Cardiology Research and Practice

Heart Failure 2013

Guest Editors: Gregory Giamouzis, Filippos Triposkiadis, Vasiliki V. Georgiopoulou, Dimitrios Farmakis, Dirk Westermann, and John Skoularigis

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Editorial Board

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Hindawi Publishing Corporation
Cardiology Research and Practice
Volume 2013, Article ID 342316, 2 pages
http://dx.doi.org/10.1155/2013/342316

Editorial

Heart Failure 2013

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Received 21 November 2013; Accepted 21 November 2013

The heart failure "growing epidemic" is an important public health issue that the health care systems of all developed countries are facing. Over the last decade, the annual number of heart failure hospitalizations has almost doubled with approximately 50% of patients being rehospitalized within 6 months of discharge [1]. The complex array of physiologic, psychological, social, and health care delivery issues makes it a challenging chronic disease to manage. To implement cost-effective strategies to curb the epidemic, better understanding of the underlying pathophysiological mechanisms as well as novel diagnostic and therapeutic approaches is needed.

In this special issue we have invited a few papers that address such issues and explain why, despite the emergence of novel therapeutic approaches that promise life prolongation and hospital length reduction, this patient population will still be needing rehospitalization and will often have a poor prognosis. This special issue is the extension of an effort that was initiated in 2011 with the first heart failure-focused issue, [2] coupled with a second focused issue a year later [3].

We have divided this issue into 4 categories: the pathophysiology section, the pharmacological treatment section, the nonpharmacological treatment section, and the comorbidity section.

According to the ejection fraction, patients with heart failure have traditionally been divided into two different groups: heart failure with preserved and heart failure with reduced ejection fraction. In recent years, accumulating studies showed that increased mortality and morbidity rates of these two groups are nearly equal. Although heart failure with preserved ejection fraction (formerly called "diastolic heart failure") is an increasingly frequent condition of heart failure worldwide, its pathophysiology has not been sufficiently elucidated. This is thought to be the most significant reason for a lack of established treatment methods in this patient population. In the *pathophysiology section*, K. Komamura and colleagues provide a comprehensive review of the similarities and differences between the pathogenesis and pathophysiology of diastolic and systolic heart failure.

Shedding light in a very similar topic, in the *pharmacological section*, J. Li and colleagues focus on the tested as well as the promising therapeutic options that are currently studied in patients with heart failure with preserved ejection fraction and provide a brief discussion on the pathophysiological mechanisms and diagnostic options that are helpful to increase our understanding of these novel therapeutic strategies. In an original study, A. Orea-Tejeda et al. evaluate the effect of ivabradine on endothelial function in diastolic and right heart failure patients. Ivabradine is an $I(f)$ ion current inhibitor that has proved to reduce mortality in patients with systolic heart failure by slowing heart rate without decreasing myocardial contractility but has not been tested in patients with preserved ejection fraction. Diastolic and right heart failure patients underwent photoplethysmography, a simple, low-cost optical technique that can evaluate vascular function, before and after induced ischemia and before and 6 months after treatment with ivabradine (mean 12.5 mg a day). Ivabradine administration significantly improved endothelial function (shear stress) in this patient population.

The accurate impact of exercise on coronary artery disease patients with left ventricular dysfunction is still debatable. In the *non-pharmacological treatment section*, M. Khosravi and colleagues study the effects of cardiac rehabilitation on echocardiography parameters in coronary artery disease patients with left ventricular dysfunction. Following an eight-week exercise-based rehabilitation program, all subjects significantly increased their left ventricular ejection fraction and peak exercise capacity without experiencing any serious cardiac complication.

A shared understanding of medical conditions between patients and their health care providers has been shown to improve self-care and outcomes [4]. In the *comorbidity section*, we demonstrate how certain comorbid conditions may affect patients' decision-making capacity and interfere with their ability to comply with treatment requirements, recognize and self-manage disease worsening symptoms [5]. Sleep disordered breathing, encompassing both obstructive and central sleep apnea, has been associated with increased cardiovascular morbidity and mortality. It occurs in almost half of all heart failure patients and is linked to hypertension, arrhythmia, impaired glucose tolerance, cerebrovascular disease, and ischemic heart disease. Despite the high prevalence and significant morbidity associated with this comorbid condition, our awareness and understanding of sleep disordered breathing remain incomplete [6]. E. Stopford and colleagues outline the available evidence linking sleep disordered breathing and cardiovascular disease and discuss the potential consequences and management in the heart failure population in particular.

We hope that the readers of the journal will find the topics as interesting and important as we did.

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References

[1] G. Giamouzis, A. Kalogeropoulos, V. Georgiopoulou et al., "Hospitalization epidemic in patients with heart failure: risk factors, risk prediction, knowledge gaps, and future directions," *Journal of Cardiac Failure*, vol. 17, no. 1, pp. 54–75, 2011.

[2] G. Giannakoulas, G. Giamouzis, F. Triposkiadis, J. Butler, and D. Westermann, "Heart failure," *Cardiology Research and Practice*, vol. 2011, Article ID 159608, 2 pages, 2011.

[3] G. Giamouzis, G. Giannakoulas, J. Butler, J. A. Elefteriades, C. Tschope, and F. Triposkiadis, "Heart failure 2012," *Cardiology Research and Practice*, vol. 2012, Article ID 126324, 3 pages, 2012.

[4] A. S. Malik, G. Giamouzis, V. V. Georgiopoulou et al., "Patient perception versus medical record entry of health-related conditions among patients with heart failure," *American Journal of Cardiology*, vol. 107, no. 4, pp. 569–572, 2011.

[5] C. N. Marti, V. V. Georgiopoulou, G. Giamouzis et al., "Patient-reported selective adherence to heart failure self-care recommendations: a prospective cohort study: the atlanta cardiomyopathy consortium," *Congestive Heart Failure*, vol. 19, pp. 16–24, 2013.

[6] V. Bhalla, V. V. Georgiopoulou, A. P. Kalogeropoulos et al., "Contemporary outcomes of optimally treated heart failure patients with sleep apnea. Case for urgency in evaluation of newer interventions? From the atlanta cardiomyopathy consortium," *International Journal of Cardiology*, vol. 165, pp. 366–368, 2013.

Hindawi Publishing Corporation
Cardiology Research and Practice
Volume 2013, Article ID 201713, 4 pages
http://dx.doi.org/10.1155/2013/201713

Clinical Study

The Impacts of Cardiac Rehabilitation Program on Echocardiographic Parameters in Coronary Artery Disease Patients with Left Ventricular Dysfunction

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Received 23 May 2013; Revised 21 September 2013; Accepted 2 November 2013

Academic Editor: Vasiliki Georgiopoulou

Introduction. The accurate impact of exercise on coronary artery disease (CAD) patients with left ventricular dysfunction is still debatable. We studied the effects of cardiac rehabilitation (CR) on echocardiography parameters in CAD patients with ventricular dysfunction. *Methods*. Patients with CAD who had ventricular dysfunction were included into an exercise-based rehabilitation program and received rehabilitation for eight weeks. All subjects underwent echocardiography before and at the end of the rehabilitation program. The echocardiography parameters, including left ventricular ejection fraction (LVEF), LV end-diastolic (LVEDD) and end-systolic diameters (LVESD), and peak exercise capacity measured in metabolic equivalents (METs), were assessed. *Results*. Seventy patients (mean age = 57.5 ± 10.2 years, 77.1% males) were included into the study. At the end of rehabilitation period, the LVEF increased from 45.14 ± 5.77% to 50.44 ± 8.70% ($P < 0.001$), and the peak exercise capacity increased from 8.00 ± 2.56 to 10.08 ± 3.00 METs ($P < 0.001$). There was no significant change in LVEDD (54.63 ± 12.96 to 53.86 ± 8.95 mm, $P = 0.529$) or in LVESD (38.91 ± 10.83 to 38.09 ± 9.04 mm, $P = 0.378$) after rehabilitation. *Conclusion*. Exercise training in postmyocardial infarction patients with ventricular dysfunction could have beneficial effects on cardiac function without adversely affecting LV remodeling or causing serious cardiac complications.

1. Introduction

Coronary artery diseases (CAD) are the leading cause of mortality in elderly individuals in developing countries. They account for nearly 50 percent of all deaths per year in Iran [1]. Also, they cause significant morbidity and impair the patient's quality of life [2, 3]. Various echocardiographic parameters have been shown to provide cardiac dysfunction in CAD patients, such as left ventricular volumes and ejection fraction which are strongly related to prognosis of cardiac diseases [4]. Cardiac rehabilitation (CR) is an acceptable treatment strategy adding to the basic medical plan for the patients with CAD. A multifactorial rehabilitation program includes six basic cores which are (1) baseline patient assessment, (2) nutritional counseling and weight management, (3) aggressive coronary risk-factor management, (4) psychosocial management, (5) physical activity counseling, and (6) exercise training. Several studies showed the beneficial effects of CR for CAD patients [5]. According to previous meta-analyses on the effects of exercise-based rehabilitation in

patients with CAD, a reduction in total and cardiac mortality and morbidity occurred after CR [6–8]. In this regard, a controlled study on patients with myocardial infarction (MI) with reduced ventricular function treated with cardiac exercised base rehabilitation revealed that oxygen uptake increased by the exercise, but end-diastolic and end-systolic myocardial wall thickness yielded no significant change indicating that the training program had no deleterious effects on left ventricular (LV) volume, function, or wall thickness [9]. Additionally, there are studies that indicate no adverse changes in left ventricle remodeling in patients with ejection fraction of more than 50% [10]. However, in another study, Jugdutt et al. followed the patients after acute MI that had underwent 12 weeks CR program and found that further cardiac functional and topographic deteriorations occur after exercise programs in patients with more severe LV asynergy [11]. The accurate impact of exercise in patients with advanced ventricular dysfunction seems to be debatable. We hypothesized that exercise-based cardiac rehabilitation programs improve echocardiographic parameters in patients with LV dysfunction. Therefore, we aimed to study the effect of rehabilitation program on the echocardiography parameters of CAD patients who had LV dysfunction.

2. Methods and Materials

2.1. Patients and Settings. This self-controlled trial was conducted on CAD patients referring to Isfahan Cardiovascular Research Center, Isfahan, Iran, between 2011 and 2012. Adult patients after coronary artery bypass grafting (CABG), percutaneous coronary angioplasty (PCA), or MI, with New York Heart Association classes II and III and ejection fraction between 30% and 50% and with LV dysfunction, were included into the study. The patients started the rehabilitation program one month after CABG and MI and two months after PCA. Patients with severe ventricular dysfunction (ejection fraction < 30%), unstable cardiac symptoms, change in medication within the preceding three months, recurrent ischemia, concurrent pulmonary disease, uncontrolled arrhythmia, or sever musculoskeletal disease were not included to the study. Also patients who had taken part in less than half of the rehabilitation sessions or had poor echo window were excluded from the study. The study was approved by the Ethics Committee of the Isfahan University of Medical Sciences and all patients signed a written inform consent before entering the study.

2.2. Rehabilitation Program. The rehabilitation program consisted of 20 sessions, scheduled over 8 weeks, 2 to 3 times per week. All participants follow both ergometer and treadmill. They allocate a predefined time in each exercise modality. Each session was about 1.5 hour; the first 10–20 minutes began with a warm-up followed by 20–40 minutes of aerobic exercise and finished with a 10-minute cool down; the patients had 20-minute relaxation at the end of each session [11]. Each session consists of at least 30 minutes aerobic exercise including about 20 minutes treadmill and 10 minutes ergoline cycling. In this part heart monitoring and control of blood pressure have been done. Patients had stretch activities for warm-up and cool-down phases. The intensity of the exercise was calculated according to the determined risk (patients age, underlying disease severity, and exercise test result) [12, 13], between 60 and 85% of the maximum heart rate (HR) according to Naughton protocol achieved on the basic exercise test [14]. Also the load and velocity of the exercise increased during the sessions. According to patients' underlying disease and capacity and the result of exercise test, we increase gradually both load and velocity. In the first three sessions the patients had heart monitoring supervised by a cardiologist. All patients received psychological, nutritional, and smoking cessation consult. In addition, weekly educational sessions were held during the eight weeks of comprehensive rehabilitation program, both for patients and their families. These consisted of explanations on cardiovascular diseases, its risk factors, diagnoses and treatment approaches, medications with their complications, stress reduction methods, and advice on a healthy lifestyle including smoking cessation, nutrition, and physical activity.

2.3. Assessments. At baseline and at the end of the rehabilitation period, cardiac peak exercise capacity measured in metabolic equivalents (METs) was evaluated and Doppler-echocardiography was performed. Standard views, including the parasternal long-axis, short-axis at the papillary muscle level, and apical 4- and 2-chamber views were recorded. Left ventricular ejection fraction (LVEF) and end-systolic and end-diastolic diameters (LVESD and LVEDD) were measured according to Simpsons model. The Doppler-echocardiographic studies were all performed by the same cardiologist who was blinded to the study. Also, the patients' demographic date, medical history, and presence of heart failure were recorded.

2.4. Statistical Analysis. The data were analyzed using the SPSS software (version 16.0) for windows. Quantitative and qualitative variables are presented as mean ± SD and number (%), respectively. Paired t-test was used for comparing LVEF, end-systolic/diastolic diameters, and the peak exercise capacities before and after the treatment. A P value of <0.05 was considered significant in all analyses.

3. Results

During the study period, 140 patients enrolled to the rehabilitation program from which 84 patients had EF between 30% and 50%. A total of 82 patients agreed and enrolled to the study and 70 patients completely attended the rehabilitation sessions (mean age = 57.5 ± 10.2 years, 77.1% males). Demographic data of the patients are presented in Table 1. All the patients were taking aspirin, beta blockers, and statins. Also, 30 patients had heart failure.

At the end of the rehabilitation period, the LVEF increased from 45.14 ± 5.77% to 50.44 ± 8.70% ($P < 0.001$) and the peak exercise capacity increased from 8.00 ± 2.56 to 10.08 ± 3.00 METs ($P < 0.001$). But no significant change was observed in LVEDD or LVESD after rehabilitation ($P > 0.05$), and the patients had no cardiac complications (Table 2).

Table 1: Demographic data of the patients.

Age (years)	57.5 ± 10.24
Male/female	54/16 (77.1% M)
Hypertension	26 (37.3%)
Diabetes mellitus	24 (34.3%)
Hyperlipidemia	37 (52.9%)
Smoking	8 (11.4%)
Family history	47 (67.1%)
CABG	36 (51.4%)
PTCA	17 (24.3%)
Beta blockers	48 (68.5%)
Statins	56 (80.0%)
Aspirin	61 (87.14%)

Data are presented as the mean ± SD or number (%); CABG: coronary artery bypass grafting; PTCA: percutaneous transluminal coronary angioplasty.

Table 2: Echocardiographic data of patients before and after the rehabilitation period.

	Before CR	After CR	*P* value
LVEF (%)	45.14 ± 5.77	50.44 ± 8.70	<0.001
METs	8.00 ± 2.56	10.08 ± 3.00	<0.001
LVESD (mm)	38.91 ± 10.83	38.09 ± 9.04	0.378
LVEDD (mm)	54.63 ± 12.96	53.86 ± 8.95	0.529
Maximum heart rate	45.19 ± 98.13	56.17 ± 69.13	0.15
Test duration and recovery	20.5 ± 81.14	06.6 ± 17.15	0.57

Data are presented as mean ± SD. CR: cardiac rehabilitation; LVEF: left ventricular ejection fraction; METs: peak exercise capacity measured in Metabolic equivalents; LVESD: left ventricular end-systolic diameter; LVEDD: left ventricular end-diastolic diameter.

4. Discussion

The epidemic of our era is CAD and it is estimated to be the single most important disease in the world in the terms of mortality, morbidity, disability, and economy even until 2020. Therefore cardiac preventive programs are the special need of our century. The meta-analysis evaluating the trials on coronary patients treated with exercise-based rehabilitation concluded that all of the coronary risk factors were improved and recurrent MI was reduced by about 20 percent after a year of rehabilitation program, also the mortality rate was reduced with longer follow-up after taking part in the programs [6, 15]. However the effect of CR on ventricular remodeling especially in patients with lower ejection fraction is still debatable [10]. This study originates in Iran, which is a highly understudied population in cardiac rehabilitation. Given the increasing prevalence of CAD and noncommunicable diseases worldwide, this study was needed to document the efficacy of cardiac rehabilitation in Iranian population. In our study, we applied rehabilitation program for CAD patients with ventricular dysfunction. Our study population had the ejection fraction of about less than 50% before entering into the study that was improved significantly after rehabilitation. Moreover, peak exercise capacity was significantly improved in our patients. Also, LVESD and LVEDD had no clinical or statistical change after the program. These results show that, among the patients with LV dysfunction, exercise-based rehabilitation is beneficial and has no detrimental effects on ventricular remodeling.

In rehabilitation programs several techniques are indicated for blood pressure control, smoking cessation, lipid lowering, diabetes and obesity control, and lifestyle modification. Although exercise training affects synthesize of free radicals, it increases the work capacity without a concomitant increase in free radical production. This fact indicates that physical activity could be performed with less oxidative stress. Also physical training reduced insulin resistance in post-MI patients with hyperinsulinemia and homocysteine level in patients with normal lipid profile which reduce the CAD risk for 20 to 30%. In this regard the review indicated that fibrinolysis improved as well as myocardial perfusion after physical training and improves systolic function and ejection fraction by increasing the muscle strength due to increasing heart rate during sympathic states caused by exercise [16].

Our results are consistent with the studies on patients with ejection fraction greater than 50% which indicated that exercise-based rehabilitation program does not have adverse impact on LV remodeling [10]. Also, study on the patients with advanced LV dysfunction (ejection fraction of less than 25%) shows that exercise training improves exercise capacity, has no adverse effect on ventricular remodeling, and does not cause serious cardiac complications [16]. Another study on patients with LV systolic dysfunction shows that 6-month exercise-based CR induced a combined reverse left atrial and LV remodeling as well as significant improvement in exercise functional capacity, LVEF, and early LV diastolic filling [17]. In contrast, one study on patients with Q wave MI showed that exercise training had adverse effect on ventricular asynergy and caused more shape distortion, expansion, and thinning in patients with 18% LV asynergy [11]. However, the exercise program used in their study seems not to be standard [18], and a review on 48 trials suggested that standard rehabilitation program is beneficial for all CAD patients [6]. The mechanism by which the exercise rehabilitation is beneficial for CAD patients has not been clarified yet. The described mechanisms for the effect of exercise on CAD patients are (a) improvement in endothelial function, autonomic tone, and myocardial oxygen demand, (b) modification of inflammatory markers, coagulation, and clotting factors, and (c) development of coronary collateral vessels [19, 20].

Our study had some limitations. Since we did not have control group we cannot estimate the exact effect of CR on CAD patients apart from the routine medical medication. Also, our study was not long enough to determine long-term results of CR in our patients. Therefore, controlled studies with longer follow-ups are needed in Iranian population to determine the exact effect of CR program on ventricular remodeling in CAD patients.

5. Conclusions

Cardiac rehabilitation in post-MI patients with LV dysfunction could have beneficial effects on cardiac function without

adversely affecting LV remodeling or causing serious cardiac complications. Further well-designed trials with longer follow-ups are required in this regard.

Conflict of Interests

The authors declare that they have no conflict of interests.

Acknowledgments

This study was supported by the Isfahan University of Medical Sciences as a thesis for obtaining specialty degree in Internal Medicine. The authors are thankful to Dr. Heydari H. and Dr. Mostafavi S. for helping them in rehabilitation program and Mrs. Noori H. for statistical analysis.

References

[1] N. Sarraf-Zadegan, M. Boshtam, H. Malekafzali et al., "Secular trends in cardiovascular mortality in Iran, with special reference to Isfahan," *Acta Cardiologica*, vol. 54, no. 6, pp. 327–333, 1999.

[2] E. Borowiak and T. Kostka, "Influence of chronic cardiovascular disease and hospitalisation due to this disease on quality of life of community-dwelling elderly," *Quality of Life Research*, vol. 15, no. 7, pp. 1281–1289, 2006.

[3] A. Leone, "The economic costs for the control of cardiovascular risk: an overview," *Current Pharmaceutical Design*, vol. 19, no. 13, pp. 2447–2453, 2013.

[4] S. A. Mollema, G. Nucifora, and J. J. Bax, "Prognostic value of echocardiography after acute myocardial infarction," *Heart*, vol. 95, no. 21, pp. 1732–1745, 2009.

[5] G. J. Balady, P. A. Ades, P. Comoss et al., " professionals from the American Heart Association and the American Association of Cardiovascular and Pulmonary Rehabilitation," *Circulation*, vol. 102, no. 9, pp. 1069–1073, 2000.

[6] R. S. Taylor, A. Brown, S. Ebrahim et al., "Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials," *American Journal of Medicine*, vol. 116, no. 10, pp. 682–692, 2004.

[7] P. Giannuzzi, P. L. Temporelli, U. Corrà, and L. Tavazzi, "Antiremodeling effect of long-term exercise training in patients with stable chronic heart failure: results of the exercise in left ventricular dysfunction and chronic heart failure (ELVD-CHF) trial," *Circulation*, vol. 108, no. 5, pp. 554–559, 2003.

[8] B. S. Heran, J. M. Chen, S. Ebrahim et al., "Exercise-based cardiac rehabilitation for coronary heart disease," *Cochrane Database of Systematic Reviews*, no. 7, Article ID CD001800, 2011.

[9] P. Dubach, J. Myers, G. Dziekan et al., "Effect of exercise training on myocardial remodeling in patients with reduced left ventricular function after myocardial infarction: application of magnetic resonance imaging," *Circulation*, vol. 95, no. 8, pp. 2060–2067, 1997.

[10] C. Kim, D. Y. Kim, and D. W. Lee, "The impact of early regular cardiac rehabilitation program on myocardial function after acute myocardial infarction," *Annals of Rehabilitation Medicine*, vol. 35, no. 4, pp. 535–540, 2011.

[11] B. I. Jugdutt, B. L. Michorowski, and C. T. Kappagoda, "Exercise training after anterior Q wave myocardial infarction: importance of regional left ventricular function and topography," *Journal of the American College of Cardiology*, vol. 12, no. 2, pp. 362–372, 1988.

[12] J. L. Roitman, T. LaFontaine, and A. M. Drimmer, "A new model for risk stratification and delivery of cardiovascular rehabilitation services in the long-term clinical management of patients with coronary artery disease," *Journal of Cardiopulmonary Rehabilitation*, vol. 18, no. 2, pp. 113–123, 1998.

[13] American Association of Cardiovascular and Pulmonary Rehabilitation, "Outpatient cardiac rehabilitation and secondary prevention," in *Guidelines for Cardiac Rehabilitation and Secondary Prevention Programs*, M. Williams, Ed., pp. 39–52, Human Kinetics, Champaign, Ill, USA, 1999.

[14] A. Kabir, N. Sarrafzadegan, A. Amini et al., "Impact of cardiac rehabilitation on metabolic syndrome in Iranian patients with coronary heart disease: the role of obesity," *Rehabilitation Nursing*, vol. 37, no. 2, pp. 66–73, 2012.

[15] A. M. Clark, L. Hartling, B. Vandermeer, and F. A. McAlister, "Meta-analysis: secondary prevention programs for patients with coronary artery," *Annals of Internal Medicine*, vol. 143, no. 9, pp. 659–672, 2005.

[16] J. Perk and G. Veress, "Cardiac rehabilitation: applying exercise physiology in clinical practice," *European Journal of Applied Physiology*, vol. 83, no. 4-5, pp. 457–462, 2000.

[17] F. Giallauria, G. Galizia, R. Lucci et al., "Favourable effects of exercise-based cardiac rehabilitation after acute myocardial infarction on left atrial remodeling," *International Journal of Cardiology*, vol. 136, no. 3, pp. 300–306, 2009.

[18] E. C. Kushner, "Exercise training after anterior Q wave myocardial infarction: importance of regional left ventricular function and topography," *Journal of the American College of Cardiology*, vol. 13, no. 6, p. 1451, 1989.

[19] R. Hambrecht, A. Wolf, S. Gielen et al., "Effect of exercise on coronary endothelial function in patients with coronary artery disease," *New England Journal of Medicine*, vol. 342, no. 7, pp. 454–460, 2000.

[20] J. P. Clausen and J. Trap Jensen, "Heart rate and arterial blood pressure during exercise in patients with angina pectoris. Effects of training and of nitroglycerin," *Circulation*, vol. 53, no. 3, pp. 436–442, 1976.

Hindawi Publishing Corporation
Cardiology Research and Practice
Volume 2013, Article ID 824135, 6 pages
http://dx.doi.org/10.1155/2013/824135

Review Article

Similarities and Differences between the Pathogenesis and Pathophysiology of Diastolic and Systolic Heart Failure

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Received 19 August 2013; Revised 8 October 2013; Accepted 10 October 2013

Academic Editor: Dirk Westermann

Pathophysiology of heart failure has been considered to be a damaged state of systolic function of the heart followed by a state of low cardiac output that is, systolic heart failure. Even if systolic function is preserved, left ventricular filling in diastole can be impeded and resulted in elevation of filling pressure and symptoms of heart failure. This kind of heart failure is called diastolic heart failure. Nowadays, diastolic heart failure is referred to as heart failure with preserved ejection fraction (HFpEF), whereas systolic heart failure is referred to as heart failure with reduced ejection fraction (HFrEF). In this paper, the similarities and differences between the pathogenesis and pathophysiology of diastolic and systolic heart failure were reviewed. Although diastolic heart failure is a common condition of heart failure worldwide, its pathophysiology has not been sufficiently elucidated. This is thought to be the most significant reason for a lack of established treatment methods for diastolic heart failure. We hope to proceed with future studies on this topic.

1. Introduction

Pathophysiology of heart failure has been considered to be a damaged state of systolic function of the heart followed by a state of low cardiac output (systolic heart failure). However, even if systolic function is preserved, left ventricular filling in diastole is impeded due to various factors. This condition leads to congestive heart failure due to the rise in left ventricular end-diastolic pressure and the decrease in cardiac output. This kind of pathophysiology is now known as diastolic heart failure [1, 2]. In recent years, diastolic heart failure caused by the affected left ventricle has become a clinical issue [3]. Nowadays, diastolic heart failure is referred to as heart failure with preserved ejection fraction (HFpEF), whereas systolic heart failure is referred to as heart failure with reduced ejection fraction (HFrEF). This is because evaluating accurate pathophysiology and diagnosis of diastolic heart failure is in fact difficult.

2. Diastolic Dysfunction

Diastole of the left ventricle is composed of isovolumic relaxation and ventricular filling. Relaxation of the left ventricle is an active process that occurs as a result of energy-dependent uptake of intracellular calcium by the sarcoplasmic reticulum, whose concentration has risen during the systolic phase.

Relaxation of the left ventricle is impaired in a disease state caused by energy metabolism disorders or calcium-handling abnormalities such as myocardial ischemia and myocardial hypertrophy. Left ventricular filling phase abnormality, namely, elevation of left ventricular stiffness, influences left ventricular flow dynamics during filling phase and is commonly caused by myocardial fibrosis or hypertrophy.

When left ventricular diastolic function is impaired, cardiac output is reduced because the left ventricle is not filled enough in diastole due to left ventricular inflow obstruction. By contrast, to compensate for reduced cardiac output, increasing the inflow pressure to the left ventricle (and consequently left ventricular end-diastolic pressure) becomes necessary, which in turn increases left atrial pressure. As a result, left ventricular dysfunction easily and directly causes pulmonary congestion.

The end-systolic pressure-volume relationship is the same as a normal heart in diastolic heart failure, but the end-diastolic pressure-volume relationship shifts upwards (Figure 1(a)) [3]. As a result, left ventricular end-diastolic

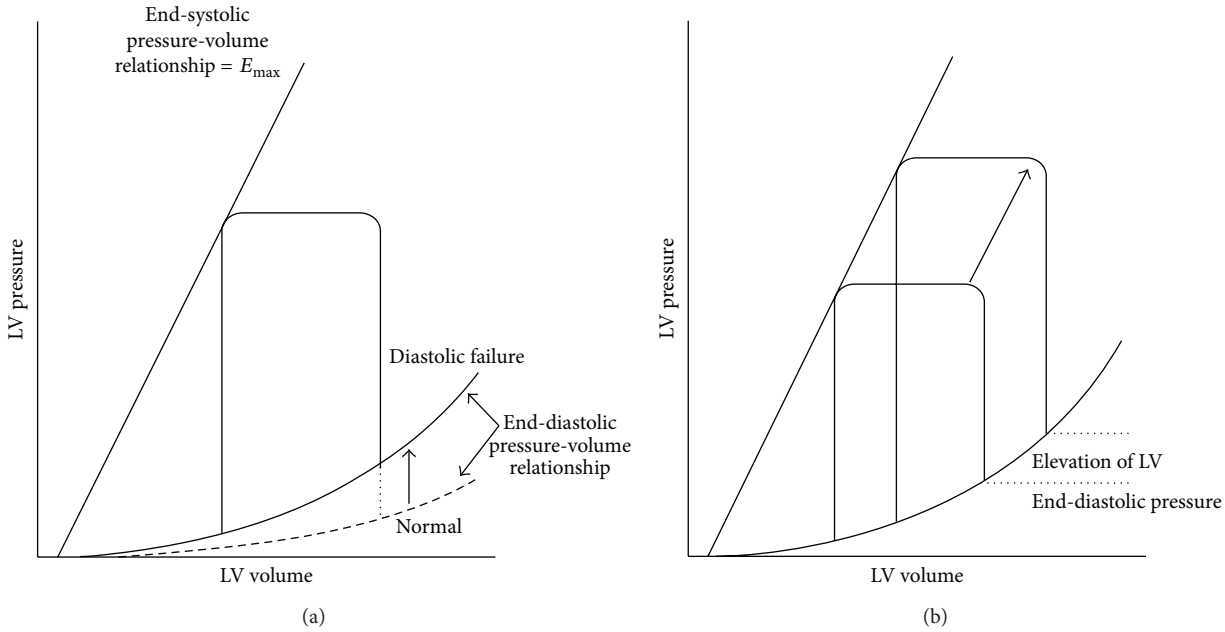

Figure 1: (a) The end-systolic pressure-volume relationship is the same as a normal heart in diastolic heart failure, but the end-diastolic pressure-volume relationship shifts upwards. As a result, left ventricular end-diastolic pressure rises. (b) In pathologies with diastolic dysfunction, when an abrupt increase in blood pressure occurs, the pressure-volume loop shifts to the upper right without decrease in E_{max}. Therefore, pulmonary congestion is induced as a result of the significant increase in left ventricular end-diastolic pressure. LV: left ventricular.

pressure rises. In pathologies with diastolic dysfunction, when an abrupt increase in blood pressure occurs, the pressure-volume loop shifts to the upper right without decrease in E_{max} (absolute index of contractibility). Therefore, pulmonary congestion is induced as a result of the significant increase in left ventricular end-diastolic pressure (Figure 1(b)).

By contrast, in systolic dysfunction, left ventricular contractile function decreases and E_{max} gets smaller (Figure 2). Meanwhile, the end-diastolic pressure-volume relationship shifts downwards rather than remaining unchanged. To maintain cardiac output, the pressure-volume loop shifts right due to increase in preload. Therefore, the left ventricular pressure-volume loop operates on the steep part of the end-diastolic pressure-volume curve, consequently causing end-diastolic pressure to rise.

3. Are Diastolic Dysfunction and Systolic Dysfunction Separate Diseases?

In diastolic dysfunction, contractility of whole left ventricle is considered normal. However, the contractile velocity in systole measured with tissue Doppler decreased in both systolic and diastolic dysfunction [4]. Furthermore, local contractility in longitudinal direction is known to be impaired locally in diastolic heart failure [5]. Recent findings suggest that contractility decreases even in diastolic heart failure in myocardium level. By contrast, diastolic function is also impaired in systolic heart failure and has been shown to decrease exercise tolerance and be one of the determinants of prognosis [6]. Therefore, diastolic and systolic heart failure are not considered to be independent and separate entities. The single syndrome hypothesis of heart failure is therefore advocated (Figure 3) [1]. In that hypothesis, heart failure is a single continuous disease spectrum and systolic and diastolic heart failure are phenotypes at two extremes.

Thus, there is the "grey zone" in diagnosing HFrEF with LVEF of 45 to 50% or 45 to 55%. In other words, some of HFpEF with LVEF of 45 to 55% might be diagnosed as HFrEF rather than HFpEF. As shown in Figure 3, a phenotype of heart failure comprised of some extent of systolic dysfunction and some extent of diastolic function. Heart failure with LVEF of 45 to 55% would be located in the middle of the continuum of disease spectrum.

By contrast, some researchers have advocated that diastolic function is not something that should only be noted in the pathogenesis of diastolic heart failure, but should be widely viewed as a determinant of pathophysiology in heart failure [7]. Heart dysfunction that occurs as a result of heart disease causes diastolic dysfunction. Among such cases there exist patients with concurrent systolic dysfunction. Furthermore, a portion of patients with heart dysfunction clinically exhibit symptoms of heart failure. Among them, those with significant systolic dysfunction where the main pathology is systolic heart failure, and diastolic dysfunction, are said to have diastolic heart failure.

4. The Diagnostic Criteria for Diastolic Heart Failure

Definition of systolic heart failure is reduction of the left ventricular ejection fraction. Thus, its diagnosis is quite easy. By contrast, diagnosis of diastolic heart failure is difficult

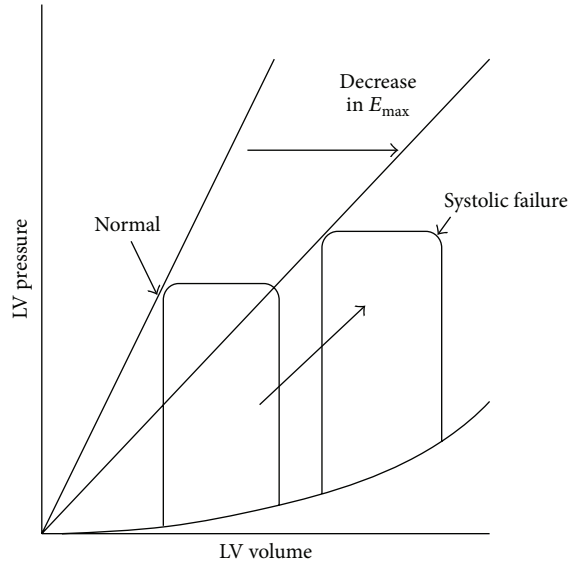

Figure 2: In systolic dysfunction, LV contractile function decreases and E_{max} gets smaller. Meanwhile, the end-diastolic pressure-volume relationship shifts downwards rather than remaining unchanged. To maintain cardiac output, the pressure-volume loop shifts right due to increase in preload. Therefore, the LV pressure-volume loop operates on the steep part of the end-diastolic pressure-volume curve, consequently causing end-diastolic pressure to rise. LV: left ventricular.

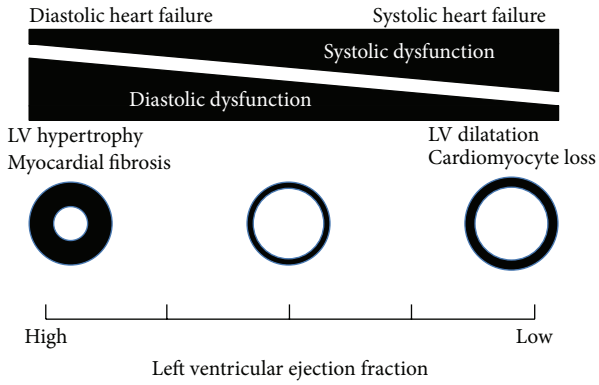

Figure 3: Diastolic and systolic heart failure are not considered to be independent and separate entities. Heart failure is a single continuous disease spectrum and systolic and diastolic heart failure are phenotypes at two extremes.

since there are no simple and reliable criteria. Therefore, diastolic heart failure can be clinically diagnosed when clinical symptoms and findings of heart failure are exhibited and decrease in left ventricular ejection fraction is none or minimal.

The American College of Cardiology Foundation and the American Heart Association define diastolic heart failure as a condition having the typical signs and symptoms of heart failure with a normal left ventricular ejection fraction, without valvular abnormalities on echocardiography [8]. Vasan and Levy define diastolic heart failure as (1) exhibiting clinical symptoms of congestive heart failure, (2) having normal left ventricular systolic function during congestive heart failure (left ventricular ejection fraction of 45 to 50% and above), and (3) having left ventricular diastolic dysfunction. Those that meet all these items and who have congestive heart failure that is not caused by valvular heart disease, cor pulmonale, or primary volume overload are considered as "definite diastolic heart failure (definite DHF)" cases. Currently, accurate diagnosis of (3) needs cardiac catheterization, which could be skipped in a common clinical situation.

Diastolic heart failure is strongly suspected (probable DHF) when conditions (1) and (2) are met [9]. When diagnosing diastolic heart failure, it is important to perform a careful exclusion of valvular heart disease, pericardial disease, right heart failure, intracardiac tumor, congenital heart disease, and high-output cardiac failure. Zile et al. demonstrated that diastolic functional abnormalities caused an increase in left ventricular filling pressure and clinical symptoms of congestive heart failure using cardiac catheterization for patients with heart failure with preserved ejection fraction and patients with diastolic heart failure [10, 11]. The currently accepted criteria for diagnosis of diastolic heart failure are essentially a clinical diagnosis. Thus, it is important to understand that there are possibilities that diastolic heart failure means somewhat broader range than what diastolic heart failure exactly stands for.

5. Diastolic Heart Failure from the Perspective of Clinical Features

According to reports by Owan et al. and Bhatia et al., roughly half of hospitalizations for heart failure are due to diastolic heart failure [12, 13]. Compared with systolic heart failure, diastolic heart failure is seen more often in the elderly and women and accompanied by hypertension and anemia. Comorbidity rate of obesity, diabetes, and chronic kidney disease (CKD) in diastolic heart failure is high, but not particularly higher than in systolic heart disease. In general, both diastolic and systolic heart failure exhibit distinctive subjective symptoms and objective findings of heart failure including dyspnea, edema, and malaise. Symptoms of diastolic heart failure typically include dyspnea due to pulmonary congestion, particularly shortness of breath, paroxysmal atrial fibrillation, and rapidly developing dyspnea induced by tachycardia, all of which are common initial symptoms. By contrast, in systolic heart failure, symptoms and signs due to general malaise and organ hypoperfusion associated with decreased cardiac output are frequently seen.

The main differences between diastolic and systolic heart failure are the presence of contractile dysfunction and left ventricular remodeling (Table 1). In systolic heart failure, progressive ventricular dilatation, or eccentric cardiac hypertrophy, can be seen. By contrast, diastolic heart failure exhibits concentric ventricular remodeling without dilatation or concentric cardiac hypertrophy. The tissue Doppler E/E′ ratio (early mitral inflow peak velocity/early diastolic mitral annular velocity) is an established diastolic function index that is not affected by hemodynamic load, but increases in

Table 1: Comparison of systolic and diastolic heart failure.

	Systolic heart failure	Diastolic heart failure
LV remodeling	 Eccentric hypertrophy	 Concentric remodeling Concentric hypertrophy
LV end-diastolic volume	↑	→
LV end-diastolic pressure	↑	↑
LV ejection fraction	↓	→
LV dP/dt	↓	→
LV stiffness	→	↑
E/E'	↑	↑
LA dilatation	+	+
BNP or NT-proBNP	↑	↑

LV: left ventricular; E/E': early mitral flow velocity/early diastolic mitral annular velocity ratio; LA: left arterial; BNP: brain natriuretic peptide.

both diastolic and systolic heart failure. Pattern of pulmonary vein flow and E/A (ratio of early to late mitral inflow peak velocity) are also established as major diastolic functional indices, though they are rather dependent on hemodynamic status [14].

In recent years, several reports on important association of various biomarkers for heart failure and subtypes of heart failure have been published [15–19]. According to those reports, plasma B-type natriuretic peptide (BNP) concentration in patients with HFpEF is lower than that in patients with HFrEF [15]. Nonetheless, at a given level of BNP, the prognosis in patients with HFpEF is as poor as in those with HFrEF [15]. Not only BNP and N-terminal proBNP (NT-proBNP) but also high sensitive troponin T (hsTnT) was significantly associated with the risk for HFrEF [16]. On the other hand, growth differentiation factor 15 (GDF15), cystatin C, and urinary albumin excretion were significantly associated with the risk for HFpEF [16, 17]. Researchers suggest that biomarkers relevant to myocardial injury (TnT) and myocardial stress (BNP, NT-proBNP, and midregional proadrenomedullin) have significant relation with HFrEF [17–19] and biomarkers relevant to extracellular matrix remodeling (Galectin-3 and GDF15) have significant relation with HFpEF [17–19].

6. The Pathogenesis of Diastolic Heart Failure

The histological features of systolic heart failure include myocardial hypertrophy, loss of myocardial cells, and restructuring of the extracellular matrix. Meanwhile, significant myocardial fibrosis together with myocardial hypertrophy is typical in diastolic heart failure. Myocardial fibrosis is thought to be the main factor in increased stiffness [14].

Mechanical stimulation to the myocardium is the main factor of myocardial hypertrophy, while myocardial fibrosis may be caused by humoral factors such as various cytokines, growth factors, and hormones. In hypertensive HFpEF model rats, oxidative stress was increased and angiotensin II was produced within the arterial walls due to high blood pressure. This resulted in fibroblast activation and increased production of transforming growth factor-β via macrophage infiltration and activation mediated by monocyte chemotactic protein-1. The resulting perivascular inflammation is reported to be the cause of reactive fibrosis of myocardium [14–16]. In Dahl salt-sensitive rat HFpEF models, it was found that endothelin, together with angiotensin II, is an important mediator of myocardial fibrosis [17].

In addition to the quantitative increase in collagen and distribution abnormalities, qualitative changes are also involved in increased myocardial stiffness caused by fibrosis. In Dahl salt-sensitive rat HFpEF models, the increase in the ratio of stiff type I collagen to type III collagen, which is highly distensible, and increased collagen cross-linking are reported to important factors of increased myocardial stiffness [18].

In diastolic heart failure, myocardial stiffness of cardiomyocytes per se also increases. Detailed mechanism for this remains unclear but is thought to be due to changes in structural proteins associated with myocardial hypertrophy. Titin, which is a giant sarcomeric protein, acts as a molecular spring and plays a large part in the distensibility of cardiomyocytes during diastole. However, in diastolic heart failure, compared with systolic heart failure, the ratio of large, distensible N2A isoforms small, rigid N2B isoforms to was found to decrease [19].

7. Therapeutic Options

To date, angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARB), beta-blockers, and statins have been tried for HFpEF. Although they are authorized for optimal treatment for HFrEF, none of them can provide the optimal treatment for HFpEF [2]. ACEI perindopril was tested for HFpEF patients for the first time in PEP–CHF trial [20]. It showed no difference in mortality and/or hospitalization rate for heart failure. CHARM-preserved trial, in which ARB candesartan was tested for

cardiovascular mortality and heart failure hospitalizations, failed to demonstrate a beneficial effect on cardiovascular death but observed fewer heart failure hospitalizations in the candesartan group [21]. I-PRESERVE was so far the largest trial for HFpEF using ARB irbesartan or placebo. Mortality or hospitalization rate for cardiovascular causes was again not improved by irbesartan [22]. In OPTIMIZE-HF registry, discharge use of beta-blockers exerted no effect on one-year mortality or hospitalization rate in HFpEF patients [23]. A preliminary report suggested statin therapy to be beneficial in HFpEF with lower mortality rate [24].

A neutral outcome in HFpEF compared with a positive outcome in HFrEF, as occurred with ACEIs, ARBs, and beta-blockers, might be compatible with flawed study design. However, a positive outcome in HFpEF compared with a neutral outcome in HFrEF, as occurred with statins, can no longer be attributable to study design but supports different signal transductions driving myocardial remodeling in HFpEF and HFrEF [25].

Several compounds seem to be promising for drug target of HFpEF. Phosphodiesterase 5 inhibitors (PDE5I) increase cGMP level, attenuate adrenergic stimulation, reduce ventricular-arterial stiffening, antagonize maladaptive chamber remodeling, improve endothelial function, and reduce pulmonary vascular resistance [26–30]. The PDE5I sildenafil is currently being tested in the RELAX trial, which evaluates the effects of PDE5I on exercise capacity, functional status, and ventricular function [31]. A preliminary open-label trial documented improvements in exercise capacity and the E/E' ratio in HFpEF treated with spironolactone [32]. Aldosterone antagonists are currently being actively investigated for HFpEF in the clinical situation. Chamber stiffness is altered by the extracellular matrix like collagen. Alagebrium chloride (ALT-711) is a novel agent that breaks glucose cross-links and improves ventricular and vascular compliance in animal experiments and reduces blood pressure and vascular stiffness in humans [33, 34]. Small open-label trial revealed that ALT-711 was associated with reduced LV mass and improved diastolic filling [35]. Diastolic dysfunction in HFpEF may be related to abnormalities in energy availability or utilization in myocytes [36–38]. Recently, abnormal ATP phosphocreatine shuttle kinetics in HFpEF was demonstrated, and similar results were recently also reported [37, 39]. Currently, a novel therapy targeting energy utilization is under investigation [40].

8. Conclusion

Despite the fact that diastolic heart failure is a common condition of heart failure, its precise definition still remains unclear. Therefore, the similarities and differences between the pathogenesis and pathophysiology of diastolic and systolic heart failure have not been sufficiently elucidated. This is thought to be the most significant reason for a lack of established treatment methods for diastolic heart failure. We hope to proceed with future studies on this paper.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this article.

References

[1] M. Ouzounian, D. S. Lee, and P. P. Liu, "Diastolic heart failure: mechanisms and controversies," *Nature Clinical Practice Cardiovascular Medicine*, vol. 5, pp. 375–386, 2008.

[2] M. T. Maeder and D. M. Kaye, "Heart failure with normal left ventricular ejection fraction," *Journal of the American College of Cardiology*, vol. 53, no. 11, pp. 905–918, 2009.

[3] B. A. Borlaug and W. J. Paulus, "Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment," *European Heart Journal*, vol. 32, no. 6, pp. 670–679, 2011.

[4] E. H. García, E. R. Perna, E. F. Farías et al., "Reduced systolic performance by tissue Doppler in patients with preserved and abnormal ejection fraction: new insights in chronic heart failure," *International Journal of Cardiology*, vol. 108, no. 2, pp. 181–188, 2006.

[5] G. Yip, M. Wang, Y. Zhang, J. W. H. Fung, P. Y. Ho, and J. E. Sanderson, "Left ventricular long axis function in diastolic heart failure is reduced in both diastole and systole: time for a redefinition?" *Heart*, vol. 87, no. 2, pp. 121–125, 2002.

[6] S. J. Skaluba and S. E. Litwin, "Mechanisms of exercise intolerance: insights from tissue Doppler imaging," *Circulation*, vol. 109, no. 8, pp. 972–977, 2004.

[7] K. Yamamoto, Y. Sakata, T. Ohtani, Y. Takeda, and T. Mano, "Heart failure with preserved ejection fraction: what is known and unknown," *Circulation Journal*, vol. 73, no. 3, pp. 404–410, 2009.

[8] S. A. Hunt, W. T. Abraham, M. H. Chin et al., "ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society," *Circulation*, vol. 112, no. 12, pp. e154–e235, 2005.

[9] R. S. Vasan and D. Levy, "Defining diastolic heart failure: a call for standardized diagnostic criteria," *Circulation*, vol. 101, no. 17, pp. 2118–2121, 2000.

[10] M. R. Zile, W. H. Gaasch, J. D. Carroll et al., "Heart failure with a normal ejection fraction: is measurement of diastolic function necessary to make the diagnosis of diastolic heart failure?" *Circulation*, vol. 104, no. 7, pp. 779–782, 2001.

[11] M. R. Zile, C. F. Baicu, and W. H. Gaasch, "Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle," *The New England Journal of Medicine*, vol. 350, no. 19, pp. 1953–1959, 2004.

[12] T. E. Owan, D. O. Hodge, R. M. Herges, S. J. Jacobsen, V. L. Roger, and M. M. Redfield, "Trends in prevalence and outcome of heart failure with preserved ejection fraction," *The New England Journal of Medicine*, vol. 355, no. 3, pp. 251–259, 2006.

[13] R. S. Bhatia, J. V. Tu, D. S. Lee et al., "Outcome of heart failure with preserved ejection fraction in a population-based study," *The New England Journal of Medicine*, vol. 355, no. 3, pp. 260–269, 2006.

[14] S. F. Nagueh, C. P. Appleton, T. C. Gillebert et al., "Recommendations for the evaluation of left ventricular diastolic function by echocardiography," *European Journal of Echocardiography*, vol. 10, no. 2, pp. 165–193, 2009.

[15] D. J. van Veldhuisen, G. C. Linssen, T. Jaarsma et al., "B-type natriuretic Peptide and prognosis in heart failure patients with preserved and reduced ejection fraction," *Journal of the American College of Cardiology*, vol. 61, no. 14, pp. 1498–1506, 2013.

[16] F. P. Brouwers, R. A. de Boer, P. van der Harst et al., "Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND," *European Heart Journal*, vol. 34, pp. 1424–1431, 2013.

[17] R. Santhanakrishnan, J. P. Chong, T. P. Ng et al., "Growth differentiation factor 15, ST2, high-sensitivity troponin T, and N-terminal pro brain natriuretic peptide in heart failure with preserved vs. reduced ejection fraction," *European Journal of Heart Failure*, vol. 14, pp. 1338–1347, 2012.

[18] R. R. J. van Kimmenade and J. L. Januzzi Jr., "Emerging biomarkers in heart failure," *Clinical Chemistry*, vol. 58, no. 1, pp. 127–138, 2012.

[19] H. K. Gaggin and J. L. Januzzi Jr., "Biomarkers and diagnostics in heart failure," *Biochimica et Biophysica Acta*, 2013.

[20] J. G. F. Cleland, M. Tendera, J. Adamus, N. Freemantle, L. Polonski, and J. Taylor, "The perindopril in elderly people with chronic heart failure (PEP-CHF) study," *European Heart Journal*, vol. 27, no. 19, pp. 2338–2345, 2006.

[21] S. Yusuf, M. A. Pfeffer, K. Swedberg et al., "Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-preserved trial," *The Lancet*, vol. 362, no. 9386, pp. 777–781, 2003.

[22] B. M. Massie, P. E. Carson, J. J. McMurray et al., "Irbesartan in patients with heart failure and preserved ejection fraction," *The New England Journal of Medicine*, vol. 359, no. 23, pp. 2456–2467, 2008.

[23] A. F. Hernandez, B. G. Hammill, C. M. O'Connor, K. A. Schulman, L. H. Curtis, and G. C. Fonarow, "Clinical effectiveness of beta-blockers in heart failure. Findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) Registry," *Journal of the American College of Cardiology*, vol. 53, no. 2, pp. 184–192, 2009.

[24] H. Fukuta, D. C. Sane, S. Brucks, and W. C. Little, "Statin therapy may be associated with lower mortality in patients with diastolic heart failure: a preliminary report," *Circulation*, vol. 112, no. 3, pp. 357–363, 2005.

[25] W. J. Paulus and J. J. M. van Ballegoij, "Treatment of heart failure with normal ejection fraction: an inconvenient truth!," *Journal of the American College of Cardiology*, vol. 55, no. 6, pp. 526–537, 2010.

[26] B. A. Borlaug, V. Melenovsky, T. Marhin, P. Fitzgerald, and D. A. Kass, "Sildenafil inhibits β-adrenergic-stimulated cardiac contractility in humans," *Circulation*, vol. 112, no. 17, pp. 2642–2649, 2005.

[27] C. Vlachopoulos, K. Hirata, and M. F. O'Rourke, "Effect of sildenafil on arterial stiffness and wave reflection," *Vascular Medicine*, vol. 8, no. 4, pp. 243–248, 2003.

[28] S. D. Katz, K. Balidemaj, S. Homma, H. Wu, J. Wang, and S. Maybaum, "Acute type 5 phosphodiesterase inhibition with sildenafil enhances flow-mediated vasodilation in patients with chronic heart failure," *Journal of the American College of Cardiology*, vol. 36, no. 3, pp. 845–851, 2000.

[29] G. D. Lewis, J. Lachmann, J. Camuso et al., "Sildenafil improves exercise hemodynamics and oxygen uptake in patients with systolic heart failure," *Circulation*, vol. 115, no. 1, pp. 59–66, 2007.

[30] H. H. Chen, "Heart failure: a state of brain natriuretic peptide deficiency or resistance or both!," *Journal of the American College of Cardiology*, vol. 49, no. 10, pp. 1089–1091, 2007.

[31] M. M. Redfield, K. L. Lee, and E. Braunwald, "Evaluating the effectiveness of Sildenafil at improving health outcomes and exercise ability in people with diastolic heart failure (The RELAX Study)," NCT00763867, 2008, http://clinicaltrials.gov/.

[32] K. R. Daniel, G. Wells, K. Stewart, B. Moore, and D. W. Kitzman, "Effect of aldosterone antagonism on exercise tolerance, doppler diastolic function, and quality of life in older women with diastolic heart failure," *Congestive Heart Failure*, vol. 15, no. 2, pp. 68–74, 2009.

[33] P. V. Vaitkevicius, M. Lane, H. Spurgeon et al., "A cross-link breaker has sustained effects on arterial and ventricular properties in older rhesus monkeys," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 3, pp. 1171–1175, 2001.

[34] D. A. Kass, E. P. Shapiro, M. Kawaguchi et al., "Improved arterial compliance by a novel advanced glycation end-product crosslink breaker," *Circulation*, vol. 104, no. 13, pp. 1464–1470, 2001.

[35] W. C. Little, M. R. Zile, D. W. Kitzman, W. G. Hundley, T. X. O'Brien, and R. C. Degroof, "The effect of alagebrium chloride (ALT-711), a novel glucose cross-link breaker, in the treatment of elderly patients with diastolic heart failure," *Journal of Cardiac Failure*, vol. 11, no. 3, pp. 191–195, 2005.

[36] B. A. Borlaug, V. Melenovsky, S. D. Russell et al., "Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction," *Circulation*, vol. 114, no. 20, pp. 2138–2147, 2006.

[37] T. T. Phan, K. Abozguia, G. Nallur Shivu et al., "Heart failure with preserved ejection fraction is characterized by dynamic impairment of active relaxation and contraction of the left ventricle on exercise and associated with myocardial energy deficiency," *Journal of the American College of Cardiology*, vol. 54, no. 5, pp. 402–409, 2009.

[38] D. W. Kitzman, M. B. Higginbotham, F. R. Cobb, K. H. Sheikh, and M. J. Sullivan, "Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism," *Journal of the American College of Cardiology*, vol. 17, no. 5, pp. 1065–1072, 1991.

[39] C. S. Smith, P. A. Bottomley, S. P. Schulman, G. Gerstenblith, and R. G. Weiss, "Altered creatine kinase adenosine triphosphate kinetics in failing hypertrophied human myocardium," *Circulation*, vol. 114, no. 11, pp. 1151–1158, 2006.

[40] M. Frenneaux, "Perhexiline therapy in heart failure with preserved ejection fraction syndrome," NCT00839228, 2009, http://clinicaltrials.gov/.

Hindawi Publishing Corporation
Cardiology Research and Practice
Volume 2013, Article ID 356280, 9 pages
http://dx.doi.org/10.1155/2013/356280

Review Article

The Association of Sleep Disordered Breathing with Heart Failure and Other Cardiovascular Conditions

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Received 13 July 2013; Revised 7 October 2013; Accepted 30 October 2013

Academic Editor: Dimitrios Farmakis

An abundance of evidence exists in support of primary and secondary prevention for tackling the scourge of cardiovascular disease. Despite our wealth of knowledge, certain deficiencies still remain. One such example is the association between sleep disordered breathing (SDB) and cardiovascular disease. A clear body of evidence exists to link these two disease entities (independent of other factors such as obesity and smoking), yet our awareness of this association and its clinical implication does not match that of other established cardiovascular risk factors. Here, we outline the available evidence linking SDB and cardiovascular disease as well as discussing the potential consequences and management in the cardiovascular disease population.

1. Sleep Disordered Breathing and Cardiovascular Disease

1.1. Opening Statement. Sleep disordered breathing (SDB), encompassing both obstructive and central sleep apnoea, has been associated with increased cardiovascular morbidity and mortality. It occurs in half of all heart failure patients and is linked to hypertension, arrhythmia, impaired glucose tolerance, cerebrovascular disease, and ischaemic heart disease [1–3]. Despite the high prevalence and significant morbidity associated with SDB, our awareness and understanding of this condition remain incomplete.

1.2. Introduction. An abundance of evidence exists in support of primary and secondary prevention for tackling the scourge of cardiovascular disease. Despite our wealth of knowledge, certain deficiencies still remain. One such example is the association between SDB and cardiovascular disease. A clear body of evidence exists to link these two disease entities (independent of other factors such as obesity and smoking) yet our awareness of this association and its clinical implication does not match that of other established cardiovascular risk factors [4, 5]. Here, we outline the available evidence linking SDB and cardiovascular disease as well as discussing the potential consequences and management in the cardiovascular disease population.

2. Sleep Disordered Breathing and Its Apnoeic Subtypes: Obstructive or Central?

Sleep apnoea can be defined as the cessation of breathing during sleep which lasts for at least 10 seconds, on five or more occasions per hour, and which leads to tiredness during the daytime [6]. Presenting symptoms may include morning headaches, unrefreshing sleep, and the effects of increased daytime somnolence (poor concentration, mood changes, and reduced libido). In over 80% of cases, however, individuals suffering from sleep apnoea will be completely unaware of their condition and it is often their partners that report classical snoring symptoms. The gold standard method for confirming nocturnal apnoea and diagnosing SDB is full polysomnography, comprising of multiple recorded variables including thoracoabdominal movement, oxygen saturation, electrocardiography and respiratory airflow. In clinical practice, however, sleep studies typically involve more time- and cost-effective methods such as pulse oximetry. A 4% or greater fall in oxygen saturations correlates with a 10-second pause or apnoea [6].

The severity of sleep apnoea is assessed using the apnoea-hypopnoea index (AHI), which represents the number of apnoeic or hypopnoeic (reduction in oronasal airflow amplitude by ≥30% for a period of at least 10 seconds) episodes per hour of sleep. Sleep apnoea can be classified as mild (AHI = 5–15), moderate (AHI = 15–30), or severe (AHI ≥ 30) [6]. Sleep apnoea is further categorised according to the underlying mechanism of apnoea [2]. Obstructive sleep apnoea (OSA) is the most prevalent form of sleep apnoea amongst the general population and involves recurrent collapse of the pharyngeal airway leading to reduction or cessation in oropharyngeal airflow and subsequent arousal (Figure 1) [2, 4, 7]. Central sleep apnoea (CSA) is not caused by occlusion of the pharynx but rather an autonomic-mediated reduction of ventilation due to a fall in the partial pressure of carbon dioxide below the threshold needed to stimulate breathing. Once this hypocapnic threshold is breached, ventilation decreases and the carbon dioxide level increases. This homeostatic mechanism maintains stable levels of serum carbon dioxide and pH [2].

A combination of the two apnoeic pathologies can occur in some patients, defined as mixed sleep apnoea. Obstructive apnoeas can lead to an impaired homeostatic response to hypercapnia and the subsequent development of central apnoeas. This happens primarily in heart failure patients with the exact mechanism not fully understood. Obstructive and central apnoea can also combine to produce complex sleep apnoea. This occurs when patients with OSA treated with continuous positive airway pressure (CPAP) convert to central apnoeic episodes; again believed to be a consequence of impaired homeostatic mechanisms [8].

3. How Is Sleep Disordered Breathing Related to Cardiovascular Disease?

The prevalence of SDB in the general population is estimated to be between 5 and 10% [4, 6, 9]. This figure rises to be between 30–83%, 30–58%, and 50–80% in hypertensive patients, ischaemic heart disease patients, and the heart failure population, respectively [5, 10, 11]. Evidence supports the role of SDB in the development and progression of cardiovascular disease and vice versa. The exact mechanisms for this association are not fully defined but have been widely postulated.

4. Pathophysiology: How Does SDB Contribute to Cardiovascular Disease?

Normal sleep physiology involves a reduction in sympathetic nervous system activity combined with an increase in parasympathetic tone. The combined effect is a decrease in heart rate, stroke volume, and systemic vascular resistance so reducing cardiac output, blood pressure, and myocardial workload during sleep. In SDB, this usual cardiovascular quiescence is disrupted through the mechanisms outlined below (Figure 2) [5].

(1) Hypoxia. Hypoxic episodes may directly impair cardiac contraction and diastolic relaxation by reducing oxygenation and hence cardiac efficiency. In addition, intermittent hypoxia may create oxygen-free radicals and activate inflammatory pathways so causing hypertension by direct effects on vascular endothelium, independent of sympathetic tone [11].

(2) Repeated Arousals during Sleep. In SDB, termination of apnoeic episodes is accompanied by a sudden and brief arousal from sleep, with an accompanying increase in sympathetic activity, reduction in vagal tone, and resultant peripheral vasoconstriction [5, 12]. This is evidenced by an increase in urinary catecholamines in patients with untreated OSA, which returns to normal levels after effective therapy [3]. Therefore, during sleep patients will experience surges in heart rate and blood pressure accompanying brief episodes of arousal.

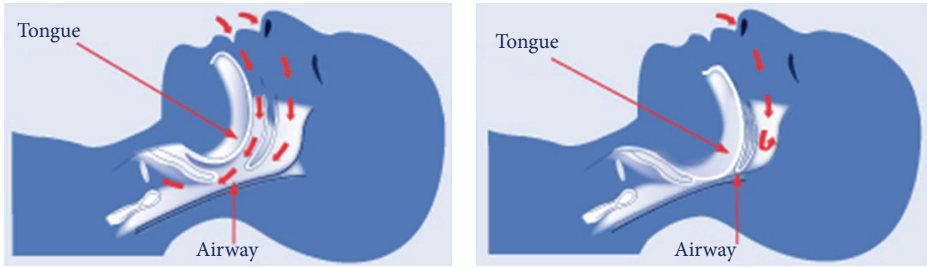
(3) Exaggerated Negative Intrathoracic Pressure. In OSA there is ineffective inspiration due to attempts to inspire against a fully or partially collapsed pharynx, so increasing the inspiratory negative intrathoracic pressure. The resultant greater venous return to the right side of the heart increases cardiac preload and work [5].

5. Sleep Disordered Breathing: The Clinical Implications

The causative mechanisms of obstructive and central type sleep apnoea differ, but the physiological and hence cardiovascular sequelae can be considered in unison [12]. However, there are several difficulties with definitively relating the physiological changes associated with SDB to the development and progression of clinical cardiovascular disease. Firstly, a multitude of confounding factors are shared between the two. For example, obesity is a common characteristic of patients suffering from sleep apnoea (specifically OSA) but is also implicated in the development of cardiovascular conditions such as hypertension and ischaemic heart disease [3, 4]. Complicatedly, CSA arises as a *consequence* of heart failure, and once present, may further exacerbate cardiovascular disease progression [2, 4]. Secondly, studies have suffered from small sample population sizes and differing inclusion criteria and methodology [1, 4, 13]. However, despite these difficulties, there is increasing evidence supporting the causal relationship between SDB and the subsequent development and progression of cardiovascular disease that is independent of other factors [1, 4, 11].

6. Hypertension

The repeated arousals that occur with apnoeic episodes result in an increase in heart rate and blood pressure, typically 5–7 seconds following an apnoea [9, 14]. Evidence indicates that the repeated apnoeas not only cause the temporary nocturnal increases in blood pressure but, over time, inflict chronic alterations in blood pressure leading to persistent daytime hypertension. Indeed, incident hypertension has been found to be three times as common in SDB patients as compared with that in the general population [14]. Alongside increased sympathetic tone, apnoea increases the expression of vascular adhesion molecules, alters cytokine levels, promotes



(a) (b)

Figure 1: Mechanism of airway obstruction in OSA. (a) demonstrates normal breathing; (b) shows posterior movement of the tongue producing OSA.

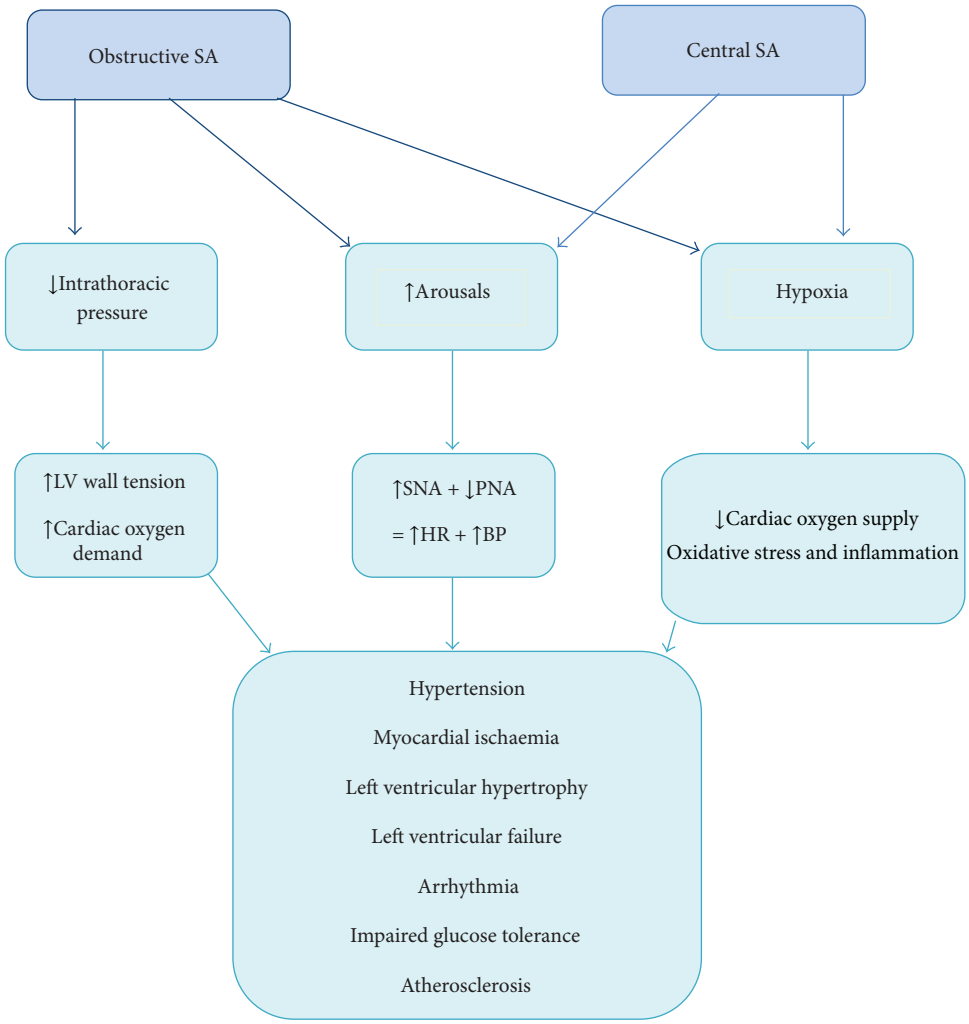


Figure 2: Summary of the physiological mechanisms contributing to cardiovascular disease in SDB. SA: sleep apnoea; SNA: sympathetic nervous activity; PNA: parasympathetic nervous activity.

oxidation of low density lipoproteins, and impairs endothelial cell function, which may further augment hypertension and contribute towards an atherosclerotic process [5].

A cross-sectional analysis of 6,132 subjects who underwent polysomnography at home showed a definite association between OSA and hypertension with the prevalence of hypertension increasing in proportion to the AHI [15]. A further prospective study revealed a 2.89-fold increase in hypertension for AHI = 15 compared with AHI = 0 over a 4–8-year time period [14]. Studies employing animal models have also demonstrated this relationship. Dogs exposed to repeated obstructive episodes over a 1–3-month period

developed a significant increase in blood pressure during sleep and wakefulness [16].

OSA may also predispose to resistant hypertension defined as a blood pressure persisting above 140/90 mmHg despite lifestyle intervention and the use of three or more pharmacological agents, one of which should be a diuretic [17]. Greater than 60% of patients with resistant hypertension are at high risk for OSA in accordance with the Berlin Questionnaire, but the actual polysomnographic diagnosis is greater; about 70% of females and 90% of males with resistant hypertension have OSA [18–20]. Combinations of mechanisms mediated through OSA are likely to be responsible for the predisposition to resistant hypertension. These may include increased levels of endothelin (a potent vasoconstrictor), hyperaldosteronism, and increased sympathetic drive. Notably, patients with resistant hypertension with a high risk of OSA are almost two times more likely to have primary hyperaldosteronism [21].

There is accumulating evidence in support of CPAP in the management of resistant hypertension. The use of nightly CPAP for a two-month period can produce significant reductions in both systolic and diastolic BP in patients with resistant hypertension and, similarly, compliance with CPAP may normalise nocturnal blood pressure patterns [21, 22]. However, these studies are relatively small, with most of the current evidence for CPAP reserved for the general hypertensive population rather than treatment-resistant hypertension.

7. Pulmonary Hypertension

As well as systemic hypertension, pulmonary hypertension is associated with sleep disordered breathing. This is likely to be via similar mechanisms as described for systemic hypertension including the effects of increased sympathetic activity. Additionally, negative intrathoracic pressure during apnoeic or hypopnoeic episodes amplifies venous return to the right heart accentuating pulmonary artery blood flow. Alongside preload, increased afterload due to pulmonary arteriolar remodelling and increased reactivity to hypoxia is also thought to contribute [23].

Pulmonary hypertension, which tends to be mild, may have a prevalence of up to 40% in the OSA population with evidence to support using nocturnal CPAP for reducing pulmonary artery pressures [23]. A study of 49 patients with polysomnography proven OSA but with normal lung function tests found that 6 patients had evidence of pulmonary hypertension at rest (defined as mean pulmonary artery pressure >20 mmHg) whilst 39 patients developed pulmonary hypertension during exercise. 25 of these 39 patients had elevated pulmonary capillary wedge pressures whilst none had raised pulmonary vascular resistance. Therefore, mild pulmonary hypertension commonly occurs in OSA patients, especially during exercise, and is probably mediated by left ventricular (LV) diastolic impairment resulting in raised pulmonary capillary wedge pressures [23, 24]. Conversely, a quarter of patients with pulmonary hypertension may suffer from OSA. A recent study assessed 169 patients with known pulmonary hypertension for SDB. 45 patients (27 OSA, 18 CSA) were found to have AHI > 10, with a mean of 20 [25].

8. Ischaemic Heart Disease

The link between SDB and coronary artery disease (CAD) is primarily derived from studies of OSA. Following correction for confounding factors such as age, sex, BMI, hypertension, hypercholesterolaemia, diabetes mellitus, and current smoking, the prevalence of CAD is still higher in patients with OSA. The prospective Sleep Heart Health Study revealed that subjects with a moderate to high AHI (>11) were 1.42 times more likely to develop CAD when compared with patients in the lowest AHI quartile. Likewise, there is a significantly higher prevalence of OSA in patients with angiographic evidence of CAD when compared to control patients with normal coronary arteries. The overall prevalence of OSA in the CAD population is estimated to be in the region of 30 to 58% compared with 2–4% for the general population [26–29].

Patients with SDB are more likely to have cardiac events during nocturnal hours [30]. Acute coronary syndromes (ACS) are more frequent during night time in OSA patients as opposed to the well-documented diurnal pattern of presentation in the general population [31]. The converse relationship is also true. In a study of 19 patients with sleep-onset ACS, 89% were found to have moderate or severe SDB (AHI > 15) [32]. Although an abundance of evidence exists to support the relationship between OSA and ischaemic heart disease, it is less clear whether this association is due to a direct effect of the apnoeic episodes on the myocardium during sleep or whether it is a consequence of the combined pathological processes induced by repeated apnoeas over time. A community-based study of patients without CAD has demonstrated elevated background levels of high-sensitivity troponin in 65% of subjects with OSA. Troponin levels correlated directly with severity of OSA and prognosis [33]. An earlier study of OSA patients discovered that ST-depression during sleep was relatively common and that a significant reduction in ST-depression could occur on application of nasal CPAP [34].

The effect of hypoxia on the cardiac function is not as straightforward as it may first appear. Significant research data advocates exposing the heart to repeated episodes of hypoxia to protect it from ischaemic damage through preconditioning of the myocardium. This process aids to regulate critical transcription factors within the cardiac endothelium and also promotes development of coronary collaterals, a phenomenon well-documented in patients with chronic myocardial ischaemia [35, 36].

The development of hypertension, of which SDB may be a causative factor, along with LV hypertrophy which is also associated with SDB may further accentuate the relationship between CAD and SDB; both conditions act as risk factors for ischaemic events. In addition, hypoxia induces the release of inflammatory mediators such as C-reactive protein, fibrinogen, interleukin-6, and adhesion molecules, all of which have a postulated role in the development of

CAD [3, 5]. Coronary thrombus may also arise secondary to a hypercoagulable state induced via a number of mechanisms:

(1) superoxide release from neutrophils depleting nitric oxide bioavailability,

(2) increased catecholamine levels promoting platelet activation and aggregation,

(3) hypertension induced hypercoagulability.

9. Heart Failure

Current evidence strongly supports an association between heart failure and SDB. Studies consistently report SDB prevalence of 50% or higher in the chronic heart failure population [5, 12, 37]. Both types of apnoea syndrome are implicated in heart failure. In one study, very severe SDB (AHI > 44 per hour) occurred in 49% of patients (37% CSA, 12% OSA) with a LV ejection fraction of less than 45% [38]. The particularly high prevalence of SDB in this population can be attributed mainly to CSA which arises as a *consequence* of heart failure [4]. CSA develops in heart failure patients through increased LV filling pressures that lead to pulmonary congestion and activation of irritant receptors within the lungs, stimulating hyperventilation and producing hypocapnoea [12]. Once carbon dioxide levels fall below a critical threshold, breathing ceases. A self-perpetuating cycle of hyperventilation-apnoea episodes ensues, typically associated with frequent arousals from sleep [2].

Heart failure, in turn, may worsen as a consequence of SDB. Right ventricular (RV) preload is increased (as discussed earlier) and hypoxia induced pulmonary arterial vasoconstriction produces increased RV afterload; the combined effect results in RV distension, a leftward shift of the interventricular septum, and a subsequent impedance to LV filling and diminution of stroke volume. Similarly, increased systemic vascular resistance may impair LV function [5].

Outcomes are worse in heart failure patients with SDB. The 3-year mortality rate in heart failure patients with untreated SDB is double that of non-SDB subjects, even when allowing for age, LV ejection fraction, and New York Heart Association functional class [39]. Similarly, the median survival of systolic heart failure patients with CSA is 45 months compared with 90 months for those without CSA. Even for patients with mild heart failure the concurrent incidence of SDB significantly increases mortality [40]. Patients with mild heart failure and CSA have a 39% mortality rate at five years compared to 11% in non-SDB patients with mild heart failure [41]. The aetiology of heart failure may also determine the risk from underlying SDB. In a prospective analysis, the presence of moderate to severe sleep apnoea (AHI ≥ 15) in ischaemic heart failure significantly increased mortality when compared to those without SDB, whilst no appreciable difference was demonstrated in nonischaemic cardiomyopathy patients [42].

The effect of cardiac resynchronisation therapy (CRT) in patients with severe heart failure and SDB has also been studied. CRT decreases the number of apnoea-hypopnoea episodes, reduces the maximum apnoea-hypopnoea duration, and results in higher minimal oxygen saturations. These physiological benefits are not seen in the OSA or patients without SDB. The benefit seen in CSA appears to be dependent on a good clinical and haemodynamic response to CRT [43, 44].

10. Arrhythmias

Apnoeic episodes have a tendency to induce bradycardias through increased vagal activity, whilst the subsequent postapnoea period can be associated with tachycardic episodes due to hyperventilation and sympathetic stimulation [12, 13]. The repeated surges in sympathetic nervous activity have been shown to precipitate abnormal remodelling of the atrium which in turn predisposes to the development of supraventricular arrhythmias [14]. Indeed, atrial fibrillation (AF) is four times more prevalent in patients with severe OSA (AHI > 30) than in matched patients without SDB [29]. In a recent study, twelve-month recurrence rates of AF following successful cardioversion were 82% for patients with untreated SDB, 42% for OSA patients treated with CPAP, and 53% in the control group that never had a sleep study, thereby advocating CPAP for the prevention of recurrent AF [45]. Separately, atrial overdrive pacing was previously attempted to ameliorate CSA by preventing bradycardia and augmenting cardiac output, but this effect was not reproducible [46, 47].

The risk of ventricular arrhythmias increases with SDB. Polysomnograms have shown an almost 18-fold increase in the relative risk of arrhythmias within 90 seconds of a respiratory disturbance compared with normal breathing, with nonsustained ventricular tachycardia making up 76% of the arrhythmic episodes [48]. Also, SDB significantly increases the risk of ventricular arrhythmias in patients with implantable cardioverter-defibrillators (ICD). A prospective study of appropriate ICD therapy (antitachycardia pacing or shock therapy for ventricular tachycardia or ventricular fibrillation) over a one-year period in patients with SDB ($n = 26$) and without SDB ($n = 19$) demonstrated significantly more appropriate ICD therapies for patients with SDB (73% versus 47%). This was solely due to an increase in arrhythmias occurring between midnight and 6 a.m. with no difference in ICD therapies during waking hours [49].

11. Endothelial Dysfunction

Chronic intermittent hypoxia can contribute to endothelial dysfunction independent of other risk factors [50–52]. Endothelial dysfunction encompasses prothrombotic and inflammatory processes, impairment of endothelial repair mechanisms related to reduced nitric oxide availability, and increased vasoconstriction. Increased serum levels of adhesion molecules and inflammatory markers including ICAM-1, VCAM-1, E-selectin, and CRP have been measured in subjects with moderate-severe OSA independent of coexisting cardiovascular risk factors such as diabetes mellitus, hypertension, and smoking status [50]. Intermittent hypoxia caused by OSA promotes oxygen radical formation that leads to activation of transcription factors that upregulate the expression of adhesion molecules [52]. The role of these adhesion molecules is well established in the process of

atherosclerosis. Also, there is reduced expression of proteins that regulate production of endothelial nitric oxide (eNOS) as well as the increase in the markers of inflammation and oxidative stress (cyclooxygenase-2, inducible NOS, and nitrotyrosine) in subjects with OSA compared to control subjects [50, 53, 54]. Adherence to CPAP for 4 weeks can reverse the downregulation of eNOS and the upregulation of markers of oxidative stress and inflammation with normalisation of circulating and exhaled markers of oxidative stress in patients with OSA [52, 55].

12. Cerebrovascular Disease

OSA is an independent risk factor for stroke. Patients presenting following a stroke or transient ischaemic attack are 3 to 4 times more likely to have OSA than matched control subjects, and silent infarction (infarction in the absence of stroke symptoms) occurs in 25% of OSA subjects compared with only 6.7% of control subjects [56, 57].

The brain requires a steady and continuous supply of oxygen in order to function. Measurements of cerebral blood flow velocity (middle cerebral artery) in subjects with OSA during apnoeic episodes demonstrate an increase in flow during the apnoea itself with a resultant decrease below baseline velocity on termination of the apnoea, which typically persists for one minute before return to baseline. During these hypoxic episodes, levels of brain adenosine triphosphate have been shown to decrease whereas inorganic phosphate levels increase [58]. These transient changes in cerebral blood flow may have detrimental effects on memory, spatial learning, and attention, particularly in patients with moderate-severe OSA [59–61]. In addition to the *transient* alterations in cerebral blood flow velocity during apnoeic episodes, changes in autoregulation may produce a more *permanent* impairment of cerebral blood flow velocity. This is associated with a higher incidence of stroke as well as poorer outcomes after stroke. An impaired cerebral blood flow response to changes in arterial pressure, particularly the sharp decrease in blood pressure following apnoea, can leave the brain vulnerable to ischaemia [62, 63].

In addition to changes in cerebral blood flow velocity and autoregulation, the cerebral vasculature will also be exposed to the same cascade of events that have been discussed regarding the peripheral vasculature: prothrombotic and inflammatory changes, vasoconstriction, and endothelial dysfunction. Therefore, the cerebral vascular system is also predisposed to atherosclerotic processes in the same way as the peripheral system. Specific to the obstructive form of sleep apnoea, there is evidence to suggest that physical vibration of the carotid arteries during snoring can also contribute to endothelial damage and atherosclerosis [64].

13. Does Treating SDB Improve CVD Outcomes?

Current evidence is largely based on observational studies with a dearth of robust randomised control trial data.

CPAP is a recognised treatment for the symptoms of OSA and has a clear role in the management of acute heart failure. Fixed pressure CPAP has consistently resulted in improved left ventricular ejection fraction (LVEF) and a decrease in sympathetic nervous system activation in patients with OSA [65]. A one-month randomised controlled trial of CPAP in patients with heart failure and severe OSA showed an increase in LVEF of 9% in the CPAP arm [66]. This was reaffirmed by a significant 2.5% increase in LVEF in heart failure patients (baseline LVEF < 45% and AHI > 10) after three months of optimal CPAP therapy. The benefit from CPAP therapy was significantly greater in individuals with a baseline LVEF >30% in this study. However, Epworth Sleepiness Scale Scores (a score from 0 to 24 which attempts to measure subjective daytime sleepiness based on patient responses to an eight-stem questionnaire), quality of life, New York Heart Association functional class, and 6-minute walking distance did not show significant improvement [67].

CPAP also appears to improve patient outcomes. Long-term (>5 years) prospective observational studies of middle-aged and elderly patients with OSA suggest increased mortality and risk of cardiovascular events in patients untreated with CPAP compared to those on treatment. The risk of cardiovascular events is not increased in patients with OSA treated with CPAP when compared to patients without OSA, so implicating a cardioprotective role for CPAP [5, 68, 69]. The short-term improvements in blood pressure, pulmonary hypertension, burden of AF, and coronary ischaemia have already been discussed but longer-term data is awaited.

CSA has been identified as a poor prognosticator in heart failure. There is less data to support CPAP in the context of CSA but application of CPAP can reduce the frequency of central apnoeic episodes and improve quality of life. A randomised controlled trial of CPAP for 66 heart failure patients (29 with and 37 without CSA) over a five-year period demonstrated a significantly reduced mortality and cardiac transplantation rate for patients with CSA receiving CPAP. CPAP did not affect mortality or the cardiac transplantation rate in subjects without CSA [70]. These findings were not subsequently replicated in a larger randomised controlled trial in which 258 heart failure patients with CSA were randomly assigned to a CPAP arm or a non-CPAP arm. Although follow-up demonstrated significant improvement in exercise capacity, apnoeic episodes, oxygen saturations, norepinephrine levels, and LVEF, the overall morbidity (cardiac transplant rate) and mortality were not significantly different between the two groups. Post hoc analysis revealed a possible improvement in transplant-free survival if the AHI was suppressed below 15. Therefore, the data remains equivocal in support of CPAP improving life expectancy in heart failure patients with CSA [71, 72].

Despite the lack of evidence for using positive airway pressure treatment to improve long-term outcomes in heart failure patients with CSA, the reduction in apnoeic episodes and improvement in symptoms merit continued CPAP usage. A 2012 meta-analysis of the available literature for the treatment of CSA recommends the use of CPAP as well as positive airway pressure delivery using an adaptive servoventilator (ASV) [73]. ASV is a device that continuously monitors the patient's breathing pattern enabling delivery of ventilatory support on detection of reduced or absent breathing and

withdrawal of this support once the patient's breathing has normalised. There is efficacy of ASV in heart failure patients with CSA and, in particular, improvement in patient compliance compared with CPAP, which is often poorly tolerated. Indeed, there is alleviation of SDB in heart failure patients with OSA treated with CPAP or CSA treated with ASV as well as improvement in LV systolic function, RV systolic function, and reverse LV remodelling consistent with overall enhancement of cardiac performance [74]. Although there is evidence to support the use of CPAP and ASV in patients with heart failure, the studies to date are relatively small and of short duration. For these findings to be transferrable to wider clinical practice more robust and larger scale studies are required to address the longer-term effects on morbidity and mortality [75].

14. Conclusions

The prevalence of SDB is increased throughout the cardiovascular disease spectrum when compared to the general population and its presence is associated with poor prognostic outcomes. Despite the growing body of evidence illustrating this point, SDB is still underdiagnosed; research indicates that over 85% of individuals with clinically significant and treatable SDB have never been diagnosed and its relationship with cardiovascular disease states is poorly recognised [4, 5, 12]. In raising awareness of this relationship, a new target in the prevention and management of cardiovascular disease is borne. The management of SDB with positive pressure ventilation can improve not only the symptoms of sleep apnoea but also cardiovascular disease outcomes, especially for patients with heart failure. However, there is a need for larger studies (especially for CSA and mixed sleep apnoea) to confirm the long-term effects of positive pressure ventilation on cardiovascular morbidity.

Conflict of Interests

The authors declare that there is no conflict of interests.

References

[1] N. T. Ayas, G. B. J. Mancini, and J. Fleetham, "Does CPAP delay the development of cardiovascular disease in patients with obstructive sleep apnoea hypopnoea?" *Thorax*, vol. 61, no. 6, pp. 459–460, 2006.

[2] P. Bordier, "Sleep apnoea in patients with heart failure. Part I. Diagnosis, definitions, prevalence, pathophysiology and haemodynamic consequences," *Archives of Cardiovascular Diseases*, vol. 102, no. 8-9, pp. 651–661, 2009.

[3] S. F. Quan and B. J. Gersh, "Cardiovascular consequences of sleep-disordered breathing: past, present and future," *Circulation*, vol. 109, no. 8, pp. 951–957, 2004.

[4] V. K. Somers, D. P. White, R. Amin et al., "Sleep apnea and cardiovascular disease. An American Heart Association/American College of Cardiology Foundation Scientific Statement From the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing In Collaboration With the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health)," *Journal of the American College of Cardiology*, vol. 52, no. 8, pp. 686–717, 2008.

[5] T. D. Bradley and J. S. Floras, "Obstructive sleep apnoea and its cardiovascular consequences," *The Lancet*, vol. 373, no. 9657, pp. 82–93, 2009.

[6] Scottish Intercollegiate Guidelines Network, *Management of Obstructive Apnoea/Hypopnea Syndrome in Adults. A National Clinical Guideline*, British Thoracic Society, London, UK, 2003.

[7] British Lung Foundation, "Obstructive sleep apnoea," 2012, http://www.blf.org.uk/Conditions/Detail/OSA#overview.

[8] J. Wang, Y. Wang, J. Feng, B.-Y. Chen, and J. Cao, "Complex sleep apnea syndrome," *Respiratory Department of Tianjin Medical University General Hospital*, vol. 2013, pp. 633–641, 2013.

[9] T. Young, M. Palta, J. Dempsey, J. Skatrud, S. Weber, and S. Badr, "The occurrence of sleep-disordered breathing among middle-aged adults," *The New England Journal of Medicine*, vol. 328, no. 17, pp. 1230–1235, 1993.

[10] R. S. T. Leung and T. D. Bradley, "Sleep apnoea and cardiovascular disease," *The American Journal of Respiratory and Critical Care Medicine*, vol. 164, pp. 2147–2165, 2001.

[11] M. Kato, P. Roberts-Thomson, B. G. Phillips et al., "Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea," *Circulation*, vol. 102, no. 21, pp. 2607–2610, 2000.

[12] T. D. Bradley and J. S. Floras, "Sleep apnea and heart failure. Part II. Central sleep apnea," *Circulation*, vol. 107, no. 13, pp. 1822–1826, 2003.

[13] A. S. Hersi, "Obstructive sleep apnea and cardiac arrhythmias," *Annals of Thoracic Medicine*, vol. 5, no. 1, pp. 10–17, 2010.

[14] P. E. Peppard, T. Young, M. Palta, and J. Skatrud, "Prospective study of the association between sleep-disordered breathing and hypertension," *The New England Journal of Medicine*, vol. 342, no. 19, pp. 1378–1384, 2000.

[15] F. J. Nieto, T. B. Young, B. K. Lind et al., "Association of sleep-disordered breathing sleep apnea, and hypertension in a large community-based study," *Journal of the American Medical Association*, vol. 283, no. 14, pp. 1829–1836, 2000.

[16] D. Brooks, R. L. Horner, L. F. Kozar, C. L. Render-Teixeira, and E. A. Phillipson, "Obstructive sleep apnea as a cause of systemic hypertension: evidence from a canine model," *Journal of Clinical Investigation*, vol. 99, no. 1, pp. 106–109, 1997.

[17] D. A. Calhoun, D. Jones, S. Textor et al., "Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research," *Circulation*, vol. 51, no. 25, pp. 1403–1419, 2008.

[18] A. G. Logan, S. M. Perlikowski, A. Mente et al., "High prevalence of unrecognized sleep apnoea in drug-resistant hypertension," *Journal of Hypertension*, vol. 19, no. 12, pp. 2271–2277, 2001.

[19] D. A. Calhoun, M. K. Nishizaka, M. A. Zaman, and S. M. Harding, "Aldosterone excretion among subjects with resistant hypertension and symptoms of sleep apnea," *Chest*, vol. 125, no. 1, pp. 112–117, 2004.

[20] M. N. Pratt-Ubunama, M. K. Nishizaka, R. L. Boedefeld, S. S. Cofield, S. M. Harding, and D. A. Calhoun, "Plasma aldosterone is related to severity of obstructive sleep apnea in subjects with resistant hypertension," *Chest*, vol. 131, no. 2, pp. 453–459, 2007.

[21] A. G. Logan, R. Tkacova, S. M. Perlikowski et al., "Refractory hypertension and sleep apnoea: effect of CPAP on blood pressure and baroreflex," *European Respiratory Journal*, vol. 21, no. 2, pp. 241–247, 2003.

[22] M. A. Martínez-García, R. Gómez-Aldaraví, J.-J. Soler-Cataluña, T. G. Martínez, B. Bernácer-Alpera, and P. Román-Sánchez, "Positive effect of CPAP treatment on the control of difficult-to-treat hypertension," *European Respiratory Journal*, vol. 29, no. 5, pp. 951–957, 2007.

[23] D. Sajkov and R. D. McEvoy, "Obstructive sleep apnea and pulmonary hypertension," *Progress in Cardiovascular Diseases*, vol. 51, no. 5, pp. 363–370, 2009.

[24] M. Hetzel, M. Kochs, N. Marx et al., "Pulmonary hemodynamics in obstructive sleep apnea: frequency and causes of pulmonary hypertension," *Lung*, vol. 181, no. 3, pp. 157–166, 2003.

[25] R. Dumitrascu, H. Tiede, J. Eckermann et al., "Sleep apnea in precapillary pulmonary hypertension," *Sleep Medicine*, vol. 14, no. 3, pp. 247–251, 2013.

[26] Y. Peker, H. Kraiczi, J. Hedner, S. Löth, A. Johansson, and M. Bende, "An independent association between obstructive sleep apnoea and coronary artery disease," *European Respiratory Journal*, vol. 14, no. 1, pp. 179–184, 1999.

[27] T. Mooe, T. Rabben, U. Wiklund, K. A. Franklin, and P. Eriksson, "Sleep-disordered breathing in men with coronary artery disease," *Chest*, vol. 109, no. 3, pp. 659–663, 1996.

[28] D. P. White, "Pathogenesis of obstructive and central sleep apnea," *The American Journal of Respiratory and Critical Care Medicine*, vol. 172, no. 11, pp. 1363–1370, 2005.

[29] E. Shahar, C. W. Whitney, S. Redline et al., "Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the sleep heart health study," *The American Journal of Respiratory and Critical Care Medicine*, vol. 163, no. 1, pp. 19–25, 2001.

[30] Y. Ishibashi, N. Osada, H. Sekiduka et al., "Peak time of acute coronary syndrome in patients with sleep disordered breathing," *Journal of Cardiology*, vol. 53, no. 2, pp. 164–170, 2009.

[31] F. de Torres-Alba, D. Gemma, E. Armada-Romero et al., "Obstructive sleep apnea and coronary artery disease: from pathophysiology to clinical implications," *Pulmonary Medicine*, vol. 2013, Article ID 768064, 9 pages, 2013.

[32] Y. Yano, T. Ohmori, S. Kazuyuki, S. Yoichi, and K. Kazuomia, "Association of sleep onset of acute coronary syndrome with sleep apnea syndrome and abnormal diurnal variation of hemostasis and adipokine levels," *Blood Coagulation & Fibrinolysis*, vol. 23, no. 7, pp. 590–596, 2012.

[33] G. Querejeta Roca, S. Redline, N. Punjabi et al., "Sleep Apnea is associated with subclinical myocardial injury in the community: the ARIC-SHHS study," *The American Journal of Respiratory and Critical Care Medicine*.

[34] P. Hanly, Z. Sasson, N. Zuberi, and K. Lunn, "ST-segment depression during sleep in obstructive sleep apnea," *The American Journal of Cardiology*, vol. 71, no. 15, pp. 1341–1345, 1993.

[35] L. Lavie and P. Lavie, "Ischemic preconditioning as a possible explanation for the age decline relative mortality in sleep apnea," *Medical Hypotheses*, vol. 66, no. 6, pp. 1069–1073, 2006.

[36] S. Steiner, P. O. Schueller, V. Schulze, and B. E. Strauer, "Occurrence of coronary collateral vessels in patients with sleep apnea and total coronary occlusion," *Chest*, vol. 137, no. 3, pp. 516–520, 2010.

[37] A. Paulino, T. Damy, L. Margarit et al., "Prevalence of sleep-disordered breathing in a 316-patient French cohort of stable congestive heart failure," *Archives of Cardiovascular Diseases*, vol. 102, no. 3, pp. 169–175, 2009.

[38] S. Javaheri, T. J. Parker, J. D. Liming et al., "Sleep apnea in 81 ambulatory male patients with stable heart failure: types and their prevalences, consequences, and presentations," *Circulation*, vol. 97, no. 21, pp. 2154–2159, 1998.

[39] H. Wang, J. D. Parker, G. Newton et al., "Influence of obstructive sleep apnea on mortality in patients with heart failure," *Journal of the American College of Cardiology*, vol. 49, pp. 1632–1633, 2007.

[40] S. Javaheri, R. Shukla, H. Zeigler, and L. Wexler, "Central sleep apnea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure," *Journal of the American College of Cardiology*, vol. 49, no. 20, pp. 2028–2034, 2007.

[41] A. Vazir, M. J. Morrell, P. C. Hastings et al., "Central sleep apnoea predicts mortality even in patients with mild chronic heart failure: a 6-year follow-up study," *Heart*, vol. 95, article 88, 2009.

[42] D. Yumino, H. Wang, J. S. Floras et al., "Relationship between sleep apnoea and mortality in patients with ischaemic heart failure," *Heart*, vol. 95, no. 10, pp. 819–824, 2009.

[43] O. Oldenburg, L. Faber, J. Vogt et al., "Influence of cardiac resynchronisation therapy on different types of sleep disordered breathing," *European Journal of Heart Failure*, vol. 9, no. 8, pp. 820–826, 2007.

[44] A.-M. Sinha, E. C. Skobel, O.-A. Breithardt et al., "Cardiac resynchronization therapy improves central sleep apnea and Cheyne-Stokes respiration in patients with chronic heart failure," *Journal of the American College of Cardiology*, vol. 44, no. 1, pp. 68–71, 2004.

[45] R. Kanagala, N. S. Murali, P. A. Friedman et al., "Obstructive sleep apnea and the recurrence of atrial fibrillation," *Circulation*, vol. 107, no. 20, pp. 2589–2594, 2003.

[46] S. Garrigue, P. Bordier, P. Jais et al., "Benefit of atrial pacing in sleep apnea syndrome," *The New England Journal of Medicine*, vol. 346, no. 6, pp. 404–412, 2002.

[47] E. N. Simantirakis, S. E. Schiza, S. I. Chrysostomakis et al., "Atrial overdrive pacing for the obstructive sleep apnea-hypopnea syndrome," *The New England Journal of Medicine*, vol. 353, no. 24, pp. 2568–2577, 2005.

[48] K. Monahan, A. Storfer-Isser, R. Mehra et al., "Triggering of nocturnal arrhythmias by sleep-disordered breathing events," *Journal of the American College of Cardiology*, vol. 54, no. 19, pp. 1797–1804, 2009.

[49] T. Zeidan-Shwiri, D. Aronson, K. Atalla et al., "Circadian pattern of life-threatening ventricular arrhythmia in patients with sleep-disordered breathing and implantable cardioverter-defibrillators," *Heart Rhythm*, vol. 8, no. 5, pp. 657–662, 2011.

[50] A. Lurie, "Obstructive sleep apnea in adults: endothelial dysfunction in adults with obstructive sleep apnea," *Advances in Cardiology*, vol. 46, pp. 139–170, 2011.

[51] A. Atkeson, S. Y. Yeh, A. Malhotra, and S. Jelic, "Endothelial function in obstructive sleep apnea," *Progress in Cardiovascular Diseases*, vol. 51, no. 5, pp. 351–362, 2009.

[52] S. Jelic, M. Padeletti, S. M. Kawut et al., "Inflammation, oxidative stress, and repair capacity of the vascular endothelium in obstructive sleep apnea," *Circulation*, vol. 117, no. 17, pp. 2270–2278, 2008.

[53] C. Carpio, R. Álvarez-Sala, and F. García-Río, "Epidemiological and pathologenic relationship between sleep apnoea and

ischaemic heart disease," *Pulmonary Medicine*, vol. 2013, Article ID 405827, 8 pages, 2013.

[54] B. Jafari and V. Mohsenin, "Endothelial dysfunction and hypertension in obstructive sleep apnea—is it due to intermittent hypoxia?" *Journal of Cardiovascular Disease Research*, vol. 4, no. 2, pp. 87–91, 2013.

[55] A. A. El-Solh, M. J. Mador, P. Sikka, R. S. Dhillon, D. Amsterdam, and B. J. B. Grant, "Adhesion molecules in patients with coronary artery disease and moderate-to-severe obstructive sleep apnea," *Chest*, vol. 121, no. 5, pp. 1541–1547, 2002.

[56] M. E. Dyken, V. K. Somers, T. Yamada, Z.-Y. Ren, and M. B. Zimmerman, "Investigating the relationship between stroke and obstructive sleep apnea," *Stroke*, vol. 27, no. 3, pp. 401–407, 1996.

[57] K. Minoguchi, T. Yokoe, T. Tazaki et al., "Silent brain infarction and platelet activation in obstructive sleep apnea," *The American Journal of Respiratory and Critical Care Medicine*, vol. 175, no. 6, pp. 612–617, 2007.

[58] C. Rae, D. J. Bartlett, Q. Yang et al., "Dynamic changes in brain bioenergetics during obstructive sleep apnea," *Journal of Cerebral Blood Flow and Metabolism*, vol. 29, no. 8, pp. 1421–1428, 2009.

[59] Y. Li and S. C. Veasey, "Neurobiology and neuropathophysiology of obstructive sleep apnea," *NeuroMolecular Medicine*, vol. 14, no. 3, pp. 168–179, 2012.

[60] F. M. Faraci, "Protecting against vascular disease in brain," *American Journal of Physiology—Heart and Circulatory Physiology*, vol. 300, no. 5, pp. H1566–H1582, 2011.

[61] R. S. Marshall and R. M. Lazar, "Pumps, aqueducts, and drought management: vascular physiology in vascular cognitive impairment," *Stroke*, vol. 42, no. 1, pp. 221–226, 2011.

[62] D. J. Durgan and R. M. Bryan Jr., "Cerebrovascular consequences of obstructive sleep apnea," *Journal of the American Heart Association*, vol. 1, Article ID e000091, 2012.

[63] F. Urbano, F. Roux, J. Schindler, and V. Mohsenin, "Impaired cerebral autoregulation in obstructive sleep apnea," *Journal of Applied Physiology*, vol. 105, no. 6, pp. 1852–1857, 2008.

[64] J.-G. Cho, P. K. Witting, M. Verma et al., "Tissue vibration induces carotid artery endothelial dysfunction: a mechanism linking snoring and carotid atherosclerosis?" *Sleep*, vol. 34, no. 6, pp. 751–757, 2011.

[65] T. Kasai and T. D. Bradley, "Obstructive sleep apnea and heart failure: pathophysiologic and therapeutic implications," *Journal of the American College of Cardiology*, vol. 57, no. 2, pp. 119–127, 2011.

[66] Y. Kaneko, J. S. Floras, K. Usui et al., "Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea," *The New England Journal of Medicine*, vol. 348, no. 13, pp. 1233–1241, 2003.

[67] C. J. Egea, F. Aizpuru, J. A. Pinto et al., "Cardiac function after CPAP therapy in patients with chronic heart failure and sleep apnea: a multicenter study," *Sleep Medicine*, vol. 9, no. 6, pp. 660–666, 2008.

[68] M. A. Martínez-García, F. Campos-Rodríguez, P. Catalán-Serra et al., "Cardiovascular mortality in obstructive sleep apnea in the elderly: role of long-term continuous positive airway pressure treatment: a prospective observational study," *The American Journal of Respiratory and Critical Care Medicine*, vol. 186, no. 9, pp. 909–916, 2012.

[69] L. S. Doherty, J. L. Kiely, V. Swan, and W. T. McNicholas, "Long-term effects of nasal continuous positive airway pressure therapy on cardiovascular outcomes in sleep apnea syndrome," *Chest*, vol. 127, no. 6, pp. 2076–2084, 2005.

[70] D. D. Sin, A. G. Logan, F. S. Fitzgerald, P. P. Liu, and T. D. Bradley, "Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne-Stokes respiration," *Circulation*, vol. 102, no. 1, pp. 61–66, 2000.

[71] T. D. Bradley, A. G. Logan, R. J. Kimoff et al., "Continuous positive airway pressure for central sleep apnea and heart failure," *The New England Journal of Medicine*, vol. 353, no. 19, pp. 2025–2033, 2005.

[72] M. Arzt, J. S. Floras, A. G. Logan et al., "Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP)," *Circulation*, vol. 115, no. 25, pp. 3173–3180, 2007.

[73] R. N. Aurora, S. Chowdhuri, K. Ramar et al., "The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses," *Sleep*, vol. 35, no. 1, pp. 17–40, 2012.

[74] S. P. Kourouklis, E. Vagiakis, I. A. Paraskevaidis et al., "Effective sleep apnoea treatment improves cardiac function in patients with chronic heart failure," *International Journal of Cardiology*, vol. 168, no. 1, pp. 157–162, 2013.

[75] J. L. K. Brown, "Filling in the gaps: the role of noninvasive adaptive servoventilation for heart failure-related central sleep apnea," *Chest*, vol. 134, no. 1, pp. 4–7, 2008.

Hindawi Publishing Corporation
Cardiology Research and Practice
Volume 2013, Article ID 130724, 9 pages
http://dx.doi.org/10.1155/2013/130724

Review Article

Current Treatment of Heart Failure with Preserved Ejection Fraction: Should We Add Life to the Remaining Years or Add Years to the Remaining Life?

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Received 30 July 2013; Accepted 12 September 2013

Academic Editor: Gregory Giamouzis

According to the ejection fraction, patients with heart failure may be divided into two different groups: heart failure with preserved or reduced ejection fraction. In recent years, accumulating studies showed that increased mortality and morbidity rates of these two groups are nearly equal. More importantly, despite decline in mortality after treatment in regard to current guideline in patients with heart failure with reduced ejection fraction, there are still no trials resulting in improved outcome in patients with heart failure with preserved ejection fraction so far. Thus, novel pathophysiological mechanisms are under development, and other new viewpoints, such as multiple comorbidities resulting in increased non-cardiac deaths in patients with heart failure and preserved ejection fraction, were presented recently. In this review, we will focus on the tested as well as the promising therapeutic options that are currently studied in patients with heart failure with preserved ejection fraction, along with a brief discussion of pathophysiological mechanisms and diagnostic options that are helpful to increase our understanding of novel therapeutic strategies.

1. Introduction

Heart failure (HF) with preserved ejection fraction (HFPEF) has been well recognized as an increasing epidemiological and medical challenge over the last two decades [1, 2]. Studies indicate that the number of patients with HFPEF is similar or even higher compared to the number of patients with HF with reduced ejection fraction (HFREF) [3, 4]. Moreover, we do know that the mortality is similar in patients with HFPEF compared to HFREF [5]. However, the conventional medical therapies in HFREF, that are based on the strong evidence of multiple randomized controlled clinical trials (RCTs) showing a decline in mortality, have shown no favourable result in HFPEF so far [6, 7]. A recent study also showed that noncardiac deaths in HFPEF are higher than in HFREF, which could be a result of multiple complicating diseases in patients with HFPEF [8]. This review will focus on the tested and upcoming treatment options in HFPEF. Moreover, pathophysiological mechanisms and diagnostic options will also be briefly discussed in order to understand new therapeutic targets in this field.

2. Diagnosis of HFPEF

According to the latest recommendations of the European Society of Cardiology and American Heart Association [6, 7], there are, although this is still under intensive discussion, at least three criteria for the diagnosis of HFPEF: clinical signs and/or symptoms of HF, normal or mild reduction of systolic with left ventricular (LV) ejection fraction (LVEF) $> 50\%$ with normal size of LV (LV end-diastolic volume index $< 97\,\text{mL/m}^2$), and evidence of reduced diastolic LV function. This is usually determined by echocardiography (abnormalities of the mitral inflow pattern, tissue velocities (e), or the E/e ratio, left atrial volume index $> 34\,\text{mL/m}^2$, and increased LV mass index) or biomarker assessment (NT-proBNP). Other cardiac aetiologies including valvular heart disease, hypertrophic cardiomyopathy, infiltrative or

restrictive cardiomyopathy, and constrictive pericarditis have to be excluded carefully [9]. Nevertheless, today we do know that other causes next to diastolic dysfunction are also present and play an important role for many patients with HFPEF. These causes include, for example, endothelial dysfunction, chronotropic incompetence, impaired ventricular vascular coupling, and postcapillary pulmonary hypertension and may alter future therapeutic options [10].

3. Brief Introduction in the Pathophysiology of HFPEF

One leading mechanism of HFPEF is LV diastolic dysfunction. Diastolic dysfunction consists of abnormal LV active relaxation as well as increased LV passive stiffness [11]. As an energy consuming process, abnormal LV active relaxation is related to ischemia of cardiac myocytes [12] or abnormalities in myocardial energy metabolism [13]. Furthermore, increased diastolic LV stiffness limits cardiac output by elevating LV end-diastolic pressures and decreasing stroke volumes, which has been illustrated in HFPEF by invasive and noninvasive methods at rest [11, 14] or during atrial pacing and exercise [14]. The substrate of LV stiffness seems to be excessive collagen type I deposition resulting in a stiff and noncompliant extracellular matrix (ECM) [15, 16], but also titin phosphorylation deficit [16–18] is involved in this process [19–21]. Several studies from both animals and humans showed that additional mechanisms on organ level also play an important role, such as autonomic dysfunction [22], reduced vasodilator reserves [22, 23], impaired heart rate recovery and chronotropic incompetence [22, 24], diastolic and systolic dyssynchrony [25], and abnormal ventricular vascular coupling [26, 27]. Moreover, it has been proven that the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous systems were upregulated in HFPEF and hence contribute to disease progression [28, 29]. Recently, studies focused on the molecular cell level disorder in HFPEF-like impaired nitric oxide—cyclic guanosine monophosphate (cGMP)—protein kinase G (PKG) signaling [30, 31], endothelial dysfunction [22, 32, 33], oxidative stress, and cardiac inflammation [20]. The roles of comorbidities in the HFPEF population, including arterial hypertension, coronary arterial disease (CAD), diabetes, atrial fibrillation, obesity, obstructive sleep apnoea, and chronic kidney disease (CKD), are all associated with the disease and will likely be involved in the pathophysiology [34–36]. Furthermore, patients with HFPEF are older, more often female, have less often CAD but higher rates of atrial fibrillation, and most of them have arterial hypertension [37]. All of these findings may lead to a higher noncardiac death rate of nearly 30% in HFPEF and higher non-HF hospitalizations compared to HFREF [8, 38, 39]. As a result of the diversity of the underlying mechanisms and comorbidities, HFPEF presents as a complex clinical syndrome associated with multiple pathophysiological alterations rather than one single entity [40]. Taken together, this makes treating HFPEF a clinical challenge.

4. Pharmacological Treatment

The exact mechanisms of HFPEF are still under investigation. Nevertheless, there are several clinical trials in the HFPEF population targeting on clinical symptoms, exercise capacity, diastolic dysfunction, and quality of life (QoL). While there are tested treatments improving these outcomes, no confirmed positive outcomes in regard to mortality were obtained from all pharmacological therapies including diuretics, beta-blockers, RAAS antagonists, digitalis, HMG-CoA-reductase inhibitors (statins), nondihydropyridine calcium channel blockers, and phosphodiesterase-5 inhibition (PDE-5 inhibition) so far.

4.1. Diuretics. Up to now, the data about the effect on long-term prognosis of diuretics in HFPEF are still limited. In the Hong Kong Diastolic Heart Failure Study [41], diuretics (furosemide or thiazide) alone or combined with ramipril or irbesartan were evaluated in 150 patients with LVEF > 45%. Diuretic use alone was associated with improvement of symptoms and QoL significantly, while the addition of ramipril or irbesartan provided only slight additional beneficial effects. There was no survival benefit or reduction in HF hospitalization in this rather small study. Importantly, in one ALLHAT substudy, chlorthalidone reduced the incidence of new-onset hospitalization in patients with HFPEF significantly compared to patients treated with amlodipine and doxazosin. The occurrence of new-onset HFPEF was also smaller compared to lisinopril [42]. Similar results were demonstrated by HYVET (Hypertension in the Very Elderly Trial); indapamide combined with or without perindopril showed a significant HF reduction by 64% in patients of 80 years of age or older, which suggests that many suffered indeed from HFPEF. With the lack of evidence in mortality reduction, according to current guidelines [6, 7], diuretics should be used only for relief of symptoms (breathlessness and edema) due to sodium and water retention in patients with HFPEF. Nevertheless, diuretics are still an important cornerstone in daily clinical routine.

4.2. Renin-Angiotensin System (RAS) Antagonists. It is well known that three large RCTs have failed to reduce morbidity and mortality in patients with HFPEF. The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved trial [43], which showed only moderate reduction in HF hospitalization, when assessing the reduction of mortality and morbidity, showed a 30% reduction in the risk of death at 1 year ($P < 0.001$) but only a 9% reduction ($P > 0.055$) over the full-duration followup of 38 months in median. The Perindopril for Elderly People with Chronic Heart Failure (PEP-CHF) study [44] showed that angiotensin-converting enzyme inhibitors (ACEI) resulted in improved symptoms and exercise capacity and HF hospitalization but no reduction in long-term morbidity and mortality. This may result from insufficient power for lower enrolment and event rates than anticipated. Moreover, the Irbesartan in heart failure with preserved systolic function (I-Preserve) trial [45], which showed no reduction in the

primary composite outcome of death or cardiovascular hospitalization. Recently, a propensity-matched inception cohort study showed that angiotensin receptor blocker (ARB) use obtained no improved clinical outcomes in real-world older (mean age of 80 years) HFPEF patients [46]. A meta-analysis of trials was reported regarding whether pharmacological agents improved exercise capacity, LV diastolic function, and survival benefit in patients with HFPEF [47]. From 18 RCTs and 12 observational studies, data of 53,878 patients were analysed. After 18.6-month followup, all-cause mortality was unimproved both in RCTs and observational studies. However, there were tendencies in these studies toward marginal benefits in primary outcomes. Considering these neutral results may be due to a bias of selection or underpowered data or high crossover rates which concealed a real benefit [48]. Recently, additional two large rigorous registry studies gave us a glimpse of the hope. An observational analysis conducted by Lund and colleagues with the Swedish Heart Failure registry showed that RAS antagonists may reduce all-cause mortality in patients with HFPEF [49]. In this trial, 16,216 patients with HFPEF (LVEF ≥ 40%, mean age 75 years; 46% women) were assessed in an age-matched and propensity score-matched cohort balanced on 43 variables. 12,543 patients treated with RAS antagonists (ACEI or ARB) and 3,673 without RAS antagonists as control group. In the matched HFPEF cohort, the treated patients versus those untreated in 1-year survival was 77% (95% CI, 75%–78%) versus 72% (95% CI, 70%–73%), respectively, (hazard ratio (HR) 0.91, 95% CI, 0.85–0.98; $P = 0.008$). In the overall HFPEF cohort, the treated patients in crude 1-year survival was 86% (95% CI, 86%-87%) versus 69% (95% CI, 68%–71%) in untreated patients (HR 0.90, 95% CI, 0.85–0.96; $P = 0.001$). In the HFPEF dose analysis, the HR was 0.85 in > 50% of target dose group versus in untreated group (95% CI, 0.78–0.83; $P < 0.001$), while HR was 0.94 in <50% of target dose group versus in untreated group (95% CI, 0.87–1.02; $P = 0.14$). It is notable in this study the LVEF ≥ 40% for HFPEF diagnosis may include the subgroup of 40–50% which represents systolic dysfunction [50]. This lax enrolment might increase more benefits of RAS antagonists than in those with LVEF ≥ 50%, as mentioned by the author that the subgroup of LVEF 40–50% have a tendency of more reduction in mortality compared to those LVEF > 50% [49]. Another similar study evaluated ACEI therapy in > 65 years older patients with HFPEF [51]. Date of patients from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) and link to Medicare, 1,337 eligible patients (mean LVEF = 55%, mean age of 81 years, 64% women) receiving ACEI were matched by propensity scores to 1,337 patients not receiving ACEI. Initiation of ACEI was linked with a 9% modest reduction in all-cause mortality or HF hospitalization during 2.4 years of followup in median (HR 0.91, 95% CI, 0.84–0.99; $P = 0.028$). However, there is also limitation in observational studies that the decision to use the agents depends on patient factors instead of using the agents in random [52]. Recently, LCZ696, the combination of ARB (valsartan) and neprilysin inhibitors (AHU377), acts as a promising drug in hypertension and HF [53–55]. Neprilysin is able to attenuate biological active of brain natriuretic peptide (BNP), and atrial natriuretic peptide (ANP), LCZ696, increasing natriuretic peptides by inhibiting this enzyme, might result in favourable cardiovascular effects [55]. LCZ696 now is evaluated in a phase II study (The PARAMOUNT study) in patients with HFPEF [56]. All 301 patients based on a clinical diagnosis of HFPEF (LVEF ≥ 45%), with increased plasma concentration of N-terminal prohormone brain natriuretic peptide (NT-proBNP) > 400 pg/mL. 149 patients were randomly assigned to LCZ696 group, and 152 patients to valsartan group. Finally, 134 and 132 patients were included in LCZ696 and valsartan group, respectively, in total 36-week analysis of the primary endpoint. Compared with the valsartan group, the LCZ696 group achieved a 23% ($P = 0.005$) reduction in plasma NT-proBNP level after the first 12 weeks, while only 15% ($P = 0.20$) over the full 36-week followup. In addition, LCZ696 had beneficial effects on symptoms. All of the above, although suggested some benefits, required more appropriately powered RCTs in the future. Nonetheless, on the other hand, there are also no harmful pieces of evidence of RAS antagonists in patients with HFPEF. According to current guidelines, it is reasonable to use RAS antagonists for hypertension treatment in HFPEF [6, 7]. In other words, the application of RAS antagonists is not because they are of benefit in HFPEF, but for most patients with HFPEF have the indication for RAS antagonists related to comorbidities, such as arterial hypertension and diabetes [57].

4.3. Mineralocorticoid Receptor Antagonists (MRAs) or Aldosterone Receptor Antagonist (ARAs). There is growing evidence to suggest that mineralocorticoid receptor antagonists (MRAs) are beneficial for the patients with HFREF. The RALES trial [58] initiated a wide use of MRAs in severe HFREF patients. Additionally, the EPHESUS study [59] led to the widespread use of these agents in postmyocardial infarction patients with HF. The EMPHASIS-HF study [60], thus, changed current guidelines with expanded use of MRAs to patients with mild HFREF. For patients with HFPEF, a small RAAM-PEF trial showed echocardiographic improvement of diastolic function and a decrease in serum markers of collagen turnover [61]. More recently, the Aldo-DHF trial investigated the efficacy of spironolactone in 422 patients with HFPEF (LVEF ≥ 50%) and mild symptoms. Spironolactone was demonstrated as the first MRA to show an improvement in diastolic function in patients with HFPEF, despite no effects on maximal exercise capacity improvement, symptoms relief, or QoL increase. However, because of a relative "healthy or young" study population, as well as the treatment period might be too short to provide useful data on clinical benefit, the Aldo-DHF trial was not powered to evaluate the role of spironolactone in HF hospitalizations or mortality [62]. An ongoing much larger TOPCAT study [63], which tries to answer whether spironolactone is of benefit in the reduction of cardiovascular death, aborted cardiac arrest, and hospitalization for HF compared with placebo in 3,445 patients with HFPEF (LVEF > 45%), will provide more data in this issue.

4.4. Beta-Blockers. Beta-blockers were thought of as keystone in the treatment of HFREF [6, 7]. However, the exact effect of beta-blockers treatment on patients with HFPEF still remains unclear. In the Swedish Doppler-echocardiographic study (SWEDIC), carvedilol showed echocardiographic improvement in diastolic function [64]. Nevertheless, exercise capacity [65] and mortality within beta-blockers-treated HFPEF patients remain unchanged in other RCTs [66–68]. Recently, the results of Japanese Diastolic Heart Failure (J-DHF) study were published [67]. In this study, 245 patients with HF and LVEF > 40% were randomly divided into carvedilol group and control group (without carvedilol). The primary endpoints of this study are composite of cardiovascular death and hospitalization for HF. During 3.2 years of followup in median, the endpoints occurred in 29 patients in the carvedilol group and in 34 patients in the control group (HR 0.90, 95% CI, 0.55–1.49; $P = 0.6854$). The results of any cardiovascular death and unplanned cardiovascular hospitalization were 38 patients in the carvedilol group and 52 in the control group (HR 0.77, 95% CI, 0.50–1.17; $P = 0.2178$), respectively. This study suggested that carvedilol could not improve prognosis of patients with HFPEF. However, the editorial of this study considered that the numbers of patients were probably too small to show significant differences, so they tried to pool the data of three similar small studies together and demonstrated that beta-blockers could reduce all-cause mortality in the HFPEF population [57]. This should be reassessed by another ongoing b-Preserve trial, which aimed to enroll 1,200 patients with HFPEF randomized to metoprolol or placebo therapy and to clarify the long-term effect of beta-blocker treatment in the HFPEF population [69].

4.5. Phosphodiesterase-5 Inhibition (PDE-5 Inhibition). Sildenafil, as a typical agent of selective PDE-5 inhibition, is currently permitted for group 1 pulmonary arterial hypertension treatment. Recently, there are increased numbers of trials to evaluate the effects of sildenafil in chronic HF. Guazzi and his coworkers studied 44 patients with HFPEF (LVEF ≥ 50%) and pulmonary hypertension (pulmonary artery systolic pressure > 40 mm Hg). Compared with placebo, sildenafil significantly reduced mean pulmonary artery pressure and right atrial pressure, but also improved right ventricular function and symptoms [70]. Furthermore, they conducted another study in HF to demonstrate that sildenafil could improve LV diastolic function and cardiac geometry [71]. In contrast, the RELAX trial showed a different result [72]. This study aimed to evaluate the role of PDE-5 inhibition in improvement of clinical status and exercise capacity in diastolic HF. 216 patients with HFPEF (LVEF > 50%), associated with reduced exercise capacity and increased NT-BNP or elevated invasively measured LV filling pressures, were assigned to sildenafil group ($n = 113$) or placebo ($n = 103$). The primary endpoint of this study is evaluation in peak oxygen consumption after 24 weeks of therapy. Secondary endpoints were change in 6-minute walk distance and clinical status assessment. The result showed that sildenafil failed to achieve improvement in exercise capacity in patients with HFPEF. As far as now, studies on PDE-5 inhibition in HFPEF are mainly focused on clinical status improvement or symptom relief instead of mortality reduction. However, as pointed by Kitzman that improvements in symptom among HF patients might diverge from improvements in mortality. The best examples are using positive inotropic drugs in the treatment of HFREF, which resulted in the most effective improvement in symptom but worsened survival, while using beta-blockers, which worsen the symptom acutely, brings a significant reduction in mortality [73]. Thus, although exercise capacity is an important clinical endpoint and might be improved by PDE-5 inhibition in the HFPEF population, the efficacy of PDE-5 inhibition on survival benefit still needs to be evaluated in further large RCTs.

4.6. Nondihydropyridine Calcium Channel Blockers (Non-DHP CCBs). In patients with HFPEF, the effects of nondihydropyridine calcium channel blockers (non-DHP CCBs) are still unknown. Published trials in this field were mainly focused on improvement of LV diastolic function and symptom relief with treatment of verapamil [74, 75]. A recent substudy of the ASCOT (the Anglo-Scandinavian Cardiac Outcomes Trial) trial demonstrated that patients receiving the amlodipine-perindopril regimen had better diastolic function than an atenolol-thiazide regimen [76]. However, it is unclear whether amlodipine or perindopril has the more important effect in this analysis.

4.7. Other Medications. Digoxin, compared with placebo in the digitalis investigation group (DIG) trial, showed neutral result in mortality among patients with HFPEF [77]. However, findings from a more recent study were at odds with the previous neutral results. Meyer and his coworkers found a statistically significant benefit including mortality or hospitalization with digoxin treated group after 2 years of followup, compared with placebo group in patients with HFPEF and in patients with HFREF. However, at the end of the analysis period (median 3.2 years), no significant difference was seen between digoxin and placebo in either the HFPEF group or HFREF group. This result probably was caused by the higher digoxin doses and crossover design [78]. Digoxin is only recommended for control of the rapid ventricular rate during atrial fibrillation in patients with HFPEF.

Statins, as anti-inflammatory agents, have been well demonstrated as a first-line therapy in CAD and hyperlipidemia. Neutral findings have been reported in the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trial regarding the efficacy of statins in patients with HFREF [79]. However, Fukuta et al. reported a significant relative risk reduction in mortality in patients with HFPEF (LVEF > 50%) treated with statins and followed for 21 months [80]. Recent studies also suggested that statins therapy seems to be associated with improved survival benefit in patients with HFPEF [81–84]. This effect remains unclear because only some small observational studies were performed so far.

The Ranolazine for the Treatment of Diastolic Heart Failure (RALI-DHF) trial, that was focused on the effect

of ranolazine in patients with HFPEF, is undergoing now [85]. As an antianginal agent and late sodium channel inhibitor, ranolazine might improve LV diastolic function through inhibition of late sodium current or probably a direct effect on myofilament cross-bridge kinetics and myofilament sensitivity to calcium [86].

A recent epidemiological study showed that the decrease of vitamin D is associated with hypertension, LV hypertrophy, and diastolic dysfunction [87]. An additional study revealed vitamin D regulates renin transcription and the RAAS regulation by activating the vitamin D receptor [88]. An ongoing research in the Vitamin D CHF trial is currently under investigation for the change of plasma renin activity by administration of high-dose vitamin D in a stable chronic HF group [89].

Ivabradine, a drug that inhibits the I_f channel in sinus node, has been found to improve LV systolic and diastolic function in an angiotensin II-induced HF mouse [90]. Ivabradine might be a novel therapeutic concept for HFPEF through effects that improve vascular stiffness, LV contractility, and diastolic function [91]. It is currently also under investigation in patients with HFPEF [92].

Relaxin was evaluated in the treatment of acute HF patients in the RELAX-AHF study lately [93]. Relaxin might play a role in potential benefits in patients with HFPEF due to additional properties including antifibrosis, anti-inflammatory, and anti-ischemic [94].

The combination of hydralazine and isosorbide dinitrate (HISDN) has been recommended to reduce morbidity and mortality for African Americans with advanced HFREF [6, 7]. However, experimental research indicated that diastolic function and exercise capacity could be improved by HISDN [95]. In addition, a study of Vasodilators on Cardiac Function in Diastolic Heart Failure aims to assess the potential benefits of HISDN treatment in the HFPEF population [96].

5. Nonpharmacological Treatment

As evidence-based recommendation by current guidelines, regular exercise is implemented in patients with stable HFREF [6, 7]. Recently, the results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study illustrated that exercise capacity and QoL were improved by exercise training (ET) in patients with mild HFPEF. This finding is probably linked with reversed atrial remodeling and LV diastolic function improvement [97]. However, some recent studies suggested that the improvement of exercise capacity and QoL might come from nonheart organs. Haykowsky and his colleagues found the exercise capacity improvement may mainly be due to peripheral mechanisms (microvascular and/or skeletal muscle function improvement) in elderly stable compensated HFPEF patients [98]. Another study published by Kitzman and his colleagues demonstrated similar results; after 16 weeks of ET, the increase in peak VO_2 was disassociated with endothelial dependent flow-mediated arterial dilation (FMD) and carotid artery stiffness [99]. Fujimoto and his coworkers found that one year of endurance training failed to improve the cardiac output [100]. These studies suggested that ET plays an important role in the improvement of exercise capacity and QoL in the HFPEF population. The mechanisms are probably associated with increased function of metabolically active skeletal muscles instead of cardiac factors [101]. Other nonpharmacological treatments are focused on device therapies. The RESET study aimed to assess the potential benefit of rate-adaptive pacing (RAP) in patients with mild-to-moderate HFPEF based on the prevalence of chronotropic incompetence in HFPEF but failed to enroll sufficient patients [102]. Moreover, the increase in parasympathetic tone has been suggested as a treatment for autonomic dysfunction in patients with HFPEF by carotid sinus stimulation [103]. The clinical safety and efficacy of chronic baroreflex therapy in patients with HFPEF is being evaluated in the CVRx Health Outcomes Prospective Evaluation for Heart Failure with EF ≥ 40% (HOPE4HF) trial [104]. In addition, some patients with severe HFPEF may be associated with interatrial dyssynchrony. Left atrial (LA) pacing therapy might have beneficial effects on restoration of LV active filling and decrease of LA pressure. This will be assessed in a randomized, controlled crossover "LEAD" study recently [105]. Finally, cardiac resynchronization therapy has been developed since dyssynchrony is common in HFPEF. But this still needs further powerful evidence [106, 107].

6. Conclusions

Compared with HFREF, HFPEF is associated with a similar prevalence and mortality, yet no effective treatment has been achieved in RCTs. This may be attributed to unrevealed pathophysiological mechanisms, multiple comorbidities existence, and high noncardiac deaths. Although treatment options remain unclear concerning mortality in patients with HFPEF, most of these patients have significant co-morbidities which are strongly associated with mortality, as well as these comorbidities including hypertension, CAD, diabetes, and CKD. Importantly, these comorbidities have to be treated effectively under the guidance of evidence-based medicine. Therefore, we should identify and treat these comorbidities positively instead of waiting for the new findings of treatments in HFPEF [108]. Likewise, while regarding the goal of treatment, HFPEF patients are often older, and improvements of endpoints such as functional exercise capacity and QoL may be more important than mortality only. Fortunately, putting aside mortality, current results of clinical trials in patients with HFPEF have shown positive evidence of exercise capacity improvement [47]. But despite all this, new pathophysiological concepts and improved diagnostic algorithms are still needed to generate new therapeutic options in the future. Finally, it is necessary to continue further ongoing studies that could be helpful to increase our understanding of the pathophysiology and develop novel therapeutic strategies in the HFPEF population.

References

[1] T. E. Owan, D. O. Hodge, R. M. Herges, S. J. Jacobsen, V. L. Roger, and M. M. Redfield, "Trends in prevalence and outcome

of heart failure with preserved ejection fraction," *The New England Journal of Medicine*, vol. 355, no. 3, pp. 251–259, 2006.

[2] C. S. P. Lam, E. Donal, E. Kraigher-Krainer, and R. S. Vasan, "Epidemiology and clinical course of heart failure with preserved ejection fraction," *European Journal of Heart Failure*, vol. 13, no. 1, pp. 18–28, 2011.

[3] F. P. Brouwers, R. A. de Boer, P. van der Harst et al., "Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND," *European Heart Journal*, vol. 34, no. 19, pp. 1424–1431, 2013.

[4] B. A. Steinberg, X. Zhao, P. A. Heidenreich et al., "Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes," *Circulation*, vol. 126, no. 1, pp. 65–75, 2012.

[5] Meta-Analysis Global Group in Chronic Heart Failure, "The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis," *European Heart Journal*, vol. 33, no. 14, pp. 1750–1757, 2012.

[6] J. J. McMurray, S. Adamopoulos, S. D. Anker et al., "ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC," *European Heart Journal*, vol. 33, no. 14, pp. 1787–1847, 2012.

[7] C. W. Yancy, M. Jessup, B. Bozkurt et al., "2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines," *Circulation*, 2013.

[8] M. M. Chan and C. S. Lam, "How do patients with heart failure with preserved ejection fraction die?" *European Journal of Heart Failure*, vol. 15, no. 6, pp. 604–613, 2013.

[9] B. A. Borlaug and W. J. Paulus, "Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment," *European Heart Journal*, vol. 32, no. 6, pp. 670–679, 2011.

[10] P. M. Becher, D. Lindner, N. Fluschnik, S. Blankenberg, and D. Westermann, "Diagnosing heart failure with preserved ejection fraction," *Expert Opinion on Medical Diagnostics*, vol. 7, no. 5, pp. 463–474, 2013.

[11] M. R. Zile, C. F. Baicu, and W. H. Gaasch, "Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle," *The New England Journal of Medicine*, vol. 350, no. 19, pp. 1953–2018, 2004.

[12] T. E. Vanhecke, R. Kim, S. Z. Raheem, and P. A. McCullough, "Myocardial ischemia in patients with diastolic dysfunction and heart failure," *Current Cardiology Reports*, vol. 12, no. 3, pp. 216–222, 2010.

[13] T. T. Phan, K. Abozguia, G. Nallur Shivu et al., "Heart failure with preserved ejection fraction is characterized by dynamic impairment of active relaxation and contraction of the left ventricle on exercise and associated with myocardial energy deficiency," *Journal of the American College of Cardiology*, vol. 54, no. 5, pp. 402–409, 2009.

[14] D. Westermann, M. Kasner, P. Steendijk et al., "Role of left ventricular stiffness in heart failure with normal ejection fraction," *Circulation*, vol. 117, no. 16, pp. 2051–2060, 2008.

[15] A. González, B. López, R. Querejeta, E. Zubillaga, T. Echeverría, and J. Díez, "Filling pressures and collagen metabolism in hypertensive patients with heart failure and normal ejection fraction," *Hypertension*, vol. 55, no. 6, pp. 1418–1424, 2010.

[16] C. Franssen, N. Hamdani, C. A. Ottenheijm, and W. J. Paulus, "Relative importance of titin and collagen for myocardial stiffness in metabolic risk-induced heart failure with preserved ejection fraction," *Journal of the American College of Cardiology*, vol. 61, no. 10, pp. E696–E696, 2013.

[17] J. Díez, R. Querejeta, B. López, A. González, M. Larman, and J. L. Martínez Ubago, "Losartan-dependent regression of myocardial fibrosis is associated with reduction of left ventricular chamber stiffness in hypertensive patients," *Circulation*, vol. 105, no. 21, pp. 2512–2517, 2002.

[18] K. T. Weber, C. G. Brilla, and J. S. Janicki, "Myocardial fibrosis: functional significance and regulatory factors," *Cardiovascular Research*, vol. 27, no. 3, pp. 341–348, 1993.

[19] S. Heymans, E. Hirsch, S. D. Anker et al., "Inflammation as a therapeutic target in heart failure? A scientific statement from the Translational Research Committee of the Heart Failure Association of the European Society of Cardiology," *European Journal of Heart Failure*, vol. 11, no. 2, pp. 119–129, 2009.

[20] D. Westermann, D. Lindner, M. Kasner et al., "Cardiac inflammation contributes to changes in the extracellular matrix in patients with heart failure and normal ejection fraction," *Circulation*, vol. 4, no. 1, pp. 44–52, 2011.

[21] W. J. Paulus and C. Tschope, "A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation," *Journal of the American College of Cardiology*, vol. 62, no. 4, pp. 263–271, 2013.

[22] B. A. Borlaug, V. Melenovsky, S. D. Russell et al., "Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction," *Circulation*, vol. 114, no. 20, pp. 2138–2147, 2006.

[23] T. Boonyasirinant, P. Rajiah, R. M. Setser et al., "Aortic stiffness is increased in hypertrophic cardiomyopathy with myocardial fibrosis. Novel insights in vascular function from magnetic resonance imaging," *Journal of the American College of Cardiology*, vol. 54, no. 3, pp. 255–262, 2009.

[24] T. T. Phan, G. N. Shivu, K. Abozguia et al., "Impaired heart rate recovery and chronotropic incompetence in patients with heart failure with preserved ejection fraction," *Circulation*, vol. 3, no. 1, pp. 29–34, 2010.

[25] J. Wang, K. M. Kurrelmeyer, G. Torre-Amione, and S. F. Nagueh, "Systolic and diastolic dyssynchrony in patients with diastolic heart failure and the effect of medical therapy," *Journal of the American College of Cardiology*, vol. 49, no. 1, pp. 88–96, 2007.

[26] M. M. Redfield, S. J. Jacobsen, B. A. Borlaug, R. J. Rodeheffer, and D. A. Kass, "Age- and gender-related ventricular-vascular stiffening: a community-based study," *Circulation*, vol. 112, no. 15, pp. 2254–2262, 2005.

[27] C. S. P. Lam, V. L. Roger, R. J. Rodeheffer et al., "Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota," *Circulation*, vol. 115, no. 15, pp. 1982–1990, 2007.

[28] D. W. Kitzman, W. C. Little, P. H. Brubaker et al., "Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure," *Journal of the American Medical Association*, vol. 288, no. 17, pp. 2144–2150, 2002.

[29] K. Hogg and J. McMurray, "Neurohumoral pathways in heart failure with preserved systolic function," *Progress in Cardiovascular Diseases*, vol. 47, no. 6, pp. 357–366, 2005.

[30] L. van Heerebeek, N. Hamdani, I. Falcao-Pires et al., "Low myocardial protein kinase G activity in heart failure with

preserved ejection fraction," *Circulation*, vol. 126, no. 7, pp. 830–839, 2012.

[31] L. van Heerebeek, C. P. Franssen, N. Hamdani, F. W. Verheugt, G. A. Somsen, and W. J. Paulus, "Molecular and cellular basis for diastolic dysfunction," *Current Heart Failure Reports*, vol. 9, no. 4, pp. 293–302, 2012.

[32] E. Akiyama, S. Sugiyama, Y. Matsuzawa et al., "Incremental prognostic significance of peripheral endothelial dysfunction in patients with heart failure with normal left ventricular ejection fraction," *Journal of the American College of Cardiology*, vol. 60, no. 18, pp. 1778–1786, 2012.

[33] C. S. Lam and D. L. Brutsaert, "Endothelial dysfunction: a pathophysiologic factor in heart failure with preserved ejection fraction," *Journal of the American College of Cardiology*, vol. 60, no. 18, pp. 1787–1789, 2012.

[34] F. Edelmann, R. Stahrenberg, G. Gelbrich et al., "Contribution of comorbidities to functional impairment is higher in heart failure with preserved than with reduced ejection fraction," *Clinical Research in Cardiology*, vol. 100, no. 9, pp. 755–764, 2011.

[35] D. Abramov, K.-L. He, J. Wang, D. Burkhoff, and M. S. Maurer, "The impact of extra cardiac comorbidities on pressure volume relations in heart failure and preserved ejection fraction," *Journal of Cardiac Failure*, vol. 17, no. 7, pp. 547–555, 2011.

[36] S. Ather, W. Chan, B. Bozkurt et al., "Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction," *Journal of the American College of Cardiology*, vol. 59, no. 11, pp. 998–1005, 2012.

[37] M. T. Maeder and D. M. Kaye, "Heart failure with normal left ventricular ejection fraction," *Journal of the American College of Cardiology*, vol. 53, no. 11, pp. 905–918, 2009.

[38] M. R. Zile, W. H. Gaasch, I. S. Anand et al., "Mode of death in patients with heart failure and a preserved ejection fraction: results from the Irbesartan in Heart Failure with Preserved Ejection Fraction study (I-Preserve) trial," *Circulation*, vol. 121, no. 12, pp. 1393–1405, 2010.

[39] D. W. Kitzman and M. W. Rich, "Age disparities in heart failure research," *Journal of the American Medical Association*, vol. 304, no. 17, pp. 1950–1951, 2010.

[40] T. T. Phan, G. N. Shivu, K. Abozguia, M. Gnanadevan, I. Ahmed, and M. Frenneaux, "Left ventricular torsion and strain patterns in heart failure with normal ejection fraction are similar to age-related changes," *European Journal of Echocardiography*, vol. 10, no. 6, pp. 793–800, 2009.

[41] G. W. K. Yip, M. Wang, T. Wang et al., "The Hong Kong diastolic heart failure study: a randomised controlled trial of diuretics, irbesartan and ramipril on quality of life, exercise capacity, left ventricular global and regional function in heart failure with a normal ejection fraction," *Heart*, vol. 94, no. 5, pp. 573–580, 2008.

[42] B. R. Davis, J. B. Kostis, L. M. Simpson et al., "Heart failure with preserved and reduced left ventricular ejection fraction in the antihypertensive and lipid-lowering treatment to prevent heart attack trial," *Circulation*, vol. 118, no. 22, pp. 2259–2267, 2008.

[43] S. Yusuf, M. A. Pfeffer, K. Swedberg et al., "Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial," *The Lancet*, vol. 362, no. 9386, pp. 777–781, 2003.

[44] J. G. F. Cleland, M. Tendera, J. Adamus, N. Freemantle, L. Polonski, and J. Taylor, "The perindopril in elderly people with chronic heart failure (PEP-CHF) study," *European Heart Journal*, vol. 27, no. 19, pp. 2338–2345, 2006.

[45] B. M. Massie, P. E. Carson, J. J. McMurray et al., "Irbesartan in patients with heart failure and preserved ejection fraction," *The New England Journal of Medicine*, vol. 359, no. 23, pp. 2456–2467, 2008.

[46] K. Patel, G. C. Fonarow, D. W. Kitzman et al., "Angiotensin receptor blockers and outcomes in real-world older patients with heart failure and preserved ejection fraction: a propensity-matched inception cohort clinical effectiveness study," *European Journal of Heart Failure*, vol. 14, no. 10, pp. 1179–1188, 2012.

[47] D. J. Holland, D. J. Kumbhani, S. H. Ahmed, and T. H. Marwick, "Effects of treatment on exercise tolerance, cardiac function, and mortality in heart failure with preserved ejection fraction: a meta-analysis," *Journal of the American College of Cardiology*, vol. 57, no. 16, pp. 1676–1686, 2011.

[48] J. McMurray, "Renin angiotensin blockade in heart failure with preserved ejection fraction: the signal gets stronger," *European Heart Journal*, vol. 27, no. 19, pp. 2257–2259, 2006.

[49] L. H. Lund, L. Benson, U. Dahlstrom, and M. Edner, "Association between use of renin-angiotensin system antagonists and mortality in patients with heart failure and preserved ejection fraction," *Journal of The American Medical Association*, vol. 308, no. 20, pp. 2108–2117, 2012.

[50] J. C. Fang, "Heart failure therapy: what should clinicians believe?" *Journal of The American Medical Association*, vol. 308, no. 20, pp. 2144–2146, 2012.

[51] M. Mujib, K. Patel, G. C. Fonarow et al., "Angiotensin-converting enzyme inhibitors and outcomes in heart failure and preserved ejection fraction," *The American Journal of Medicine*, vol. 126, no. 5, pp. 401–410, 2013.

[52] U. Khalid and A. Deswal, "Lack of definitive evidence for the use of renin-angiotensin system antagonists for heart failure with preserved ejection fraction," *Evidence-Based Medicine*, 2013.

[53] J. Gu, A. Noe, P. Chandra et al., "Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi)," *Journal of Clinical Pharmacology*, vol. 50, no. 4, pp. 401–414, 2010.

[54] T. G. von Lueder, S. J. Sangaralingham, B. H. Wang et al., "Renin-Angiotensin blockade combined with natriuretic Peptide system augmentation: novel therapeutic concepts to combat heart failure," *Circulation Heart Failure*, vol. 6, no. 3, pp. 594–605, 2013.

[55] S. Mangiafico, L. C. Costello-Boerrigter, I. A. Andersen, A. Cataliotti, and J. C. Burnett Jr., "Neutral endopeptidase inhibition and the natriuretic peptide system: an evolving strategy in cardiovascular therapeutics," *European Heart Journal*, vol. 34, no. 12, pp. 886–893, 2013.

[56] S. D. Solomon, M. Zile, B. Pieske et al., "The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial," *The Lancet*, vol. 380, no. 9851, pp. 1387–1395, 2012.

[57] D. J. van Veldhuisen and J. J. McMurray, "Pharmacological treatment of heart failure with preserved ejection fraction: a glimpse of light at the end of the tunnel?" *European Journal of Heart Failure*, vol. 15, no. 1, pp. 5–8, 2013.

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

[59] B. Pitt, W. Remme, F. Zannad et al., "Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction," *The New England Journal of Medicine*, vol. 348, no. 14, pp. 1309–1321, 2003.

[60] F. Zannad, J. J. V. McMurray, H. Krum et al., "Eplerenone in patients with systolic heart failure and mild symptoms," *The New England Journal of Medicine*, vol. 364, no. 1, pp. 11–21, 2011.

[61] A. Deswal, P. Richardson, B. Bozkurt, and D. L. Mann, "Results of the Randomized Aldosterone Antagonism in heart failure with Preserved Ejection Fraction trial (RAAM-PEF)," *Journal of Cardiac Failure*, vol. 17, no. 8, pp. 634–642, 2011.

[62] F. Edelmann, R. Wachter, A. G. Schmidt et al., "Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial," *Journal of The American Medical Association*, vol. 309, no. 8, pp. 781–791, 2013.

[63] A. S. Desai, E. F. Lewis, R. Li et al., "Rationale and design of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial: a randomized, controlled study of spironolactone in patients with symptomatic heart failure and preserved ejection fraction," *American Heart Journal*, vol. 162, no. 6, pp. 966–e10, 2011.

[64] A. Bergström, B. Andersson, M. Edner, E. Nylander, H. Persson, and U. Dahlström, "Effect of carvedilol on diastolic function in patients with diastolic heart failure and preserved systolic function. Results of the Swedish Doppler-Echocardiographic study (SWEDIC)," *European Journal of Heart Failure*, vol. 6, no. 4, pp. 453–461, 2004.

[65] V. M. Conraads, M. Metra, O. Kamp et al., "Effects of the long-term administration of nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with diastolic dysfunction: results of the ELANDD study," *European Journal of Heart Failure*, vol. 14, no. 2, pp. 219–225, 2012.

[66] D. J. van Veldhuisen, A. Cohen-Solal, M. Böhm et al., "Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: data from SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure)," *Journal of the American College of Cardiology*, vol. 53, no. 23, pp. 2150–2158, 2009.

[67] K. Yamamoto, H. Origasa, M. Hori, and J. D. Investigators, "Effects of carvedilol on heart failure with preserved ejection fraction: the Japanese Diastolic Heart Failure Study (J-DHF)," *European Journal of Heart Failure*, vol. 15, no. 1, pp. 110–118, 2013.

[68] W. S. Aronow, C. Ahn, and I. Kronzon, "Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction ≥40% treated with diuretics plus angiotensin-converting enzyme inhibitors," *American Journal of Cardiology*, vol. 80, no. 2, pp. 207–209, 1997.

[69] J. Zhou, H. Shi, J. Zhang, Y. Lu, M. Fu, and J. Ge, "Rationale and design of the β-blocker in heart failure with normal left ventricular ejection fraction (β-PRESERVE) study," *European Journal of Heart Failure*, vol. 12, no. 2, pp. 181–185, 2010.

[70] M. Guazzi, M. Vicenzi, R. Arena, and M. D. Guazzi, "Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study," *Circulation*, vol. 124, no. 2, pp. 164–174, 2011.

[71] M. Guazzi, M. Vicenzi, R. Arena, and M. D. Guazzi, "PDE5 inhibition with sildenafil improves left ventricular diastolic function, cardiac geometry, and clinical status in patients with stable systolic heart failure: result of a 1-year, prospective, randomized, placebo-controlled study," *Circulation*, vol. 4, no. 1, pp. 8–17, 2011.

[72] M. M. Redfield, H. H. Chen, B. A. Borlaug et al., "Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial," *Journal of The American Medical Association*, vol. 309, no. 12, pp. 1268–1277, 2013.

[73] D. W. Kitzman, "Understanding results of trials in heart failure with preserved ejection fraction: remembering forgotten lessons and enduring principles," *Journal of the American College of Cardiology*, vol. 57, no. 16, pp. 1687–1689, 2011.

[74] J. F. Setaro, B. L. Zaret, D. S. Schulman, H. R. Black, and R. Soufer, "Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance," *American Journal of Cardiology*, vol. 66, no. 12, pp. 981–986, 1990.

[75] M. J. Hung, W. J. Cherng, L. T. Kuo, and C. H. Wang, "Effect of verapamil in elderly patients with left ventricular diastolic dysfunction as a cause of congestive heart failure," *International Journal of Clinical Practice*, vol. 56, no. 1, pp. 57–62, 2002.

[76] R. J. Tapp, A. Sharp, A. V. Stanton et al., "Differential effects of antihypertensive treatment on left ventricular diastolic function: an ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) substudy," *Journal of the American College of Cardiology*, vol. 55, no. 17, pp. 1875–1881, 2010.

[77] A. Ahmed, M. W. Rich, J. L. Fleg et al., "Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial," *Circulation*, vol. 114, no. 5, pp. 397–403, 2006.

[78] P. Meyer, M. White, M. Mujib et al., "Digoxin and reduction of heart failure hospitalization in chronic systolic and diastolic heart failure," *American Journal of Cardiology*, vol. 102, no. 12, pp. 1681–1686, 2008.

[79] J. Kjekshus, E. Apetrei, V. Barrios et al., "Rosuvastatin in older patients with systolic heart failure," *The New England Journal of Medicine*, vol. 357, no. 22, pp. 2248–2261, 2007.

[80] H. Fukuta, D. C. Sane, S. Brucks, and W. C. Little, "Statin therapy may be associated with lower mortality in patients with diastolic heart failure: a preliminary report," *Circulation*, vol. 112, no. 3, pp. 357–363, 2005.

[81] M. Ouzounian, J. V. Tu, P. C. Austin, A. Chong, P. P. Liu, and D. S. Lee, "Statin therapy and clinical outcomes in heart failure: a propensity-matched analysis," *Journal of Cardiac Failure*, vol. 15, no. 3, pp. 241–248, 2009.

[82] M. Roik, "Statin therapy in patients with heart failure and preserved left ventricular function," *Circulation Journal*, vol. 73, no. 7, p. 1359, 2009.

[83] F. Tehrani, R. Morrissey, A. Phan, C. Chien, and E. R. Schwarz, "Statin therapy in patients with diastolic heart failure," *Clinical Cardiology*, vol. 33, no. 4, pp. E1–E5, 2010.

[84] D. Gomez-Garre, M. L. Gonzalez-Rubio, P. Munoz-Pacheco, A. Caro-Vadillo, P. Aragoncillo, and A. Fernandez-Cruz, "Rosuvastatin added to standard heart failure therapy improves cardiac remodelling in heart failure rats with preserved ejection fraction," *European Journal of Heart Failure*, vol. 12, no. 9, pp. 903–912, 2010.

[85] C. Jacobshagen, L. Belardinelli, G. Hasenfuss, and L. S. Maier, "Ranolazine for the treatment of heart failure with preserved ejection fraction: background, aims, and design of the RALI-DHF study," *Clinical Cardiology*, vol. 34, no. 7, pp. 426–432, 2011.

[86] J. D. Lovelock, M. M. Monasky, E.-M. Jeong et al., "Ranolazine improves cardiac diastolic dysfunction through modulation of myofilament calcium sensitivity," *Circulation Research*, vol. 110, no. 6, pp. 841–850, 2012.

[87] S. U. Nigwekar, I. Bhan, and R. Thadhani, "Nutritional vitamin D in dialysis patients: what to D-iscern?" *Nephrology Dialysis Transplantation*, vol. 26, no. 3, pp. 764–766, 2011.

[88] J. P. Forman, J. S. Williams, and N. D. L. Fisher, "Plasma 25-hydroxyvitamin D and regulation of the renin-angiotensin system in humans," *Hypertension*, vol. 55, no. 5, pp. 1283–1288, 2010.

[89] US National Library of Medicine, "Study to investigate the effects of vitamin D administration on plasma renin activity in patients with stable Chronic Heart Failure (VitD-CHF)," 2010, http://clinicaltrials.gov/ct2/show/NCT01092130.

[90] P. M. Becher, D. Lindner, K. Miteva et al., "Role of heart rate reduction in the prevention of experimental heart failure: comparison between if-channel blockade and β-receptor blockade," *Hypertension*, vol. 59, no. 5, pp. 949–957, 2012.

[91] J. C. Reil, M. Hohl, G. H. Reil et al., "Heart rate reduction by If-inhibition improves vascular stiffness and left ventricular systolic and diastolic function in a mouse model of heart failure with preserved ejection fraction," *European Heart Journal*, vol. 34, no. 36, pp. 2839–2849, 2012.

[92] US National Library of Medicine, "If channel blockade with ivabradine in patients with diastolic heart failure," 2008, http://clinicaltrials.gov/ct2/show/NCT00757055.

[93] J. R. Teerlink, G. Cotter, B. A. Davison et al., "Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial," *The Lancet*, vol. 381, no. 9860, pp. 29–39, 2013.

[94] S. L. Teichman, E. Unemori, J. R. Teerlink, G. Cotter, and M. Metra, "Relaxin: review of biology and potential role in treating heart failure," *Current Heart Failure Reports*, vol. 7, no. 2, pp. 75–82, 2010.

[95] R. M. Wilson, D. S. de Silva, K. Sato, Y. Izumiya, and F. Sam, "Effects of fixed-dose isosorbide dinitrate/hydralazine on diastolic function and exercise capacity in hypertension-induced diastolic heart failure," *Hypertension*, vol. 54, no. 3, pp. 583–590, 2009.

[96] US National Library of Medicine, "Vasodilator therapy for heart failure and preserved ejection fraction," 2012, http://clinicaltrials.gov/ct2/show/NCT01516346.

[97] F. Edelmann, G. Gelbrich, H.-D. Dngen et al., "Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise Training in Diastolic Heart Failure) pilot study," *Journal of the American College of Cardiology*, vol. 58, no. 17, pp. 1780–1791, 2011.

[98] M. J. Haykowsky, P. H. Brubaker, J. M. John, K. P. Stewart, T. M. Morgan, and D. W. Kitzman, "Determinants of exercise intolerance in elderly heart failure patients with preserved ejection fraction," *Journal of the American College of Cardiology*, vol. 58, no. 3, pp. 265–274, 2011.

[99] D. W. Kitzman, P. H. Brubaker, D. M. Herrington et al., "Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial," *Journal of the American College of Cardiology*, vol. 62, no. 7, pp. 584–592, 2013.

[100] N. Fujimoto, A. Prasad, J. L. Hastings et al., "Cardiovascular effects of 1 year of progressive endurance exercise training in patients with heart failure with preserved ejection fraction," *American Heart Journal*, vol. 164, no. 6, pp. 869–877, 2012.

[101] S. J. Keteyian, "Exercise training in patients with heart failure and preserved ejection fraction: findings awaiting discovery," *Journal of the American College of Cardiology*, vol. 62, no. 7, 2013.

[102] D. A. Kass, D. W. Kitzman, and G. E. Alvarez, "The restoration of chronotropic competence in heart failure patients with normal ejection fraction (RESET) study: rationale and design," *Journal of Cardiac Failure*, vol. 16, no. 1, pp. 17–24, 2010.

[103] B. Olshansky, H. N. Sabbah, P. J. Hauptman, and W. S. Colucci, "Parasympathetic nervous system and heart failure pathophysiology and potential implications for therapy," *Circulation*, vol. 118, no. 8, pp. 863–871, 2008.

[104] D. Georgakopoulos, W. C. Little, W. T. Abraham, F. A. Weaver, and M. R. Zile, "Chronic baroreflex activation: a potential therapeutic approach to heart failure with preserved ejection fraction," *Journal of Cardiac Failure*, vol. 17, no. 2, pp. 167–178, 2011.

[105] G. Laurent, J. C. Eicher, A. Mathe et al., "Permanent left atrial pacing therapy may improve symptoms in heart failure patients with preserved ejection fraction and atrial dyssynchrony: a pilot study prior to a national clinical research programme," *European Journal of Heart Failure*, vol. 15, no. 1, pp. 85–93, 2013.

[106] E. S. Chung, R. P. Katra, S. Ghio et al., "Cardiac resynchronization therapy may benefit patients with left ventricular ejection fraction >35: a PROSPECT trial substudy," *European Journal of Heart Failure*, vol. 12, no. 6, pp. 581–587, 2010.

[107] M. Penicka, V. Kocka, D. Herman, H. Trakalova, and M. Herold, "Cardiac resynchronization therapy for the causal treatment of heart failure with preserved ejection fraction: insight from a pressure-volume loop analysis," *European Journal of Heart Failure*, vol. 12, no. 6, pp. 634–636, 2010.

[108] S. J. Shah and M. Gheorghiade, "Heart failure with preserved ejection fraction: treat now by treating comorbidities," *Journal of the American Medical Association*, vol. 300, no. 4, pp. 431–433, 2008.

Hindawi Publishing Corporation
Cardiology Research and Practice
Volume 2013, Article ID 603913, 5 pages
http://dx.doi.org/10.1155/2013/603913

Research Article

Effect of Ivabradine on Endothelial Function in Diastolic and Right Heart Failure Patients

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Received 18 June 2013; Revised 12 August 2013; Accepted 28 August 2013

Academic Editor: Gregory Giamouzis

Background. Ivabradine is an If ion current inhibitor that has proved to reduce mortality in patients with systolic heart failure by slowing heart rate without decreasing myocardial contractility. Photoplethysmography is a simple, low-cost optical technique that can evaluate vascular function and detect changes in blood flow, pulse, and swelling of tissular microvascular space. *Objective*. To evaluate the effect of ivabradine on endothelial function by photoplethysmography in diastolic and right heart failure patients. *Methodology*. 15 patients were included (mean age of 78.1 ± 9.2 years) with optimally treated diastolic and right heart failure. They underwent photoplethysmography before and after induced ischemia to evaluate the wave blood flow on the finger, using the maximum amplitude time/total time (MAT/TT) index. Two measurements were made before and after oral Ivabradine (mean 12.5 mg a day during 6 months of followup). *Results*. In the study group, the MAT/TT index was 29.1 ± 2.2 versus 24.3 ± 3.2 ($P = 0.05$) in basal recording and 30.4 ± 2.1 versus 23.3 ± 2.9 ($P = 0.002$), before versus after ischemia and before versus after Ivabradine intervention, respectively. *Conclusions*. Ivabradine administration improves endothelial function (shear stress) in diastolic and right heart failure patients.

1. Background

Diastolic dysfunction has been associated with symptoms of congestive heart failure in patients with preserved left ventricular ejection fraction [1]. In the largest single-center study with approximately 36, 000 outpatients with normal LVEF, some authors have shown that diastolic dysfunction is an independent predictor of all-cause mortality [2].

In outpatients with heart failure with preserved ejection fraction (HFpEF) at the baseline echocardiogram, worsening of diastolic function in a follow-up study is also an independent predictor of all-cause mortality [3]. In addition, Achong showed that improvement in diastolic function was associated with increased survival ($P = 0.05$) in a mixed cohort of inpatients and outpatients with normal or mild systolic dysfunction [4], while the more advanced the stage is, the higher the filling pressures and the worse the outcomes are [5].

In patients with atrial fibrillation, if diastolic function was assessed, it was based on deceleration time of mitral E-wave velocity and tissue Doppler imaging (i.e., peak early mitral inflow velocity/diastolic early tissue velocity [E/e']) [6].

Ivabradine added to recommended treatment, improved the outcome of heart failure patients reducing cardiovascular death and hospitalizations rate [7]. In patients with coronary disease and left ventricular dysfunction also the benefit was observed [8]. In experimental studies, ivabradine have been demonstrated that reduces fibrosis and improve endothelial function [9–12].

Ivabradine also has demonstrated a favorable effect on LV remodeling after 8 months of followup as well as and antianginal effect [13].

Hyperemic coronary blood flow velocity also increases after ivabradine treatment, probably because the diastolic period is prolonged (per cardiac beat and per minute). It has been speculated that the most probable explanation of the improvement of ventricular relaxation caused by ivabradine treatment could be its effect on coronary blood flow velocity during hyperemia [14].

To evaluate the effect of ivabradine on endothelial function by photoplethysmography in patients with right heart failure and preserved ejection fraction, we performed this open-label clinical trial.

2. Methods

2.1. Study Population. This open-label clinical trial included ambulatory patients who came to the Heart Failure Clinic of the Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán." Patients were recruited if they were men or nongravid women with more than 18 years of age with a confirmed diagnosis of stable heart failure with preserved ejection fraction in New York Heart Association functional classes II to III. Candidates were excluded if they had had myocardial infarction, unstable angina or a history of myocardial revascularization (percutaneous transluminal coronary angioplasty or aortocoronary bypass grafts), cerebrovascular events during the previous 3 months, dysfunctional prosthetic heart valve, obstructive or nonobstructive cardiomyopathy, uncorrected congenital heart disease, active myocarditis, a history of resuscitation from sudden death, or severe arrhythmias.

Heart failure was established by signs and symptoms as well as echocardiographic and radioisotopic ventriculography findings. Preserved ejection fraction was defined as a left ventricular ejection fraction ≥ 50%, LVEDVI < 97 mL/m^2, left atrial diameter > 40 mL/m^2, tissue doppler E/E′ > 15 echo-blood flow Doppler E/A in >50 years <0.5, and DT in >50 years >280 ms [15]. Right ventricular dysfunction was defined as ejection fraction ≤ 35% measured by radioisotopic ventriculography [16, 17].

All patients received standard heart failure therapy and their comorbidities (diuretics, angiotensin-converting enzyme inhibitors, angiotensin II antagonists, aldosterone receptor blockers, digitalis, and beta-adrenoreceptor blockers), at their maximum doses tolerated. Some patients that developed atrial fibrillation also received digital.

2.2. Study Design. This was an investigator-initiated, single center, single-arm, open-label clinical trial.

After baseline measurements, in addition to conventional therapy, patients received an average of ivabradine 12.5 mg (10–15 mg) a day, according their tolerance during 6 months of follow-up [18, 19]. Patients underwent 2D and Doppler echocardiograms and radioisotopic (rest/effort) left and right ventriculography before and after oral ivabradine.

Table 1: Demographic and clinical characteristics of the CHF patients.

Variables	$N = 15$
Age (years)	78.1 ± 9.2
Female (%)	73.3
Arterial hypertension (%)	73.3
Hypothyroidism (%)	53.3
Diabetes mellitus (%)	33.3
COPD (%)	33.3
Dyslipidemia (%)	26.6
End Stage Kidney disease (%)	26.6
Functional class (NYHA):	
II	60
III	40

2.2.1. Photoplethysmography. A baseline digital photoplethysmographic wave was recorded for 30 seconds. The forearm was then compressed with a sphygmomanometer cuff for 5 minutes using a pressure of 30 mmHg above the systolic arterial pressure recorded (ischemic phase). The compression was then released and the digital photoplethysmographic wave was recorded for 120 seconds. The wave was analyzed at 30-second intervals for comparison with the baseline values. The most representative waves were selected from the recording of each interval, and the maximum amplitude time (MAT) and total time (TT) were measured in order to calculate the MAT/TT index. A MAT/TT index of less than 30 was considered normal, as proposed in other studies [20, 21].

Cardiologists who performed the echocardiograms and radioventriculography did not have access to patients' information.

2.3. Statistical Analysis. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as percentages. To compare the changes from baseline to 6 months, a paired t-test was used. A P value of <0.05 was considered statistically significant. All analyses were performed using a commercially available package (SPSS for Windows, version 17.0 SPSS Inc.).

3. Results

Fifteen patients (73.6% female) were studied. Arterial hypertension and hypothyroidism (under treatment and well controlled) were the most common comorbidities with patients in functional classes (NYHA) II and III (Table 1). It is important to note that COPD and ESKD patients were not excluded from the study. Concomitant medication was as follows: diuretic (73%) and adrenergic beta blocker receptor (BB, 73%) agents were the most commonly employed; 46.6% also received mineralocorticoid receptor antagonists (MRAmedications) and angiotensin-converting-enzyme inhibitors (ACEIs)/angiotensin receptors blockers (ARB).

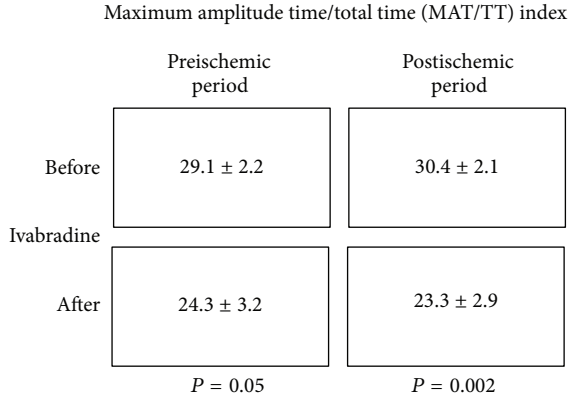

Figure 1: Pre and after ischemic period, before and after 6 months of follow-up of oral ivabradine.

Patients received an average of 12.5 (range 10–15) mg/day during the 6 months of followup. It was particularly interesting that heart rate did not decrease in any patients below the 10% recommended (88 versus 82 beats/min) in the literature in spite of the top doses received.

Figure 1 shows the maximum amplitude time/total time (MAT/TT) index before and after the followup. A significant increase in pre- and post-ischemic periods after ivabradine administration is evident when basal values are compared with those at the end of followup.

Improvement of the endothelial-dependent vasodilatation expressed by significant changes observed in the photoplethysmographic curves occurred concurrently. All patients had some degree of clinical improvement, 8/9 (88.8%) from NYHA III to II and 4/6 (66.6%) from II to I, respectively, although this did not achieve statistical significance ($P = 0.08$).

With respect to cardiac structural changes, in the echocardiographic study, only right ventricular diastolic diameter (40.5 ± 7.8 versus 36.4 ± 5.3; $P = 0.05$) was significantly different after the followup. There was also a reduction of 8.15% in the systolic pulmonary arterial pressure (59.6 ± 8.4 versus 54.9 ± 10.2; $P = 0.05$).

4. Discussion

Approximately 50% of patients with heart failure (HF) have normal or preserved left ventricular ejection fraction (HFPEF) [22], and their prognosis is similar to that of patients with HF with reduced LVEF (HFREF) [22, 23]. Left ventricular diastolic dysfunction (LVDD) plays an important role in patients with HFPEF [24] and could be due to structural and molecular abnormalities of the cardiovascular system. These abnormalities include myocardial ischemia, cardiac hypertrophy, cardiac inflammation [25], and ventricular vascular stiffening, in part due to the reduced effects of nitric oxide and impaired endothelial function [26]. Borlaug et al. recently demonstrated that global cardiovascular reserve functions, including endothelial function, are impaired in subjects with HFNEF who have hypertension, a very frequent cause of HF [27]. In HFREF, coronary endothelial function is also impaired [28], and it has been reported that peripheral endothelial dysfunction is associated with the severity of HF symptoms and clinical outcome in patients with HFREF [29, 30]. Moreover, vascular stiffness and resistance with elevated blood pressure has been proposed as a potential important noncardiac factor in patients with HFpEF [31].

Endothelial dysfunction has been shown to be involved in the pathogenesis of HF, mainly HFREF. Several studies have reported that peripheral endothelial dysfunction is associated with the clinical outcome in patients with HFREF [30]. Borlaug et al. recently reported that subjects with HFpEF had limited arterial vasodilator response to exercise, which might impair cardiac output reserve under stress [32].

Peripheral endothelial function is impaired in patients with HFpEF, and when it is evaluated as a reactive hyperemia by peripheral arterial tonometry (RH-PAT), it significantly correlates with future cardiovascular events. Peripheral endothelial function is thus an independent predictor after adjusting various clinical parameters [33]. Indeed, the prognostic impact of the reactive hyperemia index in patients with HFpEF suggests that endothelial dysfunction may not be a passive finding, but may rather play an active and important pathophysiologic role in HFpEF [32]. When matched in patients and controls for diabetes and hypertension, more endothelial dysfunction was found in patients with HFPEF, who were notably more obese than controls [34].

The results of the systolic heart failure treatment with the If inhibitor ivabradine trial (SHIFT) showed that treatment with ivabradine added to conventional therapy for HF was associated with an 18% reduction in the relative risk for the primary composite endpoint of cardiovascular death or hospitalization for worsening HF ($P < 0.0001$) [7]. It also had a positive effect on LV remodelling in the echocardiographic substudy of the BEAUTIFUL (morBidity-mortality EvAlUaTion of the If inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) study [8].

In experimental studies, ivabradine has been demonstrated to reduces fibrosis and improve endothelial function [9–12], together with its antiischemic and antianginal effects [13] which could explain why all our patients improved their functional class, possibly associated with increased hyperemic coronary blood flow velocity. It may also be explained by the prolonged diastolic period (per cardiac beat and per minute). Moreover, we can speculate that the endothelial-dependent vasodilatation expressed by the significant changes observed in the photoplethysmographic curves in peripheral and coronary territories plays an important role in improving coronary blood reserve as has already been described [35, 36], and flow velocity may have a direct effect on coronary vessels and reduced ventricular wall tension, with improvement of ventricular relaxation [14], added to diminished right ventricular diastolic diameter with significant reduction of arterial pulmonary pressure, which probably reflects improved coronary perfusion pressure (aortic mean pressure/coronary sinus ratio).

In experimental postinfarction settings, both cardiac [37] and pulmonary vascular [38] endothelial dysfunction may

contribute to the development of heart failure through endocardial and myocardial capillary endothelial abnormalities [39] and could explain the impaired left ventricular relaxation in pressure-overload hypertrophy [40].

Preserved ejection fraction is present in almost 50% of heart failure patients and is cause of half of HF hospitalizations, and traditional HF treatment is not effective. A recently published pathophysiology-based novel pharmacotherapy for these patients considers spironolactone, aliskiren, and neprilisyn as therapeutic options for HFPEF because of their anti-hypertrophic and anti-fibrotic effects [41]. Combined ventricular and vascular stiffening involving both the systemic and pulmonary circulations, plays a role in the pathophysiology of HFpEF [42, 43]. Thus, the effects of ivabradine on endothelial function, that we observed, may represent a major advantage when it is used to treat left diastolic dysfunction because of its secondary impact on pulmonary arterial hypertension and damaged right ventricular function.

5. Limitations

The number of patients studied was small, and the intervention period was short. It is probable that a longer followup would show changes in variables such as left ventricular diastolic diameter and other structural characteristics. In addition, the lack of direct quantification of pulmonary pressures is a drawback.

Our findings support continued investigation into the effects of ivabradine on right ventricular function, systemic arterial pressure, and systolic pulmonary arterial pressure in heart failure patients with preserved ejection fraction. More studies are required to evaluate the effects observed on a larger number of patients for a longer period.

References

[1] W. Aljaroudi, M. C. Alraies, C. Halley et al., "Impact of progression of diastolic dysfunction on mortality in patients with normal ejection fraction," *Circulation*, vol. 125, no. 6, pp. 782–788, 2012.

[2] M. Senni, C. M. Tribouilloy, R. J. Rodeheffer et al., "Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991," *Circulation*, vol. 98, no. 21, pp. 2282–2289, 1998.

[3] B. G. Angeja and W. Grossman, "Evaluation and management of diastolic heart failure," *Circulation*, vol. 107, no. 5, pp. 659–663, 2003.

[4] P. M. Mottram and T. H. Marwick, "Assessment of diastolic function: what the general cardiologist needs to know," *Heart*, vol. 91, no. 5, pp. 681–695, 2005.

[5] C. M. Halley, P. L. Houghtaling, M. K. Khalil, J. D. Thomas, and W. A. Jaber, "Mortality rate in patients with diastolic dysfunction and normal systolic function," *Archives of Internal Medicine*, vol. 171, no. 12, pp. 1082–1087, 2011.

[6] H. Okura, Y. Takada, T. Kubo et al., "Tissue Doppler-derived index of left ventricular filling pressure, E/E′, predicts survival of patients with non-valvular atrial fibrillation," *Heart*, vol. 92, no. 9, pp. 1248–1252, 2006.

[7] K. Swedberg, M. Komajda, M. Böhm et al., "Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study," *The Lancet*, vol. 376, no. 9744, pp. 875–885, 2010, Erratum in *The Lancet*, vol. 376, p. 1988, 2010.

[8] C. Ceconi, S. B. Freedman, J. C. Tardif et al., "Effect of heart rate reduction by ivabradine on left ventricular remodeling in the echocardiographic substudy of BEAUTIFUL," *International Journal of Cardiology*, vol. 146, no. 3, pp. 408–414, 2011.

[9] P. Mulder, S. Barbier, A. Chagraoui et al., "Long-term heart rate reduction induced by the selective If current inhibitor ivabradine improves left ventricular function and intrinsic myocardial structure in congestive heart failure," *Circulation*, vol. 109, no. 13, pp. 1674–1679, 2004.

[10] E. I. Dedkov, W. Zheng, L. P. Christensen, R. M. Weiss, F. Mahlberg-Gaudin, and R. J. Tomanek, "Preservation of coronary reserve by ivabradine-induced reduction in heart rate in infarcted rats is associated with decrease in perivascular collagen," *American Journal of Physiology—Heart and Circulatory Physiology*, vol. 293, no. 1, pp. H590–H598, 2007.

[11] P. Milliez, S. Messaoudi, J. Nehme, C. Rodriguez, J.-L. Samuel, and C. Delcayre, "Beneficial effects of delayed ivabradine treatment on cardiac anatomical and electrical remodeling in rat severe chronic heart failure," *American Journal of Physiology—Heart and Circulatory Physiology*, vol. 296, no. 2, pp. H435–H441, 2009.

[12] M. Vercauteren, J. Favre, P. Mulder, F. Mahlberg-Gaudin, C. Thuillez, and V. Richard, "Protection of endothelial function by long-term heart rate reduction induced by ivabradine in a rat model of chronic heart failure," *European Heart Journal*, vol. 28, supplement, p. 48, 2007.

[13] G. Riccioni, N. Vitulano, and N. D'Orazio, "Ivabradine: beyond heart rate control," *Advances in Therapy*, vol. 26, no. 1, pp. 12–24, 2009.

[14] E. I. Skalidis, M. I. Hamilos, G. Chlouverakis, E. A. Zacharis, and P. E. Vardas, "Ivabradine improves coronary flow reserve in patients with stable coronary artery disease," *Atherosclerosis*, vol. 215, no. 1, pp. 160–165, 2011.

[15] W. J. Paulus, C. Tschöpe, J. E. Sanderson et al., "How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology," *European Heart Journal*, vol. 28, no. 20, pp. 2539–2550, 2007.

[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] J. F. Setaro, M. W. Cleman, and M. S. Remetz, "The right ventricle in disorders causing pulmonary venous hypertension," *Cardiology Clinics*, vol. 10, no. 1, pp. 165–183, 1992.

[18] F. M. Sarullo, G. Fazio, D. Puccio et al., "Impact of "off-label" use of ivabradine on exercise capacity, gas exchange, functional class, quality of life, and neurohormonal modulation in patients with ischemic chronic heart failure," *Journal of Cardiovascular Pharmacology and Therapeutics*, vol. 15, no. 4, pp. 349–355, 2010.

[19] A. Schuster and W. H. W. Tang, "Ivabradine in heart failure: to SHIFT or not to SHIFT," *Current Heart Failure Reports*, vol. 8, no. 1, pp. 1–3, 2011.

[20] J. T. Kuvin, A. R. Patel, K. A. Sliney et al., "Assessment of peripheral vascular endothelial function with finger arterial

pulse wave amplitude," *American Heart Journal*, vol. 146, no. 1, pp. 168–174, 2003.

[21] A. Aldama, H. Álvarez, A. Rodríguez, and B. Reyes, "Evaluación cualitativa de la morfología de la señal fotopletismográfica en el diagnóstico de la insuficiencia arterial," *Revista Cubana de Investigaciones Biomédicas*, vol. 27, no. 1, 2008.

[22] R. S. Bhatia, J. V. Tu, D. S. Lee et al., "Outcome of heart failure with preserved ejection fraction in a population-based study," *The New England Journal of Medicine*, vol. 355, no. 3, pp. 260–269, 2006.

[23] T. E. Owan, D. O. Hodge, R. M. Herges, S. J. Jacobsen, V. L. Roger, and M. M. Redfield, "Trends in prevalence and outcome of heart failure with preserved ejection fraction," *The New England Journal of Medicine*, vol. 355, no. 3, pp. 251–259, 2006.

[24] M. R. Zile, C. F. Baicu, and W. H. Gaasch, "Diastolic heart failure: abnormalities in active relaxation and passive stiffness of the left ventricle," *The New England Journal of Medicine*, vol. 350, no. 19, pp. 1953–1959, 2004.

[25] J. Matsubara, S. Sugiyama, T. Nozaki et al., "Pentraxin 3 is a new inflammatory marker correlated with left ventricular diastolic dysfunction and heart failure with normal ejection fraction," *Journal of the American College of Cardiology*, vol. 57, no. 7, pp. 861–869, 2011.

[26] M. Ouzounian, D. S. Lee, and P. P. Liu, "Diastolic heart failure: mechanisms and controversies," *Nature Reviews Cardiology*, vol. 5, pp. 375–386, 2008.

[27] B. A. Borlaug, T. P. Olson, C. S. P. Lam et al., "Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction," *Journal of the American College of Cardiology*, vol. 56, no. 11, pp. 845–854, 2010.

[28] S. H. Kubo, T. S. Rector, A. J. Bank, R. E. Williams, and S. M. Heifetz, "Endothelium-dependent vasodilation is attenuated in patients with heart failure," *Circulation*, vol. 84, no. 4, pp. 1589–1596, 1991.

[29] M. A. AlZadjali, V. Godfrey, F. Khan et al., "Insulin resistance is highly prevalent and is associated with reduced exercise tolerance in non-diabetic patients with heart failure," *Journal of the American College of Cardiology*, vol. 53, no. 9, pp. 747–753, 2009.

[30] D. Fischer, S. Rossa, U. Landmesser et al., "Endothelial dysfunction in patients with chronic heart failure is independently associated with increased incidence of hospitalization, cardiac transplantation, or death," *European Heart Journal*, vol. 26, no. 1, pp. 65–69, 2005.

[31] G. Cotter, M. Metra, O. Milo-Cotter, H. C. Dittrich, and M. Gheorghiade, "Fluid overload in acute heart failure—re-distribution and other mechanisms beyond fluid accumulation," *European Journal of Heart Failure*, vol. 10, no. 2, pp. 165–169, 2008.

[32] B. A. Borlaug, V. Melenovsky, S. D. Russell et al., "Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction," *Circulation*, vol. 114, no. 20, pp. 2138–2147, 2006.

[33] E. Akiyama, S. Sugiyama, Y. Matsuzawa et al., "Incremental prognostic significance of peripheral endothelial dysfunction in patients with heart failure with normal left ventricular ejection fraction," *Journal of the American College of Cardiology*, vol. 60, no. 18, pp. 1778–1786, 2012.

[34] C. S. Lam and D. L. Brutsaert, "Endothelial dysfunction: a pathophysiologic factor in heart failure with preserved ejection fraction," *Journal of the American College of Cardiology*, vol. 60, no. 18, pp. 1787–1789, 2012.

[35] M. B. Britten, A. M. Zeiher, and V. Schächinger, "Microvascular dysfunction in angiographically normal or mildly diseased coronary arteries predicts adverse cardiovascular long-term outcome," *Coronary Artery Disease*, vol. 15, no. 5, pp. 259–264, 2004.

[36] B. A. Herzog, L. Husmann, I. Valenta et al., "Long-term prognostic value of 13N-ammonia myocardial perfusion positron emission tomography added value of coronary flow reserve," *Journal of the American College of Cardiology*, vol. 54, no. 2, pp. 150–156, 2009.

[37] X.-L. Qi, D. J. Stewart, H. Gosselin et al., "Improvement of endocardial and vascular endothelial function on myocardial performance by captopril treatment in postinfarct rat hearts," *Circulation*, vol. 100, no. 12, pp. 1338–1345, 1999.

[38] A. Ben Driss, C. Devaux, D. Henrion et al., "Hemodynamic stresses induce endothelial dysfunction and remodeling of pulmonary artery in experimental compensated heart failure," *Circulation*, vol. 101, no. 23, pp. 2764–2770, 2000.

[39] D. Popov, A. Sima, D. Stern, and M. Simionescu, "The pathomorphological alterations of endocardial endothelium in experimental diabetes and diabetes associated with hyperlipidemia," *Acta Diabetologica*, vol. 33, no. 1, pp. 41–47, 1996.

[40] P. A. MacCarthy and A. M. Shah, "Impaired endothelium-dependent regulation of ventricular relaxation in pressure-overload cardiac hypertrophy," *Circulation*, vol. 101, no. 15, pp. 1854–1860, 2000.

[41] D. M. Konstantinou, Y. S. Chatzizisis, and G. D. Giannoglou, "Pathophysiology-based novel pharmacotherapy for heart failure with preserved ejection fraction," *Pharmacology & Therapeutics*, 2013.

[42] C. S. P. Lam, V. L. Roger, R. J. Rodeheffer et al., "Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota," *Circulation*, vol. 115, no. 15, pp. 1982–1990, 2007.

[43] C. S. P. Lam, V. L. Roger, R. J. Rodeheffer, B. A. Borlaug, F. T. Enders, and M. M. Redfield, "Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study," *Journal of the American College of Cardiology*, vol. 53, no. 13, pp. 1119–1126, 2009.