CXCR4 and CCR2, the receptors for stromal cell-derived factor- (SDF-)1α and monocyte chemoattractant protein-(MCP-)1, respectively. SDF-1α is a CXC chemokine known to play a critical role in the trafficking of hematopoietic cells and stem cell progenitors and in maintaining hematopoietic stem cell niches in bone marrow [43]. SDF-1α expression has been shown to increase under hypoxic conditions [44] and thus may serve to attract stem cells to sites of tissue injury. Its expression is significantly upregulated in experimental rat and mouse models of myocardial infarction [45–47], in cardiac tissue of patients with myocardial ischemia [48], and in experimental CVB3-induced myocarditis (own unpublished data). Abbott et al. [47] could demonstrate that administration of AMD3100, which specifically blocks the binding of SDF-1α to its endogenous receptor CXCR4, diminished bone marrow cells recruitment after myocardial infarction, strongly suggesting a requirement for SDF-1α in bone marrow cell recruitment to the infarcted heart. Forced expression of SDF-1α in the heart by adenoviral gene delivery 48 hours after myocardial infarction doubled bone marrow cells recruitment over myocardial infarction. However, gene transfer of SDF-1α did not enhance recruitment in the absence of myocardial infarction, suggesting that SDF-1α can augment, but is not singularly sufficient for bone marrow cells recruitment to the heart. The importance of the SDF-CXCR4 axis in cardiac homing of MSCs has been demonstrated by CXCR-overexpressing MSCs showing improved targeted cardiac migration and engraftment of MSCs [49].

MCP-1 is upregulated upon myocardial infarction [50] and is induced in experimental CVB3-induced myocarditis [51], by which its cardiac expression correlates with the infiltration of mononuclear cells in the heart. Though, the importance of cardiac MCP-1 expression for the cardiac homing of MSCs follows from a study of Belema-Bedada et al. [52] which demonstrated that directed expression of MCP-1 in the myocardium led to specific homing of MSCs to the heart. In addition, they could show that MCP-1-mediated MSC migration depends on CCR2/FROUNT signaling in the MSC, by which the adapter molecule FROUNT is required for polarization, cytoskeletal reorganization, and clustering of CCR2 on the cell surface of MSCs. Besides the induction of cardiac chemokine expression, inflammation also triggers the expression of chemokine receptors on the MSCs. Only a small proportion of MSCs strongly expresses functionally active CXCR4 receptor [53]. Shi et al. [54] demonstrated that a cocktail of cytokines resulted in upregulation of both cell surface and intracellular CXCR4, increasing *in vitro* migration capacity to SDF-1α and homing to the bone marrow of irradiated NOD/SCID mice. Croitoru-Lamoury et al. [55] showed that TNF-α, IFN-γ, and IFN-β influence the expression of chemokines and their receptors in MSCs. This was further confirmed by Ponte et al. [40] demonstrating that TNF-α stimulation of MSCs increases chemotaxis towards chemokines but not towards growth factors. These data suggest that the mobilization of MSCs and their subsequent homing to injured tissues may depend on the systemic and local inflammatory state.

Numerous *in vivo* studies have shown that MSCs have the capacity to migrate from the blood, across endothelial cells into injured tissues. Many of the molecules, including integrins, selectins, and chemokine receptors, known to be involved in the tethering, rolling, adhesion, and transmigration of leukocytes from the bloodstream into tissues are also expressed on MSCs. MSCs express the integrins α1, α2, α3, α4, α5, αv, β1, β3, and β4, and approximately 50% of human MSCs are thought to express the integrin very late antigen-(VLA-)4 ($\alpha 4\beta 1$, CD49d) [56]. The importance of VLA-4 in the adherence of human MSCs to endothelial cells, under shear flow conditions, follows from the observation that the use of a neutralizing antibody to this integrin decreased MSC binding to endothelial cells. On the other hand, it was observed that treating endothelial cells with a blocking antibody to its counterpart adhesion molecule, VCAM-1, induced a similar decrease in MSC adherence. Both findings indicate the importance of the VLA-4/VCAM-1 axis for firm MSC adherence to endothelial cells.

MSCs also express the adhesion molecules VCAM-1, ICAM-1, ICAM-3, ALCAM, and endoglin/CD105 [57]. Segers et al. [58] demonstrated that activation of both

cardiac microvascular endothelial cells and MSCs with TNF-α or IL-1β before adhesion, increased the adhesion of MSCs to endothelial cells under shear stress concentration dependently. In agreement, *in vivo*, activation of MSCs with TNF-α before injection significantly enhanced cardiac homing of MSCs. TNF-α-induced adhesion could be completely blocked by pretreating either cardiac microvascular endothelial cells or MSCs with anti-VCAM-1 monoclonal antibodies but not by anti-ICAM-1 antibodies. Therefore, the adhesion of circulating MSCs in the heart appears to be an endothelium-dependent process and to be sensitive to modulation by activators of both MSCs and the endothelium. Inflammation and the expression of VCAM-1 but not of ICAM-1 on both MSCs and cardiac microvascular endothelial cells appear to have a regulatory effect on MSC homing in the heart. Furthermore, Rüster et al. [56] showed that MSCs display a coordinated rolling and adhesion behavior on endothelial cells similar to peripheral blood mononuclear cells for which they equally required P-selectin and VCAM-1/VLA-4. This involved rapid extension of podia, rolling, and subsequent firm adhesion was increased when endothelial cells were prestimulated with TNF-α.

A comparison between the cell adhesion molecule expression profile of the mobilized, circulating MSCs, and tissue-derived MSCs may provide further insight into the potential mechanisms of MSC homing.

The expression of chemokine receptors [49, 59] and integrins [60, 61] on MSCs is not only beneficial for cardiac migration/adhesion, but also for MSC survival and cardiac engraftment. However, the impact of inflammation on MSC survival and cardiac engraftment is beyond the scope of this review.

Upon adhesion, MSCs migrate through the endothelium. At present, little is known about the mechanism of MSC transendothelial migration and which adhesion molecules are involved. MSCs do not express PECAM-1/CD31, which is required in leukocyte transmigration across the endothelium. So, although the rolling and adhesion of MSCs on the endothelium are similar to those of leukocytes, it seems that MSCs use different adhesion molecules for transendothelial migration. Schmidt et al. [62] investigated the mechanism of transendothelial migration *in vitro* using a coculture of MSCs on an endothelial monolayer and analyzed direct interactions. An increasing flattened morphology of the MSCs, starting 30 minutes upon coculture was followed by total integration into the monolayer after 2 hours. *In vivo*, using isolated heart perfusions with gold-labelled MSCs and electron microscopy, they detected that MSCs exhibited direct cell-cell contacts. Tight junctions between the endothelial cells became abolished resulting in a distinct split between the cells. MSCs developed tight cell-cell contacts and became integrated into the endothelial wall of the capillary vessel. Finally, confocal laser scanning microscopy revealed that 30 minutes of MSC perfusion was sufficient to observe transmigration across the endothelium of approximately 30% of the cells. This percentage rose to 50% after 60 minutes and remained nearly unchanged thereafter. This finding is important in view of exposure times of MSCs in clinical settings. Steingen et al. [63] demonstrated that the time course of adhesion, integration, and transmigration depends on the endothelial phenotype and is most effective in venous vessels of the myocardium. Furthermore, they showed that transmigration not only requires the interaction of VCAM-1 and VLA-4, as verified by blocking experiments, but also triggers the clustering of beta1 integrins.

After transmigrating across the endothelium, MSCs have to traffic through the extracellular matrix (ECM) to first infiltrate sites of tissue damage. MSCs strongly express and synthesize matrix metalloproteinase 2 (MMP-2), membrane type 1 MMP (MT1-MMP), tissue inhibitor of metalloproteinase 1 (TIMP-1), and TIMP-2 [64]. *In situ* zymographies infer the activation of gelatinases at sites of MSC invasion into myocardial tissue [63]. The ability of MSCs to traverse reconstituted human basement membranes was effectively blocked in the presence of synthetic MMP inhibitors. Detailed studies by RNA interference revealed that gene knock-down of MMP-2, MT1-MMP, or TIMP-2 substantially impaired MSC invasion whereas silencing of TIMP-1 enhanced cell migration, indicating opposing roles of both TIMPs in this process. Moreover, the inflammatory cytokines TGF-β1, IL-1β, and TNF-α upregulated MMP-2, MT1-MMP, and/or MMP-9 production in these cells, resulting in a strong stimulation of chemotactic migration through ECM whereas the chemokine SDF-1α exhibited minor effects on MMP/TIMP expression and cell invasion [64].

In summary, the homing of MSCs to the heart in inflammatory cardiomyopathy is triggered on different levels as outlined in Figure 1.

1.4. Route of Administration. Since MSCs have the capacity to home to injured tissue, intravenous application may be considered for inflammatory cardiomyopathy and might even have advantages over intracoronary or transendocardial application despite their reduced cardiac engraftment [65]. Indeed, via intravenous application, also the spleen could be reached. The spleen is the reservoir of monocytes which are recruited into the inflammatory heart via interaction of the chemokine MCP-1, released by the heart, with its cognate receptor CCR2, present on monocytes [51]. In case of myocardial infarction, 40% to 70% of monocytes acutely recruited to the infarct originate from a splenic reservoir [66]. Retrieved in the heart, cells then assume a central role in orchestrating the healing wound [67]. However, an excessive inflammatory response is deleterious. As shown for myocardial infarction where splenectomy or the arrested release of monocytes from the splenic reservoir via angotensin-converting enzyme inhibition reduced the recruitment into the healing infarct and improved the myocardial infarction outcome [68], an anti-inflammatory impact via MSCs on the splenic monocyte reservoir in the context of inflammatory cardiomyopathy could be further beneficial in addition to the direct MSC-mediated cardioprotective effects, favoring intravenous application.

In case of Coxsackievirus B3-induced inflammatory cardiomyopathy, the filtration of viral particles during acute infection takes place in the spleen [69] and pre-B, B cells,

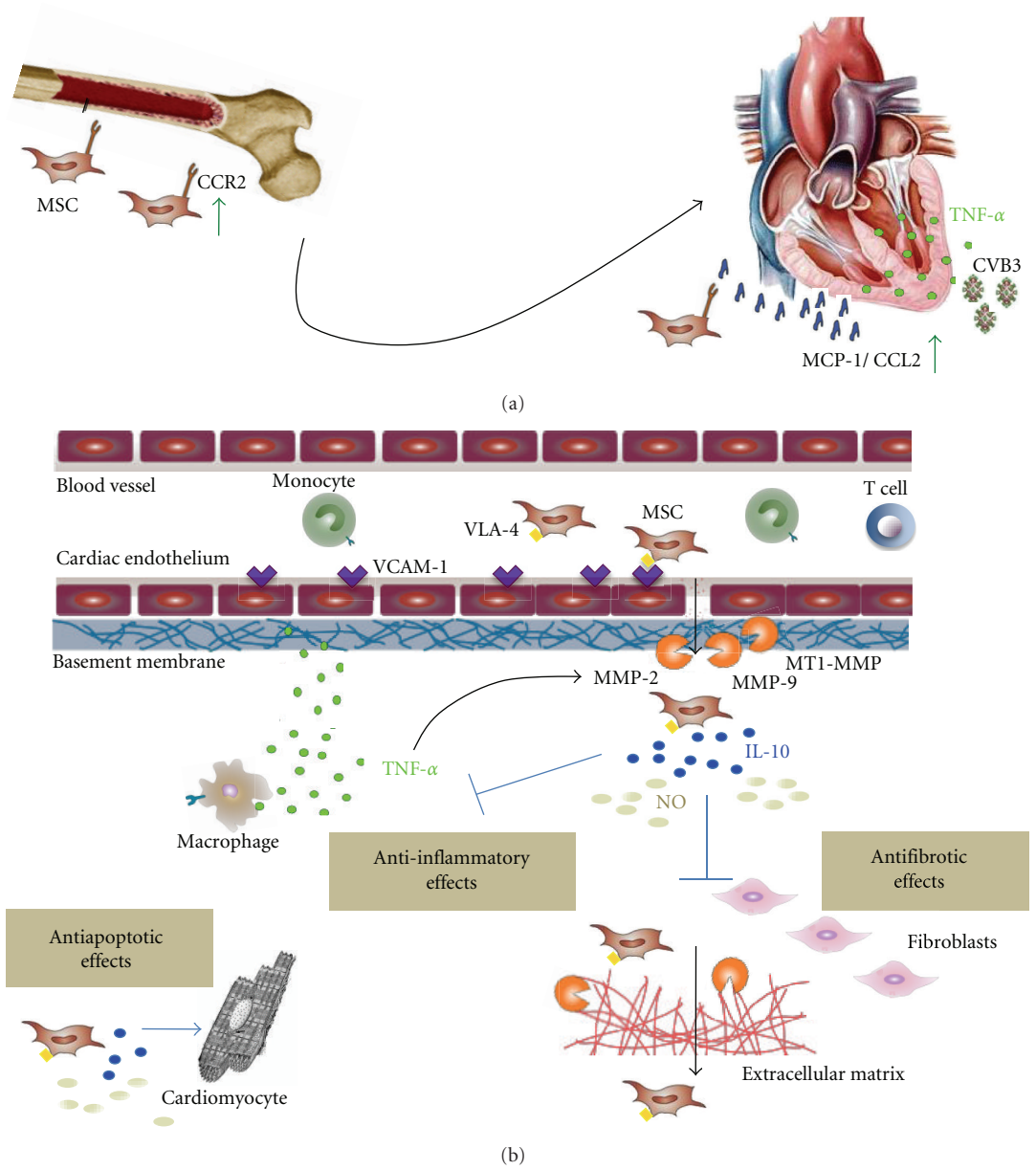

Figure 1: Proposed pathways how inflammation induces cardiac homing of mesenchymal stem cells. (a) TNF-α and/or Coxsackievirus B3 (CVB3) trigger the induction of cardiac expression of monocyte chemoattractant protein-1 (MCP-1) also known as CCL2. At the same time, the expression of the corresponding chemokine receptor CCR2 is induced on mesenchymal stem cells (MSCs), stimulating cardiac migration. (b) TNF-α induces vascular cellular adhesion molecule- (VCAM-)1 expression on the cardiac endothelium. The VLA-4/VCAM-1 axis is important for firm MSC adherence to endothelial cells. Next, MSCs transmigrate through the endothelium which also requires the interaction of VCAM-1 and VLA-4. Finally, MSCs invade through the basement membrane and the extracellular matrix (ECM) via their secretion of matrix metalloproteinase- (MMP-)2, MMP-9, and membrane type 1 MMP (MT1-MMP), which are upregulated by TNF-α. In the heart, MSCs can exert cardioprotective effects, including their anti-inflammatory, antifibrotic, and antiapoptotic features, among others, via interleukin- (IL-)10 and nitric oxide (NO).

CD4+ helper T cells, and Mac-1+ macrophages are infected [70]. Homing of MSCs to the spleen might influence the condition of immune cells, including their activity [13], apoptosis [71], as well as their viral infection [14, 70] and potentially also their homing capacity [13]. The MSC-mediated dissemination of infected immune cells in the spleen might therefore reduce the infiltration of infected immune cells in the heart and consequently lead to a decrease in cardiac damage.

Finally, the ease of application, as well as the finding that MSCs transmigration is most effective in venous vessels of the myocardium [63], favor the intravenous route of administration.

2. Conclusion and Perspectives

In conclusion, consistent evidence from *in vitro* and *in vivo* experimental studies support a promoted cardiac homing

of MSCs under inflammatory cardiomyopathy. This finding together with the activation of MSCs via cytokines, and the immunomodulatory properties of MSCs, make MSCs an attractive cell source for the treatment of inflammatory cardiomyopathy. The investigation of endogenous cardiac homing in patients with inflammatory cardiomyopathy versus control patients, currently ongoing in our working group, is needed to confirm these experimental findings in a patient setting and will underscore the potential use of intravenous application of MSCs for the treatment of inflammatory cardiomyopathy. Finally, the importance of adhesion molecules for cardiac homing of MSCs and the immunosuppressive effect of MSCs, position the use of antiadhesion therapies for inflammatory cardiomyopathy in perspective.

Abbreviations

CVB:	Coxsackievirus
DCM:	Dilated cardiomyopathy
DCMi:	Inflammatory dilated cardiomyopathy
ECM:	Extracellular matrix
IFN:	Interferon
IL:	Interleukin
iNOS:	Inducible nitric oxide synthase
MMP:	Matrix metalloproteinase
MT1-MMP:	Membrane type 1-MMP
MSC:	Mesenchymal stem cell
NO:	Nitric oxide
SDF-1α:	Stromal derived factor-1 alpha
TIMP:	Tissue inhibitor of metalloproteinase
TNF-α:	Tumor necrosis factor-alpha
TGF:	Transforming growth factor
VCAM-1:	Vascular cell adhesion molecule-1
VLA-4:	Very late antigen-4.

Acknowledgments

This paper was supported by the Berlin-Brandenburg Center for Regenerative Therapies—BCRT (Bundesministerium für Bildung und Forschung—0313911) to C. Tschöpe, and by the DFG Sonderforschungsbereich Transregio-19 B5 to C. Tschöpe.

References

[1] H. T. Aretz, M. E. Billingham, W. D. Edwards et al., "Myocarditis. A histopathologic definition and classification," *The American Journal of Cardiovascular Pathology*, vol. 1, no. 1, pp. 3–14, 1987.

[2] A. Frustaci, M. A. Russo, and C. Chimenti, "Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study," *European Heart Journal*, vol. 30, no. 16, pp. 1995–2002, 2009.

[3] U. Kühl, M. Pauschinger, P. L. Schwimmbeck et al., "Interferon-β treatment eliminates cardiotropic viruses and improves left ventricular function in patients with myocardial persistence of viral genomes and left ventricular dysfunction," *Circulation*, vol. 107, no. 22, pp. 2793–2798, 2003.

[4] A. Staudt, L. R. Herda, C. Trimpert et al., "Fcgamma-receptor IIa polymorphism and the role of immunoadsorption in cardiac dysfunction in patients with dilated cardiomyopathy," *Clinical Pharmacology and Therapeutics*, vol. 87, no. 4, pp. 452–458, 2010.

[5] N. Nagaya, K. Kangawa, T. Itoh et al., "Transplantation of mesenchymal stem cells improves cardiac function in a rat model of dilated cardiomyopathy," *Circulation*, vol. 112, no. 8, pp. 1128–1135, 2005.

[6] H. C. Quevedo, K. E. Hatzistergos, B. N. Oskouei et al., "Allogeneic mesenchymal stem cells restore cardiac function in chronic ischemic cardiomyopathy via trilineage differentiating capacity," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 33, pp. 14022–14027, 2009.

[7] C. Yerebakan, A. Kaminski, A. Liebold, and G. Steinhoff, "Safety of intramyocardial stem cell therapy for the ischemic myocardium: results of the Rostock trial after 5-year follow-up," *Cell Transplantation*, vol. 16, no. 9, pp. 935–940, 2007.

[8] J. M. Hare, J. H. Traverse, T. D. Henry et al., "A randomized, double-blind, placebo-controlled, dose-escalation study of intravenous adult human mesenchymal stem cells (prochymal) after acute myocardial infarction," *Journal of the American College of Cardiology*, vol. 54, no. 24, pp. 2277–2286, 2009.

[9] J. Van Ramshorst, J. J. Bax, S. L. M. A. Beeres et al., "Intramyocardial bone marrow cell injection for chronic myocardial ischemia: a randomized controlled trial," *Journal of the American Medical Association*, vol. 301, no. 19, pp. 1997–2004, 2009.

[10] J. H. Li, N. Zhang, and J. A. Wangi, "Improved anti-apoptotic and anti-remodeling potency of bone marrow mesenchymal stem cells by anoxic pre-conditioning in diabetic cardiomyopathy," *Journal of Endocrinological Investigation*, vol. 31, no. 2, pp. 103–110, 2008.

[11] C. Mias, O. Lairez, E. Trouche et al., "Mesenchymal stem cells promote matrix metalloproteinase secretion by cardiac fibroblasts and reduce cardiac ventricular fibrosis after myocardial infarction," *Stem Cells*, vol. 27, no. 11, pp. 2734–2743, 2009.

[12] J. M. Sorrell, M. A. Baber, and A. I. Caplan, "Influence of adult mesenchymal stem cells on in vitro vascular formation," *Tissue Engineering—Part A*, vol. 15, no. 7, pp. 1751–1761, 2009.

[13] G. Ren, L. Zhang, X. Zhao et al., "Mesenchymal stem cell-mediated immunosuppression occurs via concerted action of chemokines and nitric oxide," *Cell Stem Cell*, vol. 2, no. 2, pp. 141–150, 2008.

[14] S. van Linthout, K. Savvatis, K. Miteva et al., "Mesenchymal stem cells improve murine acute Coxsackievurs B3-induced myocarditis," *European Heart Journal*, 2010.

[15] S. Ohnishi, B. Yanagawa, K. Tanaka et al., "Transplantation of mesenchymal stem cells attenuates myocardial injury and dysfunction in a rat model of acute myocarditis," *Journal of Molecular and Cellular Cardiology*, vol. 42, no. 1, pp. 88–97, 2007.

[16] D. J. Prockop, "Marrow stromal cells as stem cells for nonhematopoietic tissues," *Science*, vol. 276, no. 5309, pp. 71–74, 1997.

[17] M. F. Pittenger, A. M. Mackay, S. C. Beck et al., "Multilineage potential of adult human mesenchymal stem cells," *Science*, vol. 284, no. 5411, pp. 143–147, 1999.

[18] S. E. Haynesworth, M. A. Baber, and A. I. Caplan, "Cell surface antigens on human marrow-derived mesenchymal cells are detected by monoclonal antibodies," *Bone*, vol. 13, no. 1, pp. 69–80, 1992.

[19] S. Ohnishi, H. Sumiyoshi, S. Kitamura, and N. Nagaya, "Mesenchymal stem cells attenuate cardiac fibroblast proliferation and collagen synthesis through paracrine actions," *FEBS Letters*, vol. 581, no. 21, pp. 3961–3966, 2007.

[20] X. Xu, Z. Xu, Y. Xu, and G. Cui, "Selective down-regulation of extracellular matrix gene expression by bone marrow derived stem cell transplantation into infarcted myocardium," *Circulation Journal*, vol. 69, no. 10, pp. 1275–1283, 2005.

[21] L. Li, Y. Zhang, Y. Li et al., "Mesenchymal stem cell transplantation attenuates cardiac fibrosis associated with isoproterenol-induced global heart failure," *Transplant International*, vol. 21, no. 12, pp. 1181–1189, 2008.

[22] X. X. Jiang, YI. Zhang, B. Liu et al., "Human mesenchymal stem cells inhibit differentiation and function of monocyte-derived dendritic cells," *Blood*, vol. 105, no. 10, pp. 4120–4126, 2005.

[23] M. Krampera, L. Cosmi, R. Angeli et al., "Role for interferon-γ in the immunomodulatory activity of human bone marrow mesenchymal stem cells," *Stem Cells*, vol. 24, no. 2, pp. 386–398, 2006.

[24] P. A. Sotiropoulou, S. A. Perez, A. D. Gritzapis, C. N. Baxevanis, and M. Papamichail, "Interactions between human mesenchymal stem cells and natural killer cells," *Stem Cells*, vol. 24, no. 1, pp. 74–85, 2006.

[25] R. Meisel, A. Zibert, M. Laryea, U. Göbel, W. Däubener, and D. Dilloo, "Human bone marrow stromal cells inhibit allogeneic T-cell responses by indoleamine 2,3-dioxygenase-mediated tryptophan degradation," *Blood*, vol. 103, no. 12, pp. 4619–4621, 2004.

[26] G. Xu, Y. Zhang, L. Zhang, G. Ren, and Y. Shi, "The role of IL-6 in inhibition of lymphocyte apoptosis by mesenchymal stem cells," *Biochemical and Biophysical Research Communications*, vol. 361, no. 3, pp. 745–750, 2007.

[27] K. H. Schuleri, L. C. Amado, A. J. Boyle et al., "Early improvement in cardiac tissue perfusion due to mesenchymal stem cells," *American Journal of Physiology*, vol. 294, no. 5, pp. H2002–H2011, 2008.

[28] J. Oswald, S. Boxberger, B. Jørgensen et al., "Mesenchymal stem cells can be differentiated into endothelial cells in vitro," *Stem Cells*, vol. 22, no. 3, pp. 377–384, 2004.

[29] S. C. Hung, R. R. Pochampally, S. Y. C. Chen, S. C. Hsu, and D. J. Prockop, "Angiogenic effects of human multipotent stromal cell conditioned medium activate the PI3K-Akt pathway in hypoxic endothelial cells to inhibit apoptosis, increase survival, and stimulate angiogenesis," *Stem Cells*, vol. 25, no. 9, pp. 2363–2370, 2007.

[30] T. Kinnaird, E. S. Burnett, M. Shou et al., "Local delivery of marrow-derived stromal cells augments collateral perfusion through paracrine mechanisms," *Circulation*, vol. 109, no. 12, pp. 1543–1549, 2004.

[31] W. R. Prather, A. Toren, M. Meiron, R. Ofir, C. Tschope, and E. Horwitz, "The role of placental-derived adherent stromal cell (PLX-PAD) in the treatment of critical limb ischemi," *Cytotherapy*, vol. 11, no. 4, pp. 427–434, 2009.

[32] N. Nagaya, T. Fujii, T. Iwase et al., "Intravenous administration of mesenchymal stem cells improves cardiac function in rats with acute myocardial infarction through angiogenesis and myogenesis," *American Journal of Physiology*, vol. 287, no. 6, pp. H2670–H2676, 2004.

[33] H. Sheng, Y. Wang, Y. Jin et al., "A critical role of IFNγ in priming MSC-mediated suppression of T cell proliferation through up-regulation of B7-H1," *Cell Research*, vol. 18, no. 8, pp. 846–857, 2008.

[34] G. Ren, X. Zhao, L. Zhang et al., "Inflammatory cytokine-induced intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in mesenchymal stem cells are critical for immunosuppression," *Journal of Immunology*, vol. 184, no. 5, pp. 2321–2328, 2010.

[35] I. Oh, K. Ozaki, K. Sato et al., "Interferon-γ and NF-κB mediate nitric oxide production by mesenchymal stromal cells," *Biochemical and Biophysical Research Communications*, vol. 355, no. 4, pp. 956–962, 2007.

[36] H. M. Razavi, J. A. Hamilton, and Q. Feng, "Modulation of apoptosis by nitric oxide: implications in myocardial ischemia and heart failure," *Pharmacology and Therapeutics*, vol. 106, no. 2, pp. 147–162, 2005.

[37] R. Zell, R. Markgraf, M. Schmidtke et al., "Nitric oxide donors inhibit the coxsackievirus B3 proteinases 2A and 3C in vitro, virus production in cells, and signs of myocarditis in virus-infected mice," *Medical Microbiology and Immunology*, vol. 193, no. 2-3, pp. 91–100, 2004.

[38] K. Kemp, E. Gray, E. Mallam, N. Scolding, and A. Wilkins, "Inflammatory cytokine induced regulation of superoxide dismutase 3 expression by human mesenchymal stem cells," *Stem Cell Reviews and Reports*, vol. 6, no. 4, pp. 548–559, 2010.

[39] G. Chamberlain, J. Fox, B. Ashton, and J. Middleton, "Concise review: mesenchymal stem cells: their phenotype, differentiation capacity, immunological features, and potential for homing," *Stem Cells*, vol. 25, no. 11, pp. 2739–2749, 2007.

[40] A. L. Ponte, E. Marais, N. Gallay et al., "The in vitro migration capacity of human bone marrow mesenchymal stem cells: comparison of chemokine and growth factor chemotactic activities," *Stem Cells*, vol. 25, no. 7, pp. 1737–1745, 2007.

[41] J. Ringe, S. Strassburg, K. Neumann et al., "Towards in situ tissue repair: human mesenchymal stem cells express chemokine receptors CXCR1, CXCR2 and CCR2, and migrate upon stimulation with CXCL8 but not CCL2," *Journal of Cellular Biochemistry*, vol. 101, no. 1, pp. 135–146, 2007.

[42] M. Honczarenko, Y. I. Le, M. Swierkowski, I. Ghiran, A. M. Glodek, and L. E. Silberstein, "Human bone marrow stromal cells express a distinct set of biologically functional chemokine receptors," *Stem Cells*, vol. 24, no. 4, pp. 1030–1041, 2006.

[43] M. Kucia, K. Jankowski, R. Reca et al., "CXCR4-SDF-1 signalling, locomotion, chemotaxis and adhesion," *Journal of Molecular Histology*, vol. 35, no. 3, pp. 233–245, 2004.

[44] D. J. Ceradini, A. R. Kulkarni, M. J. Callaghan et al., "Progenitor cell trafficking is regulated by hypoxic gradients through HIF-1 induction of SDF-1," *Nature Medicine*, vol. 10, no. 8, pp. 858–864, 2004.

[45] A. T. Askari, S. Unzek, Z. B. Popovic et al., "Effect of stromal-cell-derived factor 1 on stem-cell homing and tissue regeneration in ischaemic cardiomyopathy," *The Lancet*, vol. 362, no. 9385, pp. 697–703, 2003.

[46] K. Pillarisetti and S. K. Gupta, "Cloning and relative expression analysis of rat stromal cell derived factor-1 (SDF-1): SDF-1 α mRNA is selectively induced in rat model of myocardial infarction," *Inflammation*, vol. 25, no. 5, pp. 293–300, 2001.

[47] J. D. Abbott, Y. Huang, D. Liu, R. Hickey, D. S. Krause, and F. J. Giordano, "Stromal cell-derived factor-1α plays a critical role in stem cell recruitment to the heart after myocardial infarction but is not sufficient to induce homing in the absence of injury," *Circulation*, vol. 110, no. 21, pp. 3300–3305, 2004.

[48] M. H. Yamani, N. B. Ratliff, D. J. Cook et al., "Peritransplant ischemic injury is associated with up-regulation of stromal cell-derived factor-1," *Journal of the American College of Cardiology*, vol. 46, no. 6, pp. 1029–1035, 2005.

[49] D. Zhang, G. C. Fan, X. Zhou et al., "Over-expression of CXCR4 on mesenchymal stem cells augments myoangiogenesis in the infarcted myocardium," *Journal of Molecular and Cellular Cardiology*, vol. 44, no. 2, pp. 281–292, 2008.

[50] S. Schenk, N. Mal, A. Finan et al., "Monocyte chemotactic protein-3 is a myocardial mesenchymal stem cell homing factor," *Stem Cells*, vol. 25, no. 1, pp. 245–251, 2007.

[51] Y. Shen, W. Xu, Y. I. W. Chu, Y. Wang, Q. S. Liu, and S. I. D. Xiong, "Coxsackievirus group B type 3 infection upregulates expression of monocyte chemoattractant protein 1 in cardiac myocytes, which leads to enhanced migration of mononuclear cells in viral myocarditis," *Journal of Virology*, vol. 78, no. 22, pp. 12548–12556, 2004.

[52] F. Belema-Bedada, S. Uchida, A. Martire, S. Kostin, and T. Braun, "Efficient homing of multipotent adult mesenchymal stem cells depends on FROUNT-mediated clustering of CCR2," *Cell Stem Cell*, vol. 2, no. 6, pp. 566–575, 2008.

[53] R. F. Wynn, C. A. Hart, C. Corradi-Perini et al., "A small proportion of mesenchymal stem cells strongly expresses functionally active CXCR4 receptor capable of promoting migration to bone marrow," *Blood*, vol. 104, no. 9, pp. 2643–2645, 2004.

[54] M. Shi, J. Li, L. Liao et al., "Regulation of CXCR4 expression in human mesenchymal stem cells by cytokine treatment: role in homing efficiency in NOD/SCID mice," *Haematologica*, vol. 92, no. 7, pp. 897–904, 2007.

[55] J. Croitoru-Lamoury, F. M. J. Lamoury, J. J. Zaunders, L. A. Veas, and B. J. Brew, "Human mesenchymal stem cells constitutively express chemokines and chemokine receptors that can be upregulated by cytokines, IFN-β, and copaxone," *Journal of Interferon and Cytokine Research*, vol. 27, no. 1, pp. 53–64, 2007.

[56] B. Rüster, S. Göttig, R. J. Ludwig et al., "Mesenchymal stem cells display coordinated rolling and adhesion behavior on endothelial cells," *Blood*, vol. 108, no. 12, pp. 3938–3944, 2006.

[57] M. Krampera, G. Pizzolo, G. Aprili, and M. Franchini, "Mesenchymal stem cells for bone, cartilage, tendon and skeletal muscle repair," *Bone*, vol. 39, no. 4, pp. 678–683, 2006.

[58] V. F. M. Segers, I. Van Riet, L. J. Andries et al., "Mesenchymal stem cell adhesion to cardiac microvascular endothelium: activators and mechanisms," *American Journal of Physiology*, vol. 290, no. 4, pp. H1370–H1377, 2006.

[59] J. Huang, Z. Zhang, J. Guo et al., "Genetic modification of mesenchymal stem cells overexpressing ccr1 increases cell viability, migration, engraftment, and capillary density in the injured myocardium," *Circulation Research*, vol. 106, no. 11, pp. 1753–1762, 2010.

[60] H. Song, W. Chang, S. Lim et al., "Tissue transglutaminase is essential for integrin-mediated survival of bone marrow-derived mesenchymal stem cells," *Stem Cells*, vol. 25, no. 6, pp. 1431–1438, 2007.

[61] S. W. Song, W. Chang, B. W. Song et al., "Integrin-linked kinase is required in hypoxic mesenchymal stem cells for strengthening cell adhesion to ischemic myocardium," *Stem Cells*, vol. 27, no. 6, pp. 1358–1365, 2009.

[62] A. Schmidt, D. Ladage, C. Steingen et al., "Mesenchymal stem cells transmigrate over the endothelial barrier," *European Journal of Cell Biology*, vol. 85, no. 11, pp. 1179–1188, 2006.

[63] C. Steingen, F. Brenig, L. Baumgartner, J. Schmidt, A. Schmidt, and W. Bloch, "Characterization of key mechanisms in transmigration and invasion of mesenchymal stem cells," *Journal of Molecular and Cellular Cardiology*, vol. 44, no. 6, pp. 1072–1084, 2008.

[64] C. Ries, V. Egea, M. Karow, H. Kolb, M. Jochum, and P. Neth, "MMP-2, MT1-MMP, and TIMP-2 are essential for the invasive capacity of human mesenchymal stem cells: differential regulation by inflammatory cytokines," *Blood*, vol. 109, no. 9, pp. 4055–4063, 2007.

[65] T. Freyman, G. Polin, H. Osman et al., "A quantitative, randomized study evaluating three methods of mesenchymal stem cell delivery following myocardial infarction," *European Heart Journal*, vol. 27, no. 9, pp. 1114–1122, 2006.

[66] F. K. Swirski, M. Nahrendorf, M. Etzrodt et al., "Identification of splenic reservoir monocytes and their deployment to inflammatory sites," *Science*, vol. 325, no. 5940, pp. 612–616, 2009.

[67] N. G. Frangogiannis, C. W. Smith, and M. L. Entman, "The inflammatory response in myocardial infarction," *Cardiovascular Research*, vol. 53, no. 1, pp. 31–47, 2002.

[68] F. Leuschner, P. Panizzi, I. Chico-Calero et al., "Angiotensin-converting enzyme inhibition prevents the release of monocytes from their splenic reservoir in mice with myocardial infarction," *Circulation Research*, vol. 107, no. 11, pp. 1364–1373, 2010.

[69] D. Matteucci, A. Toniolo, and P. G. Conaldi, "Systemic lymphoid atrophy in coxsackievirus B3-infected mice: effects of virus and immunopotentiating agents," *Journal of Infectious Diseases*, vol. 151, no. 6, pp. 1100–1108, 1985.

[70] K. Klingel, S. Stephan, M. Sauter et al., "Pathogenesis of murine enterovirus myocarditis: virus dissemination and immune cell targets," *Journal of Virology*, vol. 70, no. 12, pp. 8888–8895, 1996.

[71] J. Plumas, L. Chaperot, M. J. Richard, J. P. Molens, J. C. Bensa, and M. C. Favrot, "Mesenchymal stem cells induce apoptosis of activated T cells," *Leukemia*, vol. 19, no. 9, pp. 1597–1604, 2005.

SAGE-Hindawi Access to Research
Cardiology Research and Practice
Volume 2011, Article ID 739702, 4 pages
doi:10.4061/2011/739702

Case Report

Multimodality Imaging of Chronic Ischemia

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Received 31 August 2010; Accepted 5 October 2010

Academic Editor: Gregory Giamouzis

Although ischemic cardiomyopathy is commonly caused by chronic obstructive coronary disease, the mechanism of the cause is still under investigation. We present echocardiographic strain, magnetic resonance, and histology findings in a chronic ischemia model in preclinical study. This case illustrates the features of multimodality imaging in chronic obstructive coronary disease and gives us great insight into understanding the mechanism of ischemic cardiomyopathy.

1. Introduction

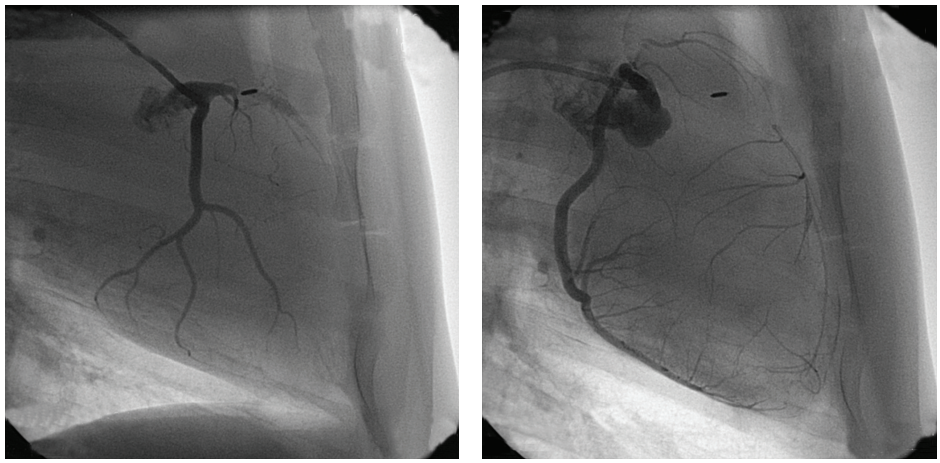
Ischemic cardiomyopathy, the most frequent cause of heart failure, is commonly caused by chronic obstructive coronary disease. The cardiomyocyte response to ischemia, the mechanism for ischemic cardiomyopathy, is still under investigation. On the other hand, imaging devices have developed rapidly over the past decade. We present successful images taken in a model with chronic coronary disease describing characteristic features of chronic ischemia.

2. Case Report

A Yorkshire pig (26 Kg) was studied for 2 months after a chronic implantation of customized occluder on the proximal left anterior descending (LAD) artery. Briefly, under isoflurane anesthesia, surgical access was achieved through the third left intercostal space. A plastic occluder of fixed diameter and 18 G copper wire were deployed around the proximal segment of the LAD. This model progresses a total occlusion of LAD artery with rich collaterals and minimum scar formation within 1 to 3 months after the occluder implantation. The study was performed in accordance with the Guidelines for the Care and Use of Laboratory Animals and was approved by the Subcommittee on Research Animal Care at Mount Sinai School of Medicine. Steady anesthesia using propofol 6 mg/kg/hr IV was maintained throughout each study point.

Coronary angiogram (CAG), left ventriculography (LVG), and echocardiography were performed at 2 weeks, 1 month, and 2 months. Although CAG showed only stenosis of LAD with normal flow at 2 weeks and 1 month with normal LVG and echocardiography, the stenosis developed to total occlusion with Rentrop grade 2 collateral flow from right coronary artery and antegrade bridge collateral flow at 2 months (Figure 1). At the point of occlusion, LVG showed slightly depressed anterior wall motion with ejection fraction (EF) of 59%.

Echocardiography at 2 months confirmed this abnormality (EF 58%). Using prototype Q-lab software (Philips Medical Systems, Andover, MA), two-dimensional images were analyzed for strain analysis using a speckle-tracking algorithm. Circumferential and radial strain (CS and RS, resp.) were analyzed at the level of papillary muscles, and both strain rates at anterior region showed relatively decreased but sustained value compared with other regions. (mean CS −19% versus −26%, mean RS 30% versus 46%, resp.) (Figure 2). After the echocardiography, the pig was transported to the magnetic resonance (MR) facility under anesthesia. Using a 1.5 Tesla magnet (Sonata, Siemens Medical Solutions, Erlangen, Germany), and with electrocardiographic gating, the same plane as during transthoracic



(a) (b)

Figure 1: Coronary angiography at 2 months. (a) Totally occluded left anterior descending artery with bridge collateral flow . (b) Rentrop degree 2 collateral flow from right coronary artery to left anterior descending artery.

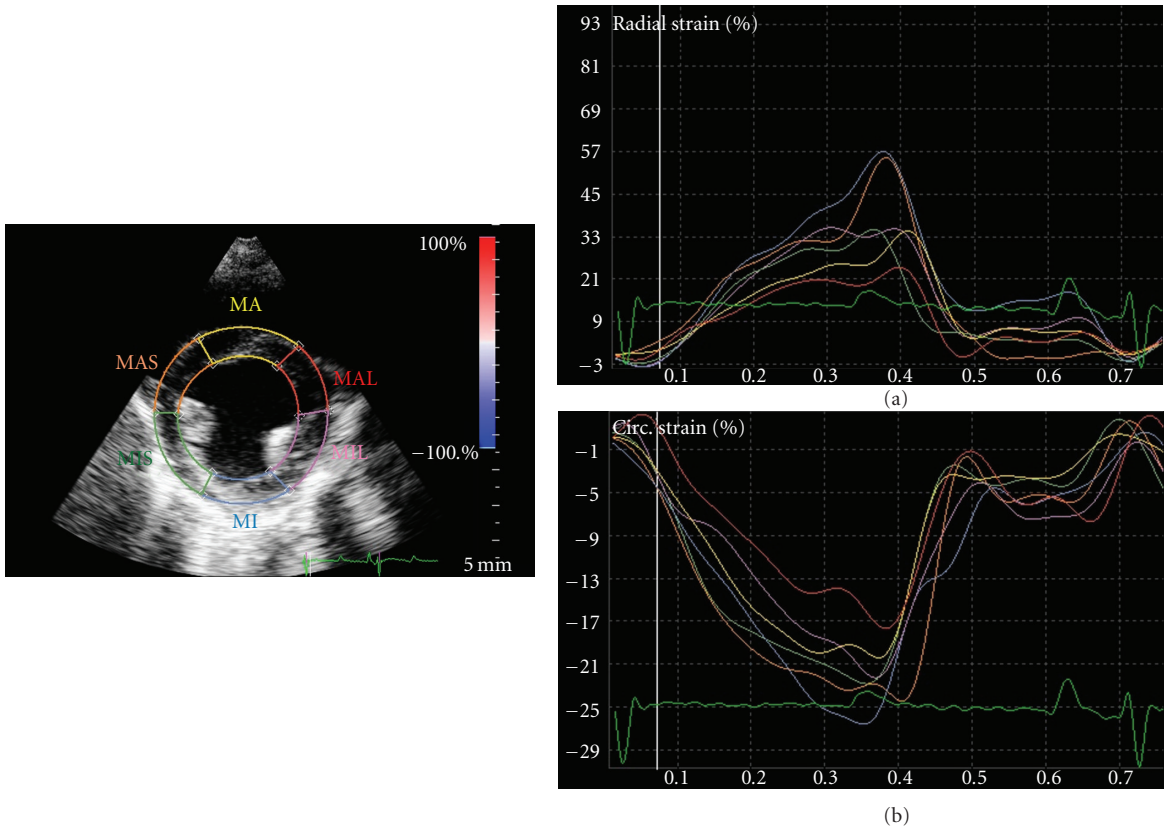


Figure 2: Strain analysis of equally divided six parts at the level of papillary muscles. Yellow and red lines are defined as anterior wall. Both radial strain (a) and circumferential strain (b) showed relatively decreased, yet preserved, strain rate compared with other regions.

echocardiography study was obtained. Delayed enhancement imaging was performed 15 minutes after the administration of 0.2 mmol/kg gadopentetate dimeglumine. T2-weighted image revealed limited intensified area in the subendocardium layer of the anterior wall, which indicates the presence of edema. However, no delayed enhancement was detected at the same region (Figure 3).

After a deep anesthesia with isoflurane, the pig was sacrificed and heart was sliced and subjected to triphenyltetrazolium chloride (TTC) staining to delineate the scar

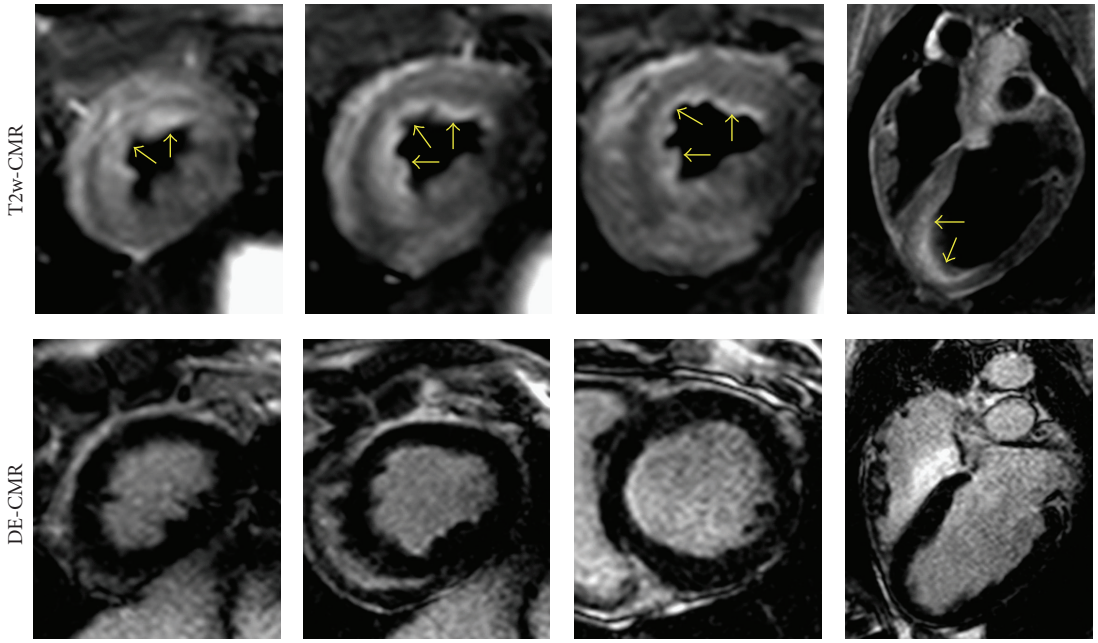


Figure 3: Corresponding short axis and long axis images obtained by CMR. T2w-CMR images showed uptake in the anterior wall (arrows), indicating myocardial edema from ischemia mainly in subendocardium (upper row). However, no specific change was found in delayed enhancement images (lower row). CMR: cardiac magnetic resonance DE: delayed enhancement.

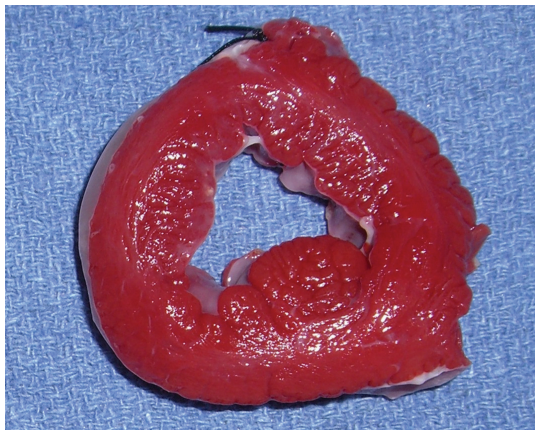


Figure 4: No macroscopic infarction was seen in postmortem TTC-stained myocardium. TTC: triphenyltetrazolium chloride.

area, and one of the slices was divided into 3 layers (endo, mid, and epi) to separately analyze the histopathological profile of each by hematoxylin and eosin (H&E), Masson's trichrome, and TUNEL stainings for further histological evaluation. No significant infarction was observed in TTC staining (Figure 4); however, H&E and Masson's trichrome stainings presented interstitial fibrosis in foci surrounded by apparently healthy myocardial tissue, as indicated by the presence of cardiomyocytes (Figures 5(a) and 5(b)). Furthermore, TUNEL staining showed ongoing mild apoptosis (Figure 5(c)), which was comparable with previous report in hibernated myocardium [1]. Both fibrosis and apoptosis were more apparent towards subendocardium, implying more impaired perfusion of subendocardium in hibernating myocardium.

3. Discussion

In this study, characteristic features of hibernated myocardium were successfully depicted using multiimaging modalities. Formative mechanism of hibernated myocardium is presumed as a complex adjustment to repetitive ischemia-reperfusion [2]. Although this is supported by changing patterns of flow-function relationship, no evidence of ongoing ischemia has been shown by in vivo imaging. Thus, our results further confirm the "adjustment to repetitive ischemia-reperfusion" hypothesis. Myocardial edema without delayed enhancement in cardiac MR suggests ischemia without irreversible change and can be regarded as a part of the process of adapting to chronically restricted blood flow over time. Decreased but maintained CS and RS in strain analysis can also be interpreted as an ischemic state of myocardium with preserved viability [3]. The above observation was further supported by the presence of no apparent infarction in TTC staining together with mild ongoing apoptosis as well as low-extent fibrosis.

3.1. Limitation. Due to the rather rapid progress of total occlusion when compared to humans, the ischemic response might be intensified in this model which led to the characteristic MR image. If we had performed resting perfusion with cardiac MR, it could have illustrated the reduction in flow.

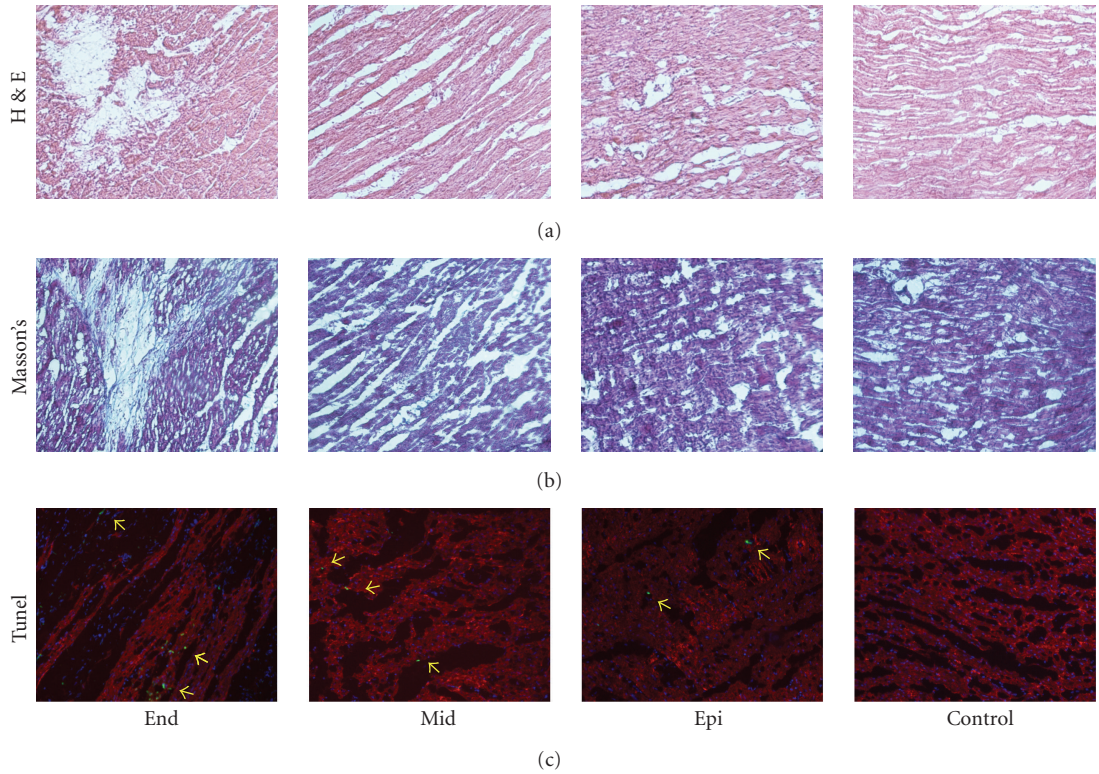


Figure 5: (a, b): General histopathology as assessed by H&E (upper) reveals cardiac lesion. Further characterization by Masson's trichrome (middle) staining shows interstitial fibrosis, which is more severe towards the subendocardium. (c) TUNEL staining for apoptosis analysis of myocardial tissue sections. TUNEL positive nuclei are stained with FITC (green; arrows). Cardiomyocytes were identified by α actinin immunostaining (red). Nuclei were stained with DAPI (blue). Percentages of TUNEL positive nuclei were 0.40%, 0.26%, 0.12%, and 0.03% for endo, mid, epi, and control endo, respectively. H&E: hematoxylin and eosin, FITC: fluorescein isothiocyanate, DAPI: 4'-6'-diamidino-2-phenylindole.

4. Conclusion

We believe that this study is the first to show characteristic features of concurrent multiple images from an identical animal that brought out development of ischemia in chronic obstructive coronary disease. Despite a case report from only one animal, this report gives us a comprehensive understanding in images of chronic ischemia, and at the same time, provides great insight into understanding the mechanism of ischemic cardiomyopathy.

Acknowledgment

This paper was supported by Grants from the National Institutes of Health (1P20HL100396 and 5R01HL083156).

References

[1] C. Chen, L. Ma, D. R. Linfert et al., "Myocardial cell death and apoptosis in hibernating myocardium," *Journal of the American College of Cardiology*, vol. 30, no. 5, pp. 1407–1412, 1997.

[2] G. Heusch, R. Schulz, and S. H. Rahimtoola, "Myocardial hibernation: a delicate balance," *American Journal of Physiology*, vol. 288, no. 3, pp. H984–H999, 2005.

[3] M. Becker, A. Lenzen, C. Ocklenburg et al., "Myocardial deformation imaging based on ultrasonic pixel tracking to identify reversible myocardial dysfunction," *Journal of the American College of Cardiology*, vol. 51, no. 15, pp. 1473–1481, 2008.

SAGE-Hindawi Access to Research
Cardiology Research and Practice
Volume 2011, Article ID 173102, 7 pages
doi:10.4061/2011/173102

Research Article

Noninvasive Detection of Left-Ventricular Systolic Dysfunction by Acoustic Cardiography in Atrial Fibrillation

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Received 13 August 2010; Accepted 30 September 2010

Academic Editor: Filippos Triposkiadis

Objectives. Assessment of left ventricular (LV) systolic function in patients with atrial fibrillation can be difficult. Acoustic cardiography provides several parameters for quantifying LV systolic function. We evaluated the ability of acoustic cardiography to detect LV systolic dysfunction in patients with and without atrial fibrillation. *Design*. We studied 194 patients who underwent acoustic cardiography and cardiac catheterization including measurement of angiographic ejection fraction (EF) and maximum LV dP/dt. LV systolic dysfunction was defined as LV maximum dP/dt < 1600 mmHg/s. Acoustic cardiographic parameters included electromechanical activation time (EMAT) and the systolic dysfunction index (SDI). *Results*. Acoustic cardiography detected systolic dysfunction with high specificity and moderate sensitivity with similar performance to EF (sensitivity/specificity without afib: EMAT 30/96, SDI 40/90, EF at 35% 30/96; sensitivity/specificity with afib: EMAT 64/82, SDI 59/100, EF at 35% 45/82). *Conclusions*. Acoustic cardiography can be used for diagnosis of LV systolic dysfunction in atrial fibrillation.

1. Introduction

Atrial fibrillation is a highly prevalent arrhythmia, particularly in patients with heart failure. Atrial fibrillation significantly increases with age in patients with heart failure, and the prevalence increases from <10% in those with New York Heart Association (NYHA) functional class I to almost 50% in those patients with NYHA class IV [1, 2]. It is estimated that two-thirds of patients with heart failure are over 65 years old and 4.5 times more likely to have atrial fibrillation in men and 5.9 times more likely in women [3]. Assessing systolic function in atrial fibrillation is especially important since both pharmacological and device-based therapies exist. However, due to the beat-to-beat variations in preload with atrial fibrillation, assessment of left ventricular systolic function is difficult. Systolic function is most commonly assessed using the ejection fraction (EF) measured by angiographic, echocardiographic, or radionuclide methods with varying success as schemas continue to be developed to improve accuracy during atrial fibrillation [4–6]. In addition, invasive or imaging technologies such as cardiac magnetic resonance to quantify systolic function are expensive and not always readily available.

Acoustic cardiography (Audicor, Inovise Medical, Inc., Beaverton, OR) records and algorithmically interprets simultaneous digital ECG and acoustic data by using the same array of electrodes used for a standard ECG. However, in the V3 and V4 positions, it employs dual sensors that acquire both ECG and sound data. Measuring systolic time intervals and diastolic heart sounds, acoustic cardiography allows reliable assessment of hemodynamics [7–10]. Parameters produced by this technique include those to assess systolic function [11] including EMAT (electrical mechanical activation time, Q wave onset to the S1 interval), the presence of a third heart sound (S3), and SDI (systolic dysfunction index, a combination of EMAT, S3, QRS duration and QR interval). This diagnostic method is particularly appropriate in environments, where echocardiography or invasive assessment of LV function is not available [12] or when serial measurements are desired.

The goal of the present paper was to evaluate the use of acoustic cardiography as a rapid, noninvasive method to assess LV systolic dysfunction (LVSD) in a population with atrial fibrillation that also underwent invasive diagnostic evaluation. We tested the hypothesis that acoustic cardiography could discriminate those patients with and without LV dysfunction independent of whether or not they also had atrial fibrillation.

2. Materials and Methods

2.1. Subjects. The local Medical Ethics Committee approved the study. After obtaining written informed consent from each patient, we evaluated a convenience sample of 194 patients who underwent diagnostic cardiac catheterization. Patients were without food for at least 6 hours. Short-acting diuretics were withheld on the morning of the catheterization but other cardiac drugs were administered as usual.

All the subjects had measurement of left-ventricular EF and LV end-diastolic pressure (LVEDP). Left-ventricular maximum dP/dt (i.e., LV max(dP/dt)) was measured using a manometer-tipped catheter (Volcano Inc., Parker, TX, USA) in 108 patients and a fluid-filled catheter in the remaining 86. LV max(dP/dt) was calculated automatically (Schwarzer GmbH Medical Equipment, Munich, Germany) in normally conducted beats. Only recordings with a minimum of at least 4 normally conducted beats were used including in patients with atrial fibrillation. Values of LV max(dP/dt) of <1600 mmHg/s were considered to be a marker of LVSD [13–15]. Left ventricular ejection fraction was calculated using monoplane ventriculography. Measurements of right atrial, right ventricular and pulmonary artery systolic and wedge pressures were performed with multipurpose catheters.

2.2. Acoustic Cardiography. Acoustic cardiography data were recorded immediately prior to cardiac catheterization with the patient in a supine position. This quantitative method provides parameters for assessing both systolic and diastolic LV function. In the present study, we evaluated two systolic parameters—the electromechanical activation time (EMAT) and the systolic dysfunction index (SDI). EMAT measures the time interval from the onset of the QRS complex to the point of maximum intensity of the first heart sound. Therefore, EMAT indicates the amount of time required for the LV to generate sufficient force to close the mitral valve and reflects the velocity of force generated during systole. The SDI combines EMAT, QRS duration, QR interval and the strength of the third heart sound into one parameter (SDI = transform (QRS duration $*$ QR interval $*$ S3 strength $*$ EMAT/RR interval)). The SDI value undergoes a nonlinear transformation and is then reported as a value between 0 and 10, where SDI > 5 indicates systolic dysfunction defined as EF < 50%, and SDI > 7.5 indicates EF < 35% and elevated filling pressure. The SDI was developed on separate learn and test sets of invasive cardiac catheterization data that provided both EF and LV end-diastolic pressure. The acoustic cardiographic parameters are calculated from a 10-second recording of data that typically involves averaging of measurements from 8 to 12 beats. We hypothesized that EMAT and SDI could be used to detect LVSD.

2.3. Statistical Analysis. Data are presented as mean values and standard deviations with minimum and maximum values as ranges for continuous variables. Categoric data are presented as exact numbers and proportions. We tested the null hypothesis for continuous data using the unpaired T-test for patients with and without atrial fibrillation and a priori chose alpha <0.05 to indicate statistical significance. We also generated ROC curves to determine the diagnostic sensitivities and specificities for LVSD and to calculate positive and negative likelihood ratios. Unlike positive and negative predictive values, positive and negative likelihood ratios are independent of the prevalence of the abnormality in the population being tested [16]. To avoid dividing by zero, we set the positive likelihood ratio equal to sensitivity in the cases in which specificity was 100%.

3. Results

There were a total of 194 subjects recruited for this study. The mean age of the 155 subjects without atrial fibrillation was 62.6 ± 11.8 years (range: 22 to 86 years), and 102 (66%) of the subjects were men, whereas the mean age of the 39 patients with atrial fibrillation was 67.3 ± 10.7 years (range: 43 to 85 years) and 32 (82%) were men.

One hundred three (66%) of the subjects without atrial fibrillation had LVSD (a LV max(dP/dt) < 1600 mmHg/s), while 22 (56%) of the subjects with atrial fibrillation had LVSD. In the population without atrial fibrillation, the LV max(dP/dt) was 1474 ± 479 mmHg/s (range: 480 to 2928 mmHg/s) and 1589 ± 534 mmHg/s (range: 648 to 2832 mmHg/s) in the group with atrial fibrillation. Table 1 shows that the subjects with LVSD had significantly lower mean values of EF, larger end-diastolic and end-systolic volumes, and greater mean values of EMAT and the systolic dysfunction index. Heart rate was significantly higher and EMAT longer in the populations with atrial fibrillation independent of whether there was LVSD or not.

Figure 1 shows the means and 95% confidence intervals of EMAT, the systolic dysfunction index and EF. In both the patients with and without atrial fibrillation, EMAT and the systolic dysfunction index discriminate between the presence versus the absence of LVSD, as does the ejection fraction. Figure 1 also reveals that EMAT is higher in patients with atrial fibrillation compared to those in sinus rhythm both with and without LVSD suggesting that atrial fibrillation alone impairs LV contractility. The ROC curves in Figure 2 reveal that EMAT and SDI are similar in performance for the groups with and without atrial fibrillation.

Table 2 shows sensitivities, specificities and the likelihood ratios for EMAT, SDI, and EF at common thresholds to detect LV systolic dysfunction in groups with and without atrial fibrillation. Note the similar performances for EMAT and SDI independent of the presence of atrial fibrillation. Specificities were high for all populations for EMAT and SDI, with moderate sensitivities (ranging from 30 to 64).

Table 1: Demographic and clinical characteristics.

Parameter	No Afib, No LVSD ($N = 52$)	No Afib, LVSD ($N = 103$)	Afib, No LVSD ($N = 17$)	Afib, LVSD ($N = 22$)
Age (years)	$63.8 \pm 11.6, 27 - 81$	$62.0 \pm 12.0, 22 - 86$	$66.7 \pm 11.2, 43 - 85$	$67.7 \pm 10.4, 43 - 85^{*}$
Male (%)	63%	67%	82%	82%
Height (cm)	$170 \pm 10, 141 - 190$	$169 \pm 9.1, 149 - 196$	$173 \pm 11, 152 - 192$	$172 \pm 10.6, 150 - 190$
Weight (kg)	$80.1 \pm 19.4, 52 - 148$	$78.9 \pm 15.0, 51 - 117$	$91.4 \pm 24.4, 49 - 160$	$86.5 \pm 22.0, 53 - 132$
Heart rate (bpm)	$75.3 \pm 16.0, 42 - 129$	$74.5 \pm 14.9, 43 - 142$	$99.0 \pm 28.6, 56 - 149^{*}$	$90.7 \pm 14.8, 68 - 119^{*}$
QRS duration (ms)	$96.4 \pm 16.1, 59 - 143$	$121 \pm 36.1, 68 - 235^{\wedge}$	$90.2 \pm 9.8, 74 - 102$	$110 \pm 26.1, 81 - 171^{\wedge}$
QTc interval (ms)	$418 \pm 28.7, 319 - 465$	$430 \pm 32.8, 372 - 528^{\wedge}$	$407 \pm 29.1, 374 - 466$	$404 \pm 33.4, 321 - 483^{*}$
EMAT (ms)	$83.7 \pm 16.5, 58 - 164$	$100 \pm 19.7, 60 - 164^{\wedge}$	$101 \pm 16.8, 79 - 147^{*}$	$116 \pm 20.5, 88 - 164^{\wedge *}$
SDI	$3.2 \pm 1.6, 0.8 - 7.4$	$4.9 \pm 2.6, 0.7 - 10^{\wedge}$	$3.8 \pm 0.7, 2.7 - 4.6$	$6.0 \pm 2.1, 2.9 - 10^{\wedge}$
LV EDP (mmHg)	$19.9 \pm 6.5, 4 - 37$	$18.6 \pm 7.6, 4 - 39$	$16.4 \pm 7.4, 5 - 27$	$15.1 \pm 6.6, 8 - 37^{*}$
LV max (dP/dt) (mmHg/s)	$2039 \pm 301, 1608 - 2928$	$1189 \pm 238, 480 - 1584^{\wedge}$	$2090 \pm 342, 1632 - 2832$	$1201 \pm 254, 648 - 1584^{\wedge}$
LV ejection fraction (%)	$62.3 \pm 14.0, 19 - 83$	$43.4 \pm 18.3, 8 - 84^{\wedge}$	$57.1 \pm 21.1, 10 - 86$	$40.7 \pm 19.2, 15 - 81^{\wedge}$
EDV (ml)	$116 \pm 35.3, 51 - 206$	$155 \pm 63.4, 47 - 337^{\wedge}$	$107 \pm 32.5, 50 - 146$	$144 \pm 59.7, 25 - 264^{\wedge}$
ESV (ml)	$51.1 \pm 24.3, 18 - 135$	$96.0 \pm 56.8, 19 - 261^{\wedge}$	$49.9 \pm 29.5, 19 - 113$	$97.5 \pm 59.7, 40 - 186^{\wedge}$

Afib: atrial fibrillation; LV EDP: left ventricular end-diastolic pressure; EDV: end-diastolic volume; EMAT: electromechanical activation time; ESV: end-systolic volume; LVSD: left ventricular systolic dysfunction, defined as LV max(dP/dt) < 1600 mmHg/s; SDI: systolic dysfunction index.
$^{\wedge}P < .05$ compared across LV systolic dysfunction groups; $^{*}P < .05$. No Afib compared to Afib within the same LV systolic dysfunction group.

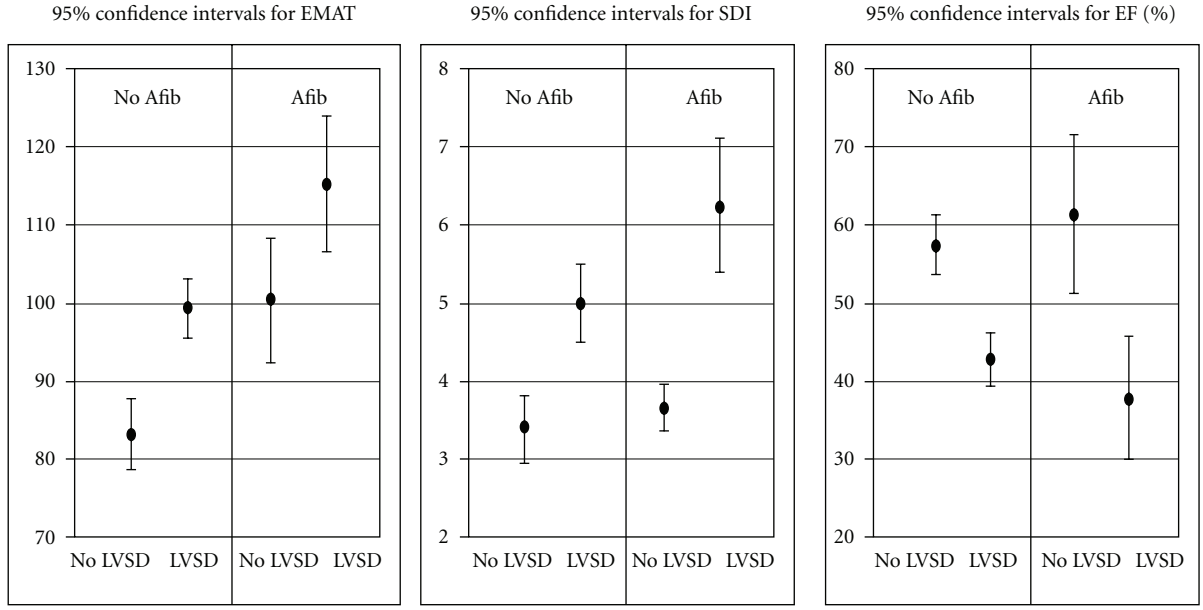

Figure 1: The means and 95% confidence intervals for electromechanical activation time (EMAT), the systolic dysfunction index (SDI) and ejection fraction (EF) for populations with and without left ventricular systolic dysfunction (LVSD). Afib: atrial fibrillation; EMAT: electromechanical activation time, msec; SDI: systolic dysfunction index; EF: ejection fraction, %; LVSD: left ventricular systolic dysfunction, defined as LV max(dP/dt) < 1600 mmHg/s.

Ejection fraction had reduced specificities at similar sensitivities to the acoustic cardiographic parameters.

4. Discussion

Noninvasive methods are often employed to identify patients with LVSD. Echocardiography measures several systolic parameters but the beat-to-beat variations in preload with atrial fibrillation make accuracy difficult. A study by Gosselink [17] found that varying left ventricular performance during atrial fibrillation is determined by cycle length-dependent contractile mechanisms including postextrasystolic potentiation and mechanical restitution, but that beat-to-beat changes in preload consistent with the Starling mechanism are diminished after long and short preceding intervals. Another study using simultaneous biplane views of the left ventricle concludes that systolic function can be accurately assessed in atrial fibrillation by averaging 2 beats with equal subsequent cycle lengths greater than 500 ms [18]. Dubrey [19] found that in atrial fibrillation the average

Table 2: Performances of EMAT, SDI, and EF to detect LVSD.

Parameter	Group	% Sensitivity	% Specificity	Pos LR	Neg LR
EMAT@110	No AFib	30	96	7.8	1.4
	Afib	64	82	3.6	2.3
SDI@5.0	No Afib	40	90	4.0	1.5
	Afib	59	100	59	2.4
EF@35%	No Afib	30	96	7.8	1.4
	Afib	45	82	2.6	1.5
EF@50%	No Afib	69	81	3.6	2.6
	Afib	64	76	2.7	2.1

EMAT: electromechanical activation time, msec; SDI: systolic dysfunction index; EF: ejection fraction, %; LVSD: left ventricular systolic dysfunction, defined as LV max(dP/dt) < 1600 mmHg/s, Afib: atrial fibrillation, Pos LR: positive likelihood ratio, Neg LR: negative likelihood ratio.

number of beats required to determine cardiac output using Doppler measurements was approximately 13 beats (ranging 4 to 17 beats) or three times that required in sinus rhythm. Therefore, the time required and skill necessary to perform echocardiographic examinations in patients with atrial fibrillation are quite high.

Cardiac magnetic resonance imaging (CMRI) has superior interobserver and intraobserver variability than echocardiography and is the preferred technique by some clinicians for volume and ejection fraction estimation in heart failure patients due to its three-dimensional technique for nonsymmetric ventricles and excellent image quality [20]. But recent literature is mixed on its routine use in the management of atrial fibrillation for evaluation of systolic function. In a recent review of cardiovascular imaging in atrial fibrillation, Wazni et al. recommend the use of CMRI for precise visualization of left atrial and pulmonary vein anatomy [21] but recommend echocardiography for clinical management.

The acoustic cardiography method is a rapid and inexpensive test and does not have the above limitations inherent in echocardiography or cardiac magnetic resonance imaging. The procedure needed to obtain EMAT and SDI requires no more time, effort, or technical skill than that needed for recording a standard 12-lead ECG, and the analysis of the data is fully automated [22]. The parameters are reproducible and represent an average over the 10-second recording. This averaging of values over multiple cardiac cycles improves their performance by minimizing the effect of varying preceding RR intervals as demonstrated for systolic time intervals over 30 years ago [23, 24].

In the present paper, we defined left ventricular systolic dysfunction as LV max(dP/dt) <1600, a threshold value similar to that used by other investigators [13–15]. Left-ventricular maximum dP/dt is sensitive to changes in contractility and is affected to a lesser extent by both preload and afterload [25, 26]. Left ventricular max(dP/dt) may be delayed and may follow the opening of the aortic valve in patients with severe LVSD or with marked vasodilatation with very low aortic diastolic pressures. Its sensitivity to preload is greater in ventricles with enhanced contractility, but is reduced in LVSD [27]. Nevertheless, reduced LV max(dP/dt) is clinically important because of its association with a poor prognosis [28–30].

EMAT also reflects the rate of left ventricular pressure development since it measures the time required to close the mitral valve. EMAT is similar to LV max(dP/dt) in that it is influenced by preload via the Starling mechanism invoked by left-ventricular filling pressure. However, EMAT is not affected by afterload resulting from changing systemic vascular resistance or aortic valvular obstruction. In this way, EMAT can be a robust measurement in atrial fibrillation even with other concurrent disease conditions. The systolic dysfunction index combines EMAT with QRS duration, the QR interval, and the strength of the third heart sound. It was developed to provide good detection of systolic dysfunction at values above 5.0, and above 7.5 detects systolic dysfunction with elevated filling pressures [31]. As a continuous variable SDI can provide a means to track changes in systolic function and filling pressures.

Diminished LV max(dP/dt) is a well-established and accurate marker of LV systolic dysfunction. The present study has shown that acoustic cardiographic parameters discriminate well between normal versus low values of LV max(dP/dt) in patients with atrial fibrillation. However, it would be useful to know if these parameters also identify patients who are at increased risk of adverse clinical outcomes. Nonacute heart failure patients ($n = 128$) were studied using acoustic cardiography and echocardiography (personal communication, M. Zuber). They were followed for 27.1 ± 14.8 months and all heart failure events and all-cause deaths were recorded (24 events total). Echocardiographic and acoustic cardiographic measurements were evaluated for sensitivity at 90% specificity and the corresponding odds ratios. Echocardiographic parameters had lower sensitivity (T deceleration time 26% at 180 ms; EF 17% at 45%; E/E′ ratio 18% at 15; E/A 25% at 1.8) than the acoustic cardiographic parameters (EMAT 38% at 120 ms; SDI 45% at 5.0). The echocardiographic measurements also had lower odds ratios (ranging from 0.4 for T deceleration time to 2.2 for E/E′ ratio) than acoustic cardiographic parameters (ranging from 5.9 for EMAT to 7.5 for SDI). This study would indicate that both EMAT and SDI have superior prognostic value over the traditional echocardiographic measurements.

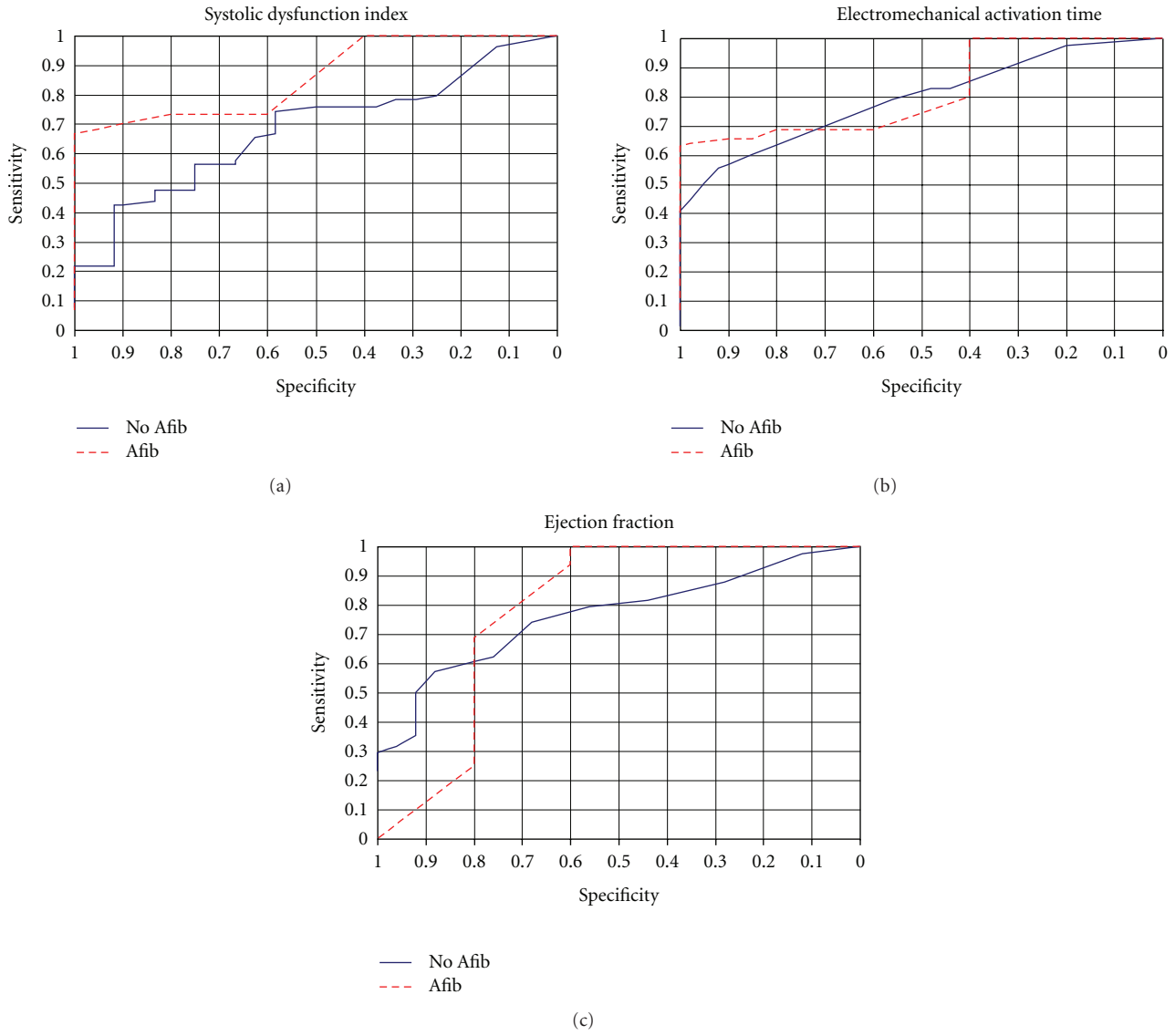

Figure 2: Receiver-operating characteristic (ROC) curves are presented for electromechanical activation time, the systolic dysfunction index and ejection fraction for populations with (red curve) and without atrial fibrillation (blue curve). Afib: atrial fibrillation.

In another study of patients hospitalized for acute heart failure ($n = 45$), acoustic cardiographic recordings were taken within 24 hours of admission, before discharge and 2 weeks after discharge [32]. Adverse post-discharge events were cardiac death or rehospitalization for heart failure. Patients were followed for 242 ± 156 days. Predischarge and 2-week postdischarge %EMAT (defined as EMAT divided by the R-R interval) was significantly associated with adverse post-discharge events, with or without adjustment for age, gender, left ventricular EF, E/E′ by Doppler echocardiography, and serum N-terminal probrain natriuretic peptide.

We conclude that acoustic cardiography detects left ventricular systolic dysfunction in patients with atrial fibrillation. This is particularly important when repeat assessment is desired and in situations where invasive (cardiac catheterization) or noninvasive (echocardiographic or cardiac magnetic resonance imaging) assessment of LV function is not feasible or readily available.

5. Limitations of the Study

Although it is similar to older methods used to obtain systolic time intervals, acoustic cardiography is a relatively new method of quantifying cardiac function and has limited routine use. There was not a control group of healthy subjects due to the fact that this was an invasive cardiac catheterization study. Not all the recordings of left ventricular dP/dt were performed with manometer-tipped catheters. Left ventricular ejection fraction was calculated using monoplane ventriculography. Although short-acting diuretics were withheld on the morning of the catheterization, the subjects varied with respect to the types and

dosages of other cardiac drugs that they were receiving. Since beta adrenergic blockers, vasodilators, ACE inhibitors and other cardiac drugs influence ventricular performance, this pharmacological variability may have affected our results.

Conflict of Interests

Dr. P. Arand is an employee of Inovise Medical, Inc. The remaining authors have no conflict of interests and will have no financial gain from the writing or the publication of this paper.

Acknowledgment

The authors thankfully acknowledge the assistance of Dr. Peter Bauer, Inovise Medical, Inc., Beaverton, OR for data analysis support.

References

[1] W. H. Maisel and L. W. Stevenson, "Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy," *American Journal of Cardiology*, vol. 91, no. 6, pp. 2D–8D, 2003.

[2] G. M. de Ferrari, C. Klersy, P. Ferrero et al., "Atrial fibrillation in heart failure patients: prevalence in daily practice and effect on the severity of symptoms. Data from the ALPHA study registry," *European Journal of Heart Failure*, vol. 9, no. 5, pp. 502–509, 2007.

[3] I. Savelieva and A. J. Camm, "Atrial fibrillation and heart failure: natural history and pharmacological treatment," *Europace*, vol. 5, no. 1, pp. S5–S19, 2004.

[4] C.-L. Wang, W.-J. Ho, N. Luqman, L.-A. Hsu, and C.-T. Kuo, "Biplane assessment of left ventricular function during atrial fibrillation at beats with equal subsequent cycles," *International Journal of Cardiology*, vol. 113, no. 1, pp. 54–60, 2006.

[5] T. Tabata, R. A. Grimm, N. L. Greenberg et al., "Assessment of LV systolic function in atrial fibrillation using an index of preceding cardiac cycles," *American Journal of Physiology—Heart and Circulatory Physiology*, vol. 281, no. 2, pp. H573–H580, 2001.

[6] M. Iwase, T. Aoki, M. Maeda, M. Yokota, and H. Hayashi, "Relationship between beat to beat interval and left ventricular function in patients with atrial fibrillation," *International Journal of Cardiac Imaging*, vol. 3, no. 4, pp. 217–226, 1988.

[7] B. Moyers, M. Shapiro, G. M. Marcus et al., "Performance of phonoelectrocardiographic left ventricular systolic time intervals and B-type natriuretic peptide levels in the diagnosis of left ventricular dysfunction," *Annals of Noninvasive Electrocardiology*, vol. 12, no. 2, pp. 89–97, 2007.

[8] M. Roos, S. Toggweiler, P. Jamshidi et al., "Noninvasive detection of left ventricular systolic dysfunction by acoustic cardiography in cardiac failure patients," *Journal of Cardiac Failure*, vol. 14, no. 4, pp. 310–319, 2008.

[9] M. Shapiro, B. Moyers, G. M. Marcus et al., "Diagnostic characteristics of combining phonocardiographic third heart sound and systolic time intervals for the prediction of left ventricular dysfunction," *Journal of Cardiac Failure*, vol. 13, no. 1, pp. 18–24, 2007.

[10] M. Roos, S. Toggweiler, M. Zuber, P. Jamshidi, and P. Erne, "Acoustic cardiographic parameters and their relationship to invasive hemodynamic measurements in patients with left ventricular systolic dysfunction," *Congestive Heart Failure*, vol. 12, supplement 1, pp. 19–24, 2006.

[11] S. J. Shah and A. D. Michaels, "Hemodynamic correlates of the third heart sound and systolic time intervals," *Congestive Heart Failure*, vol. 12, supplement 1, pp. 8–13, 2006.

[12] P. Erne, "Beyond auscultation—acoustic cardiography in the diagnosis and assessment of cardiac disease," *Swiss Medical Weekly*, vol. 138, no. 31-32, pp. 439–452, 2008.

[13] C. F. Baicu, M. R. Zile, G. P. Aurigemma, and W. H. Gaasch, "Left ventricular systolic performance, function, and contractility in patients with diastolic heart failure," *Circulation*, vol. 111, no. 18, pp. 2306–2312, 2005.

[14] Y. Yabe and S. Yoshimura, "Effect of inosine on left ventricular performance and its clinical significance," *Japanese Heart Journal*, vol. 22, no. 6, pp. 915–928, 1981.

[15] B. Gremmler, M. Kunert, H. Schleiting, K. Kisters, and L. J. Ulbricht, "Relation between N-terminal pro-brain natriuretic peptide values and invasively measured left ventricular hemodynamic indices," *Experimental and Clinical Cardiology*, vol. 8, no. 2, pp. 91–94, 2003.

[16] A. M. Weissler, "A perspective on standardizing the predictive power of noninvasive cardiovascular tests by likelihood ratio computation: 2. Clinical applications," *Mayo Clinic Proceedings*, vol. 74, no. 11, pp. 1072–1087, 1999.

[17] A. T. M. Gosselink, P. K. Blanksma, H. J. G. M. Crijns et al., "Left ventricular beat-to-beat performance in atrial fibrillation: contribution of Frank-Starling mechanism after short rather than long RR intervals," *Journal of the American College of Cardiology*, vol. 26, no. 6, pp. 1516–1521, 1995.

[18] C.-L. Wang, W.-J. Ho, N. Luqman, L.-A. Hsu, and C.-T. Kuo, "Biplane assessment of left ventricular function during atrial fibrillation at beats with equal subsequent cycles," *International Journal of Cardiology*, vol. 113, no. 1, pp. 54–60, 2006.

[19] S. W. Dubrey and R. H. Falk, "Optimal number of beats for the Doppler measurement of cardiac output in atrial fibrillation," *Journal of the American Society of Echocardiography*, vol. 10, no. 1, pp. 67–71, 1997.

[20] N. G. Bellenger, M. I. Burgess, S. G. Ray et al., "Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance. Are they interchangeable?" *European Heart Journal*, vol. 21, no. 16, pp. 1387–1396, 2000.

[21] O. M. Wazni, H.-M. Tsao, S.-A. Chen et al., "Cardiovascular imaging in the management of atrial fibrillation," *Journal of the American College of Cardiology*, vol. 48, no. 10, pp. 2077–2084, 2006.

[22] S. Toggweiler, M. Zuber, R. Kobza et al., "Improved response to cardiac resynchronization therapy through optimization of atrioventricular and interventricular delays using acoustic cardiography: a pilot study," *Journal of Cardiac Failure*, vol. 13, no. 8, pp. 637–642, 2007.

[23] P. Kligfield, "Systolic time intervals in atrial fibrillation and mitral stenosis," *British Heart Journal*, vol. 36, no. 8, pp. 798–805, 1974.

[24] A. Cieslinski, W. K. K. Hui, and P. J. Oldershaw, "Interaction between systolic and diastolic time intervals in atrial fibrillation," *British Heart Journal*, vol. 51, no. 4, pp. 431–437, 1984.

[25] D. T. Mason, "Usefulness and limitations of the rate of rise of intraventricular pressure (dp/dt) in the evaluation of myocardial contractility in man∗," *The American Journal of Cardiology*, vol. 23, no. 4, pp. 516–527, 1969.

[26] H. P. Krayenbuehl, W. Rutishauser, P. Wirz, I. Amende, and H. Mehmel, "High-fidelity left ventricular pressure measurements for the assessment of cardiac contractility in man," *The American Journal of Cardiology*, vol. 31, no. 4, pp. 415–427, 1973.

[27] H. D. Schmidt and H. Hoppe, "Preload dependence of dP/dt max, V(CE) max and calculated V max compared to the inotropic sensitivity of these indices of cardiac contractility," *Basic Research in Cardiology*, vol. 73, no. 4, pp. 380–393, 1978.

[28] T. J. Kolias, K. D. Aaronson, and W. F. Armstrong, "Doppler-derived dP/dt and -dP/dt predict survival in congestive heart failure," *Journal of the American College of Cardiology*, vol. 36, no. 5, pp. 1594–1599, 2000.

[29] R. Yamauchi-Kohno, T. Miyauchi, T. Hoshino et al., "Role of endothelin in deterioration of heart failure due to cardiomyopathy in hamsters: increase in endothelin-1 production in the heart and beneficial effect of endothelin-A receptor antagonist on survival and cardiac function," *Circulation*, vol. 99, no. 16, pp. 2171–2176, 1999.

[30] J. S. Dubiel, P. Petkow-Dimitrow, G. Kałuza, and T. Horzela, "Prognostic value of selected hemodynamic parameters featuring left ventricular systolic and diastolic function in patients with dilated cardiomyopathy," *Polskie Archiwum Medycyny Wewnetrznej*, vol. 88, no. 6, pp. 392–400, 1992.

[31] P. Arand, A. D. Michaels, M. Kontos, R. Warner, M. Gasperina, and S. Hesler, "Combined ECG and heart sounds parameters identifies patients with systolic dysfunction with or with-out elevated pressure. Heart Failure Society of America (HFSA)," *Journal of Cardiac Failure*, vol. 13, no. 6, p. S184, 2007.

[32] T. Chao, S. Sung, H. Cheng et al., "Electromechanical activation time in the prediction of discharge outcomes in patients hospitalized with acute heart failure syndrome," Submitted.

SAGE-Hindawi Access to Research
Cardiology Research and Practice
Volume 2011, Article ID 201962, 4 pages
doi:10.4061/2011/201962

Case Report

A Case of Isolated Left Ventricular Noncompaction with Basal ECG-Tracing Strongly Suggestive for Type-2 Brugada Syndrome

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Received 7 August 2010; Accepted 30 September 2010

Academic Editor: Gregory Giamouzis

Isolated left ventricular noncompaction (ILVNC) is a cardiomyopathy caused by intrauterine arrest of compaction of the myocardial fibres and meshwork, an important process in myocardial development. ILVNC is clinically accompanied by depressed ventricular function, arrhythmias, and systemic embolization. We reported a case of ILVNC with basal ECG-tracing strongly suggestive for type-2 Brugada syndrome (BrS). Up to now, this is the first report investigating the association between ILVNC and this particular ECG pattern.

1. Introduction

Isolated left ventricular noncompaction (ILVNC) is a relatively newly defined disorder of the endomyocardium characterized by prominent ventricular trabeculations and deep intertrabecular recesses [1]. Clinical manifestations include a depressed left ventricular function, ventricular arrhythmia, and systemic embolization [2, 3]. ILVNC has been reported to be associated with several electrocardiographic changes such as ST depression and flat or negative T waves, bundle branch block, and Wolff-Parkinson-White (WPW) syndrome [2–4]. To the best of our knowledge, Brugada syndrome (BrS) has not been reported on previously. We described a case of ILVNC with basal ECG tracing strongly suggestive for type-2 BrS.

2. Case Report

We reported the case of a 59-year-old man with basal ECG tracing strongly suggestive for type-2 BrS Figure 1(c). He had virtually no cardiac complaint or any medication before. On physical examination, his heart rate was 70 beats/min, blood pressure was 130/80 mmHg, and body temperature was 36.1°C. Cardiopulmonary findings were normal. Haematological and biochemical tests were within normal limits.

Patient underwent a transthoracic echocardiogram (TTE) that excluded arrhythmogenic right ventricular dysplasia, septal ischemia, ventricular aneurysm, and fast repolarization and showed noncompaction areas in both ventricles. This exam revealed the existence of two layers of myocardium—a thin, compacted, epicardial layer and a thick, noncompacted endocardial zone. The inner layer consisted of multiple myocardial trabeculations and deep intratrabecular recesses communicating with the left ventricular cavity Figures 1(a) and 1(b). The ratio of systolic thickness of noncompacted to compacted myocardium layers was above 2.0 (N/C > 2.0). In the colour-Doppler the deep intertrabecular recesses were filled with blood from the ventricular cavity. This finding was confirmed by nuclear magnetic resonance (NMR).

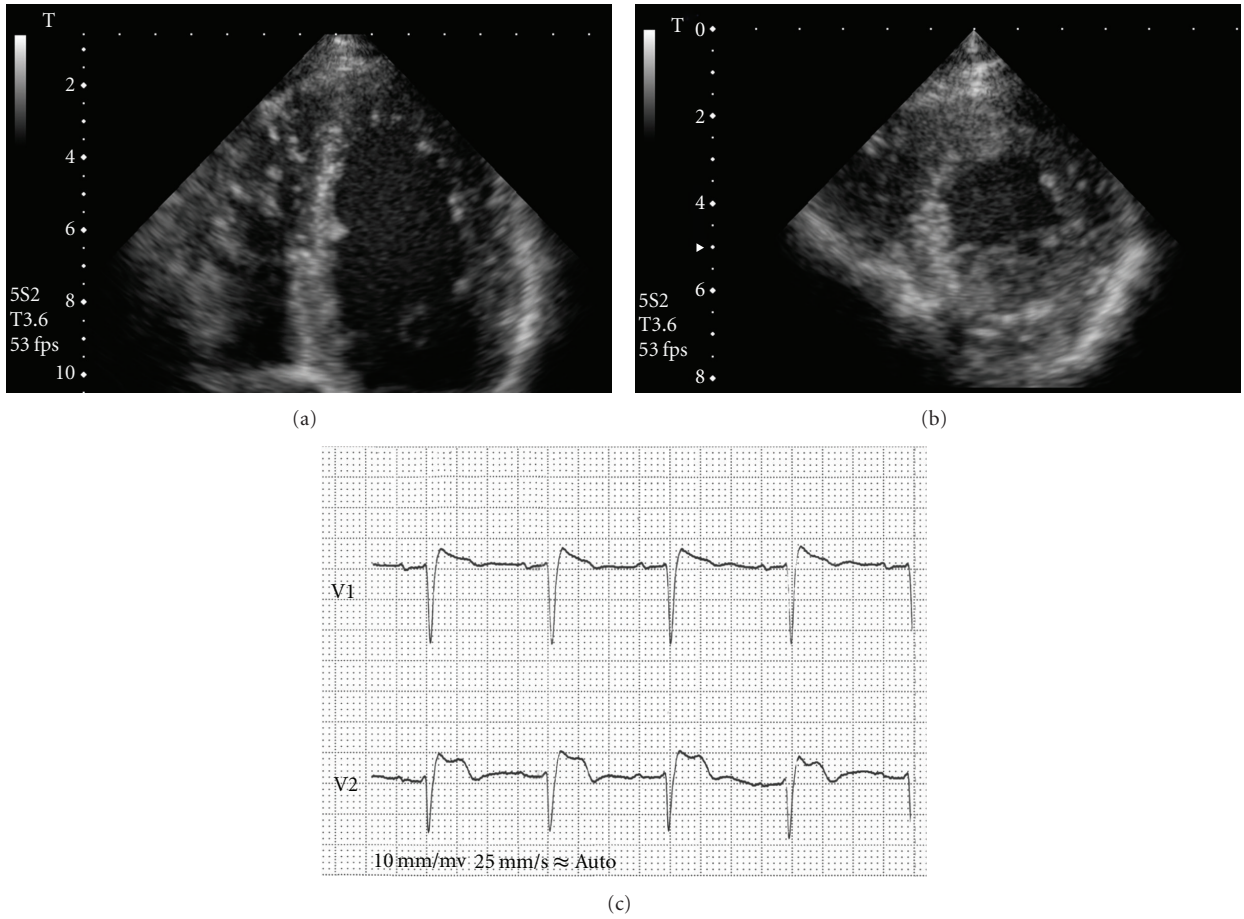

Figure 1: (a) Four-chamber view showing left and right ventricular noncompaction. The inner noncompacted layer is thick and hyperechogenic, and the outer is compacted and echolucent. This appearance is more markedly visible on the left ventricle's lateral wall and apex and on the right ventricle's free wall and apex. (b) Left ventricular short axis view showing noncompacted areas in the apex. (c) Type-2 ECG pattern with ST-segment elevation followed by a positive T wave in V1 and V2 consistent with Brugada syndrome.

The Holter ECG did not reveal any ipercinetic arrhythmias but confirmed ST-segment elevation in the right precordial leads (V1 and V2). Treadmill stress test according to the Bruce protocol was normally sustained for BP and ECG ischemic findings. During the recovery phase the saddleback-type ST-segment elevation in V1 and V2 changed into a coved-type ECG. The ventricular tachycardia elicited by the flecainide test was hemodynamically stable and normalized without medication.

Based on the dynamic ECG changes (conversion from saddleback- to coved-type ECG) and exercise-induced ventricular tachycardia showing a left bundle branch block pattern, a diagnosis of asymptomatic Brugada syndrome was made.

The patient was sent to an arrhythmologic center for the electrophysiological study.

3. Discussion

ILVNC is a rare congenital cardiomyopathy characterized by excessively prominent trabecular meshwork and deep intratrabecular recesses within the left ventricle, sometimes also affecting the right ventricle and interventricular septum [4, 5]. The predominant clinical features are heart failure, arrhythmias, embolic events, and sudden cardiac death (SCD) [4]. By definition, ILVNC occurs in the absence of other structural heart diseases. The gold standard for the ILVNC diagnosis is the echocardiographic examination. Because of an increasing awareness and interest in this disorder, and advances in echocardiographic imaging, reported cases have increased.

Although the etiology of ILVNC has not been fully investigated, this disorder is thought to result from an arrest in endomyocardial morphogenesis during the embryonic period [1]. During early embryonic life, the heart is a loose interwoven meshwork of muscle fibers. The developing myocardium gradually condenses, and the large spaces within the trabecular meshwork flatten or disappear [6].

The ECG of the previously reported patients with ILVNC showed ST depression and flat or negative T waves, bundle branch block, WPW syndrome, and various patterns of arrhythmia [2–4]. A high incidence of WPW syndrome

was found in children [4]. A basal ECG tracing strongly suggestive for type-2 BrS accompanied by ILVNC has not yet been reported.

Brugada syndrome (BrS; OMIM 601144) is an autosomal dominant arrhythmogenic pathology characterized by syncope and SCD. This pathology, defined by some authors as "Idiopathic ventricular fibrillation," is actually understood as a channelopathy probably consecutive to mutations on *SCN5A* gene (3p21-23) encoding the cardiac sodium channel's α-subunit [7].

BrS manifests with syncope and cardiac arrest, typically occurring in the third and fourth decade of life, and usually at rest or during sleep. This eventuality called for an aggressive therapeutic strategy in all patients with BrS and, since no pharmacological treatment of proven efficacy still is available, it led to implantable cardioverter defibrillator (ICD) implants.

According to a recent consensus conference [8], BrS is diagnosed in presence of the following diagnostic criteria.

(1) Type-1 ECG pattern with ST-segment elevation in more than one right precordial lead, followed by a negative T wave plus one of the following conditions documented ventricular fibrillation; self-terminating polymorphic ventricular tachycardia; a family history of SCD (<45 years); coved-type ECGs in family members; electrophysiological inducibility; syncope or nocturnal agonal respiration.

(2) Appearance of type-2 ECG pattern with ST-segment elevation in more than one right precordial lead upon challenge with a sodium channel blockers (Flecainide or Ajmaline), followed by a positive or biphasic T wave that results in a saddleback configuration.

(3) Appearance of type-3 ECG pattern characterized by ST-segment elevation ($\leq$1 mm) in more than one lead either with a coved-type or a saddleback morphology, with conversion to type 1 after challenge with a sodium channel blocker.

In their initial report on eight patients, Brugada et al. emphasized the lack of structural cardiac abnormalities [9]. However, there is probably an overlap between Brugada syndrome and other nosographic entities. It is reported in the literature the association between the typical V1–V3 segment elevation and right bundle branch block in some patients with arrhythmogenic right ventricular cardiomyopathy (ARVC; OMIM 107970) [10, 11]. Molecular genetic studies identified five allelic variants cosegregating with dilated cardiomyopathy (DCM) [12, 13]. Some authors reported structural degeneration (fibrosis) and apoptosis during the analysis of myocardial biopsies of patients with clinical diagnosis of Brugada syndrome and an SCN5A mutation [14]. Taken as a whole, these studies suggest that at least some SCN5A mutations manifest as both excitability and structural derangement.

In the presented case, there was no conclusive proof of the aetiology and the coexistence of the Brugada-type electrocardiographic pattern and ILVNC might be coincidental. However, the case is consistent with the consideration that up to now none of the autopsies in Brugada patients turned out to present a normal heart.

On a clinical basis, the possible coexistence of the Brugada syndrome with structural myocardial alterations should always be considered and it advocates the need of careful echo and NMR studies on all BrS patients.

References

[1] R. Jenni, E. Oechslin, J. Schneider, C. Attenhofer Jost, and P. A. Kaufmann, "Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy," *Heart*, vol. 86, no. 6, pp. 666–671, 2001.

[2] R. H. Pignatelli, C. J. McMahon, W. J. Dreyer et al., "Clinical characterization of left ventricular noncompaction in children: a relatively common form of cardiomyopathy," *Circulation*, vol. 108, no. 21, pp. 2672–2678, 2003.

[3] M. Ritter, E. Oechslin, G. Sütsch, C. Attenhofer, J. Schneider, and R. Jenni, "Isolated noncompaction of the myocardium in adults," *Mayo Clinic Proceedings*, vol. 72, no. 1, pp. 26–31, 1997.

[4] F. Ichida, Y. Hamamichi, T. Miyawaki et al., "Clinical features of isolated noncompaction of the ventricular myocardium: long-term clinical course, hemodynamic properties, and genetic background," *Journal of the American College of Cardiology*, vol. 34, no. 1, pp. 233–240, 1999.

[5] E. N. Oechslin, C. H. Attenhofer Jost, J. R. Rojas, P. A. Kaufmann, and R. Jenni, "Long-term follow-up of 34 adults with isolated left ventricular noncompaction: a distinct cardiomyopathy with poor prognosis," *Journal of the American College of Cardiology*, vol. 36, no. 2, pp. 493–500, 2000.

[6] D. Sedmera, T. Pexieder, M. Vuillemin, R. P. Thompson, and R. H. Anderson, "Developmental patterning of the myocardium," *Anatomical Record*, vol. 258, no. 4, pp. 319–337, 2000.

[7] B. Begoña, R. Brugada, J. Brugada, and P. Brugada, "Brugada syndrome," *Progress in Cardiovascular Diseases*, vol. 51, pp. 1–22, 2008.

[8] C. Antzelevitch, P. Brugada, M. Borggrefe et al., "Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association," *Circulation*, vol. 111, pp. 659–670, 2005.

[9] P. Brugada and J. Brugada, "Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report," *Journal of the American College of Cardiology*, vol. 20, no. 6, pp. 1391–1396, 1992.

[10] B. Martini, A. Nava, G. Thiene et al., "Ventricular fibrillation without apparent heart disease: description of six cases," *American Heart Journal*, vol. 118, no. 6, pp. 1203–1209, 1989.

[11] B. Martini, A. Nava, B. Canciani, and G. Thiene, "Right bundle branch block, persistent ST segment elevation and sudden cardiac death," *Journal of the American College of Cardiology*, vol. 22, no. 2, p. 633, 1993.

[12] S. W. Carveth, D. Olson, and J. Bechtel, "Emergency medical care system. Lincoln (Neb) mobile heart team," *Archives of Surgery*, vol. 108, no. 4, pp. 528–530, 1974.

[13] T. M. Olson, V. V. Michels, J. D. Ballew et al., "Sodium channel mutations and susceptibility to heart failure and atrial fibrillation," *Journal of the American Medical Association*, vol. 293, no. 4, pp. 447–454, 2005.

[14] A. Frustaci, S. G. Priori, M. Pieroni et al., "Cardiac histological substrate in patients with clinical phenotype of Brugada syndrome," *Circulation*, vol. 112, no. 24, pp. 3680–3687, 2005.

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Cardiology Research and Practice
Volume 2011, Article ID 342302, 6 pages
doi:10.4061/2011/342302

Clinical Study

Efficiency and Safety of Prolonged Levosimendan Infusion in Patients with Acute Heart Failure

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Received 1 November 2010; Revised 10 January 2011; Accepted 3 February 2011

Academic Editor: Gregory Giamouzis

Background. Levosimendan is an inotropic drug with unique pharmacological advantages in patients with acute heart failure. Scope of this study is to determine whether longer infusion patterns without the hypotension-inducing loading dose could justify an effective and safe alternative approach. *Methods*. 70 patients admitted to the emergencies with decompensated chronic heart failure received intravenously levosimendan without a loading dose up to 72 hours. Clinical parameters, BNP (Brain Natriuretic Peptide) and signal-averaged-ECG data (SAECG) were recorded up to 72 hours. *Results*. The 48-hour group demonstrated a statistically significant BNP decrease ($P < .001$) after 48 hours, which also maintained after 72 hours. The 72-hour group demonstrated a bordeline decrease of BNP after 48 hours ($P = .039$), necessitating an additional 24-hour infusion to achieve significant reduction after 72 hours ($P < .004$). SAECG data demonstrated a statistically significant decrease after 72 hours ($P < .04$). Apart from two deaths due to advanced heart failure, no major complications were observed. *Conclusion*. Prolonged infusion of levosimendan without a loading dose is associated with an acceptable clinical and neurohumoral response.

1. Introduction

Levosimendan is recognized as an inotropic drug used in acute or decompensated chronic heart failure with innovative characteristics. It is not a β-adrenergic agonist which would have energy-consuming and proarrhythmic effects. It is rather a mild PDE inhibitor in clinical relevant doses [1] and mainly a Ca-dependant troponine-I sensitizer resulting in energetically beneficial contractility of the cardiac muscle. Furthermore, there is also an ATP-dependant K-channel activation which causes peripheral vasodilation [2]. A cardioprotective mechanism via the ATP-K channels and the phenomenon of preconditioning is also under research. Pharmacokinetically, levosimendan acts for prolonged time, since its two major metabolites OR-1855 and OR-1896 have half-life time of 70–80 hours [3]. This pharmacological profile offers an ideal medical option in acute heart failure with preserved or borderline systolic blood pressure [4]. Standard pattern of infusion consists of a loading dose and a continuous 24-hour i.v. infusion. In some cases, the vasodilatory action causes an early hypotension resulting in withdrawal of drug or coadministration with a β-agonist with all the possible risks of this combination [5]. The goal of this observational study was primarily to determine whether a prolonged and beyond the 24-hour infusion pattern without the loading dose could be efficient and safe for patients in acute or decompensated heart failure. For this reason, we administrated a prolonged levosimendan infusion for 24, 48, or 72 hours creating three subgroups.

Clinical and neurohormonal responses were measured with simple bedside parameters derived from physical examination [6] and serial measurements of BNP [7] and SAECG. Safety was determined by the presence of major or minor complications and onset of new arrhythmias [8].

2. Methods

2.1. Patients. Study population consisted of patients admitted to hospital between March 2003 and December 2006 suffering from acute heart failure or decompensated chronic heart failure. The clinical status of those patients was III or IV according to the NYHA classification. All patients were resistant to optimal medical therapy and did need support of an inotropic agent. Diagnosis of heart failure was confirmed by the contribution of physical examination, previous history, but mainly by transthoracic echocardiography and thoracic X-rays. Ejection fraction less than 45% in echocardiogram was documented in all patients. Retrospective analysis of the heart failure aetiology was performed.

As for the exclusion criteria, patients with an acute coronary syndrome, cardiac shock with systolic blood pressure under 85 mmHg resistant to volume administration, hypertrophic cardiomyopathy, benign or life-threatening tachyarrhythmias with heart rate over 120/min, and electrolytic abnormalities did not participate.

2.2. Study Protocol. The study protocol included quantitative analysis in three different subgroups of main population determined by clinical evaluation after 24-hour intervals. All participants took next to their standard medication (diuretics, oxygen, ACEs or ARBs, digoxin, and β-blockers in minor dose) an infusion of levosimendan of 0.05 μg/min/Kg uptitrated in two hours to 0.1 μg/min/Kg for 24 hours. In the interval, if there was no contraindication, the uptitration could achieve the dose of 0.2 μg/min/Kg.

24-hour and 48-hour time points after initial infusion were crucial. It should be decided if levosimendan could be stopped or continued according to bedside clinical criteria. The subjective criterion of patient's well-being and the absence of pathologic signs on auscultation of the pneumonal areas or the absence of S3 gallop were cut points for the discontinuation of levosimendan infusion. Patients, who continued the infusion, did so for a duration of 72 hours. The exclusion criteria of recruitment had the same power during the infusion time, so that management could be safe. In some complications, like hypotension or tachyarrhythmia, it was up to investigator to treat the complication and to decide for the next step of the study.

2.3. Measurements. All patients were measured for several countable variables. Blood pressure and heart rate were determined at baseline and at 24, 48, and 72 hours, respectively.

A resting ECG was performed at the above-mentioned time points confirming also the possible arrhythmogenic complications. In cases a confirmation of heart failure was needed, a transthoracic echo was performed.

As far for the neurohormonal response of the therapy, we used measurements of brain natriuretic peptide (BNP) by means of the microspheric ELISA analysis (MEIA) method. Blood samples of 6 mL were taken at the beginning time point of the infusion, at 48 hours and at 72 hours independently on the subgroup a patient belonged to.

After an addition of 0.1 mL transylol for preserving protein molecules, these samples were centrifuged at 3000 cycles/min for 5 minutes. The serum taken was frozen on -20° Celsius for retrospective BNP measurements. BNP normal range was assumed under the value of 100 pg/mL.

On the study, a signal averaged ECG was used (Marquette model 5000). *P*-wave filtered, QRS filtered duration, root mean square voltage, the last 40 msec, and the duration of voltage $<40\,\mu$V at 40 Hz were determined at baseline, 48 and 72 hours, respectively. Normal ranges of the above mentioned variables are QRS filtered duration <120 msec, RMS the last 40 msec $>20\,\mu$V, and duration of low voltage at 40 Hz <38 msec.

Confirming an assumption of BNP response, we decided to determine two cut points. Relative BNP decrease of >60% was evaluated as a good neurohormonal response.

BNP decrease <20% or increase was evaluated as no response. The values between the two cut points were characterized as moderate responses.

Changes in QRS-filtered duration observed in this clinical study were evaluated with the assumption that variations in QRS complex duration could represent respective variations in left ventricular dimensions. So, decreases in QRS-filtered duration >10 msec were regarded as good response. Increases in QRS-filtered duration were evaluated as no response and the values in between as moderate ones.

The well-being status was evaluated by means of clinical examination and subjective confirmation of the patient at 24 and 48 hours of infusion. This semicountable variable was the determinator of continuation of levosimendan treatment.

Major complications were confirmed for the whole duration of the study and a period of a month followed. A continuous ECG monitoring during the infusion protocol confirmed the arrhythmias observed.

2.4. Statistics. Countable variables were demonstrated with minimum, maximum, mean, and standard deviation values. Differences in countable variables were evaluated with the nonparametric paired *t*-test of Wilcoxon.

Correlation between countable variables was evaluated with linear regression analysis. To confirm a comparison between the subgroups, we used the Kolmogorov-Smirnov and the Mann-Whitney tests.

Uncountable variables were evaluated in a descriptive manner and the correlation between them with the Chi-square test accompanied by the Phi or Cramer's V test. In all the tests the null hypothesis is rejected at confidence level of 5%. SPSS.12 version statistical package was used.

2.5. Ethical Considerations. The protocol was approved by the Institutional Review Board of our center and was performed in accordance with institutional guidelines and the Declaration of Helsinki. All patients gave written informed consent before entering the study.

Table 1: Demographic statistics at baseline of the study population.

	Mean ± St. dv.	Range
Age (years)	63.7 ± 1.4	[36–88]
Mean arterial pressure (mmHg)	87.8 ± 15.1	[72–126]
Heart rate (min^{-1})	76.5 ± 10.5	[56–100]
BNP (pg/mL)	1104 ± 124	[51–4000]
Ejection fraction (%)	33.5 ± 6.3	[22–43.3]
P-wave duration (msec)	180 ± 10	[78–322]
QRS filtered duration (msec)	149 ± 4.1	[71–265]

Data are presented as Mean ± Standard deviation.

Table 2: BNP and QRS filtered duration variations after 72 hours.

Parameter		Response		
		Good	Moderate	Low
Relative BNP difference at 72 hours	%	44.3	24.3	28.6
	N	*N* = 31	*N* = 17	*N* = 20
Difference of QRS filtered duration at 72 hours	%	15.7	30.0	27.1
	N	*N* = 11	*N* = 21	*N* = 19

3. Results

3.1. Demographics. Descriptive variables are presented in Table 1. The population consisted mainly of male participants (82.9%), not allowing to perform adequate sex-related statistical analysis. Regarding the aetiology of the heart failure, we observed a population with 64.3% suffering from coronary artery disease and with 35.7% from nonischemic dilated cardiomyopathy.

BNP mean baseline value was 1105 pg/mL, confirming a study population with severe heart failure with low mean ejection fraction at baseline (33.5 ± 6.3%) and high mean enddiastolic left ventricular diameter (6.81 ± 0.81 mm). Mean *P* wave was elevated at baseline (180 ± 9.5 msec) and mean QRS duration filtered (149 ± 4.1 msec) was quite higher than normal range, even if bundle branch block was present.

3.2. Neurohormonal Response. Relative BNP difference and QRS duration filtered at 72 hours are shown below (Table 2).

It is obvious by the data derived that using the specific infusion pattern, there was a 68.6% of good or moderate BNP and a 45.7% of good or moderate QRS response.

Considering the two main end-point parameters overall, there was a statistically significant BNP decrease at 48 hours after baseline ($P < .001$), which continued at 72 hours, and a significant decrease of QRS filtered duration at 72 hours ($P = .04$). (Figures 1 and 2). However, crosstabulation of the QRS duration and the BNP response did not show any statistically significant correlation ($P > .1$).

There were established three subgroups depending on the duration of infusion of 24 hours ($n = 14$), 48 hours ($n = 35$), or 72 hours ($n = 21$).

3.2.1. Levosimendan Infusion of 24 h. The 24-hour infusion subgroup had a mean percentage relative difference on BNP at 72 hours of 15.3% and mean difference on QRS duration at 72 hours of 0.8 msec per patient. There were no statistical significance in any measured parameter ($P > .1$) according to the Wilcoxon test for paired differences (Table 3).

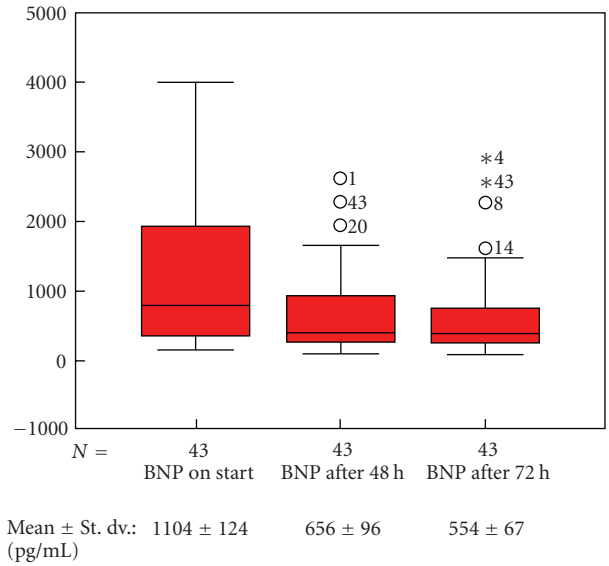

Figure 1: Changes of BNP after onset of levosimendan.

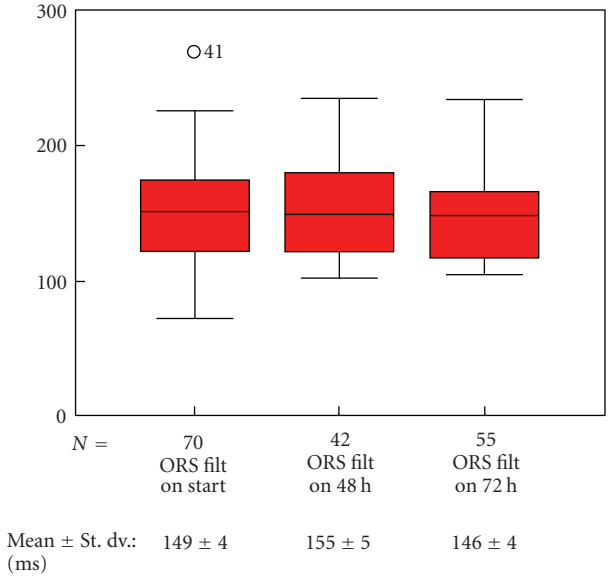

Figure 2: Changes of filtered QRS duration after onset of levosimendan.

3.2.2. Levosimendan Infusion of 48 h. Patients with 48-hour infusion had a statistically significant decrease on BNP beginning at 48 hours ($P < .0001$), which continued at 72 hours ($P < .0001$).

This finding indicates an enormous neurohormonal response with 48-hour infusion of levosimendan without loading dose. The mean percentage relative difference of BNP at 72 hours showed a decrease of 43%, which is a

Table 3: Demographic statistics of the three subgroups (24h, 48h, and 72h infusion).

	Infusion	Start	48 h	72 h
BNP-Concentration (pg/mL)	24 h-Group	1114 ± 320	494 ± 101 ($P > .1$)	545 ± 95 ($P > .1$)
	48 h-Group	1215 ± 193	748 ± 151 ($P < .0001$)	568 ± 104 ($P < .0001$)
	72 h-Group	912 ± 159	601 ± 18 ($P < .04$)	535 ± 29 ($P = .004$)
QRS Duration (msecs)	24 h-Group	151 ± 6	159 ± 12 ($P > .1$)	169 ± 5 ($P > .1$)
	48 h-Group	145 ± 6	159 ± 8 ($P > .1$)	140 ± 6 ($P = .06$)
	72 h-Group	153 ± 8	145 ± 10 ($P > .1$)	147 ± 6 ($P = .05$)

Data are presented as Mean ± Standard Deviation.

quite acceptable percent. QRS duration had on average a borderline significant decrease at 72 hours of −10.96 msecs per patient ($P = .065$), which might indirectly indicate a decrease of left ventricular dimensions.

3.2.3. Levosimendan Infusion of 72 h. Patients with 72-hour infusion had a borderline significant decrease on BNP beginning at 48 hours ($P = .039$) and a statistically significant decrease at 72 hours ($P < .004$). This finding shows a good neurohormonal response with 48-hour infusion of levosimendan without loading dose with the necessity to follow 24-hour infusion additionally, so that the decrease could achieve a significant range. Mean percentage relative difference of BNP at 72 hours was 31%. QRS filt duration had on average a borderline significant decrease at 72 hours of −7.4 msecs per patient ($P = .049$).

Trying a general correlation between the countable parameters of difference of QRS filtered duration at 72 hours and BNP relative difference at 72 hours, there was a linearity only in cases with adverse response for the two variables (R-squared = 0.01). Crosstabulation analysis of the two 48- and 72-hour infusion patterns demonstrated that at 48-hour infusion there was an obvious correlation between good QRS responders and good BNP responders (P value of χ-square test = .05). This statistical result was determined by the respective adjusted residuals of the data analysis.

At 72-hour infusion, the correlation was biased with non-BNP responders to have also a moderate QRS filtered duration response ($P > .1$).

According to the Kolmogorov-Smirnov test and the Mann-Whitney analysis, the demographics of two subgroups of the population were compared. Without differences on the characteristics, those who have taken 48-hour infusion demonstrated at least good or moderate QRS filtered duration—at acceptable BNP—response, representing a subpopulation with good neurohormonal profile (Figure 3).

3.3. Safety. As for the complications, there were not patients who had to discontinue the study due to hypotension or other minor complication. Two patients died due to advanced heart failure (asystole without successful reanimation). New onset of atrial flutter, atrial fibrillation or ventricular tachycardia was not observed, indicating a study population with low short-term arrhythmogenic profile according to the continuous ECG monitoring.

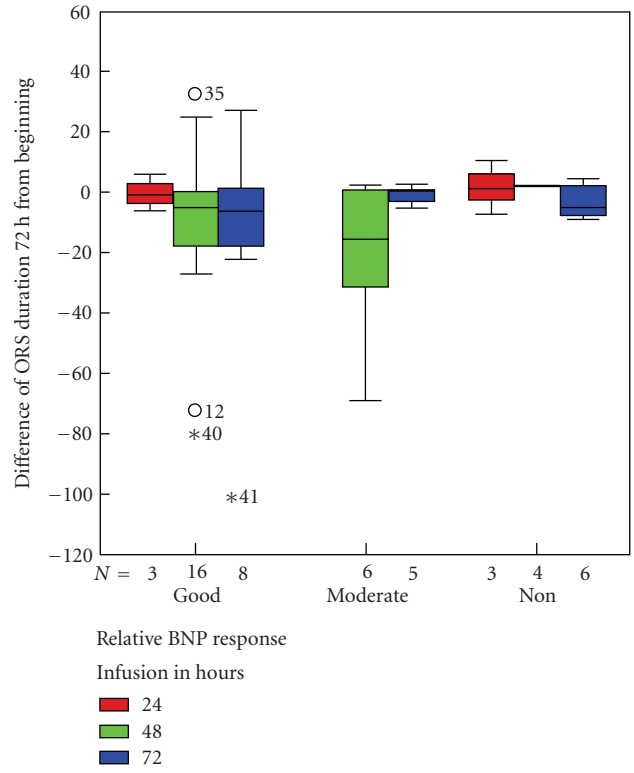

Figure 3: Differences of BNP response and filtered QRS duration between infusion groups.

All patients survived achieved a weaning status by inotropic agents without the necessity of withdrawal until their discharge. Within a period of a month, one patient was presented with acute renal exacerbation, and three others needed to be rehospitalised for exacerbated heart failure.

4. Discussion

In this study, we tried to demonstrate efficiency and safety of an alternative infusion pattern of levosimendan in acute heart failure. The critically ill patients of this condition have most of the time a borderline preserved systolic pressure. So, it is important to prevent the patient from hypotension, which could induce hypoperfusion. Levosimendan has on start an enormous peripheral vasodilatory effect, which causes hypotension [9].

In this view, participants were not given the loading dose at the beginning, but a continuous dose was administrated up to 72 hours depended on the clinical response.

BNP is widely recognized as a therapeutic tool of responsiveness in patients with heart failure [10]. In our study, we used BNP as a reliable marker of efficiency [11].

It was obvious from the data analysis that those patients who were given 72-hour infusion had the necessity for such a long infusion. They did not achieve clinical improvement at 48 hours, so they had to continue with another 24-hour infusion. The population studied were patients with advanced heart failure, since mean value was generally above 1000 pg/mL. This means that the percent of decrease of BNP was, respectively, not so enormous like in other trials [12], in which the mean value was about 500–800 pg/mL. We think that the achieved mean values of 31–43% are acceptable improvement [13], concerning that all patients survived did not have symptoms or re-exacerbation of their clinical status.

The other basic bound of our study was the investigation of safety of such infusion patterns. As for the complications observed, there was no indication that we had arrhythmogenic effect of the agent. The two deaths were due to advanced heart failure and could be accepted by the condition of acute heart failure [14].

The signal averaged ECG is an examination which has a good specificity in predicting monomorphic ventricular tachycardia in patients with chronic heart failure. Its power is obvious in patients after myocardial infarct [15]. There are also studies with patients of dilated cardiomyopathy [16], which mention the role of signal-averaged ECG. However, in the last years, the role of this examination has diminished [17].

The scope was to show that levosimendan did not at least change the parameters of this examination, so that a neutral effect could be confirmed. Indeed, the study showed that in good BNP responders there was a subpopulation whose QRS filtered duration not only was unchanged but also decreases. The finding of this observation cannot be evaluated exactly but indicates a subpopulation with good clinical and neurohormonal response. Further studies should be conducted to investigate the correlation between BNP and filtered QRS duration variations.

Considering the results of this study, it could be said that levosimendan is an inotropic drug, which allows an infusion of more than 24 hours. There is also an opposed opinion [18], which supports that there is no need of prolonged infusions, since the metabolites of levosimendan have long half-life period. The problem is that sometimes patients admitted are critically ill and the target of treating them efficiently is difficult to achieve.

We need an inotropic agent like levosimendan with an acceptance of β-blocker coadministration, or at least at low doses, with non-β-agonist effect and energetically beneficial. Furthermore, at this clinical condition, a drug-induced hypotension could be unnecessary. So, patterns without loading dose could be beneficial.

Limitations of the study are its design, which does not have perspective analysis and randomization of groups in an objective manner. It is an observational study with the additional limitation of small period of followup of the variables measured.

Another limitation is the absence of hemodynamic data [19, 20], which could support adequately the scope of the study. This could be the goal of a future study in the same way of using alternative infusion patterns.

The subgroup observed in this study with the beneficial profile should be followed in time with the hope to stratify the cumulative risk of mortality or morbidity in heart failure [21].

Acknowledgment

G. Aidonidis (University of Duisburg-Essen, Germany; Aristotle University of Thessaloniki, Greece), I. Kanonidis (Aristotle University of Thessaloniki, Greece), V. Koutsimanis (Aristotle University of Thessaloniki, Greece), T. Neumann (University of Duisburg-Essen, Germany), R. Erbel (University of Duisburg-Essen, Germany), and G. Sakadamis (Aristotle University of Thessaloniki, Greece) are all on behalf of the Competence Network of Heart Failure.

References

[1] A. Lehmann, J. Boldt, and J. Kirchner, "The role of Ca++-sensitizers for the treatment of heart failure," *Current Opinion in Critical Care*, vol. 9, no. 5, pp. 337–344, 2003.

[2] M. S. Nieminen, J. Akkila, G. Hasenfuss et al., "Hemodynamic and neurohumoral effects of continuous infusion of levosimendan in patients with congestive heart failure," *Journal of the American College of Cardiology*, vol. 36, no. 6, pp. 1903–1912, 2000.

[3] R. Takahashi, M. A. H. Talukder, and M. Endoh, "Inotropic effects of OR-1896, an active metabolite of levosimendan, on canine ventricular myocardium," *European Journal of Pharmacology*, vol. 400, no. 1, pp. 103–112, 2000.

[4] M. Sharma and J. R. Teerlink, "A rational approach for the treatment of acute heart failure: current strategies and future options," *Current Opinion in Cardiology*, vol. 19, no. 3, pp. 254–263, 2004.

[5] M. Packer, "REVIVE II. Metanalysis—Selected adverse events," American Heart Association. Scientific Sessions, 2005.

[6] A. Nohria, S. W. Tsang, J. C. Fang et al., "Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure," *Journal of the American College of Cardiology*, vol. 41, no. 10, pp. 1797–1804, 2003.

[7] A. Gegenhuber, T. Mueller, F. Firlinger, K. Lenz, W. Poelz, and M. Haltmayer, "Time course of B-type natriuretic peptide (BNP) and N-terminal ProBNP changes in patients with decompensated heart failure," *Clinical Chemistry*, vol. 50, no. 2, pp. 454–456, 2004.

[8] S. Mavrogeni, G. Giamouzis, E. Papadopoulou et al., "A 6-month follow-up of intermittent levosimendan administration effect on systolic function, specific activity questionnaire, and arrhythmia in advanced heart failure," *Journal of Cardiac Failure*, vol. 13, no. 7, pp. 556–559, 2007.

[9] P. Põder, J. Eha, S. Sundberg et al., "Pharmacodynamics and pharmacokinetics of oral levosimendan and its metabolites in patients with severe congestive heart failure: a dosing interval study," *Journal of Clinical Pharmacology*, vol. 44, no. 10, pp. 1143–1150, 2004.

[10] A. S. Maisel et al., "The diagnosis of acute congestive heart failure: role of BNP measurements," *Heart Failure Reviews*, vol. 8, no. 4, pp. 327–334, 2003.

[11] G. Giamouzis, G. Giannakoulas, K. Tsarpalis et al., "Natriuretic peptide-guided levosimendan therapy for heart failure: a promising new approach," *International Journal of Cardiology*, vol. 128, no. 1, pp. 91–93, 2008.

[12] P. Arruda et al., "Long term effect of levosimendan upon BNP levels in patients with decompensated heart failure," *Critical Care Medicine*, vol. 32, no. 12, supplement, 2004.

[13] G. Gianakoulas, G. Giannoglou, V. Vassilikos et al., "Clinical significance of acute neorohormonal respons after levosimendan treatment," *American Journal of Cardiology*, vol. 98, pp. 1123–1124, 2006.

[14] M. S. Nieminen, M. Böhm, M. R. Cowie et al., "Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology," *European Heart Journal*, vol. 26, no. 4, pp. 384–416, 2005.

[15] American College of Cardiology Expert Consensus Document, "Signal- averaged Electrocardiography," *Journal of the American College of Cardiology*, vol. 27, no. 1, pp. 238–249, 1996.

[16] D. Provan and A. Krentz, Eds., *Oxford Handbook of Clinical and Laboratory Investigation*, Oxford University Press, Oxford, UK, 2003.

[17] L. Toivonen, M. Viitasalo, S. Sundberg, J. Akkila, and L. Lehtonen, "Electrophysiologic effects of a calcium sensitizer inotrope levosimendan administered intravenously in patients with normal cardiac function," *Journal of Cardiovascular Pharmacology*, vol. 35, no. 4, pp. 664–669, 2000.

[18] L. De Luca, W. S. Colucci, M. S. Nieminen, B. M. Massie, and M. Gheorghiade, "Evidence-based use of levosimendan in different clinical settings," *European Heart Journal*, vol. 27, no. 16, pp. 1908–1920, 2006.

[19] J. Lilleberg, M. Laine, T. Palkama, M. Kivikko, P. Pohjanjousi, and M. Kupari, "Duration of the haemodynamic action of a 24-h infusion of levosimendan in patients with congestive heart failure," *European Journal of Heart Failure*, vol. 9, no. 1, pp. 75–82, 2007.

[20] J. G. F. Cleland, N. Freemantle, A. P. Coletta, and A. L. Clark, "Clinical trials update from the American Heart Association: REPAIR-AMI, ASTAMI, JELIS, MEGA, REVIVE-II, SURVIVE, and PROACTIVE," *European Journal of Heart Failure*, vol. 8, no. 1, pp. 105–110, 2006.

[21] A. Varro and J. G. Papp, "Classification of positive inotropic actions based on electrophysiologic characteristics: where should calcium sensitizers be placed?" *Journal of Cardiovascular Pharmacology*, vol. 26, no. 1, pp. S32–S44, 1995.

SAGE-Hindawi Access to Research
Cardiology Research and Practice
Volume 2011, Article ID 837238, 7 pages
doi:10.4061/2011/837238

Review Article

Exercise Training for Heart Failure Patients with and without Systolic Dysfunction: An Evidence-Based Analysis of How Patients Benefit

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Received 23 July 2010; Accepted 19 September 2010

Academic Editor: Javed Butler

Significant benefits can be derived by heart failure patients from exercise training. This paper provides an evidence-based assessment of expected clinical benefits of exercise training for heart failure patients. Meta-analyses and randomized, controlled trials of exercise training in heart failure patients were reviewed from a search of PubMed, Cochrane Controlled Trial Registry (CCTR), CINAHL, and EMBASE. Exercise training improves functional capacity, quality of life, hospitalization, and systolic and diastolic function in heart failure patients. Heart failure patients with preserved systolic function (HFnEF) participating in exercise training studies are more likely to be women and are 5–7 years older than their systolic heart failure (CHF) counterparts. All patients exhibit low functional capacities, although in HFnEF patients this may be age related, therefore subtle differences in exercise prescriptions are required. Published works report that exercise training is beneficial for heart failure patients with and without systolic dysfunction.

1. Background

Exercise training has become an accepted adjunct therapy for patients with systolic heart failure. Recent data have shown that exercise is considered beneficial for heart failure patients in terms of improved mortality and morbidity [1], quality of life [2, 3], functional capacity [4], and improved cardiac [5] and vascular function [6]. Characteristics of heart failure patients who participate in community-based prevalence and exercise training studies may be different with the latter likely to be younger and predominantly male [1, 4, 7, 8]. North American [9], European [10], and Australian [11] guidelines on the use of exercise training in heart failure patients have been developed, although subtle differences exist between the various guidelines. Subtle differences may also exist in the demographics of heart failure patients with abnormal systolic function (CHF) and heart failure patients with normal left ventricular ejection fraction (HFnEF). CHF patients are normally defined as having left ventricular ejection fraction <50% and impaired diastolic filling, while HFnEF patients have a normal (>50%) ejection fraction but impaired diastolic filling.

The aims of this work were to review highlighted differences between the demographics of heart failure patients participating in prevalence studies and those completing exercise training studies. Moreover demographic data were presented for systolic heart failure patients and those with heart failure with preserved systolic function. This work also aimed to provide a clinical update on the benefits of exercise training in heart failure patients.

2. Methods

Data relating to exercise training protocols in heart failure patients and subsequent outcomes were reviewed. Pub Med (MEDLINE), Medscape, EMBASE, CINAHL, and Cochrane Controlled Trials Registry were searched up until June 2010. Reference lists of papers found were scrutinized for new references. North American, European, and Australian heart failure treatment guidelines were also sourced. Search terms used were combinations of the terms *exercise training*, *heart failure*, *left ventricular dysfunction*, *physical training*, *resistance training*, *guidelines, position stands, systematic reviews*,

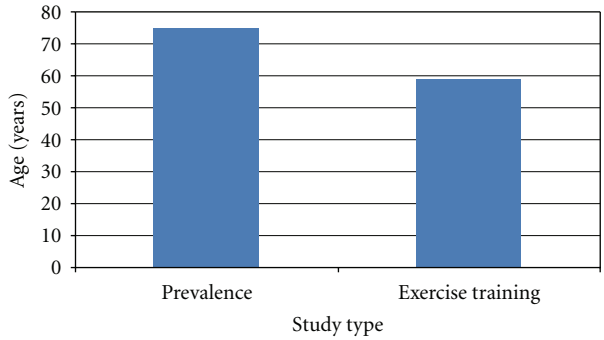

Figure 1: Age comparison of heart failure patients in both prevalence and exercise studies.

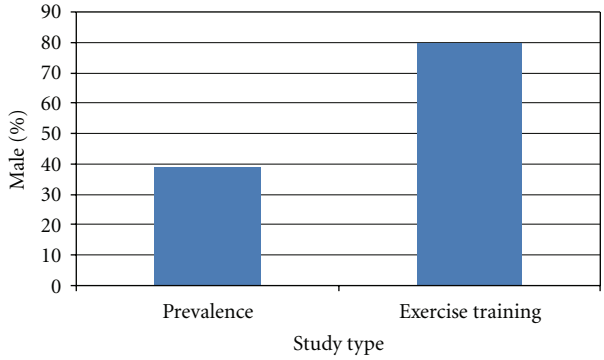

Figure 2: Gender comparison of heart failure patients in both prevalence and exercise studies.

meta-analysis, quality of life, functional capacity, mortality, morbidity, cardiac function, heart failure with preserved systolic function, safety, cytokine expression, brain natriuretic peptide, and *aerobic exercise*. There were no restrictions on the year of publication. We examined the latest editions of relevant journals that were not yet available on electronic databases. The reference lists of identified articles were subsequently scrutinized and relevant articles were included. Information on clinical variables was archived in a database. Community-based heart failure prevalence studies were also sought to draw comparisons with exercise studies in heart failure patients.

Outcome measures fell into three categories: demographics, clinical measures, and public health issues. *Demographics:* age and gender of heart failure patients enrolled in community-based prevalence versus exercise training studies. *Clinical measures:* mortality and morbidity rates, functional capacity, quality of life, cardiac function, cytokine, and brain natriuretic peptide (BNP) expression in those who did and did not undertake exercise training. *Public Health:* number needed to treat, cost-effectiveness, safety, and minimization of adverse events during exercise training.

3. Results

3.1. Demographics of Heart Failure Patients in both the Community and in Exercise Training Studies.. Heart failure patients who participate in exercise training research tend to be younger (Figure 1) and twice as likely to be male (Figure 2) compared to those heart failure patients studied in prevalence research [1, 12]; the latter appear to provide a better representation of heart failure patients in the community, suggesting exercise studies may be prone to participant selection bias.

> *Evidence suggests younger, male heart failure patients are more likely to participate in exercise training due to possible selection bias.*

3.2. Demographics of CHF and HFnEF Patients Participating in Exercise Training Studies.. Data from exercise training studies of heart failure patients [4] reports CHF patients are younger, mean 59 ± 7 years**,** and more likely to be male (79%) compared to HFnEF patients, mean age 65 ± 5 years and 50% male.

> *Evidence suggests CHF patients participating in exercise training are younger and more likely to be male.*

3.3. Clinical or Prognostic Characteristics

3.3.1. Mortality and Hospitalization Benefits. A meta-analysis of exercise training programs in heart failure patients (ExTraMATCH) reported benefits in terms of mortality and hospitalization [1]. A subanalysis of this study revealed the reduction in overall and cardiac mortality and hospitalization appears to be more likely in sicker patients, specifically those with lower left ventricular ejection fraction, New York Heart Association class III/IV, ischemic cardiomyopathy, lower peak VO_2, and those over 60 years of age. In terms of these exercise training program characteristics, these mortality benefits appear to be more apparent in those patients that adhere to an exercise training program for 28 weeks or more [1]. All studies included in the ExTraMATCH meta-analysis used cycling as the training modality. In comparison the largest (2,300 patients) randomized, controlled study of exercise training in heart failure patients to date, the heart failure ACTION (HF-ACTION) study [8], reported nonsignificant reductions in mortality and hospitalization, especially in those who do not have factors highly prognostic of mortality. Specifically, duration of baseline cardiopulmonary exercise testing, left ventricular ejection fraction, Beck Depression Inventory II score, and history of atrial fibrillation or flutter were identified as highly prognostic of the primary endpoint of all-cause mortality or hospitalization. After adjusting for prognostic hence exercise training was found to reduce the incidence of all-cause mortality or all-cause hospitalization by 11%. The data from ExTraMATCH and HF-ACTION appear to contrast one another, while the former showed a mortality benefit that was most obvious in the sickest patients, the latter only showed a mortality benefit once the patients with prognostic symptoms had been removed from the analysis.

Evidence equivocal for mortality and hospitalization benefits and also whether disease severity predicts which patients may benefit most.

3.3.2. Functional Capacity. Meta-analysis reported that heart failure patients can typically expect to improve their functional capacity by 15%–17% following exercise training [4] and this is a powerful predictor of prognosis in this population [13]. Peak VO_2 values >13-14 mL/kg/min may confer a 50% cardiac mortality reduction, while a 1 mL/kg/min increase may be associated with a 10% lower cardiac mortality [14]. Peak VO_2 changes appear to be independent of the type of exercise training undertaken, for example, aerobic, intermittent or resistance training [4]. In comparison, the (HF-ACTION) study [8] reported only a 4% improvement in peak VO_2. Meta-analysis data was generated from generally smaller, single site studies which often had facilitated good short-term exercise training adherence rates. HF-ACTION trial authors reported poor adherence in the early part of the training program, and the multicentre study design may have affected the magnitude of change in peak VO_2. Moreover, the meta-analysis data was generated mainly from short (<3 month) duration studies with only two studies >12 months duration [15, 16], while HF-ACTION reported both 3 month and 12 month data. Twelve months is a difficult period to retain patients, due to either attrition, illness, or death, and also maintain exercise adherence in those who do not withdraw from the study. It has been suggested that exercise training studies tend to overestimate the size of change in peak VO_2 of exercise training participants [17], due to variations in patient motivation and the impracticality of blinding exercise training subjects. The more robust design of HF-ACTION may have minimized the overestimation of peak VO_2 and therefore changes were smaller, but perhaps more reliable. Only one published exercise training study in HFnEF has provided functional capacity data to date suggesting the size of the change in peak VO_2 may be similar, or even greater, to that seen in CHF patients.

Evidence suggest functional capacity undoubtedly improves, but what is uncertain is the size of change in Peak VO_2 which is likely to be between 4%–15%.

3.3.3. Quality of Life (QOL). In a systematic review of exercise training in heart failure patients, QOL assessment was improved in 11 of 16 randomized controlled studies [2]. A more recent meta-analysis of 35 randomized controlled trials, reported that heart failure patients can expect an improvement of nearly 10 points in Minnesota living with heart Failure Questionnaire scores following exercise training [3].

Evidence is unequivocal for improvement in quality of life.

3.3.4. Cardiac (Systolic) Function. A recent meta-analysis [5] showed that exercise training improved left ventricular ejection fraction (LVEF), end-diastolic volume (EDV), and end-systolic volume (ESV) in patients with heart failure. The weighted mean difference (WMD) of LVEF was significantly improved after aerobic exercise training (9 trials, 538 patients, WMD = 2.59%; 95% confidence interval (CI) 1.44% to 3.74%), EDV (371 patients; WMD = −11.49 mL; 95% CI −19.95 to −3.02 mL), and ESV (371 patients; WMD = −12.87 mL; 95% CI −17.80 to −7.93 mL. The authors concluded that aerobic training, but not combined aerobic and strength training, or isolated strength training reverse LV remodelling in clinically stable individuals with heart failure. Other data suggest that high intensity (95% peak heart rate) aerobic interval walking will confer even greater improvements in systolic function (baseline LVEF 28%, posttraining LVEF 38%) [18].

Evidence suggests exercise training will improve systolic function and should be predominantly aerobic, and if tolerated, intermittent high intensity, in nature as this will convey the greatest improvements in systolic function.

3.4. Cardiac (Diastolic) Function. Published randomized, controlled trials of exercise training in heart failure patients with outcome measures of diastolic function, assessed by tissue Doppler have reported variable results. The work of Belardinelli [15] showed improvements in isovolumic relaxation time (ms), early and late diastolic filling in a 2-month exercise training study of heart failure patients with moderate-severe systolic function. Similarly improved left ventricular diastolic stiffness [19] and reduced filling pressure (E/Ea ratio) [18] in heart failure patients has been reported in two other randomized, controlled trials of exercise training.

Evidence suggests exercise training may enhance diastolic function.

3.5. Circulating Levels of Proinflammatory Cytokines. Several small randomized controlled trials have conducted analyses of the effect of different forms of exercise training (high versus low intensity, cycling versus electrical stimulation, or respiratory muscle training) on serum measures of proinflammatory cytokines in patients with congestive heart failure. Interleukin-6 (IL-6) and tumour necrosis factor-alpha are the two most commonly studied proinflammatory cytokines [20–27]. A recent, elegant review clarified the role of IL-6 as a fuel (glucose) sensor [28]. As glucose metabolism may be affected in heart failure patients, especially during exercise Pederson's review may explain some of the varied effects of exercise training on IL-6.

Evidence—equivocal for reducing systemic levels of inflammatory cytokines.

3.6. Brain Natriuretic Peptide (BNP) Levels. BNP levels are also raised in the circulation of patients with chronic heart failure (CHF) and may be related to disease severity or poor management [29]. B-type natriuretic peptide (BNP) is a cardiac neurohormone released as pre-pro-BNP and then enzymatically cleaved to N-terminal-proBNP and BNP

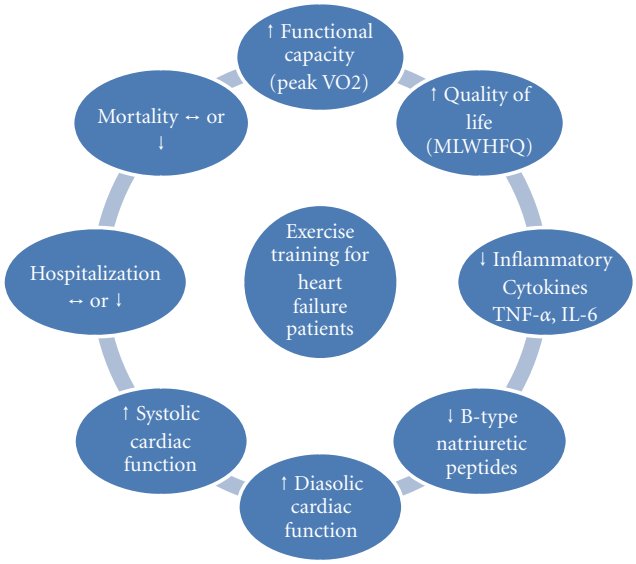

Figure 3: Clinical or prognostic markers of change in heart failure patients undertaking exercise training.

upon ventricular myocyte stretch. Blood measurements of BNP have been used to identify patients with heart failure [29, 30]. Currently, BNP assay is used as a diagnostic and prognostic aid in congestive heart failure. In general, a BNP level <100 pg/mL excludes acutely decompensated heart failure [29]. A recent systematic review in order to establish whether exercise training of CHF patients has an effect on circulating BNP levels [31]. Meta-analysis of randomized, controlled trials showed that exercise training had a favourable effect on BNP −79 pg/mL 95% C.I. (−141 to −17) $P = .01$ and NT-proBNP −621 pg/mL 95% C.I. (−844 to −398) $P < .00001$. Two of the included studies had low weekly energy expenditure (<400 Kcal/week) and changes in BNP and NT-pro-BNP were not significant in these studies [32, 33]. Patients who did not undergo training showed no changes, suggesting blunting of adrenergic overactivity and of natriuretic peptide overexpression [31].

> *Evidence unequivocal that B-type natriuretic peptides are reduced following exercise training, moreover a minimum weekly energy expenditure (circa 400 Kcal·week^{-1}) may be required to elicit changes in B-type natriuretic peptides.*

A summary of clinical markers of heart failure prognosis can be seen in Figure 3.

3.7. Public Health Issues

3.7.1. Number Needed to Teat (NNT) to Prevent 1 Death. As peak VO_2 is a strong predictor of prognosis [13] and heart failure patients undertaking exercise training may expect a 4%–15% improvement in peak VO_2. An associated mortality benefit has been reported [1, 15], although HF-ACTION data suggest these benefits remain equivocal. A systematic review calculated the number of heart failure patients that need to undertake exercise training in order to prevent one death is 17 over two years [1]. This value corresponds to 34 patients over a 12 month period.

> *Evidence suggests that 34 heart failure patients need to be provided with exercise training for 12 months to prevent one death from exercise training over this period.*

3.7.2. Cost-Effectiveness. Cost of treatment will always be a consideration in clinical decision making. Table 1 describes the estimated cost-effectiveness of three therapies for heart failure. To highlight the example the cost has been calculated for conducting a heart failure specific exercise program in Australia (in mid-2010), in both a supervised hospital setting and home-based setting (Table 1). A salary of AUS$ 60 K p.a. for a full-time graduate exercise physiologist is typical, and would be required to manage 34 patients, however start-up equipment costs of AUS$ 5–10 K have not been included in the estimation as these and other ongoing costs have been excluded. A home exercise program may require only 1 day per week of the same exercise physiologist to telephone patients to verify progress, but little or no equipment—the next section addresses home exercise in more detail. We have used examples cited on the University of Toronto's evidence-based medicine website [34] of trials of a beta-1 selective blocker [35] and the diuretic Aldactone [36]. When we compare treatment costs to prevent mortality in one patient, we can see that hospital-based exercise is comparable in cost to beta-blockade but noticeably less cost-effective than Aldactone, while home exercise training is clearly more cost-effective than beta-blockade but not Aldactone.

> *Evidence suggests exercise training, especially home-based, is a cost effective adjunct treatment.*

3.7.3. Safety. Exercise may increase the risk of sudden cardiac death [38]. While both exercise training and the heart failure condition each convey an increased risk of sudden death or adverse event, the published works in this field are yet to identify as single death that could be directly linked to exercise exertion in over 100,00 patient-hours of exercise training [4]. For this reason odds ratios for heart failure patients have not been calculated. Data from the HF-ACTION trial were zero deaths per 1,000 exercise tests and 0.45 nonfatal major CV events per 1,000 exercise tests (95% CI 0.11–1.81). Recent data suggest that although, sudden cardiac death (SCD) and cardiac events are more prevalent in the morning hours, data do not exist to suggest the time of day exercise training is conducted may not increase the risk of SCD or other adverse events [38].

Supervised outpatient trials may proffer better adherence rates than home exercise, possibly due to poor motivation and concerns about safety [39]. Strategies that improve home exercise compliance require regular patient contact and methods of verifying patient adherence. Nevertheless it is possible to sustain peak VO_2 and quality of life (QOL) in a "Home" exercise program 12 months after outpatient cardiac rehabilitation discharge [16, 40]. A recent systematic review

Table 1: Relative costs of various treatments for one mortality avoided.

Treatment	Number Needed to Treat per annum	Estimated Cost (AUS$) per annum
Beta-Blockade [35]	72	65 K
Aldactone (Spironolactone) [36]	4.5	5 K
Hospital based exercise training [37]	34	60 K
Home based exercise training	N/A	12 K

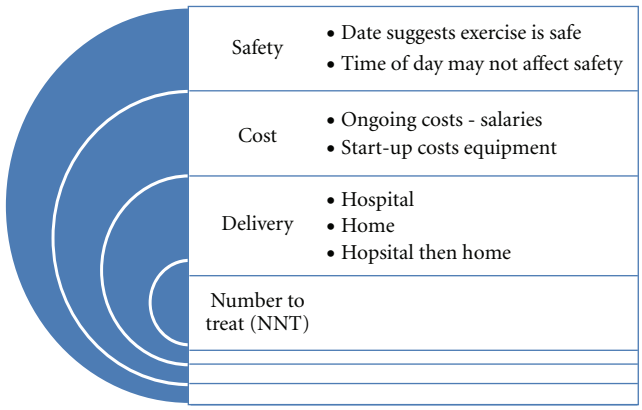

Figure 4: Public health issues associated with exercise training programs for heart failure patients.

reported that home exercise for heart failure patients may elicit similar magnitude of change in peak VO_2 compared to hospital based programs, although some of the data was generated from combined hospital and home exercise studies [40]. A tailored exercise program may optimise health benefits while minimising risk of exertional events. Periodic measurement of functional capacity, either directly or indirectly may protect against under- or overestimating the optimal training intensity.

> *Evidence suggests exercise training is safe for heart failure patients, but home exercise is most beneficial when it follows a supervised, hospital-based program.*

A summary of public health issues related to heart failure exercise training can be seen in Figure 4.

4. Discussion

A chronological history of exercise training for heart failure patients makes interesting reading. Prior to the 1990's the advice almost unequivocally given to heart failure patients was to avoid physical exertion. A handful of studies prior to the 1990's suggested exercise training was safe and possibly beneficial in reducing dyspnea and improving mood. In the 1990's and 2000's numerous studies and several meta-analyses have highlighted the importance of regular physical activity in improving not only improving physical fitness and quality of life, but also cardiac and blood vessel function and systemic inflammatory and neurohormonal markers of heart failure. Moreover exercise appears to be safe and most people with heart failure, with the exception of New York Heart Association class IV and some other high risk-heart failure patient categories, should be advised to regularly exercise.

The change in consensus of opinion towards safety and efficacy of exercise training was based upon data synthesis from many small- to medium-sized trials. Notably, meta-analysis [1] had suggested significant mortality and hospitalization benefits could be derived from exercise training heart failure patients, however closer analysis of the data suggested statistical significance of mortality and hospitalization was absent if the study of Belardinelli [15] was removed from the meta-analysis. Then, in late 2008 data was released from the HF-ACTION study [8] the largest (2,300 patients) exercise training study of heart failure patients to date. HF-ACTION reported nonsignificant reductions in mortality and hospitalization. After adjusting for highly prognostic predictors, exercise training was associated with modest significant reductions for both mortality and heart failure hospitalization. These findings together with the cost and efficacy data presented in this paper suggest exercise has a beneficial role in the nonpharmacological management of heart failure.

5. Conclusions

Differences exist in the demographics of participants of prevalence and exercise training studies in heart failure patients. Exercise training is safe, effective, and not cost prohibitive. Evidence shows exercise training-induced improvements are possible in many indicators of heart failure patient prognosis; functional capacity, quality of life, systolic and diastolic function, BNP and NT-pro-BNP expression. Nevertheless it remains questionable whether exercise training reduces cardiac deaths and hospitalisation and whether disease severity predicts which patients are most likely to benefit.

References

[1] M. F. Piepoli, C. Davos, D. P. Francis, and A. J. Coats, "Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH)," *British Medical Journal*, vol. 328, article 189, 2004.

[2] F. Lloyd-Williams, F. S. Mair, and M. Leitner, "Exercise training and heart failure: a systematic review of current evidence," *British Journal of General Practice*, vol. 52, no. 474, pp. 47–55, 2002.

[3] B. A. F. van Tol, R. J. Huijsmans, D. W. Kroon, M. Schothorst, and G. Kwakkel, "Effects of exercise training on cardiac performance, exercise capacity and quality of life in patients with heart failure: a meta-analysis," *European Journal of Heart Failure*, vol. 8, no. 8, pp. 841–850, 2006.

[4] N. Smart and T. H. Marwick, "Exercise training for patients with heart failure: a systematic review of factors that improve mortality and morbidity," *American Journal of Medicine*, vol. 116, no. 10, pp. 693–706, 2004.

[5] M. J. Haykowsky, Y. Liang, D. Pechter, L. W. Jones, F. A. McAlister, and A. M. Clark, "A meta-analysis of the effect of exercise training on left ventricular remodeling in heart failure patients. The benefit depends on the type of training performed," *Journal of the American College of Cardiology*, vol. 49, no. 24, pp. 2329–2336, 2007.

[6] R. Hambrecht, L. Hilbrich, S. Erbs et al., "Correction of endothelial dysfunction in chronic heart failure: additional effects of exercise training and oral L-arginine supplementation," *Journal of the American College of Cardiology*, vol. 35, no. 3, pp. 706–713, 2000.

[7] G. S. Bleumink, A. M. Knetsch, M. C. J. M. Sturkenboom et al., "Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure—the Rotterdam Study," *European Heart Journal*, vol. 25, no. 18, pp. 1614–1619, 2004.

[8] C. M. O'Connor, D. J. Whellan, K. L. Lee et al., "Efficacy and safety of exercise training in patients with chronic heart failure HF-ACTION randomized controlled trial," *Journal of the American Medical Association*, vol. 301, no. 14, pp. 1439–1450, 2009.

[9] S. A. Hunt, D. W. Baker, M. H. Chin et al., "ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure)," *Journal of the American College of Cardiology*, vol. 38, no. 7, pp. 2101–2113, 2001.

[10] P. Giannuzzi, "Recommendations for exercise training in chronic heart failure patients," *European Heart Journal*, vol. 22, no. 2, pp. 125–135, 2001.

[11] A. Tonkin, P. Barter, J. Best et al., "National heart foundation of Australia and the cardiac society of Australia and New Zealand: position statement on lipid management—2005," *Heart, Lung & Circulation*, vol. 14, no. 4, pp. 275–291, 2005.

[12] E. F. Philbin, T. A. Rocco Jr., N. W. Lindenmuth, K. Ulrich, and P. L. Jenkins, "Systolic versus diastolic heart failure in community practice: clinical features, outcomes, and the use of angiotensin-converting enzyme inhibitors," *American Journal of Medicine*, vol. 109, no. 8, pp. 605–613, 2000.

[13] D. Mancini, T. LeJemtel, and K. Aaronson, "Peak VO2: a simple yet enduring standard," *Circulation*, vol. 101, no. 10, pp. 1080–1082, 2000.

[14] T. Kavanagh, D. J. Mertens, L. F. Hamm et al., "Peak oxygen intake and cardiac mortality in women referred for cardiac rehabilitation," *Journal of the American College of Cardiology*, vol. 42, no. 12, pp. 2139–2143, 2003.

[15] R. Belardinelli, D. Georgiou, G. Cianci, and A. Purcaro, "Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome," *Circulation*, vol. 99, no. 9, pp. 1173–1182, 1999.

[16] R. S. McKelvie, K. K. Teo, R. Roberts et al., "Effects of exercise training in patients with heart failure: the Exercise Rehabilitation Trial (EXERT)," *American Heart Journal*, vol. 144, no. 1, pp. 23–30, 2002.

[17] T. Meyer, J. Scharhag, and W. Kindermann, "Peak oxygen uptake: myth and truth about an internationally accepted reference value," *Zeitschrift fur Kardiologie*, vol. 94, no. 4, pp. 255–264, 2005.

[18] U. Wisløff, A. Støylen, J. P. Loennechen et al., "Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study," *Circulation*, vol. 115, no. 24, pp. 3086–3094, 2007.

[19] G. Malfatto, G. Branzi, G. Osculati et al., "Improvement in left ventricular diastolic stiffness induced by physical training in patients with dilated cardiomyopathy," *Journal of Cardiac Failure*, vol. 15, no. 4, pp. 327–333, 2009.

[20] S. Adamopoulos, A. J. S. Coats, F. Brunotte et al., "Physical training improves skeletal muscle metabolism in patients with chronic heart failure," *Journal of the American College of Cardiology*, vol. 21, no. 5, pp. 1101–1106, 1993.

[21] S. Adamopoulos, J. Parissis, D. Karatzas et al., "Physical training modulates proinflammatory cytokines and the soluble Fas/soluble Fas ligand system in patients with chronic heart failure," *Journal of the American College of Cardiology*, vol. 39, no. 4, pp. 653–663, 2002.

[22] V. M. Conraads, P. Beckers, J. Bosmans et al., "Combined endurance/resistance training reduces plasma TNF-α receptor levels in patients with chronic heart failure and coronary artery disease," *European Heart Journal*, vol. 23, no. 23, pp. 1854–1860, 2002.

[23] A. Ferraz, E. A. Boochi, R. S. Meneghelo, I. I. Umeda, and N. Salvarane, "Sensitive C-reactive protein is reduced by exercise training in chronic heart failure patients: a prospective, randomized, controlled study," *Circulation*, vol. 110, pp. 793–794, 2004.

[24] S. Gielen, V. Adams, S. Möbius-Winkler et al., "Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure," *Journal of the American College of Cardiology*, vol. 42, no. 5, pp. 861–868, 2003.

[25] A. I. Karavidas, K. G. Raisakis, J. T. Parissis et al., "Functional electrical stimulation improves endothelial function and reduces peripheral immune responses in patients with chronic heart failure," *European Journal of Cardiovascular Prevention and Rehabilitation*, vol. 13, no. 4, pp. 592–597, 2006.

[26] J. P. LeMaitre, S. Harris, K. A. A. Fox, and M. Denvir, "Change in circulating cytokines after 2 forms of exercise training in chronic stable heart failure," *American Heart Journal*, vol. 147, no. 1, pp. 100–105, 2004.

[27] D. Xu, B. Wang, Y. Hou, H. Hui, S. Meng, and Y. Liu, "The effects of exercise training on plasma tumor necrosis factor-alpha, blood leucocyte and its components in congestive heart failure patients," *Zhonghua Nei Ke Za Zhi*, vol. 41, no. 4, pp. 237–240, 2002.

[28] B. K. Pedersen and M. A. Febbraio, "Muscle as an endocrine organ: focus on muscle-derived interleukin-6," *Physiological Reviews*, vol. 88, no. 4, pp. 1379–1406, 2008.

[29] P. A. McCullough, "B-type natriuretic peptide and its clinical implications in heart failure," *The American heart hospital journal*, vol. 2, no. 1, pp. 26–33, 2004.

[30] P. Jourdain, F. Funck, E. Canault et al., "Value of brain peptide in the management of suspected cardiac failure in the emergency room," *Archives des Maladies du Coeur et des Vaisseaux*, vol. 95, no. 9, pp. 763–767, 2002.

[31] N. A. Smart and M. Steele, "Systematic review of the effect of aerobic and resistance exercise training on systemic brain natriuretic peptide (BNP) and N-terminal BNP expression in heart failure patients," *International Journal of Cardiology*, vol. 140, pp. 260–265, 2010.

[32] J. A. Butterfield, S. C. Faddy, P. Davidson, and B. Ridge, "Exercise training in patients with stable chronic heart failure: effects on thoracic impedance cardiography and B-type natriuretic peptide," *Journal of Cardiopulmonary Rehabilitation and Prevention*, vol. 28, no. 1, pp. 33–37, 2008.

[33] S. Jónsdóttir, K. K. Andersen, A. F. Sigurosson, and S. B. Sigurosson, "The effect of physical training in chronic heart failure," *European Journal of Heart Failure*, vol. 8, no. 1, pp. 97–101, 2006.

[34] Uo. Toronto, "More on number needed to treat," 2008, http://www.cebm.net/index.aspx?o=1025.

[35] A. Hjalmarson, S. Goldstein, B. Fagerberg et al., "Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF)," *Journal of the American Medical Association*, vol. 283, no. 10, pp. 1295–1302, 2000.

[36] B. Pitt, F. Zannad, W. J. Remme et al., "The effect of spironolactone on morbidity and mortality in patients with severe heart failure," *New England Journal of Medicine*, vol. 341, no. 10, pp. 709–717, 1999.

[37] Website UoTEbm, "Glossary- moreon number needed to treat," 2008, http://www.cebm.net/index.aspx?o=1025.

[38] P. D. Thompson, B. A. Franklin, G. J. Balady et al., "Exercise and acute cardiovascular events: placing the risks into perspective a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology," *Circulation*, vol. 115, no. 17, pp. 2358–2368, 2007.

[39] K. M. Smith, H. M. Arthur, R. S. McKelvie, and J. Kodis, "Differences in sustainability of exercise and health-related quality of life outcomes following home or hospital-based cardiac rehabilitation," *European Journal of Cardiovascular Prevention and Rehabilitation*, vol. 11, no. 4, pp. 313–319, 2004.

[40] R. Hwang and T. Marwick, "Efficacy of home-based exercise programmes for people with chronic heart failure: a meta-analysis," *European Journal of Cardiovascular Prevention and Rehabilitation*, vol. 16, no. 5, pp. 527–535, 2009.

SAGE-Hindawi Access to Research
Cardiology Research and Practice
Volume 2011, Article ID 532620, 6 pages
doi:10.4061/2011/532620

Research Article

Effect of Exercise Training on Interleukin-6, Tumour Necrosis Factor Alpha and Functional Capacity in Heart Failure

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Received 5 October 2010; Revised 12 January 2011; Accepted 14 January 2011

Academic Editor: Gregory Giamouzis

Background. We pooled data from four studies, to establish whether exercise training programs were able to modulate systemic cytokine levels of tumour necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6). A second aim was to establish if differences in ExT regimens are related to degree of change in cytokines and peak VO_2. *Methods*. Data from four centres relating to training protocol, exercise capacity, and cytokine measures (TNF-alpha and IL-6) were pooled for analysis. *Results*. Data for 106 CHF patients were collated (98 men, age 62 ± 10 yrs, wt 79 ± 14 Kg). Patients were moderately impaired (peak VO_2 16.9 ± 4.4 mls/kg/min), with moderate LV systolic dysfunction (EF $30 \pm 6.9\%$), 78% (83) had ischaemic cardiomyopathy. After ExT, peak VO_2 increased 1.4 ± 3.4 ml/kg/min ($P < .001$), serum TNF-alpha decreased 1.9 ± 8.6 pg/ml ($P = .02$) and IL-6 was not significantly changed (0.5 ± 5.4 pg/ml, $P = .32$) for the whole group. Baseline and post-training peak VO_2 changes were not correlated with change in cytokine levels. *Conclusions*. Exercise training reduces levels TNF-alpha but not IL-6 in CHF. However, across a heterogenic patient group, change in peak VO_2 was not correlated with alterations in cytokine levels. While greater exercise volume (hours) was superior in improving peak VO_2, no particular characteristic of ExT regimes appeared superior in effecting change in serum cytokines.

1. Introduction

Inflammatory activation with increased serum cytokine levels has been described by several authors as an important factor in the progression of the syndrome of chronic heart failure (CHF) [1–3]. In multifactorial analyses, elevated levels of tumour necrosis factor-(TNF-) alpha and interleukin-(IL-) 6 have been identified as prognostic heart failure markers [4–6]. Cytokines act as catabolic factors involved in the pathogenesis of muscle wasting and cardiac cachexia [3, 7], and increased levels of serum TNF-alpha have been identified in patients with reduced skeletal muscle cross-sectional area and peripheral muscle strength [1]. There also exists a statistical significant association between elevated serum cytokine levels (especially TNF-alpha) and New York Heart Association (NYHA) functional class as well as exercise intolerance [2]. Inflammatory cytokines may alter skeletal muscle histology and have a negative impact on left ventricular remodelling and cardiac contractility [2, 3, 8]. The inflammatory response is also associated with progression of atherosclerosis [9], oxidative stress [10], NO impairment [11], vasoconstriction, endothelial cell apoptosis [12], and adverse vascular remodelling [13].

Exercise training has been documented to improve the inflammatory profile in CHF by inhibition of cytokine-chemokine production, regulation of monocyte activation and adhesion, inhibition of inflammatory cell-growth signals and growth factor production, reduction of soluble apoptosis signalling molecules [12], and attenuation of monocyte-endothelial cell adhesive interaction [14]. A study of 277 patients with coronary artery disease reported a significant 41% reduction in high-sensitivity C-reactive protein following exercise training [15]. A recent study of four-month duration, utilizing combined endurance/resistance

Table 1: Studies identified in PUBMED, MEDLINE search.

Study	Subjects(Control)	Year	Cytokines measured	% △ VO_2	Mode of Exercise
Adamapoulos et al. [23]	12	2001	Soluble adhesion molecules	13	Home bike
Adamopoulos et al. [12]	24	2002	TNF-alpha, Interleukin-6	15	Home bike
Conraads et al. [16]	23 (12)	2002	TNF-alpha, Interleukin-6	7.5	Bike and resistance training
Ferraz et al. [21]#	30 (10)	2004	TNF-alpha, Interleukin-6	23	Bike
Gielen et al. [2]	20 (10)	2003	TNF-alpha, Interleukin-1, 6 and beta In both serum and skeletal muscle	29	Bike
Karavidas et al. [24]	16 (8)	2006	TNF-alpha, Interleukin-6, 10	7.5*	Electrical stimulation
Larsen et al. [22]#	28	2001	TNF-alpha, Interleukin-6,8	8*	Aerobic endurance training and home bike
Larsen et al. [25]	25	2008	Plasma Chromogranin A (CgA)	8*	Aerobic endurance training and home bike
Laoutaris et al. [26]	38	2007	TNF-alpha, Interleukin-6	12	Low versus high intensity inspiratory muscle training
LeMaitre et al. [17]#	46	2004	TNF-alpha, Interleukin-6	3	Bike and electrical stimulation
Niebauer et al. [27]	18 (9)	2005	TNF-alpha Interleukin-6, e-selectin	11	Bike
Smart [28]#	22	2008	TNF-alpha, Interleukin-6, brain natriurietic peptide (BNP)	20	Bike
Xu et al. [18]	60 (28)	2002	TNF-alpha	Unknown	Unknown

* % change in 6-minute walk distance (Peak VO_2 not measured). #Study used in this paper.

training demonstrated reduced TNF-alpha receptor levels (TNFR1 and TNFR2) and a significant (7.5%) increase in peak VO_2 in patients with ischemic cardiomyopathy, although changes in IL-6 and TNF-alpha were not apparent [16]. This effect on circulating levels of TNF-alpha receptors is also reported after 6 weeks of cycle ergometry [17]. In this study, there were no alterations in IL-6, C-reactive protein (CRP), or TNF-alpha. In addition, electrical muscle stimulation provided no changes in any of the aforementioned cytokines. Larsen et al. [8] reported an 11% increase in peak VO_2 following 3 months of endurance training; TNF-alpha was significantly reduced, and this decrease was significantly correlated to the increase in peak VO_2. Adamopoulos [14] reported a 13% increase in functional capacity with a 12-week cycle ergometry training program, which correlated with lower levels of soluble adhesion molecules. The authors later reported a strong and highly significant correlation between improvements in peak VO_2 (15%) and reduction in TNF-alpha, soluble TNFR-1 and -2, and IL-6 [12]. Plasma TNF-alpha is also documented to decrease after twice daily 6-minute walk tests in NYHA II/III heart failure patients [18]. A recently published study reported absent von Willebrand factor (vWF) release upon exercise testing in heart failure patients; this normalised following 6 months of exercise training; other plasma endothelial markers were unaltered [19].

Changes in skeletal muscle, but not systemic expression of TNF-alpha, IL-1-beta, and IL-6 have been reported in heart failure patients undertaking a regimen of 10 minutes cycling, 4–6 times daily for 6 months [2]. This exercise program resulted in large changes in functional capacity (29%), nearly twice the mean expected increment (17%) shown from our review of 81 heart failure exercise training studies [20]. This study suggested the existence of a cytokine cascade where levels may be changed at altered rates in different tissues. As heart failure exercise training studies are often small, we sought by pooling data from four studies to establish whether exercise training programs were able to modulate systemic cytokine levels. A second aim was to establish if differences in ExT regimens are related to the degree of change in cytokines and peak VO_2.

2. Methods

We searched PUBMED and MEDLINE for exercise training studies in heart failure patients that had measured one or more of the proinflammatory cytokines. The full list of studies is summarized in Table 1. The focus of this work was interleukin-6 and TNF-alpha as these cytokines were measured in 10 exercise training studies, the correspondence authors of which were contacted for their cooperation in collaboration. Authors were requested to provide individual patient data from their study; four centres provided data (Table 2). One study was a conference proceedings abstract [21]. Sufficient data were not available to analyse changes in other cytokines.

Table 2: Clinical characteristics and pharmacotherapy of the 106 patients.

Clinical characteristics	
Age (Years)	61.8 ± 9.9
Male (%)	98 (92.5)
Body mass (kg)	78.7 ± 13.7
Peak VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$)	16.9 ± 4.4
Diabetes (%)	11 (10)
Previous myocardial infarction (%)	86 (81)
Atrial fibrillation (%)	27 (26)
NYHA class II/III	49/57
LVEF (%)	30 ± 6.9
Medications	
Beta-blocker (%)	44 (42)
ACE-inhibitor/antagonist (%)	95 (90)
Digoxin (%)	67 (63)
Nitrates (%)	40 (38)

2.1. Blood Sampling and Analysis. In 3 studies, plasma or serum samples were obtained by venipuncture (arterial cannula used in Larsen's study) and stored on ice. In all studies, venipuncture collections were taken between 0900, and 1200, at least 24 hours and not more than 5 days after the last exercise session, thus negating the effects of the intervention. Within one hour, samples were centrifuged at 4°C, 1500–2000 RPM for 10 minutes, and then separated into aliquots and stored at between −75°C and −80°C. Concentrations of IL-6 or TNF-alpha were measured by commercially available enzyme-linked immunosorbent assays (ELISAs) (R&D systems Minneapolis, Minnesota) in all 4 studies. The intra- and interassay coefficients of variation were <10% for all assays. In one study, 16 healthy, male volunteers of approximately the same age (62 ± 5 years) served as controls [22] although this data was not included in our analyses.

2.2. Metabolic Exercise Testing and Exercise Training. All four collaborating investigators completed baseline and posttraining metabolic exercise tests to establish functional capacity.

Larsen and Smart used cycle ergometers with a 15 W and 10 W per min stepped protocol, respectively; LeMaitre and Ferraz used a modified Bruce treadmill protocol.

One study used a regime of supervised aerobic exercise training 3 times per week. Two studies used supervised cycle ergometry as the primary mode of exercise training [21, 22], and one study used both home-based and neuromuscular stimulation of the legs [17].

2.3. Data Extraction. Mode of training, program duration and exercise intensity were examined. Baseline and post-training cytokine levels, peak VO_2, left ventricular ejection fraction (LVEF), clinical, demographic, and pharmacological characteristics of patients are shown in Table 2.

Table 3: Exercise program parameters and change in primary outcome measures in the 4 studies.

	Ferraz	Larsen	LeMaitre	Smart
Weeks	24	12	6	16
Minutes/Wk	135	90	150	90
Freq. sessions/Wk	3	3	5	3
Intensity (% max)	67	80	70	70
Total hours	54	54	15	48

2.4. Statistical Analysis. Paired student t-tests were used to analyse baseline and postintervention changes in cytokines and peak VO_2. ANOVA (2×4) was used to analyse differences between the four datasets. Pearson correlation coefficients were established for change in cytokines and peak VO_2. Univariate and multivariate regression analysis with change in TNF-alpha as the dependent variable were used to determine factors leading to cytokine change. Data are expressed as mean +/− standard deviation unless otherwise stated. Significance was accepted at the 5% level ($P < .05$).

3. Results

3.1. Baseline Measures. The four collaborating authors provided data on 106 patients (98 male, age 62 ± 10 yrs, body weight 79 ± 14 Kg). Patients were moderately impaired (peak VO_2 16.9 ± 4.4 mls/kg/min), with moderate LV systolic dysfunction (EF 30 ± 6.9%). Seventy eight % (83) had an ischaemic cardiomyopathy (Table 2). Adherence data relating to training regimes were 87.2 ± 1.9% [21] and 85 ± 12% [28] and were unavailable for the other 2 studies.

3.2. Training Regimes. Regimes varied between 3 and 5 exercise sessions per week, at an intensity of 58–80% of peak VO_2. Program durations were between 6 and 24 weeks, 90–150 minutes per week, and total program hours varied between 15 and 54 hours (Table 3).

3.3. Pooled Posttraining Changes. After training, peak VO_2 increased by 1.4 ± 3.4 mL/kg/min or 9% ($P < .001$) from 16.9 ± 4.4 to 18.4 ± 4.5, serum TNF-alpha decreased from a baseline value of 13 ± 15.2 pg/mL by 1.9 ± 8.6 pg/mL ($P = .02$), and IL-6 increased slightly from a baseline value of 7.8 ± 11.4 pg/mL by 0.5 ± 5.4 pg/mL ($P = .32$). Cytokine changes for each study can be seen in Figure 1. Body weight was unchanged following exercise training. None of the clinical, demographic, or pharmacologic variables were correlated with changes in circulating IL-6 or TNF-alpha following training. The correlations between change in posttraining peak VO_2 and changes in TNF-alpha ($r = 0.023$, $P = .82$) and IL-6 ($r = -0.12$, $P = .21$) were not significant. Change in TNF-alpha was correlated with exercise session duration and anerobic threshold (both $r = 0.21$, $P = .31$), univariate but not multivariate analysis identified that previous myocardial infarction, longer exercise session duration, and higher body mass index predicted change in TNF-alpha ($r^2 = 0.18$, $P = .001$).

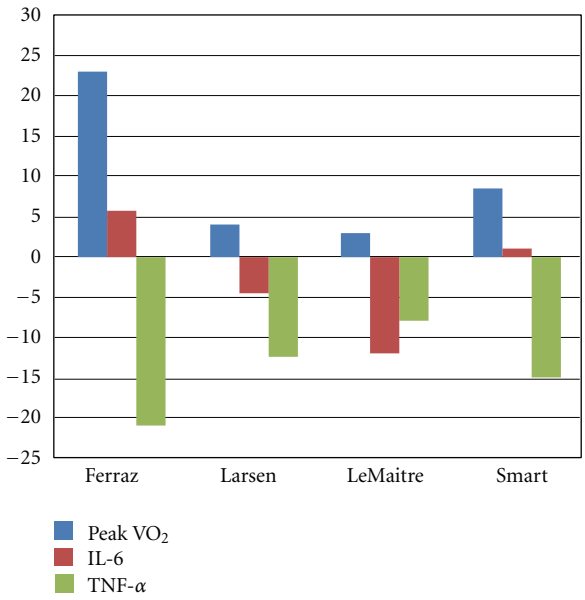

Figure 1: Change in cytokines and peak VO_2 across the four studies.

3.4. Optimal Exercise Program Components for Peak VO_2 and Cytokine Changes. A total exercise program duration of 54 hours appeared to be superior than 15 or 18 hours in effecting change in peak VO_2 ($P < .001$); however, no difference was seen for change in cytokine levels. The longest program duration resulted in a greater increment in peak VO_2 compared to 12 weeks ($P = .003$) and 6 weeks ($P = .001$), while peak VO_2 or 6-minute walk distance was unchanged in the ExT programs of 6 and 12 weeks duration.

4. Discussion

Pooled data from four studies demonstrated that alterations in levels of the cytokines IL-6 and TNF-alpha are not necessarily uniform. Increments in peak VO_2 following exercise training are widely accepted; however, they may be unrelated to changes in cytokine levels. Moreover, changes in particular cytokines appear to be independent of one another. One cannot be sure about the variable effects of the different program parameters and exercise adherence rates; nevertheless, the mean change in functional capacity from the four studies was 8%, suggesting that cumulatively the four exercise programs provided stimulus for a possible favourable change in cytokine expression. Interpretation of this pooled data is limited by the fact that several other centres did not supply data. Table 2 suggests that study participants showed heterogeneity for age, peak, VO_2 and beta-blocker use.

4.1. Expectations of Favourable Changes in Cytokine Expression. Moderate endurance activity in frail, elderly, but otherwise healthy persons has previously been reported to influence circulating cytokine levels [29]. As our patients had mild to moderate heart failure, it is not surprising to observe that levels of systemic TNF-alpha were decreased after training, thereby initiating anti-inflammatory effects. The finding that IL-6 was unchanged after training is more puzzling. However, one study has suggested that IL-6 produced by exercising muscle is thought to exert an anti-inflammatory effect [30]. These data suggest that production and removal of TNF-alpha and IL-6 may be, at least partially, from independent mechanisms and may have opposing effects (inflammatory versus anti-inflammatory). Recent clinical trials have not shown benefit from treatments that target TNF-alpha. A clinical trial of etanercept (a TNF-alpha antagonist) therapy has cast doubt on the role of cytokines in the pathogenesis of heart failure [31]. There are then implications for health professionals or researchers in the process of designing an exercise program for heart failure patients. Primary end points of CHF exercise programs should perhaps not include lowering cytokine levels as they may represent surrogate markers of efficacy; this may be particularly true in patients with milder degrees of CHF. In this population, program design may be better focussed on the parameters such as program frequency (sessions/week), duration (number of weeks), and intensity that may have a greater effect on peak VO_2 changes. Peak VO_2 improvement from exercise training may be linked to attenuated levels of oxidative stress which in turn may attenuate cytokine expression. Previous work in healthy older adults [32] and heart failure patients [33] has shown intermittent exercise programs to be at least more effective in improving peak VO_2 than a continuous regime that would produce greater cumulative oxidative stress. In our work, peak VO_2 was not significantly changed in patients who exercised despite utilizing a reasonable volume of exercise to elicit functional capacity changes.

In heart failure, the effect of inflammation, which may be due partly to inactivity, may manifest in the terminal disease phase. The study by Adamopoulos et al. [14] may provide the best evidence to date linking change in peak VO_2 and cytokines in heart failure patients. The small cytokine change shown in our studies may be due to the fact that our patients exhibited mild to moderate heart failure symptoms. The participants in the study of Adamopoulos et al. [14] exhibited moderate to severe symptoms. In addition, our participants had higher left ventricular ejection fractions (30% versus 24%) than those of Adamopoulos et al. [14]. Exercise training has been shown to significantly reduce the local muscle expression of TNF-alpha, IL-1-beta, IL-6, and iNOS in the skeletal muscle of CHF patients [8]. In turn, physical exercise has been shown to improve both basal endothelial nitric oxide (NO) formation and agonist-mediated endothelium-dependent vasodilation of the skeletal muscle vasculature in patients with CHF. The correction of endothelium dysfunction is associated with a significant increase in exercise capacity [34]. These local anti-inflammatory and systemic effects of exercise may attenuate the catabolic wasting process associated with CHF progression [3]. In addition to an overall beneficial effect on exercise capacity, combined endurance/resistance exercise training has an anti-inflammatory effect in patients with heart disease [16]. These skeletal muscle and anti-inflammatory changes may explain why alterations in TNF-alpha levels are most likely to be observed in patients with moderate or severe heart failure.

4.2. Conclusions. Exercise training reduces levels of TNF-alpha but not IL-6 in CHF. However, across a heterogenic patient group, change in peak VO_2 was not correlated with alterations in cytokine levels. While greater exercise volume (number of hours) was superior in improving peak VO_2, no particular characteristic of ExT regimes appeared superior in effecting change in serum cytokines.

Acknowledgment

This work is supported in part by an MBF Research Grant Award 2003 and a scholarship from the National Heart Foundation of Australia.

References

[1] J. Niebauer, "Inflammatory mediators in heart failure," *International Journal of Cardiology*, vol. 72, no. 3, pp. 209–213, 2000.

[2] S. Gielen, V. Adams, S. Möbius-Winkler et al., "Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure," *Journal of the American College of Cardiology*, vol. 42, no. 5, pp. 861–868, 2003.

[3] S. D. Anker and S. Von Haehling, "Inflammatory mediators in chronic heart failure: an overview," *Heart*, vol. 90, no. 4, pp. 464–470, 2004.

[4] J. Orús, E. Roig, F. Perez-Villa et al., "Prognostic value of serum cytokines in patients with congestive heart failure," *Journal of Heart and Lung Transplantation*, vol. 19, no. 5, pp. 419–425, 2000.

[5] M. Rauchhaus, W. Doehner, D. P. Francis et al., "Plasma cytokine parameters and mortality in patients with chronic heart failure," *Circulation*, vol. 102, no. 25, pp. 3060–3067, 2000.

[6] A. Deswal, N. J. Petersen, A. M. Feldman, J. B. Young, B. G. White, and D. L. Mann, "Cytokines and cytokine receptors in advanced heart failure: an analysis of the cytokine database from the Vesnarinone Trial (VEST)," *Circulation*, vol. 103, no. 16, pp. 2055–2059, 2001.

[7] S. D. Anker, W. Steinborn, and S. Strassburg, "Cardiac cachexia," *Annals of Medicine*, vol. 36, no. 7, pp. 518–529, 2004.

[8] A. I. Larsen, S. Lindal, P. Aukrust, I. Toft, T. Aarsland, and K. Dickstein, "Effect of exercise training on skeletal muscle fibre characteristics in men with chronic heart failure. Correlation between skeletal muscle alterations, cytokines and exercise capacity," *International Journal of Cardiology*, vol. 83, no. 1, pp. 25–32, 2002.

[9] D. Tousoulis, M. Charakida, and C. Stefanadis, "Inflammation and endothelial dysfunction as therapeutic targets in patients with heart failure," *International Journal of Cardiology*, vol. 100, no. 3, pp. 347–353, 2005.

[10] S. Ichihara, Y. Yamada, G. Ichihara et al., "Attenuation of oxidative stress and cardiac dysfunction by bisoprolol in an animal model of dilated cardiomyopathy," *Biochemical and Biophysical Research Communications*, vol. 350, no. 1, pp. 105–113, 2006.

[11] O. Parodi, R. De Maria, and E. Roubina, "Redox state, oxidative stress and endothelial dysfunction in heart failure: the puzzle of nitrate-thiol interaction," *Journal of Cardiovascular Medicine*, vol. 8, no. 10, pp. 765–774, 2007.

[12] S. Adamopoulos, J. Parissis, D. Karatzas et al., "Physical training modulates proinflammatory cytokines and the soluble Fas/soluble Fas ligand system in patients with chronic heart failure," *Journal of the American College of Cardiology*, vol. 39, no. 4, pp. 653–663, 2002.

[13] S. Adamopoulos, J. T. Parissis, and D. T. Kremastinos, "New aspects for the role of physical training in the management of patients with chronic heart failure," *International Journal of Cardiology*, vol. 90, no. 1, pp. 1–14, 2003.

[14] S. Adamopoulos, J. Parissis, C. Kroupis et al., "Physical training reduces peripheral markers of inflammation in patients with chronic heart failure," *European Heart Journal*, vol. 22, no. 9, pp. 791–797, 2001.

[15] R. V. Milani, C. J. Lavie, and M. R. Mehra, "Reduction in C-reactive protein through cardiac rehabilitation and exercise training," *Journal of the American College of Cardiology*, vol. 43, no. 6, pp. 1056–1061, 2004.

[16] V. M. Conraads, P. Beckers, J. Bosmans et al., "Combined endurance/resistance training reduces plasma TNF-α receptor levels in patients with chronic heart failure and coronary artery disease," *European Heart Journal*, vol. 23, no. 23, pp. 1854–1860, 2002.

[17] J. P. LeMaitre, S. Harris, K. A. A. Fox, and M. Denvir, "Change in circulating cytokines after 2 forms of exercise training in chronic stable heart failure," *American Heart Journal*, vol. 147, no. 1, pp. 100–105, 2004.

[18] D. Xu, B. Wang, Y. Hou, H. Hui, S. Meng, and Y. Liu, "The effects of exercise training on plasma tumor necrosis factor-alpha, blood leucocyte and its components in congestive heart failure patients," *Zhonghua Nei Ke Za Zhi*, vol. 41, no. 4, pp. 237–240, 2002.

[19] L. W. E. Sabelis, P. J. Senden, R. Fijnheer et al., "Endothelial markers in chronic heart failure: training normalizes exercise-induced vWF release," *European Journal of Clinical Investigation*, vol. 34, no. 9, pp. 583–589, 2004.

[20] N. Smart and T. H. Marwick, "Exercise training for patients with heart failure: a systematic review of factors that improve mortality and morbidity," *American Journal of Medicine*, vol. 116, no. 10, pp. 693–706, 2004.

[21] A. Ferraz, E. A. Boochi, R. S. Meneghelo, I. I. Umeda, and N. Salvarane, "High sensitive C-reactive protein is reduced by exercise training in chronic heart failure patients: a prospective, randomized, controlled study," *Circulation*, vol. 110, pp. 793–794, 2004.

[22] A. I. Larsen, P. Aukrust, T. Aarsland, and K. Dickstein, "Effect of aerobic exercise training on plasma levels of tumor necrosis factor alpha in patients with heart failure," *American Journal of Cardiology*, vol. 88, no. 7, pp. 805–808, 2001.

[23] S. Adamopoulos, A. J. Coats, F. Brunotte et al., "Physical training improves skeletal muscle metabolism in patients with chronic heart failure," *Journal of the American College of Cardiology*, vol. 21, no. 5, pp. 1101–1106, 1993.

[24] A. I. Karavidas, K. G. Raisakis, J. T. Parissis et al., "Functional electrical stimulation improves endothelial function and reduces peripheral immune responses in patients with chronic heart failure," *European Journal of Cardiovascular Prevention and Rehabilitation*, vol. 13, no. 4, pp. 592–597, 2006.

[25] A. I. Larsen, K. B. Helle, M. Christensen, J. T. Kvaloy, T. Aarsland, and K. Dickstein, "Effect of exercise training on chromogranin A and relationship to N-ANP and inflammatory cytokines in patients with chronic heart failure," *International Journal of Cardiology*, vol. 127, no. 1, pp. 117–120, 2008.

[26] I. D. Laoutaris, A. Dritsas, M. D. Brown et al., "Immune response to inspiratory muscle training in patients with chronic heart failure," *European Journal of Cardiovascular Prevention and Rehabilitation*, vol. 14, no. 5, pp. 679–685, 2007.

[27] J. Niebauer, A. L. Clark, k. M. Webb-Peploe, and A. J. Coats, "Exercise training in chronic heart failure: effects on pro-inflammatory markers," *European Journal of Heart Failure*, vol. 7, no. 2, pp. 189–193, 2005.

[28] N. Smart, "Effects of exercise training on functional capacity, quality of life, cytokine and brain natriuretic peptide levels in hart failure patients," *Journal of Medical and Biological Sciences*, vol. 2, no. 1, 2008.

[29] J. S. Greiwe, B. Cheng, D. C. Rubin, K. E. Yarasheski, and C. F. Semenkovich, "Resistance exercise decreases skeletal muscle tumor necrosis factor α in frail elderly humans," *FASEB Journal*, vol. 15, no. 2, pp. 475–482, 2001.

[30] A. M. W. Petersen and B. K. Pedersen, "The anti-inflammatory effect of exercise," *Journal of Applied Physiology*, vol. 98, no. 4, pp. 1154–1162, 2005.

[31] D. L. Mann, J. J. V. McMurray, M. Packer et al., "Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL)," *Circulation*, vol. 109, no. 13, pp. 1594–1602, 2004.

[32] N. Morris, G. Gass, M. Thompson, G. Bennett, D. Basic, and H. Morton, "Rate and amplitude of adaptation to intermittent and continuous exercise in older men," *Medicine and Science in Sports and Exercise*, vol. 34, no. 3, pp. 471–477, 2002.

[33] K. Meyer, L. Samek, M. Schwaibold et al., "Interval training in patients with severe chronic heart failure: analysis and recommendations for exercise procedures," *Medicine and Science in Sports and Exercise*, vol. 29, no. 3, pp. 306–312, 1997.

[34] R. Hambrecht, E. Fiehn, C. Weigl et al., "Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure," *Circulation*, vol. 98, no. 24, pp. 2709–2715, 1998.

SAGE-Hindawi Access to Research
Cardiology Research and Practice
Volume 2011, Article ID 798658, 6 pages
doi:10.4061/2011/798658

Research Article

Progression of Left Ventricular Dysfunction and Remodelling under Optimal Medical Therapy in CHF Patients: Role of Individual Genetic Background

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Received 25 October 2010; Accepted 25 November 2010

Academic Editor: Javed Butler

Background. Neurohormonal systems play an important role in chronic heart failure (CHF). Due to interindividual heterogeneity in the benefits of therapy, it may be hypothesized that polymorphisms of neurohormonal systems may affect left ventricular (LV) remodelling and systolic function. We aimed to assess whether genetic background of maximally treated CHF patients predicts variations in LV systolic function and volumes. *Methods and Results*. We prospectively studied 131 CHF outpatients on optimal treatment for at least six months. Echocardiographic evaluations were performed at baseline and after 12 months. Genotype analysis for ACE I/D, β1adrenergic receptor (AR) Arg389Gly, β2AR Arg16Gly, and β2AR Gln27Glu polymorphisms was performed. No differences in baseline characteristics were detected among subgroups. ACE II was a significant predictor of improvement of LV end-diastolic and end-systolic volume ($P = .003$ and $P = .002$, respectively) but not of LV ejection fraction (LVEF); β1AR389 GlyGly was related to improvement of LVEF ($P = .02$) and LV end-systolic volume ($P = .01$). The predictive value of polymorphisms remained after adjustment for other clinically significant predictors ($P < .05$ for all). *Conclusions*. ACE I/D and β1AR Arg389Gly polymorphisms are independent predictors of reverse remodeling and systolic function recovery in CHF patients under optimal treatment.

1. Introduction

Chronic heart failure (CHF) is a major cause of morbidity and mortality [1]. Approximately 5 million Americans and more than 10 million Europeans have CHF, with an incidence approaching 1% of the population among people over 65 years of age [2]. It is a progressively debilitating condition and despite treatment, only half of the patients survive more than five years after diagnosis [3].

Left ventricular remodeling is a key process determining disease progression and affecting outcome in this condition. Several multicenter trials in patients with CHF have shown a survival benefit from the use of ACE inhibitors, beta-blockers, and aldosterone antagonists; such effects were associated with so-called reverse remodeling, in which the therapy promoted a return to a better left ventricular size and shape [4–7]. However, significant heterogeneity exists in the benefits to individual subjects. Great attention has therefore been devoted to the genetic makeup of the renin-angiotensin-aldosterone system (RAAS) and the beta-adrenergic system: understanding the functional role of these variants is a main aim of current research. One of the most comprehensively studied polymorphisms is ACE I/D, which is localized in the ACE gene. The DD genotype is implicated in numerous pathological conditions considered to be key risk factors for heart failure [8, 9]. Similarly, polymorphisms of β adrenergic receptors have been regarded as implicated in the variation of cardiac response to sympathetic drive. The aim of the present study was to assess whether the genetic background of the individual patient might predict changes

in left ventricular systolic function and volumes within a population of stable CHF outpatients under optimal medical treatment.

2. Methods

2.1. Study Population. A series of 148 consecutive outpatients with CHF was recruited from the Heart Failure Clinic of the Cardiology Department at Verona City Hospital. The local ethics committee approved the protocol and each patient gave written informed consent before participation in the study. The criteria for enrollment were a diagnosis of dilated cardiomyopathy of diverse etiology with a left ventricular ejection fraction <45%, stable clinical conditions, and optimal medical treatment at the maximally tolerated dosages according to the most recent CHF international guidelines for at least six months. All subject were followed up prospectively for one year and underwent two complete echocardiographic evaluations, at the beginning and at the end of followup.

2.2. Genotyping. A 2 mL blood sample was collected in an EDTA-containing tube and was kept at −80°C until the deoxyribonucleic acid (DNA) was isolated. We identified the following polymorphisms: ACE I/D, β1 adrenergic receptor (AR) Arg389Gly, β2AR Arg16Gly, and β2AR Gln27Glu. The gene polymorphisms studied were amplified using polymerase chain reactions (PCRs) and processed by restriction enzymes when needed. The procedure used to prepare DNA for PCR from whole blood was based on that described by Walsh et al. [10] for forensic material. Putative DD genotypes were further confirmed using the ACE 2 primer, which eliminates mistyping that can occur with a two-primer system. The PCR results were scored by two independent investigators unaware of patient identity. PCRs were run for 35 cycles: 30 seconds at 94°, 45 seconds at 56°, and 2 minutes at 72°. The product was subjected to electrophoresis in a 1.5% agarose gel and stained with ethidium bromide.

2.3. Statistical Analysis. Data were expressed by mean ± standard deviation (SD) for continuous variables or by number and percentage for categorical variables. Intergroup comparisons of % changes in left ventricular ejection fraction and volumes (% difference between end and beginning of followup: ΔLVEF, ΔLVEDV, ΔLVESV) were made using Student's *t*-test for unpaired data. Univariate and multivariate logistic regression analyses were used to determine the relationship between clinical and genetic variables and ΔLVEF, ΔLVEDV, and ΔLVESV. Commercially available statistical software was used (Statview 5.0, Abacus Concepts Inc; SAS 6.12, SAS Institute, Cary, North Carolina). A P value < .05 was considered statistically significant.

3. Results

3.1. Clinical Characteristics of the Study Population. During the observation period, six patients died, and one patient was lost to followup, while ten patients underwent implantation of a biventricular pacemaker, and were therefore excluded from further analyses because of the well-known resynchronization therapy effects on left ventricular remodeling and systolic function; 131 patients completed the study. The clinical baseline characteristics of study population are summarized in Table 1. Most patients were men, aged 63.2 ± 9 years old, and with a CHF of mainly ischemic (60.7%) or idiopathic origin (34.9%). At baseline mean left ventricular ejection fraction (LVEF) was 33 ± 7%, mean left ventricular end-diastolic volume (LVEDV) 266 ± 98 mL, and mean left ventricular end-systolic volume (LVESV) 181 ± 86 mL. No statistically significant differences in baseline characteristics were detected among the genotype subgroups.

Table 1: Baseline characteristics of study population.

Variable	
Age (yrs)	63.2 ± 9
Male gender *n* (%)	107 (82)
NYHA functional class	2.2 ± 0.7
SBP (mm Hg)	127 ± 15
DBP (mm Hg)	79 ± 8
Heart Rate (beats/min)	67 ± 11
S-Na^+ (mEq/L)	139 ± 3
S-Creatinine (μmol/L)	105 ± 25
Hb (g/dL)	13.9 ± 1.3
Treatment *n* (%)	
Diuretics	117 (90)
ACE inhibitors/ARBs	127 (97)
Beta blockers	110 (84)
Spironolactone	31 (24)
Statins	90 (69)
Echocardiography	
LVEF (%)	33 ± 7
LVEDV (mL)	266 ± 98
LVESV (mL)	181 ± 86
Genotypes, *n*	
ACE II/ ID, DD	20/111
β1 AR389 ≥1 Arg/GlyGly	31/100
β2 16 GlyGly/ ≥ 1 Arg	57/74
β2 27 GlnGln/ ≥ 1 Glu	51/80

Data are expressed as mean ± SD or number (%). Abbreviations: NYHA: New York Heart Association; SBP: systolic blood pressure; DBP: diastolic blood pressure; Hb: hemoglobin; ARBs: angiotensin II receptor blockers; LVEF: left ventricular ejection fraction; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume.

3.2. Echocardiography. At one-year followup mean LVEF was 36 ± 9%; 8% of patients completely recovered their systolic function with an improvement of LVEF to a value >50%. We found that 45% of patients had a reduction of LVEDV > 10%, while only 21% increased their LVEDV >10%. A reduction of LVESV > 10% was found in 47% of subjects, whereas 25% of patients worsened, showing an increase in volume > 10%.

Association between Genetic Polymorphisms and Changes in LV Function and Volumes.. The relations between genetic

Table 2: Changes in echocardiographic parameters according to ACE and βAR genotypes.

		ΔLVEF	ΔLVEDV	ΔLVESV
ACE	II versus ID, DD	7/3	−16/0*	−19/0*
β1AR389	≥1Arg versus GlyGly	7/−7*	16/−3*	24/−6†
β2AR16	GlyGly versus ≥1Arg	0/6	−2/−3	−1/−5
β2AR27	GlnGln versus ≥1Glu	3/0	−3/−3	−4/−3

ΔLVEF (left ventricular ejection fraction), ΔLVEDV (left ventricular end diastolic volume), and ΔLVESV (left ventricular end systolic volume) are calculated as the percentage difference between followup and baseline left ventricular ejection fraction and volumes, respectively. Comparisons were made using the Student's t-test for unpaired data. *$P < .05$; †$P < .01$.

Table 3: Clinical predictors of ΔLVEF at one year follow-up (multivariate analysis).

Variable	P-value
Age (yrs)	.07
Nonischemic etiology	.006
NYHA functional class	.04
Diuretic dose (mg)	NS
S-Creatinine (μmol/L)	NS
Baseline LVEF (%)	<.0001

Abbreviations as in Table 1.

polymorphisms and variations in LVEF, LVEDV, and LVESV are described in Table 2. The ACE II genotype had a reduction of LVEDV and LVESV of 16% and 19%, respectively, while in ID/DD group there was no significant variation in left ventricular volumes over followup ($P < .05$ for both comparisons). β1AR389 GlyGly genotype was related to an improvement in LVEF of 7%, while the β1AR389 ≥ 1Arg group showed a decrease of 7% (intergroup comparison $P < .05$). Moreover, β1AR389 ≥1Arg was associated with a worsening of ventricular volumes with an LVEDV increase of 16% and an LVESV increase of 24%, whereas the β1AR389 GlyGly group showed a slight improvement of both LVEDV and LVESV ($P < .05$ and $P < .01$, resp., for intergroup comparisons). Genotypes of the β2AR 16 and β2AR 27 showed no significant changes in left ventricular systolic function or volumes over time.

3.3. Clinical Predictors of Remodeling. At the univariate analysis, significant predictors of improving LVEF were age ($P = .018$, $r = -0.13$), NYHA class ($P = .01$, $r = -0.15$), serum creatinine ($P = .01$, $r = -0.14$), diuretic dose ($P = .03$, $r = -0.12$), baseline LVEF ($P = .001$, $r = -0.22$), and nonischemic etiology ($P = .0003$). At the multivariate analysis, independent clinical predictors of improvement in systolic function were lower NHYA class, lower baseline LVEF, and nonischemic etiology (Table 3). Significant clinical predictors of changes in left ventricular volumes were systolic blood pressure, baseline LVEDV, and baseline LVESV, while at the multivariate analysis independent predictors of ΔLVEDV were only higher values of baseline LVEDV ($P = .0006$) and baseline LVESV ($P = .004$); systolic blood pressure was the only independent predictor of ΔLVESV ($P = .04$).

3.4. Genetic Predictors of Remodeling. ACE I/D was significantly correlated with ΔLVEDV and ΔLVESV, while we did not observe any association with ΔLVEF (Table 4). At the multivariate analyses it was significantly and independently related to both ΔLVEDV ($P = .03$) and ΔLVESV ($P = .028$), even after adjustment for baseline left ventricular volumes and systolic blood pressure. β1AR 389 was associated with both ΔLVEF and ΔLVESV, but not with ΔLVEDV. At the multivariate analyses it proved a significant predictor for both ΔLVEF ($P = .03$) and ΔLVESV ($P = .02$), even after adjustment for etiology, NYHA class, baseline values of LVEF, and LVESV and systolic blood pressure ($P < .05$ for both). β2AR 16 was only a borderline predictor of ΔLVEF at the univariate analysis, but lost its power at the multivariate analysis, while β2AR 27 was not associated with reverse remodeling or improvement in systolic function (Table 4).

4. Discussion

In the present study we analyzed the impact of genetic polymorphisms of the β adrenergic system and RAAS on ventricular remodeling and systolic function in a population of 131 CHF outpatients who had already been on optimal treatment for this condition for at least six months. Interestingly, at one year followup, we observed a significant improvement in left ventricular volumes and systolic function in about half and one fourth of patients, respectively. Importantly, along with clinical predictors of reverse remodeling and systolic function recovery such as baseline conditions and CHF etiology, we found that ACE I/D and β1AR 389 polymorphisms were independent predictors of functional and/or volumetric improvement, suggesting an important genetic background to disease progression and response to therapy. Because the benefits in terms of remodeling of beta blockers and ACE inhibitors are already evident after only three months of treatment [11, 12], to find an improvement after one year in subjects who had already been on optimal treatment for at least six months is a very remarkable result.

4.1. ACE Polymorphism. The ACE gene I/D polymorphism is one of the most comprehensively studied genetic variants in the field of cardiovascular disease. This polymorphism consists of the insertion (I) or deletion (D) of a 287-bp DNA fragment in intron 16 of the ACE gene. Serum and cardiac tissue levels of ACE and angiotensin II are related to ACE I/D polymorphism, with lower activation of RAAS in II subjects [13–15]. Previous studies report increased prevalence of DD genotype in CHF patients as compared with controls [16] and the same genotype is associated with increased mortality in patients with CHF [17]. In the present study we found that ACE gene polymorphism is a good predictor of left ventricular remodeling, being significantly, and independently related to both ΔLVEDV and ΔLVESV, even after adjustment for baseline values of volumes. The II genotype was significantly correlated

Table 4: Genetic predictors of echocardiographic changes at one year followup (univariate and multivariate analyses, see text for details).

Genotypes	Univariate analysis P-value			Multivariate analysis P-value		
	ΔLVEF	ΔLVEDV	ΔLVESV	ΔLVEF	ΔLVEDV	ΔLVESV
ACE II versus. ID/DD	NS	NS	.003	—	.03	.028
β1AR389 ≥ 1Arg versus GlyGly	.02	.02	NS	.03	NS	.02
β 2AR16 GlyGly versus ≥ 1Arg	.05	.05	NS	NS	NS	NS
β 2AR27 GlnGln versus ≥ 1Glu	NS	NS	NS	NS	NS	NS

Abbreviations as in Table 1.

with an improvement in left ventricular volumes, with a reduction of both LVEDV and LVESV. This observation is in accordance with previous studies from our group showing a genotype-dependent response to ACE-inhibitors and spironolactone in CHF patients [18, 19]. Nevertheless, even in the most unfavourable genetic conditions there is an important effect on disease progression of inhibition with maximal pharmacological therapy for CHF, as shown by the stability of left ventricular volumes in the majority of patients. Previous studies investigating the association between the ACE genotype and cardiac function in CHF patients assessed the negative impact of the DD group. McNamara et al. [20] evaluated the interaction between ACE inhibitor therapy and the effect of the ACE genotype on survival, finding that higher doses of ACE inhibitors diminished the impact of the ACE D allele. Our results further suggest the presence of a pathophysiological pathway from the ACE gene to increased levels of ACE and variations in cardiac function, supporting the hypothesis that ACE genotype modulates the progression and response to therapy in CHF.

4.2. β1AR 389 Polymorphism. The β1AR is the predominant β-adrenergic receptor expressed on the cardiomyocyte and is responsive to circulating epinephrine and to local norepinephrine derived from cardiac sympathetic nerves [21]. Two common polymorphisms of β1AR in the human population lead to either a glycine (β1AR Gly389) or an arginine (β1AR Arg389) at amino acid position 389, where the latter variation is characterized by increased function. The β1AR Arg389 polymorphism has been therefore considered a possible risk factor for heart failure, since it results in an increase of approximately 200% in agonist-stimulated activity in transfected cells as compared with the β1AR Gly389 receptor [22]. Its synergic effect with other polymorphisms has been estimated to represent some degree of increased risk of CHF, whereas the β1AR Arg389 genotype alone was not associated with heart failure [23]. In the present study we found that β1AR Arg389 genotype is an independent predictor of worsening systolic function and LVESV, while the β1AR Gly389 genotype was not associated with substantial changes.

Previous studies investigating the potential relationship between genotype and response to beta-blockers have reported contrasting results. Some have found no effect of beta adrenergic system polymorphisms on survival in CHF patients treated with beta blockers [24, 25]. Chen et al. [26] found that after treatment with carvedilol, patients with Arg/Arg genotype had a significantly greater improvement in LVEF compared to Gly389 carriers, whereas there were no differences attributable to other β1 and β2 adrenergic receptor polymorphisms. Taken together, these observations suggest that the β1AR Arg389 genotype could play a key role in promoting remodeling of the left ventricle, even in conditions of maximal medical therapy, and could identify patients at particularly high risk. Nevertheless, it should be said that this genotype characterises a minority of CHF patients, probably too few to allow extensive evaluation of the effect of the polymorphism on progression of CHF.

4.3. β2 Polymorphism. β2 receptors are also implicated in adrenergic signalling, even though norepinephrine released from sympathetic nerves shows a much lower affinity to these receptors than to β1. Our results revealed how β2AR Gly16 genotype is a borderline predictor for variation in LVEF (P = .05), while β2AR27 polymorphism is not significantly related to either systolic function or volumetric variation.

It is important to emphasize that in a highly progressive disease like CHF, most patients on standard treatment for this condition remained stable or even underwent a functional and volumetric improvement. Moreover, a significant percentage of patients had a complete recovery of systolic function. Many studies have already explored genotypes of RAAS and the adrenergic system as possible risk factors for CHF. In this research we rather analyzed how genetic background is related to progression of CHF, and found that functional and volumetric improvements were at least in part and independently related to genetic polymorphisms of neurohormonal systems. Understanding the mechanisms underlying the pharmacogenetic interaction between polymorphisms and treatment could predict which patients will respond best to beta-blockers and ACE inhibitors. Gene variation analyses will probably never completely prefigure drug responsiveness in a complex condition like CHF, but hopefully in the future they could help to select patients for treatment in a more specific way, evaluating ethnic and interindividual differences.

Our study has some limitations. The main one is the modest number of subjects in a few genotype groups. Because of the different frequencies of alleles in the population, several polymorphisms are difficult to recruit for investigation. To measure the impact of genetic variation in a multifactorial disease in which heterogeneous mechanisms and numerous interactions are implicated, larger trials are certainly needed. Moreover, analysis of the duration of the disease will be necessary, since the progression of CHF

and response to therapy are modulated by the grade of hypertrophy and interstitial fibrosis [27–29].

In conclusion, our results indicate that stable and maximally treated patients with CHF can improve their left ventricular systolic function and volumes according to specific baseline clinical and genetic variables. Some genetic variations may be more important in the progression of CHF than in its predisposition. Therefore, genetic polymorphisms could indeed be at least in part responsible for interindividual variation in progression of the disease as well as in response to therapy; whether genotyping may help to target therapy and improve clinical management of CHF patients can only be confirmed by large, randomized trials.

Financial Support

The authors received financial support from university of Verona.

Conflict of Interests

The authors declare that there is no conflict of interests to report.

References

[1] S. A. Hunt, W. T. Abraham, M. H. Chin et al., "2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the Aamerican College of Cardiology Foundation/American Heart Association Task Force on practice guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation," *Circulation*, vol. 119, no. 14, pp. e391–e479, 2009.

[2] D. Lloyd-Jones, R. J. Adams, T. M. Brown et al., "Executive summary: heart disease and stroke statistics—2010 update: a report from the american heart association," *Circulation*, vol. 121, no. 7, pp. e46–e215, 2010.

[3] M. M. Givertz, "Underlying causes and survival in patients with heart failure," *New England Journal of Medicine*, vol. 342, no. 15, pp. 1120–1122, 2000.

[4] J. N. Cohn, "Structural basis for heart failure: ventricular remodeling and its pharmacological inhibition," *Circulation*, vol. 91, no. 10, pp. 2504–2507, 1995.

[5] M. A. Pfeffer, E. Braunwald, L. A. Moye et al., "Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction—results of the survival and ventricular enlargement trial," *New England Journal of Medicine*, vol. 327, no. 10, pp. 669–677, 1992.

[6] S. A. Hall, C. G. Cigarroa, L. Marcoux, R. C. Risser, P. A. Grayburn, and E. J. Eichhorn, "Time course of improvement in left ventricular function, mass and geometry in patients with congestive heart failure treated with beta-adrenergic blockade," *Journal of the American College of Cardiology*, vol. 25, no. 5, pp. 1154–1161, 1995.

[7] M. Cicoira, L. Zanolla, A. Rossi et al., "Long-term, dose-dependent effects of spironolactone on left ventricular function and exercise tolerance in patients with chronic heart failure," *Journal of the American College of Cardiology*, vol. 40, no. 2, pp. 304–310, 2002.

[8] A. Pfeufer, K. J. Osterziel, H. Urata et al., "Angiotensin-converting enzyme and heart chymase gene polymorphisms in hypertrophic cardiomyopathy," *American Journal of Cardiology*, vol. 78, no. 3, pp. 362–364, 1996.

[9] J. Higaki, S. Baba, T. Katsuya et al., "Deletion allele of angiotensin-converting enzyme gene increases risk of essential hypertension in Japanese men: the Suita study," *Circulation*, vol. 101, no. 17, pp. 2060–2065, 2000.

[10] P. S. Walsh, D. A. Metzger, and R. Higuchi, "Chelex 100 as a medium for simple extraction of DNA for PCR-based typing from forensic material," *BioTechniques*, vol. 10, no. 4, pp. 506–513, 1991.

[11] W. J. Remme, G. Riegger, P. Hildebrandt et al., "The benefits of early combination treatment of carvedilol and an ACE-inhibitor in mild heart failure and left ventricular systolic dysfunction. The carvedilol and ACE-inhibitor remodelling mild heart failure evaluation trial (CARMEN)," *Cardiovascular Drugs and Therapy*, vol. 18, no. 1, pp. 57–66, 2004.

[12] R. S. Khattar, R. Senior, P. Soman, R. van der Does, and A. Lahiri, "Regression of left ventricular remodeling in chronic heart failure: comparative and combined effects of captopril and carvedilol," *American Heart Journal*, vol. 142, no. 4, pp. 704–713, 2001.

[13] L. Tiret, B. Rigat, S. Visvikis et al., "Evidence, from combined segregation and linkage analysis, that a variant of the angiotensin I-converting enzyme (ACE) gene controls plasma ACE levels," *American Journal of Human Genetics*, vol. 51, no. 1, pp. 197–205, 1992.

[14] A. H. J. Danser, F. H. M. Derkx, H. W. Hense, X. Jeunemaître, G. A. J. Riegger, and H. Schunkert, "Angiotensinogen (M235T) and angiotensin-converting enzyme (I/D) polymorphisms in association with plasma renin and prorenin levels," *Journal of Hypertension*, vol. 16, no. 12, pp. 1879–1883, 1998.

[15] B. R. Winkelmann, M. Nauck, B. Klein et al., "Deletion polymorphism of the angiotensin I-converting enzyme gene is associated with increased plasma angiotensin-converting enzyme activity but not with increased risk for myocardial infarction and coronary artery disease," *Annals of Internal Medicine*, vol. 125, no. 1, pp. 19–25, 1996.

[16] M. V. Raynolds, M. R. Bristow, E. W. Bush et al., "Angiotensin-converting enzyme DD genotype in patients with ischaemic or idiopathic dilated cardiomyopathy," *Lancet*, vol. 342, no. 8879, pp. 1073–1075, 1993.

[17] B. Andersson and C. Sylvén, "The DD genotype of the angiotensin-converting enzyme gene is associated with increased mortality in idiopathic heart failure," *Journal of the American College of Cardiology*, vol. 28, no. 1, pp. 162–167, 1996.

[18] M. Cicoira, L. Zanolla, A. Rossi et al., "Failure of aldosterone suppression despite angiotensin-converting enzyme (ACE) inhibitor administration in chronic heart failure is associated with ACE DD genotype," *Journal of the American College of Cardiology*, vol. 37, no. 7, pp. 1808–1812, 2001.

[19] M. Cicoira, A. Rossi, S. Bonapace et al., "Effects of ACE gene insertion/deletion polymorphism on response to spironolactone in patients with chronic heart failure," *American Journal of Medicine*, vol. 116, no. 10, pp. 657–661, 2004.

[20] D. M. McNamara, R. Holubkov, L. Postava et al., "Pharmacogenetic interactions between angiotensin-converting enzyme inhibitor therapy and the angiotensin-converting enzyme deletion polymorphism in patients with congestive heart failure," *Journal of the American College of Cardiology*, vol. 44, no. 10, pp. 2019–2026, 2004.

[21] M. R. Bristow, "Why does the myocardium fail? Insights from basic science," *Lancet*, vol. 352, no. 1, pp. 8–14, 1998.

[22] D. A. Mason, J. D. Moore, S. A. Green, and S. B. Liggett, "A gain-of-function polymorphism in a G-protein coupling domain of the human β1-adrenergic receptor," *Journal of Biological Chemistry*, vol. 274, no. 18, pp. 12670–12674, 1999.

[23] K. M. Small, L. E. Wagoner, A. M. Levin, S. L. R. Kardia, and S. B. Liggett, "Synergistic polymorphisms of β- and α-adrenergic receptors and the risk of congestive heart failure," *New England Journal of Medicine*, vol. 347, no. 15, pp. 1135–1142, 2002.

[24] H. L. White, R. A. de Boer, A. Maqbool et al., "An evaluation of the beta-1 adrenergic receptor Arg389Gly polymorphism in individuals with heart failure: a MERIT-HF sub-study," *European Journal of Heart Failure*, vol. 5, no. 4, pp. 463–468, 2003.

[25] A. J. Sehnert, S. E. Daniels, M. Elashoff et al., "Lack of association between adrenergic receptor genotypes and survival in heart failure patients treated with carvedilol or metoprolol," *Journal of the American College of Cardiology*, vol. 52, no. 8, pp. 644–651, 2008.

[26] L. Chen, D. Meyers, G. Javorsky et al., "Arg389Gly-β1-adrenergic receptors determine improvement in left ventricular systolic function in nonischemic cardiomyopathy patients with heart failure after chronic treatment with carvedilol," *Pharmacogenetics and Genomics*, vol. 17, no. 11, pp. 941–949, 2007.

[27] J. N. Cohn, R. Ferrari, and N. Sharpe, "Cardiac remodeling-concepts and clinical implications: a consensus paper from an International Forum on Cardiac Remodeling," *Journal of the American College of Cardiology*, vol. 35, no. 3, pp. 569–582, 2000.

[28] B. H. Greenberg, "Effects of angiotensin converting enzyme inhibitors on remodeling in clinical trials," *Journal of Cardiac Failure*, vol. 8, no. 6, pp. S486–S490, 2002.

[29] P. W. Armstrong, "Left ventricular dysfunction: causes, natural history, and hopes for reversal," *Heart*, vol. 84, supplement 1, pp. i15–i17, 2000.

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Cardiology Research and Practice
Volume 2011, Article ID 806795, 7 pages
doi:10.4061/2011/806795

Review Article

Development of Bioartificial Myocardium Using Stem Cells and Nanobiotechnology Templates

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Received 4 October 2010; Accepted 16 November 2010

Academic Editor: Javed Butler

Cell-based regenerative therapy is undergoing experimental and clinical trials in cardiology, in order to limit the consequences of decreased contractile function and compliance of damaged ventricles following myocardial infarction. Over 1000 patients have been treated worldwide with cell-based procedures for myocardial regeneration. Cellular cardiomyoplasty seems to reduce the size and fibrosis of infarct scars, limit adverse postischemic remodelling, and improve diastolic function. The development of a bioartificial myocardium is a new challenge; in this approach, tissue-engineered procedures are associated with cell therapy. Organ decellularization for bioscaffolds fabrication is a new investigated concept. Nanomaterials are emerging as the main candidates to ensure the achievement of a proper instructive cellular niche with good drug release/administration properties. Investigating the electrophysiological properties of bioartificial myocardium is the challenging objective of future research, associating a multielectrode network to provide electrical stimulation could improve the coupling of grafted cells and scaffolds with host cardiomyocytes. In summary, until now stem cell transplantation has not achieved clear hemodynamic benefits for myocardial diseases. Supported by relevant scientific background, the development of myocardial tissue engineering may constitute a new avenue and hope for the treatment of myocardial diseases.

1. Introduction

Ischemic myocardial disease, the main cause of heart failure, is a major public health and economic problem. Given the aging population, heart failure is becoming a bigger clinical issue and bigger financial burden [1, 2]. Thus, research in heart failure is of relevant interest and importance, involving specialities as cellular and molecular biology, tissue engineering, genetics, biophysics, and electrophysiology.

2. Cellular Cardiomyoplasty

The recent progress in cellular and molecular biology allows the development of new therapies for heart failure. One of the most innovative consists in the transplantation of stem cells into the myocardium for heart muscle regeneration. This approach is called "cellular cardiomyoplasty" [3, 4]. Adult myocardium cannot effectively repair after infarction due to the limited number of stem cells. Thus, most of the injury is irreversible [5]. For this reason, cell transplantation strategies for heart failure have been designed to replace damaged cells with cells that can induce angiogenesis in order to recover hibernating and stunned myocardium or to grow new fibers creating contractile tissue that will perform cardiac work, either in ischemic or nonischemic cardiomyopathies.

Grafting of healthy cells into the diseased myocardium holds enormous potential as an approach to cardiovascular pathology. The functional goal of cell transplantation is to contribute to improve systolic and diastolic ventricular functions and to reverse the postischemic remodeling process responsible for ventricular chambers dilatation [5].

The encouraging results of experimental studies [6–10] have opened the way to the clinical application of cellular cardiomyoplasty in patients with akinetic and nonviable postinfarction scar and low ejection fraction and in patients

presenting idiopathic and chagasic cardiomyopathies [11–14]. Cultured autologous cells do not raise immunological, ethical, tumorogenesis, or donor availability problems. Thus, the development of cell therapy for heart failure is progressing according to a rigorous scientific methodology, from observation to experimentation to a careful evaluation of preliminary clinical results.

Current possibilities in cell therapy for myocardial regeneration are the transplantation into the damaged myocardium of different types of stem cells as autologous myoblasts (originating from a skeletal muscle biopsy) [15], bone marrow stem cells [16], peripheral blood stem cells [17], vascular endothelial cells [18], mesothelial cells (removed from a biopsy of the omentum) [19], adipose tissue stem cells [20], umbilical cord cells, induced pluripotent stem cells (iPSCs), and embryonic pluripotent cells [21]. There is a tendency to use bone marrow cells for myocardial regeneration since this approach avoids the 3-week cell-culture procedure and the risk of ventricular arrhythmias and sudden death observed after skeletal myoblast transplantation.

Tissue engineering using biological and synthetic matrix is now associated with cell therapy, the goal is to develop a bioartificial myocardium [22–27]. The MAGNUM Clinical Trial (Myocardial Assistance by Grafting a New Upgraded bioartificial Myocardium) is under development by our group [28].

3. Indications

3.1. Ischemic Cardiomyopathy. Clinical application for cell transplantation should be in patients presenting a cardiac dysfunction due to left or right ventricular myocardial infarction. The cells are generally implanted during catheter-based or surgical revascularization procedures. The objective of cellular cardiomyoplasty (CMP) is to limit infarct expansion and cardiac remodelling and regenerate the myocardium. Patients with ischemic mitral valve regurgitation can also be treated with stem cells [4, 29].

3.2. Nonischemic Cardiomyopathies. Non ischemic dilated cardiomyopathies and Chagas disease are also major causes of heart failure, with high mortality rates [2, 13]. Cell transplantation could offer new hopes in this disease by restoring impaired heart function, since the grafted cells appear to better survive in the host myocardium because myocardial irrigation in these pathologies is not severely impaired. Stem cells are injected after catheterization of the coronary arteries. New indications include diabetic and pediatric cardiomyopathies.

4. Mechanisms of Action

The many proposed mechanisms of action of cellular cardiomyoplasty are reduction of the size and fibrosis of infarct scars, limitation of adverse postischemic ventricular remodeling, improvement of ventricular wall thickening and compliance, and increase of regional myocardial contractility. Bone marrow cells principally induce angiogenesis and vasculogenesis. Mesenchymal bone marrow cells and induced pluripotent stem cells (iPSCs) are of great interest, since these cells can differentiate in cardiac cells [30].

The initial clinical trials of cell transplantation after a myocardial infarction have reported only limited improvements in ventricular function. Ongoing studies showed survival of the implanted cells, but no study showed active participation of the implanted cells in the force generation. This may be due to the lack of electrophysiological connections between the implanted cells and the host myocardium and lack of the gap junction protein (connexin 43).

In summary, the mechanisms of action of cell therapy seem to be

(i) reduction of the size and fibrosis of infarct scars,

(ii) improvement of myocardial viability,

(iii) limitation of global ventricular dilatation (positive remodelling),

(iv) improvement of ventricular wall compliance and diastolic function,

(v) paracrine effects (antiapoptotic and angiogenic).

5. Cell Delivery

The technical approach used to implant the cells should influence the efficacy of cellular CMP. Cell mortality after transplantation seems to be important when they are grafted in the center of high-fibrotic ischemic scars, since there are limitations of oxygen and nutrients supply to the chronic ischemic myocardium. Implanting the cells mainly in the peri-infarct areas may improve the rate of surviving cells, thus the size of the infarct scar may undergo a centripetal reduction [4].

Periodically repeated cell injections should be necessary to progressively reduce the infarct scars in ischemic cardiomyopathies [31] or to gradually improve the diseased myocardium in nonischemic cardiomyopathies. This approach should be boosted by the development of a new generation of specific catheters for percutaneous cell implantations [14].

Intracoronary and endoventricular catheter-based cell delivery procedures for therapeutic angiogenesis and myogenesis have been performed. Nevertheless, the quantity of the cells injected in the target infarcted area is unknown, despite the use of myocardial mapping to identify the pathologic myocardium. The success is largely dependent on many technical considerations namely the risk of cell ≪regurgitation≫ at the injection site and the precise localization of the postischemic scar and the peri-infarct areas [14].

A new diagnostic-therapeutic device for local myocardial treatment has been created by our group, called "CELL-FIX" catheter [32]. This system includes a method and apparatus to identify by electrophysiology the infarcted area and to simultaneously deliver the cells, stabilizing by vacuum the scar at the moment of the cell injection with the needle. In

fact, the Cell-Fix catheter includes a fixing "sucker" system to the endocardium, in the form of a suction cup; this "umbrella" is retracted inside the exterior tube of the distal part of the catheter during the introduction and progression of the device into the arteries. Importantly, during cell delivery the umbrella avoids the risk of ventricular wall perforation by the catheter at the level of the myocardial infarction. This complication was already observed in clinical cases treated with current available catheters.

Experimental studies using the Cell-Fix catheter have demonstrated a minimal loss of the injected material in beating hearts treated after myocardial infarction [32].

6. Hypoxic Preconditioning of Stem Cells

Hypoxic preconditioning of stem cells before transplantation into the infarcted heart seems to be useful to promote cell survival and to increase their therapeutic potential. Cell cultures can be performed under low oxygen conditions; flasks can be transferred to a hypoxic incubators (e.g., Xvivo; Biospherix, Lacona, NY), allowing for uninterrupted cell culture and passaging in a controlled atmosphere of 5% O_2 and 5% CO_2 balanced with nitrogen [33]. Under hypoxic conditions, the cells grow faster, thus hypoxia seems to give an initial boost followed by regular stimuli for growth.

Animal studies demonstrated that hypoxic preconditioning enhances the capacity of mesenchymal stem cells to repair infarcted myocardium, attributable to reduced cell death and apoptosis of implanted cells, increased angiogenesis/vascularization, and paracrine effects [34]. In summary, cell preconditioning using reduced oxygen tension to expand cells in the cultures is of relevant interest for the treatment of ischemic heart disease, since these cells could survive better after transplantation in the ischemic myocardium.

7. Development of Bioartificial Myocardium

The objective of cellular cardiomyoplasty is to regenerate the myocardium by the implantation of living cells. However, in ischemic disease, the extracellular matrix is also pathologically modified. Therefore, it could be important to associate a procedure aiming at regenerating both myocardial cells and the extracellular matrix. We are currently working to evaluate the potential of a biodegradable tridimensional matrix seeded with cells and grafted onto the infarcted ventricle [22].

Shortly after myocardial infarction, inflammatory cells such as neutrophils, monocytes, and macrophages infiltrate the infarcted zone, and then the necrotic myocytes in the injured myocardium are replaced by collagen fibers. This process uniformly occurs in the whole infarcted area and determines the degree of early infarct expansion. Prevention of the dilation, secondary to LV remodelling, can increase cardiac performance [5].

There are two types of collagen fibers in the normal adult heart, types I and III, produced by fibroblasts and myofibroblasts. The fiber type I represents 80% of collagen protein in the heart, and type III is near to 10%. These fibers provide structural support and give the heart properties that include stiffness and resistance to deformation; they have also shown an important role as a link between contractile elements of adjacent myocytes, carrying some information useful for cell function. In the infarcted zone, the extracellular myocardial matrix is modified; collagen type I decreases from 80% to 40%. Experimental and clinical studies performed by our group in ischemic patients showed that bone marrow cell therapy associated with the surgical implantation onto the epicardium of a cell-seeded collagen type I matrix prevented myocardial wall thinning and limited postischemic remodelling [22, 28]. In addition, collagen matrix as a delivery vehicle significantly reduced the relocation of transplanted MSCs to remote organs and noninfarcted myocardium [35].

8. Clinical Perspectives

Followup of congestive heart failure patients has mobilized a growing number of research teams over the past years. Medical treatment particularly with ACE inhibitors combined to beta and aldosterona blockers, heart rate reduction using drugs like Ivabradine [36], and electrophysiological procedures like multisite pacing for atrial-biventricular resynchronization and implantable defibrillators have proven to be effective, improving the prognosis of heart failure patient. However, these treatments remain palliative in many patients, and a lot of cardiovascular diseases still evolve towards the deficiency of the cardiac muscle [1].

Cardiac transplantation remains the only curative treatment of congestive heart failure but has remained limited in its application secondary to shortage of donated organs, age of recipients, and other strict selection criteria. Surgical alternatives for refractory heart failure such as left ventricular geometry/remodeling interventions and dynamic cardiomyoplasty also remain limited in their applicability as well [3, 37]. Cardiomyoplasty, in which the latissimus dorsi muscle is used to create an LV wrap, has been proposed by our group at the earliest 80s, but nowadays it remains dedicated to patients with right ventricular dysfunction and relatively preserved LV function [38].

Implantable cardiac assist devices are still in evolution. While mechanical support continues to improve, intrinsic disadvantages remain, such as thromboembolism, the need for careful anticoagulation, infection, lack of physiological response, durability, and power supply [39]. Xenotransplantation is in the early phase of research with no clinical applications as of yet.

Historically, tissue regeneration techniques based in cell transplantation technology had been used for the treatment of hemopathies (chronic lymphocytic leukemia, aplastic anaemia, immunodeficiencies, and myeloma), in ophthalmology (transplantation of limbal stem cells for corneal regeneration), and in orthopedics (implantation of chondrocytes for articular defects). Current clinical investigations concern the following specialities: endocrinology (transplantation of stem cells in diabetes mellitus), neurology (Alzheimer and Parkinson diseases), hepatology

(implantation of hepatocytes as a bridge to liver transplantation), myology (transplantation of myoblasts in Duchenne dystrophy), dermatology (implantation of cultured keratinocytes and fibroblasts in burned patients), and peripheral vascular diseases (implantation of angiogenic stem cells in critical limb ischemia). Transplanted neurally induced embryonic stem cells can differentiate into myelin-forming cells and provide a potential therapy for severely injured peripheral nerves and spinal cord traumatic injury [40].

Engineered organs are in development. Regenerative medicine uses combinations of cells and/or biomaterials to encourage regeneration of healthy tissue and offers an alternative approach for the replacement of lost or deficient organs. Promising results have already been obtained in urology, in children with neurogenic bladder caused by myelomeningocele. Human clinical trials are ongoing in both children and adults to further evaluate the safety and efficacy of this technology for regenerating bladders [41].

The prevalence of severe heart failure and the clear clinical limitations of conventional interventions have encouraged the development of new methods based on the regeneration of the pool of myocardial contractile cells. This approach is supported by recent advances in cellular and molecular biology. New technologies for cell implantation, derived from interventional cardiology procedures, are emerging. Intracoronary and endoventricular catheter-based cell delivery for therapeutic angiogenesis and myogenesis have been performed [14, 16, 17].

Cell transplantation is becoming recognized as a viable strategy to improve myocardial viability and limit infarct growth. The major challenges for future research programs are the preconditioning for predifferentiation of stem cells before transplantation the optimization of the rate of surviving cells after myocardial implantation associating angiogenic therapy (growth factors and/or bone-marrow derived cells) [42, 43] with myogenic cells (skeletal muscle cells and bone marrow mesenchymal stem cells) [44].

The improvement of host-cell interactions (mechanical and electrical coupling) is of great importance and interest. To achieve this goal, we have associated electrostimulation (cardiac resynchronization therapy) with stem cell transplantation in ischemic hearts [45]. The development of a bioartificial myocardium is a new challenge; in this approach, tissue engineered procedures are associated with cell therapy [25, 27]. The preliminary results of the MAGNUM Clinical Trial (Myocardial Assistance by Grafting a New Upgraded bioartificial Myocardium) are encouraging [28] (Figure 1).

9. Organ Decellularization for Bioscaffold Fabrication

The use of synthetic and naturally-derived scaffolds for bioengineering of solid organs has been limited due to a lack of an integrated vascular network. Natural bioscaffolds constitute a new approach for tissue engineering. Fabrications of a bioscaffold system with intact vascular tree are in development in specialities such as hepatology, cardiology, and ophthalmology. Animal-donor organs and tissues have been perfused with decellularization solutions to selectively remove the cellular component of the tissue and leave an intact extracellular matrix and vascular network. The vascular tree demonstrated sequential fluid flow through a central inlet vessel that branched into an extensive capillary bed and coalesced back into a single outlet vessel.

9.1. Hepatology. Human liver cells have been used to engineer miniature livers. These livers successfully function in a laboratory setting like human livers. To engineer the organ, animal livers were treated with a mild detergent to remove all cells; this process is called decellularization, leaving only the collagen "skeleton" or support structure. The original cells are then replaced with two types of cells: immature liver cells known as progenitors and endothelial cells that line blood vessels. The cells were introduced into the liver skeleton through a large vessel that feeds a system of smaller vessels in the liver. This network of vessels remains intact after the decellularization process. The liver is next placed in a bioreactor, a special equipment that provides a constant flow of nutrients and oxygen throughout the organ. After a week in the bioreactor system, it was documented the progressive formation of human liver tissue, as well as liver-associated function. This results in a widespread cell growth inside the bioengineered organ. The engineered organs can be grown from the patients' own cells, so there is no risk of rejection. Bioengineered livers could also be useful for evaluating the safety of new drugs; this approach would more closely mimic drug metabolism in the human liver [46].

9.2. Cardiology. A bioartificial heart is a theoretical alternative to transplantation or mechanical left ventricular support. Generating a bioartificial heart requires engineering of cardiac architecture, appropriate cellular constituents, and pump function. Hearts were decellularized by coronary perfusion with detergents, preserving the underlying extracellular matrix, and producing an acellular, perfusable vascular architecture, competent acellular valves, and intact chamber geometry. To mimic cardiac cell composition, these constructs were reseeded with cardiac or endothelial cells. Constructs were maintained for up to 28 days by coronary perfusion in a bioreactor that simulated cardiac physiology. At day 4, macroscopic contractions were observed. At day 8, under physiological load and electrical stimulation, constructs generated pump function (equivalent to about 2% of adult or 25% of 16-week fetal heart function) in a modified working heart preparation [47].

9.3. Ophthalmology. Corneal transplantation is a common transplant procedure performed to improve visual acuity by replacing the opaque or distorted host tissue by clear healthy donor tissue. However, its clinical utility is limited due to a lack of high-quality donor corneas. Bioengineered neocorneas, created using an expandable population of human donor-derived corneal endothelial cells (HCECs), address this current shortage. Studies were performed to investigate the feasibility of bioengineering corneal tissue constructs by

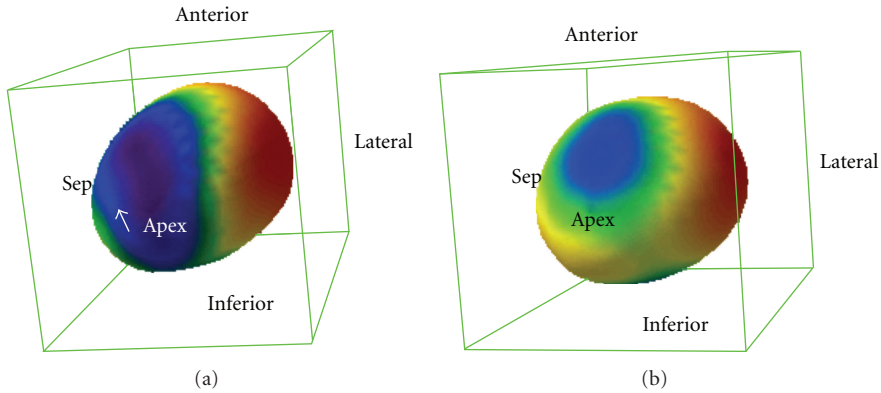

Figure 1: (a) MAGNUM Clinical Trial: Ischemic heart disease patient, 3D representation of the preoperative radioisotopic SPECT Tc^{99m} sestamibi imaging, showing the chronic infarction area (blue stain). (b) Same patient, followup at 18 months showing the improvement of myocardial viability and function (60% of reduction of the infarcted area, in blue) after stem cell therapy associated with the implantation onto the infarct scar of a cell-seeded collagen matrix.

seeding the cells on decellularized human corneal stroma. HCECs were removed from the discarded corneas of eye donors by enzymatic digestion. Donor corneal stromas were cut to 120–200 microm thickness slices using a microtome and then decellularized. To engineer neocorneas, HCECs were seeded on decellularized human corneal stromas. The resulting constructs were placed in growth medium for 14 days. Seeded cells retain expression of the functional markers Na(+)/K(+)-ATPase and zona occludens ZO-1; in addition, constructs demonstrated biomechanical properties similar to those of normal corneas. These results indicate that construction of neocorneas, using HCECs derived from discarded donor corneas and decellularized thin-layer corneal stromas, may create a new source of high-quality corneal tissue for transplantation [48].

In summary, all these studies demonstrate a novel yet simple and scalable method to obtain whole organ-vascularized bioscaffolds with potential for liver, kidney, heart, pancreas, intestine, and other organs' bioengineering. These bioscaffolds can further provide a tool to study cells in their natural three-dimensional environment, which is superior for drug discovery platform compared with cells cultured in two-dimensional petridishes.

10. Bioengineered Cardiac Nanobiomaterials

Until now, the optimal cell-matrix combination for robust and sustained myocardial restoration has not been identified. We are evaluating bioengineered nanobiomaterials with polymer-based elastomeric membranes to obtain a controlled drug release myocardium patch with additional features, such as local cell attraction (proangiogenic activity) and cell differentiation and delivery (precardiomyocytes). Random injections of stem cells into the heart have proven rather insufficient due to poor cell retention and survival. In order to engraft and function more effectively, bioengineered tissues require some degree of early vascularisation. Hence, more evolved tissue constructs must be produced involving more efficient vascularisation strategies.

Our group is developing a bioengineered platform consisting in obtaining preconditioned electrostimulated stem cells to resist their implantation into a highly stressed tissue [49]. Cells are incorporated in this newly designed biodegradable scaffolds that will support cell survival, proper cardiomyogenic differentiation, and early extracellular instruction. This construct should induce vascularisation to ensure rapid tissue remodelling and regeneration into a newly functional myocardium.

Good progress in the design and fabrication of synthetic biomaterials with biomimetic characteristics has been accomplished in the field of nanotechnology for direct applications in biomedicine. The main purpose of these materials is to display structural and functional properties similar to extracellular matrices, containing truly three-dimensional nanonetworks and eventual control in the delivery and effective concentration of "therapeutic drugs" [50–52].

Nanomaterials are emerging as the main candidates to ensure the achievement of a proper instructive cellular niche with good drug release/administration properties. Synthetic nanomaterials are attractive platforms because of their pure composition, predictive toxicology, target specificity, low manufacturing costs, and control in degradability. Proteins, peptides, and polysaccharides are top on the list for their versatility in nanomaterial design and fabrication [53, 54].

Investigating the electrophysiological properties of bioartificial myocardium is the challenging objective of future research. A multielectrode network to provide electrical stimulation could be included in order to improve the coupling of grafted stem cells and scaffolds with host cardiomyocytes, the goal being to improve the local properties of ischemic myocardium. In summary, until now stem cell transplantation has not achieved clear hemodynamic benefits for myocardial diseases [55]. Supported by relevant scientific background, the development of myocardial tissue engineering may constitute a new avenue and hope for the treatment of myocardial diseases [56, 57].

References

[1] M. Jessup and S. Brozena, "Heart failure," *The New England Journal of Medicine*, vol. 348, no. 20, pp. 2007–2018, 2003.

[2] G. S. Bleumink, A. M. Knetsch, M. C. J. M. Sturkenboom et al., "Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure—the Rotterdam Study," *European Heart Journal*, vol. 25, no. 18, pp. 1614–1619, 2004.

[3] J. C. Chachques, A. Shafy, F. Duarte et al., "From dynamic to cellular cardiomyoplasty," *Journal of Cardiac Surgery*, vol. 17, no. 3, pp. 194–200, 2002.

[4] J. C. Chachques, C. Acar, J. Herreros et al., "Cellular cardiomyoplasty: clinical application," *Annals of Thoracic Surgery*, vol. 77, no. 3, pp. 1121–1130, 2004.

[5] M. A. Pfeffer and E. Braunwald, "Ventricular remodeling after myocardial infarction: experimental observations and clinical implications," *Circulation*, vol. 81, no. 4, pp. 1161–1172, 1990.

[6] J. S. Wang, D. Shum-Tim, J. Galipeau, E. Chedrawy, N. Eliopoulos, and R. C. J. Chiu, "Marrow stromal cells for cellular cardiomyoplasty: feasibility and potential clinical advantages," *Journal of Thoracic and Cardiovascular Surgery*, vol. 120, no. 5, pp. 999–1006, 2000.

[7] D. Orlic, J. Kajstura, S. Chimenti et al., "Mobilized bone marrow cells repair the infarcted heart, improving function and survival," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 18, pp. 10344–10349, 2001.

[8] D. A. Taylor, B. Z. Atkins, P. Hungspreugs et al., "Regenerating functional myocardium: improved performance after skeletal myoblast transplantation," *Nature Medicine*, vol. 4, no. 8, pp. 929–933, 1998.

[9] C. Rajnoch, J. C. Chachques, A. Berrebi, P. Bruneval, M. O. Benoit, and A. Carpentier, "Cellular therapy reverses myocardial dysfunction," *Journal of Thoracic and Cardiovascular Surgery*, vol. 121, no. 5, pp. 871–878, 2001.

[10] C. M. Verfaillie, R. Schwartz, M. Reyes, and Y. Jiang, "Unexpected potential of adult stem cells," *Annals of the New York Academy of Sciences*, vol. 996, pp. 231–234, 2003.

[11] J. C. Chachques, B. Cattadori, J. Herreros et al., "Treatment of heart failure with autologous skeletal myoblasts," *Herz*, vol. 27, no. 7, pp. 570–578, 2002.

[12] H. K. Haider, A. C. K. Tan, S. Aziz, J. C. Chachques, and E. K. W. Sim, "Myoblast transplantation for cardiac repair: a clinical perspective," *Molecular Therapy*, vol. 9, no. 1, pp. 14–23, 2004.

[13] F. Vilas-Boas, G. S. Feitosa, M. B. P. Soares et al., "Early results of bone marrow cell transplantation to the myocardium of patients with heart failure due to chagas disease," *Arquivos Brasileiros de Cardiologia*, vol. 87, no. 2, pp. 159–166, 2006.

[14] E. C. Perin, H. F. R. Dohmann, R. Borojevic et al., "Transendocardial, autologous bone marrow cell transplantation for severe, chronic ischemic heart failure," *Circulation*, vol. 107, no. 18, pp. 2294–2302, 2003.

[15] J. C. Chachques, J. Herreros, J. Trainini et al., "Autologous human serum for cell culture avoids the implantation of cardioverter-defibrillators in cellular cardiomyoplasty," *International Journal of Cardiology*, vol. 95, no. 1, pp. S29–S33, 2004.

[16] C. Stamm, B. Westphal, H. D. Kleine et al., "Autologous bone-marrow stem-cell transplantation for myocardial regeneration," *The Lancet*, vol. 361, no. 9351, pp. 45–46, 2003.

[17] V. Schächinger, B. Assmus, M. B. Britten et al., "Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction: final one-year results of the TOPCARE-AMI trial," *Journal of the American College of Cardiology*, vol. 44, no. 8, pp. 1690–1699, 2004.

[18] D. A. Narmoneva, R. Vukmirovic, M. E. Davis, R. D. Kamm, and R. T. Lee, "Endothelial cells promote cardiac myocyte survival and spatial reorganization: implications for cardiac regeneration," *Circulation*, vol. 110, no. 8, pp. 962–968, 2004.

[19] B. Bourahla, A. Shafy, O. Meilhac, I. Elmadbouh, J. B. Michel, and J. C. Chachques, "Mesothelial cells vs. skeletal myoblasts for myocardial infarction," *Asian Cardiovascular and Thoracic Annals*, vol. 18, no. 2, pp. 153–160, 2010.

[20] V. Planat-Bénard, C. Menard, M. André et al., "Spontaneous cardiomyocyte differentiation from adipose tissue stroma cells," *Circulation Research*, vol. 94, no. 2, pp. 223–229, 2004.

[21] I. Kehat, L. Khimovich, O. Caspi et al., "Electromechanical integration of cardiomyocytes derived from human embryonic stem cells," *Nature Biotechnology*, vol. 22, no. 10, pp. 1282–1289, 2004.

[22] M. Cortes-Morichetti, G. Frati, O. Schussler et al., "Association between a cell-seeded collagen matrix and cellular cardiomyoplasty for myocardial support and regeneration," *Tissue Engineering*, vol. 13, no. 11, pp. 2681–2687, 2007.

[23] I. Kutschka, I. Y. Chen, T. Kofidis et al., "Collagen matrices enhance survival of transplanted cardiomyoblasts and contribute to functional improvement of ischemic rat hearts," *Circulation*, vol. 114, no. 1, pp. I167–I173, 2006.

[24] O. Schussler, C. Coirault, M. Louis-Tisserand et al., "Use of arginine-glycine-aspartic acid adhesion peptides coupled with a new collagen scaffold to engineer a myocardium-like tissue graft," *Nature Clinical Practice Cardiovascular Medicine*, vol. 6, no. 3, pp. 240–249, 2009.

[25] T. Eschenhagen and W. H. Zimmermann, "Engineering myocardial tissue," *Circulation Research*, vol. 97, no. 12, pp. 1220–1231, 2005.

[26] T. Kofidis, P. Akhyari, J. Boublik et al., "In vitro engineering of heart muscle: artificial myocardial tissue," *Journal of Thoracic and Cardiovascular Surgery*, vol. 124, no. 1, pp. 63–69, 2002.

[27] J. Leor and S. Cohen, "Myocardial tissue engineering: creating a muscle patch for a wounded heart," *Annals of the New York Academy of Sciences*, vol. 1015, pp. 312–319, 2004.

[28] J. C. Chachques, J. C. Trainini, N. Lago, M. Cortes-Morichetti, O. Schussler, and A. Carpentier, "Myocardial assistance by grafting a new bioartificial upgraded myocardium (MAGNUM trial): clinical feasibility study," *Annals of Thoracic Surgery*, vol. 85, no. 3, pp. 901–908, 2008.

[29] C. Spadaccio, E. Chachques, M. Chello, E. Covino, J. C. Chachques, and J. Genovese, "Predifferentiated adult stem cells and matrices for cardiac cell therapy," *Asian Cardiovascular and Thoracic Annals*, vol. 18, no. 1, pp. 79–87, 2010.

[30] K. Takahashi, K. Tanabe, M. Ohnuki et al., "Induction of pluripotent stem cells from adult human fibroblasts by defined factors," *Cell*, vol. 131, no. 5, pp. 861–872, 2007.

[31] J. J. Gavira, E. Nasarre, G. Abizanda et al., "Repeated implantation of skeletal myoblast in a swine model of chronic myocardial infarction," *European Heart Journal*, vol. 31, no. 8, pp. 1013–1021, 2010.

[32] J. C. Chachques, A. Azarine, E. Mousseaux, M. El Serafi, M. Cortes-Morichetti, and A. F. Carpentier, "MRI evaluation of local myocardial treatments: epicardial versus endocardial (Cell-Fix catheter) injections," *Journal of Interventional Cardiology*, vol. 20, no. 3, pp. 188–196, 2007.

[33] T. Fink, L. Abildtrup, K. Fogd et al., "Induction of adipocyte-like phenotype in human mesenchymal stem cells by hypoxia," *Stem Cells*, vol. 22, no. 7, pp. 1346–1355, 2004.

[34] X. Hu, S. P. Yu, J. L. Fraser et al., "Transplantation of hypoxia-preconditioned mesenchymal stem cells improves infarcted heart function via enhanced survival of implanted cells and angiogenesis," *Journal of Thoracic and Cardiovascular Surgery*, vol. 135, no. 4, pp. 799–808, 2008.

[35] W. Dai, S. L. Hale, G. L. Kay, A. J. Jyrala, and R. A. Kloner, "Delivering stem cells to the heart in a collagen matrix reduces relocation of cells to other organs as assessed by nanoparticle technology," *Regenerative Medicine*, vol. 4, no. 3, pp. 387–395, 2009.

[36] M. Böhm, K. Swedberg, M. Komajda et al., "Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial," *The Lancet*, vol. 376, no. 9744, pp. 886–894, 2010.

[37] A. Carpentier, J. C. Chachques, and P. Grandjean, Eds., *Cardiac Bioassist*, Futura Publishing, New York, NY, USA, 1997.

[38] J. C. Chachques, P. G. Argyriadis, G. Fontaine et al., "Right ventricular cardiomyoplasty: 10-year follow-up," *Annals of Thoracic Surgery*, vol. 75, no. 5, pp. 1464–1468, 2003.

[39] L. W. Stevenson, L. W. Miller, P. Desvigne-Nickens et al., "Left ventricular assist device as destination for patients undergoing intravenous inotropic therapy: a subset analysis from REMATCH (Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure)," *Circulation*, vol. 110, no. 8, pp. 975–981, 2004.

[40] L. Cui, J. Jiang, L. Wei et al., "Transplantation of embryonic stem cells improves nerve repair and functional recovery after severe sciatic nerve axotomy in rats," *Stem Cells*, vol. 26, no. 5, pp. 1356–1365, 2008.

[41] R. Soler, C. Fullhase, and A. Atala, "Regenerative medicine strategies for treatment of neurogenic bladder," *Therapy*, vol. 6, no. 2, pp. 177–184, 2009.

[42] J. C. Chachques, F. Duarte, B. Cattadori et al., "Angiogenic growth factors and/or cellular therapy for myocardial regeneration: a comparative study," *Journal of Thoracic and Cardiovascular Surgery*, vol. 128, no. 2, pp. 245–253, 2004.

[43] D. W. Losordo and S. Dimmeler, "Therapeutic angiogenesis and vasculogenesis for ischemic disease: part I: angiogenic cytokines," *Circulation*, vol. 109, no. 21, pp. 2487–2491, 2004.

[44] K. A. T. Carvalho, L. C. Guarita-Souza, C. L. K. Rebelatto et al., "Could the coculture of skeletal myoblasts and mesenchymal stem cells be a solution for postinfarction myocardial scar?" *Transplantation Proceedings*, vol. 36, no. 4, pp. 991–992, 2004.

[45] A. Shafy, T. Lavergne, C. Latremouille, M. Cortes-Morichetti, A. Carpentier, and J. C. Chachques, "Association of electrostimulation with cell transplantation in ischemic heart disease," *Journal of Thoracic and Cardiovascular Surgery*, vol. 138, no. 4, pp. 994–1001, 2009.

[46] P. M. Baptista, G. Orlando, S. H. Mirmalek-Sani, M. Siddiqui, A. Atala, and S. Soker, "Whole organ decellularization—a tool for bioscaffold fabrication and organ bioengineering," in *Proceedings of the 31st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC '09)*, pp. 6526–6529, September 2009.

[47] H. C. Ott, T. S. Matthiesen, S. K. Goh et al., "Perfusion-decellularized matrix: using nature's platform to engineer a bioartificial heart," *Nature Medicine*, vol. 14, no. 2, pp. 213–221, 2008.

[48] J. S. Choi, J. K. Williams, M. Greven et al., "Bioengineering endothelialized neo-corneas using donor-derived corneal endothelial cells and decellularized corneal stroma," *Biomaterials*, vol. 31, no. 26, pp. 6738–6745, 2010.

[49] J. A. Genovese, C. Spadaccio, E. Chachques et al., "Cardiac pre-differentiation of human mesenchymal stem cells by electrostimulation," *Frontiers in Bioscience*, vol. 14, pp. 2996–3002, 2009.

[50] S. Chen, S. Hilcove, and S. Ding, "Exploring stem cell biology with small molecules," *Molecular BioSystems*, vol. 2, no. 1, pp. 18–24, 2006.

[51] C. E. Semino, "Can we build artificial stem cell compartments?" *Journal of Biomedicine and Biotechnology*, vol. 3, pp. 164–169, 2003.

[52] J. C. Rodríguez Hernández, M. S. Sánchez, J. M. Soria, J. L. Gómez Ribelles, and M. M. Pradas, "Substrate chemistry-dependent conformations of single laminin molecules on polymer surfaces are revealed by the phase signal of atomic force microscopy," *Biophysical Journal*, vol. 93, no. 1, pp. 202–207, 2007.

[53] E. Genové, C. Shen, S. Zhang, and C. E. Semino, "The effect of functionalized self-assembling peptide scaffolds on human aortic endothelial cell function," *Biomaterials*, vol. 26, no. 16, pp. 3341–3351, 2005.

[54] J. C. Rodríguez Hernández, A. Serrano Aroca, J. L. Gómez Ribelles, and M. Monleón Pradas, "Three-dimensional nanocomposite scaffolds with ordered cylindrical orthogonal pores," *Journal of Biomedical Materials Research Part B*, vol. 84, no. 2, pp. 541–549, 2008.

[55] S. N. Zhang, A. J. Sun, J. B. Ge et al., "Intracoronary autologous bone marrow stem cells transfer for patients with acute myocardial infarction: a meta-analysis of randomised controlled trials," *International Journal of Cardiology*, vol. 136, no. 2, pp. 178–185, 2009.

[56] E. C. Martinez and T. Kofidis, "Myocardial tissue engineering: the quest for the ideal myocardial substitute," *Expert Review of Cardiovascular Therapy*, vol. 7, no. 8, pp. 921–928, 2009.

[57] J. C. Chachques, "Cellular cardiac regenerative therapy in which patients?" *Expert Review of Cardiovascular Therapy*, vol. 7, no. 8, pp. 911–919, 2009.

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Cardiology Research and Practice
Volume 2011, Article ID 830279, 5 pages
doi:10.4061/2011/830279

Clinical Study

Response to Cardiac Resynchronization Therapy: The Muscular Metabolic Pathway

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Received 5 October 2010; Accepted 23 November 2010

Academic Editor: Filippos Triposkiadis

Background. Changes in peripheral muscle in heart failure lead to a shift from aerobic to early anaerobic metabolism during exercise leading to ergoreflex overactivation and exaggerated hyperventilation evaluated by the VE/VCO_2 slope. *Methods*. 50 patients (38 males, 59 ± 12 years) performed cardio-pulmonary exercise test with gaz exchange measurement and echocardiographic evaluation before and 6 months after CRT. *Results*. The peak respiratory exchange (VCO_2/VO_2) ratio was significantly reduced from 1.16 ± 0.14 to 1.11 ± 0.07 ($P < .05$) and the time to the anaerobic threshold was increased from 153 ± 82 to 245 ± 140 seconds ($P = .01$). Peak VO_2, VE/VCO_2, peak circulatory power and NYHA were improved after CRT (13 ± 4 to16 ± 5 ml/kg/min ($P < .05$), 45 ± 16 to 39 ± 13 ($P < .01$), 1805 ± 844 to 2225 ± 1171 mmHg.ml/kg/min ($P < .01$) and 3 ± 0.35 to 1.88 ± 0.4 ($P = .01$)). In addition, left ventricular ejection fraction and end-systolic volumes were improved from 24 ± 8 to 29 ± 7% ($P < .01$) and from 157 ± 69 to 122 ± 55 ml ($P < .01$). *Conclusion*. We suggest that CRT leads to an increase in oxidative muscular metabolism and postponed anaerobic threshold reducing exaggerated hyperventilation during exercise.

1. Introduction

It remains unclear how cardiac resynchronization therapy (CRT) improves symptom status in heart failure population. CRT is one of the major treatment for patients suffering from refractory heart failure (HF) despite an optimal drug regimen [1]. Huge previous trialsconfirmed improvement in both symptom status (NYHA class) and remodelling parameters (left ventricular (LV) ejection fraction, mitral regurgitation, and LV end-systolic volume) [2]. In addition, objective functional parameters are improved by CRT (peak oxygen uptake, 6-minute walking test, peak workload, exercise duration) [3]. It was well confirmed that heart failure patients present an exaggerated hyperventilationcharacterised by an increase in the slope relating the minute ventilation to carbon dioxide production (VE/VCO_2) leading to early fatigue and breathlessness during the effort [4].

Physiopathological determinants of such an hyperventilation remain unclear. Nevertheless, an important cause of hyperpnea during effort is the enlargement of physiological dead space and ventilation-perfusion mismatch by alveolar hypoperfusion from hemodynamic dysfunction. Another determinant is the early cardiorespiratory reflex dysregulation. This was evidenced by increased peripheral and central chemosensitivity, impaired sympathovagal balance with sympathetic predominance, and depressed baroreflex circulation control [5, 6]. In addition, in heart failure population, the skeletal musculature has been extensively investigated. Muscle bulk is known to be reduced, and abnormalities of muscle function, histologic features, and metabolism have all been described [7]. In particular, both reduction in capillary density and shift from slow-twitch-type 1 muscular fibres to fast-twitch-type 2 fibres were found. It leads to depressed oxidative capacity by a reduction in mitochondrial density and increases the glycogenolytic metabolism, the carbon dioxide production, and the respiratory exchange ratio at peak of the exercise (VCO_2/VO_2) [8]. These muscular modifications are associated with an overactivation of

the peripheral ergoreflex leading to an early hyperventilation during exercise (the "muscle hypothesis") [9].

We suggest that reduction in exaggerated hyperventilation during exercise in HF population after CRT is linked to an improvement in musculature metabolism, which results in increasing oxidative metabolism, reducing the respiratory exchange ratio at peak of the exercise, and improving the time to anaerobic threshold (AT).

2. Methods

Fifty consecutive refractory HF patients were enrolled in this single center investigation. All those patients matched the following criteria: indication for CRT implantation according to current indications (QRS duration >120 ms, LV ejection fraction <35%, NYHA symptom class II-III or IV, and optimal heart failure medical regimen) [10]. Complete echocardiographic evaluation including LV volume measurements and a cardiopulmonary exercise were realized before and 6 months after CRT implantation. Patients with history of chronic lung diseases were excluded.

2.1. Echocardiographic Measurement. Echocardiograms were loaded into a computer system (Echopac, GE), and all measurements were obtained for all patients at baseline and 6 months after implantation. Echocardiograms were analyzed by a single experienced sonographer.

Sample loops were analyzed off line on an Echopac computer workstation to obtain end-diastolic (EDV) and end-systolic LV (ESV) volumes using the methods of disks. Ejection fraction was calculated as follows: (EDV − ESV)/EDV × 100%. Mitral regurgitation was evaluated according to the European Society of Echocardiography [11].

2.2. Testing Procedure and Data Collection. A symptom-limited exercise test with ventilatory expired gas analysis using a cycle ergometer with a 10 Watts/minute protocol was performed in all patients in an air conditioned room (Ergo Card, Medisoft, Sorinnes, Belgium). Continuous standard 12 lead electrocardiograms, manual blood pressure measurements, and heart rate recordings were monitored at every stage. Data for oxygen consumption (VO_2), carbon dioxide production (VCO_2), minute ventilation (VE), respiratory rate (RR), and work load were collected continuously throughout the exercise. Oxygen and carbon dioxide sensors were calibrated using gases with known oxygen, nitrogen, and carbon dioxide concentrations prior to each test. Ventilatory efficiency was obtained by the linear regression slope relating VE to VCO_2 from the beginning to the peak of the effort [12]. Peak VO_2 was used as an index of exercise capacity.

The peak circulatory power was measured as an evaluation of the cardiac pumping function by the product of the peak VO_2 and the systolic blood pressure as described by Cohen-Solal et al. [13]. The respiratory exchange ratio (RER) was measured by the rapport between the carbon dioxide production (VCO_2) and the oxygen consumption (VO_2). The peak RER was used in this study. The anaerobic threshold was assessed using Wasserman's method. All exercises were realized after written agreements of patients.

2.3. Subgroup Analysis. the responders and the nonresponders to the CRT were characterized. The responder subgroup was defined as having a telesystolic LV volume reduction greater than 15% after CRT [14].

2.4. Statistical Analysis. Paired t tests were used to compare differences between parameters at baseline and after CRT. All statistical tests with a P value of <.05 were considered to be significant. Continuous variables are summarized by mean ± SD.

3. Results

3.1. Patients. Baseline characteristics of patients included are summarized in Table 1. Heart failure etiology was ischaemic in 46% and nonischaemic in 54%. Patients had severely depressed LV function with a mean LV ejection fraction of 24 ± 8%. Mean NYHA symptom class was $2,98 \pm 0,35$, and mean QRS duration was 154 ± 35 ms. Mean values of peak VO_2 and VE/VCO_2 slope were 13 ± 4 ml/kg/minute and 45 ± 16. Mean maximal work load at peak of the exercise and the mean peak circulatory power were 78 ± 28 Watts and 1805 ± 744 mmHg·ml/kg/min. Mean peak RER was ml/min, $1,16 \pm 0,14$. EDV and ESV were 205 ± 79 ml and 157 ± 69 ml, respectively. Mean mitral regurgitation grade was $1,49 \pm 1$.

3.2. 6-Month Followup after CRT. At 6 months, mean values of NYHA,peak VO_2, VE/VCO_2 slope and RER at the peak were $1,88 \pm 0,4$ ($P < .01$), 16 ± 5 ml/kg/min ($P < .05$), 39 ± 13 ($P < .01$) and $1,11 \pm 0,07$ ($P < .05$), respectively. Mean time to anaerobic threshold was improved from 153 ± 82 to 245 ± 140 seconds ($P = .01$). Left ventricular remodelling parameters were significantly improved. Mean values of EDV, ESV, and ejection fraction were 175 ± 71 ml ($P < .01$), 122 ± 55 ml ($P < .01$), and 31 ± 8% ($P < .01$), respectively. Efficient biventricular pacing was assessed by CRT control at 6 months.

3.3. Subgroup Analysis. 23 patients (18 males, 61 ± 10 years) (46%) were included in the nonresponder subgroup. Major HF etiology was ischaemic in 56%, and mean QRS duration was 144 ± 39 ms.

In this population, NYHA symptom was improved from $2,83 \pm 0,5$ to $2 \pm 0,34$ ($P < .01$). Peak VO_2, Ve/VCO_2 slope, RER, and RR did not change (13 ± 2 to 15 ± 5 ml/kg/min, 46 ± 10 to $41 \pm 8,1$, $14 \pm 0,14$ to $1,1 \pm 0,07$, and 30 ± 4 to 27 ± 4/min, respectively; $P > .05$). Mean time to anaerobic threshold was not significantly increased from 183 ± 90 to 225 ± 122 seconds ($P > .05$). No significant increase in exercise duration and peak workload was found 6 months after CRT. Rest HR was decreased from 77 ± 16 bpm to 73 ± 9 bpm ($P > .05$), and peak circulatory power did not change from 1733 ± 480 to 2021 ± 803 mm Hg·ml/kg/min ($P > .05$). In this subgroup, LV tele-systolic, ejection fraction

Table 1: Population characteristics before and after CRT.

	Baseline	6-month followup	P
Subjects	50		
Male	38 (76%)		
Female	12 (24%)		
Age, yrs	59 ± 12		
Left ventricular ejection fraction, %	24 ± 8	29 ± 7	<.01
Etiology			
Ischaemic	23 (46%)		
Nonischaemic	27 (54%)		
SBP at rest, mmHg	108 ± 18	107 ± 17	>.05
SBP at peak, mmHg	131 ± 22	135 ± 28	>.05
HR at rest, bpm	81 ± 18	73 ± 11	<.05
HR at peak, bpm	116 ± 23	114 ± 27	>.05
Peak of VO_2, ml/kg/min	13 ± 4	16 ± 5	<.05
VE/VCO_2 slope	45 ± 16	39 ± 13	<.05
AT (seconds)	153 ± 82	245 ± 140	.01
AT VO_2	10 ± 2	12 ± 4	<.05
Peak CP, mmHg·ml/kg/min	1805 ± 744	2225 ± 1071	<.01
Maximal work load, Watts	78 ± 28	86 ± 26	<.05
Peak RER	1, 16 ± 0, 14	1, 11 ± 0, 07	<.05
Peak respiratory rate, /min	30 ± 8	27 ± 6	.01
Exercise duration, seconds	406 ± 175	449 ± 164	.01
NYHA class	2, 98 ± 0, 35	1, 88 ± 0, 4	<.01
Left ventricular end-systolic volume, ml	157 ± 69	122 ± 55	<.01
Left ventricular end-diastolic volume, ml	205 ± 79	175 ± 71	<.01
Mitral regurgitation, grade	1.49 ± 1	1.12 ± 0.9	<.05
QRS duration, ms	154 ± 35		
Beta-blocker, %	95		
Diuretic, %	83		
Angiotensin-converting enzym inhibitor, %	85		

AT: anaerobic threshold, CP: circulatory power, HR: heart rate, Ms: milliseconds, NYHA: New York Heart Association, RER: respiratory exchange ratio, SBP: Systolic blood pressure, VCO_2: carbon dioxide production, VE: minute ventilation, VO_2: oxygen consumption, and yrs: years.

and mitral regurgitation were measured from 26 ± 7 to 27 ± 8%, from 137 ± 0, 11 to 143 ± 44 ml, and from 1, 06 ± 0, 87 to 0, 89 ± 0, 96 (all $P > .05$).

27 patients (20 males, 58 ± 14 years) (54%) were included in the responder subgroup. QRS duration at baseline was 162 ± 29 ms and an ischaemic cause was found in 37%.

NYHA symptom class was improved from 3 ± 0, 3 to 1, 78 ± 0, 42 ($P < .01$). Peak HR was decreased from 85 ± 21 to 71 ± 13 bpm ($P < .05$). Peak VO_2, VE/VCO_2 slope, RER, RR, exercise duration, peak circulatory power, peak workload, and peak respiratory rate were improved from 14 ± 5 to 16 ± 5 ml/kg/min ($P < .05$), 45 ± 20 to 38 ± 15 ($P < .01$), 1, 17 ± 0, 14 to 1, 11 ± 0, 07 ($P < .05$), 31 ± 11 to 27 ± 7/min ($P < .05$), 409 ± 200 to 460 ± 193 seconds ($P < .05$), 1862 ± 907 to 2384 ± 1235 mmHg·ml/kg/min ($P = .01$), 78 ± 31 to 89 ± 33 watts ($P < .01$), and 31 ± 10 to 27 ± 7/min ($P < .05$). Mean time to anaerobic threshold was improved from 133 ± 5 to 261 ± 154 seconds ($P = .01$). In addition, LV ejection fraction, telesystolic volume, and mitral regurgitation were improved from 22 ± 8 to 34 ± 7% ($P < .01$), 173 ± 81 to 106 ± 59 ml ($P < .01$), and from grade 1, 83 ± 0, 94 to 1, 3 ± 0, 76 ($P < .01$), respectively.

4. Discussion

Reduction in the RER at peak (despite significant increase in exercise parameters) and improvement in the time to AT suggest a postponed muscular anaerobic metabolism during exercise 6 months after CRT, in particular in responder subgroup.

It was clearly confirmed that patients suffering from heart failure have muscular dysfunctions leading to an early anaerobic metabolism with a high production in carbon dioxide and a reduction in the oxygen consumption during exercise [15]. Skeletal muscle blood flow is limited in HF population probably due to a combination of low cardiac output and increased peripheral resistance as sympathetic tone overactivation and endothelial dysfunction leading to a reduction in muscular capillary density [16, 17].

There is also evidence of a reduced percentage of slow-twitch-type 1 fibres with high oxidative enzyme content and an increased percentage of type 2 B fibres with high glycolytic capacity. In addition, previous trials confirmed a reduction in oxidative enzyme activity and in mitochondrial density and a phosphocreatine depletion leading to lactate accumulation. In response to metabolic distress in exercising muscle an exaggerated ergoreflex activation was found. This leads to excessive reflex sympathetic tone. Large previous trials confirmed an important ergoreflex overactivation in heart population correlated with exaggerated hyperventilation during exercise [18, 19]. This model represents the "muscle hypothesis."

In our investigation, the ventilatory response evaluated by the linear regression slope relating the minute ventilation to the carbon dioxide production was significantly improved in particular in the responder subgroup as previously described [20]. In addition, heart rate at rest and peak respiratory rate were reduced after CRT implantation, in particular in the responder subgroup, suggesting a reduction in sympathetic tone. 95% of patients were treated with beta blockers before and after CRT without increase during followup. Heart rate reduction was previously described in a study by Wasserman et al. after CRT ($P < .001$ compared with baseline in the CRT-on group and $P < .01$ in the CRT-off group) [21]. The effects of long-term beta blockade were demonstrated in heart failure population with a reduction in both ventilatory parameters (peak minute ventilation, peak carbon dioxide production, and respiration rate) and haemodynamic parameters (LV ejection fraction, heart rate and blood pressure) [22].

In addition, left ventricular volumes and ejection fraction were improved as well as the peak circulatory power. This simple haemodynamic noninvasive parameter was described to be a close approach of the "cardiac power" (production of both the cardiac output and the main blood pressure) for the evaluation of the cardiac pumping function. The peak CP was measured by the product of the peak VO_2 and the SBP at peak of the exercise as described previously. It was confirmed that the peak CP is a strong prognostic marker in heart failure population. It incorporates arteriovenous difference, heart rate, stroke volume, and blood pressure responses at peak of the exercise [13]. Haemodynamic condition was clearly improved after CRT implantation, in particular for the responder subgroup.

In the nonresponder subgroup, no significant improvement was found in the haemodynamic parameters (LV ejection fraction, peak circulatory power) associated with a nonsignificant improvement in both exercise capacity and ventilatory response. In addition, in this population no significant decrease in peak RER and in time to AT was found, suggesting a persistent early muscular anaerobic metabolism.

We suggest that CRT leads to an improvement in peripheral blood flow by better haemodynamic conditions. It could lead to a shift from fast-twitch-type 2 B fibres to slow-twitch-type 1 fibres with an increase in oxidative metabolism, in mitochondrial density, and in oxygen consumption and in reduction in carbon dioxide production resulting in a postponed AT and in lower peak RER.

Muscular biopsies with mitochondrial density, oxidative enzymes, and capillary density measurements are needed to confirm our data. We could correlate biopsy results with ventilatory response and time to AT after CRT. The lack of histology support was the main limitation in our investigation. In addition, this prospective study was not a randomized control trial.

5. Conclusion

CRT improves haemodynamic condition and exercise capacity and reduces the ventilatory response during effort. In addition, CRT decreases the peak respiratory exchange ratio suggesting the possibility of increased efficiency of energy production in skeletal muscle with less anaerobic metabolism by a shift from a glycolytic to an oxidative metabolism. Link between the improvement in the peak RER, the ventilatory data, and the haemodynamic parameters suggests a reduction in the sympathetic tone explained by a decrease in the ergoreflex activity. But, large further studies are needed to confirm our data.

References

[1] W. T. Abraham, W. G. Fisher, A. L. Smith et al., "Cardiac resynchronization in chronic heart failure," *The New England Journal of Medicine*, vol. 346, no. 24, pp. 1845–1853, 2002.

[2] J. G. F. Cleland, J.-C. Daubert, E. Erdmann et al., "The effect of cardiac resynchronization on morbidity and mortality in heart failure," *The New England Journal of Medicine*, vol. 352, no. 15, pp. 1539–1549, 2005.

[3] T. De Marco, E. Wolfel, A. M. Feldman et al., "Impact of cardiac resynchronization therapy on exercise performance, functional capacity, and quality of life in systolic heart failure with QRS prolongation: COMPANION trial substudy," *Journal of Cardiac Failure*, vol. 14, no. 1, pp. 9–18, 2008.

[4] K. K. Witte and A. L. Clark, "Why does chronic heart failure cause breathlessness and fatigue?" *Progress in Cardiovascular Diseases*, vol. 49, no. 5, pp. 366–384, 2007.

[5] N. P. Buller and P. A. Poole-Wilson, "Mechanism of the increased ventilatory response to exercise in patients with chronic heart failure," *British Heart Journal*, vol. 63, no. 5, pp. 281–283, 1990.

[6] P. Ponikowski, D. P. Francis, M. F. Piepoli et al., "Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis," *Circulation*, vol. 103, no. 7, pp. 967–972, 2001.

[7] M. F. Piepoli, A. C. Scott, A. Capucci, and A. J. S. Coats, "Skeletal muscle training in chronic heart failure," *Acta Physiologica Scandinavica*, vol. 171, no. 3, pp. 295–303, 2001.

[8] H. Drexler, U. Riede, T. Munzel, H. Konig, E. Funke, and H. Just, "Alterations of skeletal muscle in chronic heart failure," *Circulation*, vol. 85, no. 5, pp. 1751–1759, 1992.

[9] A. J. S. Coats, A. L. Clark, M. Piepoli, M. Volterrani, and P. A. Poole-Wilson, "Symptoms and quality of life in heart failure: the muscle hypothesis," *British Heart Journal*, vol. 72, no. 2, pp. S36–S39, 1994.

[10] K. Dickstein, P. E. Vardas, A. Auricchio et al., "2010 Focused Update of ESC Guidelines on device therapy in heart failure: an update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC Guidelines for cardiac and resynchronization therapy—developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association," *Europace*, vol. 12, no. 11, pp. 1526–1536, 2010.

[11] A. Vahanian, H. Baumgartner, J. Bax et al., "Guidelines on the management of valvular heart disease: the task force on the management of valvular heart disease of the European society of cardiology," *European Heart Journal*, vol. 28, no. 2, pp. 230–268, 2007.

[12] R. Arena, J. Myers, S. S. Aslam, E. B. Varughese, and M. A. Peberdy, "Technical considerations related to the minute ventilation/carbon dioxide output slope in patients with heart failure," *Chest*, vol. 124, no. 2, pp. 720–727, 2003.

[13] A. Cohen-Solal, J. Y. Tabet, D. Logeart, P. Bourgoin, M. Tokmakova, and M. Dahan, "A non-invasively determined surrogate of cardiac power ('circulatory power') at peak exercise is a powerful prognostic factor in chronic heart failure," *European Heart Journal*, vol. 23, no. 10, pp. 806–814, 2002.

[14] C. M. Yu, W. T. Abraham, J. Bax et al., "Predictors of response to cardiac resynchronization therapy (PROSPECT)—study design," *American Heart Journal*, vol. 149, no. 4, pp. 600–605, 2005.

[15] B. Massie, M. Conway, R. Yonge et al., "Skeletal muscle metabolism in patients with congestive heart failure: relation to clinical severity and blood flow," *Circulation*, vol. 76, no. 5, pp. 1009–1019, 1987.

[16] D. Harrington and A. J. S. Coats, "Skeletal muscle abnormalities and evidence for their role in symptom generation in chronic heart failure," *European Heart Journal*, vol. 18, no. 12, pp. 1865–1872, 1997.

[17] A. Linke, N. Schoene, S. Gielen et al., "Endothelial dysfunction in patients with chronic heart failure: systemic effects of lower-limb exercise training," *Journal of the American College of Cardiology*, vol. 37, no. 2, pp. 392–397, 2001.

[18] M. F. Piepoli, A. Kaczmarek, D. P. Francis et al., "Reduced peripheral skeletal muscle mass and abnormal reflex physiology in chronic heart failure," *Circulation*, vol. 114, no. 2, pp. 126–134, 2006.

[19] D. A. A. Grieve, A. L. Clark, G. P. McCann, and W. S. Hillis, "The ergoreflex in patients with chronic stable heart failure," *International Journal of Cardiology*, vol. 68, no. 2, pp. 157–164, 1999.

[20] J. Jaussaud, P. Blanc, N. Derval et al., "Ventilatory response and peak circulatory power: new functional markers of response after cardiac resynchronization therapy," *Archives of Cardiovascular Diseases*, vol. 103, no. 3, pp. 184–191, 2010.

[21] K. Wasserman, X. G. Sun, and J. E. Hansen, "Effect of biventricular pacing on the exercise pathophysiology of heart failure," *Chest*, vol. 132, no. 1, pp. 250–261, 2007.

[22] K. K. A. Witte, S. Thackray, N. P. Nikitin, J. G. F. Cleland, and A. L. Clark, "The effects of long-term β-blockade on the ventilatory responses to exercise in chronic heart failure," *European Journal of Heart Failure*, vol. 7, no. 4, pp. 612–617, 2005.

SAGE-Hindawi Access to Research
Cardiology Research and Practice
Volume 2011, Article ID 568918, 7 pages
doi:10.4061/2011/568918

Research Article

Dyssynchrony Assessment with Tissue Doppler Imaging and Regional Volumetric Analysis by 3D Echocardiography Do Not Predict Long-Term Response to Cardiac Resynchronization Therapy

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Received 18 August 2010; Revised 9 November 2010; Accepted 28 November 2010

Academic Editor: Dirk Westermann

Background. Currently there are no reliable predictors of response to cardiac resynchronization therapy (CRT) before implantation. We compared pre-CRT left ventricular (LV) dyssynchrony by tissue Doppler imaging (TDI) and regional volumetric analysis by 3-dimensional transthoracic echocardiography (3DTTE) in predicting response to CRT. *Methods*. Thirty-eight patients (79% nonischemic cardiomyopathy) with symptomatic heart failure who underwent CRT were enrolled. Clinical and echocardiographic responses were defined as improvement in one NYHA class and reduction in LV end-systolic volume by ≥15% respectively. Functional status was assessed by Minnesota Living with Heart Failure questionnaire and 6-minute walk distance. *Results*. In 33 patients, after CRT for 7.86 ± 2.27 months, there were 24 (73%) clinical and 19 (58%) echocardiographic responders. Functional parameters, LV dimensions, volumes and synchrony by TDI and 3DTTE improved significantly in responders. There was no difference in the number of responders and nonresponders when cut-off values for dyssynchrony by different measurements validated in other trials were applied. Area under receiver-operating-characteristic curve ranged from 0.4 to 0.6. *Conclusion*. CRT improves clinical and echocardiographic parameters in patients with systolic heart failure. The dyssynchrony measurements by TDI and 3DTTE are not comparable and are unable to predict response to CRT.

1. Introduction

Cardiac resynchronization therapy (CRT) improves functional capacity, quality of life, and reduces heart failure (HF) symptoms. CRT alone without ICD was also shown to reduce mortality in patients with severe HF [1]. Based on large clinical trials [2, 3], the current recommendations to select patients for CRT focus on electrical dyssynchrony, such as prolonged QRS duration of >120 milliseconds [4]. However, 30–40% of patients with electrical dyssynchrony do not exhibit mechanical dyssynchrony and remain as nonresponders to CRT [5]. Several studies have been done to find an echocardiographic technique that could predict a favorable response to CRT [6–10]. The goal of these studies has been to find a feasible, inexpensive, and reliable method to identify potential responders to CRT before undergoing the surgical procedure.

Mechanical dyssynchrony studied by tissue Doppler imaging (TDI) has been shown to be a reliable predictor of response after CRT in several studies [8, 11–13]. However, the results of the recent trials, including PROSPECT (predictors of response to CRT), which studied 12 different 2D transthoracic (2DTTE) echocardiographic dyssynchrony parameters, did not find any reliable parameters in predicting the response to CRT at 6 months [14, 15]. Three-dimensional transthoracic echocardiography (3DTTE) [16–20] with regional volumetric analysis is emerging as a new technique and feasible to assess dyssynchrony. Although real-time 3DTTE has been used to assess dyssynchrony, this technique has not been compared to TDI in predicting

the response to CRT [21]. We conducted this study to compare dyssynchrony measurements by TDI and regional volumetric analysis by 3DTTE and examine if these methods are efficient and reliable in predicting the long-term clinical and echocardiographic response to CRT.

2. Methods

We conducted a single-center, prospective, nonrandomized study comprising 38 consecutive patients who underwent CRT at Stanford University, California, as per recommended guidelines. All the patients signed an informed consent form and a health insurance portability and accountability act (HIPAA) form for the study. Patients with mechanical heart valve(s), pacemaker dependence, and those with technically inadequate echocardiographic images were excluded from the study. Patients underwent clinical and echocardiographic assessment prior to CRT and after 6–12 months of CRT. The clinical parameters included New York Heart Association (NYHA) functional class, 6-minute walk distance (MWD) and Minnesota Living with Heart Failure questionnaire score (MNHFQ). These patients were implanted with Medtronic ($n = 29$) (Insync Sentry, Medtronic Inc.) and St. Judes ($n = 4$) pacemaker devices. After biventricular pacemaker placement, A-V optimization was done by Ritter's method to achieve maximal end-diastolic filling duration, followed by post-CRT imaging within 24 hours of implantation. Clinical response was defined as an improvement in NYHA functional class by one class, and echocardiographic response was defined as a reduction in LV end-systolic volume (LVESV) of ≥15% after 6–12 months of CRT.

2.1. Transthoracic 2D Echocardiography. A Philips Sonos 5500, M2428A 2D Ultrasound system with an S3 transducer was used to obtain LV end-systolic and end-diastolic dimensions. Apical 4-chamber view was obtained to calculate LVESV and LV end-diastolic volume (LVEDV) to give a LVEF by Simpson's method. Mitral regurgitation was semiquantitatively assessed by color Doppler across mitral valve and graded as none (0) trace/mild (1), moderate (2), moderately severe (3), and severe (4), respectively [22].

2.2. Tissue Doppler Imaging. Dyssynchrony index by pulse-wave TDI was measured as SD of the time from beginning of QRS to the peak systolic velocity in 12 LV segments, 6 basal and 6 mid segments of inferolateral, inferoseptal, anterior, posterior, anteroseptal, and lateral walls with both CRT-on and CRT-off modes. TDI parameter was measured in 3 separate heart beats and averaged for each segment. Then SD for the 12 segments was calculated to derive a dyssynchrony index as 2 SD from the mean. An index of >32 ms from the mean was considered as significant dyssynchrony [13]. We also calculated the difference in time to peak systolic velocity between the fastest (Tf) and slowest (Ts) of 6 basal LV segments (Tf-Ts) [12] and calculated septal-lateral delay. A score of ≥65 ms was considered as significant dyssynchrony [11].

2.3. Transthoracic 3D Echocardiography. A transthoracic full-volume acquisition from apical view using Philips iE33 (Andover, MA, USA) with an X3-1 matrix array transducer was performed with CRT-on and off modes. With 2 perpendicular planes through the LV, a 3-D model of the LV was obtained, and it was subdivided into 17 volumetric segments. Sequence analysis generated the time-volume curves showing the time to the point of minimal systolic volume (Tmsv) for each segment. Q-lab program was run to derive the dyssynchrony index as SD of Tmsv of 12 (6 basal and 6 mid) and 16 (6 basal, 6 mid, and 4 apical) LV segments. It also provided the SD of Tmsv of the 12 and 16 segments as a percentage of the R-R interval.

3. Statistics

Continuous variables are presented as mean ± SD, and dichotomous data are presented as numbers and percentages. The clinical and echocardiographic parameters in responders and nonresponders at baseline, immediately after CRT and at 6–12 months after CRT were compared using Student's paired and unpaired t-tests, respectively. Categorical variables were compared with Chi-square test, and comparisons between the clinical and echocardiographic endpoints with different dyssynchrony parameters were done using analysis of variance (ANOVA). Receiver-operating characteristics curves (ROC) were generated, and the area under the curve represented the ability of the parameter to predict clinical or echocardiographic response. Correlations between different dyssynchrony measurement techniques were examined by Pearson correlation test. A P-value of ≤.05 was considered statistically significant.

4. Results

Of the 38 patients who underwent CRT, 2 patients had failed biventricular pacing, and 3 patients did not return for followup. After a median followup period of 7 months (7.86 ± 2.27 months) in 33 patients, symptoms improved in 24 (73%) patients, unchanged in 7 (21%) patients, worsened in one patient after CRT requiring cardiac transplantation, and one died and these were included as nonresponders ($n = 9$). Of the 24 clinical responders, 18 (55%) were also echocardiographic responders, 5 were clinical responders but not echocardiographic responders, and 1 patient had clinical evaluation but did not get followup echocardiogram. One patient had echocardiographic response without clinical response.

The baseline characteristics and echocardiographic measurements pre-CRT and 6-12 months after CRT are shown in Table 1. There was no significant difference in clinical response in males or females and in patients with nonischemic and ischemic CM (77% versus 57%, P = NS). There was a trend towards higher echocardiographic response in nonischemic CM than in ischemic CM (68% versus 29%, $P = .06$). Both clinical and echocardiographic responders had longer 6-MWD as compared to nonresponders before CRT, and it remained significant after long-term CRT

Table 1: Baseline characteristics and echocardiographic parameters pre-CRT and after long-term CRT.

Characteristic	Baseline	After CRT (6 m)	*P*-value
Age (years)	59.9 ± 12.5		
Gender: males	67%		
Etiology: dilated cardiomyopathy	79%		
QRS duration (ms)	161.2 ± 16.9		
Clinical parameters:			
NYHA class (1/2/3/4)	0/7/23/3	9/17/5/2	<.0005
MNLWHF score	49.7 ± 22.4	30.4 ± 22.9	<.0005
6-minute walk distance (meters)	428 ± 69	482 ± 91	<.0005
Echocardiographic parameters:			
LV end-diastolic volume (mL)	245.3 ± 128.5	192.5 ± 101.3	.006
LV end-systolic volume (mL)	188.9 ± 109.1	125.8 ± 80.3	.0002
LV ejection fraction (%)	25 ± 6	38 ± 11	.0001
LV end-diastolic diameter (cm)	6.9 ± 1.5	6.3 ± 1.5	.004
LV end-systolic diameter (cm)	6.0 ± 1.5	5.1 ± 1.6	.0008
LV fractional shortening (%)	13.3 ± 0.5	19 ± 0.9	.006
Mitral regurgitation	1.67 ± 1.1	1.32 ± 0.8	.03
TDI: SD of Tf-Ts in 12 segments (ms)	44.2 ± 14.1	34.1 ± 14.4	.0008
TDI: SD of Tf-Ts in 6 basal segments (ms)	106.3 ± 41.7	76.5 ± 35.8	.0001
TDI: SD of septal-to-lateral delay (ms)	58.1 ± 37.1	61.2 ± 36.8	.32
3D: SD of Tmsv in 6 basal segments (ms)	84.6 ± 56.4	53.9 ± 41.3	.01
3D: SD of Tmsv in 12 segments (ms)	46.3 ± 31.1	24.4 ± 20.5	.002
3D: SD of Tmsv in 16 segments (ms)	58.1 ± 35.2	35 ± 28.8	.04
3D: SD of Tmsv in 12 segments as % of R-R interval	5.8 ± 4.2%	3.1 ± 2.9%	.0004
3D: SD of Tmsv in 16 segments as % of R-R interval	7.0 ± 4.1%	4.3 ± 3.8%	.01

CRT: cardiac resynchronization therapy, LV: left ventricle, TDI: tissue Doppler imaging, Tf-Ts: difference in time to peak systolic velocity between the fastest and slowest LV segments, Tmsv: difference in longest and shortest time to minimal systolic volume in LV segments, NYHA: New York Heart Association, MNHFQ: Minnesota Living with Heart Failure questionnaire, SD: standard deviation.

(Table 1). The pre-CRT HF medications, such as beta-blockers, ACEI/ARB, diuretics, and aldosterone receptor antagonists remained the same after CRT without any significant change in their doses.

LV pacing lead was placed in posterior or postero-lateral position ($n = 24$), antero-lateral position ($n = 3$) patients, middle-cardiac-vein ($n = 4$) patients, and epicardially placed in 2 patients. There was no difference in the lead position in the clinical or echocardiographic responders and nonresponders.

4.1. Immediate Response to CRT. After initiation of CRT and AV optimization, there was no change in clinical symptoms, but there was a significant reduction in LV dyssynchrony indices measured by TDI (44.2 ± 14.1 versus 33.5 ± 13.5, $P < .05$ in 12 LV segments) and 3DTTE (46.2 ± 31.0 versus 28.3 ± 19.0, $P < .05$ in 12 LV segments). Analysis of the SD of Tmsv as a function of the R-R interval in 12 segments (5.8 ± 4.2% versus 4.5 ± 3.7%, P = NS) and 16 segments (7.0 ± 4.1% versus 5.6 ± 4.2%, P = NS) by 3DTTE did not show significant improvement. The immediate reduction in dyssynchrony score by TDI and 3DTTE did not correlate with the clinical or echocardiographic response at 6–12 months.

4.2. Predictors of Clinical Response. After CRT of 7.86 ± 2.27 months, 24 (73%) were clinical responders with improvement in 1 NYHA functional class. In these patients, there was a significant improvement in 6-MWD (Δ71 m versus Δ22 m, $P < .05$) and in MNHFQ score (Δ22 versus Δ12, $P < .05$) as compared to nonresponders.

Clinical responders were identified with 75% sensitivity and 38% specificity (ROC = 0.69) with pre-CRT QRS duration of 150 ms. Dyssynchrony score of 32 ms with TDI identified responders with a sensitivity of 75% and a specificity of 12%. The clinical response was not significantly different in those who met these cut-off values as compared to those who did not (Table 2). Echocardiographic improvement in LVESV >15% identified clinical responders (ROC = 0.88, $P < .003$) with 84% sensitivity and 86% specificity. Pre-CRT LVESV did not predict clinical response. There was no significant difference in LV dyssynchrony delta change values in clinical responders and nonresponders (Table 2).

4.3. Predictors of Echocardiographic Response. After long-term CRT, the average LVESV decreased by 27.5 ± 21.9%. There were 19 (59%) echocardiographic responders with reduction in LVESV of ≥15%, which correlated with reduction in LV end-diastolic diameter ($r = 0.6$, $P < .05$;

Table 2: Difference in left ventricular function and dyssynchrony parameters in clinical responders versus nonresponders after long-term CRT.

Variable	Clinical responders ($n = 24$) Delta change 6-months after CRT	Clinical nonresponders ($n = 9$) Delta change 6-months after CRT	P-value
LV end-diastolic volume (mL)	65 ± 59	12 ± 15	.03
LV end-systolic volume (mL)	74 ± 59	9 ± 10	.008
LV ejection fraction (%)	15 ± 8	3 ± 4	.001
LV end-diastolic diameter (cm)	0.5 ± 0.1	0.3 ± 0.6	.6
LV fractional shortening (%)	0.05 ± 0.1	0.05 ± 0.11	.9
TDI: Tf-Ts 6 basal segments (ms)	34 ± 34	18 ± 18	.24
TDI: Tf-Ts 12 segments (ms)	13 ± 12	13 ± 8	.96
TDI: septal-to-lateral delay (ms)	28 ± 26	54 ± 10	.07
3D: SD of Tmsv in 6 basal segments (ms)	51 ± 33	60 ± 81	.70
3D: SD of Tmsv in 12 segments (ms)	16 ± 13	28 ± 30	.16
3D: SD of Tmsv in 16 segments (ms)	34 ± 35	44 ± 35	.48
3D: SD of Tmsv in 12 segments as % of R-R interval	3.3 ± 2.9%	4.0 ± 4.3%	.60
3D: SD of Tmsv in 16 segments as % of R-R interval	4.4 ± 4.0%	3.5 ± 5.4%	.59

CRT: cardiac resynchronization therapy, LV: left ventricle, TDI: tissue Doppler imaging, Tf-Ts: difference in time to peak systolic velocity between the fastest and slowest LV segments, Tmsv: difference in longest and shortest time to minimal systolic volume in LV segments, SD: standard Deviation.

ROC = 0.56 for LV diameter of 5 millimeters). As compared to the echocardiographic nonresponders, the responders had significant improvement in LV volumes, ejection fraction, and LV dimensions. Overall, there was significant improvement in dyssynchrony values after CRT (Table 1); however, the absolute delta changes in LV dyssynchrony values were similar in echocardiographic responders and nonresponders (Table 3). Echocardiographic responders were identified with 77% sensitivity and 34% specificity (ROC = 0.67) with pre-CRT QRS duration of 150 ms. Dyssynchrony score of 32 ms with TDI identified responders with a sensitivity of 73% and a specificity of 15%. The echocardiographic response was not significantly different in those who met this cut-off value of dyssynchrony as compared to those who did not (Table 4).

4.4. Correlation between Dyssynchrony Indices by QRS duration, TDI, and 3D Volumetric Analysis. The pre-CRT QRS duration had significant correlation with dyssynchrony score by TDI in 12 segments ($r = 0.7$, $P = .009$) and with Tf-Ts in 6 basal segments ($r = 0.6$, $P = .01$). The dyssynchrony score by TDI in 12 LV segments correlated with septal-lateral delay ($r = 0.6$, $P < .05$) and with Tf-Ts in 6 basal segments ($r = 0.8$, $P < .05$). Similarly, dyssynchrony scores by 3D volumetric analysis in 12 LV segments and 16 segments expressed as percentage of cardiac cycle correlated significantly ($r = 0.8$, $P < .05$). However, there was no correlation between TDI and 3D measurements (Table 5).

5. Discussion

In our study, we noted improved LV systolic function and reduced LV volumes and dimensions after long-term CRT signifying reverse remodeling of LV. There was also reduction in LV dyssynchrony scores by several TDI and 3DTTE measurements after CRT; however, these did not help to identify responders before the procedure. The dyssynchrony scores by these techniques did not correlate with each other.

As seen in prior studies, there were more clinical responders than echocardiographic responders to CRT [6]. Subjective improvement in NYHA functional class was associated with objective improvement in 6-MWD as reported before [1–3, 23]. The remaining patients with only clinical response without a reduction in LVESV probably had a placebo effect after pacemaker implantation or had some beneficial effect on LV mechanics without evident significant reverse remodeling. CRT was implanted in 5 (13%) patients with NYHA functional class II symptoms, although their quality of life was significantly affected compared to their baseline and could be classified as IIIa, and opted to undergo CRT. The recent MADIT-CRT trial conducted in patients with mild heart failure symptoms showed a beneficial effect of CRT [24]. As reported in MADIT-CRT and in CARE-HF trials [25], our study also showed similar clinical and echocardiographic response in ischemic and nonischemic etiology of cardiomyopathy [26].

Echocardiographic responders showed LV reverse remodeling without significant change in dyssynchrony as compared to nonresponders. Reverse remodeling of LV with improvement in LV volumes, dimensions, and LVEF with CRT has been reproduced in several studies [3, 8, 24, 27]. LVESV is a reliable indicator of LV reverse remodeling, and it correlated with the clinical improvement in symptoms. However, pre-CRT LVESV did not identify CRT responders before implantation. The additional information on dyssynchrony by different methods did not seem to identify responders or improve the selection criteria. It is intuitive that correction of dyssynchrony is probably necessary to facilitate reverse remodeling and clinical improvement [28], but the available methods to

Table 3: Difference in left ventricular function and dyssynchrony parameters in echocardiographic responders versus nonresponders after long-term CRT.

Variable	Echocardiographic responders ($n = 19$)	Echocardiographic nonresponders ($n = 13$)	P-value
	Delta change 6-months after CRT	Delta change 6-months after CRT	
LV end-diastolic volume (mL)	71 ± 60	18 ± 26	.01
LV end-systolic volume (mL)	82 ± 58	8 ± 7	.0009
LV ejection fraction (%)	15 ± 9	6 ± 7	.01
LV end-diastolic diameter (cm)	0.7 ± 0.8	0.03 ± 0.6	.03
LV fractional shortening (%)	0.06 ± 0.1	0.03 ± 0.07	.3
TDI: Tf-Ts 6 basal segments (ms)	37 ± 34	15 ± 17	.08
TDI: Tf-Ts 12 segments (ms)	14 ± 12	10 ± 8	.36
TDI: septal-to-lateral delay (ms)	31 ± 27	41 ± 24	.43
3D: SD of Tmsv in 6 basal segments (ms)	45 ± 35	68 ± 68	.30
3D: SD of Tmsv in 12 segments (ms)	14 ± 13	27 ± 25	.13
3D: SD of Tmsv in 16 segments (ms)	35 ± 37	42 ± 33	.61
3D: SD of Tmsv in 12 segments as % of R-R interval	3.5 ± 3.0%	3.5 ± 4.0%	.97
3D: SD of Tmsv in 16 segments as % of R-R interval	3.9 ± 4.6%	4.7 ± 4.0%	.61

*$P < .05$, CRT: cardiac resynchronization therapy, LV: left ventricle, TDI: tissue Doppler imaging, Tf-Ts: difference in time to peak systolic velocity between the fastest and slowest LV segments, Tmsv: difference in longest and shortest time to minimal systolic volume in LV segments, SD: standard Deviation.

Table 4: Assessment of QRS duration and echocardiographic dyssynchrony parameters validated in other trials to predict long-term clinical and echocardiographic response.

Pre-CRT dyssynchrony parameters	Total ($n = 33$)	Clinical responders ($n = 24$)	P-value	Echocardiographic responders ($n = 19$)	P-value
QRS (ms)					
<150	9	6	0.6	6	0.7
≥150	24	18		13	
TDI septal-lateral delay (ms)					
<65	20	17	0.1	13	0.2
≥65	13	8		6	
TDI (Tf-Ts) 12 LV segments (ms)					
<32	6	5	0.5	4	0.6
≥32	27	19		15	
TDI (Tf-Ts) 6 basal LV segments (ms)					
<83	10	7	0.8	7	0.5
≥83	23	17		12	

CRT: cardiac resynchronization therapy, LV: left ventricle, TDI: tissue Doppler imaging, Tf-Ts: difference in time to peak systolic velocity between the fastest and slowest LV segments.

assess dyssynchrony are inadequate and time consuming. Until we have reliable techniques, QRS duration remains the simple choice to select patients for CRT. Although the cut-off value for selection of patients for CRT was 130 ms, a cut-off value of 150 ms was used to identify responders as patients with wider QRS had better response to CRT in a large, randomized trial such as CARE-HF, and most of the patients enrolled had QRS 150 ms [1].

In our study, on applying the cut-off values based on prior trials, the responders did not show more dyssynchrony as compared to nonresponders prior to CRT [8, 9, 11–13, 29]. The PROSPECT trial evaluated seven TDI-based dyssynchrony scores and reported variable predictive values and concluded that no single echocardiographic measure was reliable in identifying responders. Interestingly, this study also highlighted the limitations of obtaining reliable images done at different centers [14], which is currently a problem in low-volume practices, not involved in research. Despite our study being conducted in a single university setting with a high volume of CRT insertions and echocardiographers with

Table 5: Correlation between left ventricular dyssynchrony indices by QRS duration, TDI, and 3D volumetric analysis in patients undergoing CRT.

	Pearson's correlation coefficient	QRS duration (ms)	TDI: septal-to-lateral delay	TDI: Tf-Ts 6 basal segments (ms)	TDI: Tf-Ts 12 basal segments (ms)	3D: SD of Tmsv in 12 segments as % of R-R interval	3D: SD of Tmsv in 16 segments as % of R-R interval
QRS duration (ms)	Cor. coeff.	1	0.3	0.6	0.7	0.05	0.1
	P-value		0.07	<0.05	<0.05	0.8	0.5
TDI: Septal-to-lateral delay	Cor. coeff.	0.3	1	0.6	0.6	0.06	0.03
	P-value	0.07		<0.05	<0.05	0.7	0.8
TDI: Tf-Ts 6 basal segments (ms)	Cor. coeff.	0.6	0.6	1	0.8	0.05	0.2
	P-value	<0.05	<0.05		<0.05	0.7	0.2
TDI: Tf-Ts 12 basal segments (ms)	Cor. coeff.	0.7	0.6	0.8	1	0.03	0.1
	P-value	<0.05	<0.05	<0.05		0.8	0.5
3D: SD of Tmsv in 12 segments as % of R-R interval	Cor. coeff.	0.05	0.06	0.05	0.03	1	0.8
	P-value	0.8	0.7	0.7	0.8		<0.05
3D: SD of Tmsv in 16 segments as % of R-R interval	Cor. coeff.	0.1	0.03	0.2	0.1	0.8	1
	P-value	0.5	0.8	0.2	0.5	<0.05	

CRT: cardiac resynchronization therapy, TDI: tissue Doppler imaging, Tf-Ts: difference in time to peak systolic velocity between the fastest and slowest LV segments, Tmsv: difference in longest and shortest time to minimal systolic volume in LV segments, SD: standard deviation, Cor. Coeff.: correlation coefficient.

an expertise in obtaining and interpreting TDI and 3D echo images, similar limitations were encountered.

A recent study by Marsan et al. showed good correlation in dyssynchrony scores by regional volumetric analysis by 3DTTE and gated myocardial perfusion single-photon emission computed tomography [17]. Kleijn et al. compared TDI and real-time 3DTTE and reported nonagreement between the two techniques when current dyssynchrony cut-off values were applied [21]. In our study, except for the QRS and TDI values, the TDI and 3DTTE dyssynchrony measurements did not correlate significantly, consistent with our observation in previous study [19]. The likely reason may be that TDI and 3DTTE measure different events like time-to-peak systolic velocity by TDI and time-to-minimal-systolic volume by 3DTTE, and these timings may not correlate, especially in dyssynchronous LV segments.

Early improvement in LV dyssynchrony has been shown to be predictive of long-term favorable response to CRT in prior studies [26, 27, 30] unlike our study. But the goal is to identify the responders before a patient undergoes CRT procedure. Soliman et al. showed that 3DTTE dyssynchrony scores before CRT were useful in identifying long-term echocardiographic responders to CRT [20]. Multicenter studies are needed to see if this technique can reproduce similar results.

6. Limitations

The main limitation of our study is the small sample size, although studies with a larger sample such as PROSPECT yielded similar results. There are several other dyssynchrony parameters used in various studies, but we did not assess all of them. The median followup was limited to 7 months as the results of the study did not contribute to clinical decision making and were time consuming.

7. Conclusion

CRT leads to improved functional status, LV reverse remodeling, and improved synchrony between LV segments in patients with systolic HF. The dyssynchrony measurements by TDI and 3DTTE volumetric analysis do not correlate well with each other, and do not appear to be significantly related to measure of outcomes.

Acknowledgments

The authors would like to thank the staff in the echocardiography laboratory (Allan Paloma, Judy Chow and, Josephine Puryear) and the electrophysiology laboratory (Marcia Glassford, Kelly Green, and Linda Ottobani) for their invaluable support in conducting this study.

References

[1] J. G. F. Cleland, J. C. Daubert, E. Erdmann et al., "The effect of cardiac resynchronization on morbidity and mortality in heart failure," *New England Journal of Medicine*, vol. 352, no. 15, pp. 1539–1549, 2005.

[2] S. Cazeau, C. Leclercq, T. Lavergne et al., "Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay," *New England Journal of Medicine*, vol. 344, no. 12, pp. 873–880, 2001.

[3] W. T. Abraham, W. G. Fisher, A. L. Smith et al., "Cardiac resynchronization in chronic heart failure," *New England Journal of Medicine*, vol. 346, no. 24, pp. 1845–1853, 2002.

[4] G. Gregoratos, J. Abrams, A. E. Epstein et al., "ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998

Pacemaker Guidelines)," *Journal of Cardiovascular Electrophysiology*, vol. 13, no. 11, pp. 1183–1199, 2002.

[5] G. B. Bleeker, M. J. Schalij, S. G. Molhoek et al., "Relationship between QRS duration and left ventricular dyssynchrony in patients with end-stage heart failure," *Journal of Cardiovascular Electrophysiology*, vol. 15, no. 5, pp. 544–549, 2004.

[6] G. B. Bleeker, J. J. Bax, J. W. H. Fung et al., "Clinical versus echocardiographic parameters to assess response to cardiac resynchronization therapy," *American Journal of Cardiology*, vol. 97, no. 2, pp. 260–263, 2006.

[7] C. M. Yu, W. T. Abraham, J. Bax et al., "Predictors of response to cardiac resynchronization therapy (PROSPECT)—study design," *American Heart Journal*, vol. 149, no. 4, pp. 600–605, 2005.

[8] P. Sogaard, H. Egeblad, W. Y. Kim et al., "Tissue Doppler imaging predicts improved systolic performance and reversed left ventricular remodeling during long-term cardiac resynchronization therapy," *Journal of the American College of Cardiology*, vol. 40, no. 4, pp. 723–730, 2002.

[9] M. V. Pitzalis, M. Iacoviello, R. Romito et al., "Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony," *Journal of the American College of Cardiology*, vol. 40, no. 9, pp. 1615–1622, 2002.

[10] M. V. Pitzalis, M. Iacoviello, R. Romito et al., "Ventricular asynchrony predicts a better outcome in patients with chronic heart failure receiving cardiac resynchronization therapy," *Journal of the American College of Cardiology*, vol. 45, no. 1, pp. 65–69, 2005.

[11] J. J. Bax, G. B. Bleeker, T. H. Marwick et al., "Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy," *Journal of the American College of Cardiology*, vol. 44, no. 9, pp. 1834–1840, 2004.

[12] D. Notabartolo, J. D. Merlino, A. L. Smith et al., "Usefulness of the peak velocity difference by tissue Doppler imaging technique as an effective predictor of response to cardiac resynchronization therapy," *American Journal of Cardiology*, vol. 94, no. 6, pp. 817–820, 2004.

[13] C. M. Yu, W. H. Fung, H. Lin, Q. Zhang, J. E. Sanderson, and C. P. Lau, "Predictors of left ventricular reverse remodeling after cardiac resynchronization therapy for heart failure secondary to idiopathic dilated or ischemic cardiomyopathy," *American Journal of Cardiology*, vol. 91, no. 6, pp. 684–688, 2003.

[14] E. S. Chung, A. R. Leon, L. Tavazzi et al., "Results of the predictors of response to crt (prospect) trial," *Circulation*, vol. 117, no. 20, pp. 2608–2616, 2008.

[15] O. I. I. Soliman, D. A. M. J. Theuns, M. L. Geleijnse et al., "Spectral pulsed-wave tissue Doppler imaging lateral-to-septal delay fails to predict clinical or echocardiographic outcome after cardiac resynchronization therapy," *Europace*, vol. 9, no. 2, pp. 113–118, 2007.

[16] Q. Zhang, C. M. Yu, J. W. H. Fung et al., "Assessment of the effect of cardiac resynchronization therapy on intraventricular mechanical synchronicity by regional volumetric changes," *American Journal of Cardiology*, vol. 95, no. 1, pp. 126–129, 2005.

[17] N. A. Marsan, M. M. Henneman, J. Chen et al., "Real-time three-dimensional echocardiography as a novel approach to quantify left ventricular dyssynchrony: a comparison study with phase analysis of gated myocardial perfusion single photon emission computed tomography," *Journal of the American Society of Echocardiography*, vol. 21, no. 7, pp. 801–807, 2008.

[18] S. Kapetanakis, M. T. Kearney, A. Siva, N. Gall, M. Cooklin, and M. J. Monaghan, "Real-time three-dimensional echocardiography: a novel technique to quantify global left ventricular mechanical dyssynchrony," *Circulation*, vol. 112, no. 7, pp. 992–1000, 2005.

[19] S. S. Kuppahally, M. B. Fowler, R. Vagelos et al., "Worsening of left ventricular end-systolic volume and mitral regurgitation without increase in left ventricular dyssynchrony on acute interruption of cardiac resynchronization therapy," *Echocardiography*, vol. 26, no. 7, pp. 759–765, 2009.

[20] O. I. I. Soliman, M. L. Geleijnse, D. A. M. J. Theuns et al., "Usefulness of left ventricular systolic dyssynchrony by real-time three-dimensional echocardiography to predict long-term response to cardiac resynchronization therapy," *American Journal of Cardiology*, vol. 103, no. 11, pp. 1586–1591, 2009.

[21] S. A. Kleijn, J. van Dijk, C. C. de Cock, C. P. Allaart, A. C. van Rossum, and O. Kamp, "Assessment of intraventricular mechanical dyssynchrony and prediction of response to cardiac resynchronization therapy: comparison between tissue Doppler imaging and real-time three-dimensional echocardiography," *Journal of the American Society of Echocardiography*, vol. 22, no. 9, pp. 1047–1054, 2009.

[22] J. D. Thomas, "How leaky is that mitral valve? Simplified Doppler methods to measure regurgitant orifice area," *Circulation*, vol. 95, no. 3, pp. 548–550, 1997.

[23] J. B. Young, W. T. Abraham, A. L. Smith et al., "Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD trial," *Journal of the American Medical Association*, vol. 289, no. 20, pp. 2685–2694, 2003.

[24] A. J. Moss, W. J. Hall, D. S. Cannom et al., "Cardiac-resynchronization therapy for the prevention of heart-failure events," *New England Journal of Medicine*, vol. 361, no. 14, pp. 1329–1338, 2009.

[25] G. Wikstrom, C. Blomström-Lundqvist, B. Andren et al., "The effects of aetiology on outcome in patients treated with cardiac resynchronization therapy in the CARE-HF trial," *European Heart Journal*, vol. 30, no. 7, pp. 782–788, 2009.

[26] N. A. Marsan, G. B. Bleeker, R. J. van Bommel et al., "Comparison of time course of response to cardiac resynchronization therapy in patients with ischemic versus nonischemic cardiomyopathy," *American Journal of Cardiology*, vol. 103, no. 5, pp. 690–694, 2009.

[27] A. J. Bank, C. L. Kaufman, A. S. Kelly et al., "Results of the prospective Minnesota study of ECHO/TDI in cardiac resynchronization therapy (PROMISE-CRT) study," *Journal of Cardiac Failure*, vol. 15, no. 5, pp. 401–409, 2009.

[28] G. B. Bleeker, S. A. Mollema, E. R. Holman et al., "Left ventricular resynchronization is mandatory for response to cardiac resynchronization therapy: analysis in patients with echocardiographic evidence of left ventricular dyssynchrony at baseline," *Circulation*, vol. 116, no. 13, pp. 1440–1448, 2007.

[29] C.-M. Yu, H. Lin, Q. Zhang, and J. E. Sanderson, "High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration," *Heart*, vol. 89, no. 1, pp. 54–60, 2003.

[30] R. Abdelhadi, E. Adelstein, A. Voigt, J. Gorcsan, and S. Saba, "Measures of left ventricular dyssynchrony and the correlation to clinical and echocardiographic response after cardiac resynchronization therapy," *American Journal of Cardiology*, vol. 102, no. 5, pp. 598–601, 2008.

SAGE-Hindawi Access to Research
Cardiology Research and Practice
Volume 2011, Article ID 956062, 8 pages
doi:10.4061/2011/956062

Clinical Study

The Use of Epicardial Electrogram as a Simple Guide to Select the Optimal Site of Left Ventricular Pacing in Cardiac Resynchronization Therapy

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Received 1 November 2010; Revised 23 December 2010; Accepted 4 January 2011

Academic Editor: Georgios Giannakoulas

Cardiac resynchronization therapy (CRT) has been demonstrated to improve symptoms and survival in patients with left ventricular (LV) systolic dysfunction and dyssynchrony. To achieve this goal, the LV lead should be positioned in a region of delayed contraction. We hypothesized that pacing at the site of late electrical activation was also associated with long-term response to CRT. We conducted a retrospective study on 72 CRT patients. For each patient, we determined the electrical delay (ED) from the onset of QRS to the epicardial EGM and the ratio of ED to QRS duration (ED/QRS duration). After a followup of 30 ± 20 months, 47 patients responded to CRT. Responders had a significantly longer ED and greater ratio of ED/QRS duration than nonresponders. An ED/QRS duration ≥0.38 predicted a response to CRT with 89% specificity and 53% sensitivity.

1. Introduction

Cardiac resynchronization therapy (CRT) has been validated as an effective therapeutic approach for patients with drug-refractory heart failure associated with left ventricular (LV) dyssynchrony. In this population, CRT not only improves heart failure symptoms and quality of life [1, 2] but also leads to reverse remodeling [3] and reduces the risk of death [4]. Despite this unquestionable efficacy, 30% of patients do not appear to benefit from CRT, and substantial effort has been made to better identify potential responders [5, 6]. Several reports have indicated that LV lead placement at the site of latest mechanical contraction is a critical determinant of CRT outcome [7, 8]. The identification of these sites of greater dyssynchrony by echocardiography has been suggested by several authors to be associated with acute or long-term success of CRT. However, echo-guided lead positioning requires sophisticated techniques for assessment of LV dyssynchrony and selection of the site of latest mechanical activation [7, 9, 10]. The use of these techniques, during CRT, is challenging and may significantly prolong the procedure duration. Furthermore, data from the PROSPECT trial [11] illustrated the limited intra- and interobserver reproducibility of these measurements.

Another method of identifying sites of latest activation is the use of epicardial electrogram (EGM). Pacing at the site of maximal electrical delay (ED) determined electrophysiologically [12] or by electroanatomical mapping [13, 14] has been reported to result in greater acute hemodynamic response. However, data on the long-term value of this technique are very limited [12]. The goal of our study was to assess the value of the ED for the prediction of the long-term response and to determine the degree of conduction delay that was more likely to be associated with positive outcome.

2. Methods

We conducted a retrospective single-centre study on patients with a CRT device and in whom local epicardial EGM was available at the time of the procedure.

2.1. Patients' Selection. Patients were included in our study if they had successful implantation of a CRT device for drug-refractory congestive heart failure: NYHA functional class III

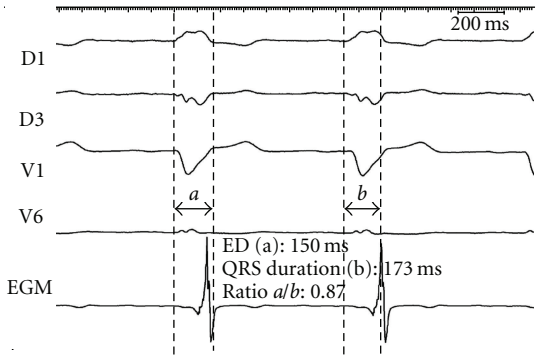


Figure 1: Recording of the epicardial EGM at the tip of the LV lead. a: QRS duration, b: electrical delay.

or IV, due to severe systolic LV dysfunction (LV ejection fraction (LVEF) ≤35% and long QRS duration (≥120 ms)) [15] and if epicardial EGMs were obtained during the procedure. Patients with severe ischemic heart disease and extensive myocardial scar (involving more than 4 LV segments) or history of lateral or posterolateral myocardial infarction who had a low likelihood of response were not considered for CRT and, therefore, were not included in our study.

2.2. Implantation Technique. Technical aspects of lead and device implantation were described in detail in previous publications [16, 17]. Efforts were made to place the LV lead in a lateral tributary of the coronary sinus. At the end of the procedure and before the LV lead was connected to the CRT device, simultaneous surface 12-lead ECG and epicardial EGMs were continuously acquired with a filter bandwidth of 0.05 to 40 Hz and 30 to 500 Hz, respectively, and displayed on a high-resolution video monitor at 100 mm/second paper speed for inspection and subsequent review (Prucka Engineering). The ED was measured from the onset of QRS to the peak of sharpest deflection of the EGM (Figure 1). We also determined the ratio of the ED to baseline QRS duration (ED/QRS duration). During the study period, the LV lead position was not modified on the basis of the ED. After the implant, each patient had a chest X-ray in the anteroposterior and left anterior oblique (LAO) views, and the final LV lead position was recorded in the latter view.

2.3. Patients' Followup. After implantation of the CRT device, patients were followed prospectively in our institution at 1, 6, and 12 months and every year thereafter. The following parameters were collected at baseline and each visit: functional status defined by NYHA class, 6-minute walked distance, and LV volumes by echocardiography: LV end-systolic volume (LVESV) and LV end-diastolic volume (LVEDV). LVEF was determined by echocardiography or nuclear angiography. When LVEF was evaluated at baseline by one of the 2 techniques, the same method was used at long-term followup. Some parameters of LV dyssynchrony were also assessed at baseline and followup, but results of these parameters will not be reported in the present study, since their value in selection of patients for CRT has not been validated by the PROSPECT trial [11]. Response to CRT was defined by either improvement of functional status by at least 2 NYHA classes alone or by one NYHA class associated with increased LVEF by at least 5% [18].

Table 1: Comparison of clinical characteristics in responders and nonresponders.

	Responders $N = 47$	Nonresponders $N = 25$	P
Age (years)	70 ± 7	72 ± 8	.36
NIDCM (%)	72	60	.29
SR at implant (%)	89	92	.72
NYHA class	3.3 ± 0.5	3.1 ± 0.7	.37
NYHA class			
Class III (%)	69	73	.71
Class IV (%)	31	27	
Baseline treatment			
Beta-blocker (%)	67	65	.91
ACE inhibitor (%)	73	81	.48
ARA (%)	22	12	.35
Diuretics (%)	98	92	.55
Spironolactone	38	42	.71
Digoxin (%)	27	31	.71
Statin (%)	40	42	.85
Treatment at followup			
Beta-blocker (%)	80	65	.17
ACE inhibitor (%)	78	65	.26
ARA (%)	29	23	.59
Diuretics (%)	98	100	1
Spironolactone	27	42	.18
Digoxin (%)	24	42	.12
Statin (%)	49	46	.82
Change of treatment during followup (%)	89	89	1
6-minute walked distance (m)	354 ± 126	348 ± 119	.88
Follow-up duration (months)	32.1 ± 20.9	27.3 ± 19.1	.35
Δ NYHA class	−1.6 ± 0.7	−0.2 ± 0.9	<.001

Abbreviations used: SR: sinus rhythm, NIDCM: nonischemic dilated cardiomyopathy, NYHA class: New York Heart Association functional class, ACE inhibitors: angiotensin converting enzyme inhibitors, ARA: angiotensin receptor antagonist, Δ NYHA: difference of NYHA class between followup and baseline.

2.4. Statistical Analysis. Categorical data are expressed as incidence, and noncategorical data are expressed as mean ± standard deviation. A comparison of categorical data was performed using the Chi-square test, and noncategorical data were compared by Student's t-test. Linear regression analysis was performed using the Pearson correlation coefficients. Logistic regression analysis was used for identification of independent predictors of long-term response to CRT. A P value < .05 was considered statistically significant.

3. Results

3.1. Baseline Characteristics. Our study population comprised 72 patients (47 men) who were implanted with a CRT device and in whom epicardial EGM was available at the time of the procedure. Mean age was 70 ± 8 years. Sixty-eight percent of patients had nonischemic dilated cardiomyopathy. Ninety percent were in sinus rhythm (SR) at the time of implant. Spontaneous baseline QRS duration was 178 ± 29 ms. Almost all patients had left bundle branch block (LBBB, $N = 69$). Only 3 patients had right bundle branch block (RBBB). Mean LVEF prior to CRT was 23 ± 8%. Six-minute walked distance was 351 ± 122 meters. Mean ED was 132 ± 36 ms, and the mean ratio of ED/QRS duration was 0.75 ± 0.17.

3.2. Long-Term Followup

3.2.1. Comparison of Baseline Characteristics between Responders and Nonresponders. After a mean followup of 30 ± 20 months, 47 patients were classified as responders and 25 as nonresponders. A comparison of patients' characteristics is summarized in Tables 1 and 2. No significant difference was observed between the 2 groups in baseline characteristics including age, nature of underlying heart disease, prevalence of SR at baseline, QRS duration, NYHA functional class, 6-minute walked distance, followup duration, and medications at baseline and followup. Optimization of medical therapy was equally frequent in both groups of patients. Baseline LVEF was higher in responders (25 ± 8% versus 20 ± 7%, $P = .01$). As expected, responders had significant improvement of their NYHA functional class and LVEF compared to baseline (Δ NYHA class = −1.6 ± 0.7, $P < .0001$, Δ LVEF = +19 ± 12%, $P < .0001$), whereas in nonresponders, there was no significant change of these same parameters at long-term followup (Δ NYHA class = −0.2 ± 0.9, $P = .63$, Δ LVEF = −0.6 ± 8%, $P = .60$). The difference between the 2 groups was statistically significant ($P < .001$). Nonresponders had significantly larger LVEDV and LVESV at baseline compared to responders (Table 2). At followup, responders exhibited significant reduction of their LV volumes (Δ LVEDV = −55 ± 72 mL, $P < .001$, Δ LVESV = −68 ± 66 mL, $P < .001$). In nonresponders, there was no significant change of LV volumes compared to baseline (Δ LVEDV = +5 ± 62 mL, $P = .73$, Δ LVESV = +5 ± 58 mL, $P = .69$). Again, the difference between the 2 groups was highly significant ($P = .002$ for Δ LVEDV and $P = .001$ for Δ LVESV).

ED was significantly longer in responders (139 ± 35 ms versus 119 ± 37 ms, $P = .03$). The ratio of ED/QRS duration was also significantly greater in responders (0.79 ± 0.16 versus 0.67 ± 0.18, $P = .005$).

3.2.2. Correlation between ED and Long-Term Outcome. Linear regression analysis showed a weak but significant positive correlation between ED and difference of LVEF from baseline to followup (Δ LVEF) ($r = +0.307$, $P = .009$) (Figure 2(a)) and also a weak but significant negative correlation with change of NYHA class from baseline to followup (Δ NYHA) (Figure 2(b)) ($r = −0.310$, $P = .008$). We also found a significant positive correlation between the ratio of ED/QRS duration and Δ LVEF ($r = +0.232$, $P = .05$) (Figure 3(a)) and a significant negative correlation with Δ NYHA ($r = −0.283$, $P = .016$) (Figure 3(b)).

Receiver operating characteristic analysis showed that an ED ≥ 150 ms predicted a response to CRT with 80% specificity and 47% sensitivity (odds ratio (OR): 3.5, confidence interval (CI): 1.1–11, $P = .025$). A ratio of ED/QRS duration ≥0.83 was associated with a response to CRT with 89% specificity and 53% sensitivity (OR: 8.3, CI: 2.2–31.7, $P = .001$).

Logistic regression analysis (Table 3) showed that, after adjustment for baseline rhythm and underlying heart disease, independent predictors of positive outcome were baseline LVEF and the ratio of ED/QRS duration.

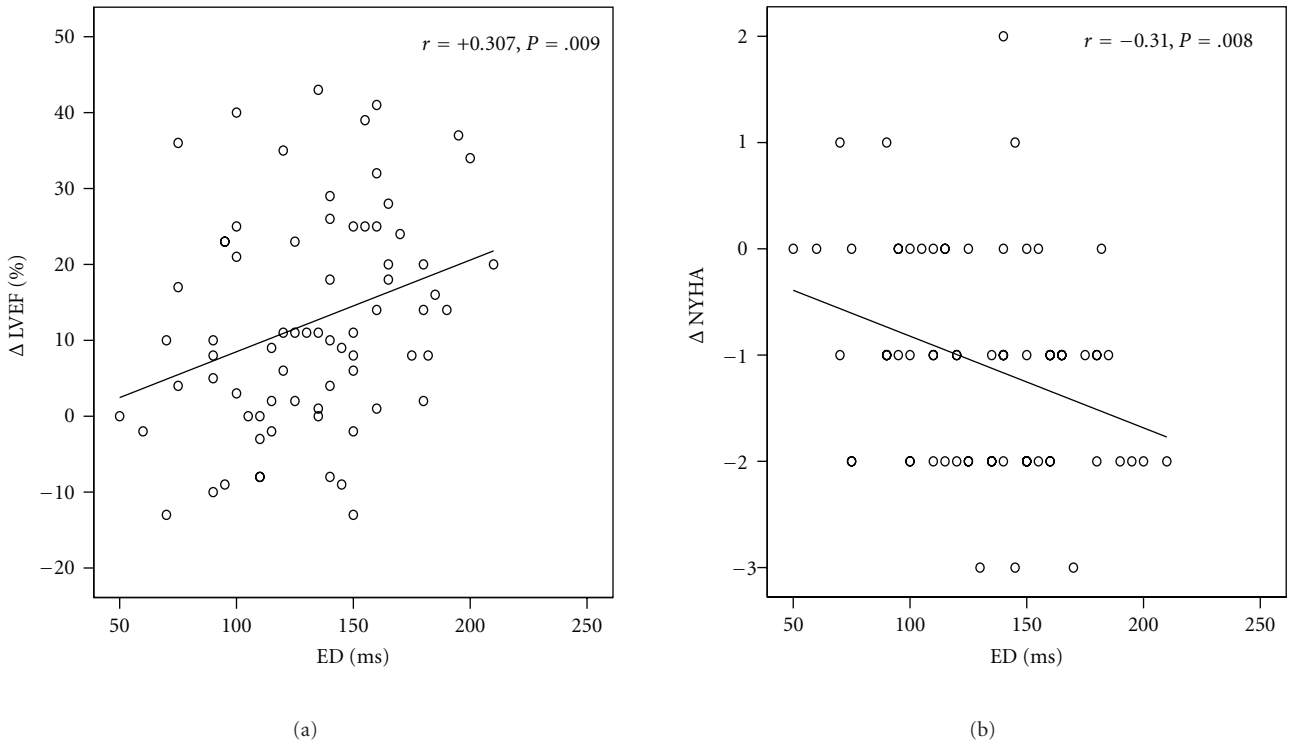
3.2.3. Comparison of Correlation between ED (or Ratio of ED/QRS Duration) and Response to CRT in Ischemic and Nonischemic Cardiomyopathy. The value of ED to predict response to CRT in patients with ischemic and nonischemic cardiomyopathy was analyzed separately (Table 4). We did not find a stronger correlation between ED and change of LVEF or NYHA class during long-term followup in patients with nonischemic dilated cardiomyopathy versus those with ischemic heart disease. The same result was observed when the correlation was examined with the ratio of ED/QRS duration.

3.2.4. Correlation between ED (or Ratio of ED/QRS Duration) and LV Lead Position in the LAO View. Figure 4 shows the distribution of ED (Figure 4(a)) and the ratio of ED/QRS duration (Figure 4(b)) based on the LV lead location in the LAO view. Almost all patients had their LV lead positioned between 1:30 and 5:00 o'clock. In 1 patient the LV lead was left in the great cardiac vein and in 2 patients, the final LV lead position was at 12:30. As shown in Figures 4(a) and 4(b), longer EDs and greater ratios ED/QRS duration were more likely to be located between 2:30 and 5:00 o'clock, but short EDs and small ratios were also observed in the same locations indicating that not all lateral sites were equal.

4. Discussion

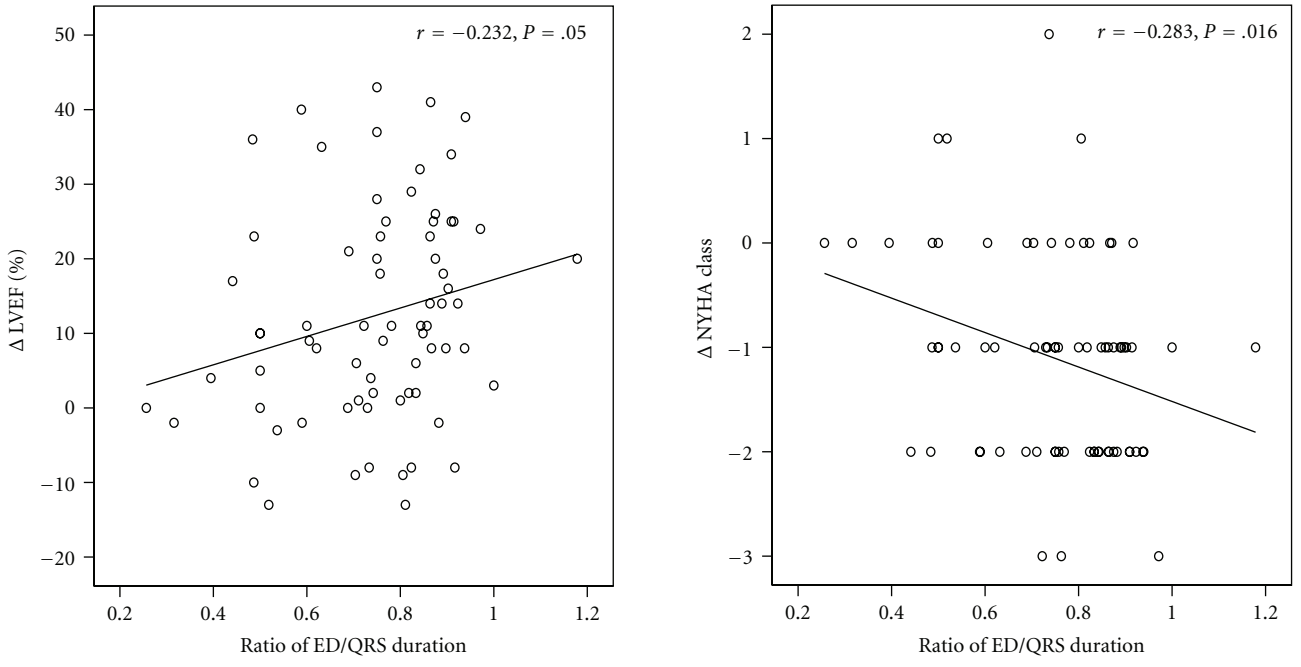
The present study demonstrates the value of intraprocedural epicardial EGM recording to direct placement of the LV lead in regions of long ED in order to increase the likelihood of long-term response to CRT. Although mechanical rather than electrical resynchronization has been suggested to be the primary determinant of hemodynamic benefit, we hypothesized that these two components are closely linked.

Controversial data from the literature raise the question whether positioning the LV lead should be guided by echocardiography to determine the site of latest mechanical contraction. Some of these reports indicate an enhanced response rate in patients in whom there is concordance between the position of the LV lead tip and the latest area of contraction [7, 9, 10, 19], whereas other investigators suggest that pacing at these sites is not always associated with



(a) (b)

Figure 2: Correlation between ED and Δ LVEF (a) and Δ NYHA class (b). Abbreviations: ED: electrical delay, Δ LVEF: difference of LVEF between long-term followup and baseline, Δ NYHA: difference of NYHA class between long-term followup and baseline.



(a) (b)

Figure 3: Correlation between ratio of ED/QRS duration and Δ LVEF (a) and Δ NYHA class (b). Abbreviations: ED: electrical delay, Δ LVEF: change in LVEF from baseline to long-term followup, Δ NYHA: change in NYHA class from baseline to long-term followup.

Table 2: Comparison of echocardiography and electrical parameters in responders and nonresponders.

	Responders	Nonresponders	*P*
Spontaneous QRS duration (ms)	177 ± 31	180 ± 26	.69
ED (ms)	139 ± 35	119 ± 37	.03
Ratio of ED/QRS duration	0.78 ± 0.15	0.68 ± 0.19	.02
LVEF (%)	25 ± 8	20 ± 7	.01
Baseline LVESV (mL)	182 ± 57	240 ± 63	<.001
Baseline LVEDV (mL)	269 ± 62	319 ± 75	.005
Δ LVEF (%)	+19.5 ± 11.9	−0.8 ± 7.7	<.001
Δ LVESV (mL)	−55 ± 72	+5 ± 62	.002
Δ LVESV (mL)	−68 ± 66	+5 ± 58	.001

Abbreviations: ED: electrical delay, LVEF: left ventricular ejection fraction, Δ LVEF: difference of LVEF between followup and baseline, LVESV: left ventricular end-systolic volume, LVEDV: left ventricular end-diastolic volume, Δ LVESV: difference of LVESV between followup and baseline, Δ LVESD: difference of LVESV between followup and baseline.

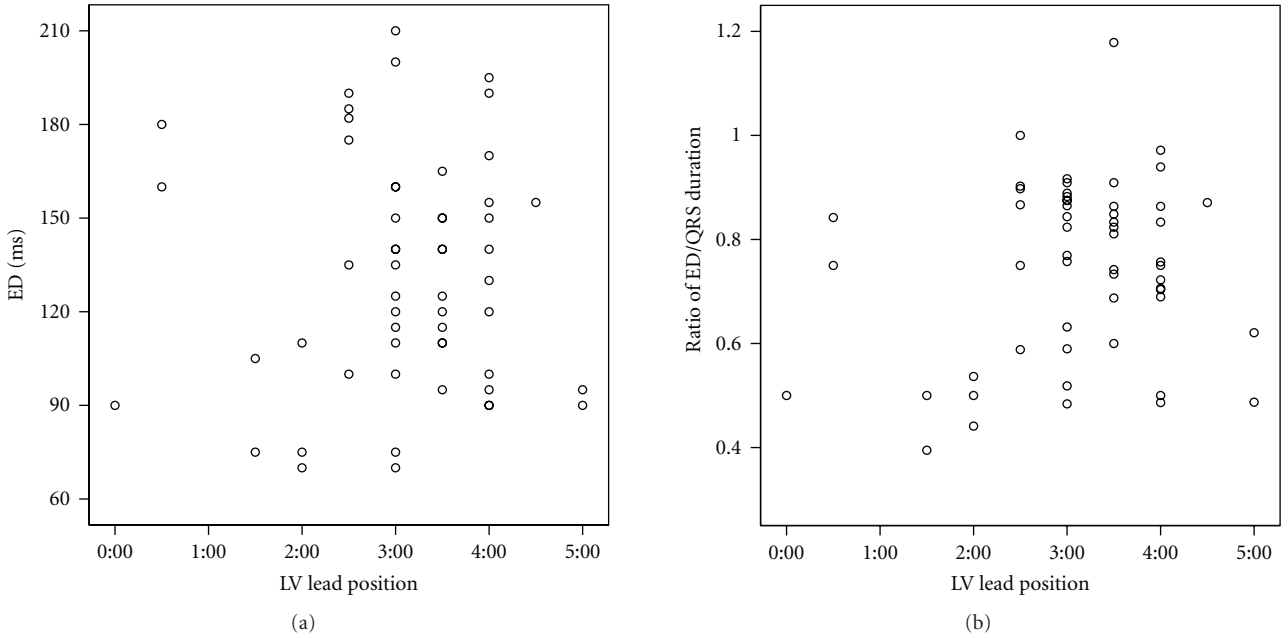


Figure 4: Distribution of ED (a) and ratios of ED/QRS duration (b) as a function of LV lead position in the LAO view. Abbreviations: ED: electrical delay, LAO: left anterior oblique.

Table 3: Multivariate predictors of response to CRT.

	OR	(95% CI)	*P*
SR at implant	1.3	0.2–10.1	.80
NIDCM	1.3	0.4–4.4	.69
LVEF	1.08	1.002–1.17	.045
Ratio of ED/QRS duration ≥0.83	6.8	1.7–27.5	.007

Abbreviations used: OR: odds ratio, CI: confidence interval, SR: sinus rhythm, NIDCM: nonischemic dilated cardiomyopathy, LVEF: left ventricular ejection fraction, ED: electrical delay.

acute or long-term response [20, 21]. On the other hand, adequate assessment of LV dyssynchrony and, more precisely, the site of latest mechanical activation requires sophisticated techniques that may prolong the implantation time, and their use is limited by high intra- and interobserver variability as illustrated by the results of the PROSPECT trial [11], whereas intraoperative assessment of ED is straightforward and can be used as a surrogate method for selection of optimal LV pacing sites.

Another method that can be used intraoperatively to select optimal sites of LV pacing is intracardiac mapping. In a human study conducted on 14 candidates for CRT, Tse et al. [13] showed the greater hemodynamic improvement by LV pacing in patients presenting with larger amount of LV area with late endocardial activation time and preserved LV myocardium measured by electroanatomical mapping.

Table 4: Comparison of the value of ED in patients with ischemic and nonischemic cardiomyopathy.

	IDCM		NIDCM	
	r	*P*	*r*	*P*
ED versus Δ LVEF	+0.39	.06	+0.20	.17
ED versus Δ NYHA	−0.44	.03	−0.26	.07
Ratio of ED/QRS duration versus Δ LVEF	+0.37	.08	+0.08	.57
Ratio of ED/QRS duration versus Δ NYHA	−0.41	.05	−0.23	.11

Abbreviations: IDCM: ischemic dilated cardiomyopathy, NIDCM: nonischemic dilated cardiomyopathy, ED: electrical delay, Δ LVEF: difference of LVEF between follow-up and baseline, Δ NYHA: difference of NYHA between follow-up and baseline, *r*: correlation coefficient determined by regression analysis, *P*: *P* value.

Previously, Singh et al. [12] reported the value of the ED to predict response to CRT defined by one-year mortality and hospitalizations for heart failure. They found that a reduced LV electrical delay less than 50% of the QRS duration was associated with worse clinical outcome within the entire patients' population as well as when stratified into ischemic and nonischemic subgroups. Our results confirm these data at longer follow-up durations using a different endpoint for response to CRT. As in the latter study, we purposely expressed, in our multivariate analysis, the ED as the percentage of the baseline QRS duration and not the absolute value, in order to eliminate a potential impact of the QRS duration on the predictive value of the local ED. Despite this adjustment, this parameter remained an independent predictor of positive outcome.

Our study population comprised patients with both ischemic and nonischemic heart disease. This could have influenced our results. Indeed, the presence of scar does not preclude electrical capture of the myocardium, but this may not translate into mechanical contraction and, therefore, may not result in effective correction of LV dyssynchrony in the presence of extensive myocardial infarction. This hypothesis has been verified by several studies using different imaging techniques of scar quantification: Bleeker et al. [22] defined LV scar burden using contrast-enhanced MRI and reported that patients who failed to respond to CRT were more likely to have transmural scar in the posterolateral region of the LV (an important target for lead placement). Ypenburg et al. [23] assessed the importance of transmural scar quantified by gated SPECT in the LV pacing target region and showed that pacing at these sites was negatively correlated to subsequent LV reverse remodeling. These observations confirm some study reports where CRT results in greater improvement of LVEF and reduction of LV end-diastolic volume in patients with nonischemic dilated cardiomyopathy compared to those with ischemic heart disease and extensive transmural scar [24].

In our series, we took every precaution not to implant CRT in patients with severe ischemic heart disease and extensive myocardial scar (involving more than 4 LV segments) or history of lateral or posterolateral myocardial infarction who had a low likelihood of response. That may explain the lack of significant difference in the prevalence of nonischemic cardiomyopathy between responders and nonresponders. Multivariate analysis of our results did not identify the nonischemic nature of the cardiomyopathy as an independent predictor of positive outcome. Furthermore, correlation between ED and long-term response was analyzed separately in patients with nonischemic cardiomyopathy and was not superior in this subgroup of patients. On the other hand, fibrosis might also be present in patients with nonischemic dilated cardiomyopathy and may also decrease the efficacy of LV pacing. MRI studies are required to quantify fibrosis in patients with nonischemic heart disease at the sites of latest mechanical contraction or greatest ED.

4.1. Lack of Correlation between ED and Sites of LV Pacing on Chest X-Ray. Our study results indicate that there is no correlation between ED and the location of the LV lead documented in the LAO view. A wide range of values of ED or ED/QRS duration are observed in the postero-lateral or lateral locations which are known as important targets for LV lead placement. This finding implies that not all LBBBs are created equal: the ventricular conduction abnormality in patients with LBBB and LV dysfunction is not a uniform conduction system lesion [25]. Both endocardial and epicardial electroanatomical mapping of LV activation disclose significant variations during intrinsic conduction in both ischemic and nonischemic cardiomyopathy [26–28]. In some patients, wavefronts from multiple directions contribute to overall LV activation. In others, activation spreads from the anterior to the inferior wall, or the reverse. Alternatively, LV epicardial activation starts from the septoapical region, spreading laterally and ending at the lateral or posterolateral base. Wavefront propagation is sometimes influenced by areas of slow conduction or lines of conduction block, some of which are fixed and correlate with areas of scar and others shift to other locations during pacing maneuvers due to their functional character. These variations, which occur with similar QRS configurations on surface ECG, may result from any combination of conduction tissue lesion, scar and fibrosis, and slow cell-to-cell conduction. Therefore, electroanatomical mapping or, more simply, local electrical delay may refine LV lead placement to achieve the best effect. Since the presumed mechanism for the efficacy of CRT is the correction of conduction delay, response is more likely when pacing is delivered at an area of greater LV conduction delay, as suggested in our study.

4.2. Study Limitations. Although we found a significant relationship between ED and long-term response to CRT, the correlation was weak. Based on our results, long ED recorded during spontaneous LBBB predicts reverse remodeling and positive clinical outcome, with good specificity but low sensitivity, which means that in the presence of ED $\geq$ 150 ms or ED/QRS duration $\geq$0.83, the likelihood of positive outcome is very high, but shorter EDs or lower ED/QRS durations do not necessarily preclude long-term improvement following

CRT. The mechanism of this finding is unclear and may result from our recording technique that was performed from the tip of the final LV lead position in a tributary of the CS indicating activation of the epicardial and not endocardial side of the left ventricle. Endocardial electroanatomical mapping might have elucidated the complex mechanism of positive response in some patients with short EDs measured from the epicardial EGM recording. It is also unknown if ED can vary at the same LV site with the level of patient's activity. On the other hand, in our study, we did not map the whole LV to determine the site of maximal electrical delay. With the use of electroanatomical mapping, we could have identified areas of latest electrical activation where LV pacing could have resulted in better outcome.

The definition of responders in our study was a pure clinical endpoint when improvement of functional status was important and a composite clinical and echocardiographic endpoint when improvement of functional status was more modest. The reason for this selection is that patients were followed at regular intervals in our institution and improvement of functional status by one NYHA class with no improvement of LVEF might have resulted from the optimization of medical therapy at each visit and not from CRT. A plethora of endpoints for response to CRT have emerged in the literature: some are merely clinical, defining response as improvement of functional status by at least one NYHA class [19, 29, 30] or including composite factors such as peak VO_2 [31, 32], quality of life score [33, 34], and 6-minute walked distance [19, 31, 33, 35], others are based on echocardiographic parameters including reduction of LV end-systolic volume by at least 15% [35–37] or improvement of LVEF by at least 5% [38, 39]. Even though our population was highly selected (mostly LBBB, nonischemic heart disease, long QRS duration), the proportion of responders in our series was in the range of that previously reported in the literature [5, 6]. With softer clinical endpoints (improvement of function status by one NYHA class), we would have expected a higher response rate. Another explanation for our result is our longer follow-up duration. On the other hand, in large CRT trials, although the cut-off value for QRS duration was usually 120–130 ms, the actual average mean QRS duration of included patients was in the range of values reported in our study (>150 ms) [18].

The small number of our patients might have been another limitation of the study. With larger number of patients, a stronger correlation might have been found between ED and response to CRT.

5. Conclusions

Selecting the LV lead position at the site of the delayed electrical activation may provide an important criterion for appropriate pacing site in patients with both ischemic and nonischemic cardiomyopathy, with high specificity but low sensitivity. Pacing at sites of increased ED is associated with long-term benefit. Gross anatomic lateral location of the LV lead is not always correlated with electrical delay and by itself is not enough to predict chronic response to CRT.

References

[1] S. Cazeau, C. Leclercq, T. Lavergne et al., "Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay," *New England Journal of Medicine*, vol. 344, no. 12, pp. 873–880, 2001.

[2] W. T. Abraham, W. G. Fisher, A. L. Smith et al., "Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure," *The New England Journal of Medicine*, vol. 346, pp. 1845–1853, 2002.

[3] G. S. Nelson, R. D. Berger, B. J. Fetics et al., "Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block," *Circulation*, vol. 102, no. 25, pp. 3053–3059, 2000.

[4] J. G. F. Cleland, J.-C. Daubert, E. Erdmann et al., "The effect of cardiac resynchronization on morbidity and mortality in heart failure," *New England Journal of Medicine*, vol. 352, no. 15, pp. 1539–1549, 2005.

[5] D. H. Birnie and A. S. L. Tang, "The problem of non-response to cardiac resynchronization therapy," *Current Opinion in Cardiology*, vol. 21, no. 1, pp. 20–26, 2006.

[6] D. A. Kass, "Cardiac resynchronization therapy," *Journal of Cardiovascular Electrophysiology*, vol. 16, supplement 1, pp. S35–S41, 2005.

[7] G. Ansalone, P. Giannantoni, R. Ricci, P. Trambaiolo, F. Fedele, and M. Santini, "Doppler myocardial imaging to evaluate the effectiveness of pacing sites in patients receiving biventricular pacing," *Journal of the American College of Cardiology*, vol. 39, no. 3, pp. 489–499, 2002.

[8] R. H. Helm, M. Byrne, P. A. Helm et al., "Three-dimensional mapping of optimal left ventricular pacing site for cardiac resynchronization," *Circulation*, vol. 115, no. 8, pp. 953–961, 2007.

[9] R. T. Murphy, G. Sigurdsson, S. Mulamalla et al., "Tissue synchronization imaging and optimal left ventricular pacing site in cardiac resynchronization therapy," *American Journal of Cardiology*, vol. 97, no. 11, pp. 1615–1621, 2006.

[10] M. Becker, R. Kramann, A. Franke et al., "Impact of left ventricular lead position in cardiac resynchronization therapy on left ventricular remodelling. A circumferential strain analysis based on 2D echocardiography," *European Heart Journal*, vol. 28, no. 10, pp. 1211–1220, 2007.

[11] E. S. Chung, A. R. Leon, L. Tavazzi et al., "Results of the predictors of response to crt (PROSPECT) trial," *Circulation*, vol. 117, no. 20, pp. 2608–2616, 2008.

[12] J. P. Singh, D. Fan, E. K. Heist et al., "Left ventricular lead electrical delay predicts response to cardiac resynchronization therapy," *Heart Rhythm*, vol. 3, no. 11, pp. 1285–1292, 2006.

[13] H.-F. Tse, K. L.F. Lee, S.-H. Wan et al., "Area of left ventricular regional conduction delay and preserved myocardium predict responses to cardiac resynchronization therapy," *Journal of Cardiovascular Electrophysiology*, vol. 16, no. 7, pp. 690–695, 2005.

[14] P. D. Lambiase, A. Rinaldi, J. Hauck et al., "Non-contact left ventricular endocardial mapping in cardiac resynchronisation therapy," *Heart*, vol. 90, no. 1, pp. 44–51, 2004.

[15] K. Dickstein, P. E. Vardas, A. Auricchio et al., "2010 Focused Update of ESC Guidelines on device therapy in heart failure," *European Heart Journal*, vol. 31, no. 21, pp. 2677–2687, 2010.

[16] J. J. Blanc, D. G. Benditt, M. Gilard, Y. Etienne, J. Mansourati, and K. G. Lurie, "A method for permanent transvenous left ventricular pacing," *Pacing and Clinical Electrophysiology*, vol. 21, no. 11 I, pp. 2021–2024, 1998.

[17] M. Fatemi, Y. Etienne, P. Castellant, and J. J. Blanc, "Primary failure of cardiac resynchronization therapy: what are the causes and is it worth considering a second attempt? A single-centre experience," *Europace*, vol. 10, no. 11, pp. 1308–1312, 2008.

[18] N. M. Hawkins, M. C. Petrie, M. I. Burgess, and J. J. V. McMurray, "Selecting patients for cardiac resynchronization therapy: the fallacy of echocardiographic dyssynchrony," *Journal of the American College of Cardiology*, vol. 53, no. 21, pp. 1944–1959, 2009.

[19] C. Ypenburg, R. J. van Bommel, V. Delgado et al., "Optimal left ventricular lead position predicts reverse remodeling and survival after cardiac resynchronization therapy," *Journal of the American College of Cardiology*, vol. 52, no. 17, pp. 1402–1409, 2008.

[20] J. W. H. Fung, Y. Y. Lam, Q. Zhang et al., "Effect of left ventricular lead concordance to the delayed contraction segment on echocardiographic and clinical outcomes after cardiac resynchronization therapy," *Journal of Cardiovascular Electrophysiology*, vol. 20, no. 5, pp. 530–535, 2009.

[21] N. Derval, P. Steendijk, L. J. Gula et al., "Optimizing hemodynamics in heart failure patients by systematic screening of left ventricular pacing sites: the lateral left ventricular wall and the coronary sinus are rarely the best sites," *Journal of the American College of Cardiology*, vol. 55, no. 6, pp. 566–575, 2010.

[22] G. B. Bleeker, T. A. M. Kaandorp, H. J. Lamb et al., "Effect of posterolateral scar tissue on clinical and echocardiographic improvement after cardiac resynchronization therapy," *Circulation*, vol. 113, no. 7, pp. 969–976, 2006.

[23] C. Ypenburg, M. J. Schalij, G. B. Bleeker et al., "Extent of viability to predict response to cardiac resynchronization therapy in ischemic heart failure patients," *Journal of Nuclear Medicine*, vol. 47, no. 10, pp. 1565–1570, 2006.

[24] G. W. Woo, S. Petersen-Stejskal, J. W. Johnson, J. B. Conti, J. A. Aranda, and A. B. Curtis, "Ventricular reverse remodeling and 6-month outcomes in patients receiving cardiac resynchronization therapy: analysis of the MIRACLE study," *Journal of Interventional Cardiac Electrophysiology*, vol. 12, no. 2, pp. 107–113, 2005.

[25] N. Varma, "Cardiac resynchronization therapy and the electrical substrate in heart failure: what does the QRS conceal?" *Heart Rhythm*, vol. 6, no. 7, pp. 1059–1062, 2009.

[26] A. Auricchio, C. Fantoni, F. Regoli et al., "Characterization of left ventricular activation in patients with heart failure and left bundle-branch block," *Circulation*, vol. 109, no. 9, pp. 1133–1139, 2004.

[27] L. M. Rodriguez, C. Timmermans, A. Nabar, G. Beatty, and H. J. J. Wellens, "Variable patterns of septal activation in patients with left bundle branch block and heart failure," *Journal of Cardiovascular Electrophysiology*, vol. 14, no. 2, pp. 135–141, 2003.

[28] P. Jia, C. Ramanathan, R. N. Ghanem, K. Ryu, N. Varma, and Y. Rudy, "Electrocardiographic imaging of cardiac resynchronization therapy in heart failure: observation of variable electrophysiologic responses," *Heart Rhythm*, vol. 3, no. 3, pp. 296–310, 2006.

[29] A. M. Duncan, E. Lim, J. Clague, D. G. Gibson, and M. Y. Henein, "Comparison of segmental and global markers of dyssynchrony in predicting clinical response to cardiac resynchronization," *European Heart Journal*, vol. 27, no. 20, pp. 2426–2432, 2006.

[30] G. B. Bleeker, M. J. Schalij, E. Boersma et al., "Relative merits of M-mode echocardiography and tissue Doppler imaging for prediction of response to cardiac resynchronization therapy in patients with heart failure secondary to ischemic or idiopathic dilated cardiomyopathy," *American Journal of Cardiology*, vol. 99, no. 1, pp. 68–74, 2007.

[31] G. Lecoq, C. Leclercq, E. Leray et al., "Clinical and electrocardiographic predictors of a positive response to cardiac resynchronization therapy in advanced heart failure," *European Heart Journal*, vol. 26, no. 11, pp. 1094–1100, 2005.

[32] C. Alonso, C. Leclercq, F. Victor et al., "Electrocardiographic predictive factors of long-term clinical improvement with multisite biventricular pacing in advanced heart failure," *American Journal of Cardiology*, vol. 84, no. 12, pp. 1417–1421, 1999.

[33] D. Notabartolo, J. D. Merlino, A. L. Smith et al., "Usefulness of the peak velocity difference by tissue Doppler imaging technique as an effective predictor of response to cardiac resynchronization therapy," *American Journal of Cardiology*, vol. 94, no. 6, pp. 817–820, 2004.

[34] S. Reuter, S. Garrigue, S. S. Barold et al., "Comparison of characteristics in responders versus nonresponders with biventricular pacing for drug-resistant congestive heart failure," *American Journal of Cardiology*, vol. 89, no. 3, pp. 346–350, 2002.

[35] J. J. Bax, G. B. Bleeker, T. H. Marwick et al., "Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy," *Journal of the American College of Cardiology*, vol. 44, no. 9, pp. 1834–1840, 2004.

[36] M. V. Pitzalis, M. Iacoviello, R. Romito et al., "Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony," *Journal of the American College of Cardiology*, vol. 40, no. 9, pp. 1615–1622, 2002.

[37] C. M. Yu, W. H. Fung, H. Lin, Q. Zhang, J. E. Sanderson, and C. P. Lau, "Predictors of left ventricular reverse remodelling after cardiac resynchronization therapy for heart failure secondary to idiopathic dilated or ischemic cardiomyopathy," *American Journal of Cardiology*, vol. 91, pp. 684–688, 2003.

[38] M. V. Pitzalis, M. Iacoviello, R. Romito et al., "Ventricular asynchrony predicts a better outcome in patients with chronic heart failure receiving cardiac resynchronization therapy," *Journal of the American College of Cardiology*, vol. 45, no. 1, pp. 65–69, 2005.

[39] J. J. Bax, T. H. Marwick, S. G. Molhoek et al., "Left ventricular dyssynchrony predicts benefit of cardiac resynchronization therapy in patients with end-stage heart failure before pacemaker implantation," *American Journal of Cardiology*, vol. 92, no. 10, pp. 1238–1240, 2003.

SAGE-Hindawi Access to Research
Cardiology Research and Practice
Volume 2011, Article ID 187434, 11 pages
doi:10.4061/2011/187434

Review Article

Focused Review on Transthoracic Echocardiographic Assessment of Patients with Continuous Axial Left Ventricular Assist Devices

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Received 2 November 2010; Accepted 17 December 2010

Academic Editor: Dirk Westermann

Left ventricular assist devices (LVADs) are systems for mechanical support for patients with end-stage heart failure. Preoperative, postoperative and comprehensive followup with transthoracic echocardiography has a major role in LVAD patient management. In this paper, we will present briefly the hemodynamics of axial-flow LVAD, the rationale, and available data for a complete and organized echocardiographic assessment in these patients including preoperative assessment, postoperative and long-term evaluation.

1. Introduction

Left ventricular assist devices (LVADs) are systems for mechanical support for patients with end-stage heart failure. They are effective in supporting the circulation for weeks to years as a bridge to transplant (BTT) or destination therapy (DT) [1–4]. The newer axial-flow devices have been designed in an effort to minimize operative risk, improve durability, and lower the risk of device-related adverse events by reducing the number of moving parts in the device and device size [5–7]. Continuous axial flow LVAD can provide effective hemodynamic support for prolonged periods, improving functional status and quality of life [8, 9]. The designation axial flow device refers specifically to the design and shape of the impeller, and therefore the route by which fluid is accelerated. The impellers of axial flow pumps generally add energy by deflecting flow in the circumferential direction. Despite their small size, these pumps can provide flows of up to 8–10 L/min, sufficient to support a large adult patient. Currently, there are two major types of axial pumps in the USA: Heartmate II (Heartmate II, Thoratec, Pleasanton, CA) and Jarvic 2000 (Jarvik, New York City, New York, USA). The Jarvik 2000 is an intraventricular axial flow pump that measures 25 mm in diameter by 55 mm in length with a weight of approximately 85 g. It consists of the pump positioned inside the left ventricular cavity and the outflow cannula which can be anastomosed to the right anterior aspect of the ascending aorta or to the descending aorta. The impeller rotates in the left ventricular cavity at speeds of 8,000 to 12,000 revolutions per minute (RPM) to deliver 2 to 7 L/min. The pulse control circuit allows the user to adjust the rotational speed of the pump manually.

The HeartMate II LVAD (Thoratec, Pleasanton, CA) is a continuous, axial-flow LVAD, positioned in succession to the left ventricle (LV). It consists of a spinning rotor pump as its lone moving part, an inflow cannula, an outflow cannula, and a single driveline that exits percutaneously towards the electronic controller [6, 7]. The inflow cannula is inserted into the apex of the LV, and the outflow cannula is anastomosed to the right anterior aspect of the ascending aorta. The LVAD pump is placed within the preperitoneal space. In both pumps, the percutaneous lead carries the electrical cable to an electronic controler and battery packs (one in the Jarvik and two in the HeartMate II), which are worn on a belt and a shoulder holster, respectively. The spinning rotor draws blood from the inflow

cannula throughout cardiac diastole and systole, propelling it into the aorta. Preoperative, postoperative, and followup transthoracic echocardiography (TTE) has a major role in LVAD patient management. In this paper, we will present briefly the hemodynamics of axial-flow LVAD, focusing on the HeartMate II, and the rationale and available data for a comprehensive echocardiographic assessment in these patients including preoperative assessment, postoperative and long-term evaluation.

LVAD Performance Parameters. The system-provided parameters of speed, power, PI, and estimated flow for the HeartMate II serve as important indicators of proper LVAD function. It is important to view each of these device parameters in the context of the patient's overall condition. Once baseline values representing a good level of patient support are established, the degree of change in a parameter usually has more clinical significance than its absolute value. Briefly, the pump speed will be determined during a speed ramp study. Pump power is a direct measurement of motor voltage and current. Increases in pump speed, flow, or physiological demand will increase pump power. Specifically, gradual power increases, power values greater than 10–12 watts, or abrupt changes in power should raise concern for possible thrombus inside the pump. When the LV contracts, the increase in ventricular pressure causes an increase in pump flow during systole. The magnitude of these flow changes is measured to produce the PI. The PI represents cardiac pulsatility and is related to the magnitude of assistance provided by the LVAD. Higher values indicate more ventricular filling or better contractility (pump is providing less support to the LV), while lower values indicate less ventricular filling or lower contractility. Pump flow is estimated based on power. Since it is a calculated value, it becomes imprecise at low and high regions of the power-flow relationship. Therefore, any increase in power not related to an increased flow, such as thrombus, will cause an erroneously high flow. Conversely, an occlusion of flow path (inflow obstruction due to malposition or suction events) will decrease power and calculated flow. In either situation, an independent assessment of pump output using the TTE should be performed.

2. Evaluation of Axial-Flow LVAD Hemodynamics

2.1. The "Tight Relation" between the LV, the Left Atrium, and the Aorta . Axial-flow pumps are connected in series to the LV by the inflow cannula, with the LV being the direct source of preload essential for LVAD output. They continuously unload the LV during the entire cardiac cycle, eliminating the isometric contraction and relaxation phases of normal cardiac activity. Although considered to be continuous flow assist devices, working in succession to the LV, the true hemodynamic profile depends on the pump speed, the LV contractility, the preload, and the afterload conditions.

The volume of flow generated by continuous flow LVAD is determined by the speed of the rotation of the pump and by the differential pressure that exists across the device. For a specified speed, flow varies inversely with the pressure difference [10]. The LVAD is connected to the circulation by the inflow conduit on the LV apex, while the outflow graft is secured to the aorta. With these connections, throughout the cardiac cycle, the pump differential pressure is equal to the aortic pressure minus the LV pressure. In other words, the flow increases with increasing LV pressure (LVAD preload), or decreasing aortic pressure (LVAD afterload). The dynamic parameter that determines the pump's differential pressure is the LV pressure, which in turn is dependent on its contractile reserve. Even a severely depressed LV will have the possibility to generate some residual rhythmic contraction that will create pulse pressure. This pressure fluctuation at the pump inflow will change the pump differential pressure, which in turn will alter the pump flow. Therefore, any residual contraction of the LV will be transduced as a flow pulse delivered to the aorta, creating, under most circumstances, pulsatile systemic flow.

At maximal speed, the LV end-diastolic volume decreases to a minimum, due to maximal decompression by the LVAD. This is comparable to a state of "hypovolemic shock." The reduced preload is translated to subphysiological LV and left atrial systolic and diastolic pressures. Furthermore, the already failing LV exposed to reduced preload decreases its contractility according to Starling's response. This minimizes the increase in LV systolic pressure, resulting in a non-significant systolic increase in LVAD preload and output. The systemic circulation is continuously supported by the maximal LVAD output, preventing significant changes in the aortic pressure and flow between systole and diastole. LV systolic pressure does not increase above aortic pressures and is insufficient to allow aortic ejection. The LV remains the direct source of LVAD preload but does not contribute independently to the cardiac output.

As pump flow decreases to submaximal values (10,000 to 11,000 rpm), pulsatility is generated. More blood is left in the ventricle, enhancing LV contractility as LV systolic pressure rises. The increased LV systolic pressure translates into increased systolic LVAD preload generating pulsatility. Under submaximal LVAD speed, systolic LV pressure does not increase above aortic pressure and is still insufficient to allow aortic ejection (aortic valve opening). The LV still does not contribute independently to cardiac output.

Reducing pump speed further increases the amount of blood left in the ventricle. LV contractility increases through the Starling's response, and the LV systolic pressure increases above aortic pressure allowing aortic valve opening and systolic ejection. Aortic valve closure (and opening) can therefore be recognized by the reappearance of the normal dicrotic notch in the aortic pressure curve.

2.2. Hemodynamic Impact of the LVAD on Right-Sided Chambers. As previously discussed, the axial-flow pumps are directly connected to the LV through the inflow cannula, making the LV the direct source of preload. The LV, in turn, receives preload from the right ventricle (RV) through the pulmonary circulation. This important concept is central to optimal pump function. Right heart dysfunction (RHD) is

a frequent concern after LVAD implantation, as it occurs in one-third of patients. It contributes significantly to postoperative morbidity and mortality [11]. The LVAD mechanically unloads the LV, resulting in subphysiological left atrial and left ventricular pressures. On the other hand, right ventricular and right atrial pressures may be elevated after LVAD implantation [5]. Excessive unloading of left heart chambers may result in a complex biphasic effect on RV function. Following LVAD implantation, there is a significant decrease in mean left atrial and mean pulmonary pressures [12]. The reduced RV afterload may therefore improve its function and total output. However, bowing of the interventricular septum away from the right ventricle into the decompressed LV may reduce the efficiency of RV contraction by destabilizing the hinge upon which the RV contracts [11, 12]. Moreover, the RV may receive excessive venous return owing to the LVAD effective forward flow through the systemic circulation, resulting in RV dilatation and dysfunction [13]. Maintaining the septum in the midline position requires maintenance of adequate or appropriate LV volume. This can result in suboptimal LVAD flow, which prevents overcirculation that could overwhelm the functional capacity of the RV. If cardiac output decreases because of lack of LV filling due to RV failure, high pulmonary resistance, or significant tricuspid regurgitation (TR), it is hazardous to attempt to improve the patient's condition by increasing pump speed. Without improvement in left ventricular inflow, increasing the speed will cause a further decrease in the size of the LV cavity compounding the leftward septal shift. This further impairs RV function and increases TR severity, decreasing the already compromised LV inflow. This worsening spiral, sometimes referred to as the "suction cascade," may cause the septum to encroach upon the inflow cannula, increasing inflow velocities, but decreasing the LVAD preload. This requires immediate intervention to avoid a vicious cycle that can eventually lead to a fatal outcome.

3. "Step by Step" Preoperative Role of Echocardiography in LVAD Patients

Transthoracic echocardiographic assessment of patient undergoing VAD insertion involves aspects related both to general echocardiographic examinations and to specific considerations associated with the LVAD. We will concentrate on specific imaging concerns pertaining to LVAD patients. For simplicity purposes, we will divide this section in three distinct parts: (1) preoperative evaluation; (2) postoperative assessment; (3) long-term echocardiographic considerations.

3.1. Preoperative Surgical Evaluation. Pre-LVAD insertion examination of the heart and large vessels is done for two main purposes: (1) evaluating suitability of patient for LVAD placement; (2) assessing significant cardiac abnormalities that could lead to postoperative complications. Important preoperative imaging include the evaluation of left heart chamber function and structure, the quantification of RV function and TR, and the assessment for aortic and mitral regurgitation. Other specific LVAD concerns are the presence of a patent foramen ovale, or the presence of intracardiac clots. These are routinely evaluated with transesophageal echocardiography in the operating room.

3.1.1. Preoperative Evaluation of the Left Heart Chambers. The evaluation of the LV function before LVAD implantation will most commonly show depressed function with either a dilated or normal sized ventricle, depending on the cause of heart failure. The LV ejection fraction (LVEF) pre-LVAD insertion is typically <25%–30%. Significant diastolic dysfunction is also usually present. The presence of a restrictive LV diastolic physiology reflects increased LV and LA pressures and, when severe, supports the indication of LVAD implantation [14]. Another common finding in patients eligible for LVAD implantation is significant functional mitral regurgitation, due to mitral annulus dilatation, and apical tethering of mitral leaflets secondary to the geometrical changes imposed on the left ventricle [15].

3.1.2. Right Ventricular Function and TR. The central role of RV function has already been discussed in detail emphasizing the importance of a proper functional evaluation of the RV before LVAD implantation. The RV is a complex structure and is incompletely visualized in any single 2D echocardiographic view. Two methods are commonly used to evaluate RV function before LVAD implantation. The first is semiquantitative assessment of RV function and dilatation, using the four chambers and inflow views. This assessment is based on visual appreciation of longitudinal and radial RV motion. A more quantitative approach was recently proposed in recent reports; the global RV fractional area change is calculated as the RV fractional area change = (RV diastolic area-RV systolic area)/RV diastolic area, with RV diastolic and systolic areas traced in the 4 chamber views [16]. An RV fractional area change (RVFAC) of 40% or higher is normal. Typically, the RVFAC in a patient needing an LVAD implantation is 20% to 30%. Patients with an RVFAC <20% are more prone to postoperative RV failure. For estimation of TR, a combination of qualitative and quantitative methods are used as described previously [17]. More than moderate TR requires surgical correction either through a TV annuloplasty or a tricuspid valve replacement [18].

3.1.3. Aortic Regurgitation. Diagnosis of significant pre- and postoperative aortic regurgitation (AR) is crucial in patients receiving an LVAD. The LVAD draws blood from the LV and ejects it into the aorta creating subphysiological LV pressures. The retrograde aorta to LV gradient increases and continues throughout the cardiac cycle, including most of the systolic phase. During maximal LVAD output, the aortic valve is permanently closed, encountering this gradient constantly. The combination of increased pressure gradient and exposure time results in increased regurgitant volume after LVAD insertion. The regurgitant volume increases LVAD preload and LV dimensions and causes secondary pump flow volume upregulation. This in turn results in further increase in blood ejection to the ascending aorta.

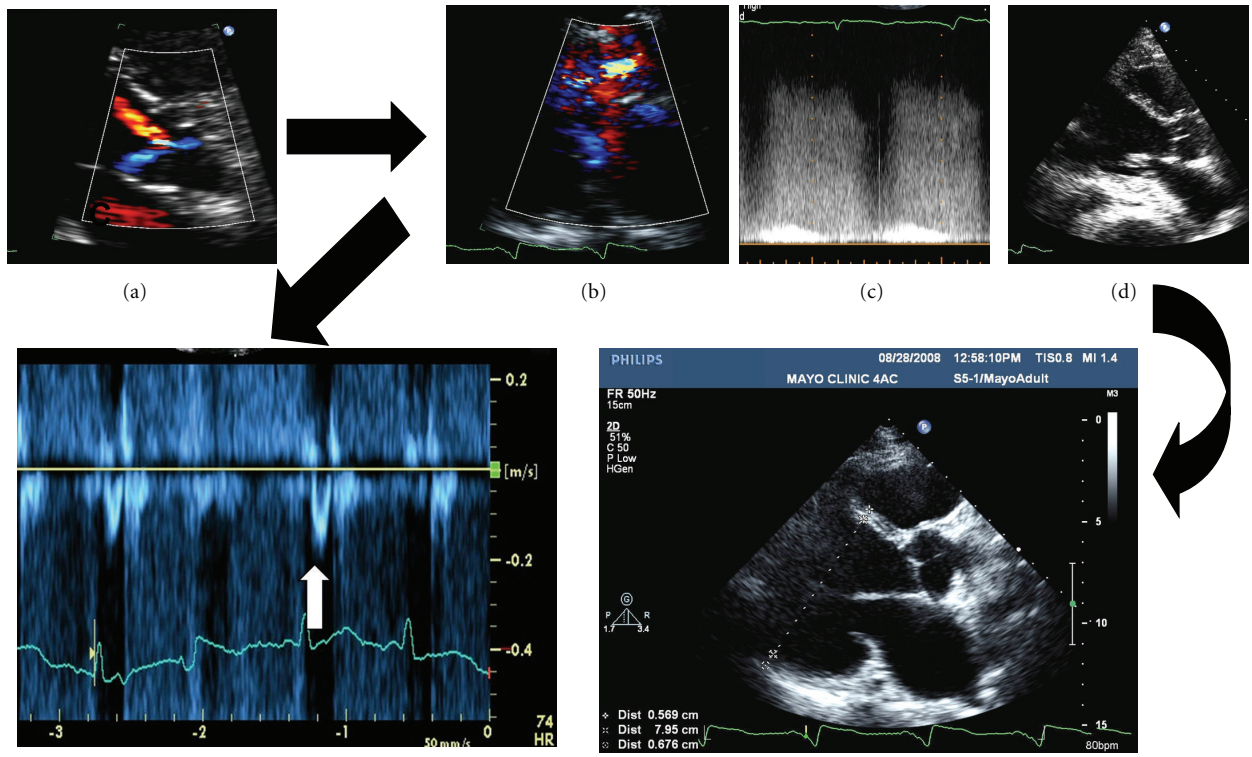

Figure 1: Aortic regurgitation after implantation. Patient presented with new onset heart failure 6 months after LVAD implantation. LVAD evaluation showed increased power and LVAD flow. (a) Pre-LVAD parasternal long axis view showing mild diastolic aortic regurgitation. (b), (c), and (d) Immediately after LVAD, blood is pumped from the LV into the aorta creating subphysiological LV pressures. The retrograde aorta to LV gradient increases and continues throughout the cardiac cycle, including most of the systolic phase. Aortic regurgitation has increased in volume and takes place during most of the cardiac cycle. (e) and (f) Six months after LVAD surgery. Aortic regurgitation deteriorated secondary to closed aortic valve encountering high retrograde pressure gradient throughout the cardiac cycle. The progressing regurgitant volume increased left ventricular diameter, which in turn amplified LVAD preload and output. Pump output spiraled up to very high levels, while actual systemic blood flow fell. The end result was a "futile cycle" consisting of high pump flow, low total cardiac output, and high left ventricular and left atrial pressures.

Pump output spirals up to very high levels, while actual systemic blood flow falls. The increased LV dimensions may result in apical tethering of mitral leaflets and functional MR. The end result is a "futile cycle" consisting of high pump flow, low total cardiac output, and high LV and LA pressures (Figure 1). In our institution, patients with significant AR as a result of structural problems of the valve undergo aortic valve replacement or surgical closure of the aortic valve leaflets (Park's stitch) [19].

3.1.4. Patent Foramen Ovale (PFO). Investigation of a Patent Foramen Ovale (PFO) should always be performed before implantation of an LVAD. Because a PFO is common (around 25% of the population), meticulous care should be taken to identify its presence. We find that the best way to identify a PFO by TTE is with the use of contrast (agitated saline or bubble study) concurrent with color Doppler. We usually perform the exam in the apical four-chamber view or the subcostal view focusing on the interatrial septum. Patients are taught to perform standard Valsalva maneuver before their echocardiographic examination: first, sustained straining against a closed epiglottis causing abdominal distension for 10 seconds before sudden release of the strain by deep inspiration. Adequate performance of Valsalva maneuver can be detected by a decrease in the left atrial and ventricular sizes with interatrial septum bulging to the left atrium. For contrast injection, we use an 18 French catheter inserted at the right antecubital vein, which is connected by an extension tube to a 3-way stopcock with two 10 mL Luer Lock syringes. One mL of patient's blood is drawn from the vein into a syringe containing 8 mL of sterile normal saline solution and 1 mL of air. The content is forcefully injected back and forth for few times between the two syringes to become a cloudy and foamy pink emulsion and then rapidly administered intravenously to the patient at baseline, before the Valsalva maneuver. Pre-LVAD implantation LA pressure surpasses the RA pressure. Because of this factor, investigation of a PFO with color Doppler echocardiography may show a left-to-right shunt, and a bubble study may not reveal a PFO due to the difficulty in producing a transient reversal of the left-to-right

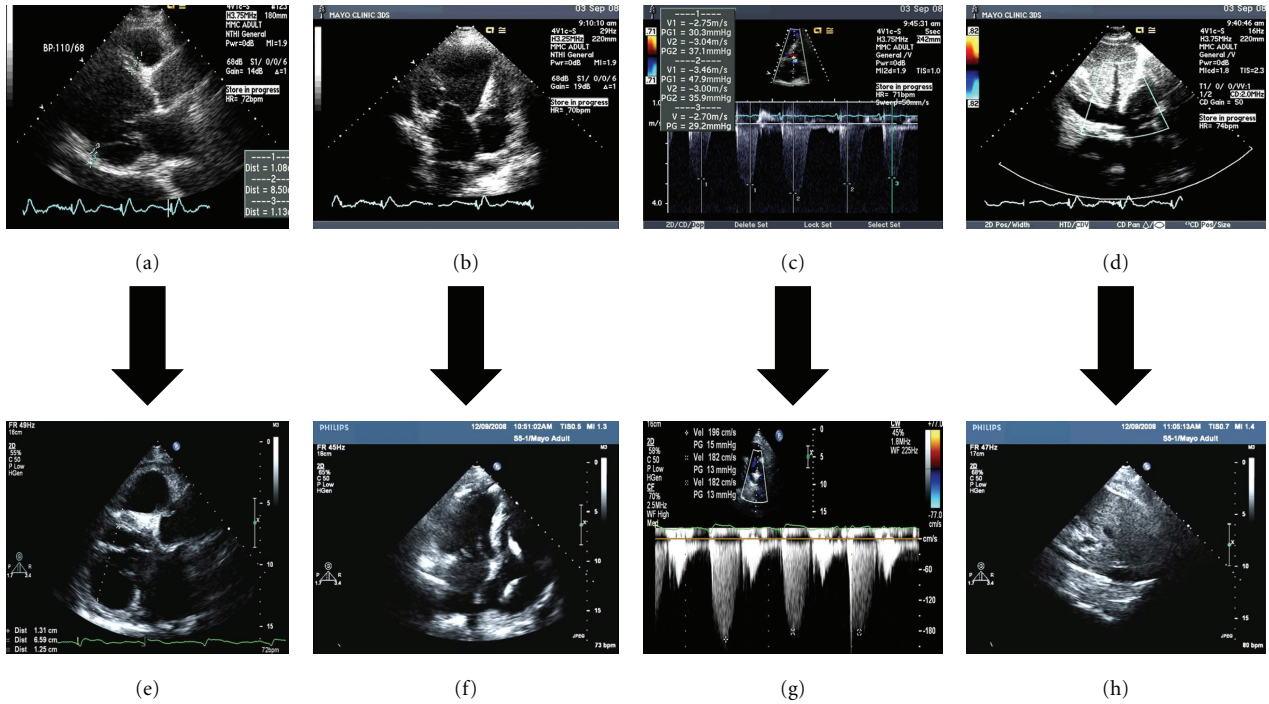

Figure 2: Interventricular dependency. Parasternal long axis view showing severely dilated LV (end-diastolic dimension 85 mm). (b) Apical 4-chamber view showing interventricular, interatrial septa shifted to the right, and increased tenting and annular dimensions of mitral valve apparatus. (c) and (d) Systolic right ventricular and right atrial pressure is increased. *The same patient two months after surgery.* (e) End-diastolic diameter decreased, and septal and posterior walls have thickened. (f) Interventricular and interatrial septa are now shifted to the left. Mitral annulus and tenting area have decreased as well as functional mitral regurgitation. (g) and (h) Systolic right ventricular and right atrial pressures have decreased significantly.

pressure gradient in the presence of left heart failure, even when a Valsalva maneuver release is correctly applied. After insertion of an LVAD, there is LV unloading with decrease of the LA pressure. This hemodynamic change, in association with maintained or increased right heart pressures, may uncover the existence of the PFO, usually with the use of intraoperative TEE. Those hemodynamic conditions can also favor a paradoxical embolism which may result in stroke or even pump thrombosis. One of the serious and more common consequences of this sequence of events is the development of severe hypoxemia due to the significant right-to-left shunt stressing the need to evaluate for PFO before and after LVAD implantation.

4. Postoperative Value of Echocardiography in LVAD Patients

Postsurgical TTE evaluation is performed for two main purposes: (1) to evaluate the surgical results of the LVAD implantation; (2) to determine reasons for postoperative hemodynamic compromises. Specifically, important routine postoperative imaging concerns include the following: (1) overall structure and function of left heart chambers; (2) quantification of RV function and TR; (3) proper inflow and outflow cannula placement.

4.1. Postoperative Evaluation of Left Heart Chambers. After LVAD insertion, the LV and the LA are unloaded with a reduction in their size [20]. Neutral or slight leftward interventricular and interatrial septa position indicates adequate LV and LA decompression (Figure 2). This appearance should persist throughout the subsequent examinations. If the LV is not decompressed after LVAD implantation, a rightward septum shift can be seen and suspicion of insufficient device ejection, or cannula obstruction should be immediately raised. In contrast, extreme leftward septal shift may indicate excessive decompression due to high pump RPM, significant tricuspid regurgitation, or RV dysfunction. Because LVAD promotes nonphysiological LV unloading, common parameters for LV function assessment such as LVEF become invalid.

4.2. Right Ventricular Function and TR. Up to one-third of patients will present with variable degrees of RV dysfunction following surgery [11]. This stresses the importance of a thorough re-examination of RV function and TR severity after LVAD insertion. The postoperative examination should follow the same protocol described in the pre-LVAD examination section. Once identified echocardiographically, TR severity should be assessed during pump flow adjustments. Such adjustments lead not only to the reduction of the TR but can also improve RV function. As part of the integrated estimation of right heart function, mean pulmonary pressure should be estimated using the mean of peak systolic tricuspid regurgitation velocity in end expiration. The right atrial pressure (RAP) should be estimated by the inferior vena cava diameter and its response to inspiration as described [21].

4.3. Assessment of Aortic and Mitral Regurgitation Severity. Estimation of AR severity should be part of every TTE evaluation as it may deteriorate secondary to the closed aortic valve encountering high retrograde pressure gradient, continued throughout the cardiac cycle. The most commonly used methods are visual estimation by color Doppler, the ratio of AR jet area to the short axis area of the LVOT at the level of the aortic annulus, and the width of the regurgitant jet at its origin relative to the dimension of the LVOT in the parasternal long axis view. For mitral regurgitation (MR), in a normally functioning LVAD system, functional MR is expected to decrease significantly. When MR persists, a thorough evaluation of its cause should be performed. In our experience, functional MR "begets" functional MR just as in patients without LVAD. Suboptimal LVAD RPM setting results in increased LV dimension, mitral valve tenting, significant mitral regurgitation, and volume overload of left ventricle, culminating in increasing LV diameter and deteriorating functional MR (Figure 3). Whenever significant functional MR is encountered, a trial of increasing RPM under echocardiographic guidance should be tried.

4.4. Inflow Cannula Evaluation. The inflow cannula and its orientation within the left ventricular apex should be visualised on the four- and two-chamber views. The cannula should be aligned with the LV inflow tract. Color Doppler is an important component of the examination. A properly aligned inflow cannula should have a laminar and unidirectional flow from the ventricle to the device. Abnormally high velocity or turbulent flow suggests obstruction of the inflow cannula. The most common reasons for obstruction to flow in the inflow cannula are thrombus or intermittent obstruction of the cannula by the ventricular wall (Figure 4) [22]. Doppler assessment of the inflow cannula should be done in the four- and two-chamber views, as they are aligned with the central axis of a properly positioned inflow cannula. Pulsed Doppler assessment should show laminar, low velocity flow, with no regurgitation. Continuous Doppler is used for measurement of the maximal velocity along the inflow pathway from the ventricle to the LVAD. Particular attention should be paid to high velocities produced by cannula obstruction, and regurgitant flow suggestive of pump malfunction. Axial-flow devices such as the HeartMate II will normally show a pulsatile inflow pattern because the pump inflow originates from the beating LV, resulting in periodic changes in flow throughout the cardiac cycle, reaching a maximum during systole, and minimum during diastole. This pattern is present even when the aortic valve does not open. Axial-flow devices show peak filling velocity between 0.7 and 2.0 m/s according to preload and the remaining pumping action of the patient's heart.

4.5. Outflow Cannula. Interrogation of the outflow cannula by TTE is technically challenging. We advocate the use of (1) high left parasternal long axis view, which shows the end-to-side anastomosis of the outflow cannula to the midascending aorta; (2) right parasternal view, with the patient lying on his right side, which shows the long axis of the outflow cannula traversing from the pump towards the right aspect of the ascending aorta. Color flow, PW, and CW Doppler are used to evaluate flow patterns of the outflow cannula. To measure flow velocity in the outflow graft, the PW sample volume should be at least 1 cm proximal to the aortic anastomosis. The peak velocity in the outflow graft in axial flow pumps usually ranges from 0.5 to 2.0 m/s, with unidirectional and slightly pulsatile flow [23], dependent on LVAD output and speed. Flow patterns of the aortic outflow cannula are significantly affected by the angle of insertion of the LVAD outflow cannula into the native aorta [24]. Connecting the LVAD outflow conduit at a shallower angle to the proximal aorta produces fewer secondary flows, lower shear stress on the aortic wall, and lower peak velocities. Sometimes velocity can be measured in the right parasternal view, with the flow directed towards the transducer.

5. Evaluation of Postoperative Hemodynamic Instability

The most common reasons for hemodynamic instability during the first postoperative days are hypovolemia (from intractable bleeding), acute RV dysfunction, cardiac tamponade, pulmonary emboli and LVAD dysfunction, most commonly secondary to impeller thrombosis [25].

Acute RV dysfunction can manifest itself in the previously described "suction cascade," including dilated hypocontractile RV, significant functional TR, small LV, and intermittent inflow cannula obstruction by the collapsed LV. Pulmonary embolism can cause acute RV dysfunction, will present in a similar way, and should be considered whenever right-sided pressures are higher than expected. Cardiac tamponade is sometimes very difficult to diagnose. Blood collections may be loculated and confined to a small area, compressing a particular chamber. Right or left atrial tamponade can occur with very small collections of blood. Right ventricular tamponade may be the consequence of a loculated substernal thrombus [25]. The unusual physiology of the LV makes the standard Doppler assessments for tamponade very challenging, since the device's echogenicity impairs thrombi visualization. On the other hand, LVAD dysfunction or thrombosis should be suspected with the following combination of findings: (1) rightward deviation of the interventricular and interatrial septum as a sign of deficient unloading of the LV and left atrium; (2) significant functional MR, due to insufficient LV unloading, mitral annular dilatation, and apical tethering of the mitral leaflets; (3) aortic valve opening every cardiac cycle due to increased LV systolic pressure; (4) decreased LVAD flow; (5) disturbed LVAD parameters, mainly increased power intake; (6) laboratory clues suggesting intravascular hemolysis (increased LDH, plasma hemoglobin, and bilirubin with decreased haptoglobin). This will be demonstrated by color, or PW Doppler evaluation of the cannula. Whenever the pump's impeller does not rotate, the LVAD system operates as a conduit connecting the ascending aorta to the left ventricular apex. Diastolic aortic pressure is higher than left ventricular diastolic pressure, and under conditions of impaired pump rotation, the pressure difference reverses the flow from the

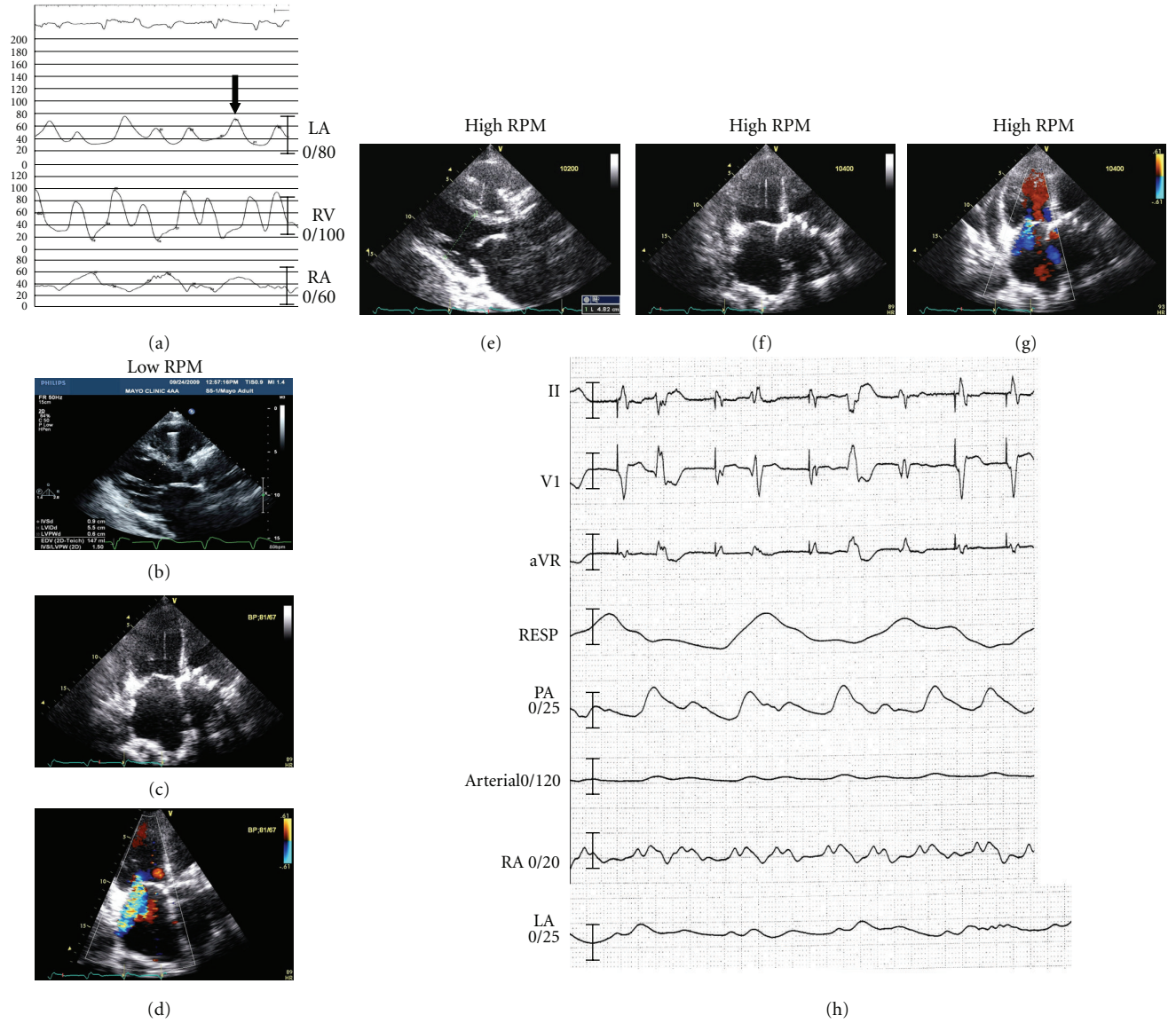

Figure 3: Severe functional mitral regurgitation. A patient presenting 17 months after LVAD implantation with failure to thrive and advanced right- and left-sided heart failure. (a) Hemodynamic right heart catheterization revealed markedly increased wedge and right atrial and ventricular pressures. Left atrial V wave (black arrow) reaching up to 70 mmHg was recorded suggesting significant functional mitral regurgitation. Echocardiographic examination during baseline RPM settings showed increased LV diameter (a), interventricular, interatrial septa shifted to the right, increased mitral annular diameter and tenting diameters (b), and severe functional mitral regurgitation. Left ventricular assist device speed was increased under echocardiographic guidance. Left ventricular middiameter decreased in size (e). Interventricular, interatrial septa shifted to the left and mitral annular and tenting diameters decreased in size (f). Functional mitral regurgitation severity decreased significantly (g). Right heart catheterization in the end of echocardiographic examination showed normal wedge, right ventricle, and right atrial pressures, and no V waves (h). Notably, cardiac output increased from 5.7 to 7.2 liters/minute after LVAD optimization.

ascending aorta through the outflow and inflow cannula and into the LV apex.

6. Long-Term Echocardiographic Considerations in Patients with LVAD

TTE is used in patients on chronic LVAD therapy for two main purposes: (1) routine LVAD optimization; (2) assessment of clinical deterioration or abnormal LVAD parameters associated with LVAD dysfunction.

6.1. Optimal LVAD Settings. The goal of LVAD implantation is to increase cardiac output while decreasing filling pressures. Optimal axial LVAD settings are still controversial. While some authors believe that maximal cardiac output and left chamber unloading are ideal, others are concerned by the long-term effects of LVAD working at maximal output [5].

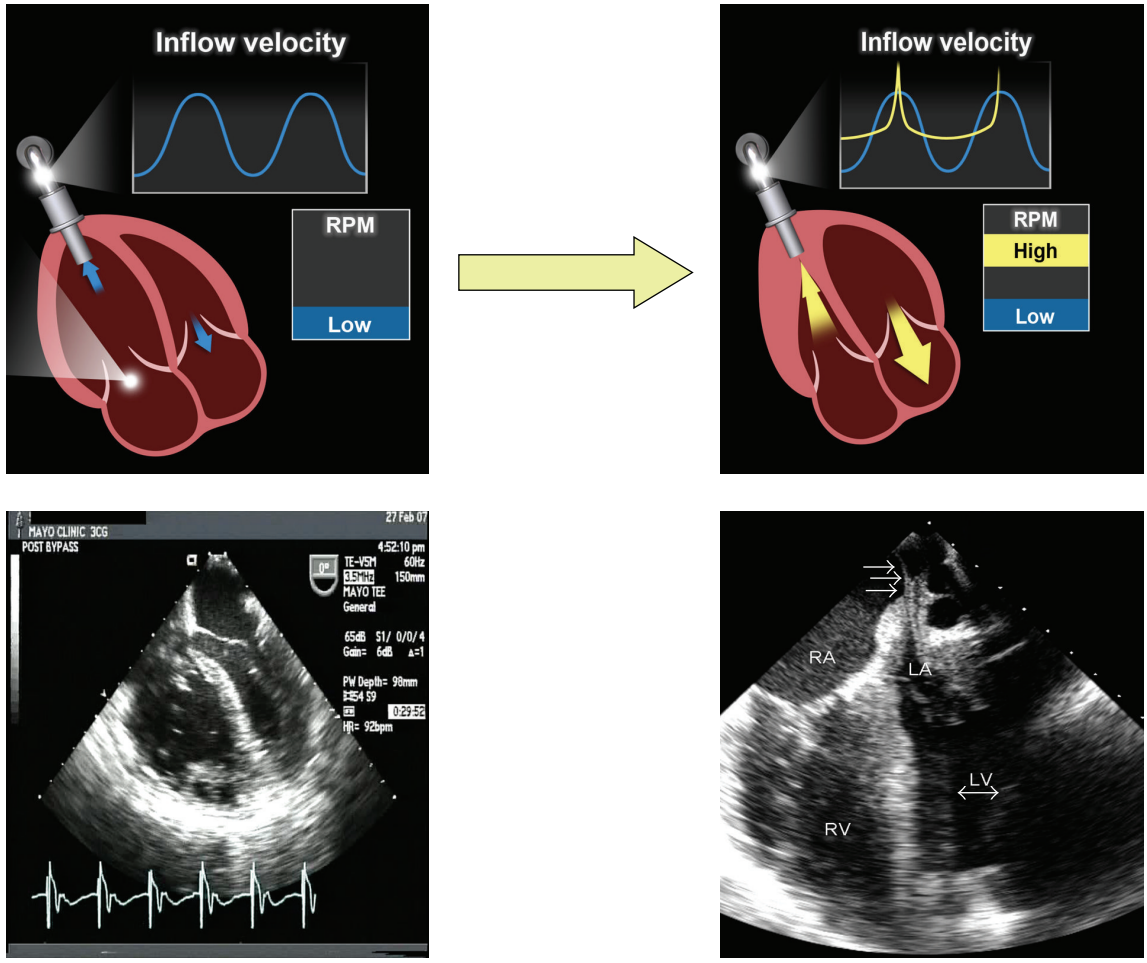

Figure 4: Inflow cannula obstruction, the "suction cascade". Four-chamber transthoracic view representing the classic "suction cascade" that can manifest itself by a dilated hypocontractile RV, significant functional TR, small left ventricle, and intermittent inflow cannula obstruction by the collapsed LV.

Possible complications of maximal LVAD output include increased prevalence of "suction events", hemolysis, stasis of blood proximal to the outflow cannula, and end-organ injury related to nonphysiologic continuous circulation. The clinical implications of continuous blood flow are currently unknown and have been a matter of significant debate. Another possible concern is stasis of blood proximal to the outflow cannula and ascending aorta anastomosis, when there is no forward flow through the aortic valve. This stagnant column of blood may theoretically result in thrombosis and embolism to coronaries or carotid arteries. Although this was described in the Jarvik 2000 axial flow device, when the outflow cannula was anastomosed to the descending aorta, it has never been reported so far with ascending aortic anastomosis [5].

The implications of this debate are obvious. If maximal cardiac output and LV decompression are the goal, the aortic valve should stay permanently closed, the interatrial septum should be shifted to the left, and flow profile in the outflow cannula will be less pulsatile. On the other hand, if pulsatility is the objective, intermittent aortic valve opening, neutral or even rightward shift of interatrial septum, and hence more flow pulsatility in the outflow cannula will be expected (Figure 5).

In our institution, the usual parameters used for estimation of proper LVAD function include (1) status of aortic valve opening; (2) interatrial and (to a lesser extent) interventricular septum position; (3) flow pulsatility in the outflow cannula; (4) TR velocity; (5) estimation of right atrial pressure; (6) LVAD system output and total cardiac output estimation.

The aortic valve opens whenever systolic LV pressure increases above the aortic pressure. Any reduction in LVAD function or speed will result in reduced LV unloading, increased LV systolic pressure reaching above aortic systolic pressure, allowing aortic valve opening, and systolic ejection. Increased native LV contractility (as encountered during stress, inotropic support, or even cardiac recovery) and increased preload may result in aortic valve opening. In case of increased afterload, the status of aortic valve opening

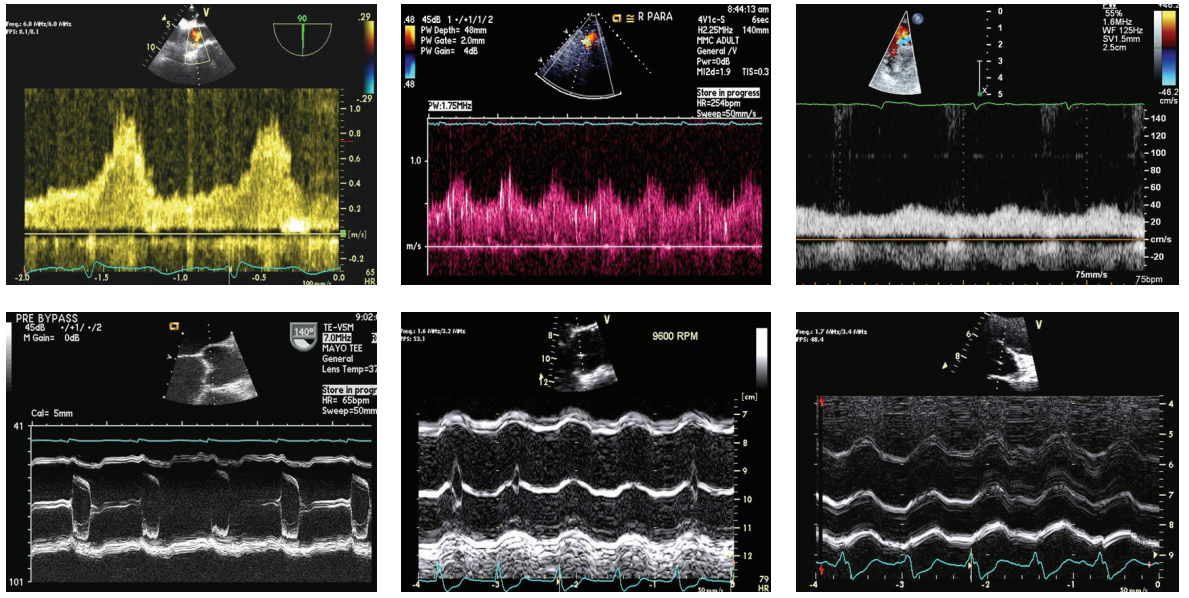

Figure 5: LVAD speed settings. Columns: (a) minimal speed; (b) submaximal speed; (c) maximal speed. Rows: (1) pulsed Doppler, outflow cannula; (2) M mode aortic valve. The status of aortic valve opening and aortic flow pulsatility depends on pump speed and output, LV contractility, preload, and afterload conditions. Reduction in LVAD speed to minimum will result in minimal unloading of the LV, increased LV systolic pressure above aortic pressure allowing pulsatile flow (a1), aortic valve opening during every cycle, seen in M mode (a2). Increasing the speed to submaximal, will unload the ventricle, reduce systolic left ventricular pressure, decrease the outflow pulsatility (b1), and result in intermittent aortic valve opening in M mode (b2). Increasing speed to maximum will unload the left ventricle even further, resulting in almost continuous aortic flow (c1), and no aortic valve opening (c2).

depends on the site of disturbance. If the reason for increased afterload is outflow cannula obstruction or kinking, the left ventricular systolic pressure will increase, but aortic pressure will decrease resulting in aortic valve opening every cycle. If on the other hand, the increased afterload is due to vasoconstriction, the aortic and left ventricle pressure will increase concomitantly, resulting in a closed aortic valve.

The position of the interatrial septum is the most sensitive measure for estimating proper decompression of left heart filling pressures. Furthermore, contrary to aortic valve opening status, it also shows the efficiency of diastolic decompression. Importantly, it should be done concurrently with estimation of right atrial pressure (using the IVC method) as increased RA pressure may cause leftward deviation of interatrial septum in the presence of high left heart filling pressure.

Pump flow, although it can be extracted from the device controller, must be directly evaluated during TTE examination. We believe that measuring the outflow cannula diameter in the right parasternal view, calculating its surface area, and multiplying it with the outflow cannula flow integral is the most reproducible method. For total cardiac output, our practice is to measure the right ventricular outflow tract (RVOT) diameter in the short axis view on the level of aortic valve and calculate its surface area. The result is multiplied by the integral of flow in the RVOT (on the same view) and the heart rate.

6.2. Assessment of Recurrent Heart Failure Associated with LVAD Dysfunction. When assessing a patient with recurrent heart failure symptoms, an integrated clinical and echocardiographic management protocol is used as a guide to recognize the cause of axial pump failure [25]. The patient is connected to the system monitor displaying a variety of system performance data including pump speed, power, pulsatility index (PI), and pump flow. Briefly, the pump speed will be determined during a speed ramp study. Pump power is a direct measurement of motor voltage and current. Increases in pump speed, flow, or physiological demand will increase pump power. Specifically, gradual power increases, power values greater than 10–12 watts, or abrupt changes in power should raise concern for possible thrombus inside the pump. When the LV contracts, the increase in ventricular pressure causes an increase in pump flow during systole. The magnitude of these flow changes is measured to produce the PI. The PI represents cardiac pulsatility and is related to the magnitude of assistance provided by the LVAD. Higher values indicate more ventricular filling or better contractility (pump is providing less support to the LV), while lower values indicate less ventricular filling or lower contractility. Pump flow is estimated based on power. Since it is a calculated value, it becomes imprecise at low and high regions of the power-flow relationship. Therefore, any increase in power not related to an increased flow, such as thrombus, will cause an erroneously high flow. Conversely, an occlusion of flow

path (inflow obstruction due to malposition or suction events) will decrease power and calculated flow. In either situation, an independent assessment of pump output using the TTE should be performed. It is however important to mention that no single monitor parameter is an adequate surrogate for monitoring the clinical status of the patient.

6.3. Evaluation of LVAD Dysfunction. LVAD malfunctions can be broadly categorized into three main groups: (1) low echocardiographically estimated pump flow and increased power values; (2) low echocardiographically estimated pump flow with normal or low power values; (3) high echocardiographically estimated pump flow with low echocardiographically estimated forward cardiac output.

6.3.1. Low Pump Flow with Increased Power Values. The reasons for this combination are pump failure or increased afterload. Pump failure may result from thrombosis, mechanical malfunction, or decreased speed settings. The echocardiographic appearance of these etiologies includes some or all of the following: (1) rightward deviation of the interventricular septum; (2) significant functional mitral regurgitation; (3) aortic valve opening every cardiac cycle; (4) spontaneous echo contrast in the left atrium or left ventricle; (5) regurgitant flow through the inflow and outflow cannula, for reasons previously discussed. Reduced speed settings will be obvious from the controler device interrogation, while presence of left ventricular or left atrial thrombus and increased power and controler calculated flow should raise suspicion for LVAD thrombosis. This differential diagnosis is clinically crucial, as LVAD thrombosis may be managed by anticoagulants or thrombolysis, while LVAD malfunction may require urgent surgery [25]. On the other hand, increased afterload differential diagnosis includes outflow cannula obstruction, outflow cannula kinking, and extreme systemic vasoconstriction [25]. Outflow cannula kinking should be suspected when there is loss of Doppler signal in the outflow cannula in any echocardiographic view [23, 25]. This can be confirmed by catheterization and contrast injection [26]. In the situation of severe systemic vasoconstriction, one should bare in mind that axial LVADs are extremely sensitive to increased afterload, resulting in decline in pump output. Differentiation of systemic vasoconstriction from mechanical complication is essential as vasoconstriction will be treated conservatively. Although most of the echocardiographic criteria for LVAD dysfunction will be present in patients with severe vasoconstriction, the aortic valve will stay closed. PW Doppler interrogation of the outflow cannula will demonstrate high velocity pulsatile forward flow, and PI will be increased [25]. The reason for this set of findings is that although LVAD output is reduced as demonstrated by the septal shift and functional MR, the impeller is still rotating, amplifying the pressure wave received from the LV. Under conditions of low pump flow, the pressure in the left ventricle is higher than normal, resulting in increased forward velocity in the outflow cannula. Although the pressure in the LV is higher than normal, the pressure in the aorta is even higher, preventing aortic valve opening and systolic ejection.

6.3.2. Low Pump Flow with Normal Current and Power Values. The combination of low pump flow with normal or low power (and low PI) values is the result of reduced LVAD preload. Reduced preload is most commonly encountered with RV failure, significant TR, or hypovolemia. Another common reason for reduced LVAD preload is inflow cannula obstruction, largely due to malposition and intermittent obstruction by the adjacent LV walls. The apical cannula should stay central, not abutting any wall. Color, CW, and PW Doppler interrogation should be done as already described. Inflow cannula obstruction will result in high velocity aliased flow at the orifice with manifest convergence area. Other rare reasons for reduced LVAD preload include mitral stenosis and ventricular fibrillation [27], which can present as recurrent heart failure episodes due to loss of RV function, resulting in reduced LVAD preload and output.

6.3.3. High Pump Flow with Low Forward Cardiac Output. Whenever the calculated total cardiac output is lower than the LVAD output, futile cycles should be suspected. The most common malfunction of the older pulsatile LVAD was inflow valve regurgitation, resulting in extremely high LVAD output, with markedly reduced total cardiac output. This combination of findings can also be encountered in patients with severe AI.

7. Conclusion

Precise transthoracic echocardiographic monitoring is mandatory and paramount to evaluate the performance of continuous flow left ventricular assist devices. This evaluation is essential for surgical planning and interventional success. Standard TTE techniques allow optimal LVAD settings during routine follow-up visits and rapid and accurate evaluation of mechanical or systemic malfunctions.

Conflict of Interest

The authors have no financial associations or relationship with an industry that might pose a conflict of interest with the submitted article.

References

[1] S. J. Park, A. Tector, W. Piccioni et al., "Left ventricular assist devices as destination therapy: a new look at survival," *Journal of Thoracic and Cardiovascular Surgery*, vol. 129, no. 1, pp. 9–17, 2005.

[2] O. H. Frazier, E. A. Rose, M. C. Dz et al., "Multicenter clinical evaluation of the HeartMate vented electric left ventricular assist system in patients awaiting heart transplantation," *Journal of Thoracic and Cardiovascular Surgery*, vol. 122, no. 6, pp. 1186–1195, 2001.

[3] O. H. Frazier, E. A. Rose, M. C. Dz et al., "Multicenter clinical evaluation of the heartmate; vented electric left ventricular assist system in patients awaiting heart transplantation," *The Journal of Heart and Lung Transplantation*, vol. 20, no. 2, pp. 201–202, 2001.

[4] E. A. Rose, A. C. Gelijns, A. J. Moskowitz et al., "Long-term use of a left ventricular assist device for end-stage heart failure,"

SAGE-Hindawi Access to Research
Cardiology Research and Practice
Volume 2011, Article ID 908921, 7 pages
doi:10.4061/2011/908921

Review Article

The Role of Device Diagnostic Algorithms in the Assessment and Management of Patients with Systolic Heart Failure: A Review

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Received 12 December 2010; Accepted 3 February 2011

Academic Editor: Gregory Giamouzis

Hospitalization due to heart failure (HF) exacerbation represents a major burden in health care and portends a poor long-term prognosis for patients. As a result, there is considerable interest to develop novel tools and strategies to better detect onset of volume overload, as HF hospitalizations may be reduced if appropriate interventions can be promptly delivered. One such innovation is the use of device-based diagnostic parameters in HF patients with implantable cardioverter defibrillators (ICD) and/or cardiac resynchronization therapy (CRT) devices. These diagnostic algorithms can effectively monitor and detect changes in patients' HF status, as well as predict one's risk of HF hospitalization. This paper will review the role of these device diagnostics parameters in the assessment and management of HF patients in ambulatory settings. In addition, the integration of these novel algorithms in existing HF disease management models will be discussed.

1. Introduction

Hospitalization for heart failure (HF) is a major health burden upon society, with an estimated prevalence of 5.8 million and an annual incidence of 55 000 in the United States alone [1]. In the United States, exacerbation of HF resulted in over 658 000 emergence room visits annually, representing a significant economic cost. In addition, hospitalization due to HF portends a poor prognosis for patients, with an estimated in-hospital mortality of 4% [2]. A major key in reducing HF hospitalization is the early recognition of HF exacerbation, which in turn may lead to prompt diagnosis and management of HF without the need for hospital visits. Unfortunately, bedside clinical parameters are often inaccurate in assessing the true volume status of HF patients [3]. Moreover, symptoms leading to HF hospitalization generally occur later in the decompensation course. For example, dyspnea due to pulmonary congestion was only reported within an average of 3 days prior to hospitalization [4]. Early recognition and prompt management of HF exacerbation has been shown to reduce hospitalization and improve quality of life for HF patients [5, 6]. As a result, there is considerable interest to develop strategies that facilitate prompt recognition and management of HF exacerbations in these patients. One such innovation is the use of device-based diagnostic parameters to assess for signs of volume overload and to predict the onset of HF exacerbation. These functions are integrated within the platforms of certain implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT) devices. They are readily accessible from routine device interrogation and are user friendly. The ever expanding indications of ICD and CRT therapy will conceivably make these device-based diagnostic parameters an indispensable tool in HF care. As such, this paper will review the current state of knowledge regarding the use of these device-based diagnostics in the assessment and management of patients with systolic HF.

2. Heart Rate Variability (HRV)

Heart rate variability arises from the interplay between the two limbs of the autonomic nervous system in order to

maintain adequate cardiac output for the body's needs. The parasympathetic input to the heart is primarily responsible for HRV [7]. In humans, chronic heart failure is known to exert deleterious alterations upon cardiac autonomic control [8]. Derangement in the homeostatic balance of the cardiac autonomic system is associated with poorer outcomes and increased mortality [9, 10]. Among patients with implanted pacing devices, continuous monitoring of HRV could be performed by measurement of the sinus rate from the atrial lead. In these devices, assessment of HRV was achieved by examining the standard deviation of the 5-minute median atrial-to-atrial depolarization interval (SDAAM). Adamson et al. first described the use of HRV as a device-based diagnostic tool in HF patients [11]. In 397 patients with systolic HF and New York Heart Association (NYHA) III or IV symptoms with an implanted CRT, measurements of SDAAM were correlated to their clinical course over an 18-month period. An SDAAM < 50 ms (averaged over 4 weeks) was associated with increased all-cause and cardiovascular mortality, with hazard ratios of 3.20 and 4.43, respectively. In addition, SDAAM were persistently depressed during the entire followup among patients who were hospitalized or died. An SDAAM > 100 ms was associated with a low risk for hospitalization. Moreover, the decline in SDAAM was found to precede HF hospitalization by a median of 16 days and returned to baseline after treatment. If changes in the patient's neurohormonal status precede development of HF symptoms, continuous monitoring of SDAAM may be a valuable tool in predicting one's future risk of HF hospitalization. Indeed, the interrelationship between HRV (as reflected by SDAAM) and HF status has been confirmed by two studies, which showed that a favourable response to CRT therapy was associated with increases in HRV and concomitant decreases of the mean heart rate [11, 12]. In current devices, measurement of SDAAM depends upon the presence of intrinsic sinus node activity. As such, the clinical use of SDAAM cannot be applied to patients with persistent atrial fibrillation (AF) or if atrial pacing is required >80% over a 24-hour period, since SDAAM cannot be accurately measured in these situations [11]. Taken together, however, measurement of HRV by SDAAM appears to be a valid clinical tool in assessing one's HF status and risk of subsequent HF hospitalization.

3. Intrathoracic Impedance

Assessment of thoracic fluid status by measuring intrathoracic impedance is the newest device-based diagnostic tool available in clinical practice. This is based on the concept that changes of fluid volume in the lungs will alter intrathoracic impedance [13, 14]. The OptiVol fluid status monitoring algorithm (Medtronic, Inc., Minneapolis, USA) is incorporated in contemporary ICD and CRT-D platforms. In these systems, intrathoracic impedance is measured between the pulse generator (usually implanted in the left pectoral region) and the right ventricular coil of the ICD lead. This vector encompasses most of the left thoracic cavity and defines the intrathoracic impedance as measured by the device. Using the concept of Ohm's law, impedance of the hemithorax cavity is measured upon delivery of a small alternating current between the pulse generator and the ICD lead. Since fluid (water, blood) is a highly conductive medium, accumulation of fluid in the lungs will lower intrathoracic impedance. A purported advantage of this algorithm is the reproducibility and consistency of repeated measurements due to the fixed positions of the two electrodes [15]. This makes data trending possible and allows clinicians to follow the pulmonary fluid status of patients over time.

The OptiVol fluid status monitor is activated ≥34 days after the index procedure in order to prevent spurious measurements due to air and edema in the healing pocket. Once active, the device will measure the intrathoracic impedance every 20 minutes between noon and 5 pm, totalling 64 recordings. These values are averaged and reported as the "daily impedance value". Daily measurements of impedance are compared to the patient's reference value, which is derived from the average of the last 4 daily impedance recordings. Negative deviations of the daily impedance value generate the OptiVol fluid index (Figure 1). The OptiVol index has a unit measurement of ohms · days and is compared to a programmable fluid index which is nominally set as 60 ohms · days. The OptiVol fluid index is plotted against time to provide two pieces of information: (i) the magnitude of the deviation from the programmable fluid index threshold; (ii) the time duration of the deviation. Pulmonary fluid retention will generate negative deviations of the daily impedance from the reference value, which is graphically depicted as deviations from the zero baseline value in the OptiVol index.

The OptiVol index only provides an indirect measurement of pulmonary congestion based on intrathoracic impedance changes. As such, false-positive and false-negative measurements can occur and need to be borne in mind when this tool is applied in clinical practice. For example, air trapping in emphysematous lungs may mask decreases in intrathoracic impedance. On the other hand, alveolar congestion from pneumonia or the presence of pleural effusions will lower daily impedance measurements even though pulmonary congestion due to elevation of left-sided cardiac pressures had not occurred. Furthermore, not all patients experience pulmonary congestion as their dominant HF exacerbation symptom. Thus, the OptiVol algorithm may not be useful in assessing patients with predominant right-sided heart failure symptoms, or those with low cardiac output despite being relatively euvolemic. In spite of these potential limitations, considerable interests exist in utilizing the OptiVol fluid index to prevent, assess, and manage heart exacerbation events due to pulmonary congestion in patients with implantable cardiac devices.

4. Clinical Data

The first proof-of-concept study of OptiVol use in humans was reported by Yu et al. in the Medtronic Impedance Diagnostics in Heart Failure Patients Trial (Mid-HeFT) [16]. A special pacemaker with an ICD lead was implanted in 33 patients with systolic HF and NYHA class III or IV symptoms. Daily intrathoracic impedance was recorded

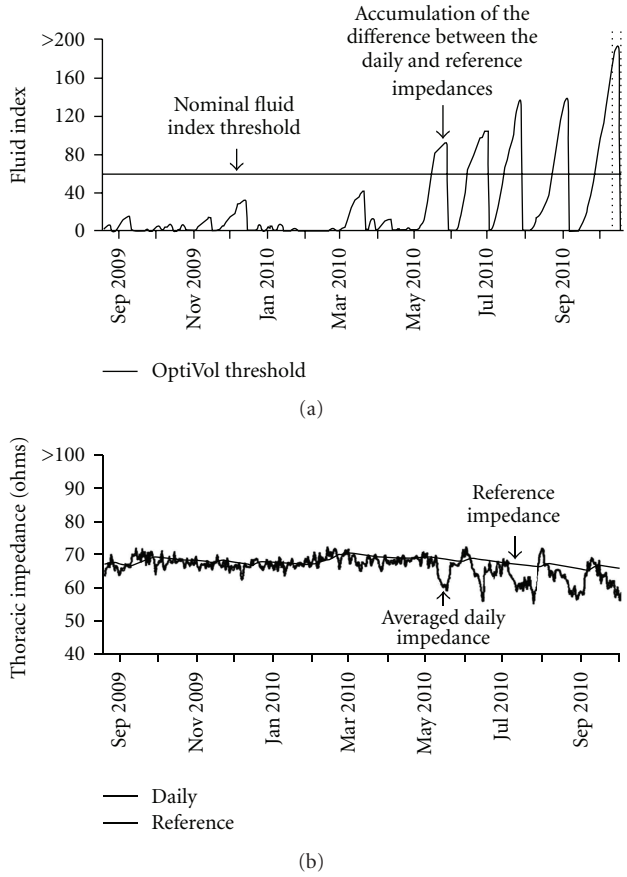

Figure 1: OptiVol fluid index. The intrathoracic impedance is measured on a daily basis and is compared to the patient's "reference" value, which is derived from the average of the last 4 daily measurements. Negative deviations from the reference value suggest a decrease in intrathoracic impedance, which may reflect pulmonary congestion. The difference between the measured intrathoracic impedance and the reference value is multiplied by time (measured in days) to generate the OptiVol fluid index, which has a unit measurement of ohms · days. The magnitude of the fluid index value is determined by (i) the absolute difference between the reference value and the measured intrathoracic impedance, and/or (ii) the time duration of the difference. The fluid index is plotted against time to graphically display the onset and duration of negative deviations of intrathoracic impedance. The nominal cut-off threshold is set as 60 ohms · days.

by the device, and physicians were blinded to these measurements. In the acute phase of the study, patients with decompensated HF were hospitalized in the coronary care unit and treated with intravenous diuretics and vasodilators. The pulmonary capillary wedge pressures (PCWP) of these patients were measured by pulmonary artery catheters every 2 hours. Intrathoracic impedance was measured by the device every 6 hours in this patient subgroup. A total of 9 patients experienced 24 hospitalizations for HF exacerbation, and PCWP measurements were recorded in 5 patients with 14 hospitalizations. A statistically significant inverse relationship was noted between the PCWP and intrathoracic impedance. As patients were being diuresed, a concomitant increase in intrathoracic impedance was noted. In addition, a statistically significant inverse correlation was demonstrated between net fluid loss during hospitalization and intrathoracic impedance. Furthermore, a decrease in intrathoracic impedance preceded the onset of dyspnea by 15.3 ± 10.3 days (mean ± standard deviation), which was considerably earlier than the actual onset of symptoms which led to hospitalization (3.0 ± 2.5 days). The drop in intrathoracic impedance which occurred before onset of HF symptoms and at HF admission were significantly reduced ($P < .001$). Thus, the authors conclude that OptiVol may help detect early onset of volume overload, which in turn may predict onset of HF exacerbation.

In the chronic phase of the study, patients were followed by an ambulatory heart function clinic on a regular basis and were managed by physicians who had no knowledge of the intrathoracic impedance measurements. If a patient was hospitalized for HF exacerbation, the intrathoracic impedance values of the preceding 30 days were used to generate the diagnostic parameters of OptiVol. The algorithm development data was derived from 7 patients (11 hospitalizations from 4 patients) and was validated in a cohort of 23 patients (13 hospitalizations from 8 patients). A receiver-operator curve ("performance curve") was constructed to assess the diagnostic sensitivity and specificity of varying thresholds for impedance changes which may predict HF hospitalization. Based on these results, a cutoff value below 60 Ω · days was able to detect impedance changes preceding HF hospitalization with a sensitivity of 76.9%. Although the specificity of this cut-off value in predicting HF hospitalization was not explicitly stated in the study, the authors reported a false-positive rate of 1.5 detections per patient-monitoring year. On the basis of this study, the nominal cut-off threshold for pulmonary congestion detection is set as 60 Ω · days in the OptiVol algorithm.

The diagnostic performance of the OptiVol algorithm in a "real-world" population was reported by Vollmann et al. from an observational registry of 373 patients implanted with the Medtronic InSync Sentry CRT-D device [18]. In this study, an audible alert was programmed when the intrathoracic impedance fell below the cut-off threshold. Patient followup included regular clinic appointments and unscheduled visits due to alert activation or clinical HF deterioration. A clinical HF exacerbation diagnosed within 2 weeks of the initial alert was classified as a "true-positive alert event". The treating physicians had knowledge of the OptiVol measurements. A total of 53 alert events occurred in 45 patients, and 53 clinical HF exacerbation events occurred in 43 patients. OptiVol was able to detect clinical HF exacerbation with an adjusted sensitivity of 60% and a positive predictive value of 60%. The false-positive detection rate was 0.2 event per patient year. In more than half of the clinical HF events (55%) which did not trigger an alert, the intrathoracic impedance had decreased below the reference value but had not crossed the programmed cut-off threshold. Thus, the authors suggested that the diagnostic sensitivity of OptiVol might be improved if the cut-off threshold values could be individualized.

Table 1: Device diagnostics parameters and algorithms from the Cardiac Compass report.

Device diagnostic parameter	Description	Algorithm
AF duration	Total amount of time spent during AF on a daily basis.	AF ≥ 6 h on ≥1 day in patients without persistent AF (7 consecutive days with ≥23 h AF).
Ventricular rate during AF	The daily average ventricular rate during AF.	AF = 24 h and the average ventricular rate ≥90 beats/min during AF on ≥1 day.
Fluid index (OptiVol)	The fluid index trend is the cumulative difference between the daily average and patient-specific reference intrathoracic impedance.	High fluid index on ≥1 day; thresholds included ≥60; ≥80; ≥ 100 Ω · days.
Patient activity	Measures the total active time per day using a capacitive accelerometer. A minute is considered active if the count exceeds a threshold equivalent to walking 70 steps/min.	Average patient activity <1 h over 1 week.
Night heart rate	Measures the ventricular rate from midnight to 4 AM.	Average night heart rate > 85 beats/min for 7 consecutive days.
Heart rate variability (HRV)	HRV is assessed by the SDAAM (standard deviation of the 5-minute median atrial rate). HRV is not measured if atrial pacing occurs >80% of the time or if the patient is in AT/AF.	HRV < 60 ms everyday for 1 week (minimum 5 consecutive days).
Percentage of CRT pacing	Percentage of biventricular pacing on each day.	Biventricular pacing <90% for 5 of 7 days.
ICD shocks for VT or VF	Records if an ICD shock was delivered for episodes detected within the VT or VF zone; includes both appropriate and inappropriate shock(s).	≥1 shock(s) during the evaluation period.

Adapted from [17].
AF = atrial fibrillation; AT/AF = atrial tachycardia/atrial fibrillation; CRT = cardiac resynchronization therapy; HF = heart failure; HRV = heart rate variability; ICD = implantable cardioverter defibrillator; VF = ventricular fibrillation; VT = ventricular tachycardia.

Programmable fluid index thresholds are available in Medtronic ICD and CRT-D platforms.

Although the use of individual HF device diagnostic parameters has been validated in multiple clinical studies, each parameter has potential limitations which may restrict its general applicability in a complex HF population. As a result, there is considerable interest in combining HF device diagnostic parameters in the management of HF patients with implanted devices. The PARTNERS HF (Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients with Heart Failure) study was a multicenter, prospective observational study which evaluated the use of combined HF diagnostic information in predicting clinical deterioration of ambulatory HF patients [17]. A cohort of 694 patients with systolic HF and NYHA III or IV symptoms with Medtronic CRT-D devices were prospectively evaluated in 100 centers in the United States. Individual HF diagnostic parameters were collected from the Cardiac Compass report (Figure 2), which consisted of (i) atrial fibrillation (AF) duration; (ii) ventricular rate during AF; (iii) fluid index (OptiVol); (iv) patient activity; (v) night heart rate; (vi) heart rate variability; (vii) percentage of CRT pacing; (viii) ICD shocks for ventricular arrhythmias (Figure 1). The definition of a "positive" event for each parameter was prespecified (Table 1). Occurrence of HF events were prospectively collected and independently adjudicated. A combined HF device diagnostic algorithm was developed by the authors and was triggered when (i) the fluid index exceeds 100 Ω · days or (ii) any 2 of the 8 prespecified parameters were positive. In total, 90 patients had 141 adjudicated HF hospitalizations with pulmonary congestion. The combined HF device diagnostic algorithm was triggered in 43% (298 of 694) of patients and in 23% (1324 of 5693) of device evaluations. Having ≥2 of the 8 criteria being positive accounted for the majority (72%) of the algorithm triggers. Importantly, patients with a positive combined HF device diagnostic were at greater risk of HF hospitalization with pulmonary congestion in the next month than those without (adjusted hazard ratio: 4.8, 95% confidence interval: 2.9 to 8.1, $P < .0001$). Among patients with a negative combined HF device diagnostic, the risk of HF hospitalization due to pulmonary congestion was 0.7% over the next 30 days. In subgroup analyses, the predictive ability of the combined HF device diagnostic algorithm was greater when device evaluations were performed monthly and semimonthly when compared to every 3 months. However, the diagnostic utility of this algorithm appeared to be limited to patients without prior HF events. These observational studies highlight the promising role of OptiVol and other device-based diagnostics in the early detection of pulmonary congestion in HF patients. Whether the use of such device diagnostics can improve outcomes in HF patients with ICD or CRT-D is currently examined by two randomized trials, the Diagnostic Trial in Heart Failure (DOT-HF) in Europe and the Prospective, Randomized Evaluation of Cardiac Compass with OptiVol in the Early

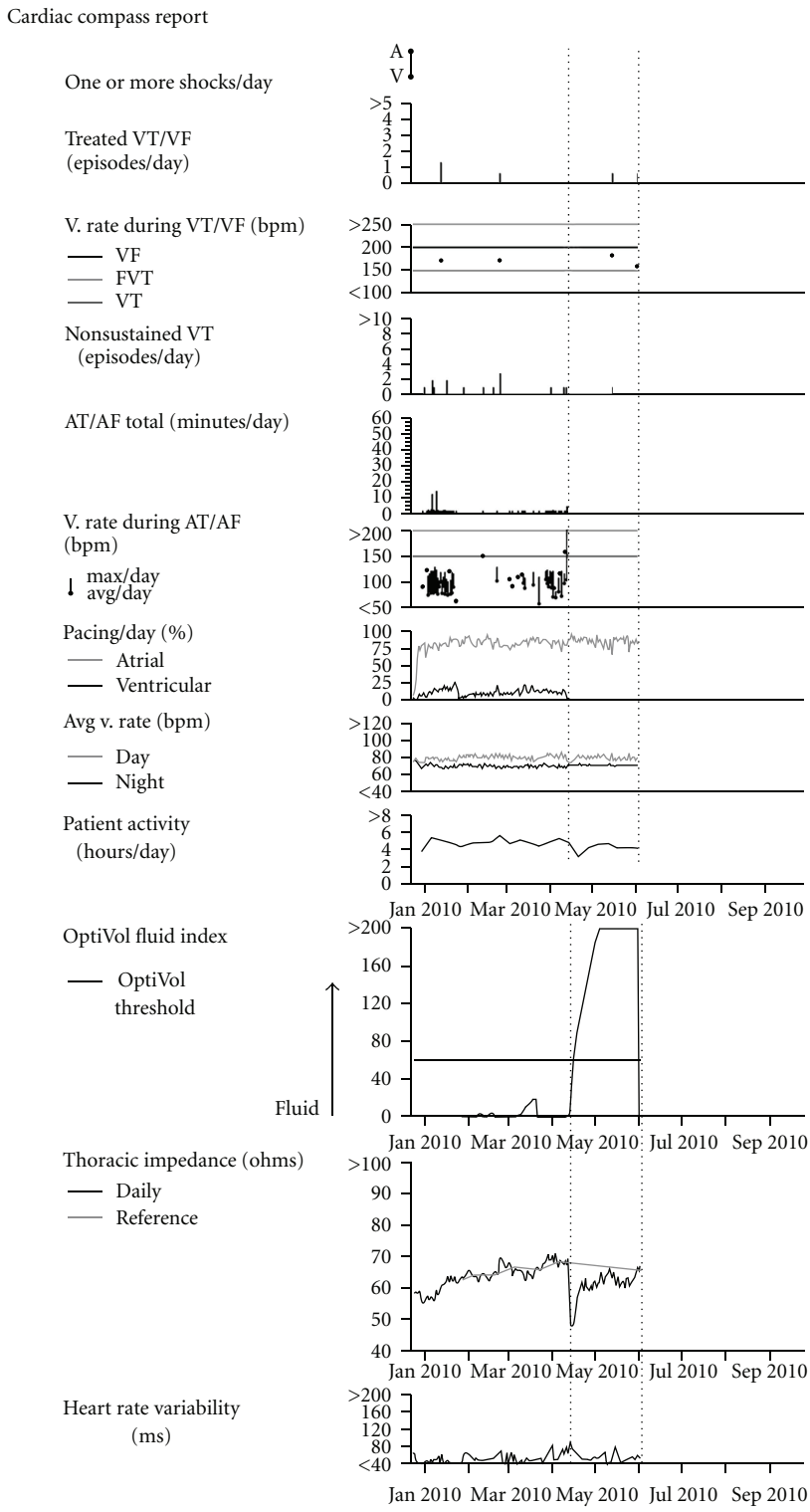

Figure 2: Cardiac Compass report. The Cardiac Compass report displays a number of device diagnostic parameters over a period of weeks to months. This allows trending of data over time, allowing clinicians to monitor the heart failure status of patients. An abnormal reading (such as a fluid index threshold crossing) may reflect a worsening of the patient's heart failure (HF) status, potentially alerting the physician to a possible HF exacerbation in the near future. The combined use of multiple device parameters may improve the diagnostic sensitivity of early HF detection.

Detection of Decompensation Events for Heart Failure (PRECEDE-HF) trial in North America.

5. Integration of Device Diagnostics into Heart Failure Clinics

The feasibility of routine OptiVol assessment in an HF disease management program was recently reported by Mullens et al. [19]. In this pilot study, changes in the fluid index were assessed in 194 HF patients with an implanted ICD or CRT-D via an online remote monitoring system (Carelink, Medtronic, Inc.). Regular Carelink uploads were reviewed by an HF clinic nurse. If the fluid index crossed the nominal threshold ($60\,\Omega \cdot$ days) for ≥ 10 days, a followup telephone call was performed by a nurse. Over a period of 4 months, 400 Carelink uploads were received and 44 fluid index threshold crossings were noted in 34 patients. Thirty-two of the 34 (97%) patients reported occurrence of "clinically relevant events" at around the time of fluid index threshold crossing, which included HF hospitalization (18%); changes in HF therapy (56%); drug and/or dietary nonadherence (38%). The incidence of clinically relevant events was not reported in the remaining 160 patients who did not cross the fluid index threshold. In this study, an internet-based program to detect fluid index threshold crossing yielded a high rate of clinically relevant events in a "real-world" population of ambulatory HF patients with implanted pacing devices. The authors concluded that use of OptiVol in an established HF program is feasible and will provide additional useful clinical information to medical providers.

6. Conclusions

The expanding implant indications for ICD and CRT will result in increasing numbers of HF patients receiving these life-saving therapies. Clinical studies had demonstrated the utility of certain device-based diagnostic parameters in assessing pulmonary congestion and in predicting one's risk of future HF hospitalization. In particular, intrathoracic impedance assessment by OptiVol is a promising tool in detecting early signs of pulmonary congestion, which in turn may reduce hospitalization with prompt recognition and treatment. The combined use of various device diagnostics has recently been shown to be a powerful predictor of short-term HF hospitalization risk. Ongoing randomized trials are being performed to evaluate whether these algorithms can improve patient outcomes. If these algorithms can indeed improve HF outcomes, how best to integrate them into existing HF disease management models will certainly become an active area of research.

Acknowledgments

Dr. R. A. Leather has received speaker honoraria from Medtronic, Inc. and has participated in research studies supported by Medtronic, Inc. Dr. P. G. Novak has received speaker honoraria from Medtronic, Inc., and has participated in research studies supported by Medtronic, Inc. Dr. L. D. Sterns has received speaker honoraria from Medtronic, Inc. He has participated in research studies supported by Medtronic, Inc. and served as a consultant for Medtronic, Inc. Dr. A. S. L. Tang has received speaker honoraria from Medtronic, Inc. and has participated in research studies supported by Medtronic. Dr. A. C. T. Ha has no conflicts of interest.

References

[1] N. L. Weintraub, S. P. Collins, P. S. Pang et al., "Acute heart failure syndromes: emergency department presentation, treatment, and disposition: current approaches and future aims: a scientific statement from the American Heart Association," *Circulation*, vol. 122, no. 19, pp. 1975–1996, 2010.

[2] W. T. Abraham, K. F. Adams, G. C. Fonarow et al., "In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE)," *Journal of the American College of Cardiology*, vol. 46, no. 1, pp. 57–64, 2005.

[3] L. W. Stevenson and J. K. Perloff, "The limited reliability of physical signs for estimating hemodynamics in chronic heart failure," *Journal of the American Medical Association*, vol. 261, no. 6, pp. 884–888, 1989.

[4] S. Chakko, D. Woska, H. Martinez et al., "Clinical, radiographic, and hemodynamic correlations in chronic congestive heart failure: conflicting results may lead to inappropriate care," *American Journal of Medicine*, vol. 90, no. 3, pp. 353–359, 1991.

[5] M. W. Rich, V. Beckham, C. Wittenberg, C. L. Leven, K. E. Freedland, and R. M. Carney, "A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure," *The New England Journal of Medicine*, vol. 333, no. 18, pp. 1190–1195, 1995.

[6] F. A. McAlister, S. Stewart, S. Ferrua, and J. J. J. V. McMurray, "Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials," *Journal of the American College of Cardiology*, vol. 44, no. 4, pp. 810–819, 2004.

[7] H. V. Huikuri, T. Mäkikallio, K. E. J. Airaksinen, R. Mitrani, A. Castellanos, and R. J. Myerburg, "Measurement of heart rate variability: a clinical tool or a research toy?" *Journal of the American College of Cardiology*, vol. 34, no. 7, pp. 1878–1883, 1999.

[8] A. Mortara, M. T. La Rovere, G. D. Pinna et al., "Arterial baroreflex modulation of heart rate in chronic heart failure: clinical and hemodynamic correlates and prognostic implications," *Circulation*, vol. 96, no. 10, pp. 3450–3458, 1997.

[9] J. Nolan, P. D. Batin, R. Andrews et al., "Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-Heart)," *Circulation*, vol. 98, no. 15, pp. 1510–1516, 1998.

[10] M. T. La Rovere, G. D. Pinna, R. Maestri et al., "Short-term heart rate variability strongly predicts sudden cadiac death in chronic heart failure patients," *Circulation*, vol. 107, no. 4, pp. 565–570, 2003.

[11] P. B. Adamson, A. L. Smith, W. T. Abraham et al., "Continuous autonomic assessment in patients with symptomatic heart failure: prognostic value of heart rate variability measured by an implanted cardiac resynchronization device," *Circulation*, vol. 110, no. 16, pp. 2389–2394, 2004.

[12] C. Fantoni, S. Raffa, F. Regoli et al., "Cardiac resynchronization therapy improves heart rate profile and heart rate variability of patients with moderate to severe heart failure," *Journal of the American College of Cardiology*, vol. 46, no. 10, pp. 1875–1882, 2005.

[13] R. V. Luepker, J. R. Michael, and J. R. Warbasse, "Transthoracic electrical impedance: quantitative evaluation of a non-invasive measure of thoracic fluid volume," *American Heart Journal*, vol. 85, no. 1, pp. 83–93, 1973.

[14] L. Wang, S. Lahtinen, L. Lentz et al., "Feasibility of using an implantable system to measure thoracic congestion in an ambulatory chronic heart failure canine model," *Pacing and Clinical Electrophysiology*, vol. 28, no. 5, pp. 404–411, 2005.

[15] L. Wang, "Fundamentals of intrathoracic impedance monitoring in heart failure," *American Journal of Cardiology*, vol. 99, no. 10, pp. S3–S10, 2007.

[16] C. M. Yu, L. Wang, E. Chau et al., "Intrathoracic impedance monitoring in patients with heart failure: correlation with fluid status and feasibility of early warning preceding hospitalization," *Circulation*, vol. 112, no. 6, pp. 841–848, 2005.

[17] D. J. Whellan, K. T. Ousdigian, S. M. Al-Khatib et al., "Combined heart failure device diagnostics identify patients at higher risk of subsequent heart failure hospitalizations. Results from PARTNERS HF (Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure) Study," *Journal of the American College of Cardiology*, vol. 55, no. 17, pp. 1803–1810, 2010.

[18] D. Vollmann, H. Nägele, P. Schauerte et al., "Clinical utility of intrathoracic impedance monitoring to alert patients with an implanted device of deteriorating chronic heart failure," *European Heart Journal*, vol. 28, no. 15, pp. 1835–1840, 2007.

[19] W. Mullens, L. P.J. Oliveira, T. Verga, B. L. Wilkoff, and W. H. Wilson Tang, "Insights from internet-based remote intrathoracic impedance monitoring as part of a heart failure disease management program," *Congestive Heart Failure*, vol. 16, no. 4, pp. 159–163, 2010.

New England Journal of Medicine, vol. 345, no. 20, pp. 1435–1443, 2001.

[5] O. H. Frazier, T. J. Myers, S. Westaby, and I. D. Gregoric, "Clinical experience with an implantable, intracardiac, continuous flow circulatory support device: physiologic implications and their relationship to patient selection," *Annals of Thoracic Surgery*, vol. 77, no. 1, pp. 133–142, 2004.

[6] B. P. Griffith, R. L. Kormos, H. S. Borovetz et al., "HeartMate II left ventricular assist system: from concept to first clinical use," *Annals of Thoracic Surgery*, vol. 71, no. 3, pp. S116–S120, 2001.

[7] O. H. Frazier, R. M. Delgado, B. Kar, V. Patel, I. D. Gregoric, and T. J. Myers, "First clinical use of the redesigned HeartMate II left ventricular assist system in the United States: a case report," *Texas Heart Institute Journal*, vol. 31, no. 2, pp. 157–159, 2004.

[8] L. W. Miller, F. D. Pagani, S. D. Russell et al., "Use of a continuous-flow device in patients awaiting heart transplantation," *New England Journal of Medicine*, vol. 357, no. 9, pp. 885–896, 2007.

[9] M. P. Siegenthaler, S. Westaby, O. H. Frazier et al., "Advanced heart failure: feasibility study of long-term continuous axial flow pump support," *European Heart Journal*, vol. 26, no. 10, pp. 1031–1038, 2005.

[10] H. A. Khalil, W. E. Cohn, R. W. Metcalfe, and O. H. Frazier, "Preload sensitivity of the jarvik 2000 and HeartMate II left ventricular assist devices," *ASAIO Journal*, vol. 54, no. 3, pp. 245–248, 2008.

[11] N. C. Dang, V. K. Topkara, M. Mercando et al., "Right heart failure after left ventricular assist device implantation in patients with chronic congestive heart failure," *Journal of Heart and Lung Transplantation*, vol. 25, no. 1, pp. 1–6, 2006.

[12] N. D. Patel, E. S. Weiss, J. Schaffer et al., "Right heart dysfunction after left ventricular assist device implantation: a comparison of the pulsatile HeartMate I and axial-flow HeartMate II devices," *Annals of Thoracic Surgery*, vol. 86, no. 3, pp. 832–840, 2008.

[13] F. Waldenberger, Y. I. Kim, S. Laycock, B. Meyns, and W. Flameng, "Effects of failure of the right side of the heart and increased pulmonary resistance on mechanical circulatory support with use of the miniaturized HIA-VAD displacement pump system," *Journal of Thoracic and Cardiovascular Surgery*, vol. 112, no. 2, pp. 484–493, 1996.

[14] B. Pinamonti, M. Zecchin, A. Di Lenarda, D. Gregori, G. Sinagra, and F. Camerini, "Persistence of restrictive left ventricular filling pattern in dilated cardiomyopathy: an ominous prognostic sign," *Journal of the American College of Cardiology*, vol. 29, no. 3, pp. 604–612, 1997.

[15] S. F. Yiu, M. Enriquez-Sarano, C. Tribouilloy, J. B. Seward, and A. J. Tajik, "Determinants of the degree of functional mitral regurgitation in patients with systolic left ventricular dysfunction: a quantitative clinical study," *Circulation*, vol. 102, no. 12, pp. 1400–1406, 2000.

[16] G. M. Scalia, P. M. McCarthy, R. M. Savage, N. G. Smedira, and J. D. Thomas, "Clinical utility of echocardiography in the management of implantable ventricular assist devices," *Journal of the American Society of Echocardiography*, vol. 13, no. 8, pp. 754–763, 2000.

[17] W. A. Zoghbi, M. Enriquez-Sarano, E. Foster et al., "Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography," *Journal of the American Society of Echocardiography*, vol. 16, no. 7, pp. 777–802, 2003.

[18] S. Chumnanvej, M. J. Wood, T. E. MacGillivray, and M. F. V. Melo, "Perioperative echocardiographic examination for ventricular assist device implantation," *Anesthesia and Analgesia*, vol. 105, no. 3, pp. 583–601, 2007.

[19] S. J. Park, K. K. Liao, R. Segurola, K. P. Madhu, and L. W. Miller, "Management of aortic insufficiency in patients with left ventricular assist devices: a simple coaptation stitch method (Park's stitch)," *Journal of Thoracic and Cardiovascular Surgery*, vol. 127, no. 1, pp. 264–266, 2004.

[20] S. C. Horton, R. Khodaverdian, P. Chatelain et al., "Left ventricular assist device malfunction: an approach to diagnosis by echocardiography," *Journal of the American College of Cardiology*, vol. 45, no. 9, pp. 1435–1440, 2005.

[21] B. J. Kircher, R. B. Himelman, and N. B. Schiller, "Noninvasive estimation of right atrial pressure from the inspiratory collapse of the inferior vena cava," *American Journal of Cardiology*, vol. 66, no. 4, pp. 493–496, 1990.

[22] J. Ferns, R. Dowling, and G. Bhat, "Evaluation of a patient with left ventricular assist device dysfunction," *ASAIO Journal*, vol. 47, no. 6, pp. 696–698, 2001.

[23] E. Catena, F. Milazzo, M. Merli et al., "Echocardiographic evaluation of patients receiving a new left ventricular assist device: the Impella® recover 100," *European Journal of Echocardiography*, vol. 5, no. 6, pp. 430–437, 2004.

[24] K. D. May-Newman, B. K. Hillen, C. S. Sironda, and W. Dembitsky, "Effect of LVAD outflow conduit insertion angle on flow through the native aorta," *Journal of Medical Engineering and Technology*, vol. 28, no. 3, pp. 105–109, 2004.

[25] E. Catena, F. Milazzo, E. Montorsi et al., "Left ventricular support by axial flow pump: the echocardiographic approach to device malfunction," *Journal of the American Society of Echocardiography*, vol. 18, no. 12, pp. 1422.e7–1422.e13, 2005.

[26] S. C. Horton, R. Khodaverdian, A. Powers et al., "Left ventricular assist device malfunction: a systematic approach to diagnosis," *Journal of the American College of Cardiology*, vol. 43, no. 9, pp. 1574–1583, 2004.

[27] M. Bedi, R. Kormos, S. Winowich, D. M. McNamara, M. A. Mathier, and S. Murali, "Ventricular arrhythmias during left ventricular assist device support," *American Journal of Cardiology*, vol. 99, no. 8, pp. 1151–1153, 2007.