Cardiology Research and Practice

Heart Failure 2012

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Editorial Board

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Editorial
Heart Failure 2012

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Heart failure has been named "the growing epidemic." 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. Understanding the epidemiology and pathophysiology of the syndrome, identifying the predictors and their strength of association with outcomes, and using the available diagnostic modalities cost-effectively are essential in order to devise effective prevention interventions and implement novel therapeutic approaches to curb this epidemic.

In this special issue, 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].

In the *pathophysiology section*, S. M. R. Kazemi-Bajestani et al. describe the opportunities and challenges of targeting the angiotensin converting enzyme 2 (ACE2)/Ang II/Ang1–7 and apelin/APJ pathways as novel therapeutic modalities in heart failure [3]. ACE2 and the apelin/APJ are two important peptide systems which exert diverse effects on the cardiovascular system. Dysregulation of such systems may be involved in the predisposition to cardiovascular diseases whereas enhancing their action may have important therapeutic effects. In the same section, D. Lindner et al. provide a comprehensive review on the protective function of signal transducer and activator of transcription 3 (STAT3) in CVB3-induced myocarditis [4]. The transcription factor (STAT3) is an important mediator of the inflammatory process, and in this original research the investigators examine the role of STAT3 in viral myocarditis and its possible role in the development to dilated cardiomyopathy.

Considering the high mortality rate and the availability of life-saving therapies like transplantation and left ventricular assist devices, accurate *prognosis determination* in HF is clinically important. Taking into account the mediocre performance of current established prediction models, such as the Seattle Heart Failure Model [5–7], the work by H. Fukuta et al. [8] on the prognostic value of left ventricular diastolic dysfunction in patients undergoing cardiac catheterization for coronary artery disease sheds light on this extremely important topic.

A shared understanding of medical conditions between patients and their health care providers has been shown to improve self-care and outcomes [9]. 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. Among others, cognitive impairment is increasingly recognized as

a common adverse consequence of HF, whereby phenomena such as microembolism, chronic or intermittent cerebral hypoperfusion, and/or impaired cerebral vessel reactivity may lead to cerebral hypoxia and ischemic brain damage. Cognitive decline in HF is characterized by deficits in one or more cognition domains, including attention, memory, executive function, and psychomotor speed. E. Dardiotis et al. [10], in a comprehensive review, underscore the importance for healthcare professionals to become familiar with assessment of cognitive performance using standardized screening instruments in their routine evaluations of HF patients.

Another comorbidity gaining increasing attention in HF patients is depression. There are several pathophysiological mechanisms as well as behavioral processes linking depression and HF. Equally important is screening for depression and there are several valid and reliable screening tools to identify patients at greater risk. Consultation should be provided by a multidisciplinary team, consisting of cardiologists, psychiatrists, and hospital or community nurses so as to carefully plan, execute, and evaluate medical intervention and implement lifestyle changes. D. Mastrogiannis et al. [11] systematically review the existing knowledge regarding current definitions, prognostic implications, pathophysiological mechanisms, and current and future treatment options in patients with depression and HF. Evidence from the literature supports the possibility of a pathophysiological relationship between cognitive impairment, depression, and HF. Yet, very few studies have sought to investigate this relationship. The paper by Z. N. Sohani and Z. Samaan reviews current literature on the association between depression and cognitive impairment in persons with HF and explores possible mechanisms explaining this complex triad [12].

Heart failure through neurohumoral activation induces alterations of cardiac metabolism, such as insulin resistance, and promotes increased utilization of noncarbohydrate substrates for energy production [13, 14]. Fasting blood ketone bodies as well as fat oxidation have been shown to be increased in this patient population. The result is depletion of myocardial ATP, phosphocreatine, and creatine kinase, leading to decreased efficiency of mechanical work. A direct approach to manipulate cardiac energy metabolism consists in modifying substrate utilization by the failing heart. Trimetazidine, perhexiline, and ranolazine directly inhibit fatty acid oxidation and have been used to increase the ischemic threshold in patients with effort angina. Current research is supporting the concept that shifting the energy substrate preference away from fatty acid metabolism and toward glucose metabolism could be an effective adjunctive treatment in patients with HF. These agents have been shown to improve both glucose metabolism and left ventricular function in diabetic patients with left ventricular dysfunction. In the *pharmacotherapy section*, we provide a systematic review, in which N. Signoretta et al. [15] discuss the beneficial therapeutic effects of modulation of cardiac metabolic substrates utilization in patients with HF.

In the *advanced heart failure section*, we provide a thorough review on the current status of mechanical circulatory support in patients with advanced HF. Management of the advanced HF patients with the numerous comorbidities [16, 17] requires a significant amount of health care resources and is becoming a major public health problem. As therapeutical strategies for HF have been refined, the number of patients suffering from the end-stage disease has expanded dramatically. Although heart transplantation still represents the gold standard therapeutical approach, the shortage of donors universally has made the implantation of mechanical circulatory support devices a well-established management for this disease. The systematic review by K. Spiliopoulos et al. [18], outlines the current status of mechanical circulatory support in this patient population.

In the *chronic follow-up section*, we deal with telemonitoring, a novel diagnostic modality that has been suggested to be beneficial for HF patients, targeting optimization of their chronic followup. Telemonitoring is viewed as a means of recording physiological data (such as body weight, heart rate, arterial blood pressure electrocardiogram recordings, and other data) by portable devices and transmitting these data remotely (via a telephone line, a mobile phone, or a computer) to a server where they can be stored, reviewed, and analyzed by the research team. In a systematic review of all randomized clinical trials evaluating telemonitoring in chronic HF, G. Giamouzis et al. [19] assess whether telemonitoring provides any substantial benefit in this patient population.

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

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Review Article

Current Status of Mechanical Circulatory Support: A Systematic Review

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Heart failure is a major public health problem and its management requires a significant amount of health care resources. Even with administration of the best available medical treatment, the mortality associated with the disease remains high. As therapeutical strategies for heart failure have been refined, the number of patients suffering from the disease has expanded dramatically. Although heart transplantation still represents the gold standard therapeutical approach, the implantation of mechanical circulatory support devices (MCSDs) evolved to a well-established management for this disease. The limited applicability of heart transplantation caused by a shortage of donor organs and the concurrent expand of the patient population with end-stage heart failure led to a considerable utilization of MCSDs. This paper outlines the current status of mechanical circulatory support.

1. Introduction

The prevalence of chronic heart failure (HF) is worldwide increasing and meanwhile averages 2.5% of the normal population [1, 2]. In Europe and the United States, more than 17 million people suffer from the disease and more than 500,000 people are yearly newly diagnosed, while the chance for a 40-year-old individual to develop HF during its lifetime approximates 20% [3]. The economic impact of the disease is important, involving in the European community approximately 1% of the total public health expenditure and up to $40 billion in the USA [4, 5].

The prognosis of chronic HF remains poor despite a lot of recent advances in medical management, interventional therapies, and surgical techniques [6–8]. It is estimated that the mortality at 5 years approaches 80%, while patients receiving inotropes have 1-year survival less than 30% [9, 10]. Although heart transplantation is the treatment of choice for patients in end-stage HF non responding to medical treatment, its applicability is limited by a shortage of donor organs [11]. Data from the Eurotransplant registry shows that in 2001 a patient on the heart transplantation waiting list would be able to undergo transplantation within one year. In 2011, in contrast, there were 1,222 patients listed and only 553 transplantations were performed. After a transient peak in the number of heart transplants in the mid-1990s, the number of reported heart transplants has remained essentially stable. In the last decade, between 3,600 and 3,850 heart transplants have been registered yearly in the (ISHLT) Transplant Registry, which represents

approximately 66% of the heart transplant procedures performed worldwide [12]. A growing number of heart transplant candidates require longterm support by a left ventricular assist device (LVAD) while they await cardiac transplantation. LVAD therapy has evolved into a standard therapy for patients with advanced HF, not only as a bridge to cardiac transplantation (BTT) but also as a bridge to decision (BTD), destination therapy (DT), or bridge to myocardial recovery (BTR) [13]. The growing excess of listed candidates without increase in the supply of donor hearts has more recently shifted the recipient population back to one of severe decompensation with high short-term mortality without intervention.

Historically, John Gibbon in 1953 was the first to introduce the idea of mechanically supporting the cardiopulmonary system, when he successfully used cardiopulmonary bypass for an atrial septal defect repair [14]. The first ventricular assist device was implanted in 1963 by DeBakey in a patient suffering a cardiac arrest following aortic valve replacement. The patient subsequently died on the fourth postoperative day. Nevertheless, DeBakey reported in 1966 the first successful implantation of a pneumatically driven VAD as bridge to recovery for 10 days in a patient sustained postcardiotomy shock. The patient ultimately survived to discharge [15]. Cooley reported soon thereafter, the first successful implantation of a pneumatically driven artificial heart as bridge to transplantation [16]. In 1984, DeVries and colleagues performed the first successful implantation of the Jarvik-7-100 total artificial heart [17]. Despite the first promising results, the incidence of thromboembolic and infectious complications remained high leading to a moratorium in 1991 regarding the use of the total artificial heart. However, in 1994, the achieved advances in the development of LVADs culminated in a Food and Drug Administration (FDA) approval of an LVAD as a bridge to transplantation treatment.

2. First-Generation Mechanical Circulatory Support

The first-generation LVADs were large pulsatile, positive displacement pumps with a lot of moving parts. The devices were limited to patients with a body surface area greater than 1.5 m^2 and were the first MCSDs initially introduced into clinical practice. The prototypes are the Novacor left ventricular assist system (LVAS, WorldHeart, Salt Lake City, Utah, USA), first implanted in a human in 1984 and used successfully as BTT in that patient, the Thoratec IVAD (implantable ventricular assist device) and the HeartMate XVE (later called HeartMate I; Thoratec Corporation, Pleasanton, Calif), which was first tested in a clinical trial in 1986 [18, 19]. The HeartMate XVE is the only long-term implantable MCSD not requiring systemic anticoagulation therapy, while the Thoratec IVAD is the only implantable MCSD approved for biventricular support.

Regarding the site of pump implantation commonly utilized pulsatile-flow MCSDs, in which the blood pump lies external to the patient are the Thoratec PVAD (paracorporeal ventricular assist device), the Berlin Heart Excor (Berlin Heart AG, Berlin, Germany) and the Toyobo LVAS (Toyobo Co Ltd, Osaka, Japan) fulfilling indications for temporary use for the BTT and BTR (Table 1). The clinical performance of MCSDs is evaluated in several studies. The landmark of those is the Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure (REMATCH) study, which evaluated the HeartMate XVE assist device compared to medical treatment in patients with end-stage heart failure [20]. This series consisted of 129 patients with heart failure of New York Heart Association (NYHA) class IV not fulfilling indications for heart transplantation. The study population was randomized to receive either a HeartMate XVE or maximum medical treatment. The 1-year survival was in the assist device group with 52% significantly higher compared to the medical treatment group, which showed a survival at 1 year of 25% and after 2 years 28% versus 8%, respectively. Major drawbacks, of the HeartMate XVE, are its large size, high device failure and infection rate of 17% and 41% respectively at 18 months of continued use [21]. A study of 280 patients after HeartMate XVE implantation performed by Lietz and colleagues confirmed the outcomes of the REMATCH study [22]. Despite an 1-year survival of 56%, the postsurgical early mortality and device failure rate at 2 years were fairly high at 27% and 73%, respectively.

Similar results regarding survival provided the non-randomized series of Rogers et al., which evaluated the performance of the Novacor LVAS. The LVAD treatment led to improved survival compared to the medical therapy, but was associated with neurologic complications approaching a stroke risk rate of 62% [23].

The first-generation MCSDs have been supplanted by newer devices because of their high device-related complications such as infections and mechanical failure arizing from their large size and the complexity of the pump function.

3. Second-Generation Mechanical Circulatory Support

The second-generation MCSDs consisted of axial pumps, which utilize continuous rather than pulsatile blood flow without valves. This continuous pulseless blood flow is physiologically entirely well-tolerated and pulseless LVADs support improves neurocognitive disturbances due to severe heart failure, just as pulsatile devices do [24]. The presence of a single-moving rotor minimizes device wear and tear resulting to mechanical stability for years. Additionally, their smaller size makes second-generation devices less prone to infections and enables the implantation in patients with small body surface areas.

Second-generation VADs include the Jarvik 2000 (Jarvik Heart, New York, NY, USA), the MicroMed DeBakey VAD (MicroMed Technologies, Woodlands, Tex, USA) and the HeartMate II (Table 1). The HeartMate II represents to date the most frequently used second-generation pump worldwide [25–28].

The outcomes of second-generation LVADs compared to those of their first-generation counterparts were evaluated

Table 1: Left ventricular assist devices currently in use.

Device	Manufacturer	Type	Approval
First generation			
Novacor LVAS	World Heart	Pulsatile	CE, FDA for BTT
Thoratec IVAD-implantable ventricular assist device	Thoratec	Pulsatile	CE, FDA for BTT in 2004
Thoratec PVAD paracorporeal ventricular assist device			CE, FDA for BTT in 1995 and for post-cardiotomy recovery (open heart surgery) in 1998.
HeartMate XVE	Thoratec	Pulsatile.	CE, FDA for BTT in 2001 and DT in 2003.
Excor (paracorporeal)	Berlin Heart	Pulsatile	CE, FDA for BTT, BTR
Toyobo LVAS (paracorporeal)	Toyobo Co Ltd	Pulsatile	Approved in Japan
Second generation			
Jarvik 2000	Jarvik Heart	Continuous	FDA for BTT; CE for BTT, BTR, DT
HeartMate II	Thoratec	Continuous	CE; FDA for BTT in 2008, DT in 2010
MicroMed DeBakey VAD	MicroMed	Continuous	CE for BTT, BTR, DT; FDA for pediatric use (BTT) of the children typ in USA
Third generation			
Levacor VAD	WorldHeart	Continuous fully magnetically levitated	In February 2011 World Heart suspended enrollment in the BTT study while it awaited notification from the FDA
HVAD	HeartWare	Continuous through centrifugal blood path and hydromagnetically suspended rotor that may be placed in the pericardial space.	CE in January 2009. US BTT trial in October 2008 and US DT trial in August 2010.
VentrAssist	Ventracor	Continuous by a hydrodynamically suspended centrifugal rotor.	CE in EU and approved in Australia. Company declared bankrupt while clinical trials for FDA approvalin 2009. Intellectual property sold to thoratec.
DuraHeart	Terumo	Magnetically levitated centrifugal pump	CE; FDA trials underway
Incor	Berlin Heart	Continuous by a magnetically suspended axial flow rotor.	CE; entered clinical trials in the US in 2009.

CE: *Conformité Européenne*; European Conformity,
FDA: food and drug administration,
USA: United States of America,
EU: European Union,
BTT: bridge to transplant,
BTR: bridge to recovery,
DT: destination therapy.

in a randomized trial comparing the Heartmate II and Heartmate XVE [25]. Survival at 2 years was significant higher (46% versus 11%) in the HeartMate II group, while the device-replacement rate was only 10% in the second-generation VAD group compared to that of 36% in the first generation VAD patients. Although the anticoagulation scheme in the HeartMate II group consisted of aspirin and warfarin, targeting an INR of 2.0-3.0, and only aspirin in the HeartMate XVE group, the risk of stroke and overall bleeding did not differ significantly between the two groups. However, the bleeding rate requiring surgical intervention in the second-generation VAD patient group was 30%. Interesting to mention is the observation that, although the enrolled patients in this trial were excluded from transplantation waiting lists, eventually 9 patients from the HeartMate XVE and 17 from the HeartMate II group underwent transplantation. The improved clinical performance of the second-generation LVADs resulted in a wider acceptance and use of the devices. Their major complications related to anticoagulation (bleeding and thrombosis) as presented in the first studies performed have been largely circumvented through technical modifications of the devices and improved anticoagulation regimes [28, 29]. A recently published standardized protocol dealing with this issue contributed to a better management of patients supported by these devises [30].

4. Third-Generation Mechanical Circulatory Support

Third-generation MCSDs provide like second-generation LVADs continuous blood flow, utilized from an axial or a centrifugal rotor. The impeller or rotor consists of a mechanism forced by hydrodynamic or electromagnetic energy, reducing in that way the moving parts and the areas of contact. The magnetic-levitation (maglev) system can be distinguished into three types: (i) external motor-driven system, (ii) direct-drive motor-driven system, and (iii) self-bearing or bearingless motor system. Through their technological advancements, third-generation MCSDs are estimated to be longer mechanically stable than their second-generation counterparts. Their smaller size approaching almost that of an AA battery enables the relative noninvasive complete intrapericardial implantation, adjacent to the heart with improved patient outcomes [31].

Third-generation MCSDS include the Levacor VAD (WorldHeart), HeartWare HVAD (HeartWare International, Inc, Framingham, Mass, USA), VentrAssist (Ventracor Ltd., Sydney, Australia, since 2010 Thoratec Corporation, Pleasanton, CA), DuraHeart (Terumo Heart Inc, Ann Arbor, Mich, USA) and the Berlin Heart Incor (Berlin Heart, Berlin, Germany, Table 1). Historically, the DuraHeart was the first third-generation device entering European clinical trials in 2004 [32]. Its performance was favorable with improved outcomes, supporting the market revolution towards extended utilization and further development of these devices. In a European multicenter study including 68 patients with advanced heart failure, who were listed for cardiac transplantation, the device was implanted as BTT. The device provided safe and reliable long-term circulatory support with survival rates at 6 and 12 months of 81 and 77%, respectively. During a mean support duration of 8 months, there was no incidence of pump mechanical failure, pump thrombosis, or hemolysis. Regarding the device related adverse events the most frequent were neurological complications (27%), right heart failure (27%) and infection, (18%) [33].

The clinical performance of the HeartWare HVAD pump (HeartWare Inc, Framingham, Mass) is evaluated in a multi-institutional trial in Europe and Australia including 23 patients. The primary end point of this bridge-to-transplant study was survival to heart transplant or survival to 180 days on the device, whichever occurred first. Actuarial survival after 6 months was 91% and 86% at the 1-year followup. The design of the HVAD pump enables a quick and less invasive implantation. The results to date demonstrate satisfactory long-term survival with excellent quality of life in this cohort [31]. Additionally, the HVAD system has been also successfully used for biventricular support [34].

The Berlin Heart Incor LVAD was evaluated in several studies, and it was associated with 1-year survival rate ranging from 53 to 63.4% and low adverse event rates, like thromboembolism ranging from 3.8 (0.1%/patient-year) to 23.2% (0.5%/patient-year) [35, 36].

In a clinical trial investigating the VentrAssist, the device reached a success rate of 82% (39.4% of patients had been successfully bridged to transplant and 42.4% of patients remained transplant eligible). The serious adverse event rates regarding infection and thromboembolism at 5 months were 0.8 and 0.12%/patient-year, respectively. Implantation resulted in improved end-organ function enhanced quality of life and reduced medication use [37].

The third-generation devices consist of smaller, potentially more reliable LVADs, which make long-term circulatory assist available to a wider range of the heart failure population, particularly those who are ineligible for transplantation or those with smaller body surface area.

5. MCSD Databases

The increasing use and the ongoing development of mechanical circulatory support, established the need for rigorous scientific data collection and registration. Therefore, in 2001 the International Society for Heart and Lung Transplantation (ISHLT) developed and implemented the MCSD Database. In 2006, the National Heart Lung and Blood Institute (NHLBI) grounded the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), a collaborative database, which collects information on MCSD implants in the USA. Data collection started on June 23, 2006, and through June 2011, more than 4,500 patients have been registered [38]. United States MCS centers designated by the Centers for Medicare and Medicaid Services (CMS) as destination therapy (DT) centers are required to enter all implants of durable devices into the INTERMACS database. With the goal of running a European registry, EUROMACS was founded on December 10, 2009 in Berlin, on the initiative of the two European centers with the largest clinical programs in the field of mechanical circulatory support—the Deutsches Herzzentrum Berlin and the Herz and Diabeteszentrum NRW Bad Oeynhausen—by 14 founding members. Additionally, the ISHLT is planing the introduction of an international MCS registry in order to collect device data from institutions worldwide.

The analysis of the INTERMACS collected data since its launch in 2006 revealed a dramatic change in the landscape of MCS support in the United States. From the year 2008, after the FDA approval of the HeartMate II continuous flow pump for BTT, there was a radical shift towards an extended use of continuous-flow pumps, being nowadays the most used devices with an implantation rate greater than 99% of adult primary LVAD implants. In addition, a gradual change has occurred during the past 5 years concerning the treatment strategies, reflected by the increased use of VAD as DT.

INTERMACS established 7 clinical profiles (Table 2) in order to facilitate the assessment of the need for MCSD therapy as well as the risk associated with MCSD implantation. This classification offers a more precise categorization of the disease severity in patients with advanced stages of HF than the traditional one provided by NYHA [39]. Regarding the disease severity of patients with MCSD-support there is a trend avoiding VAD implantation in patients in critical cardiogenic shock (INTERMACS level 1), as it was shown by the decreasing rates of critically ill patients with MCSD

Table 2: Interagency registry for mechanically assisted circulatory support (intermacs) levels (*with permission from* [39]).

Profile 1	Critical cardiogenic shock	Patient with life-threatening hypotension despite rapidly escalating inotropic support and critical organ hypoperfusion, often confirmed by worsening acidosis and/or lactate levels.
Profile 2	Progressive decline	Patient with declining function despite intravenous inotropic support, which may be manifest by worsening renal function, nutritional depletion, and inability to restore volume balance.
Profile 3	Stable but inotrope-dependent	Patient with stable blood pressure, organ function, nutrition and symptoms on continuous intravenous inotropic support (or a temporary circulatory support device or both), but demonstrating repeated failure to wean from support due to recurrent symptomatic hypotension or renal dysfunction.
Profile 4	Resting symptoms	Patient can be stabilized close to normal volume status but experiences daily symptoms of congestion at rest or during activities of daily living (ADL). Doses of diuretics generally fluctuate at very high levels. More intensive management and surveillance strategies should be considered, which may in some cases reveal poor compliance that would compromise outcomes with any therapy. Some patients may shuttle between Profiles 4 and 5.
Profile 5	Exertion intolerant	Comfortable at rest and with ADL but unable to engage in any other activity, living predominantly within the house. Patients are comfortable at rest without congestive symptoms, but may have underlying refractory elevated volume status, often with renal dysfunction. If underlying nutritional status and organ function are marginal, patient may be more at risk than INTERMACS Profile 4 and require definitive intervention.
Profile 6	Exertion limited	Patient without evidence of fluid overload is comfortable at rest, and with ADL and minor activities outside the home but fatigues after the first few minutes of any meaningful activity. Attribution to cardiac limitation requires careful measurement of peak oxygen consumption, in some cases with hemodynamic monitoring to confirm severity of cardiac impairment.
Profile 7	Advanced NYHA III	A placeholder for more precise specification in the future, this level includes patients who are without current or recent episodes of unstable fluid balance, living comfortably with meaningful activity limited to mild physical exertion.

support from 35% to 17% in the most recent INTERMACS era. Those patients may be best served with initial temporary support until stabilization and recovery from the organ dysfunction is approached [27, 40, 41].

6. Patient Selection—Outcomes

Four broad indications for an MCSD are defined, with regard to the clinical intent at the time of implantation: (i) the bridge-to-transplant intent (BTT) performed on patients eligible for transplantation, while listed for a transplant; (ii) destination therapy (DT) for patients not eligible for transplantation having refractory heart failure symptoms; (iii) bridge to decision (BTD) including patients requiring MCS with the option of reevaluation of their candidacy for transplantation after improvement of clinical parameters through the MCS, (iv) bridge to myocardial recovery (BTR) applied to patients with nonischemic heart failure, with the goal to restore myocardial function targeting the explantation of the device. The decision to apply an MCSD to a patient is often difficult, thus the criteria for referral vary greatly among institutions, but nevertheless heart failure confirmed by typical signs such as pulmonary capillary wedge pressure > 20 mm Hg, cardiac index < 2.0 L/min/m^2, or systolic blood pressure < 80 mm Hg, despite best medical management, should be present [29].

The REMATCH trial firstly, as mentioned before, proved the marked survival advantage of MCSDs over chronic medical therapy. As surgical techniques, postoperative care and devices improved, the mortality rates subsequently decreased to a level of approximately 9% in some centers [42].

According to the recently published annual report of INTERMACS for the entire patient population of primary MCS for the past 5 years, overall survival has progressively improved since 2006, exceeding 80% at 1 year. There is still a dramatic improvement in survival in favour of continuous-flow compared to pulsatile LVADs. Continuous-flow pumps (CFPs) had at 2 years a significant higher survival of 74% when compared to 43% of the pulsatile-flow pumps (PFPs) cohort. With regard to the treatment-intent the survival at 1 and 2 years is, as expected, less for DT, because those patients are generally not considered for transplantation as "rescue" therapy in the event of life threatening device complications (Figure 1) [38].

Apart from identifying the patient, who will benefit from MCS, similarly important is an adequate risk stratification in order to minimize the perioperative mortality of VAD implantation. In the literature, there are several series dealing with this issue, evaluating the accuracy and ability of risk stratification models in predicting early and late mortality associated with MCSD placement. In a study of Lietz et al. consisting of 280 HeartMate XVE recipients as DT, the patients were divided into high- and low-risk groups according to laboratory values and preoperative medical therapy [22, 43]. Low-risk patients showed a survival to discharge of 93.7% compared to that of 13.7% in the very high-risk group. Similarly after 1 year the low-risk group approached survival of 81.2%, while very high-risk patients presented a survival of only 10.7%. The performed mortality analysis demonstrated that comorbidities such as renal and hepatic insufficiency,

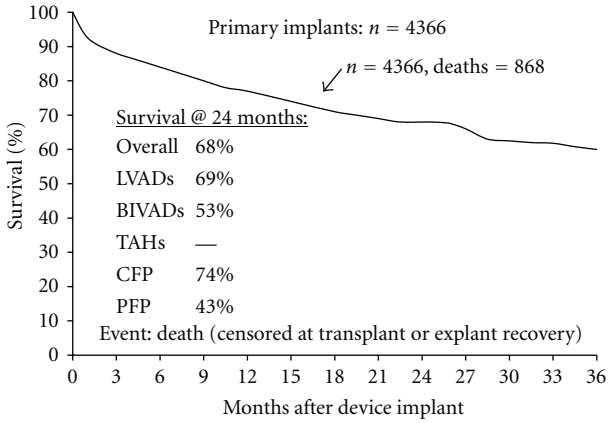

Figure 1: Actuarial survival (censored at transplant or explant/recovery) among 4,366 ventricular assist device implants from 06/23, 2006-06/30, 2011 and additionally stratified by device type, and pump type. (*with permission from: The Fourth INTERMACS Annual Report)* [32]. Abbreviations: INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support. LVAD: left ventricular assist device. BiVAD: biventricular assist device. TAH: total artificial heart. CFP: continuous-flow pumps. PFP: pulsatile-flow pumps.

right ventricle dysfunction, and poor nutritional status were independent risk factors for early mortality [8, 44, 45]. Other authors advocated the Model for End-Stage Liver Disease (MELD) score to predict perioperative and 6-month mortality after LVAD implantation [46]. Their results showed that patients with an MELD-score > 17 presented a 2.5 fold higher 6-month mortality compared to those having an MELD-score < 17. Of note is that both of the above presented studies consisted of patients with first-generation LVADs. Furthermore, these models were not derived from and have not been validated in a cohort of patients with advanced HF who are being considered for MCS. A single-center study including patients with the second-generation HearMate II assist device comparing various risk indices (Leitz- Miller, Columbia, APACHE II, INTERMACS, and Seattle Heart Failure Model (SHFM)), showed a superiority of the SHFM risk stratification model, which is a prospective validated multivariate risk-model and a tool that predicts survival of HF patients [47–51]. Summarizing, there is still need for the development of validated risk stratification models for an adequate patient selection.

According to the risk factor analysis in the recent INTERMACS annual report, during the early period (consisting of the first 3 months after implantation), the dominant mortality predictors are: clinical status of INTERMACS Level 1 (cardiogenic shock) and severe right ventricular failure sufficient to require BiVAD support (Table 4) [38]. In the constant phase (referring to the time period from 1 to 3 years after implantation), the most prominent risk factor was the presence of a first-generation pulsatile pump. The analysis evaluated subsequently subtle changes, that may occur in patient selection criteria and identified as a major change the reduction in the proportion of patients receiving continuous-flow pumps in INTERMACS Level 1 (19% versus 11%). In the most recent era, there are certain comorbid risk factors like advanced age and prior CABG-surgery, which are more prevalent. However, the fact that the expected survival (reflecting the overall risk profile in that year) has ranged from basically 81.5% to 83% for the last 3.5 years, suggests that the decrement in the strongest risk factor (INTERMACS Level 1) from 2008 to 2011 is being offset by increases in other patient comorbidities. The observation that the increase in comorbidities prevalence seems to neutralize the risk reduction effect resulting from the greater avoidance of INTERMACS Level 1 patients, while the expected 1-year survival remained relatively constant over the years (81.5% to 83%), yielded the conclusion that there is no evidence that durable device therapy is being selectively applied to lower-risk patients in the current era.

Regarding the management of patients who need biventricular support, there is in some centers ongoing interest in the total artificial heart (TAH), seeing in the device an alternative to BiVAD support, but owing to the small number of TAH patients, there is not enough data to provide a useful evaluation of the potential positive effect of TAH.

7. Adverse Events

The main critical device-related adverse events include device malfunction or failure, neurological events, bleeding, infection, and right heart failure (Table 3).

7.1. Mechanical Failure. Mechanical device malfunctions or failures have been, particularly in the first-generation devices one of the major limiting factors concerning their long-term use. Due to their complex mechanical function pulsatile flow pumps are prone to such malfunctions. Further technological development and advancements utilized in second- and third-generation devices resulted in increased mechanical reliability and durability [29]. Current continuous-flow devices consisting of only a single, nearly moving part-the impeller- sowed in clinical trials, statistically significant lower pump replacement rates in comparison to their first and second generation counterparts [25]. Through the provided unidirectional blood flow there is no longer need for valved conduits, avoiding in that way valve deterioration. The use of hydrodynamically or magnetically levitated rotors in the newest third generation assist devices may achieve even longer mechanical reliability and durability.

7.2. Neurological Events. Adverse neurological events, either of ischemic or hemorrhagic origin, are a major cause of morbidity in MCSD patients. According to the INTERMACS data, primary cerebrovascular events account for 14.1% of all deaths [27]. Continuous flow devices are associated with increased thrombogenicity, which requires appropiate anticoagulation with concomitant administration of aspirin and warfarin (current INR goal: 1.5–2.5) [30]. However, in a study evaluating the HeartMate II, the incidence of neurological adverse events was comparable to that of pulsatile pumps [29, 52]. In the literature there are

Table 3: Adverse events rates (Events/100 patient-months) in first 12 months after implant for 1092 primary LVADs (INTERMACS: June 2006–March 2009, *with permission from: Second INTERMACS annual report*) [27].

Adverse event	Events	Rate
Device malfunction	113	1.98
Bleeding	944	16.52
Cardiac/vascular		
Right heart failure	108	1.89
Myocardial infarction	4	0.07
Cardiac arrhythmia	439	7.68
Pericardial drainage	86	1.50
Hypertensiona	132	2.31
Arterial non-CNS thrombosis	20	0.35
Venous thrombotic event	83	1.45
Hemolysis	31	0.54
Infection	998	17.46
Neurologic dysfunction	164	2.87
Renal dysfunction	142	2.48
Hepatic dysfunction	52	0.91
Respiratory failure	257	4.50
Wound dehiscence	27	0.47
Psychiatric episode	112	1.96
Total "burden"	**3712**	**64.96**

CNS: central nervous system;
INTERMACS: Interagency registry for mechanical circulatory support;
LVAD: left ventricular assist device.

conflicting opinions about the adequate anticoagulation regimen that minimizes the bleeding risk and prevents thromboembolism. One advocate the "bridging" with heparin whenever a patient is subtherapeutic, while the study group of Slaughter et al. suggests that a heparin bridge might not be necessary after LVAD implantation [53]. Apart from the role of anticoagulation in the incidence of neurologic adverse events, several factors and their influence in causing strokes have been evaluated. In a recently published study including 307 consecutive patients, who underwent LVAD surgery (167 HeartMate I and 140 HeartMate II devices) at Columbia University Medical Center between November 2000 and December 2010, pre- and postoperative factors associated with neurologic complications were investigated [54]. The authors demonstrated that overall frequency of neurologic complications (NCs) including TIA after LVAD placement was 14.0% and this of ischemic/hemorrhagic cerebrovascular accident (CVA) 11.4%. The frequency of NCs was not different between patients with HeartMate I and HeartMate II devices; history of CVA and postoperative infection were independently associated with development of NCs after LVAD placement. The combination of prior CVA, preoperative sodium and albumin, postoperative sodium, hematocrit and albumin, and postoperative infection could discriminate patients who develop NCs with a discriminant probability of 76.6%. Additionally, the analysis performed for CVA patients after excluding patients with only TIA yielded similar results.

7.3. Bleeding. Analysis of the 2nd INTERMACS annual report demonstrated that bleeding, either at the site of implantation or in the gastrointestinal (GI) tract, was the second most frequent (16.52%/patient-month) adverse event (after infection) in MCSD patients [27]. On the other, bleeding events were infrequently fatal and accounted for only 6.7% of all deaths.

The association of LVAD placement and bleeding has been described in several series. Strauch et al. compared GI bleeding rates among 20 HMII, 9 HeartMate XVE, and 4 VentrAssist recipients [55]. Eight patients (40%) in the HMII group developed GI bleeding, whereas no GI bleeding occurred in the other LVAD groups.

A study of patients supported by the Novacor pulsatile LVAD—which necessitates anticoagulation—reported an incidence of nonsurgical bleeding as high as 32% [56], while a retrospective review of the European experience with the Novacor LVAD over 3 years documented a postimplantation bleeding rate of 35% (35 of 101) [57].

Theories that have been proposed to explain this association, assume that in continuous-flow LVADs, the impeller mechanism may cause von Willebrand's Factor (vWF) deformation, proteolysis, and an acquired deficiency of high molecular weight (HMW) vWF multimers, which predisposes to bleeding, especially in the setting of antiplatelet use [58]. Additionally, the utilized continuous-flow has led to more frequent incidence of atrioventricular fistulas in the GI tract, a finding also seen in another narrow pulse state like aortic stenosis [59]. Nevertheless, anticoagulation treatment must not be discounted as a factor in post-LVAD implantation bleeding.

It is likely that bleeding adverse events will decrease in frequency in light of the constantly evolvement of anticoagulation regimens with lower INR levels, the avoidance of heparin administration and the use of advanced methods of monitoring like thromboelastography.

In general, the adequate level of antiplatelet and anticoagulant treatment in order to avoid both thromboembolic and hemorrhagic adverse events is unknown and seems to be device specific.

7.4. Infection. The INTERMACS registry reported infection as the most common (17.46%/patient-month) adverse event accounting for 16.2% of all deaths, a finding which confirmed similar results from the REMATCH and HeartMate II BTT and DT trials [27]. Infection adverse events are most common within the first 3 months after placement and have a statistically significant negative influence on survival. The risk for infection after LVAD placement for long-term support is likely a multifactorial phenomenon. Newer continuous flow second- and third-generation devices are much smaller and, as the HeartMate II trials showed, associated with lower rates of pocket and driveline infections, which had been a source of morbidity and mortality. In a study performed by Martin et al., the HeartMate XVE

Table 4: Risk factors for death in 4,366 primary implant patients: 06/2006–06/2011 (*with permission from: The Fourth INTERMACS Annual* Report) [32].

Risk factors	Early hazard HR	Early hazard *P* value	Constant hazard HR	Constant hazard *P* value
Age, older	1.54[a]	<0.0001	1.30[a]	0.0001
BSA, larger	1.48[b]	0.0006		
Female			1.36	0.01
History of:				
CABG	1.84	<0.0001		
Valve surgery	1.81	0.0007		
CVA	1.74	0.005		
Bilirubin, higher	1.10[c]	<0.0001		
Creatinine, higher	1.16[d]	0.01		
BUN, higher			1.08[e]	0.001
RA pressure, higher	1.21[f]	0.0004		
Ascites	1.55	0.007		
Pulmonary hypertension			1.49	0.03
Intermacs:				
Level 1	2.87	<0.0001		
Level 2	1.84	0.001	1.35	0.01
Bridge to candidacy			1.38	0.009
Destination therapy			1.38	0.009
Pulsatile-flow LVAD			3.01	<0.0001
BiVAD	3.27	<0.0001		
Concomitant surgery	1.36	0.01		

BiVAD: biventricular assist device; BSA: body surface area; BUN: blood area nitrogen; CABG: coronary artery bypass grafting; CVA: cerebral vascular accident; HR: hazard ratio; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support;
LVAD: left ventricular assist device; RA: right atrial.
The hazard ratio denotes the increased risk: [a]from age 70 to 80; [b]of a 0.5-unit increase in BSA; [c]of a 1.0-unit increase in bilirubin; [d]of a 1.0-unit increase in creatinine; [e]of a 10-unit increase in BUN; and [f]of a 5.0-unit increase in RA pressure.

presented an increased risk for subsequent infection when used for long-term support compared to other device types, while, the HeartMate II had a decreased risk of infection compared to the other device types used in the series [60]. These findings were explained by the smaller driveline diameter found in the HeartMate II. Previously published studies comparing clinical outcomes between other types of continuous and pulsatile LVADs have not shown any differences in terms of infectious outcomes for short- or long-term support, suggesting that the flow mechanism itself does not play a role in the risk for infection [61, 62]. There are several suggestions how to minimize the driveline infection risk. These include, among others, antimicrobial device coating or device dipping in antimicrobial/antibiofilm solution (especially the driveline) or skull fixation for the transcutaneous power lead as reported by Westaby and associates [63, 64].

Furthermore, it appears that certain subgroups of patients (e.g., patients with critical cardiogenic shock) are at highest risk for infection [65]. Several authors reported that diabetes was associated with an increased risk of death regardless of the type of VAD infection [66–68].

Improvements in device design and better patient selection strategies, particularly aiming to identify individuals with genetic susceptibility to device-related infections, may further reduce this prevalent complication and increase outcomes in patients with MCSDs [65].

7.5. Right Heart Failure. Although excellent survival and outcomes were documented in patients, who receive LVADs not all patients progress smoothly, due to early right heart failure (RHF) and failure to thrive (FTT), despite hemodynamic improvements. The occurrence of RHF after LVAD placement has gained attention recently, because it is associated with significantly higher perioperative mortality and morbidity rates [69, 70]. Data from the INTERMACS shows that the need for BiVAD support is associated with marked reduction in survival [38]. The actuarial survival at 3, 6 and 12 months after device implantation was for LVAD patients 90, 86, and 80% and for BiVAD recipients 70, 62 and 55% respectively. A risk factor analysis for the entire patient population of primary MCS for the past 5 years revealed patients with severe right ventricular failure sufficient to

require BiVAD support as the most dominant early-mortality predictor (first 3 months, HR:3.27, $P < 0.0001$, Table 4). As soon as there are no established indications for BiVAD use, it is very important to identify patients, who are potentiall candidates for BiVAD support. Various predictors of post-LVAD RHF have been pruposed, yet few have been supported by multiple investigators [71, 72]. Fitzpatrick et al. developed a risk scoring system derived from analysis of 266 LVAD placements, including 5 clinical criteria: cardiac index $\leq$ 2.2 L/min·m^2, RV stroke work index $\leq$ 0.25 mmHg/L·m^2, serum creatinine $\geq$ 1.9 mg/dL, previous cardiac surgery and systolic blood pressure $\leq$ 96 mm Hg [73]. The subsequently constructed algorithm predicts the risk of RVAD in patients requiring LVAD therapy with >80% sensitivity and specificity [74]. Early RVAD implantation, based on the aforementioned algorithm, resulted in a significant higher survival to hospital discharge (51% versus 29%, $P < 0.05$), accompanied by higher survival at 1 year and long term.

8. Future Development

Second- and third-generation devices providing rotary continuous flow do not require volume compensation, but the energy transmission is still utilized percutaneously. The ideal MCSD is a fully implantable miniaturized device incorporating a transcoutaneously rechargeable battery. This is technically feasible through a transcutaneous energy transmission system (TETS). The main operation principle of the system consists of the inductive coupling of energy between an external primary and an internal subcutaneously placed secondary coil. An LVAD (LionHeart 2000 LVAD, Arrow International, Reading, Pa, USA) and a TAH (AbioCor TAH, Abiomed, Danvers, Mass, USA) are sufficiently supplied by TETS, but neither of these devices, due to other reasons not related to the TETS, is currently clinically applicable [75].

Future development of MCSD technology is being geared to the constantly changing requirements of the patients, who need or will need VAD support. As long the population of patients, who require circulatory support for end stage HF expands, future MCSDs have to be designed for long-term use, safe and less invasive implantation technique, minimizing in that way the associated morbidity.

The refinement of the clinical classification, including patient risk profiles like those proposed by the INTERMACS study and the increasing development and use of validated risk stratification models preceded further development of sophisticated therapeutic strategies. These consist in some cases of temporary circulatory support, known as bridge to bridge therapy, in order to "prepare" the patients for permanent LVAD support.

The Synergy Pocket Micro-Pump (CircuLite, Inc, Saddle Brook, NJ, USA) is the first miniaturized pump constructed to utilize partial circulatory support with a blood flow up to 4.25 L/min. It is implanted superficially in a "pacemaker-like" pocket through a small right thoracotomy. The device is currently undergoing clinical investigation at multiple centers in Europe with favourable initial results, aimed at achieving CE Mark [76]. The initial results of the clinical pilot study provide a proof of concept in at least a few cases, that temporary support provides important mid-term hemodynamic support in "less ill" patients. Additionally Circulite started to work on the development based on the Synergy Micro-Pump of a modified device for right heart support.

Another minimally invasive implantable assist device is the Symphony by Abiomed (Danvers, Mass). It is the first synchronized implantable heart pump timed to an ECG, providing in that way counter pulsation therapy through a vascular graft anastomosed to the subclavian artery. Symphony was developed to treat patients with moderate HF by improving coronary perfusion and cardiac output and aiming to stimulate the LV remodeling. The device is currently under clinical investigation (Symphony: The Implantable Counter Pulsation Device (CPD) Safety and Feasibility Trial; http://clinicaltrials.gov - ID NCT01543022).

The change in the role of LVAD support as DT away from "a last option"—treatment to in some cases an "elective" therapy is under investigation in currently running studies. The one is the Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients (ROADMAP) trial, which is a prospective, multicenter, nonrandomized, controlled, observational study to evaluate the effectiveness of the Thoratec HeartMate II Left Ventricular Assist System (LVAS) in comparison to Optimal Medical Management (OMM). The study involves ambulatory advanced HF patients not yet dependent on intravenous inotropic support, who are typically classified as INTERMACS profiles 4–6, within the existing FDA-approved indication for D T. It will include 200 patients at up to 50 sites, including experienced HeartMate II implant centers as well as community centers that care for a large volume of advanced heart failure patients. Apart from the primary above mentioned study-objective, secondary aims of the trial are to determine the accuracy of risk prediction models of a population appropriate for HeartMate II and to establish equipoise, to determine factors related to patient and physician decisions for HeartMate II, to evaluate the frequency of cross-over to other advanced HF therapies, to compare results of early versus delayed LVAD implantation, to determine the feasibility of enrolling target population and to use information to design follow-up studies; randomized trials, or additional observational studies and registries. The trial's estimated completion date is December 2015 (http://clinicaltrials.gov - ID# NCT01452802).

The second trial, the Randomized Evaluation of VAD Intervention before Inotropic Therapy (REVIVE-IT) trial, is a by the NHLBI-sponsored randomized trial of the HeartWare Ventricular Assist System (VAS) versus best medical treatment in patients with advanced HF and whose illness is not severe enough to qualify them for cardiac transplantation or permanent LVAD therapy according to current guidelines. The hypothesis of the study is that VAD therapy may improve both survival and quality of life in moderately advanced HF patients who are neither inotrope-dependent nor exercise-intolerant and have not yet developed serious complications. The pilot study will include 100 randomly assigned patients

in a 1:1 ratio to the HeartWare HVAD, or optimal medical therapy and the estimated completion date is January 2016 [31].

9. Conclusions

As the available donor hearts for transplantation remain relatively fixed and the number of patients with end stage HF is expanding, the need for long-term circulatory support is expected to increase. Meanwhile, MCS has evolved from a last resort life-saving therapy to a well established viable alternative for thousands of HF patients. The device technology has been evolving rapidly, with both frequent advancements to the particular device types and, more recently, a dramatic shift toward the use of newer generation continuous-flow miniaturized devices. In order to determine the optimal timing when the survival benefit of MCS would be greatest by the lowest surgical risk, further prospective studies are warranted to explore on the one the safety and effectiveness of MCS in less acutely ill HF patients and to develop validated risk stratification models for adequate patient selection on the other.

Conflict of Interests

The authors have no conflicts of interests to declare.

Author's Contribution

The first two authors have contributed equally.

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Research Article

Gender Differences in the Influence of Social Support on One-Year Changes in Functional Status in Older Patients with Heart Failure

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The purpose of this study was to determine the combined effects of gender and levels of social support on 1-year functional health outcomes in older persons diagnosed with heart failure (HF). Persons ≥ 65 years of age with an acute HF exacerbation (164 females; 271 males) were enrolled and followed for a year. Participants completed baseline and 12-month questionnaires containing clinical and demographic descriptive information and validated self-report measures of: (1) physical functioning (Medical Outcome Study [MOS] SF12 and Kansas City Cardiomyopathy Questionnaire [KCCQ]) and (2) social support (MOS- Social Support Survey). Women were more likely to be single, widowed or divorced, living alone and earning less annual income. At baseline, women reported significantly lower support and physical function scores. However, at 1 year there were no significant gender differences in the proportion of men or women who experienced clinically meaningful functional decline or death across the year of follow-up. In multivariable modeling, men with lower levels of social support were more likely to experience functional decline. This was not the case for women. Our findings suggest that gender-directed strategies to promote optimization of function for both men and women living with HF in their community are warranted.

1. Introduction

Heart failure (HF) is a common chronic cardiovascular disease that typically presents as episodes of acute exacerbation combined with periods of clinical stability. HF affects all ages, but in particular, is a disease of older adults. Due to its chronic nature, patients and their caregivers assume much of the daily management; thus, it is important to understand the influence of nonmedically related care factors, such as social support, on health outcomes and functionality. We know that the personal, clinical, and social profiles of persons with chronic conditions such as heart failure will vary. Older women are more likely to (a) have limited social supports, (b) be living on their own, with less financial resources, (c) not access formalized supports such as cardiac rehabilitation programs, (d) report poorer health-related quality of life, and (e) have worse physical function, in comparison to men [1–3]. Research evidence also suggests that poor levels of social support are associated with mortality and other adverse outcomes in persons with cardiac disease [4–8]. Social support is often contextualized as interpersonal transactions that provide functional support consisting of (a) emotional support (involving care, love, and empathy), (b) instrumental or tangible support (goods and services), (c) informational support (including guidance or feedback or environmental information), or (d) appraisal (information specifically related to self-evaluation and care) [2]. Some postulate that social support facilitates coping and adaption and moderates the psychological and physiological consequences of illness [9, 10].

Given that high levels of social support may promote psychological and physical well-being and good health behaviours, it is unclear whether gender differences and varying levels of social support or a combination of these factors influence functional well-being and other health outcomes for older persons with HF [11]. Therefore, the purpose of this study was to describe the effects of gender differences and social support on health outcomes, while controlling for personal demographics, disease severity, and comorbid conditions.

2. Methods

We conducted a prospective cohort study with one-year followup. The Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (Kingston, Ontario) reviewed and approved the study protocol.

2.1. Participant Sample. Potential participants were recruited from one tertiary teaching centre in Kingston, Ontario, and 3 community hospital corporations in the surrounding region. Recruitment was carried out between March 2003 and September 2007; followup continued until January 2009. Participants were included if they were aged 65 years and older and seen in the emergency department (ED) with a diagnosis of HF or HF-related complaint. The HF diagnosis was confirmed through chart review in accordance with the Framingham Criteria for Congestive Heart Failure [12]. Participants were excluded if they lived in such institutions as nursing homes, or long-term care facilities.

The study cohort consisted of 435 study participants who provided informed consent and completed baseline questionnaires. Given the observed gender distribution and loss to follow-up rate, our effective sample size achieves over 85% at a two-sided alpha = .05 to compare functional decline rates between genders if the true absolute difference is at least 10%. Furthermore, our effective sample size provides at least 80% power at alpha = .05 (two-sided) to test the association between social support and functional decline if a one standard deviation change in the social support subscale results in at least 10% difference in the proportion of patients who decline (regardless of outcome).

2.2. Data Collection Procedure. All consecutive ED discharge records were reviewed for potential participants who met inclusion criteria. Once informed consent was obtained, baseline information was collected either in hospital or obtained after discharge. Participants completed self-report questionnaires at baseline and 12 months in home and returned the package in a self-addressed envelope. If questionnaires were not returned at the designated time interval, the research coordinator contacted the participant and encouraged the participants to complete the questionnaire. In some cases, the participant provided questionnaire responses over the phone and the research coordinator completed the questionnaire. Data were entered into a secure computerized data base system maintained in the Nursing Research Unit at Kingston General Hospital, Kingston, Ontario. Data entry accuracy was verified by a second research associate. During the one-year follow-up period, survival status was determined through hospital records or through phone contact with family.

3. Measures

3.1. Primary Outcome: Physical Function. The primary outcome of interest was clinically important changes in physical function as related to (a) heart disease, measured by the physical limitation (PL) subscale score from the Kansas City Cardiomyopathy Questionnaire (KCCQ), or (b) overall health-related quality of life as measured by the physical component summary scale (PCS) of the SF-12 Health Survey.

The *Kansas City Cardiomyopathy Questionnaire (KCCQ)* is a disease-specific, 23-item questionnaire that quantifies the following domains: physical limitation, symptoms (frequency, severity, and recent change), social limitation, self-efficacy and knowledge, and quality of life. Scale scores are transformed to a 0 to 100 range by subtracting the lowest possible scale score, dividing by the range of the scale and multiplying by 100. This tool is a valid, reliable self-reported health status measure for patients with HF. Cronbach's alphas for each domain indicate high internal consistency, except for self-efficacy that has moderate internal consistency (.62) [13]. As we were most interested in physical function, we focused solely on the physical limitation (PL) score of the KCCQ. Based on the literature, we defined clinically important changes in PL as a 5-point change in score in either direction between baseline and 12 months [14, 15]. Participants were then classified accordingly: (1) improvement or maintenance of physical function, (2) decline in physical function, (3) death within the 12-month followup, (4) withdrawal from the study due to worsening illness, and (5) lost to followup/withdrawal for unknown reasons [14–16].

The physical component summary scale (PCS) of the SF-12 Health Survey was selected as a brief, patient-reported outcome for overall physical health status. The SF-12 is reliable and has been a validated tool used to measure self-reported generic functioning and well-being in numerous medical and surgical populations [17, 18]. Mean reliability coefficients are reported between .64 and .87 for the physical dimension. Using PCS scores at baseline and 12 months, a similar 5-level categorical outcome variable was created based on clinically significant changes. Based on the literature, we used a 2-point change in PCS to reflect a clinically significant change in function [19, 20]. Similar to the KCCQ-PL categorical classification, participants were classified into the 5 levels using the PCS change score.

3.2. Exposure Variable of Interest: Social Support. Social support was measured using the Medical Outcome Survey-Social Support Survey (MOS-SSS). The MOS-SSS is a 20-item self-report tool that measures four aspects of functional support including emotional/informational, tangible, affectionate, and positive social interaction [21]. Scores range from 0 to 100, with higher scores indicating higher levels of perceived support. Bennett and colleagues [2] used the MOS-SSS to measure social support to determine associations between support and health-related quality of life in 227 hospitalized HF patients. Mean overall scores (±SD) at baseline were 56 (±18.2) and 53 (±20.1) at 12 months, with a score of 76 indicating positive perceptions of support [2].

3.3. Personal Characteristics. Age, gender, income, educational level, and health habits were recorded at baseline by self-report and were used to describe the sample. Home supports such as living arrangements, housing arrangements,

and marital status were also collected, as well as health supports including access to a family physician, cardiologist/internist, details about who manages the HF, and use of HF resources.

3.4. Clinical Characteristics. Left ventricular ejection fraction (LVEF) of <40% was our primary measure of disease severity. This value was obtained from echocardiogram history during a chart review. As well, we determined to what extent participants met the Framingham Criteria for HF (major or minor). Other diseases that potentially influenced participants' functionality were identified using the Functional Comorbidity Index (FCI), a validated, self-reported tool used to identify 17 common comorbid conditions used to predict one's level of physical functional capacity [22, 23]. This tool has been validated on a cross-sectional database of 9,423 Canadian adults, using the SF-36 physical function subscale as the outcome measure [24].

4. Analysis

Data were analyzed using SPSS Version 17.0 software. All baseline and 12-month covariate and social support scales were described using standard descriptive statistics (means, standard deviation; frequencies and percentages). When 15% of any questionnaire data were not obtained, the survey data for that particular participant were considered missing. We determined the gender differences in personal and clinical variables and social support using the Chi-squared test for categorical variables and the t-test for normally distributed continuous variable scores. Logistic regression models were estimated for each subscale and overall social support score using a two-level functional outcome for each of the PL and PCS change scores: (1) maintained functional status or improved by the minimal clinically important difference and (2) died, lost to followup due to worsening illness or declined by the minimal clinically important difference. These models controlled for age and gender and were determined in the full sample and within each gender. The effect modification of gender on social support was determined through inclusion of an interaction term in each model.

The large number of participants lost to followup was addressed in two ways. First, we compared the baseline characteristics of those participants with complete 12-month data to those participants with incomplete data at 12 months, to determine if the groups were different. Secondly, we conducted a sensitivity analyses in which we compared the logistic regression model in 2 cohorts: (1) a cohort that did not include those participants that were lost to followup and (2) a cohort that included the loss to followup in the declined/died/too ill category. It should be noted that for some individuals we were able to categorize participants within the functional decline category, without questionnaire data, as they reported to the study coordinator their intent to withdraw due to worsening illness and decline. This sensitivity analysis allowed us to test the assumption that those participants lost to followup could be included in the declined/died/too ill adverse outcome group.

Table 1: Comparison of baseline characteristics of participants who completed 12-month questionnaires to those who were lost to followup or died.

	$n = 224$ Completers	$n = 211$ Noncompleters	P
Age			
Mean (SD)	77.5 (6.6)	78.7 (7.3)	.087
	n (%)	n (%)	
Gender			
Female	81 (36.2)	83 (39.3)	.495
Male	143 (63.3)	128 (60.7)	
Marital status			
Single/widowed/divorced	89 (39.7)	91 (43.1)	.472
Married/common-law	135 (60.3)	120 (56.9)	
Annual combined income			.067
≤ $40,000	131 (64,5)	124 (73.4)	
> $40,000	72 (35.5)	45 (26.6)	
LV ejection fraction			.399
≤40%	96 (51.6)	84 (47.2)	
>40%	90 (48.4)	94 (52.8)	
Comorbid conditions			.193
0–2 comorbidities	113 (57.1)	98 (50.5)	
>2 comorbidities	85 (42.9)	96 (49.5)	
Social support subscale scores	Mean (SD)	Mean (SD)	
Emotional/information	74.1 (26.7)	70.2 (27.7)	.130
Tangible	78.2 (26.9)	75.5 (31.7)	.334
Affectionate	81.7 (28.1)	79.4 (30.2)	.417
Positive social interaction	75.0 (30.1)	67.1 (33.5)	.012
Overall	76.0 (24.7)	71.7 (27.1)	.082
Functional scores			
KCCQ PL Score	52.4 (25.3)	46.6 (26.4)	.026
SF-12-PCS	30.3 (8.3)	29.7 (8.3)	.455

5. Results

Four hundred and thirty-five participants provided baseline information; 224 (52%) completed all or parts of the questionnaires at 12 months. Of the 435 who started, many eligible and consenting participants did not complete the study due to worsened illness ($n = 30$), death ($n = 54$), admission to assisted living facilities ($n = 4$), or other unknown reasons ($n = 123$). There were few significant differences in baseline characteristics between those who completed the study and those who were lost to followup (Table 1). Participants who completed the study were more likely to report higher KCCQ physical limitation scores than those who did not complete the follow-up questionnaires. Because of these results, we considered the lost-to-followup group as potentially different from those who completed, and we therefore included a separate classification for this group in relevant analyses.

Baseline participant characteristics of the total sample (completers and noncompleters combined) are described in Tables 2(a) and 2(b). The study cohort included 62% males aged 65–99 years. Female participants were more likely to

be single, widowed or divorced, living alone, and earning less annual income ($P < .01$). At baseline, men were more likely to have a LVEF ≤ 40% ($P < .01$). There were no sex differences in both the major and minor criteria for heart failure (Table 2(b)). The number of comorbid conditions were not significantly different between genders but were ranked differently with women reporting higher prevalence of asthma, angina, visual impairment, and depression and men reporting degenerative disc disease, myocardial infarction, diabetes, lung disease, and hearing impairment.

5.1. Gender Differences in Social Support. Table 3 presents the mean subscale and overall social support scores at baseline. Mean (SD) scores for females ranged from 67.3 (31.7) to 80.9 (27.0), with affectionate support being the highest subscale score. Mean (SD) scores for males ranged from 72.3 (32.9) to 80.4 (30.4), with tangible and affectionate support being the highest subscale scores. Women tended to report lower scores overall, but only tangible support was significantly lower ($P < .01$).

5.2. Functional Outcomes. Table 4 presents the KCCQ-PL and SF-12-PCS scores and the 5-level categorized variables (i.e., improved, declined, etc.), by gender. Women, in comparison to men, reported significantly lower mean PL scores (±SD) at baseline (28.7 ± 7.6 versus 30.8 ± 8.6; $P = .01$) and 12 months (30.3 ± 7.5 versus 34.2 ± 10.4; $P < .01$). Similarly, women reported significantly lower mean PCS scores (±SD) than men at baseline (45.4 ± 24.2 versus 52.1 ± 26.8; $P = .01$) and 12 months (51.0 ± 24.4 versus 61.5 ± 27.9; $P < .01$). There were no significant gender differences in the 5-level outcome variables for disease-specific and generic health outcomes at 12 months. Across the 12-month period, maintenance or improvement of functioning, as measured with either the PCS or PL, occurred in approximately 1/3 of the sample.

5.3. Social Support and Adverse Functional Outcomes. Tables 5 and 6 assess if social support predicts decline in functional outcomes after adjusting for age and sex. Overall, none of the social support domains was significantly associated with a decline in the SF-12-PCS; however, increasing levels of informational support, social and overall support were weakly and significantly associated with less decline in KCCQ-PL changes. Several sex-specific associations were identified. Men were less likely to experience disease-related functional decline with higher levels of affection support (OR .75, 95% CI .59, .96). When using the generic PCS functional outcome score as the dependent variable, levels of emotional/informational support (OR .70; 95% CI: .52, .93), affectionate support (OR .76; 95% CI: .59, .98), and positive social interaction (OR .78; 95% CI: .61, 1.00) in men were significantly associated with functional decline. There was an effect modification of gender on social support; males with high social support scores were less likely to report a functional adverse outcome, when using the PCS score as the basis for functional decline.

Sensitivity analysis, in which participants lost to followup were grouped with the functional declining group, resulted in similar findings to the aforementioned logistic regression models. Male participants were less likely to experience functional decline with more support; this was not the case for women.

6. Discussion

The purpose of this study was to describe the independent and combined effects of gender and social support on one-year functional status in older persons with HF. Women consistently reported lower levels of functioning, but over the course of the year, following an exacerbation of their illness, both women and men experienced similar levels of functional maintenance or decline. The effect of social support on maintenance of function was limited to men, where men who perceived high levels of support experienced better outcomes.

The personal, social, and clinical characteristics of participants in this cohort study were similar to those of both older persons in general and to those with HF. Women, in comparison to men, were more likely to be single and on their own, with less income. A portrait of Seniors in Canada prepared by Health Canada in 2002 reported that nearly 75% of Canadian senior men compared to 41% of Canadian senior women were married, and 46% of senior women were widowed compared to 13% of senior men. Our study grouped single and divorced individuals with those who were widowed, unlike Health Canada that compared only widowed to those who were married. This difference in grouping is likely the reason for the comparatively higher percentage of participants in our nonmarried group and is of particular relevance to this study as we were exploring the availability of support regardless of reason. Also, as expected, men were more likely to have lower left ventricular ejection fraction. Generally men, regardless of age, are more likely than women to develop systolic dysfunction and typically have lower LVEF, more severe disease, and shorter survival times [25, 26] and, consequently, may require intense and shorter duration of support to optimize their functioning within the context of their progressive disease. However, since survival times are lengthier for women, they are living longer with HF than men and, therefore, may require more long-term support.

6.1. Gender and Functional Status. Similar to other studies, our findings show that, compared to male participants, female participants reported significantly lower physical functioning, as measured by both disease-specific and generic measures and all participants reported low levels of functioning with only about one third of the sample maintaining or improving their functional level over the course of the year. In a cross-sectional, correlation study, Heo and colleagues [27] used the Duke Activity Status Index, a self-report tool, to assess the functional status of 122 HF patients. Out of a possible score ranging from 0 to 58, women reported lower functional status scores than men; mean scores (±SD) were 10.2 (±10.3) and 14.5 (±12.7), respectively ($P = .04$) [19]. Riedinger et al. [28] also demonstrated comparable results in a cross-sectional

Table 2: (a) Baseline characteristics of participants (completers and noncompleters). (b) Clinical characteristics of participants (completers and noncompleters).

(a)

	Women $n = 164$	Men $n = 271$	P
Age			
(mean, SD)	78.1 (7.0)	77.8 (7.0)	.109
	n (%)	n (%)	
Marital status			
Single/widowed/divorced	108 (65.9)	72 (26.6)	<.001
Married/common-law	56 (34.1)	199 (73.4)	
Highest educational level			
Completed high school	127 (77.4)	210 (77.5)	.907
Completed postsecondary	33 (20.1)	53 (19.6)	
Missing	4 (2.4)	8 (3.0)	
Current living arrangements			
Living alone	75 (45.7)	53 (19.6)	<.001
Living with others	88 (53.7)	218 (80.4)	
Missing	1 (.6)	—	
Geographical distance from centre			
≤50 km	151 (92.1)	239 (88.2)	.198
>50 km	13 (7.9)	32 (11.8)	
Annual combined income			<.001
≤ $40,000	111 (67.7)	144 (53.1)	
> $40,000	28 (17.1)	89 (38.8)	
Missing	25 (15.2)	38 (14.0)	
Use of other resources to manage HF[a]			.168
No	117 (71.3)	176 (64.9)	
Yes	47 (28.7)	95 (35.1)	

[a]Use of resources to manage HF includes pamphlets, books, and/or the Internet. a: resources include books, pamphlets, and the Internet.

(b)

	Women $n = 164$	Men $n = 271$	P
Major criteria			
Paroxysmal nocturnal dyspnea	37 (22.8)	71 (26.6)	.385
Orthopnea	62 (38.0)	110 (41.4)	.496
Elevated jugular venous pressure	69 (42.9)	125 (47.3)	.367
Pulmonary rales	129 (79.6)	208 (72.9)	.673
Third heart sound	10 (6.1)	22 (8.3)	.402
Cardiomegaly	76 (46.6)	139 (52.3)	.258
Minor criteria			
Pulmonary edema on chest radiograph	76 (47.2)	107 (40.4)	.167
Peripheral edema	88 (54.3)	166 (62.2)	.109
Night cough	37 (23.1)	57 (21.4)	.683
Dyspnea on exertion	124 (77.0)	213 (80.4)	.408
Hepatomegaly	3 (1.9)	9 (3.4)	.359
Pleural effusion	60 (36.8)	104 (39.1)	.636
Heart rate > 120	18 (11.3)	34 (12.8)	.646
Wgt loss > 4.5 kg in 5 days in response to diuretics	3 (1.9)	10 (3.8)	
Framingham Criteria met[a]			.219
No	19 (11.6)	22 (8.1)	
Yes	143 (87.2)	248 (91.5)	
Missing	2 (1.2)	1 (.4)	

(b) Continued.

	Women $n = 164$	Men $n = 271$	P
LV ejection fraction			.006
≤40%	54 (32.9)	126 (46.5)	
>40%	81 (49.4)	103 (38.0)	
Missing	29 (17.7)	42 (15.5)	
Comorbid conditions[b]			.068
0–2 comorbidities	72 (43.9)	139 (51.3)	
>2 comorbidities	78 (47.6)	103 (38.0)	
Missing	14 (8.5)	29 (10.7)	

[a]Diagnosis of CHF requires the simultaneous presence of at least 2 major criteria or 1 major in conjunction with 2 minor criteria which is outlined by the Framingham Criteria for congestive heart failure.
[b]The functional comorbidity index is an 18-item list of diagnoses associated with functional impairment. Median number of comorbidities for both females and males was 2.0.

Table 3: Gender differences in baseline social support scores.

	N	Baseline Mean (SD)	P
Emotional/information			.108
Women	163	69.5 (27.4)	
Men	265	73.9 (27.0)	
Tangible			.002
Women	162	71.3 (31.0)	
Men	266	80.3 (27.7)	
Affectionate support			.844
Women	161	80.9 (27.0)	
Men	265	80.4 (30.4)	
Positive social interaction			.057
Women	154	67.3 (31.7)	
Men	264	73.4 (32.0)	
Additional			.144
Women	158	67.6 (31.5)	
Men	263	72.3 (32.9)	
Overall			.068
Women	163	71.0 (24.6)	
Men	269	75.7 (26.6)	

study of 1382 age and LVEF-matched HF patients [28]. When controlling for NYHA class, age, and LVEF, women had lower mean scores (SD) than men in measures of functional status including basic activities of daily living (ADLs) ($P < .01$), intermediate ADLs ($P < .01$), and perceived general health ($P < .01$).

Qualitative research in the field has given valuable insight into patients' experiences with HF and its subsequent effects on their functional well-being [29, 30]. Bosworth et al. [29] identified 5 themes from a cross-sectional qualitative study of focus groups of male patients with HF. Symptoms, role loss, affective responses, coping, and social support were all areas patients identified as being negatively affected by their HF and consequently decreased their QOL. Similar themes were identified by Heo and colleagues [27] in an interview-based qualitative study of men and women living with HF. Participants identified personal and material supports from their significant others as having an important impact on their quality of life. Findings from our study suggest that both men and women experience considerable physical burden living with HF and that women report more limitations than men.

6.2. Gender and Maintenance of Functional Well-Being. Despite the gender differences in functional levels, no differences existed in functional maintenance or decline over one year. These results are consistent with other studies. After adjusting for disease severity, although women rated QOL worse than men in a number of domains, Riedinger et al. [28] found no significant differences between genders with respect to QOL changes. Possible explanations for our findings include (1) women started with a lower functional score, perhaps less severe disease (i.e., higher LV function) with greater opportunity for improvement and less capacity for decline, whereas men started with higher scores, more severe disease and less capacity for improvement and more capacity for decline; (2) individuals who completed the 12-month data collection period were more likely to be functioning at a higher level to begin with and, as reflected in the reported 12-month scores, were more likely to maintain or improve functioning regardless of gender; (3) the disease progression of HF is difficult to influence, and so functional decline inevitably occurs. As reflected in the physical limitation scores of the KCCQ, more participants experienced disease-related functional decline versus overall functional decline in the physical component score of the SF-12. Unfortunately, the long-term prognosis for HF is poor, with 5-year survival rates for men and women being <40%; thus, functional decline, especially which relates directly to the disease and disease impact, is expected.

6.3. Social Support and Functional Outcomes. Levels of social support at baseline had little impact on 12-month disease-specific functional outcomes; however, social support influenced 12-month generic functional outcomes. Men were significantly less likely to report a decline in general health or

Table 4: Baseline and 12-month functional scores and functional outcomes by gender.

	Women		Men		P
	n	Mean (SD)	n	Mean (SD)	
SF-12-PCS					
Baseline	160	28.7 (7.6)	263	30.8 (8.6)	.012
12 months	81	30.3 (7.5)	143	34.2 (10.4)	.003
KCCQ-PL					
Baseline	149	45.4 (24.2)	254	52.1 (26.8)	.012
12 months	80	51.0 (24.4)	137	61.5 (27.9)	.006
Functional outcomes	n	n (%)	n	n (%)	
SF-12-PCS change	164		271		.078
Maintained/improved		54 (32.9)		99 (36.5)	
Declined		13 (7.9)		20 (7.4)	
Died		12 (7.3)		42 (15.5)	
Too ill to participate		12 (7.3)		18 (6.6)	
LTFU/Missing		73 (44.5)		92 (33.9)	
KCQ-PL change	164		271		.121
Maintained/improved		46 (28.0)		72 (26.6)	
Declined		26 (15.9)		47 (17.3)	
Died		12 (7.3)		42 (15.5)	
Too ill to participate		12 (7.3)		16 (5.9)	
LTFU/Missing		68 (41.5)		94 (34.7)	

LTFU: loss to followup.

physical function, to drop out of the study due to increased illness, or to die within one year of an acute HF exacerbation when they perceived high levels of emotional/informational, affectionate, and positive social interactional support. No significant moderating effect of gender on social support and adverse outcomes were seen in women in this cohort. This is somewhat contradictory to findings reported in the literature. Similar to our study, previous literature supports the finding that increased social support has positive associations with health outcomes, however, the specifics of who benefits, and how they benefit differs between studies. Bennett et al. [2] found that the likelihood of a HF-related admission decreased by 10% for each unit increase in tangible support ($P = .05$) for both male and female participants of all ages [2]. In another study of older persons (≥65 years) with HF, absence of emotional support significantly increased the odds of cardiovascular events, defined as death or hospitalization due to cardiovascular disease, within one year of HF-related admission (OR 3.2; 95% CI: 1.4, 7.8) [5]. These associations were only found in women. Social support seems to exert an influence on selected functional outcomes and/or cardiovascular events, but the direction and strength of this influence is not clear, nor is it consistent between genders. Our study contributes novel findings about the influence of support on functionally related outcomes and the nature of the interactions between gender and support on these outcomes. Further investigation is needed to be able to identify the type and amount of support needed to assist both men and women in managing their HF.

7. Strengths and Limitations

A particular strength of this study is the detailed data captured at baseline and followup on patients with HF, a population that is usually difficult to recruit and engage in study participation. As well, we employed standardized questionnaires, allowing for comparisons across reported studies. Self-report measures are valid measures of person's perception of their illness and are related to clinical outcomes [1]. Furthermore, where possible, we ensured that participants were able to complete the self-report questionnaires. However, we do acknowledge that questionnaire completion may have been compromised by the effect of age and/or heart failure on cognitive and other abilities. Another strength of our study is that our outcome of interest was based on clinically important functional changes. Results are therefore more clinically meaningful and relevant to practice. A 52% completion rate limits the result validity; 20% of the baseline participants did not complete one-year followup due to death, or illness which emphasizes the fragility of this population. We addressed patient attrition to some extent in the sensitivity analysis. Patient attrition likely diluted relationships found between outcomes and support; however, trends found for both PL and PCS-based outcomes

Table 5: Influence of social support on decline in SF-12-PCS.

	Missing data excluded		Missing data included	
	n	OR (95% CI)	*n*	OR (95% CI)
Emotional/ informational	217		428	
Overall		.99 (.98,1.02)		.99 (.99,1.00)
Female specific		1.12 (.79,1.59)		.97 (.76,1.24)
Male specific		**.70 (.52,.93)**		**.79 (.64,.96)**
Sex interaction†		**1.58 (1.01,2.49)**		1.24 (.90,1.70)
Tangible	219		428	
Overall		1.00 (.99,1.01)		1.00 (.99,1.00)
Female specific		1.22 (.86,1.72)		1.06 (.86,1.32)
Male specific		.80 (.59,1.06)		.86 (.71,1.04)
Sex interaction†		1.52 (.97,2.40)		1.24 (.93,1.65)
Affectionate	219		426	
Overall		1.00 (.99,1.01)		1.00 (.99,1.00)
Female specific		1.37 (.91,2.05)		1.18 (.93,1.50)
Male specific		**.76 (.59,0.98)**		**.82 (.69,.99)**
Sex interaction†		**1.78 (1.10,2.87)**		**1.43 (1.06,1.94)**
Positive social interaction	216		418	
All		1.00 (1.00,1.01)		.99 (.99,1.01)
Female		1.20 (.86,1.69)		.99 (.80,1.22)
Male		**.78 (.61,1.00)**		**.82 (.69,.97)**
Interaction		**1.53 (1.01,2.32)**		1.20 (.91,1.58)
Overall	212		432	
Overall		1.00 (.99,1.01)		1.00 (.98,1.01)
Female specific		1.28 (.84,1.95)		1.04 (.80,1.36)
Male specific		.76 (.57,1.02)		**.81 (.66,1.00)**
Sex interaction†		**1.68 (1.01,2.80)**		1.28 (.92,1.79)

*OR (95% CI): odds ratios with 95% confidence intervals estimated by multiple logistic regression adjusting for age and sex. Each social support domain is modelled separately. The ORs estimate the multiplicative increase in the odds of a MCID decline in PCS per 20-point increase in the social support score. An OR < 1 indicates a protective effect of social support. ORs statistically significant at $P < .05$ are in bold font.

†The sex interaction is the female-specific OR divided by the male-specific OR. An interaction OR > 1 indicates a greater protective effect of social support for males than females.

Table 6: Influence of social support on decline in KCCQ PL score.

	Missing data excluded		Missing data included	
	n	OR (95% CI)	*n*	OR (95% CI)
Emotional/ informational	269		428	
Overall		1.00 (.99,1.01)		**.99 (.98,1.00)**
Female specific		1.08 (.78,1.50)		.91 (.71,1.16)
Male specific		.83 (.66,1.05)		**.78 (.65,.98)**
Sex interaction†		1.28 (.86,1.90)		1.14 (.83,1.57)
Tangible	269		428	
Overall		1.00 (.99,1.01)		.99 (.99,1.00)
Female specific		0.99 (.75,1.31)		.95 (.77,1.18)
Male specific		0.95 (.73,1.23)		.82 (.67,1.00)
Sex interaction†		1.03 (.71,1.51)		1.16 (.87,1.56)
Affectionate	265		426	
Overall		0.99 (.99,1.00)		1.00 (.99,1.01)
Female specific		1.00 (.73,1.37)		1.08 (.85,1.37)
Male specific		**.75 (.59, .96)**		**.80 (.66, .97)**
Sex interaction†		1.31 (.88,1.95)		1.34 (.99,1.82)
Positive social interaction	260		418	
Overall		.99 (.99,1.00)		**.99 (.99,1.00)**
Female specific		.99 (.75,1.29)		.98 (.79,1.21)
Male specific		.82 (.73,1.10)		.79 (.66,.94)
Sex interaction†		1.20 (.85,1.70)		1.24 (.94,1.64)
Overall	271		432	
Overall		1.00 (.99,1.01)		**.99 (.98,.99)**
Female specific		.97 (.69,1.37)		.96 (.74,1.25)
Male specific		.87 (.67,1.12)		**.74 (.59,.92)**
Sex interaction†		1.11 (.73,1.71)		1.30 (.92,1.84)

*OR (95% CI): odds ratios with 95% confidence intervals estimated by multiple logistic regression adjusting for age and sex. Each social support domain is modelled separately. The ORs estimate the multiplicative increase in the odds of a MCID decline in PL per 20-point increase in the social support score. An OR < 1 indicates a protective effect of social support. ORs statistically significant at $P < .05$ are in bold font.

†The sex interaction is the female specific OR divided by the male-specific OR. An interaction OR > 1 indicates a greater protective effect of social support for males than females.

were similar to that which we saw when the lost-to-followup group was excluded from the analysis. This would suggest that the relationships we found in a relatively stable HF sample could be an underestimate of the pattern in a more compromised sample.

8. Conclusions

This study reports on the gender differences in social support and its corresponding relationship to both general and disease-specific adverse functional outcomes in the HF population. The results indicate that older women report less available social support and worse physical functioning both in relation to their general health and HF. In addition, the relationship between social support and adverse functional outcomes is seemingly moderated by gender in this cohort, with men less likely to experience a decline in their health outcomes with more perceived social support. This was not the case for women. These results also show that although women report less social support than men, social support may have less of a direct influence on health outcomes and physical function and that other supportive resources such as self-care capacity and availability of formal health care supports may have a stronger impact on physical function for women. Our findings support the need for gender-sensitive care for older HF patients and further research into the complex interactions between gender, supportive resources, and functional maintenance within the context of a chronic disabling condition such as HF.

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Review Article

Does Depression Impact Cognitive Impairment in Patients with Heart Failure?

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Prevalence studies have noted the cooccurrence of cognitive decline and depression in persons with heart failure. Cognitive impairment is associated with significant mortality and deteriorated quality of life, likely due to impairments in memory and executive function, which impact a patient's ability to understand and comply with prescribed treatment plans. This is especially true in complex diseases such as heart failure. Evidence from literature supports the possibility of a pathophysiological relationship between cognitive impairment, depression, and heart failure. Yet, very few studies have sought to investigate this relationship. This paper reviews current literature on the association between depression and cognitive impairment in persons with heart failure and explores possible mechanisms explaining this complex triad.

1. Introduction

Heart failure (HF) is a complex clinical syndrome characterized by a combination of symptoms and signs including shortness of breath, fatigue, edema as well as functional and structural cardiac abnormalities [1]. HF is estimated to affect about 3.9% (95% CI 3.0, 4.7) of the population aged 55 years or older [2] and 6.7% (95% CI 5.6, 7.9) of those aged 65–84 years [3]. Other studies have shown HF prevalence to increase with age, from as low as 0.9% of individuals aged less than 65 years up to 17.4% in those aged 85 years and older [4]. The burden of HF will likely continue to increase as the population ages. In fact, HF is a leading cause of hospital readmission and mortality [5]. Though less frequently examined, decline in cognitive functioning is common in patients with HF. A systematic review and meta-analysis including over 700 patients with congestive HF showed a significant reduction in attention and memory scores in patients compared to controls suggesting that cognitive impairment (CogI) may be associated with HF [6]. Further, a systematic review including 2937 patients and 14,848 controls showed a substantial (62%) increased risk of CogI in patients with HF [7].

Research into this cooccurrence has found CogI to impart an increased risk of mortality in those with HF (adjusted relative risk (RR) = 4.9; 95% CI 2.9, 8.3) [8]. To further the burden in HF patients, many researchers have found an increased prevalence of depression in this group. Data pooled from 36 studies showed prevalence rate of depression in HF to vary from 19.3% when depression is defined based on diagnostic interviews to 33.6% for depression based on questionnaires [9]. Despite the different methods of defining depression, at minimum one in five patients with HF is affected with depression. Consistent with these findings, the prevalence of depression in patients with HF and atrial fibrillation using the Beck Depression Inventory (BDI) questionnaire was 32%. In this study depression score significantly predicted subsequent cardiovascular mortality (adjusted hazard ratio (HR) = 1.57; 95% CI 1.20, 2.07) [10].

While a relationship between depression and CogI is recognized [11–13], few studies have directly examined this association in persons with HF. We review current literature

on CogI and HF, with a focus on the contribution of depression to CogI, in HF.

2. Cognitive Impairment and Heart Failure

2.1. The Impact of Cognitive Impairment in HF Patients. CogI is commonly associated with HF, especially at an older age, with significant impact on activities of daily living and worsening HF prognosis [14, 15]. Studies have demonstrated that more than half of the patients with HF showed cognitive decline when tested using the Mini Mental State Examination (MMSE), a commonly used tool to screen for signs of CogI in older adults [16–18].

A systematic review and meta-analysis of 22 studies investigating the association between CogI and HF reported the prevalence of CogI to range from 25% to 74% in patients with HF [7]. The overall meta-analysis results from 2937 HF patients, and 14,848 controls showed a 62% increase in CogI in HF compared to controls (odds ratio (OR) = 1.62; 95% CI 1.48, 1.79; $P < 0.0001$) [7], demonstrating a clear cross-sectional association between CogI and HF. It is important to note that CogI does not necessarily indicate dementia. The Diagnostic and Statistical Manual (DSM) defines dementia as a global impairment in memory, abstract thinking, judgment, and higher executive functions that are often associated with changes in personality and social functioning as well as other psychiatric or psychotic symptoms [19]. Many patients who have CogI do not fulfill the diagnostic criteria for dementia. CogI is relatively common in the elderly, with one study reporting that 17% of individuals over the age of 65 have experienced CogI without dementia [20]. These results hint toward the possibility that CogI and HF in older individuals are a function of older age. However, this is unlikely given the numerous studies that included similar age "non-HF" control groups where the prevalence of CogI was less than that observed for the patients with HF (see previously mentioned). Furthermore, there have been studies on younger patients with HF, which also demonstrated significant CogI. One such study of 62 patients with an average age of 44.7 years (SD = 10.6 years) found patients to be impaired on half of the neuropsychological measures. Patients were most impaired on neuropsychological test aspects of reasoning and concept formation, attention, and psychomotor skills [21]. Nonetheless, the pivotal role of age in increasing risk of CogI in HF should not be denied; in this younger group, older patients performed worse on neurocognitive testing and had a poorer prognosis of HF [21].

As mentioned earlier, CogI is associated with increased mortality and deteriorated quality of life. CogI can lead to poor health related self-care [22], which can contribute to morbidity and mortality in patients with chronic HF. Health related self-care is a complex process that requires individuals to actively engage in monitoring their health and disease status and treatment aspects [22]. The presence of CogI in HF is associated with poor health-related self-care [22], which could compromise a patient's ability to understand and follow treatment plans and may lead to frequent hospitalizations in patients with HF. One study explored the precipitating factors for hospitalization in predominantly African American patients with HF and found poor compliance with the treatment of HF to be a great precipitator for hospitalization (64%) [23]. A systematic review of treatment compliance in patients with HF found the rate of poor compliance with treatment to range from 21% to 64% in different populations. Compliance rates tended to vary with education, social support, and self-confidence to maintain health status [24].

2.2. Mechanisms and Risk Factors of Cognitive Impairment in Heart Failure. A number of mechanisms responsible for CogI in HF have been reviewed [17, 25], which highlight the contribution of several risk factors such as stroke, cardioembolic abnormalities, and cerebral hypoperfusion [5]. In the following we discuss key mechanisms proposed to explain the association between CogI and HF.

2.2.1. Brain Structural Changes due to Hypoperfusion or Infarction. A possible mechanism behind the association of CogI and HF is cerebral vascular hypoperfusion that may occur after HF due to ischemia or stroke [17]. However in the presence of pathological phenomenon such as HF, certain physiological processes attempt to maintain the cerebral blood flow (CBF) homeostasis. For example, in HF where there is a reduced cardiac output, the blood is shifted away from skeletal muscles to the brain so that adequate CBF can be maintained [17, 25, 26]. However as cardiac output continues to drop in HF, the ability to maintain CBF can be compromised; a 30% reduction in CBF can lead to symptoms associated with cerebral hypoperfusion [25] that may eventually contribute to CogI. Gruhn and colleagues used Xe-133 inhalation single-photon emission computed tomography to find a 31% reduced CBF in patients with HF compared to controls [26]. Building on the work of Gruhn et al., Alves and colleagues found the specific brain regions affected by reduced CBF in HF. They report regional CBF reductions bilaterally in the precuneus and cuneus regions as well as in the right lateral temporoparietal cortex and posterior cingulate gyrus. Interestingly, this group found CogI (measured using Cambridge Mental Disorders of the Elderly Examination) to be correlated with regional CBF reductions in the posterior cingulate cortex and precuneus region, highlighting reduced CBF in specific cerebral regions as a potential link between HF and CogI [27].

In addition to compensation for lowered cardiac output, cerebrovascular reactivity, the capacity for vasodilation in the brain, is also an important mechanism in maintaining CBF [28]. Cerebrovascular reactivity may be affected in HF as seen in studies investigating patients with HF compared to controls and demonstrating significant impairment in cerebrovascular reactivity in HF patients [28]. This impairment in cerebrovascular reactivity may further contribute to hypoperfusion and CogI in HF.

Cerebral hypoperfusion may also lead to CogI through cerebral white matter degeneration (leukoaraiosis) [29]. Leukoaraiosis results in demyelination, loss of glial cells,

axon damage, and spongiosis [29]. The progression of such degenerative changes impacts different aspects of cognitive function including immediate and delayed memory, processing speed, higher executive functions, as well as global cognition [30].

2.2.2. Shared Risk Factors with Cardiovascular Diseases. In addition to specific neuronal mechanisms, it is known that patients with endometabolic disorders, including hypertension, diabetes, and hyperlipidemia, as well as conditions like small vessels disease, are at a higher risk of cardiovascular disease such as stroke. CogI may develop as a result of multiple risk factors and disorders in such individuals [17, 31–35].

2.2.3. Iatrogenic Effects on CogI in HF. Investigations into anticholinergic side effects of medication sometimes prescribed to patients with hypertension and congestive HF have found that some of these therapeutic agents are associated with CogI [36]. A longitudinal study of 13,004 participants assessed the risk of CogI with use of anticholinergic medication. CogI was determined using the MMSE. The study observed a positive dose-response relationship between anticholinergic medication use and MMSE score [36], although the change in MMSE score was relatively small and perhaps the benefits of using such medications outweigh the risks of CogI. Furthermore, medications, such as beta-blockers, prescribed in HF may contribute to neuropsychiatric disorders and worsening CogI [37]. Nonetheless the use of medications in HF and any other disease status is based on risk benefit analysis, and in the case of HF, such medications could be lifesavers, and their use is not only justified but also essential.

Overall our literature search showed that there are multiple and complex factors that may influence cognitive function in HF in addition; because patients who suffer from HF may suffer from other cardiovascular disease that have shared risk factors that can contribute to CogI, it is difficult to discern the underlying pathophysiological relationship uniquely attributed to CogI in HF.

3. Depression, Cognitive Impairment, and Heart Failure

Depression is a common psychiatric disorder characterized by the presence of low mood or loss of interests associated with several other features that are present almost daily for at least two weeks and results in impaired function [19]. Depression is prevalent in patients with HF as well as those that are cognitively impaired. This is especially true in chronically ill older patients with HF [38], in whom the prevalence of depression is greater than hospitalized older patients with other non-HF diseases (36.5% versus 17%) [39]. Meta-analysis of 27 studies reported the prevalence of depression in HF patients to range from 9% to 60% depending on the use of "liberal" or "conservative" definitions of depression. A measure was considered "conservative" if it was ascertained through an interview, review of medical charts for a formal diagnosis, or the use of screening questionnaires explicitly looking for moderate-to-severe depression [9]. The study also found that the prevalence of depression was positively correlated with poorer prognosis of HF [9]. Depression is commonly found in persons with CogI. In a systematic review of literature on HF and CogI including 22 studies, depressive symptoms were associated with CogI in 50% of the included studies [7]. Further, studies showed that depression may have a negative impact on neuropsychological tests results [7], providing an impetus for more investigation into the role of depression in HF-associated CogI.

A possible explanation of the role of depression in HF may be evident through structural brain abnormalities reported with depression in patients with HF. Studies using structural brain MRIs have attempted to find an association between structural brain lesions and depression. Greenwald and colleagues (2001) used MRI studies to explore the role of hypertension and cerebral white matter lesions and subcortical hyperintensities in depression. The authors compared depressed individuals (depression was defined based on DSM-III-R criteria) with hypertension to normotensive controls, hypertensive controls, and normotensive depressed patients. The authors found significant differences between depressed individuals with hypertension compared to controls with hypertension (deep white matter lesions rating percent distribution of 30% versus 9%; subcortical grey matter hyperintensity rating percent distribution 10% versus 0%) and depressed individuals with hypertension to depressed without hypertension (deep white matter lesions rating percent distribution of 30% versus 17%; subcortical grey matter hyperintensity percent distribution of 10% versus 0%) [40]. Another study found ischemia as the cause of white matter hyperintensities in all patients with depression [41]. These studies support a big role of cerebrovascular changes in depression that may also lead to CogI in susceptible individuals. These studies however failed to show a causative effect or the direction of association between these structural brain changes and depression.

The impact of depression on HF can also be seen through environmental and behavioral factors. Individuals with depression show poor compliance to healthy behaviours and engage in additional risks, such as smoking, sedentary behaviour, poor diet, and substance abuse, which may lead to increasing the risks of cardiovascular disease, CogI, or worsening existing conditions [9, 42, 43].

Depression in persons with CogI is marked by abnormalities on neuropsychological tests [44] including impairments in memory, attention, and executive function, such as problem solving (for a review see [45]). Patients with major depressive disorder continue to show deficits in attention and executive function even after remission [46]. A longitudinal study of 436 women found depressive symptoms to predict the occurrence of impairment in cognitive testing including episodic, immediate, and delayed memory (measured using Hopkins Verbal Learning Test immediate recall (HVLT-Imm) and delayed recall (HVLT-del)), psychomotor speed (measured using Trail Making Test (TMT)-A), and executive functioning (measured using TMT-B) [47], thus strengthening the evidence for a consistent association between

depression and CogI. Additionally, in a study of 14,089 participants, Pullicino and colleagues studied the relationship between HF and CogI. HF was characterized using self-reported orthopnea and paroxysmal nocturnal dyspnea (PND), depression was measured using the Center for Epidemiological Studies-Depression (CES-D-4) scale, and CogI was assessed using a six-item test derived from MMSE [48]. The authors reported that participants with a highly probable diagnosis of HF had a 1.51 (unadjusted OR) (95% CI 1.15, 1.96) times greater chance of having CogI than participants without HF. Similarly, those with depressive symptoms had a 1.66 (CI 1.38, 2.01) times greater likelihood of being cognitively impaired than those without depression [48]. Interestingly, when the correlation between probable HF and CogI was adjusted for comorbidities and depression, the OR became insignificant (1.25; 95% CI 0.94, 1.67). This might be due to a stronger relationship between depression and CogI or simply because HF, CogI, and depression were based on self-reported symptoms and not a clinically determined diagnosis. Such limitations are understandable in the context of large sample size. Nonetheless, this large study provides valuable data on the association between depression, CogI, and HF. Mechanistic and longitudinal studies may assist in unraveling this complex relationship.

To our knowledge, only Garcia and colleagues have explored both depression and CogI in patients with HF [44]. The authors administered ten neuropsychological tests to 116 HF patients to assess global cognitive function, attention and executive function, memory, language, and motor functioning. The Beck Depression Inventory II (BDI-II) was used to measure depression. Approximately one in five of HF patients scored positively on BDI II (a score of 14 or higher) [44]. Depression was found to predict CogI on executive function, memory, language, motor function, and global cognitive functioning following adjustment for sex, hypertension, and cardiac fitness. However, when additional demographic variables were added to the model, the association between depression and global cognitive functioning became insignificant. The added demographic variables in the full model were not explained [44].

Overall, the current literature supports the presence of an association among depression, cognitive dysfunction, and HF. In the next section we will explain potential mechanisms behind the association among depression, CogI, and HF. Figure 1 presents a schematic demonstration of the relationships discussed thus far between the three conditions.

3.1. Neural Mechanisms. With the use of neuroimaging techniques, specific brain regions have been investigated for their role in depression. Evidence from literature suggests that depression is associated with an increased occurrence of white matter hyperintensities (WHI) [45]. Sheline and colleagues used MRIs to explore brain regions with WHI in depressed patients. Compared to controls, the depressed group had a greater occurrence of WHI in the right and left superior longitudinal fasciculi, the frontooccipital fasciculus, and the left uncinate fasciculus [49]. The group also found both white and grey matter volume to be correlated with some form of CogI [49]. Other studies have also reported an association between hippocampal volume and CogI in individuals with depression [50].

These findings of cerebral structural changes in depression and CogI, taken with evidence that HF contributes to white matter hyperintensities and whole brain grey matter reductions in cortical and subcortical regions [51–53], suggest that both depression and CogI are a result of underlying structural brain changes caused by HF. However it is not clear from these studies whether depression or CogI predated HF given the shared mechanisms and risk factors. The question arises: does depression cause CogI in patients with vascular pathologies in general or worsen existing CogI as a result of HF? At this point, it is difficult to answer these questions since we do not yet have enough mechanistic or longitudinal studies to ascertain a cause and effect relationship. Additionally, as illustrated in the diagram and the plethora of potential mechanisms described, there can be several pathways underlying depression and CogI observed in patients with HF, and discerning a cause and effect relationship in the context of the multiplicity of pathways is akin to "finding a needle in haystack." In order to answer these questions, future studies should longitudinally compare persons with HF and baseline depression to HF patients without depression while controlling for other vascular, endometabolic, and inflammatory pathologies. Despite the need for such studies, they may pose feasibility challenges such as sample size given the need to adjust for multiple factors, duration of followup, attrition rate, and cost of conducting such studies. A key challenge in current studies is the use of various tools and definitions for the diagnosis of depression and CogI, which limits comparability between studies. This study of heterogeneity also makes performing well-conducted systematic review and meta-analysis exceptionally challenging.

3.2. Neurohormones. Hormones such as cortisol are known to be associated with depression and cognitive function. Elevated cortisol level was reported in current and remitted depression [54, 55] as well as nonsuppression by dexamethasone using dexamethasone suppression tests (DSTs) (for a review see [56]). Prolonged exposure to elevated cortisol levels has shown to reduce hippocampal volume in depression, which has adverse effects on verbal memory [57–59]. Although this relationship is inconsistently reported [60], a randomized controlled trial of high dose cortisol (160 mg/day) compared to low dose (40 mg/day) given to subjects for 4 days demonstrated a negative impact on verbal memory in the high cortisol dose group that was reversible [61]. Similarly, Kirschbaum and colleagues conducted two studies to investigate the relationship between cortisol and cognition. In the first study, participants were asked to take the Trier Social Stress Test. They were then given declarative memory tasks. They were also sampled for saliva to ascertain cortisol levels. The first study found a negative relationship between stress-induced cortisol level and declarative memory. In the second study, participants were assigned to a placebo group or cortisol group. The cortisol group showed

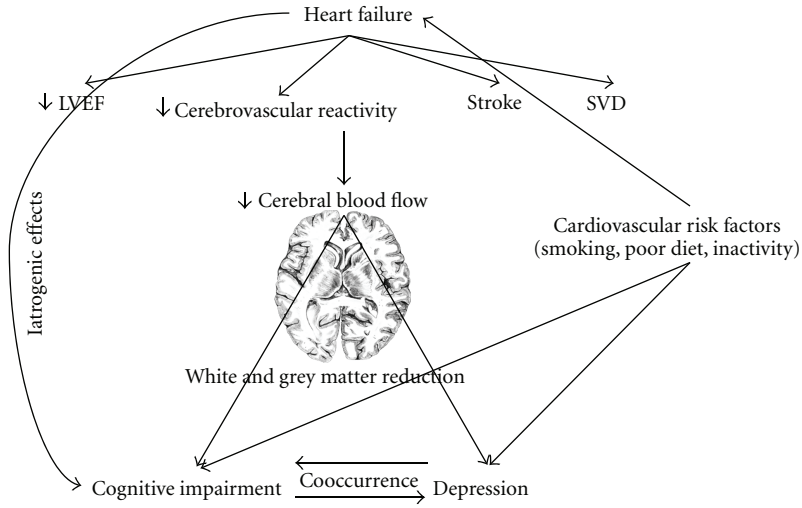

Figure 1: Relationship between CogI, depression, and HF. LVEF2: left ventricular ejection fraction; SVD: small vessels disease.

impaired performance in the declarative memory and spatial thinking tasks compared to the placebo group [62].

The effect of cortisol may also be important in HF. One study measured serum levels of cortisol and aldosterone in 294 patients with chronic HF [63] and found levels of cortisol to be elevated in HF. In addition, the authors used regression analysis to determine that cortisol and aldosterone predict increased mortality in HF (HR of highest versus lowest tertile for cortisol was 2.72 and aldosterone was 2.19). Additionally, patients with elevated cortisol and aldosterone had approximately a threefold greater risk of dying compared to patients who had median levels of both hormones. Another study, by Yamaji and colleagues, found serum cortisol to predict cardiac events in those with HF [64]. These studies although performed in HF or depression only samples may help to explain the role of cortisol and hypothalamic pituitary axis in the complex triad of depression, CogI, and HF with cortisol impacting each of these conditions. Other hormones such as atrial natriuretic peptide, adrenaline, noradrenaline, and thyroid hormone have a role in HF [65–70], and this role may extend to depression and CogI [71–74]; however these additional mechanisms are beyond the scope of this paper.

3.3. Inflammation. Emerging research in the field of inflammation and chronic diseases has shed light on the important role of cytokines in the pathogenesis of HF, depression, and CogI [75]. Elevated levels of proinflammatory cytokines, specifically IL-6, TNF-α, as well as C-reactive protein, seem to have a broad role in HF, depression, and CogI. Kubota and colleagues found elevated TNF-α and IL-6 in people with HF [76], while other studies reported similar findings in patients with depression and HF [77]. These elevated levels could relate to the HF process rather than depression in this study. But this concern was clarified by further studies of these inflammatory markers where these markers were raised in those with depression and HF compared to nondepressed with HF [78]. Similar findings have been reported in CogI [51–53]. Interestingly, one of the studies delved a bit into analysis of cytokines by sex and found that males with mild CogI had elevated serum amyloid A and C-reactive protein, while females had elevated TNF-α [79]. The role of sex is an additional factor which warrants further study in the context of depression, CogI, and HF.

Inflammatory cytokines and their role in depression and heart disease have been thoroughly reviewed [75, 80, 81]. It should be noted that depression is associated with dysregulation of immune response. A study of cellular immune activity in patients with congestive HF and depression (established using the Hamilton Rating Scale) reported that a lower IFN-gamma/IL-10 ratio was related to higher depressive symptoms. Interestingly, no difference in plasma IL-6 levels between those with high versus low depression scores [82] was seen in this study. These findings add further to the complexity of association between inflammatory markers and depression and HF.

A plausible explanation of the effect of proinflammatory cytokines in depression has been provided [83]. Briefly, increased levels of proinflammatory cytokines may reduce tryptophan, an important precursor for neurotransmitters such as serotonin with an essential role in depression. In addition, these cytokines may also affect hypothalamic-pituitary axis (HPA) leading to dysregulation of cortisol response known to impact depression, cognition, and HF as described earlier [83].

While it is interesting that the same cytokines are elevated in depression, CogI, and HF, this commonality does not confer a causative relationship. Depression in HF is associated with increased mortality (OR at 3 months = 2.5, OR at 1 year = 2.23 [84]) which could be due to the harmful effects of cytokines on the heart. Pasic, Levy, and Sullivan in their review propose that cytokines, such as TNF-α, mediate sepsis-induced alterations which ultimately reduce contractility and promote left-ventricular dysfunction among other adverse outcomes [75]. Reduced contractility and worsened HF could lead to poor cerebral perfusion ultimately causing CogI. However, the opposite

may also be true: cytokines elevated as a result of HF could play some role in the development of depression or CogI or both. Most studies reviewed to date have evaluated a binary association between depression and HF or between CogI and HF or depression and CogI. Future initiatives should seek to prospectively ascertain whether there is a causal pathway between the three conditions.

4. Treatment

The association between CogI and depression in HF is complicated, and the conditions can cooccur through many pathways. In the context of HF, hypoperfusion can cause structural changes in the brain which can lead to depression or CogI or both. Or elevated cytokines can decrease serotonin production resulting in depression and disrupt HPA regulation leading to CogI. Sometimes the HPA axis is activated in tandem with the immune system; therefore a combination of these pathways or existence of multiple pathways can also occur. If depression affects an individual's risk of either becoming cognitively impaired or worsens existing cognitive dysfunction, treatment for depression should alleviate some burden of CogI. This theory was tested in a trial of 42 patients with current depression diagnosed according to the criteria of DSM-IV-TR [85]. While some improvement in CogI did occur with antidepressant therapy, the depressed group continued to perform poorly on tests of complex tasks which required problem solving and strategic thinking [85]. Additionally, treating for depression is associated with a high rate of relapse in the presence of CogI [45]. The relapse could result from an inability to comply with depression treatment. There has been some research into whether treatments for HF improve CogI. Studies looking at heart and pacemaker transplantation to improve cardiac function have yielded inconclusive results [21, 86–88]. The discouraging results from attempts to treat CogI and depression in HF are indicative of a failure to understand all the possible interactions and should provide an impetus to continue work in this field to truly discern the cause and effect relationships.

5. Future Directions

A key challenge confronting investigators is to discern the causal mechanisms underlying the relationship between cognition, depression, and HF. What has made this endeavor particularly difficult is the possibility of several pathways that affect cognition. To make matters even more complicated, there are factors such as cognitive reserve that make CogI more easily apparent in some compared to others. Brain reserve capacity is the ability to tolerate greater cell loss due to the existence of neuronal redundancy [42]. These individuals take longer than those without such neuronal redundancy to exhibit clinical symptoms. This paper has highlighted several key questions: does depression worsen existing CogI in those with HF? Can treatment for depression change the onset of CogI in this group, and what mechanisms lead to the coexistence of these three conditions? It is very important that in the clinical care of HF patients, medical professionals be aware of the high rate of cooccurrence between HF, CogI, and depression. Health professionals treating for HF should screen for cognitive function as well as depression. Future studies should also seek to investigate neuropsychiatric rehabilitation for CogI and depression in patients with HF in improving heart function as well as reducing rates of hospitalization and mortality from HF.

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Research Article

CRT-D Therapy in Patients with Decompensated NYHA Class-Four CHF

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Background. ACC-HRS Guidelines for Cardiac Resynchronization Therapy ICD implantation (CRT-D) do not include patients with advanced nonambulatory NYHA class-four CHF due to an expectation of limited survival. There is little data available from these large multicenter randomized studies to support or refute this claim. *Purpose*. We evaluated the outcomes of patients with advanced nonambulatory NYHA class-four CHF who received CRT-D devices as an attempt to improve the clinical status and promote hospital discharge. *Methods*. Sixteen (of our six hundred and seventy CRT-D patients) were classified as advanced nonambulatory NYHA Class four inotrope/vasodilator/diuretic-dependent patients. These patients were analyzed retrospectively for weaning success to oral medications, hospital discharge, hemodynamic stability, and survival over eighteen months. *Results*. Thirteen of sixteen patients were discharged to home within two weeks of implantation. The survival to hospital discharge, as well as at six, twelve, and eighteen months was positive (ninety-four percent, seventy-five percent, sixty-nine percent, sixty-nine percent, resp.). The groups showed significant improvements in systolic blood pressure, renal function, left ventricular ejection fraction, and CHF class. *Conclusion*. CRT-D in advanced nonambulatory NYHA four patients proved feasible and beneficial. These findings suggest that the strategy merits further study.

1. Background

Chronic heart failure is a debilitating disease that continues to place an inordinate burden on the healthcare system. Management and care for the nearly five million heart failure patients in the United States alone was estimated to cost thirty-nine point two billion dollars for the year of 2010 [1, 2]. Heart failure is responsible for over one million admissions to American hospitals every year and is associated with an increased mortality [1, 2].

There have been significant contributions to the armamentarium available to physicians to help treat this disease. In addition to neurohormonal agents, cardiac resynchronization therapy (CRT) has been shown to be an effective tool in management of systolic congestive heart failure. CRT has been most effective in improving heart failure class, quality of life, left ventricular mechanics, and in reducing heart failure hospitalizations and overall mortality in patients with severe left ventricular dysfunction and a wide QRS [3, 4]. It is recognized that the beneficial impact of CRT stems from the ability of combined right ventricular and left ventricular pacing to restore both inter- and intraventricular synchrony towards normal. The result is an improvement in left ventricular geometry and mechanical function, contractility, and performance [5]. Reduction in left ventricular size and mitral regurgitation (when present) is also important for many patients [5]. Patients who benefit most are those with ejection fractions less than thirty five percent, a wide QRS (greater than one hundred twenty milliseconds), and with NYHA CHF class-three and ambulatory class-four CHF

status [3, 4]. More recent studies have also demonstrated significant benefit for patients with mild NYHA class-one and class-two CHF in the presence of a left bundle branch block QRS (greater than or equal to one hundred and thirty milliseconds) and impaired left ventricular systolic function (ejection fraction less than or equal to thirty percent) [6, 7].

All of the large CRT-D trials have excluded patients on intravenous vasoactive and/or inotropic drugs [6–9]. The reasoning behind this exclusion was the presumption that these patients were too ill to benefit from CRT-D therapy given an expectedly short survival [1]. Thus, there remains a significant knowledge gap in the possible application of CRT-D therapy to patients with advanced, nonambulatory NYHA class-four CHF. We undertook this study to better assess the feasibility and outcome of CRT-D in patients with advanced nonambulatory NYHA class-four heart failure.

2. Methods

This was a retrospective study based on a single tertiary care center's experience. The Hartford Hospital Arrhythmia Service Database followed a total of fourteen hundred and thirty-four patients. The database included six hundred and seventy patients who had received CRT-D devices from December of two thousands through March of two thousand and nine. Sixteen patients were identified from these six hundred and seventy as having been on intravenous inotropes, and/or vasodilators in combination with intravenous diuretics at the time of CRT-D implantation. These charts were then manually reviewed to define the patient's clinical status at the time of CRT-D implantation. Inability to wean from these intravenous drugs was confirmed and patients were further characterized (Table 1). Their clinical courses were followed in hospital using the inpatient record, and over 18 months (or until death) every three months through the Hartford Hospital ICD clinic database.

Weaning from intravenous medications was attempted on a daily basis. "Weaning success" was defined by transition from intravenous inotropes, vasodilators, and/or diuretics to oral medications, permitting patients to be discharged from the intensive care unit to an ambulatory cardiac bed. These patients were then followed for the next 18 months. Failure to maintain blood pressure, oxygen saturation, renal function (BUN, and creatinine), or recurrent heart failure symptoms requiring a return to previously effective intravenous medication doses was regarded at "failure to wean." "Failure to wean" patients were not eligible for transfer to a usual monitored floor bed or for discharge to home.

Patients who qualified for a CRT-D device by having a left ventricular ejection fraction of less than thirty five percent and a QRS of greater than one hundred and twenty milliseconds were offered a CRT-D device despite their nonambulatory advanced NYHA class-four status. They were aware that there were minimal data to support the use of such a device in patients with advanced CHF, but there was hope that left ventricular mechanics might improve, advancing their care to ambulatory status. Patients with systolic blood pressures of greater than ninety mmHg with an oxygen saturation of greater than ninety-five percent (with or without supplemental oxygen support) and creatinines of less than two point five milligrams percent were offered the procedure as part of our clinical practice.

Table 1: Baseline demographics.

Characteristics	Values
Total patients	16 (100%)
Male	10 (63%)
Age (years)	68.1 ± 13.1
LVEF (%)	14.7 ± 5.9
LVEDd (cm)	6.0 ± 0.7
QRS (ms)	164.1 ± 28.2
Ischemic cardiomyopathy	11 (69%)
Impaired renal function (SCr > 1.5 mg/dL)	10 (63%)
Beta blockers	10 (63%)
Ace-inhibitors	10 (63%)
Angiotensin receptor blockers	2 (12%)
Intravenous diuretics	16 (100%)
Intravenous inotropes	13 (81%)
Dobutamine	12 (75%)
Milrinone	7 (44%)
Dopamine	1 (6%)
Nesiritide	3 (19%)

All patients were in normal rhythm and received an atrial lead. All leads were implanted transvenously. The left ventricular lead was positioned within a lateral branch of the coronary sinus. The optimal position was chosen after performing biplane coronary sinus venography and by choosing a position with the greatest temporal separation measured from the onset of the QRS to the intrinsicoid deflection of the unipolar left ventricular electrocardiogram (Figure 1). The right ventricular ICD/pacing lead was positioned in the right ventricular apex or apical septum in all patients. All patients remained in the coronary care unit until the intravenous medications could be withdrawn. Inotropes and vasodilators were progressively reduced and then discontinued as the hemodynamic status of the patient permitted. Intravenous diuretics were changed to an equivalent oral (total milligram) dose after implantation. Patients were transferred from the coronary care unit to a monitored bed as soon as continuous blood pressure recording and intubation were not required, and intravenous medications could be transitioned to oral medications. Oral medications were optimized prior to hospital discharge. Patients returned for clinical assessment and device followup clinic at two weeks, one month, and every three months thereafter. All visits were recorded in our ICD database.

3. Results

The study population had a predominance of men in their late sixties with ischemic cardiomyopathies. The mean ejection fraction was fourteen point seven percent, and the mean QRS duration was one hundred and sixty-four milliseconds. All patients had a left bundle branch block QRS. A significant

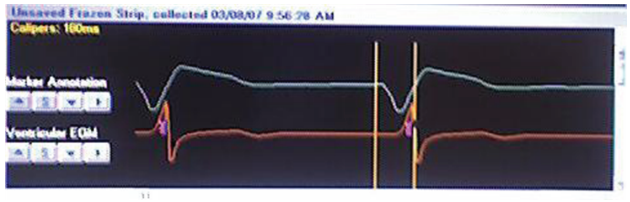

Figure 1: Cardiac electrogram measuring electrical separation (ES). Vertical lines measure ES from the beginning of the native QRS to the intrinsicoid deflection of the unipolar left ventricular electrogram in its final position (ES = 160 ms).

Table 2: Results.

Clinical variables	Pre-CRT	Post-CRT	*P* value
Systolic BP (mmHg)	92.6 ± 11.2	110.0 ± 15.8	0.0013*
Serum Cr (mg/dL)	2.12 ± 0.96	1.49 ± 0.64	0.04*
BUN (mg/dL)	55.9 ± 23.1	37.6 ± 12.8	0.011*
Dependence on Inotropes/diuretics	16 (100%)	2 (11%)	0.001*
NYHA FC	4.0 ± 0.0	3.3 ± 0.87	0.014*
Hospital stay (Days)	14.3 ± 13.3	11.4 ± 9.16	0.48

sixty-three percent of patients had concomitant renal disease (Table 1).

Survival to hospital discharge was seen in ninety-four percent of the patients (fifteen of sixteen). The single predischarge death was due to significant comorbidities including acute renal failure and ventricular tachycardia. Two patients could not be weaned from intravenous inotropes and diuretics and were transferred to hospice goals of care. Thirteen of the sixteen patients (eighty-one percent) were successfully transitioned to oral medications and discharged to home in eleven point four days (plus or minus nine point four days, Table 2). Twelve patients (seventy-five percent) were alive at six months, and eleven patients (sixty-nine percent) were alive and living at home at both twelve and eighteen months after implantation. Five of the sixteen patients (thirty-one percent) received appropriate therapy for sustained ventricular tachycardia during followup. There were also significant improvements in the hemodynamic profile and patient status: systolic blood pressure increased 17.4 millimeters of mercury ($P = 0.013$), creatinine declined 0.63 milligrams per deciliter ($P = 0.04$); BUN declined 18.3 per deciliter ($P = 0.01$, and New York Heart Association Functional Class improved by 0.7 ($P = 0.014$, Table 2).

4. Discussion

Multiple CRT trials have shown improvement in left ventricular mechanics, congestive heart failure symptoms, patient quality of life, and survival in patients with advanced NYHA class-three and ambulatory class-four heart failure. Patients included in these studies also had significant left ventricular dysfunction (LVEF less than or equal to thirty-five percent) and a wide QRS [3, 4]. Similar benefits have more recently been shown in patients with less severe (NYHA class-one and two) CHF, a left ventricular ejection fraction of less than thirty percent, with a left bundle branch block pattern QRS of greater than one thirty milliseconds [6, 10]. In MADIT CRT, the single criterion of a left bundle branch block QRS separated those who gleaned benefit from CRT-D from those who did not benefit [6]. It was reasoned that left bundle branch QRS morphology is a marker in many patients for left ventricular dys-synchrony. Dys-synchrony, when present, may be rectified by resynchronization, which can improve cardiac performance and clinical status. Patients with decompensated NYHA class-four CHF have been excluded from these major studies despite having a wide QRS and a left ventricular ejection fraction of less than or equal to thirty-five percent [1, 6, 10].

A few small studies have evaluated CRT as a possible weaning/salvage therapy in this very ill population. They have demonstrated the possibility of CRT support enabling successful weaning from intravenous inotropes in hospitalized NYHA class-four CHF patients [11–14]. The largest study to date included twenty inotrope-dependent patients who were treated with CRT devices as an attempt to provide additional hemodynamic support for weaning [11]. Three of these patients had CRT-D devices. The authors report a remarkable clinical recovery after CRT with cessation of catecholamine support in all twenty patients. There was a six-month survival of eighty percent, with a fifty-five percent eighteen-month survival [11].

Our study differs from this study by Milliez and colleagues. Our sixty-nine percent eighteen month survival stands out against the fifty-five percent eighteenmonth survival reported by Milliez et al. [11] It is possible that the Milliez study patients were more ill than our patients. Three of the deaths in the Milliez study were sudden and occurred in patients without an ICD, while all of our patients received CRT-D devices. Five of our sixteen patients (thirty-one percent) received appropriate (antitachycardia pacing and/or shock) therapy for sustained ventricular tachycardia during followup. It is possible that some of the deaths seen in the Milliez study were due to cardiac arrhythmias in patients who had not received CRTD devices.

Studies performed at other centers have demonstrated favorable outcomes for inotrope-dependent patients who were treated with cardiac resynchronization pacing therapy enabling weaning from intravenous inotropes to oral medications [11–14]. Our study agrees with the results of these other small reports and expands on the potential usefulness and effectiveness of CRT-D implantation in this population.

5. Conclusion

Our study reports on the survivability and effectiveness of CRT-D therapy in a patient population typically excluded from CRT-D studies. Ninety-four percent of patients were discharged from hospital, while eighty percent were discharged to home care, and sixty-nine percent of patients remained alive and home at both twelve and eighteen months after implantation. It is significant that almost one-third (thirty-one percent) of our patients received appropriate therapy for sustained ventricular tachycardia from their

devices during the eighteen-month followup. These results emphasize the effectiveness of CRT-D therapy in improving hemodynamics and permitting a transition from an intravenous dependent hospital-bound status, to an ambulatory dischargeable status in some patients. Survival in out patients was sixty nine percent at eighteen months.

Despite the small size and retrospective nature of our study, we hope that this will serve as a catalyst for larger randomized controlled studies to better understand the role of CRTD therapy in patients with decompensated advanced NYHA class-four CHF.

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Review Article

Depression in Patients with Cardiovascular Disease

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It has been widely suggested that depression negatively affects patients with cardiovascular disease. There are several pathophysiological mechanisms as well as behavioral processes linking depression and cardiac events. Improvements in nursing and medical care have prolonged survival of this patient population; however, this beneficial outcome has led to increased prevalence of depression. Since mortality rates in chronic heart failure patients remain extremely high, it might be as equally important to screen for depression and there are several valid and reliable screening tools that healthcare personnel could easily employ to identify patients at greater risk. Consultation should be provided by a multidisciplinary team, consisting of cardiologists, psychiatrists, and hospital or community nurses so as to carefully plan, execute, and evaluate medical intervention and implement lifestyle changes. We aim to systematically review the existing knowledge regarding current definitions, prognostic implications, pathophysiological mechanisms, and current and future treatment options in patients with depression and cardiovascular disease, specifically those with heart failure.

1. Introduction

During the past decades, researchers have documented a significant negative impact of depression on various outcomes in patients with cardiovascular disease (CVD). Apart from the cardiac disease itself it is not uncommon that these patients experience the burden of another condition such as depression, often contributing to the worsening of their somatic illness, thus, entrapping them in a possible vicious circle.

Minor forms of depression have been reported in 20% of patients after an acute myocardial infarction (AMI), while rates of major depression vary between 16% and 45% of patients after an AMI [1, 2]. Approximately two-fifths of patients with angina suffer from depression [3]. The incidence increases in patients following coronary artery bypass graft surgery [4–6]. Depressive symptoms appear to be associated with severe functional limitation in patients with chronic heart failure (CHF) after discharge [7], and functional limitation may be viewed as a behavioural factor

affecting the progression of the disease. However, it is not clear whether there is a distinct link between depression and cardiac events as well as their chronological sequence. Some authors have proposed that depression may be both an antecedent and a consequence in patients with CHF [8–10].

Huffman et al. reported that depression is associated with a 60% increase in the onset of cardiac diseases in a population of healthy men and women [11]. In another study, Carney et al. found that patients with major depressive disorder (MDD) who had undergone cardiac catheterization were more likely to have acute cardiovascular or ischemic events compared to non-MDD patients (77.7% versus 34.9%, relative risk 2.2, $P < 0.02$) [1]. Finally, a clinical diagnosis of depression has been found to be a strong predictor of death in patients after a recent myocardial infarction (MI) [12].

We aim to systematically review the existing knowledge regarding current definitions, prognostic implications, pathophysiological mechanisms, and current and future treatment options in patients with depression and cardiovascular disease.

2. Unveiling Depression

2.1. Definition. According to the fourth revised edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [13], there are several criteria that need to be met in order to diagnose a single episode of major depression. The patient has to present with either depressed mood or loss of interest or pleasure during an at least two-week period along with another four additionalsymptoms: fatigue or loss of energy; diminished ability to think/concentrate; insomnia or hypersomnia; feelings of worthlessness, excessive or inappropriate guilt; recurrent thoughts of death or suicidal ideation; psychomotor agitation or retardation; significant weight loss or weight gain. The above should not be due to substance use or a medical condition. Significant distress or impairment should be present and should not be accompanied by a bereavement. In Table 1 all DSM-IV-TR criteria are presented along with the corresponding criteria according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [14]. However, the severity of depression varies and there are also other similar forms such as atypical depression or dysthymia that should not be overlooked.

It should also be noted that caution must be exercised in this particular population, since symptoms such as fatigue, dyspnea, exhaustion, and disturbed sleep occur commonly and may be confused for depressive symptoms.

2.2. Diagnosing Depression. In caseswhen depression is suspected in patients with cardiovascular diseases, a referral to a psychiatric clinician should be made. It could be argued that the formal diagnosis of depression should be performed by appropriately trained clinicians; nevertheless, it is widely apparent in the literature that many patients are dealt with as depressed based on numerous diagnostic tools that are utilized by nonpsychiatric clinicians.

Several instruments have been constructed and have been broadlyused: the Beck Depression Inventory (BDI) and BDI-II [15, 16], the Mental Health Diagnostic Interview Schedule [17], the Symptom CheckList-90 Revised (SCL-90-R) [18], the Hospital Anxiety and Depression Scale (HADS) [19], the Schedule for Clinical Assessment in Neuropsychiatry [20], the Medical Outcome Study-Depression (MOS-D) [21], the Zung Self-Rating Depression Scale [22], the Geriatric Depression Scale (GDS) [23], the Centre for Epidemiologic Studies-Depression Scale (CES-D) [24], the General Health Questionnaire (GHQ) [25], the Hamilton Rating Scale for Depression (HAM-D) [26], the Montgomery and Asberg Depression Rating Scale (MADRS) [27], and the Cardiac Depression Scale (CDS) [28].

These instruments largely address the need to assess whether patients suffer from depression when conducting epidemiological studies. Since it would be difficult, time consuming, and costly to conduct structured clinical interviews, especially in large scale trials, the above scales and questionnaires are being used successfully in everyday clinical practice.

3. Physiologic Mechanisms and Elements of Pathophysiology

Several potential physiological mechanisms linking depression and adverse cardiac events have been proposed and they are eloquently presented in the literature [11, 29]. Among these mechanisms there are increased platelet activity and aggregation, inflammation, heart rhythm disturbances, elevated levels of catecholamines, and endothelial dysfunction.

3.1. Platelet Activity and Aggregation. Serotonin seems to play a role in clot formation, since it can bind to 5-hydroxytryptamine (5-HT) receptors on platelets, causing the release of precoagulant factors, thus promoting platelet aggregation [30]. Also, Laghrissi-Thode et al. demonstrated that increased platelet activation is present in depressed patients regardless of the presence of coronary heart disease (CHD) [31]. It is also known that activated platelets enhance progression of atherosclerotic plaques and depressed patients have been shown to have increased levels of platelet induced chemotactic and mitogenic factors, as discussed in detail by Nemeroff et al. [32, 33].

3.2. Inflammation. Depression has been found to be associated with elevated levels of interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α). These proinflammatory cytokines play a key role in the process of atherosclerosis [34]. Also, it has been shown that levels of C-reactive protein (CRP), IL-6, and TNF-α were higher in patients with coronary artery disease (CAD) and were linked to an increased risk of adverse cardiac events and mortality [35–37]. These findings have been supported by another meta-analysis, which concluded that this pattern existed in both clinical and community-based samples as well as in the studies which used either clinical interviews or self-report measures of depression [38]. Also, cytokines may also influence, in turn,

Table 1: ICD-10 (version 2010) and DSM-IV-TR criteria for depression.

Depressive episode according to ICD-10	Major depressive disorder according to DSM-IV-TR
Generally, the patient should present for at least 2 weeks with the following.	(1) At least one of the two main symptoms and five or more of the additional symptoms present during the same 2-week period
(a) Main symptoms	(a) Main symptoms
(i) Lowering of mood	(i) Depressed mood
(ii) Reduction of energy	(ii) Loss of interest or pleasure
(iii) Decrease in activity	(b) Additional symptoms
(b) Additional symptoms	Fatigue or loss of energy
(i) Reduced capacity for enjoyment, interest and concentration	Decreased ability to think or concentrate, indecisiveness
(ii) Marked tiredness after even minimum effort	Insomnia or hypersomnia
(iii) Disturbed sleep	Feelings of worthlessness or excessive, inappropriate guilt
(iv) Diminished appetite	Recurrent thoughts of death or recurrent suicidal ideation
(v) Reduced self-esteem and self-confidence	Psychomotor agitation or retardation
(vi) Ideas of guilt or worthlessness	Significant weight loss or weight gain
	(2) Symptoms do not meet the criteria for a mixed episode
(c) Somatic symptoms (i) Loss of interest and pleasurable feelings (ii) Waking in the morning several hours before the usual time (iii) Depression is worst in the morning (iv) Marked psychomotor retardation, agitation (v) Loss of appetite (vi) Weight loss (vii) Loss of libido	(3) Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas (4) Symptoms are not due to direct physiological effects of a substance (i.e., drug or medication abuse) or medical condition (i.e., hypothyroidism) (5) Symptoms are not better accounted for by a bereavement (e.g., after the loss of a loved one); they persist for more than 2 months or are characterized by marked functional imparment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.
Mild depressive episode: Two or three of the above symptoms are usually present. The patient is usually distressed by these but will probably be able to continue with most activities	
Moderate depressive episode: Four or more of the above symptoms are usually present and the patient is likely to have great difficulty in continuing with ordinary activities.	
Severe depressive episode without psychotic symptoms: An episode of depression in which several of the above symptoms are marked and distressing, typically loss of self-esteem and ideas of worthlessness or guilt. Suicidal thoughts and acts are common and a number of "somatic" symptoms are usually present.	

Adopted with permission from the American Psychiatric Association and the WHO (ID: 87085).

the release of reactive oxygen and nitrogen species by microglia and astrocytes which may promote oxidative stress as well as enhance inflammatory pathways within the brain and such effects in morphology have also been found in patients with major depression [39].

3.3. Heart Rhythm Disturbances. In a recent meta-analysis, low heart beat rate observed in post-MI patients with depression has been associated with higher mortality, possibly because of the risk of enhancing the incidence of arrhythmias in this population [40]. Depression has also been found to be related with longer QT intervals, decreased baroreflex cardiac control and ventricular arrhythmias [41]. Lower heart rate variability (HRV) may indicate decreased parasympathetic tone, which allows sympathetic nerves to provide stimulation and possibly provoke ventricular arrhythmias.

3.4. Catecholamines. Veith et al. provided evidence that norepinephrine (NE) was significantly elevated into vascular and extravascular compartments of patients with depression compared to controls while both had similar plasma NE clearance rates, suggesting increased sympathetic nervous system activity [42]. Catecholamines cause vasoconstriction, arrhythmia, increased blood pressure, and platelet activation, all of which are contributing factors of cardiovascular instability [33].

3.5. Endothelial Dysfunction. The impaired endothelial function, usually appearing with aging, has been suggested as a contributing factor to the development, progression, and clinical manifestations of atherosclerosis [43]. Elevated symptoms of depression compared to nondepression in CHD patients have been associated with diminished flow-mediated dilation of the brachial artery, an index of endothelial function that is related to coronary vessel dysfunction [44]. Impaired nitric oxide (NO) function, a marker of endothelial dysfunction, has been reported in depressed patients [45]. NO is involved in several physiological activities including inflammation and vasodilation and impaired NO production can lead to vascular thrombosis and atherosclerosis [46].

4. Behavioral Mechanisms

It can be argued that patients with depression may exercise less and live a sedentary life, are less compliant with diet and drug treatment, and are more likely to consume alcohol and tobacco. As Gottlieb et al. reported, patients with depression may perceive that their quality of life (QoL) is lower and tend to underestimate their functional status [47]. However, objective assessment of physical functioning showed that depressed patients with heart failure (HF) had less exertion on exercise with lower respiratory quotient compared to nondepressed patients with HF. This finding could be of use when determining patients' functional class according to New York Heart Association (NYHA) criteria, as some depressed patients may report more severe physical status [48].

Similarly, Cheok et al. found that depressed patients at baseline in the Identifying Depression As a Comorbid Condition (IDACC) project [49] reported lower QoL as measured by different instruments: the Assessment of Quality of Life (AQoL) [50] and the Short Form-36 (SF-36) [51]. They found that depressive symptoms were related to younger age, female gender, unemployment, divorce or separation, and a lower educational level.

Compliance is another issue of great concern in patients with CVDs. Due to the fact that many patients are over 60 years old and suffering from other diseases as well, the number of medications may be increased with a number of them taken several times daily. In a study of elderly patients with HF, compliance rate was reported to be as low as 10% [52]. This strong association between noncompliance and depression was evident in a meta-analysis where nondepressed patients were three times more likely to adhere to their medical treatment compared to depressed patients [53].

Nevertheless, there is still much debate on whether depression itself, impaired cognition or associatedsequelae such as poor adherence to drug treatment, lack of exercise, sedentary life, and so on are responsible for adverse outcomes in CVD patients.

5. Prognosis

Around 20% of patients present with MDD and a larger portion may have subthreshold depressive symptoms [3, 6, 54, 55]. Depression is associated with increased morbidity, even greater than the impact that left ventricular function and ischemia have on CAD [56]. Another 15% to 23% of patients after an MI and in ACSs have depression and depression in this population increases mortality three times [57]. Lower QoL can be predicted in hospitalized ACS patients by the degree of depression [58].

In another study by Sherwood et al., it was found that severity of depressive symptoms but not use of antidepressants was related to increased likelihood of death or cardiovascular rehospitalization in HF patients [59]. In accordance with these findings, in a recent prospective study of 1006 patients with a mean follow-up period of 972 days, depression rather than antidepressants' use was independently associated with increased mortality in HF patients (hazard ratio HR: 1.34; 95% confidence interval: 1.08–1.68) [60].

Increased mortality, readmission rates, and cardiac events have also been associated with depression in patients undergoing CABG [61, 62]. Depressed HF patients experience a twofold increase in mortality risk [8], whereas depression worsens health status and increases hospitalization rates [9, 10, 63].

An interesting feature that has been brought to surface is the fact that onset of depression is related to morbidity and cardiac events, with patients presenting postcardiac event depression being at greater risk. Several studies showed that even after controlling for age, sex, education level, and left ventricular ejection fraction (LVEF) among others, depression is predictive of mortality and recurrent cardiovascular events [64–67]. According to an explanation offered by Spijkerman et al. [68] and Goodman et al. [69], new onset of depression may be associated with more severe state of cardiac disease or different risk factors compared to recurrent depression [70].

Faller et al., in a study of 231 HF patients with a median follow-up period of 986 days (IQR = 664–1120 days), found that major but not minor depression was associated with shorter survival rates (HR: 3.3; 95% CI = 1.8–6.1, Wald χ^2 = 15.2, $P < 0.001$ versus HR: 1.6; 95% CI = 0.8–3.1, Wald χ^2 = 1.6, $P = 0.20$) compared to nondepressed patients, regardless of sex [71]. 2847 community-dwelling people with CHD or congestive heart failure (CHF) ($n = 450$) and without any CVDs ($n = 2397$) were studied by Penninx et al. in order to investigate the effect of depression on cardiac mortality [72]. During 50 months of followup, depressed older people had significantly higher risk of mortality. Patients with CVDs and minor or major depression had 1.6 and 3.0 times greater relative risk (RR) of mortality compared to nondepressed CVD patients (95% CI = 1.0–2.7 and 95% CI = 1.1–7.8, resp.), with the risk being almost fourfold in the subgroup of CHD patients (RR = 3.9; 95% CI = 1.3–11.8). Similarly, non-CVD individuals with minor or major depression were more likely to die compared to non-CVD, non depressed individuals (RR = 1.5; 95% CI = 0.9–2.6 and RR = 3.9; 95% CI = 1.08–1.68, resp.).

6. Brief Considerations in Stroke Patients

According to the World Health Organization, it is estimated that 15 million people every year experience stroke with

a third not surviving and another third having a permanent disability [43]. Stroke may have several detrimental physical and psychological effects both on patients and their caregivers as well. Among these effects, depression is commonly found in this population [73]. In a systematic review by Poynter et al., it was found that prevalence of depression in women was higher in 35 among 47 studies included; however, reasons for this finding are inconclusive [74]. The need for early recognition and diagnosis of poststroke depression (PSD) is emphasized in the literature [75]. In a study by Schmid et al. who followed a group of 367 stroke patients with and without depression for 12 weeks, it was found that dependence after stroke was independently associated with increased age, stroke severity but not baseline depression [76]. The authors also reported significant association between cognition and neurological impairment with functioning. PSD may lead to poor quality of life, worse prognosis, and increased mortality. Morris et al. and Ellis et al. found that PSD patients have higher mortality rates (3.4- and 1.88-fold risk, resp.) [10, 77]. Management strategies in PSD patients do not differ from those implemented in CVD patients with depression.

7. Treatment

According to the clinical guidelines (number 90 and 91, October 2009) issued by the National Institute for Health and Clinical Excellence (NICE) regarding treatment and management of depression in adults generally and adults with chronic physical health problems, respectively, there are several therapeutic approaches, varying from individual, computerized, or group cognitive behavioral therapy (CBT), interpersonal therapy (IPT), medications, or combinations of the above [78, 79].

7.1. Pharmaceutical Approaches. Several agents may be administered to patients suffering from depression. Some of the most frequently given include monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs).

MAOIs and TCAs are generally avoided in patients with cardiovascular diseases since trials in antidepressants' use have shown adverse cardiac effects in patients without established heart disease [80–82]. In addition, they increase heart rate, cause orthostatic hypotension, impede cardiac conduction, and increase the risk of arrhythmias [83–85].

In one study, SSRIs have been shown to be safe for patients suffering from CVDs [86]. Nevertheless, the use of these drugs could still cause potential drug-to drug interactions, since some SSRIs are metabolized by P450 liver enzymes, which metabolize drugs prescribed for treating certain CVDs. In another trial, investigators reported fluoxetine to be safe and effective in patients with stable CHD [87].

Sertraline was also found to be safe in patients hospitalized for AMI or unstable angina [88]. The authors reported that sertraline was superior to placebo mainly in a group of patients with severe recurrent depression. In a larger and more recent randomized, double-blind, placebo-controlled trial of sertraline that lasted 12 weeks (Sertraline Against Depression and Heart Disease in Chronic Heart Failure—SADHART-CHF), the drug was found safe; nevertheless, the administered doses (50 to 200 mg/day) did not significantly reduce depression, measured with HAM-D, compared to placebo [89].

The same scale was utilized in another study of citalopram by Fraguas et al. [90]. Apart from HAM-D, authors employed the MADRS and weekly visits by a psychiatrist. Generally, patients tolerated well this agent without any significant effects on left ventricular ejection fraction (LVEF), blood pressure, heart rate, or pulmonary function in this population of older people with heart failure. A concern about the suitability of HAM-D was raised by the authors who suggested that the MADRS may be more suitable for the evaluation of antidepressant effects in patients with HF and MDD.

Contrary to previous findings, clinical benefits derived in a Canadian study (Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy—CREATE) evaluating citalopram alone and combined with interpersonal psychotherapy (IPT) [91]. Two hundred eighty-four patients with coronary artery disease (CAD) and major depression were allocated in four groups, receiving either IPT plus clinical management and citalopram ($n = 67$), IPT plus clinical management with placebo ($n = 75$), clinical management and citalopram ($n = 75$), or clinical management with placebo ($n = 67$). It was found that citalopram was effective and safe (effect size 0.33 in mean changes) after a 12-week period of drug use in this population that was required to have at least a score of 20 or higher in the HAM-D, meaning that the participants were more likely to be severely depressed. On the other hand, IPT did not exhibit any benefits over the usual clinical management which was a 20-minute, nonpsychotherapeutic intervention evaluating medication's adverse effects and depression symptoms.

Controlled-release paroxetine was studied in a pilot double blind, randomized, placebo-controlled study by Gottlieb et al. in a small population of patients with chronic heart failure [92]. At twelve weeks of followup, paroxetine-CR was associated with significant improvement in depression (69% versus 23%, $P = 0.018$) and improvements in psychological aspects of quality of life but not physical. In another trial, safety of paroxetine versus nortriptyline was examined [93]. By obtaining and analyzing baseline 24-hour ECG and 24-hour ECGs at the end of the second and sixth week of drug treatment, the authors concluded that paroxetine is a safer option in a population of patients with ischemic heart disease (IHD) and MDD, since nortriptyline had a greater vagolytic function, negatively influencing heart rate variability by prolonging R-R intervals.

Prevention of depression was studied in a double-blind randomized controlled trial which evaluated the efficacy of escitalopram in post-acute coronary syndromes (ACSs) patients [81]. There were no significant adverse events in the treatment group. A multivariate analysis revealed that the absence of escitalopram and a higher score in HAM-D scale were the only elements associated with development

of depression in these patients who did not have clinical depression at baseline. Only two of the 120 patients treated with escitalopram developed depression versus ten in control group ($P = 0.022$).

In the Myocardial Infarction and Depression Intervention Trial (MIND-IT), a multicenter, double-blind, randomized controlled study, 91 post-MI patients (recruitment after 3 to 12 months post-MI) with depression were allocated to treatment with mirtazapine or placebo during a 24-week period [94]. Patients from both groups reported adverse effects such as fatigue, dizziness, headache, and appetite changes and there had been incidents of heart failure ($n = 1$), angina pectoris ($n = 1$), and atrial fibrillation ($n = 1$) in the intervention group. The number of hospitalizations was similar between the two groups (10 versus 8) and ECG characteristics such as PR and QRS duration and QTc interval did not show significant changes. Although scores in HAM-D did not show any substantial changes, statistically significant improvements were found in the depression subscale of the Symptom Check List 90 (dSCL-90) and the Clinical Global Impression (CGI) scale ($F = 3.88$, $P = 0.02$ and $F = 3.87$, $P = 0.05$, resp.).

Kerber at al. studied symptom remission in depressed patients with and without heart disease (HD), while administering different combinations of agents: bupropion sustained release plus escitalopram, venflaxine extended release plus mirtazapine, and escitalopram plus placebo [95]. In thissingle-blinded, prospective randomized trial, HD patients had similar remission rates (40% versus 38.2%, $P = 0.556$) and response rates (50% versus 52.1%, $P = 0.805$) and demonstrated fewer side effects at the 12th and 28th treatment week, indicating that heart disease may not influence the therapeutic effects of antidepressants and their use is safe. However, the number of HD patients included was small ($n = 40$) with a mean age of 42 years old and heart condition was self-reported.

In another review of several studies in animals and humans [75], erythropoietin (EPO) was found to have beneficial effects on hippocampus-dependent memory and antidepressant-like effects that seem to be attributable to neuriological actions of EPO rather than increase of red cell mass. The authors conclude that, although studies on this area are still small scaled, EPO may be a promising add-on treatment for mood disorders.

In conclusion, it should be emphasized that a great number of studies performed on various drugs may be underpowered to efficiently address safety in CVD patients and some of them were of short duration. Thus, more studies are needed in this area.

7.2. Psychotherapy. Cognitive behavioural therapy (CBT) and interpersonal therapy (IPT) are two forms of psychotherapy that are employed in managing depression. CBT is based on the idea that individuals' thoughts cause their feelings and behaviour, not external things such as people, situations, or events. The benefit of this fact is that the way someone thinks can be changed in order to feel and act better even if the situation does not change. Emphasis is also placed on problem solving and on increasing the time and frequency of pleasurable activities [96].

IPT is a short-term supportive psychotherapy that focuses on the connection between interactions that people have and the development of psychiatric symptoms. There are several types of interventions that are commonly used in IPT: a focus on emotions; exploration of client's resistance to treatment; discussion of patterns in client's relationships and experiences; detailed past history; emphasis on client's current interpersonal experiences; exploration of the relationship between the client and the therapist; the identification of the client's wishes. IPT focuses on the ways in which a person's current relationships and social context cause or maintain symptoms instead of trying to explore the wider sources of the symptoms and aims at rapid symptom reduction and improved social adjustment.

The goals of IPT in the treatment of depression are to diagnose depression explicitly and educate the patient about depression, its causes, and the various treatments available for it; to identify the interpersonal context of depression as it relates to symptom development; to develop strategies for the patient to follow in coping with the depression. The targeted approach of IPT has demonstrated improvement for patients with problems ranging from mild situational depression to severe depression with a recent history of suicide attempts [97–101].

8. Future Research Directions

Our knowledge base concerning depression in patients with cardiac diseases is increasingly enriched by valuable studies on this area. However, not all pieces of the puzzle are there yet.

It is not quite clear, for example, whether there are any coincidental physiologic factors found in depressed patients that may or not affect the progression ofheart disease per se. Also, another issue of concern may be the timing of diagnosing depression in patients with CVDs, as well as the use of a screening modality suitable for each heart condition. Also, it is hoped and widely expressed in the literature that advances in technology and genetics will allow us to image molecules that may be implicated in the pathophysiology of the brain activity in depressed patients and confirm possible areas in chromosomes that are hypothesized to be linked with depression.

Finally, it is encouraging to know that the National Institute of Mental Health (NIMH), acknowledging the importance of depression, has awarded researchers at the University of Pittsburgh School of Medicine a three-year, half a million dollars grant to develop an intervention strategy for simultaneously treating congestive heart failure and major depression. This future study will be designed to compare the impact of a "blended" depression/heart failure care management programs versus traditional heart failure care management program on cardiovascular morbidity and mortality, health-related quality of life, mood symptoms, health care costs, and a variety of other outcomes of interest, further enhancing our existing understanding.

9. Conclusions

It has been widely suggested in the literature that depression negatively affects patients with cardiovascular diseases. There are several pathophysiologic mechanisms linking depression and cardiac events as well as behavioral processes. Improvements in nursing and medical care have prolonged survival of this patient population; however, this beneficial outcome may have led to increased prevalence of depression. Since mortality rates in treated CHF patients remain extremely high, it might be as equally important to screen for depression and there are several valid and reliable screening tools that healthcare personnel, such as nurses, could easily employ in order to identify patients at greater risk. Identification is the first step to take. Consultations should follow by a multidisciplinary team, consisting of cardiologists, psychiatrists, and hospital or community nurses so as to carefully plan, execute, and evaluate drug treatment, medical interventions, and necessary lifestyle changes of cardiac patients who suffer from any form of depression.

Authors' Contributions

D. Mastrogiannis and G. Giamouzis have contributed equally.

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Review Article

Telemonitoring in Chronic Heart Failure: A Systematic Review

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Heart failure (HF) is a growing epidemic with the annual number of hospitalizations constantly increasing over the last decades for HF as a primary or secondary diagnosis. Despite the emergence of novel therapeutic approached that can prolong life and shorten hospital stay, HF patients will be needing rehospitalization and will often have a poor prognosis. Telemonitoring is a novel diagnostic modality that has been suggested to be beneficial for HF patients. Telemonitoring is viewed as a means of recording physiological data, such as body weight, heart rate, arterial blood pressure, and electrocardiogram recordings, by portable devices and transmitting these data remotely (via a telephone line, a mobile phone or a computer) to a server where they can be stored, reviewed and analyzed by the research team. In this systematic review of all randomized clinical trials evaluating telemonitoring in chronic HF, we aim to assess whether telemonitoring provides any substantial benefit in this patient population.

1. Introduction

Heart failure (HF) is a growing epidemic, especially in the western world. Over the last decade, the annual number of hospitalizations has increased from 800,000 to over a million for HF as a primary diagnosis and from 2.4 to 3.6 million for HF as a primary or secondary diagnosis [1]. Approximately 50% of HF patients are rehospitalized within 6 months of discharge and with the aging of the population this trend will continue to rise [2, 3]. Understanding the epidemiology and pathophysiology of the syndrome [4], identifying the predictors and their strength of association with outcomes, and cost-effectively using the available diagnostic modalities are essential in order to devise effective preventive interventions and implement novel therapeutic approaches to curb this epidemic [5–8]. Despite, however, the emergence of novel therapeutic approached that can prolong life and shorten hospital stay [9–13], these patients will be needing rehospitalization and will often have a poor prognosis [2].

In Europe, it is estimated that at least 10 million people suffer from chronic HF [14, 15], and in the United States another 400.000–700.000 patients are diagnosed annually [16], while 1 in 9 death certificates (277,193 death) in 2007 mentioned HF [17]. The healthcare costs are equally high; in one study, it is reported that $30 billion were spent in the USA in 2007 [18].

Telemonitoring is a novel diagnostic modality that has been suggested to be beneficial for HF patients [19, 20]. Telemonitoring is viewed as a means of recording physiological data (such as body weight, heart rate, arterial blood pressure

Table 1: Inclusion and exclusion criteria.

Inclusion criteria
Randomized controlled trials (RCT)
Trials conducted in the previous ten years
At least one device that measures physiological data provided by the researchers for home use
Intended (per protocol) follow-up period of at least 6 months
Exclusion criteria
Papers that published protocols
Papers that published feasibility data
Papers that published pilot studies
Review papers
Papers not in English

(BP) electrocardiogram (ECG) recordings, and other data) by portable devices and transmitting these data remotely (via a telephone line, a mobile phone, or a computer) to a server where they can be stored, reviewed, and analyzed by the research team.

In this systematic review of all randomized clinical trials evaluating telemonitoring in chronic HF, we aim to assess whether telemonitoring provides any substantial benefit in this patient population.

2. Methods

We searched in Medline, SpringerLink, Scopus, Cinahl, and Embase for trials that examined efficacy and efficiency of telemonitoring modalities in chronic HF patients. Keywords used in the search included: home care, telemedicine, telemetry, telemonitoring and telehealth combined with chronic heart failure. This yielded 3378, 322, 288, 130, and 48 papers respectively. The search lasted for two months and ended in November 2011. Two of the researchers read all available titles and abstracts and eliminated duplicate articles. Only randomized controlled trials were included that had a follow-up period of at least six months, clearly stated a means of telemonitoring, and were conducted in the previous ten years. We excluded feasibility or pilot studies which primarily report preliminary findings of ongoing trials, usually, in a small number of patients. Table 1 summarizes inclusion and exclusion criteria. In Figure 1, the selection process is depicted.

3. Study Characteristics

We identified 12 randomized controlled trials that met our inclusion criteria (Tables 2 and 3). Sample sizes varied from 57 [33] to 710 [32] patients. The age of the participants covered a wide range from 44 [29] to 86 years [21]. In most of the studies, the functional status of the participants according to New York Heart Association's (NYHA) classification was reported (I–IV) apart from two studies [22, 30]. Two studies were multinational [24, 27], four were conducted in the USA [21, 22, 29–31], and the remaining six in Europe [21, 23, 25, 28, 32, 33].

In most of the studies, the follow-up period ranged from 6 to 12 months, while in one study participants were followed for 26 months (median value) [32]. Three studies did not clearly state left ventricular ejection fraction (LVEF) [22, 25, 30] and in all of the remaining studies, LVEF was under 40% except for one (LVEF: $35 \pm 15\%$) [21].

Domestic telephone line was the preferred means for data transmission in most of the studies, while, in two studies cell phones were utilized [23, 32], pointing out that mobile and portable options offered by technology are being increasingly adopted in health care.

Researchers collected several physiological data. In the study by Wade and colleagues [22], body weight and BP were measured. In the study by Dendale and colleagues [21], weight, arterial blood pressure, and heart rate were monitored, while in the studies by Scherr and colleagues [23] and Giordano and colleagues [28], patients also reported the dosage of drugs taken. Goldberg et al. [29] and Soran et al. [31] recorded weight along with questions regarding HF symptoms. Cleland et al. [27] and Koehler et al. [32] monitored weight, arterial blood pressure, and ECG. In the study by Mortara et al. [24], collection of data included blood results, dyspnea score, asthenia score, edema score in addition to weight, heart rate, and systolic blood pressure. Pulse oximetry was recorded in two studies along with weight, BP, heart rate and questions regarding symptoms [25, 30]. Finally, Antonicelli et al. [33] also measured 24-hour urine output.

With regard to primary endpoints, they were similar across studies. Researchers were mostly interested in mortality (all-cause and/or cardiovascular mortality), rehospitalization, or visits to emergency department, expressed either as bed-days per year or days alive and out of hospital, and, thirdly, there were combined endpoints including the above.

4. Findings

In all included studies, baseline characteristics of the participants did not differ significantly between intervention and control groups. Three studies reported reduced hospitalization rates in telemonitoring groups that reached statistical significance [23, 28, 33], and another four studies also found reductions in hospitalization rates in favor of telemonitoring without, however, reaching statistical significance [21, 27, 28, 30]. In four studies there were more rehospitalizations in telemonitoring groups compared to usual care groups, but statistical significance was either not reported [25] or was not important [22, 31, 32]. Therefore, it could be argued that survival rates may occur at the expense of rehospitalization rates. However, in one study, results were mixed [24]; while the telemonitoring group in Italy had fewer hospital admissions compared to Poland and UK (3% versus 11%, $P = 0.002$), the Polish telemonitoring group had more readmissions (9% versus 3%, $P = 0.13$).

With regard to all-cause mortality, three studies reported statistically significant results that favored the telemonitoring

Table 2: Study characteristics and participants' data.

Reference	Sample size	Age[†]	E.F.	Follow-up period	Transmission modality	NYHA[a] class	Study design	Place
(1) Dendale et al. [21]	160	76 ± 10	35 ± 15%	6 m	Cell phone	>II	RCT[b]	7 hospitals in Belgium
(2) Wade et al. [22]	316	78.1	Not reported	6 m	Internet link	Not reported	RCT[b]	New York, New Jersey, Pennsylvania residents
(3) Scherr et al. [23]	120	66 (median, IQR[c] 62–72)	<38%	6 m	Mobile phone	II–IV	RCT[b]	Austria
(4) Mortara et al. [24]	461	60 ± 11	29 ± 7	12 m	Telephone line	II–IV (2.4 ± 0.6)	RCT[b]	11 centers in Italy, UK, and Poland
(5) Dar et al. [25]	182	72 (Mean) SD[d]: 12	Not reported	6 m	Telephone line	II–IV	RCT[b]	3 acute hospitals in northwest London
(6) Antonicelli et al. [26]	57	78 (Mean) SD[d]: 7		12 m	Telephone line	II–IV	RCT[b]	Italy
(7) Cleland et al. [27]	426	67 (Mean) SD[d]: 12	<40%	8 m	Telephone line	I–IV	RCT[b]	16 hospitals in Germany, UK and The Netherlands
(8) Giordano et al. [28]	460	57 ± 10	<40%	12 m	Telephone line	II–IV	RCT[b]	5 cardiovascular rehabilitation departments in Italy
(9) Goldberg et al. [29]	280	59 ± 15	<35%	6 m	Telephone line	III-IV	RCT[b]	16 heart failure centres in the USA
(10) Tompkins and Orwat [30]	390	76.1 (SD[d]: 8.1)	Not reported	6 m	Telephone line	Not reported	RCT[b]	Arizona, USA
(11) Soran et al. [31]	315	76 ± 7	23 ± 9%	6 m	Telephone line	II-III	RCT[b]	3 cites in Pittsburg, Cleveland, and Miami, USA
(12) Koehler et al. [32]	710	66.9 ± 10.7	≤35%	26 m (median)	Cell phone	II-III	RCT[b]	165 practices in Germany

[†] Age is reported in years as a mean value unless otherwise stated.
[a]NYHA: New York Heart Association, [b]RCT: randomized controlled trial, [c]IQR: interquartile range, [d]SD: standard deviation.

Table 3: Data measured, hospitalization rates and costs, primary endpoints, and all-cause mortality of trials.

	Physiological parameters measured	Cost of hospitalization per patient (telemonitoring TM group versus control group)	All-cause mortality (TM group versus control group)	Hospitalization rates or percentages (%) in TM group versus control group	Primary endpoints
Dendale et al. [21]	W[a], BP[b], HR[c]	1382€ ± 3384 versus 747€ ± 2137 ($P = 0.16$)	5% versus 17.5% ($P = 0.01$)	0.24 versus 0.42 ($P = 0.06$)	All-cause mortality
Wade et al. [22]	W[a], BP[b]	Not reported	3.7 versus 3.9 ($P = 0.96$)	34.8% versus 32.2% ($P = 0.53$)	Hospital admission, emergency department visit or death
Scherr et al. [23]	W[a], BP[b], HR[c], D[d]	Not reported	0 in intervention group, 1 in control group	54% RR[e] reduction, Confidence Interval 7 to 79%, ($P = 0.04$) in favor of intervention group	Cardiovascular mortality or rehospitalization for worsening HF[f]
Mortara et al. [24]	W[a], HR[c], SAP[g], DS[h], AS[i], OS[j], changes in therapy, blood results	Not reported	Not reported separately	Italy versus Poland and UK: 3 versus 11% ($P = 0.002$). Poland: 9 versus 3% ($P = 0.13$)	Bed-days/year, Death+hospitalization due to HF[f]
Dar et al. [25]	W[a], BP[b], HR[c], PO[k], questions about symptoms	Not reported	Not reported	36% versus 25%	Days alive and out of hospital, all-cause hospitalizations
Antonicelli et al. [26]	W[a], BP[b], HR[c], 24 h urine output, weekly ECG	Not reported	3 cases versus 5 cases, non significant	9 cases versus 25 cases ($P < 0.05$)	Rate of mortality and hospitalization
Cleland et al. [27]	W[a], BP[b], HR[c], ECG	Not reported	29% versus 27% (telephone support-TS group) versus 45% at 1st year ($P = 0.032$)	47% (TM) versus 49% (TS) versus 54%	Days lost due to death or all cause hospitalization
Giordano et al. [28]	W[a], BP[b], ECG, drug dosage	843€ ± 1733 versus 1298€ ± 2322 (−35%, $P < 0.01$)	9% versus 14%	24% versus 36% (RR = 0.57, CI: 0.38 to 0.82; $P = 0.01$)	Unplanned hospital admission for cardiovascular reason
Goldberg et al. [29]	W[a], symptom questions	Not reported	8% versus 18.4% ($P < 0.003$)	0.19 ± 0.46 versus 0.20 ± 0.30 ($P = 0.28$)	180-day hospital readmission rate
Tompkins and Orwat [30]	W[a], BP[b], HR[c], PO[k], symptom questions	12% reduction of total cost in TM group ($P = 0.14$)	Not reported	Lower hospital admissions in TM group, incidence rate ratio = 0.87	Inpatient hospital utilization
Soran et al. [31]	W[a], symptom questions	Not reported	7.0% versus 11.2% ($P = 0.24$)	46.8% versus 42.5% ($P = 0.44$)	Cardiovascular death or rehospitalization for heart failure
Koehler et al. [32]	W[a], BP[b], ECG,	Not reported	54 cases versus 55 cases (hazard ratio 0.97, CI = 0.67 to 1.41, $P = 0.87$)	486 events versus 394 events (hazard ratio 1.12, CI = 0.91 to 1.37, $P = 0.29$)	Death from any cause

[a]W: weight, [b]BP: arterial blood pressure, [c]HR: heart rate, [d]D: dosage of heart failure medication, [e]RR: relative risk, [f]HF: heart failure [g]SAP: systolic arterial pressure, [h]DS: dyspnoea score, [i]AS: asthenia score, [j]OS: oedema score, [k]PO: pulse oximetry.

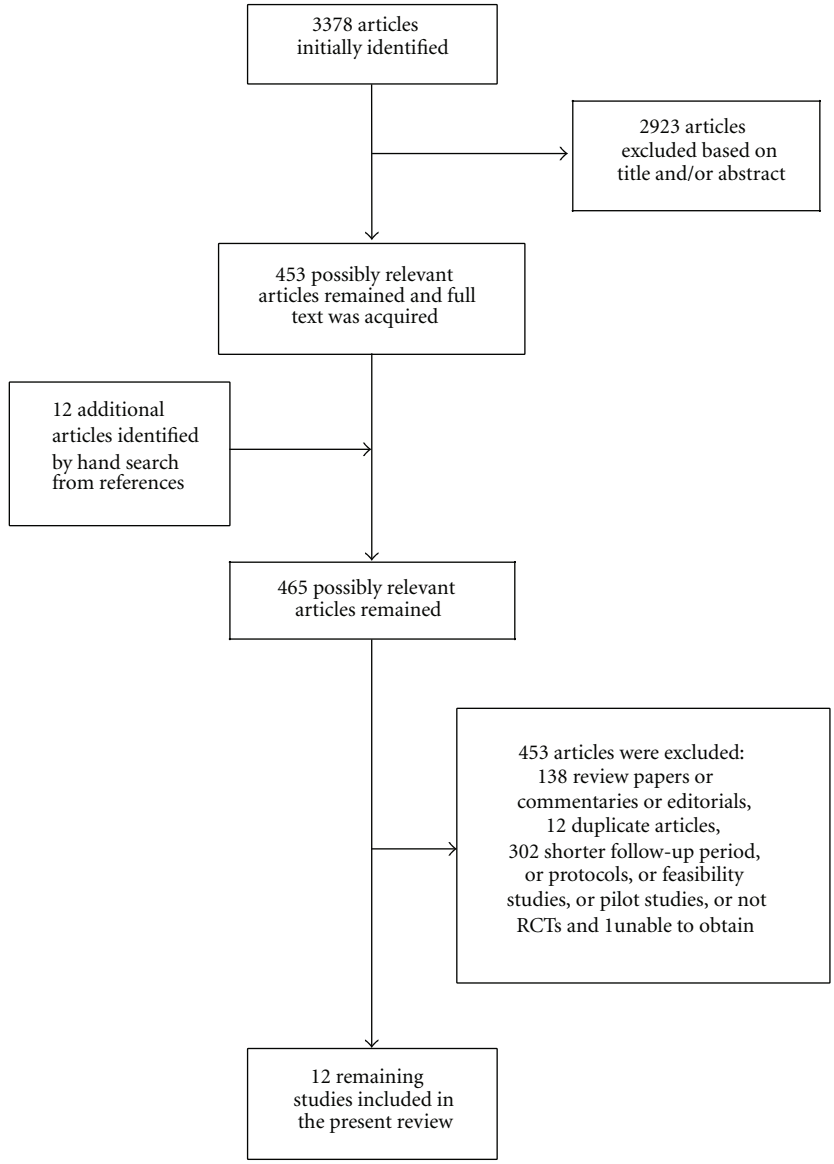

Figure 1: Flowchart of study search.

group [21, 28, 29]. In two of these studies, mean age was relatively low (Table 2). This might implicate that younger age could be associated with better survival through improved adherence to medication plan. In the first study by Goldberg et al. [29], compliance was reported to be as high as 98.5%, while in the study by Giordano et al. [28], the authors report only that a nurse offered strategies to enhance compliance, without stating any rates of compliance. Compliance has been measured in the past and in one study by De Lusignanet et al. [34] 75% of the patients recorded their weight sufficiently and blood pressure was measured at 90% of the time in the study. Medication adherence is another key-factor in this patient population. Wu et al. [35] examined World Health Organization' multidimensional adherence model (MAM) in 134 patients with a mean age of 61 ± 11 years. This model encompasses five dimensions: (1) socioeconomic factors, (2) health care system-related factors, (3) condition-related factors, (4) treatment-related factors, and (5) patient-related factors. In their multivariate analyses, worse NYHA functional class, more barriers to medication adherence (i.e., forgetting to take their medication, cost of medication), minority ethnicity, lower financial status, and lack of perceived social support, but not age nor gender, were associated with worse objectively measured medication adherence.

In other four trials, fewer deaths were reported in the telemonitoring group in comparison to the usual care, however, these results were not statistically significant [22, 26, 31, 32]. In concordance with these positive findings, another study reported that there was no death in the telemonitoring group compared to one death in the control group [23]. In three studies all-cause mortality was not reported [24, 25,

30]. Finally, one study reported a death rate of 29% in the telemonitoring group, 27% in the telephone support group, and 45% in the usual care group at the first year ($P = 0.032$) [27].

Another issue that was investigated in three studies was the cost of hospitalization calculated per patient. One study found statistically significant reduction in the telemonitoring group compared to the usual care group (€ 843 ± 1733 versus € 1298 ± 2322, 35% reduction, $P < 0.01$) [28]. In Tompkins and Orwat's study [30], there was also a 12% reduction in the telemonitoring group ($P = 0.14$). In contrast, Dendale et al. [21] reported increased costs associated with the telemonitoring group (€ 1382 ± 3384 versus € 747 ± 2137, $P = 0.16$).

5. Discussion

Since an aspect of medicine is the continuing attempt to provide better care to people and HF patients in particular, it is worth trying to identify the way and means to improve their quality of life through the best available evidence-based knowledge. There are several meta-analyses in the literature that offer an interpretation of findings after a statistical process of different trials. These results are based on solid mathematical procedures, offered by a computer program. In our opinion, there will always be a degree of error involved, inherent in all human processes. That is, despite the effort of all esteemed researchers, there will still be discrepancies in study designs which may render them not absolutely comparable. There are inclusion and exclusion criteria differences among studies, functional status differences, outcome measure discrepancies, and so on.

Currently available trial results may seem rather ambiguous and confusing. Nevertheless, it appears that the above-presented randomized controlled trials tend to be in favor of telemonitoring. It could be argued that in some studies sample sizes were small and thus underpowered to detect significant associations. Importantly, however, an improved quality of life—a soft end-point gaining more and more clinical significance—has been reported in all studies, whereas telemonitoring was highly acceptable by chronic HF patients.

Key components that patients with HF encounter through their contact with healthcare services should be sample in order to design larger scale studies that could test their value. Small-sized trials may provide some insight; however, this should always be verified by larger trials. In the field of telemonitoring, protocols should be clear beforehand. It may be of great importance in case participants are asked to monitor their status daily or every other day. Patient education is also important and documentation of learning goals and results should be provided, a task that can be undertaken by experienced nurses.

Another urgent need is the identification of patients that would actually be benefited by such interventions. Since the resources are getting scarce and in a time when cutbacks and cost reductions are getting bigger, sustainability of telemonitoring approaches seems difficult. Consequently, a key factor that will influence the future implementation of telemonitoring strategies is the availability of human and economic resources.

Disclaimer

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Authors' Contribution

G. Giamouzis and D. Mastrogiannis have contributed equally to this paper.

Conflict of Interests

The authors declare that there is no conflict of interests.

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Review Article

Cognitive Impairment in Heart Failure

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Cognitive impairment (CI) is increasingly recognized as a common adverse consequence of heart failure (HF). Although the exact mechanisms remain unclear, microembolism, chronic or intermittent cerebral hypoperfusion, and/or impaired cerebral vessel reactivity that lead to cerebral hypoxia and ischemic brain damage seem to underlie the development of CI in HF. Cognitive decline in HF is characterized by deficits in one or more cognition domains, including attention, memory, executive function, and psychomotor speed. These deficits may affect patients' decision-making capacity and interfere with their ability to comply with treatment requirements, recognize and self-manage disease worsening symptoms. CI may have fluctuations in severity over time, improve with effective HF treatment or progress to dementia. CI is independently associated with disability, mortality, and decreased quality of life of HF patients. It is essential therefore for health professionals in their routine evaluations of HF patients to become familiar with assessment of cognitive performance using standardized screening instruments. Future studies should focus on elucidating the mechanisms that underlie CI in HF and establishing preventive strategies and treatment approaches.

1. Introduction

Heart failure (HF) is a major and growing health problem in the developed world that affects 1-2% of the adult population and 6–10% of people over the age of 65 [1, 2]. HF is associated with frequent hospital admissions, reduced quality of life, significant morbidity, and increased mortality [3–6]. It is estimated that elderly HF patients have high readmission rates ranging from 40 to 50% within 6 months [7]. Significant predictors of HF decompensation and high readmission rates include patients' poor compliance with therapy and diet restrictions, and their failure to recognize early symptoms of HF deterioration which may be the consequences of cognitive impairment (CI) and poor insight [8].

Several studies have demonstrated that CI is particularly common in HF with 30% to 80% of patients with HF experiencing some degree of cognitive impairment [9, 10]. This wide range in CI prevalence estimates is believed to be the result of diverse study designs, HF severity, age of patients, sample sizes, neuropsychological tests, and diagnostic criteria between different studies. HF adversely affects various aspects of cognitive functioning, including attention, learning ability and delay recall, working memory, executive function, and psychomotor speed [9–11]. Areas of cognition less affected are the language domain and possibly visuospatial functions although both domains have not been adequately investigated in patients with HF [12]. Most of the patients with HF and CI suffer from mild impairment in cognition whereas about 25% may have moderate-to-severe CI [9]. In addition, HF severity has been linked to increased risk of CI [13], while effective treatment of HF, use of ACE inhibitors, and physical activity lead to improvement in cognitive performance [14] which imply that CI may fluctuate in severity and can also be modified to some degree.

In this paper, we outline the spectrum of cognitive functional domains and describe the specific patterns of cognitive decline and their consequences in patients with HF. We also discuss the current understanding of the underlying mechanisms that affect neuronal function in HF and finally we provide suggestions for future research in this field.

2. Cognition and Cognitive Impairment

Cognition is a collective term for higher cortical functions such as thinking, remembering, knowing, planning, and analyzing. Cognition is crucial for a person to become aware of his/her situation, needs, and goals and meet the challenges of daily life [15]. Cognitive functioning encompasses various specific aspects referred to as cognitive domains that include memory, attention, executive functioning, psychomotor speed, language, and visuospatial ability. Positron emission tomography and functional MRI have shown that each cognitive domain involves diverse and often overlapping parts of the brain.

Several measures of cognitive functioning are available. A measure of global cognition that is often used by the clinicians as a screening instrument is the Mini-Mental State Examination (MMSE). MMSE is a 30-point test that provides information about orientation, working and episodic memory, attention, calculation, naming, copying, language comprehension, and visuospacial construction. Very often, however, a more detailed neuropsychological assessment is required. For this purpose, a number of neuropsychological tests are available, designed for the assessment of different cognitive domains and the calculation of cognitive dysfunction severity.

CI is a broad term that generally describes a decline in cognitive functions. The severity of this impairment may range from mild symptoms to severe cognitive deficits that may warrant the diagnosis of dementia. Mild cognitive impairment is described as a transition phase between normal ageing and dementia. This syndrome reflects the clinical situation in which a person has subjective complaints of CI as well as objective measurements of cognitive decline (around 1.5 standard deviations below normative data) along with intact daily functioning [16]. Mild cognitive impairment may involve single or multiple domain deficits (with or without memory impairment). Individuals with mild cognitive impairment are in increased risk of progression to dementia [17]. Dementia is characterized by progressive impairment in more than one cognitive domain. Routine laboratory tests for dementia include measurement of liver, renal and thyroid function, vitamin B12 levels, and imaging of the brain (CT or MRI). After excluding reversible causes, four common dementia syndromes, that is, Alzheimer's disease, vascular dementia, dementia with Lewy body, and frontotemporal dementia, account for 90% of all cases. These dementias have distinct clinical features, cognitive profiles, and imaging abnormalities [18].

3. Pathophysiology of CI in HF

The exact pathophysiologic mechanisms that underlie the development of CI in a proportion of patients with HF continue to be investigated and much research is conducted in the field. Studies have provided evidence that the clinically detected CI in patients with HF can be the outcome of structural or neurodegenerative changes which cannot be reversed and/or functional neuronal dysfunction which may progress to neuronal cell death or improve in response to treatment.

Cerebral and systemic hemodynamics seem to influence the development of CI in patients with HF. Cerebral blood flow (CBF), estimated with single-photon emission computed tomography (SPECT), was reduced about 30% in patients with severe HF (NYHA class III/IV) [19]. In another study the degree of CI in HF was related to regional CBF reductions particularly in the posterior cortical areas of the brain [20]. Interestingly, CBF in patients with severe HF was restored after heart transplantation [19]. These data suggest that cognitive performance in patients with HF appears to be closely related to the measurements of cerebral perfusion.

Cerebral perfusion is mediated by a number of factors including cardiac output and cerebrovascular reactivity. Low systolic blood pressure was shown to be an independent predictor of CI in HF patients [21]. In addition, low cardiac output was associated with impairment in cognitive performance [22–26] and dementia [27]. Furthermore, cerebrovascular reactivity, measured as the response to cerebral vasodilatory effects of carbon dioxide, was found to be impaired in patients with HF and correlated with left ventricular ejection fraction and NYHA class [28]. It appears therefore that low cardiac output, low systolic blood pressure, and impaired cerebral neurohormonal autoregulatory mechanisms in HF result in a decrease in cerebral blood flow that may account for the neuroanatomic and neuropsychological changes [29].

Another aspect of the pathophysiology of CI in HF is the development of cerebral abnormalities as a result of chronic hypoperfusion or stroke [30–33]. Cardiac output was shown to be associated with lower brain volumes and information speed processing [24]. In addition, some brain regions including the frontal cortex and parahippocampal gyrus, which are considerably implicated in cognition, seem to be more vulnerable in patients with HF [34]. MRI studies have also revealed [35] that HF patients have increased frequencies of focal brain abnormalities ranging from multiple cortical or subcortical infarcts to small vessel disease with white-matter lesions and lacunar infarcts with cerebral embolism and hypoperfusion being the most plausible mechanisms [36]. The location of the lesions in each individual with HF is likely to determine the domain specific impairment and these differences among patients with HF may account for the inconsistencies between the studies regarding the impairment of specific domains. In addition to location, lesion load and the ensuing cortical atrophy are also important determinants of cognitive impairment. Imaging techniques that integrate lesion location and burden would be valuable tools in predicting the cognitive consequences of HF.

4. Impairment of Cognitive Domains in Heart Failure

In most studies investigating the association between HF and cognitive performance using various neuropsychological tests, the term CI was used without specifying if the criteria for mild CI or specific dementias in each individual were met. In contrast, associations of CI, either global or in a specific

domain, were searched by comparing the test scores between patients and controls or normative data [9, 11, 12, 37]. This approach may account for the inconsistencies between the studies regarding the prevalence of CI and the impaired domains. In the following section we briefly describe the main cognitive domains and the identified CI profiles in HF patients.

4.1. Memory. Memory is a basic cognitive function, which includes three main stages: registration, storage, and retrieval. Several types of memory exist, each involving different brain areas. The most important types for clinical use are the episodic memory which refers to the memory of specific personal events and experiences and the semantic memory which reflects the memory of meanings and general knowledge. Memory involves structures mainly within the medial temporal lobe, such as the hippocampal region, the entorhinal, perirhinal, and parahippocampal cortex [38]. Other regions related to memory include diencephalic nuclei, the mammillary bodies, portions of the thalamus, and prefrontal areas. Memory loss is a usual complaint of many elderly people. Interview questions regarding the patient's personal life and public events are useful for an initial screen of memory problems. The California Verbal Learning Test (CVLT) and the Rey Auditory Verbal Learning Test (AVLT) are memory tests that require learning and immediate recall (immediate memory) of lists of words repeatedly presented. Then a second list of words is presented. After some time has elapsed the patient is asked to recall the first list (delay memory) [39]. Episodic memory impairment, which is manifested as impaired ability to acquire, encode, and retrieve new information, is the main cognitive deficit in Alzheimer's disease and is directly related to mesial temporal lobe atrophy [40]. Semantic memory is assessed through category fluency tests, picture-naming tests and word-picture matching tests. Deficits in semantic memory may be present in Alzheimer's disease or more prominently in semantic dementia [41]. In HF several studies have revealed cognitive deficits in both the initial learning of information and the delay recall of that information at a later time point [11, 13, 42–53]. However, some other studies did not confirm a decline in initial learning scores [54–56].

4.2. Attention-Working Memory-Psychomotor Speed. Attention is the ability to concentrate and focus selectively on a stimulus without being distracted by the background noise. Intact attention is essential for the patient's performance in other cognitive tasks. Working memory is a function of attention important for information processing. It refers to the ability to maintain and manipulate information temporarily in the mind and then retrieve it accurately in a few seconds, for instance, our ability to remember a phone number within a period of 30 seconds. The prefrontal cortex is considered the major brain structure involved in working memory. However, various other brain areas including parietal cortex, subcortical, and cerebellar regions also participate in working memory [57]. Serial subtractions of 7 from 100 are an easy and frequently used test for detecting attention problems. Attention and working memory can also be assessed using the digit span forwards and backwards and the Trail-Making-Test-A (TMT-A) in which individuals are instructed to connect sequential numbers by drawing lines. Impairment of attention and working memory is a feature of various medical conditions, including delirium and dementia. Another important aspect of cognition is the speed of information processing or else the psychomotor speed. It refers to the reaction time between a stimulus and the subsequent response. It represents a basic cognitive domain that affects other domains, especially executive functions. Processing speed is globally distributed in the brain and is dependent on the connectivity of nearly all cortical regions. It is believed that subcortical areas play an important role in this cognitive process [58]. Psychomotor slowing is characteristic of vascular, subcortical, and multi-infarct dementia [59, 60]. The Digit Symbol Substitution Test (DSST) is a useful test for the assessment of psychomotor speed. This test consists of 9 digit-symbol pairs. The patient is given an array of digits and is required to write the corresponding symbol beneath each digit as fast as possible. Another test used for the assessment of processing speed is the TMT-A and TMT-B. TMT-B also has a considerable executive function component. Deficits in attention, working memory, and speed of processing were detected in patients with HF in most studies [11–13, 42–47, 50, 52, 56, 61–64] but not all [44, 47, 48, 54, 65]. Given that these domains are mainly affected in vascular dementia it is possible that CI in HF and vascular dementia may share similar pathophysiologic mechanisms [66].

4.3. Executive Functions. Executive functioning refers to the cognitive abilities needed for daily life. Under this term, a wide range of cognitive processes and behavioral competencies are included, some of them being verbal reasoning, problem solving, planning, multitasking, cognitive flexibility and the ability to deal with novelty [67]. These skills primarily involve the frontal and prefrontal cortex. Complex cortical and subcortical circuits were also recognized to participate in executive functioning [68]. Deficits in executive functions are associated with a decline in one's ability to fulfill the requirements of everyday life. These deficits are common and occur early in the course of frontotemporal and vascular dementia. A number of tests are available for evaluating executive functions. The Stroop Test, the TMT-B, the letter fluency test and the Wisconsin Card Sorting Test (WCST) are commonly, used tests in clinical studies [69]. In patients with HF, the majority of studies found significant impairment in measures of executive functioning [11, 43, 44, 49, 51, 52, 61, 64], whereas two studies did not confirm such deficits [13, 20].

4.4. Language. Language deficits are quite common in dementias. Patients usually complain of difficulties in word finding and naming. They may use related words instead of the target word, have trouble following instructions or staying on a conversation. Patients also have impairment in word recognition in reading and writing [70]. The main brain regions for language are Broca's area, which is related to motor aspects of speech and Wernicke's area, which is responsible for language perception. These two regions are connected to each other and to temporal, prefrontal, and

parietal regions, forming a complex network involved in language function. Evaluation of language domain includes assessment of naming, repetition, following commands, verbal fluency, reading and writing. Boston Naming Test (BNT), Benton Controlled Oral Word Association Test (COWAT), Token Test, and semantic fluency task are some useful neuropsychological tests for examination of language function. It should be noted that language disturbance can interfere with the patient's performance in other cognitive domains. Compared to other domains, there has been little work on language deficits in patients with HF. Two studies reported impaired performance on language measures in patients with HF [20, 52].

4.5. Visuospatial Function. Visuospatial function refers to the visual perception of the environment and the spatial relationships between the objects. Common manifestations of visuospatial deficits include impairment in navigation and topographical orientation and difficulty in dressing, recognizing familiar faces, or grasping objects [71]. The neural network that mediates visuospatial cognition is widely distributed and includes areas of parietal lobes, occipital cortex, lateral prefrontal cortex, medial and inferior temporal cortex, basal ganglia, and white-matter tracts. Neuropsychological tests for the assessment of visuospatial functions include Benton Facial Recognition Test (FRT), Judgement of Line Orientation Test (JLO), and Block Design Test. The Clock Drawing Test (CDT) is also widely used for evaluation of visuospatial and constructional ability. Deficits in visuospatial perception and construction are a prominent manifestation of Alzheimer's disease. In patients with HF some studies noticed visuoperceptual deficits [47, 49, 53]. Another study, however, did not replicate this finding [52].

Given the high occurrence of deficits in cognitive function in patients with HF and their prognostic value in the course of HF, adequate assessment and early detection of CI is essential. HF patients with CI may have diverse patterns of cognitive domain involvement which can be understood considering the pathophysiology of CI in HF where a concomitant and uneven involvement of multiple brain areas occurs. All these cognitive domains should be included in the assessment of CI in HF in order to achieve both reliability and sensitivity.

Most studies have used various measures of cognitive functioning, and currently there is no consensus among investigators regarding the optimum neuropsychological tests to assess patients with HF. Brief screening instruments such as the MMSE or the Montreal Cognitive Assessment (MoCA) can be easily administered by health professionals in the outpatient clinical practice to confirm the presence of cognitive impairment. Brief tests, however, may be insufficient in identifying subtle cognitive deficits and more detailed neuropsychological assessment will be required. On the other hand, implementation of comprehensive series of tests requires specific training for administration and interpretation, is time consuming, and consequently may affect performance and compliance of participants. Future studies therefore should focus on validating a screening instrument that combines brevity, ease of use, and sensitivity to detect in HF patients the presence of cognitive impairment in each specific domain.

5. Severity Progression of CI

The prevalence of CI severity in HF patients with CI has not been adequately addressed in the literature. In addition, no standard criteria were used for delineating between mild, moderate, and severe CI in the studies. Most of the patients with HF and CI in these studies had mild impairment in cognition, whereas about 25% had moderate-to-severe CI [9, 56, 72]. Furthermore, the degree of cognitive decline in HF patients appears to correlate with the severity of HF. Zuccalà et al. [23] in a study of 57 patients with HF described a nonlinear relationship between left ventricular ejection fraction and MMSE scores. Interestingly, a greater decrease in rate of MMSE scores was revealed for ejection fraction (EF) values <30%. A similar relationship between measures of verbal memory and EF drop below 30% was noted by another group in patients older than 63 years [73]. Likewise, other studies found that decrease in cardiac output [21, 25], long duration of HF [74], and higher New York Heart Association (NYHA) class of the disease [75] parallel the severity of cognitive impairment.

Another important issue which has received much attention lately is whether cognitive impairment in patients with HF progresses to dementia over time, remains stable, or even remit. In an important population-based cohort study [27] Qiu et al. investigated the progression to dementia of 205 individuals with HF over a 9-year follow-up period. At baseline assessment HF patients, although nondemented, had lower cognitive performance measured by MMSE test compared to controls. These patients, in the long-term follow-up, were at increased risk of progression to dementia (HR: 1.84, C.I.: 1.35–2.51) or Alzheimer's disease (HR: 1.80, C.I.: 1.25–2.61). Interestingly, the use of antihypertensive drugs seemed to counteract the effect of HF on dementia risk. Another study in patients aged >80 years examined the relationship between HF and the change over time of specific cognitive domains. It was shown that measures of episodic memory decline more in HF patients compared to the group without HF [47].

Finally, some studies reported improvements in cognitive performance of HF patients over time which could be attributed to improvement of cerebral hypoperfusion and consequently neuronal function due to optimum management of heart failure [76, 77], initiation of ACE inhibitors [14], or implementation of exercise training programs [64].

6. Impact of CI in HF

Deficits in attention, learning, memory, executive functions, and psychomotor speed observed in high prevalence in patients with HF may impair their ability to carry out self-care and adhere to treatment requirements. Such deficits may also compromise patients' capacity to recognize HF worsening symptoms and make appropriate decisions about their health care [8]. In a recent study [78] mild CI was a significant predictor of lower self-care management and

self-confidence scores with other determinants of self-care being severity of HF and presence of comorbidities. In addition, HF patients with CI had greater difficulty with medication management [79], were less likely to participate in outpatient treatment programs [74], and failed to recognize early symptoms and make the appropriate self-care decisions [80, 81]. As a result, these patients were at increased risk of HF decompensation, unplanned hospital admissions or even death [82]. These data suggest that CI may ultimately represent a risk factor of suboptimal health care and worse outcome of HF patients. Impairments in attention, judgment, and speed of information processing should be taken into account when treatment strategies are planned.

A number of studies in patients with HF also examined the impact of CI on disability in daily activities, mortality, and quality of life. The functional independence in daily activities was investigated in a large multicentre study in patients with HF. The study revealed that CI was associated with a sixfold increase in functional disability (OR: 6.49; 95% C.I.: 4.39–9.59) independently of any potential confounders such as age, sex, comorbidities, medications or low blood pressure [83]. Dependence and increased disability are known predictors of raised mortality and increased hospital readmission rates. CI was also associated with increased risk of mortality. In a study investigating the in-hospital mortality among HF patients, CI was found to increase the mortality by five times (Relative Risk (RR): 4.9; 95% C.I.: 2.9–8.3) after adjusting for multiple confounders [84]. CI, therefore, seems to represent a hidden comorbidity with an adverse impact on disease course, influencing the burden of disease, survival rates, and resource consumption. Finally, cognitive decline that accompanies HF may negatively affect many aspects of daily life and the patients' perceptions of quality of life and well-being. In a recent study [85], significant determinants of the patients' quality of life included disease severity, age, depressive symptoms, and memory measures although the latter accounted only for a small amount of the observed variance.

7. Therapeutic Implications

A small number of studies have addressed the influence of HF treatment on cognitive performance of patients with HF. In a retrospective database analysis of 1220 patients with HF, the use of ACE inhibitors was associated with improvement in cognitive performance (OR: 1.57; 95% C.I.: 1.18–2.08). Furthermore, the probability of improvement increased with higher dosages of ACE inhibitors and longer duration of treatment [14]. In addition, the same group of investigators reported [86] that the use of digoxin also improved cognitive performance among older patients with HF, reaching an OR of 1.69 (95% CI: 1.20–2.38). In another study of 50 patients with severe HF that were reassessed 6 weeks after the introduction of the appropriate medications, it was shown that effective treatment of HF patients according to their needs with diuretics, ACE inhibitors, cardiotonic medication (such as digoxin), and antiarrhythmic drugs had beneficial effects in patients' cognitive performance and in particular in attentional and visuospatial scores [87]. These studies provided valuable evidence that specific medications used in HF such as ACE inhibitors and digoxin as well as optimal HF therapy may have beneficial effects on cognitive performance of HF patients. However, further research is needed mainly from randomized trials in order to confirm these results and establish possible favorable role of various medications on cognition.

Some studies also examined the role of nonpharmacological approaches on cognition in patients with HF. In agreement with pharmacological treatments invasive methods were also demonstrated to improve cognition. It was reported that impaired cognitive function in patients with HF was significantly improved after heart transplantation [42, 65]. Of note, pacemaker implantation in bradycardic patients was associated with improvement in verbal cognitive function [88]. Two studies tested the impact physical activity on cognitive function of HF patients. As expected, physical activity was demonstrated to have beneficial effects on cognitive performance [64, 89]. Finally, the efficacy of cognitive training intervention known as cognitive rehabilitation on mental performance was evaluated in patients with HF. The authors through structured cognitive training programs designed to improve several aspects of cognition found significant improvements on measures of working memory, psychomotor speed, executive function, and memory [90]. These interesting results should be further investigated especially in larger randomized controlled trials.

There are no current studies examining the effects of the acetylcholinesterase inhibitors (i.e., the group of medications licensed for the symptomatic treatment of Alzheimer's disease) on cognitive performance of patients with HF. Given that acetylcholinesterase inhibitors were also found efficacious in vascular dementia, a similar effect might be expected in patients with HF. Other approaches such as repetitive transcranial magnetic stimulation [91] could also be considered for CI in HF.

In summary, optimal HF treatment through pharmacological or invasive approaches ameliorates cognition among patients with HF. Effective control of vascular risk factors should also be achieved considering the pathophysiology of CI in HF. Patients should be encouraged to participate in cognitive, physical, and social activities in order to improve their cognitive performance.

8. Conclusions

Cognitive impairment is particularly common in HF and is increasingly regarded as an independent prognostic factor of HF outcome since it exerts significant effects on quality of life, disability, morbidity, and mortality of patients with HF.

HF patients may present with deficits in attention, learning ability and delay recall, working memory, executive function, and psychomotor speed. They may have fluctuations in their cognition over time, depending on the effective management of HF, but they are at increased risk of progression to dementia. However, more conclusive evidence especially from prospective longitudinal studies is required for the establishment of the long-term course of CI in HF

patients and the possibility of emergence of modifiable risk factors and new targets for intervention.

CI in HF seems to result from structural changes in the brain cortex and white-matter due to microembolism, chronic or intermittent cerebral hypoperfusion, and impaired flow regulation in small vessels which lead to cerebral hypoxia and ischemic brain damage. Along with the neurodegenerative component, there is also a functional and consequently modifiable component of neuronal dysfunction due to decreased cerebral blood flow which may account for the improvements of cognitive performance after effective treatment of HF. Future studies are needed to provide further insights into the relationship between CI and tissue structural abnormalities and neuronal dysfunction.

Furthermore, a priority for researchers is the identification of a screening instrument sensitive to the cognitive profile of HF and easy to use in the clinical setting. With increasing awareness that CI can worsen HF outcome, health professionals should recognize the importance of early identification and management of patients at risk of CI and become familiar with assessment of cognitive performance in their routine evaluations.

Authors' Contribution

E. Dardiotis and G. Giamouzis have contributed equally to this work.

Conflict of Interests

The authors declare no conflict of interests.

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Research Article

Protective Function of STAT3 in CVB3-Induced Myocarditis

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The transcription factor signal transducer and activator of transcription 3 (STAT3) is an important mediator of the inflammatory process. We investigated the role of STAT3 in viral myocarditis and its possible role in the development to dilated cardiomyopathy. We used STAT3-deficent mice with a cardiomyocyte-restricted knockout and induced a viral myocarditis using Coxsackievirus B3 (CVB3) which induced a severe inflammation during the acute phase of the viral myocarditis. A complete virus clearance and an attenuated inflammation were examined in both groups WT and STAT3 KO mice 4 weeks after infection, but the cardiac function in STAT3 KO mice was significantly decreased in contrast to the infected WT mice. Interestingly, an increased expression of collagen I was detected in STAT3 KO mice compared to WT mice 4 weeks after CVB3 infection. Furthermore, the matrix degradation was reduced in STAT3 KO mice which might be an explanation for the observed matrix deposition. Consequently, we here demonstrate the protective function of STAT3 in CVB3-induced myocarditis. Since the cardiomyocyte-restricted knockout leads to an increased fibrosis, it can be assumed that STAT3 signalling in cardiomyocytes protects the heart against increased fibrosis through paracrine effects.

1. Introduction

Acute viral myocarditis is a frequent cause of sudden cardiac death and can later progress to dilated cardiomyopathy (DCM) due to the chronic inflammatory process. On the one hand, the inflammatory process is needed to control the acute viral infection, but, on the other hand, prolonged inflammation in the subacute phase of the disease will lead to adverse cardiac remodelling. This is mainly characterised with an accumulation of cardiac collagen as well as a deregulation of matrix metalloproteinases, known to be important for collagen degradation and for modulating the inflammatory process [1, 2]. Despite our growing knowledge about viral myocarditis, it remains challenging to diagnose and especially treat patients with viral myocarditis [3, 4]. Therefore, we need to understand more about the inflammatory process in the acute phase of viral myocarditis to tailor future treatment strategies to limit the progression to DCM.

One of the potent regulators of inflammation is the signal transducer and activator of transcription 3 (STAT3) which is activated in response to extracellular proteins such as cytokines. The members of the IL-6-type cytokine family bind to plasma membrane receptor complexes containing the signal transducing 130 kDa glycoprotein (gp130) that are ubiquitously expressed in most tissues including the heart. Ligand binding to this receptor subsequently leads to the phosphorylation of STAT3 which is then translocated into the nucleus [5]. This family of cytokines is named after the prominent member IL-6 which leads to an increased phosphorylation of STAT3 [6]. Several studies have implicated that STAT3 is essential for hypertrophy and cytoprotection in the heart [7–9]. While its role in acute viral myocarditis is still unknown, it is interesting that the signalling via

the gp130/STAT3 pathway is profoundly altered in the myocardium of patients with DCM [10]. It was observed that IL-6 expression as well as STAT3 phosphorylation was decreased in the myocardium of patients with DCM. Interestingly, the myocardial IL-6 expression decreases, whereas the circulating level of IL-6 was increased in patients with heart failure [11, 12]. Moreover, several experimental studies have been performed with a cardiomyocyte-restricted knockout of STAT3 [13]. In general, the cardiomyocyte-restricted STAT3 KO leads to an age-induced fibrosis. Beyond 9 months, the STAT3 KO mice show increased interstitial fibrosis, and, at 12 months, the hearts were dilated [14, 15], suggesting a role for STAT3 in cardiac remodelling and the progression to DCM.

Here, we study the effect of cardiomyocyte-restricted knockout of STAT3 in viral myocarditis to evaluate its role during inflammation as well as adverse cardiac remodelling in experimental viral myocarditis.

2. Material and Methods

2.1. Study Design. Mice with the cardiomyocyte-restricted STAT3 deletion were generated on a CB6FI genetic background as described previously [14] and kept under standard conditions. Male STAT3 KO and WT animals were infected with 10^6 plaque-forming units of CVB3 intraperitoneally (all mice were 6 weeks old at the day of infection). Infected mice were compared with saline-treated mice of both groups 10 and 28 days after infection. This investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the US NIH (NIH Publication number 85-23, revised 1996).

2.2. Hemodynamic Measurements and Surgical Procedures. Four weeks after infection with CVB3, all animals were anesthetized (thiopental 125 mg/g i.p.), intubated, and artificially ventilated. A 1.2 F-mircoconductance pressure catheter (SciSence, Ontario, Canada) was positioned in the left ventricle via the right carotid artery for continuous registration of pressure-volume loops in a closed-chest model as described previously [16].

Global function was quantified by heart rate (bpm), cardiac output (mL/min), stroke volume (μL), stroke work (μL · mmHg), and ejection fraction (%). Systolic function was assessed by end systolic pressure, P_{es} (mmHg), left ventricular contractility dP/dt_{max} (mmHg/s), and end systolic volume V_{es} (μL). Diastolic performance was measured by end diastolic pressure P_{ed} (mmHg), left ventricular relaxation dP/dt_{min} (mmHg/s), left ventricular relaxation time Tau (ms), and end diastolic volume V_{ed} (μL).

Hearts of sacrificed animals were removed and immediately frozen in liquid nitrogen and stored at −80°C for later biological or immunohistochemical analyses.

2.3. RNA Isolation and Gene Expression Analysis. Frozen tissue sections were minced in Trizol and further disrupted during 10 minutes of vigorous shaking. To extract the RNA, chlorophorm was added, mixed, and centrifuged. The aqueous phase containing the RNA was collected in a separate tube, and isopropanol was added. For precipitation, the RNA solution was centrifuged 15 minutes at 4°C at high speed. The RNA pellet was then further purified using the RNeasy Mini Kit (Qiagen) according to manufacturer's protocol. One μg of RNA was reverse transcribed into cDNA using the High Capacity Kit (Applied Biosystems) and then further diluted to a final concentration of 5 ng/μL cDNA.

The relative quantification of mRNA levels were carried out on a 7900 TaqMan systems (Applied Biosystem). To assess the mRNA expression of the target genes, real-time PCR was performed using 5 μL of the gene expression master mix (Applied Biosystems) and 0.5 μL of the gene expression assay for IL-1β (Mm00434228_m1), IL-6 (Mm00446190_m1), TNF-α (Mm00443258_m1), IL-10 (Mm00439616_m1), TGF-β (Mm00441724_m1), ANF (Mm01255747_g1), MMP13 (Mm00439491_m1), TIMP1 (Mm00441818_m1) (each includes forward and reverse primers as well the fluorescently FAM-labelled probe) from Applied Biosystems, and 1 μL of cDNA in a final volume of 10 μL. Quantification of the house keeping gene 18S (Hs99999901_s1) as an internal control was performed for each sample. Data were normalized to 18S RNA level as an endogenous control and are expressed using the formula $2^{-\Delta\Delta Ct}$ in comparison to the corresponding untreated controls. CVB3 copy numbers were detected using a forward primer (CCCTGAATGCGGCTAATCC) and a reverse primer (ATTGTCACCATAAGCAGCCA) in a final concentration of 60 ng/μL as well as a FAM-labelled MGB probe (FAM-TGCAGCGGAACCG) in a final concentration of 5 pM.

2.4. Histological Measurements. Pieces of heart were either embedded in Tissue-Tek or paraffin. Sections embedded in Tissue-Tek were stained with antibodies directed against CD3 (goat anti-CD3; Santa-Cruz), VCAM (rat anti-VCAM; Pharmingen), collagen I (rabbit anti-ColI; Chemicon), and collagen III (rabbit anti-ColIII; Calbiochem). The paraffin sections were used for Mac3 staining using a specific antibody directed against Mac3 (rat anti-Mac3; Pharmingen).

For VCAM and Mac3 staining a biotinylated secondary rabbit anit-rat antibody and for CD3 staining a biotinylated secondary rabbit anti-goat antibody was used followed by visualization with a biotin-streptavidin-peroxidase technique (Vectorlabs). For visualization of ColI and ColIII staining, the Envision peroxidise technique was used (Dako).

2.5. In Situ Hybridization. Tissue sections from frozen hearts 28 days after CVB3 infection were used for detection of viral RNA with a ^{35}S-labelled CVB3-specific RNA probe as described previously [17, 18]. Briefly, hybridisation with RNA probe proceeded at 42°C for 18 hours. Slices were then washed as described [18], and nonhybridized single-strand RNA probes were digested by RNase A. Slices were autoradiographed and stained with hematoxylin/eosin.

2.6. Statistical Analysis. Data are shown as mean ± SEM. For comparison the nonparametric, Mann-Whitney U test was used. Differences were considered significant when the

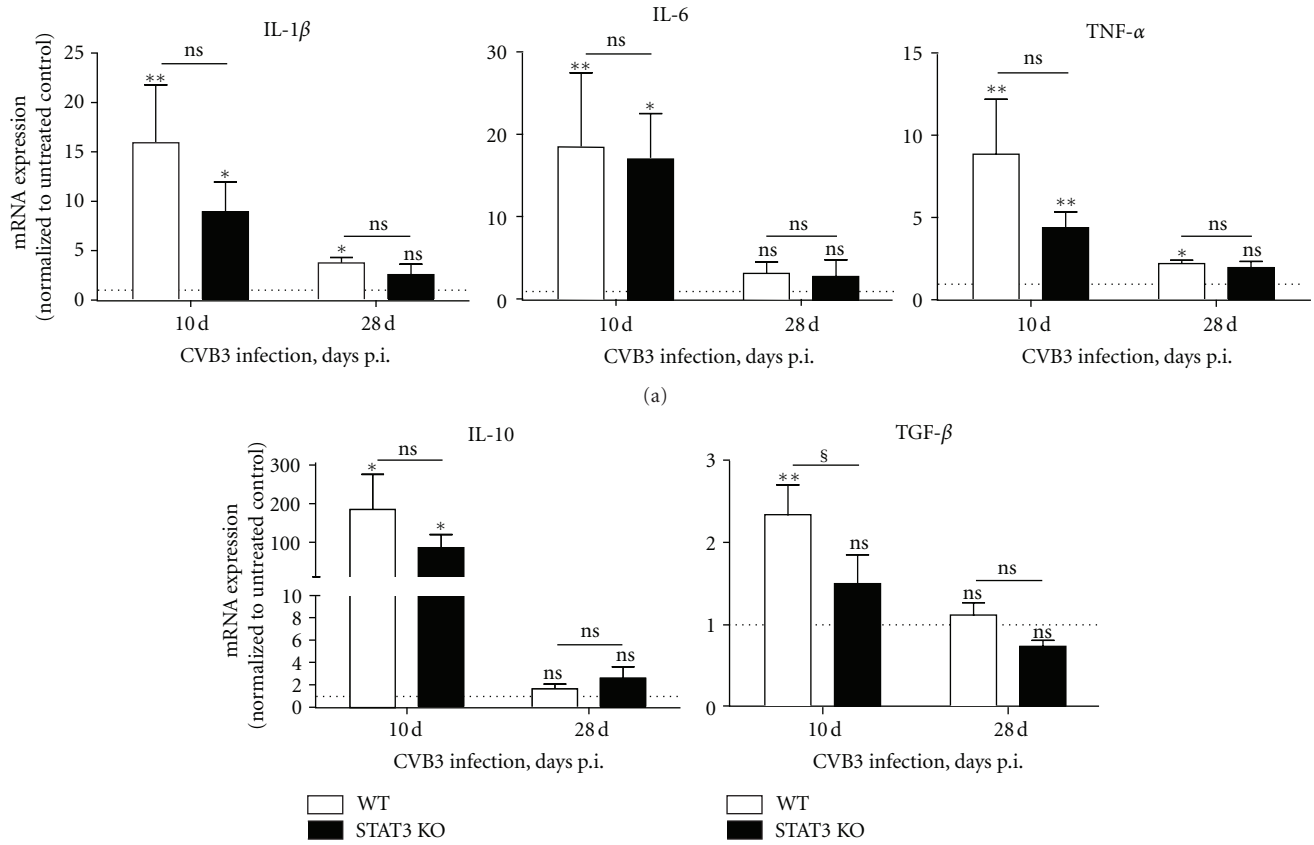

Figure 1: Cytokine expression levels in cardiac tissue of CVB3 infected mice. The mRNA expression levels are shown 10 and 28 days after CVB3 infection of WT and STAT3 KO mice. The expression data are normalized to the house-keeping gene 18S and to the expression levels of the corresponding untreated mice and expressed as x-fold over basal expression using the formula $2^{-\Delta\Delta Ct}$. *Data were compared to the expression of the corresponding untreated controls. $^*P < 0.05$; $^{**}P < 0.01$. §Data between WT and STAT3 KO mice were compared. $^{\S}P < 0.05$.

probability value P is lower than 0.05. All analyses were performed using Graph Pad Prism 5.0 software (GraphPad Software, La Jolla, CA).

3. Results

3.1. Cytokine Expression after CVB3 Infection. To study the cytokine response induced by intraperitoneal CVB3 infection, the mRNA expression levels in cardiac tissue of infected and non infected WT and STAT3 KO mice were analysed.

10 days after infection with CVB3 WT mice show a significantly increased mRNA expression level of the proinflammatory cytokines IL-1β (15.92 ± 5.86 fold, $P = 0.0043$), IL-6 (18.62 ± 8.89 fold, $P = 0.0043$), and TNF-α (8.85 ± 3.34 fold, $P = 0.0043$) compared to the expression level in cardiac tissue of untreated WT mice. Whereas, 28 days after CVB3 infection WT mice show a weaker but still significantly increased mRNA expression level of IL-1β (3.75 ± 0.57, $P = 0.0195$) and TNF-α (2.20 ± 0.21, $P = 0.0430$) compared to the expression levels in untreated controls. A raised IL-6 mRNA expression level could no longer be detected in the CVB3-infected WT mice (Figure 1(a)—white bars). The anti-inflammatory cytokines IL-10 (184.41 ± 90.69 fold, $P = 0.0357$) and TGF-β (2.33 ± 0.37 fold, $P = 0.0087$) are both significantly increased 10 days after CVB3 infection, whereas no raised mRNA expression was determined 28 days after infection (Figure 1(b)—white bars).

In the cardiac tissue of infected STAT3 KO mice, the mRNA expression of the proinflammatory cytokines IL-1β (8.95 ± 3.00 fold, $P = 0.0111$), IL-6 (17.19 ± 5.39 fold, $P = 0.0140$), and TNF-α (4.39 ± 0.96, $P = 0.0055$) was significantly increased 10 days after infection compared to the expression levels in untreated STAT3 KO mice. In contrast to the cytokine expression in WT mice, the expression of IL-1β and TNF-α in STAT3 KO mice was not longer raised 28 days after infection. However, as already shown for infected WT mice, no increased IL-6 expression was determined (Figure 1(a)—black bars). The expression of the anti-inflammatory cytokine IL-10 (85.91 ± 33.96 fold, $P = 0.0357$) was increased 10 days after CVB3 infection and decreased to a normal expression level 28 days after infection. Interestingly, an augmented TGF-β

expression was not detected in STAT3 KO mice 10 or 28 days after CVB3 infection (Figure 1(b)—black bars).

Comparing the cytokine expression of infected WT mice and infected STAT3 KO mice, only few differences were obvious. Interestingly, in infected STAT3 KO mice, TGF-β expression was not significantly increased (1.50 ± 0.35 fold, $P = 0.2766$) 10 days after infection, in contrast to the raised expression level in infected WT mice (2.33 ± 0.37 fold, $P = 0.0087$) (Figure 1(b)). Additionally, the anti-inflammatory cytokine IL-10, which is increased in both WT and STAT3 KO mice, is slightly but not significantly weaker increased in STAT3 KO mice 10 days after CVB3 infection.

3.2. Immune Cell Infiltration after CVB3 Infection. The intraperitoneal CVB3 infection leads to a significantly increased infiltration of $CD3^+$ and $Mac3^+$ cells in cardiac tissue of WT as well as STAT3 KO mice. In general, 10 days after CVB3 infection, more infiltrated cells were determined than 28 days after infection.

In WT mice, the number of infiltrated $CD3^+$ (18.30 ± 6.06 fold, $P = 0.0043$) and $Mac3^+$ (31.19 ± 9.02 fold, $P = 0.0043$) cells were significantly increased 10 days after CVB3 infection compared to the control animals. In comparison to the inflammation occurring 10 days after infection, the number of $CD3^+$ cells was slightly but not significantly decreased to 6.40 ± 1.45 fold ($P = 0.0070$) compared to untreated controls 28 days after infection. In contrast, the number of infiltrated $Mac3^+$ cells was strongly and significantly ($P = 0.0046$) reduced from 31.19 ± 9.02 fold 10 days after infection to 3.72 ± 1.29 fold ($P = 0.028$ compared to untreated controls) 28 days after infection (Figure 2—white bars).

In the cardiac tissue of infected STAT3 KO mice, a significantly increased number of $CD3^+$ cells (14.48 ± 4.38 fold, $P = 0.0003$) was observed 10 days after CVB3 infection which was significantly reduced ($P = 0.0379$) to an 4.90 ± 1.03 fold increase ($P = 0.0182$) compared to untreated controls 28 days after infection. In contrast, the number of infiltrated $Mac3^+$ cells 10 days after CVB3 infection (14.48 ± 4.86 fold, $P = 0.0006$) was slightly but not significantly reduced (8.86 ± 2.12 fold, $P = 0.0091$) 28 days after infection (Figure 2—black bars).

No differences were found comparing the number of infiltrated $CD3^+$ cells between WT and STAT3 KO mice. Interestingly, the significantly reduced infiltration of $Mac3^+$ cells in cardiac tissue of CVB3-infected WT comparing day 10 and 28 after infection could not be demonstrated in the cardiac tissue of infected STAT3 KO mice. There, the number of $Mac3^+$ cells was not significantly decreased after 28 days compared to 10 days. Even more $Mac3^+$ cells were found in cardiac tissue of CVB3-infected STAT3 KO mice compared to CVB3-infected WT mice (WT: 3.72 ± 1.29 fold versus STAT3 KO: 8.86 ± 2.12 fold, $P = 0.0232$) 28 days after infection.

3.3. Virus Load and Clearance. Intraperitoneal CVB3 infection resulted in a high viral genome quantity in cardiac tissue of both infected groups 10 days after infection determined by gene expression analysis. No viral genome was detected in non infected control animals. No significant difference was determined in viral genome quantity comparing infected WT mice ($(151 \pm 88) \times 10^3$ copy numbers) and infected STAT3 KO mice ($(30 \pm 18) \times 10^3$ copy numbers). Similarly, 28 days after infection, the copy number of viral genome in infected WT mice (18 ± 10) and infected STAT3 KO mice (16 ± 5) revealed no differences. Therefore, a nearly complete virus clearance was demonstrated for both WT and STAT3 KO mice 28 days after CVB3 infection. The complete virus clearance was further confirmed using *in situ* hybridisation which stains virus replication with a radioactively labelled CVB3-specific probe. There, no viral genome was detected in infected wild-type or STAT3 KO mice 28 days after infection.

3.4. Expression of Adhesion Molecule VCAM. The expression of the vascular cell adhesion molecule VCAM was analysed using cryosections of untreated and CVB3-infected WT and STAT3 KO mice 28 days after infection. Whereas the VCAM expression was not raised in infected WT mice compared to their untreated controls (1.28 ± 0.46 fold, $P = 0.5536$), a significant increase was determined in STAT3 KO mice (5.00 ± 1.38 fold, $P = 0.0290$). Therefore, the significantly higher VCAM expression in infected STAT3 KO mice compared to infected WT mice was obvious ($P = 0.0250$) (Figure 3).

3.5. Hemodynamic Data. The infected WT and the infected STAT3 KO mice were hemodynamically characterized 28 days after infection and compared to the hemodynamic function of their respective non infected controls.

As shown in Table 1, the global function in infected WT and infected STAT3 KO mice is restricted compared to the respective controls. Both WT and STAT3 KO revealed a significantly reduced cardiac output and stroke work induced by CVB3 infection. Furthermore, the ejection fraction is significantly reduced in infected STAT3 KO mice and slightly but not significantly reduced in infected WT mice. Moreover, CVB3 infection resulted in impaired systolic and diastolic function indicated by significantly reduced P_{es} and dP/dt_{max} as well as significantly increased P_{ed}, dP/dt_{min}, and Tau in WT as well as in STAT3 KO mice.

Interestingly, compared to their respective controls, infected STAT3 KO mice reveal a significantly more impaired global, systolic, and diastolic function. The ejection fraction is reduced to 78% in infected WT animals and significantly more decreased to 57% in infected STAT3 KO mice. Moreover, the end systolic pressure P_{es} was reduced to 87% in infected WT and to 60% in infected STAT3 animals. Furthermore, the end diastolic pressure P_{ed} was 2.7-fold higher in infected WT mice and even 5-fold increased in infected STAT3 KO mice compared to their respective controls.

3.6. ANF as Marker for Heart Failure. Since atrial natriuretic factor (ANF) is known as a marker for heart failure, we examined the mRNA expression level of ANF which was higher expressed in cardiac tissue of infected WT (7.20 ± 3.54 fold, $P = 0.0823$) and STAT3 KO (5.11 ± 1.18 fold, $P = 0.0079$) mice as in control animals. Interestingly, in infected

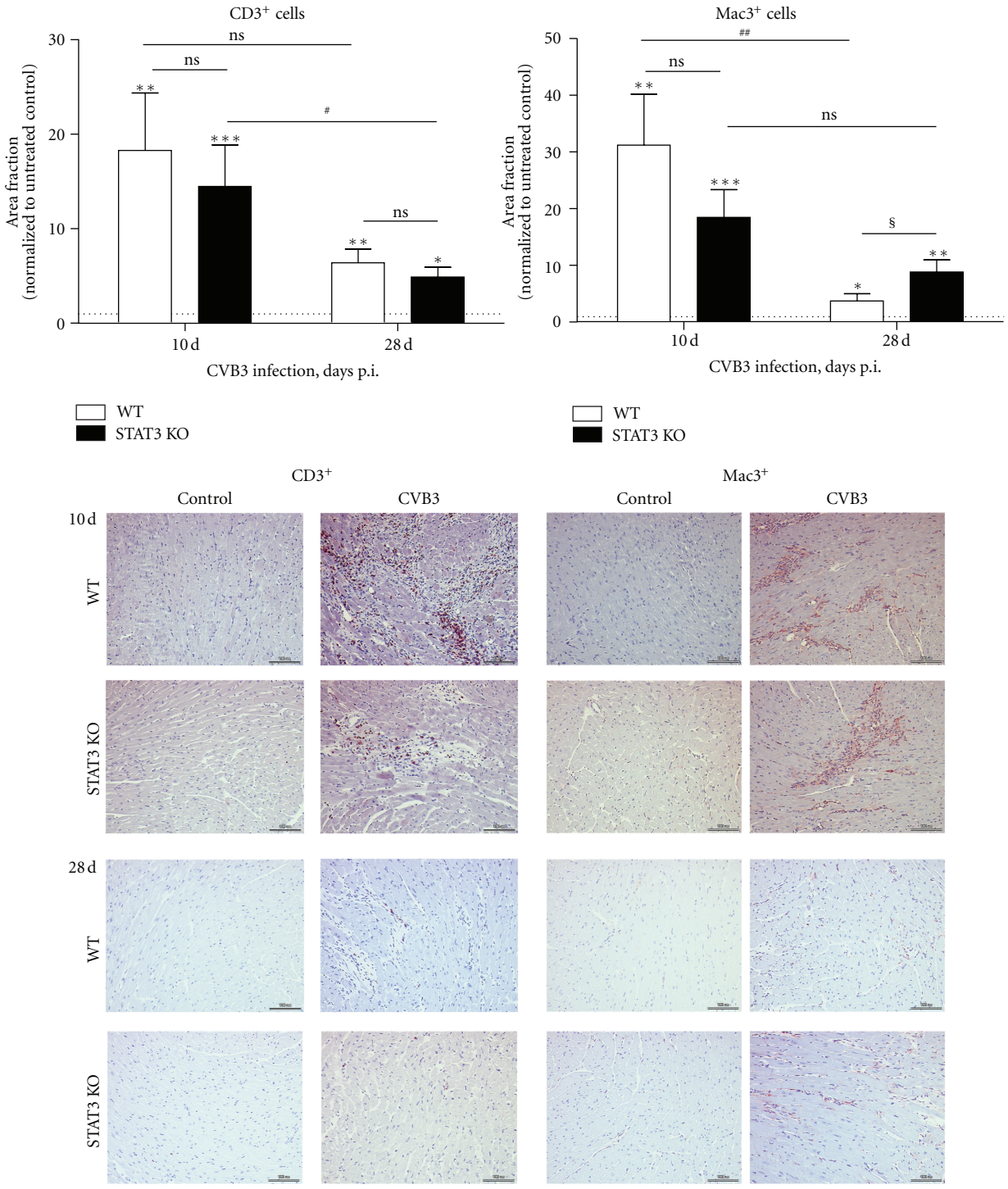

Figure 2: Cell infiltration in cardiac tissue 10 and 28 days after CVB3 infection. Data are expressed as area fraction of tissue sections after staining with antibodies directed against CD3 or Mac3. Data were normalized to corresponding untreated controls and expressed as x-fold over basal level. *Data were compared to the corresponding untreated controls. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$. §Data between WT and STAT3 KO mice were compared. $^{\S}P < 0.05$. #Data between 10 or 28 days were compared. $^{\#}P < 0.05$; $^{\#\#}P < 0.01$.

WT mice, ANF expression was nearly reduced to the normal expression level (2.72 ± 1.29 fold, $P = 0.9371$) 28 days after infection. Whereas, the increased ANF expression level remained unchanged in STAT3 KO mice (9.37 ± 2.62 fold, $P = 0.0476$) and revealed a significant higher expression ($P = 0.0160$) of ANF in cardiac tissue of infected STAT3 KO mice compared to infected WT 28 days after infection (Figure 4).

Table 1: Animal characteristics and hemodynamic measurements 28 days after CVB3 infection.

	WT	WT-CVB3	STAT3 KO	STAT3 KO-CVB3
Body weight [g]	29 ± 2	23 ± 1	28 ± 1	22 ± 1
Heart weight [g]	0.15 ± 0.03	0.09 ± 0.01	0.11 ± 0.01	0.09 ± 0.01
Global function				
Heart rate [bpm]	434 ± 30	404 ± 14	353 ± 90	420 ± 12
Cardiac output [mL/min]	15 ± 1	11 ± 1*	14 ± 1	8 ± 1*†
Stroke volume [μL]	31 ± 4	29 ± 2	30 ± 1	22 ± 2
Stroke work [μL · mmHg]	3589 ± 116	2384 ± 117**	3331 ± 173	1631 ± 125*††
Ejection fraction [%]	67 ± 3	52 ± 2	68 ± 2	39 ± 2**††
Systolic function				
P_{es} [mmHg]	123 ± 6	100 ± 1*	122 ± 11	74 ± 9*†
dP/dt_{max} [mmHg/s]	9640 ± 786	6663 ± 325*	9415 ± 637	3422 ± 202**††
V_{es} [μL]	28 ± 2	31 ± 3	26 ± 2	47 ± 5*†
Diastolic function				
P_{ed} [mmHg]	4.0 ± 0.8	11.0 ± 1.2*	3.7 ± 0.3	18.7 ± 3.0*†
dP/dt_{min} [mmHg/s]	−7873 ± 319	−4757 ± 240**	−7813 ± 131	−2818 ± 216**††
Tau [ms]	11.7 ± 0.3	15.2 ± 0.4*	11.3 ± 0.7	17.8 ± 0.8**†
V_{ed} [μL]	49 ± 5	57 ± 3	48 ± 3	74 ± 4**††

* Significantly different versus respective control.
† Significantly different versus WT-CVB3.

3.7. Extracellular Matrix Alteration. Regarding the regulation of extracellular matrix cryosections of cardiac tissue from CVB3 infected and not infected mice were stained with antibodies directed against collagen I or collagen III.

No increased area fraction of collagen III was determined 10 or 28 days after infection, whereas collagen I deposition in the cardiac tissue was induced by CVB3. 10 days after infection, significantly increased collagen I content was measured in both infected WT (3.45 ± 0.66 fold, $P = 0.0043$) and infected STAT3 KO mice (3.79 ± 1.00 fold, $P = 0.0006$). Interestingly, 28 days after infection, the collagen I content in infected WT mice (1.24 ± 0.27 fold) was reduced to the collagen I level comparably to non infected control animals. Whereas, this reduced collagen I content could not be detected in infected STAT3 KO mice 28 days after infection. There, the area fraction of collagen I was still significantly increased by 5.88 ± 1.82 fold compared to the untreated controls which revealed a significant difference between infected WT and infected STAT3 KO mice ($P = 0.0014$). Furthermore, the Col I/ColIII ratio displays a CVB3-induced increase 10 days after infection. In WT mice, this increase dropped significantly down to the normal level 28 days after infection, whereas, in infected STAT3 KO mice, the CVB3-induced increase remains unchanged 28 days after infection which reveals a significant distinction ($P = 0.0077$) between infected WT and infected STAT3 KO mice (Figure 5(a)). Consequently, CVB3 infection resulted in increased fibrosis in STAT3 KO compared to WT mice.

Additionally, we further examined the mRNA expression levels of the ECM-degrading system. The mRNA expression of the collagenase MMP13 was not significantly increased 10 days after infection, whereas the expression of the endogenous inhibitor TIMP1 was significantly increased (WT: 37.42 ± 17.78 fold, $P = 0.0043$; STAT3 KO: 51.59 ± 28.97 fold, $P < 0.0001$) which is then reduced to an only slightly increased expression 28 days after infection (WT: 3.07 ± 0.93 fold, $P = 0.2168$; STAT3 KO: 4.47 ± 1.54 fold, $P = 0.0485$) and revealed no distinction between WT and STAT3 KO mice. In contrast, the mRNA expression of MMP13 in STAT3 KO mice is significantly reduced (0.39 ± 0.08 fold, $P = 0.0121$) 28 days after CVB3 infection, whereas the MMP13 expression in infected WT mice remains unchanged.

Concerning the MMP13/TIMP1 ratio, the CVB3-induced significant reduction of ECM degradation is clearly demonstrated for WT and STAT3 KO mice 10 days after infection but revealed no difference between both. Interestingly, this inhibition of ECM degradation was still demonstrated in infected STAT3 KO mice 28 days after infection but was not longer determined in infected WT animals.

4. Discussion

To study the relevance of the signal transducer and activator of transcription molecule 3 (STAT3) in CVB3-induced myocarditis, we examined mice with a cardiomyocyte-restricted STAT3 deletion. We show for the first time that STAT3 KO induces adverse cardiac remodelling leading to DCM in the subacute phase of viral myocarditis, while no change was seen in the acute phase when cardiomyocyte-restricted STAT3 KO was compared to wild-type. This was interestingly associated with increased cardiac inflammation followed by an exaggerated remodelling process in cardiomyocyte-restricted STAT3 KO mice and deregulating the matrix degradation system.

Acute CVB3 infection leads to a robust inflammation in cardiac tissue of wildtype mice, which is demonstrated by

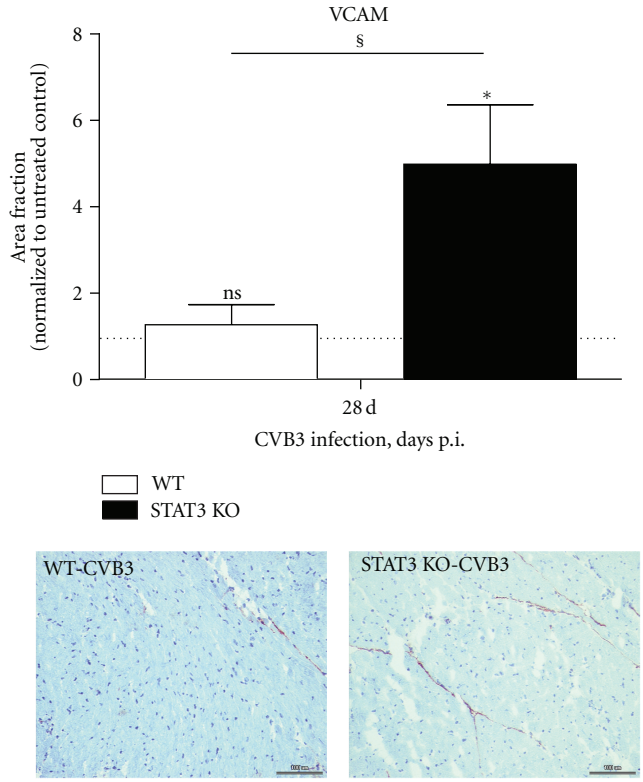

Figure 3: VCAM expression in cardiac tissue of CVB3 infected mice. The expression level was examined at cryosections of control or infected mice. The expression is shown as area fraction and was normalized to the corresponding untreated mice and expressed as x-fold over basal expression. *Data were compared to the expression of the corresponding untreated controls. $^{*}P < 0.05$; §Data between WT and STAT3 KO mice were compared. $^{\S}P < 0.05$.

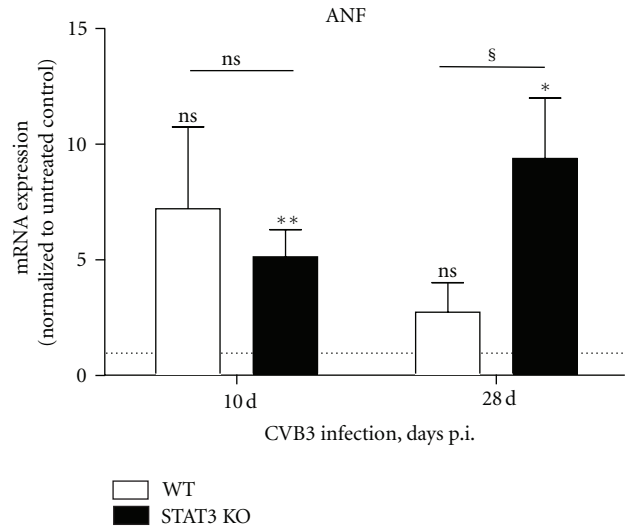

Figure 4: ANF expression in cardiac tissue of CVB3 infected mice. The mRNA expression level is shown 10 and 28 days after CVB3 infection of WT and STAT3 KO mice. The expression data are normalized to the house-keeping gene 18S and to the expression levels of the corresponding untreated mice and expressed as x-fold over basal expression using the formula $2^{-\Delta\Delta Ct}$. *Data were compared to the expression of the corresponding untreated controls. $^{*}P < 0.05$; $^{**}P < 0.01$. §Data between WT and STAT3 KO mice were compared. $^{\S}P < 0.05$.

high numbers of infiltrated inflammatory cells and highly increased expression of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α 10 days after infection [1, 19, 20]. It is previously described for the mouse strain C57/BL6j that the virus does not induce a chronic ongoing inflammation [20] and animals recover from myocarditis. In line with these findings, the wild-type animals show a reduced number of invaded cells and decreased mRNA expression of cytokines 28 days after viral infection. Furthermore, nearly a complete virus clearance was detected 28 days after infection. Controlling inflammation therefore was associated with no adverse cardiac remodelling which can be demonstrated by no collagen accumulation as well as nearly normal LV function 28 day after infection in wild-type animals.

STAT3 is well known as a transcription activator of IL-6 [21, 22]. Since the STAT3 KO is restricted to cardiomyocytes [14], in cardiac tissue of infected STAT3 KO mice, a highly upregulated IL-6 expression was detected due to the infiltration of inflammatory cells still expressing STAT3 in this animal model. Compared to the infected wild-type mice, the mRNA expression levels of IL-1β, IL-6, and TNF-α as well as the number of infiltrating immune cells revealed no distinction in STAT3 KO mice 10 days after infection. While inflammation was controlled and therefore resolved in wild-type animals between day 10 and 28, in STAT3 KO mice, the number of invaded Mac3^{+} cells was not reduced significantly after the acute phase despite viral genome was also extinguished. The finding that endothelial activation demonstrated as increased vascular cell adhesion molecule (VCAM) expression level on endothelial cells in cardiac tissue of STAT3 KO mice is increased accommodates with the unchanged number of infiltrated Mac3^{+} cells found 28 days after infection. The specific effects of cardiomyocyte-restricted STAT3 KO on endothelial VCAM expression levels have to be revealed in future studies, but it is intriguing to speculate that altered myocyte to endothelial crosstalk may be involved in this upregulation of VCAM and therefore fuel cardiac inflammation.

The previously reported characterisation of the cardiomyocyte-restricted STAT3 KO mice in comparison to wild-type mice revealed development of cardiac fibrosis in aging KO mice which was associated with the impaired cardiac function [14, 15]. Left ventricles of aging wild-types and STAT3 KO reveal an increased expression of profibrotic genes such as collagen-Iα1, connective tissue growth factor (CTGF), and TIMP1 which could be the reason for the age-dependent interstitial fibrosis [14]. Here, 10 days after CVB3 infection the wild-type and STAT3 KO animals revealed a similar increase of interstitial collagen I in cardiac tissue, whereas the amount of collagen III was not affected by CVB3 resulting in an increased Col I/Col III ratio. This reveals that cardiac inflammation which controls cardiac

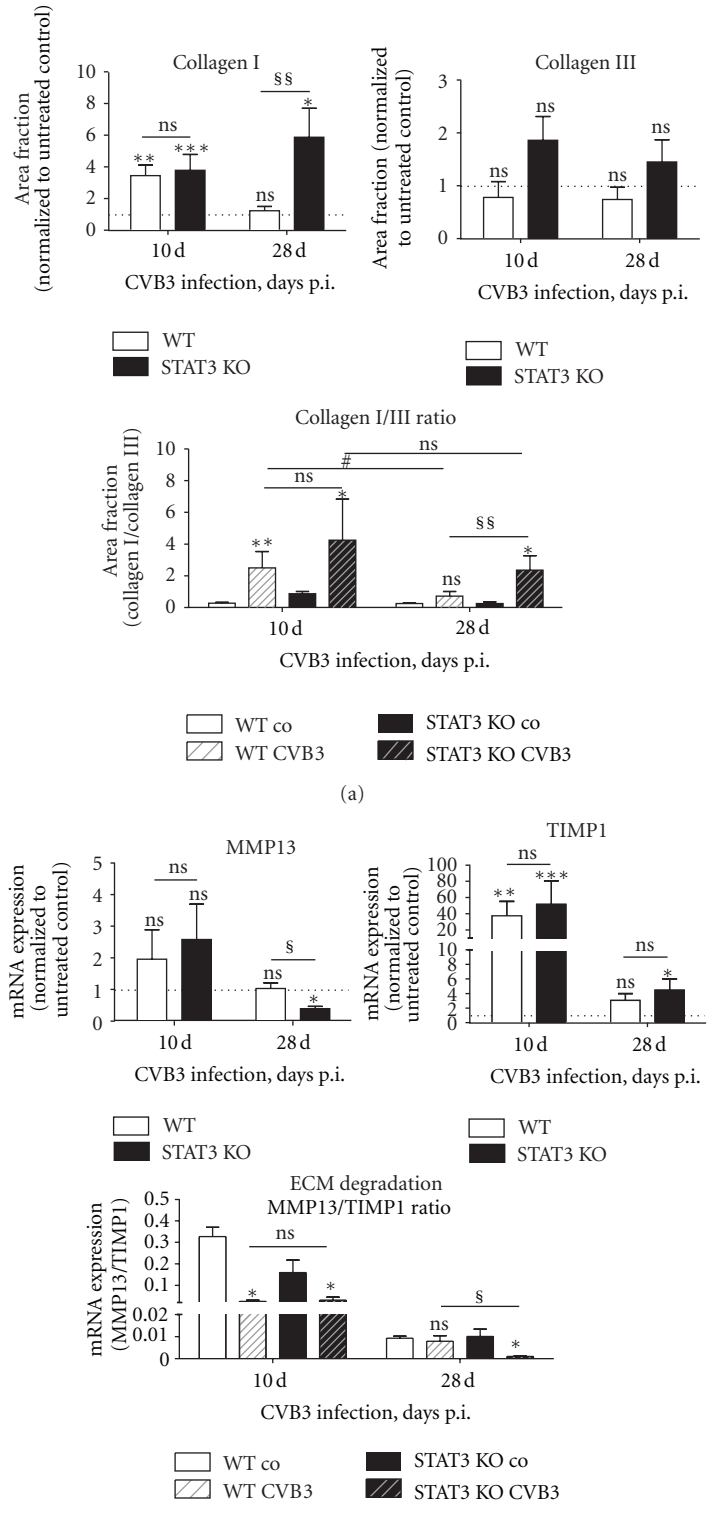

Figure 5: Collagen expression and expression of the ECM degrading system in cardiac tissue of CVB3-infected mice. The area fractions of collagen I and collagen III are shown 10 and 28 days after CVB3 infection of WT and STAT3 KO mice as x-fold compared to the corresponding untreated controls. The mRNA expression data of MMP13 and TIMP1 are normalized to the house-keeping gene 18S and to the expression levels of the corresponding untreated mice and expressed as x-fold over basal expression using the formula $2^{-\Delta\Delta Ct}$. The ratios were calculated without previous normalization to the untreated controls. * Data were compared to the expression of the corresponding untreated controls. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$. §Data between WT and STAT3 KO mice were compared. $^{\S}P < 0.05$; $^{\S\S}P < 0.01$. $^{\#}$Data between 10 or 28 days were compared. $^{\#}P < 0.05$.

remodelling was not differently regulated in the acute phase of myocarditis in this animal model.

However, this increased Col I/Col III ratio declined to normal levels in infected wild-type mice 28 days after infection. In contrast, in STAT3 KO mice the CVB3 infection resulted in a Col I/Col III ratio still being upregulated after 28 days. This ongoing fibrosis in infected STAT3 KO resulted in impaired cardiac function, since collagen is known to depress cardiac function in experimental models as well as in patients with cardiomyopathies [23, 24].

To further investigate the distinct mechanisms of this changed remodelling in response to inflammation, we investigated the regulation of the matrix degradation system [25].

In the acute phase, an increased expression of TIMP1, which is an endogenous inhibitor of the ECM-degrading matrix metalloproteinases [26, 27], prevents collagen degradation and thus revealed matrix deposition in both wild-type and STAT3 KO mice 10 days after infection. One of the most abundant matrix metalloproteases in the cardiac tissue is the collagenase MMP13. Interestingly, reduced MMP13 expression found in infected STAT3 KO mice 28 days after infection is consistent with the increased collagen I protein content in infected STAT3 KO mice 28 days after infection. The deposition and degradation of ECM is a finely balanced equilibrium between the degrading enzymes and their endogenous inhibitors [28, 29]. To clarify the ECM degradation activity in the infected cardiac tissue, the MMP13/TIMP1 ratio reveals a significantly reduced degradation activity in infected STAT3 KO mice 28 days after infection compared to the infected wild-type animals. Concerning the influence of the cardiomyocyte-restricted STAT3 KO on the regulation of ECM, it could be assumed that cardiomyocytes release paracrine factors to influence the ECM regulation. The presence of those paracrine factors was confirmed by the finding that the cell culture supernatant of isolated cardiomyocytes from STAT3 KO animals induced a higher fibroblast proliferation compared with wild-type cardiomyocytes supernatant, as shown earlier [14]. Since cardiac fibroblasts are the most prominent producers of ECM proteins as well as of the ECM degradation system, the paracrine effects shown for fibroblast proliferation can also be assumed for regulation of ECM deposition or degradation by cardiac fibroblasts [30–33].

Conventional knockout of the STAT3 gene leads to embryonic lethality at embryonic day 6.5 [13]. Therefore, the cardiomyocyte-restricted KO was chosen to study the protective function of STAT3 against CVB3-induced myocarditis *in vivo*. It has already been shown that the IL-6 cytokine family using the Jak/STAT pathway protects cardiomyocytes from apoptotic cell death in response to serum starvation or ischemia and induces hypertrophy in cardiomyocytes [34, 35]. In previous studies, the cardiac function of the cardiomyocyte-restricted STAT3 KO mice has been analysed. At a young age, the cardiac structure and function are apparently normal but an age-related increase in cardiac apoptosis and fibrosis has been described [14, 15]. The cardiomyocyte-restricted deletion of receptor subunit gp130, which also prevents STAT3 signalling, also leads to a dilated ventricle after pressure overload [36].

In the present study, we used CVB3 to induce heart failure. The hemodynamic characterisation clearly shows a significantly reduced cardiac function of CVB3-infected STAT3 KO mice compared to CVB3-infected wild-type mice 28 days after infection. These findings are in line with the described cardiac dysfunction of cardiomyocyte-restricted STAT3 KO mice after myocardial infarction or doxorubicin-induced cardiomyopathy [14, 15]. After myocardial infarction, the KO mice revealed a larger infarct size as well as a more pronounced deterioration in systolic dysfunction [14]. In another study, they demonstrated that animals with the cardiomyocyte-restricted STAT3 KO are more susceptible to doxorubicin-induced cardiac injury and develop heart failure. Thus, STAT3 deletion leads to impaired cardiac function after myocardial infarction and doxorubicin-induced cardiomyopathy. Here, we demonstrate for the first time that STAT3 deletion also leads to an aggravated cardiac function in viral myocarditis induced by CVB3. Furthermore, the cardiac-specific overexpression of STAT3 in transgenic mice protected against doxorubicin-induced apoptosis and therefore is another evidence that STAT3 may protect hearts from injuries caused by different stressors [37].

In conclusion, the present study revealed new insights in the protective function of STAT3 expressed in cardiomyocytes after CVB3-induced myocarditis. There and in other cardiac damages such as myocardial infarction or doxorubicin-induced cardiomyopathy, STAT3 in cardiomyocytes prevents uncontrolled fibrosis and clinical progression to DCM. Therefore, STAT3 seems to be a crucial factor for the resolution of viral myocarditis.

Acknowledgments

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Review Article

Targeting the ACE2 and Apelin Pathways Are Novel Therapies for Heart Failure: Opportunities and Challenges

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Angiotensin-converting enzyme 2 (ACE2)/Ang II/Ang 1–7 and the apelin/APJ are two important peptide systems which exert diverse effects on the cardiovascular system. ACE2 is a key negative regulator of the renin-angiotensin system (RAS) where it metabolizes angiotensin (Ang) II into Ang 1–7, an endogenous antagonist of Ang II. Both the prolonged activation of RAS and the loss of ACE2 can be detrimental as they lead to functional deterioration of the heart and progression of cardiac, renal, and vascular diseases. Recombinant human ACE2 in an animal model of ACE2 knockout mice lowers Ang II. These interactions neutralize the pressor and subpressor pathologic effects of Ang II by producing Ang 1–7 levels *in vivo*, that might be cardiovascular protective. ACE2 hydrolyzes apelin to Ang II and, therefore, is responsible for the degradation of both peptides. Apelin has emerged as a promising peptide biomarker of heart failure. The serum level of apelin in cardiovascular diseases tends to be decreased. Apelin is recognized as an imperative controller of systemic blood pressure and myocardium contractility. Dysregulation of the apelin/APJ system may be involved in the predisposition to cardiovascular diseases, and enhancing apelin action may have important therapeutic effects.

1. Introduction

Angiotensin-converting enzyme 2 (ACE2)/Ang II/Ang 1–7 and apelin/APJ are two important peptide systems with diverse and fundamental cardiovascular protective effects that may prevent or reverse a variety of vascular and cardiac disorders [1–3]. ACE2 is a monocarboxypeptidase which effectively plays a key role as the central negative regulator of the renin-angiotensin system (RAS). ACE2 is of particular interest because it is an essential component of RAS which is possibly implicated in metabolizing angiotensin (Ang) II into Ang 1–7 [4]. These interactions counteract the pathologic effects of Ang II by producing Ang 1–7, that is known to be cardiovascular protective. Ang II impairs cardiovascular function and enhances pressor and subpressor pathologic consequences, and hence Ang 1–7 protects against these pathological processes [1, 2].

Apelin is an endogenous peptide that is widely expressed in various organs as a 77 amino acid preproapelin. Several active fragments of apelin have been known (apelin-36, apelin-19, apelin-17, apelin-16, apelin-13, and apelin-12) which relatively share similar biological activities. In addition to the possibility of application of apelin as a heart failure (HF) biomarker, apelin also has direct biological effects including vasodilatory and inotropic effects [5]. Several previous studies have shown the cardioprotective effect of ACE2 and apelin in all three steps of primary, secondary and tertiary prevention of HF (Figures 1 and 2). In this paper we summarize the current literature regarding the cardiovascular effects of ACE2 and apelin and their possible therapeutic applications.

2. Role of ACE2 and Apelin in Systemic and Pulmonary Hypertension

Several previous studies demonstrated that ACE2 can modulate blood pressure. Daily infusion of recombinant human

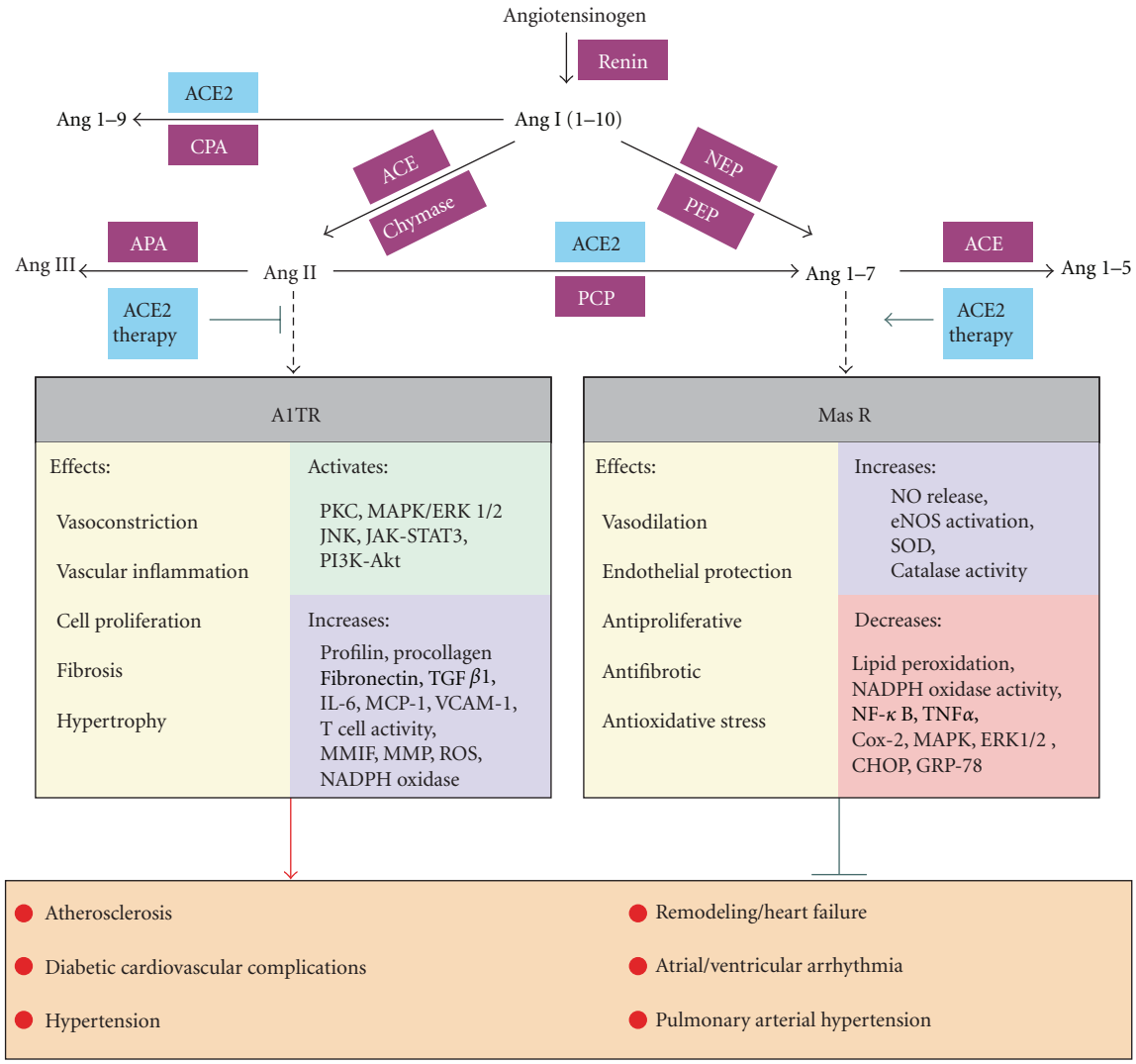

Figure 1: The enzymatic cascade involved in the renin-angiotensin system, key receptor systems, and the biological effects mediated by Ang II and Ang 1–7. Solid black lines, enzymatic pathways; Broken lines, peptide agonist interacting with its key receptor; Green arrow, stimulatory effects; Red arrow, pathologic effects; Green bars; inhibitory effects. ACE2: angiotensin-converting enzyme; Akt: protein kinase B; Ang: angiotensin; APA: aminopeptidase A; AT1R Ang II type 1 receptor; CHOP: CCAAT/enhancer binding protein homologous protein; Cox-2: cyclooxygenase-2; CPA: carboxypeptidase A; eNOS: endothelial synthase; ERK: extracellular signal-regulated kinase; GRP-78: glucose regulated protein; IL-6: interleukin-6; JAK-STAT: Janus Kinase- signal transducer and activator of transcription system; JNK: C-jun-N-terminal kinase; MAPK: mitogen activated protein kinase; Mas R: Ang 1–7 receptor; MCP-1: monocyte cheomattractant protein 1; MMIF: macrophage migration inhibitory factor; MMP: matrix metalloproteinase; NADPH: nicotinamide adenine dinucleotide phosphate; NEP: neutral endopeptidase; NF-kappaB: nuclear factor kappa-light-chain-enhancer of activated B cells; NO: nitric oxide; PCP: prolyl carboxypeptidase (also known as angiotensinase C); PEP: prolyl endopeptidase; PI3K: phosphatidylinositol 3-kinases; PKC: protein kinase C; ROS: reactive oxygen species; SOD: superoxide dismutase; TGFβ1, transforming growth factorβ1; TNF α: tumor necrosis factor α; VCAM-1: vascular cell adhesion molecule-1.

ACE2 (rhACE2) (2 mg/kg^{-1}/d^{-1}) reduces the Ang II-induced hypertension in mice, by reducing Ang II-mediated activation of enhanced extracellular signal-regulated kinase 1/2 (ERK1/2), protein kinase C (PKC) pathways and renal fibrosis [6]. It is suggested that ACE2 expression is decreased in the spontaneously hypertensive rats before the marked onset of hypertension [7]. It is believed that impaired renal level of ACE2 contributes to hypertension in humans [8]. Exposure of cultured human umbilical artery smooth muscle cells (HUASMCs) to Ang II results in a significant increase in the mRNA and protein expression of profilin-1, recently linked to cytoskeleton remodeling by activation of the hypertrophic signaling through mitogen activated protein kinase (MAPK), ERK1/2 and C-jun-N-terminal kinase (JNK), in conjunction with reduced ACE2 activity [9]. Enhanced profilin-1 expression and MAPK signaling in HUASMCs in response to Ang II was noticeably reduced by rhACE2 in an Ang 1–7-dependent manner [9]. Improvement of ACE2

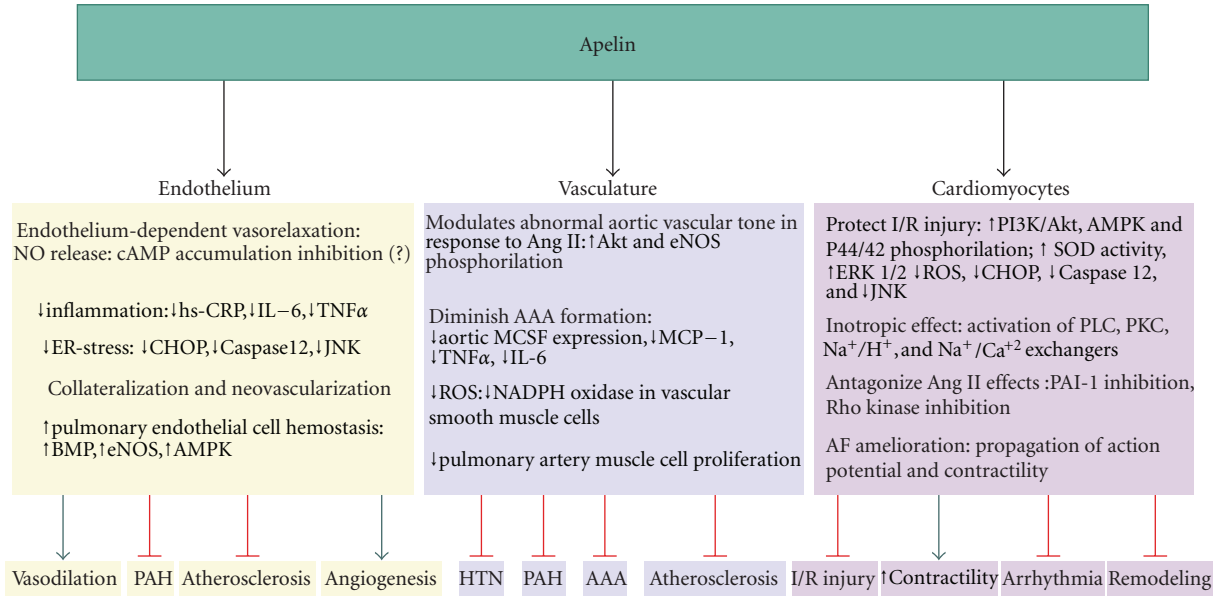

Figure 2: Diverse effects of apelin on cardiovascular system. Black arrows, effects of apelin on various targets; Green arrows and red bars, favorable stimulatory and inhibitory effects of apelin on cardiovascular system respectively; AAA: abdominal aorta aneurysm; AF: atrial fibrillation; Akt: protein kinase B; AMPK: adenosine monophosphate-activated protein kinase; BMP: bone morphogenetic protein; CHOP: CCAAT/enhancer binding protein homologous protein; eNOS: endothelial synthase; hs-CRP: high sensitivity C-reactive protein; ER-stress: endoplasmic reticulum stress; ERK: extracellular signal-regulated kinase; HTN: hypertension; I/R: ischemia reperfusion; IL-6: interleukin 6; JNK: C-jun-N-terminal kinase; MCSF: macrophage colony stimulating factor; MCP-1: monocyte cheomattractant protein 1; NADPH: nicotinamide adenine dinucleotide phosphate; NO: nitric oxide; PAH: pulmonary arterial hypertension; PI3K: phosphatidylinositol 3-kinases; PKC:protein kinase C; PLC: Phospholipase-C; ROS: reactive oxygen species; SOD: superoxide dismutase; TNFα: tumor necrosis factor.

expression and reduced profilin-1 levels were associated with an overt suppression of ERK1/2 and JNK phosphorylation in aortas of spontaneously hypertensive rats [9].

ACE2 overexpression results in increased expression of various antihypertensive components of the RAS including Ang 1–7/Mas and AT2R. Vascular transgenic overexpression of ACE2 results in reduction of arterial blood pressure [10, 11] and an attenuated response to Ang II infusion [10]. Central nervous system overexpression of ACE2 also was proved to be protective against Ang II induced hypertension [12]. Wysocki et al. (2010) showed that acute Ang II infusion-induced hypertension can be prevented by rhACE2 pre-treatment (2 hrs before the Ang II infusion) in mice. This antihypertensive effect of rhACE2 was associated with a decrease in plasma Ang II and increases in plasma Ang 1–7 levels. However, the antihypertensive effect of rhACE2 was shown to be independent of Ang 1–7 in this study [13]. Wysocki et al. concluded that circulatory decrease of Ang II was the driving cause of decreased hypertension, rather than increased levels of Ang 1–7 [13]. This acute antihypertensive effect of ACE2 seems promising for management of the patients with hypertension.

Reduced circulating levels of apelin have been demonstrated in the patients with essential hypertension [14, 15]. Genetic variation in apelin likely contributes to essential hypertension and the onset of aged hypertension [16]. Tatemoto et al. (2001) showed that arterial pressure after the administration of apelin-12, apelin-13, and apelin-36 at a dose of 10 nmol/kg resulted in a reduction in arterial blood pressure [17]. Cheng et al. (2003) examined dose response curves of apelin (10, 20, and 40 nmol/kg) in rats and concluded that apelin is an arterial and venous dilator *in vivo* [18]. Japp et al. (2008) showed nitric oxide (NO)-dependent vasodilatory effect of apelin in 24 healthy volunteers *in vivo* [19]. However, the long-term effects of manipulating the apelin pathway and its effect on blood pressure are unknown.

Several studies focused on the role of ACE2 and apelin in amelioration of pulmonary arterial hypertension (PAH). Ang II is of fundamental importance to development and progression of PAH, due to its vasoconstrictive, fibrotic, and proliferative effects [20]. Left ventricular failure/remodeling is one of the frequent consequences of PAH which may aggravate the global function of the heart. The ability of ACE2 to combat the fibrosis/proliferative effects of Ang II on lung and right ventricle (RV) supported the beneficial role of ACE2 in PAH treatment [20]. ACE2 overexpression [21] and ACE2 activation by 1-[(2-dimethylamino) ethylamino]-4-(hydroxymethyl)-7-[(4-methylphenyl) sulfonyl oxy]-9H-xanthene-9-one (XNT) [22] ameliorate RV systolic failure, decrease the adverse effects of Ang II, and attenuate pro-inflammatory cytokines in PAH mice. There is promising evidence of rhACE2 on improvement of RV load-stress (pulmonary artery banded (PAB)) of early HF [23]. rhACE2 administered to PAB mice for two weeks prevented load-induced RV systolic and diastolic dysfunction [23]. The exceptional increasing effect of rhACE2 on RV [23] shows

the remarkable property of ACE2 for potentially complex patients with isolated RVHF.

Apelin/APJ is highly expressed in pulmonary vasculature [24]. Chandra et al. (2011) reported significantly lower serum apelin levels in patients with PAH compared to control subjects [25]. Apelin expression also decreases in the pulmonary endothelial cells of the patients with PAH [26]. It was shown that PAH in mice may originate from the disruption of apelin signaling which is mediated by decreased activation of adenosine monophosphate-activated protein kinase and endothelial synthase (eNOS) [25]. Pyr-Apelin-13 treatment has been reported to downregulate Ang II and endothelin-1 and could therefore attenuate RV hypertrophy and diastolic dysfunction in rats with PAH [27]. Alastalo et al. (2011) have elegantly shown that apelin could have both autocrine and paracrine effects against PAH in pulmonary vasculature [26]. Bone morphogenetic protein-mediated apelin autocrine production results in enhanced pulmonary arterial endothelial survival, proliferation, and migration which can protect the vasculature against PAH. Importantly, apelin autocrine function against PAH is based on attenuation of the pulmonary arterial smooth muscle cells response to growth factors and by promoting apoptosis [26].

3. Role of ACE2 and Apelin in Diabetes (DM) and Diabetic Cardiovascular Complications

Attenuation of Ang II-induced glomerular mesangial cell proliferation, oxidative stress, and collagen IV protein synthesis is thought to be the critical steps in ACE2-related protection of diabetic nephropathy [28, 29]. Even in non-diabetic mice loss of ACE2 contributes to increase in renal lipid peroxidation product formation and activation of MAPK and ERK 1/2 in glomeruli [30]. ACE2 mRNA has been shown to be reduced by more than half in both the glomeruli and proximal tubules of the diabetic patients compared to controls [31]. ACE2 treatment is believed to be critical in protection against diabetes induced nephropathy. rhACE2 treatment attenuated high glucose in cultured primary rat mesangial cells [32]. The potential role of Ang II in the induction of kidney injury in ACE2 knocked out mice has been reported [33]. In addition to the possibility of renal protective role of rhACE2 due to its antihypertensive effect in diabetic subjects, rhACE2 also attenuates diabetic nephropathy via blockade of Ang II-induced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity in mesangial cells [32]. Bindom et al. (2010) have elegantly shown that ACE2 gene therapy in mice results in reduced fasting blood glucose and glucose tolerance improvement in a diabetic mice model [34]. They also proved that ACE2 overexpression in diabetic mice significantly reduces apoptosis which can be prevented by Ang 1–7 receptor blockade [34], further supporting the link between ACE2 and diabetic glycemic control [34, 35].

Several studies have shown an association between apelin levels and overt diabetes [36]. Erdem et al. (2008) demonstrated that plasma apelin was lower in newly diagnosed and untreated patients with DM II compared to healthy controls [37]. Soriguer et al. (2009) showed the association between apelin levels and glucose concentrations and insulin sensitivity in diabetic patients suggesting the role of apelin in diabetes pathogenesis [38]. Furthermore, diabetic mice exhibited downregulation of apelin receptors and depressed aortic vascular tone [39]. However, Rittig et al. (2011) examined the association between apelin and atherosclerosis indicators (intima media thickness) in 344 subjects with an increased risk for DM II and did not show any association to diabetes risk pattern [40].

The effect of apelin in DM control has been shown in some animal studies. Intracerebroventricular injection of apelin in mice leads to improved glucose homeostasis via NO-dependent pathway [41]. Injection of apelin-13 (400 pmol/kg) for 10 weeks considerably reduced the pancreas endoplasmic reticulum (ER) stress in Akita mice, a model of DM I, which leads to modification of pancreatic islet mass reduction and preservation of insulin content [42]. This important effect of apelin-13 in type 1 diabetes was mediated by inhibition of inositol requiring enzyme 1-α and JNK pathways, suggesting apelin effects on two important pathways of ER stress and cell death, respectively [42]. In mice with metabolic syndrome, apelin restores glucose tolerance and increases glucose utilization [43]. Apelin treatment has a favorable effect on vascular function in diabetic mice. Apelin treatment remarkably adjusts the abnormal aortic vascular reactivity in response to Ang II and acetylcholine in DM II mice by increasing the phosphorylation of Akt and eNOS [39]. Apelin may improve the glycemic status and insulin sensitivity of the patients and also can ameliorate vascular functions of diabetic patients.

4. Role of ACE2 and Apelin in Vascular Inflammation and Atherosclerosis

The effect of vascular inflammation in the initiation and progression of atherosclerosis/cardiovascular diseases has been well recognized. Gene transfer of ACE2 suppresses the expression of macrophage migration inhibitory factor, a proinflammatory cytokine associated with insulin resistance, in endothelial cells stimulated by Ang II [44]. ACE2 deficiency contributes to enhanced atherosclerotic plaque formation and also increases proinflammatory cytokines, including interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and vascular cell adhesion molecule-1, which defined the key role of ACE2 in modulation of inflammation-dependent atherosclerosis development [44]. Remarkable effects of rhACE2 on attenuation of Ang II-induced T-lymphocyte-mediated inflammation can be considered as an evidence for antiinflammatory/anti-atherosclerotic effects of ACE2 [45].

ACE2 reduced atherosclerosis progression in apolipoprotein E knockout mice probably by inhibition of reactive oxygen species (ROS) subsequent activities [46]. Association between ACE2 antiatherosclerotic effects and disturbance of Ang II/Ang 1–7 peptides has been proved [47]. Zhang et al. (2010) suggested the downregulation of the ERK-p38, Janus kinase-signal transducer and activator of transcription

system (JAK-STAT), and Ang II-induced ROS-nuclear factor kappa light chain enhancer of activated B cells (NF-kappaB) signaling pathways and upregulation of the phosphatidylinositol 3 kinases-protein kinase B (PI3K-Akt) pathway subsequent to ACE2 therapy in rabbits [48]. It has been shown that overexpression of ACE2 can readily stabilize the atherosclerotic plaques probably due to protective effects of Ang 1–7 [49]. Hence we concluded that ACE2 is essential to prevent or delay the development of atherosclerosis. The plaque stabilizing effect of ACE2 seems promising for prevention of acute coronary syndromes (ACS).

Plasma levels of apelin inversely correlated to inflammatory markers (C-reactive protein and IL-6) in hemodialysis patients [50]. Apelin treatment in mice models of abdominal aorta aneurysm (AAA) clearly demonstrated its anti-inflammatory effects that could attenuate AAA formation [51]. Injected apelin can reduce the mRNA levels of pro-inflammatory markers (MCP-1, macrophage inflammatory protein-1α, IL6 and tumor necrosis factor-α) [51]. Apelin attenuates ultraviolet B-induced edema and inflammation in mice and play an important role in stabilization of the tissue [52]. Apelin exerts acute anti-inflammatory effects on the vascular system; the results are promising and if these results can be extrapolated in chronic models, it can be a proper therapeutic modality for prevention of inflammation in the process of atherosclerosis. Pitkin et al. (2010) have shown an increase in apelin expression in atherosclerotic coronary artery, with the additional peptide localizing to the atherosclerotic plaque [53]. Apelin receptor was also found to be present within the atherosclerotic plaque and to have a similar distribution to its ligand [53]. Increased content of apelin and its receptor might be an indicator of increased anti-inflammatory activation of macrophages thereby limiting plaque instability. Due to lack of data and contradictory findings, the exact role of apelin on atherosclerosis plaque remains inconclusive.

5. Role of ACE2 and Apelin in Angiogenesis

The association between ACE2 and cardiac angiogenesis during the HF process has not been studied. A few studies in the cancer field have supported an important role of ACE2 in angiogenesis [54, 55]. The probable adverse antiangiogic effects of ACE2 in HF remain unclear. Apelin angiogenenic effects have been proved in few animal studies; however none of the studies targeted the effect of apelin on heart angiogenesis. Tiani et al. (2009) showed the remarkable effect of apelin on portosystemic collateralization and splanchnic neovascularization in portal hypertensive rats [56]. Treatment of human umbilical vein endothelial cells with apelin dose-dependently augments angiogenic responses [57]. Kidoya et al. (2010) indicated that apelin together with vascular endothelial growth factor (VEGF) efficiently induced functional vessels larger than with VEGF alone, in the hind limb ischemia model of mice [58]. Apelin is required factor for hypoxia-induced retinal angiogenesis in mice [59]. Available data imply that apelin is an effective factor in angiogenesis; however none of the studies have targeted coronary vessels to test the effect of apelin on their angiogenesis. If the effect of apelin on cardiac collateralization is proved in future studies, it can be considered as a valuable factor for the patients with HF, in particular ischemic HF. The probable off-or on-target effects of apelin on other organs angiogenesis, for example, retinal neovascularization/angiogenesis make interpretation problematic.

6. Role of ACE2 and Apelin in Post-Myocardial Infarction (MI) Remodeling

Post-MI remodeling and coronary artery disease are now the most common cause of HF [60]. In ACE2 deficient mice, MI leads to enhanced activation of the RAS resulting in increased cardiac mortality, adverse ventricular remodeling, and aggravated systolic function [61]. ACE2 contributes to generation of myocardial Ang 1–7 after MI which may protect the heart from ischemic consequences [61]. Loss of ACE2 in post-MI mice is associated with increased Ang II levels and ROS production. This is followed by increased matrix metalloproteinase (MMP) activation, inflammation, and activation of MAPK in ACE2-deficient hearts [61]. Der Sarkissian et al. (2008) analyzed the rats that received an intracardiac injection of lentivirus containing ACE2 cDNA followed by coronary artery ligation and found the ischemic protection of myocardium by ACE2 24 hours after the ischemic event compared to the control mice [62]. The effect of ACE2 overexpression on attenuation of left ventricular fibrosis/remodeling and systolic function was also shown one month after MI [63].

Ang II antagonist infusion for 28 days after MI results in augmented ACE2 cardiac mRNA in normotensive rats, which may be related to direct blockade of AT1R or the probable contribution of increased Ang 1–7 [64]. Attenuated cardiac hypertrophy and improved ventricular contractility both were chronic antiremodeling effects of ACE2 on ACS-induced ischemia [64]. Treatment of the rats for a same period (28 days) with C16, a selective non-peptidic ACE2 inhibitor, at a dose that inhibited myocardial ACE2 activity was associated with a significant increase in MI infarct size [65]. It seems that acute and long-term effects of ACE2 limits the infract size following ACS. ACE2 is capable to produce Ang 1–9 from Ang I [4]. Ocaranza et al. (2010) proved the efficacy of Ang 1–9 in attenuation of post-MI remodeling [66]. Further studies are needed to evaluate the effect of ACE2 on Ang 1–9 increase and its remodeling-attenuation in coronary artery disease.

Decreased levels of apelin-36 during 5 days interval following ST elevation MI have been reported [67, 68]. Weir et al. (2009) also confirmed depressed level of apelin early after MI. They showed significant increase of apelin from base line to 24 weeks after MI [69]. None of these studies found any relation between apelin levels and left ventricular function [67–69]. Kadoglou et al. (2010) showed that both groups of patients with unstable angina and acute MI had significantly lower level of apelin compared to the patients with asymptomatic coronary artery disease [70]. According to our knowledge, only decreased levels of apelin after

ACS have been proved without any relation with structural dysfunction of the heart. The therapeutic effect of apelin in the management of patients with ACS has not been examined. Evaluation of apelin role before and after acute events and its role in plaque stabilization seems to be complicated in animals, as there is no model of unstable atherosclerotic plaque-induced ACS.

The precise role of ACE2 in protection of the heart and kidney against ischemia-reperfusion (I/R) injury has not been elucidated. However, according to the association between ACE2 and MAPK [61], ACE2 protective effects against I/R injury seem probable. Simpkin et al. (2007) for the first time demonstrated the protective effects of apelin against I/R injury in rodents through the reperfusion injury salvage kinase (RISK) pathway activation [71]. In murine Langendorff model of I/R injury, apelin-13 could increase Akt and ERK1/2 phosphorylation as well as increase Akt activity at 5 and 10 min of reperfusion [72]. Activation of Akt and ERK1/2, two important members of RISK pathway, can potentially protect the heart against I/R injury [72]. Administration of apelin can partly block the ER stress-dependent apoptosis activation in rat models of I/R injury at 2 h of reperfusion which results in the heart protection against I/R injury [72]. This protection against I/R injury remained significant during time-related changes at 24 h of reperfusion [72]. Administration of apelin (30 pM) in Langendorff model of perfused isolated rat hearts favorably preserves the impaired cardiac function [73]. In rat cultured cardiomyocytes, the antioxidant activity of apelin is thought to be largely due to inhibition of ROS production, malonaldehyde activity and lactate dehydrogenase leakage and also activation of superoxide dismutase [73]. According to several previous investigations, apelin can considerably protect the heart against I/R injury. However, apelin effects against I/R injury have not been tested in humans. This promising effect of apelin can be applied in humans in the conditions that I/R injury can impair the heart function and might be a leading cause of HF. Application of apelin during the percutaneous coronary intervention and coronary artery bypass graft immediately and in early days after the procedure may have therapeutic benefits.

7. Role of ACE2 and Apelin in Arrhythmias

Atrial fibrillation (AF) is one of the most common arrhythmias among the patients with cardiovascular diseases. Down-regulation of both the mRNA and protein level of ACE2 has been shown to be associated with the development of AF in a rapid pacing-induced model [74]. They also showed higher expression of ERK1/2 cascade and also increased expression of collagen I protein in the atrial tissues with AF that is related to increased local Ang II [74]. It could be concluded that ACE2 treatment can easily protect the heart against the AF complications including fibrosis and remodeling. However the results of Donoghue et al. paper (2003) seem contradictory [75]. Donoghue et al. (2003) reported that ACE2 overexpression in the heart leads to probable gap junction remodeling, resulting in severe electrophysiological disturbances (sustained ventricular tachycardia and terminal ventricular fibrillation) and high incidence of sudden death in transgenic mice [75]. The results of Donoghue et al. has not been confirmed again by other studies, and several investigations have used ACE2 transgenic mice without increased sudden cardiac death.

Serum apelin levels are lower in the patients with AF compared to controls [76, 77]. Falcone et al. (2010) measured apelin in 93 patients with persistent AF before successful external electrical conversion. Patients with apelin levels below the median showed a hazard ratio of 3.1 of arrhythmia recurrence compared to those with high apelin levels [78]. Low plasma apelin is an independent prognostic factor for arrhythmia recurrence in the patients with AF under antiarrhythmia medication [78]. Apelin, due to its effect on the propagation of action potential and contractility in cardiomyocytes, is thought to modulate the pathophysiology of AF [79]. Apelin increases sarcomere shortening in normal as well as failing cardiomyocytes [79]. Moreover, apelin augments conduction velocity in monolayers of cultured neonatal rat cardiac myocytes [79]. According to our knowledge, the level of apelin has been investigated only in the patients with AF, and other forms of arrhythmia have not been investigated.

8. Role of ACE2 and Apelin in HF: Therapeutic Potentials

The relationship between ACE2 deficiency and failure of heart function including pathological hypertrophy, ventricular remodeling, and systolic dysfunction is well described [6, 80, 81]. In ACE2 deficient mice model of pressure overload, increased Ang II leads to severe cardiac hypertrophy [80, 82], increased activity of MAPK [82], activation of the NADPH oxidase system and oxidative stress-induced augmented MMP-mediated degradation of the extracellular matrix [80]. rhACE2 has antifibrosis properties and may attenuate expression of Ang II-induced procollagen, transforming growth factor-β1, and fibronectin [6]. The attenuating effect of rhACE2 on systolic and diastolic dysfunction [6, 81] is thought to be largely due to Ang II inhibition [6]. rhACE2 treatment blocks the Ang II-mediated activation of PKC-α, PKC-β1, ERK 1/2 and JAK-STAT in wild-type mice [6]. Ferreira et al. (2011) showed that chronic XNT infusion, an ACE2 activator, was associated with decreased cardiac collagen content, increased cardiac Ang 1–7 immunostaining and a reduction in ERK phosphorylation [83]. Ang 1–9, a known product of ACE2 activity in RAS, results in considerable reduced hypertension-induced cardiac fibrosis through modulation of collagen I expression [84]. Furthermore, Ang 1–9 attenuates Ang II-inducfed cardiomyocyte hypertrophy [85]. ACE2 by inhibiting several remodeling pathways can attenuate Ang II and pressure-overload-induced cardiomyopathy.

In HF there is hyperactivity of the sympathetic nervous system which chronically may have adverse effect on cardiac function. ACE2, Ang 1–7, and the Mas receptor exist in the brain; however, controversy remains over their relation with the cardiovascular functions [86]. There is growing interest

in the application of ACE2 in central nervous system. Xiao et al. (2011) showed that central ACE2 overexpression applies a considerable cardiac protective effect in the mice model of HF which was associated with a significant decrease in sympathetic biomarkers [87]. Brain selective human ACE2 over expression also showed to be effective for management of hypertension in transgenic mice [88]. Direct effects of central ACE2 treatment on HF improvement and also its role in hypertension attenuation are both acceptable evidence for the efficacy of ACE2 on HF management.

Arrhythmia also may occur in the patients with HF and can worsen the structural and functional status of the heart in these patients. The protective effect of ACE2 against arrhythmia in the failed heart is a subject of debate. The importance of the balance between ACE-Ang II-AT1R axis and the ACE2-Ang 1–7-Mas receptor axis in the regulation of heart cell volume has been suggested [89]. The key role of Ang 1–7 in decreasing the cell volume which results in decline in activation of swelling-activated chloride current (I_{Clswell}) suggesting a likely contribution of ACE2 in prevention of major post-ischemic cardiac arrhythmias [89]. However, De Mello (2009) mentioned the probable effect of overexpressed ACE2 on generation of early afterdepolarization especially in the patients with HF [90]. Regarding the probable arrhythmogenic effects of ACE2 in the patients with HF, it seems that precise dose adjustment based on the severity of HF may prevent this side effect.

There is growing interest regarding the protective role of apelin in HF development. Apelin level is considerably reduced in the patients with HF [91–93]. Several studies showed high expression of apelin/APJ in the heart and in vascular systems of rodents and humans [24, 93, 94]. The mechanisms by apelin reduction causes HF are becoming clearer. Gao et al. (2009) reported significant increase of apelin as an indicator of improved cardiac function from 3 to 21 days after bone marrow mononuclear cell transplantation in the patients with HF through autocrine and paracrine mechanisms [92]. Apelin reduces left ventricular preload and afterload in rodents [95] and is known to be a strong positive inotropic agent [53, 94, 96] that could be outstandingly helpful in treatment of HF. Apelin mutant mice develop HF associated with aging and pressure overload [97]. Infusion of apelin-13 [98] and apelin-12 [99] enhances myocardial function of the left anterior descending artery ligation model of HF in rats. Perfusion of isolated rat hearts with apelin-16 caused an inotropic effect with a similar time course to endothelin-1 [94]. Interestingly, apelin can present a gradually developing but sustained inotropic effect [94], which is a significant difference compared to classical β-adrenergic effects. Apelin administration to the rats in ischemic HF significantly attenuates diastolic dysfunction [96]. The involvement of phospholipase-C, PKC, Na^+/H^+ and Na^+/Ca^{2+} pumps has been proved in positive inotropic effects of apelin [94, 100, 101]. The interaction between apelin and two important regulatory pumps has been proposed to be contributed to increased inotropic effects of apelin by restoration of calcium in the cardiomyocyte cytosol.

Japp et al. (2010) investigated the acute cardiovascular effect of intrabrachial infusion of (Pyr (1)) apelin-13 in the patients with chronic HF and healthy volunteers and found vasodilatation in patients and control subjects [102]. Systemic infusions of (Pyr(1)) apelin-13 (30 to 300 nmol/min) result in elevated cardiac index, lowered mean arterial pressure and peripheral vascular resistance in HF patients and healthy control subjects [102]. Intracoronary bolus of apelin-36 leads to increased coronary blood flow and reduced peak and end-diastolic left ventricular pressures [102]. These remarkable peripheral and coronary vasodilatation effects of apelin and also its effect on cardiac output increase shows apelin as a novel medication for the patients with HF. Decreased density of apelin receptors in the heart tissues with cardiomyopathy may block the inotropic effect of apelin on the heart [53]. APJ gene also has been suggested as a modifier gene for idiopathic dilated cardiomyopathy [103]. Further investigations should focus on combination of apelin therapy with apelin receptor agonists. Synergetic effects of apelin with APJ agonists may increase the efficacy of apelin therapy for the patients with HF. However, these findings are not consistent with Atluri et al. (2007) findings in rats [98]. Atluri et al. (2007) showed increased APJ protein levels in myocardium of the rats with HF [98]. Pitkin et al. (2010) suggested [Glp65,Nle75,Tyr77][125I]-apelin-13 as a potent agent with high-affinity, saturable and reversible affect which might reflect its therapeutic efficacy in future [53].

The difference between APJ in myocardium and arterial system of the HF patients is not completely defined. Due to the dual ionotropic and hypotensive effects of apelin on the patients with HF, we need to be cautious about the application of this agent in the clinical setting. APJ agonist drugs may increase the efficacy of apelin therapy in the HF patients; however it is not clear whether APJ agonist drugs will increase the arterial hypotensive effects of apelin. Experimental evidence has established an association between Ang II and development of HF [45, 81]. Chun et al. (2008) proved that apelin signaling can antagonize Ang II actions in vascular disease by NO production and inhibiting Ang II cellular signaling [104]. Generally, apelin modulates Ang II-induced cardiovascular fibrosis [105] which may be linked to apelin ability to inhibit the plasminogen activator inhibitor type-1 production resulting in secondary changes in the expression of matrix proteins and degrading enzymes [105]. Apelin-13 inhibits Ang II-induced vascular contraction mainly through NO-dependent pathways [106]. There is evidence that apelin can be increased by blocking RAS [107] which may contribute to AT1 blocker treatment in the clinical setting [108]. This evidence led to the notion that apelin therapy may ameliorate RAS-related HF aggravating effects.

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Research Article

Prognostic Value of Left Ventricular Diastolic Dysfunction in Patients Undergoing Cardiac Catheterization for Coronary Artery Disease

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We hypothesized that left ventricular (LV) diastolic dysfunction assessed by cardiac catheterization may be associated with increased risk for cardiovascular events. To test the hypothesis, we assessed diastolic function by cardiac catheterization (relaxation time constant (Tau) and end-diastolic pressure (EDP)) as well as Doppler echocardiography (early diastolic mitral annular velocity (e') and a ratio of early diastolic mitral inflow to annular velocities (E/e')) in 222 consecutive patients undergoing cardiac catheterization for coronary artery disease (CAD). During a followup of 1364 ± 628 days, 5 cardiac deaths and 20 unscheduled cardiovascular hospitalizations were observed. Among LV diastolic function indices, Tau > 48 ms and e' < 5.8 cm/s were each significantly associated with lower rate of survival free of cardiovascular hospitalization. Even after adjustment for potential confounders (traditional cardiovascular risk factors, the severity of CAD, and cardiovascular medications), the predictive value of Tau > 48 ms and e' < 5.8 cm/s remained significant. No predictive value was observed in EDP, E/e', or LV ejection fraction. In conclusion, LV diastolic dysfunction, particularly impaired LV relaxation assessed by both cardiac catheterization and Doppler echocardiography, is independently associated with increased risk for cardiac death or cardiovascular hospitalization in patients with known or suspected CAD.

1. Introduction

Left ventricular (LV) diastolic dysfunction refers to abnormalities in relaxation, filling, and distensibility [1]. Evidence of LV diastolic dysfunction can be determined by cardiac catheterization [1]. The presence of LV diastolic dysfunction can also be estimated by Doppler echocardiography [2, 3]. Although studies have shown that LV diastolic abnormalities assessed by Doppler echocardiography are predictive of adverse prognosis in various cardiac patients [4–10], the predictive value of invasively-determined diastolic dysfunction is unclear. In the present study, we hypothesized that invasively-determined diastolic dysfunction may be associated with increased risk for cardiovascular events. To test the hypothesis, we examined the association of LV diastolic dysfunction assessed by cardiac catheterization as well as Doppler echocardiography with subsequent cardiovascular events in patients undergoing cardiac catheterization for assessment of coronary artery disease (CAD).

2. Methods

2.1. Patients. We studied 222 consecutive Japanese patients who underwent cardiac catheterization for the evaluation of CAD between January 2004 and August 2006. All the patients had symptoms suggestive of angina and/or clinical signs of CAD (positive exercise electrocardiogram and/or abnormal myocardial perfusion scintigram). No patients with acute coronary syndrome, congestive heart failure, atrial fibrillation, primary valvular diseases, idiopathic dilated or

hypertrophic cardiomyopathy, congenital heart disease, end-stage renal disease on maintenance hemodialysis, or malignant neoplasms were included. Medication status and a history of coronary revascularization were determined by review of medical records. Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg measured by indirect arm-cuff sphygmomanometry at rest or use of antihypertensive drugs. Diabetes was defined as a fasting blood glucose level >126 mg/dL or treatment with dietary modification, insulin, or oral hypoglycemic agents. Dyslipidemia was defined as low-density lipoprotein level ≥140 mg/dL, high-density lipoprotein level <40 mg/dL, and/or triglyceride level ≥150 mg/dL or treatment with antihyperlipidemic agents. Within a week before the index cardiac catheterization for this study, blood chemistry was obtained for assessment of clinical features. All the patients gave written informed consents to participate in the study, and this study was performed according to the regulations proposed by the Ethical Guidelines Committee of the Nagoya City University Graduate School of Medical Sciences.

2.2. Cardiac Catheterization. Before contrast material was injected into the LV or coronary artery, LV and aortic pressure waves were obtained with a catheter-tipped micromanometer (SPC-454D, Millar Instrument Company, Houston, TX) and recorded on a polygraph system (RMC-2000, Nihon Kohden, Inc., Tokyo, Japan) as previously reported [11]. From the recorded pressure waves, aortic systolic and diastolic pressures and LV end-diastolic pressure (EDP) were determined. A time constant of decrease in LV pressure (Tau), an index of early diastolic relaxation, was computed by applying a monoexponential fitting with zero asymptote to the LV pressure decay [12]. LV end-systolic and end-diastolic volumes were obtained from biplane left ventriculography by use of the method proposed by Chapman et al. [13] and were used for calculating ejection fraction (EF). The median values of measurements of 3 consecutive beats were used for statistical analyses.

2.3. Echocardiography. The day before the index cardiac catheterization, ultrasound examination was performed with the use of a commercially available echocardiographic machine (APLIO 80, Toshiba, Tokyo) with a 3-MHz transducer. Patients were examined at rest in the left lateral decubitus position. LV diastolic function was evaluated according to the published guideline [14]. Transmitral flow velocities during early diastole (E) and atrial contraction (A) at the mitral orifice were obtained with the use of pulsed Doppler echocardiography in the apical 4-chamber view. Deceleration time was measured as the time from the peak early filling velocity to termination of early filling. The peak early diastolic annular velocity (e') was measured with the use of pulsed Doppler echocardiography at the septal and lateral mitral annular sites. The values of e' measured at both sites were averaged. The median values of measurements of 3 consecutive beats were used for statistical analyses. LV mass was calculated from M-mode echocardiographic measurements [15] and LV mass was corrected for body surface area.

2.4. Followup. Followup was determined in October 2010 with the use of the medical record and/or at regular visit to determine the patients' vital status and any cardiovascular hospitalizations. The outcome of the present study was cardiac death (acute myocardial infarction, heart failure, and sudden cardiac death) or unscheduled admission for cardiovascular causes. Sudden cardiac death was defined as unexpected death within one hour after the onset of a new symptom, or unexpected, unobserved death.

2.5. Statistical Analysis. We used the SAS program package (SAS Institute, Cary, NC) for statistical analyses. Differences in quantitative and categorical data at baseline between groups were compared by the Student's t-test and the Fisher exact probability test. The association between continuous variables was determined by Pearson's correlation analysis. Survival curves of patients stratified by LV function indices were calculated by the Kaplan-Meier method and compared using the log-rank test. EDP of 16 mmHg, Tau of 48 ms, and EF of 50% were used as cut-off points, because these values are established thresholds for separating normal and abnormal levels [1]. In contrast, reported cut-off points of echocardiographic diastolic measures (e' and E/e') for the diagnosis of diastolic dysfunction or the prediction of adverse prognosis are variable depending on age [2] and population studied [4]. Furthermore, e' recorded at lateral mitral annular site is usually higher than e' at septal site [4]. Thus, in the present study, the best cut-off points of echocardiographic diastolic measures were explored to maximize the likelihood ratio in receiver-operating characteristic curves for the prediction of the outcome. Hazard ratio of clinical variables for the outcome was determined using the Cox proportional hazards regression analysis. To assess the independent predictive value of LV function indices, the multivariate Cox hazards regression analyses were performed including potential confounders based on the findings of previous studies and the results of univariate analyses. Multivariate model 1 included age, sex, hypertension, dyslipidemia, diabetes, and coronary revascularization after the index cardiac catheterization. Multivariate model 2 included previous history of myocardial infarction, the number of coronary arteries narrowed, EF, systolic aortic pressure, and heart rate. Multivariate model 3 included use of cardiovascular medications. Data are presented as the mean ± SD. Risk for death or cardiovascular hospitalization is presented as hazard ratio (HR) with 95% confidence interval (CI). $P < 0.05$ was considered significant.

3. Results

Based on the findings of the index coronary angiography, 50 percutaneous coronary interventions and 2 coronary artery bypass surgeries were performed. During a followup of 1364 ± 628 (median (range), 1444 (16–2433)) days, 5 cardiac deaths (4 heart failure and 1 sudden cardiac death) and 20 hospitalizations due to cardiovascular causes (15 ischemic myocardial events (14 unstable angina and 1 acute myocardial infarction), 3 heart failure, and 2 arrhythmia) were observed. Clinical, hemodynamic, and echocardiographic features of all patients and patient subgroups are shown

Table 1: Clinical, hemodynamic, and echocardiographic features of all patients and patient subgroups.

Variables	All patients ($n = 222$)	Outcomes*, no ($n = 197$)	Outcomes, yes ($n = 25$)	P value†
Age, year	67 ± 8	66 ± 8	71 ± 7	<0.01
Men	78%	79%	76%	NS
Body mass index, kg/m^2	24.1 ± 3.2	24.1 ± 3.3	24.3 ± 2.8	NS
Hypertension	49%	52%	29%	<0.05
Diabetes	40%	39%	50%	NS
Dyslipidemia	86%	84%	96%	NS
Previous myocardial infarction	60%	59%	68%	NS
Previous coronary revascularization	46%	45%	56%	NS
Coronary revascularization after the index cardiac catheterization	23%	22%	32%	NS
Serum creatinine, mg/dL	0.84 ± 0.20	0.84 ± 0.20	0.86 ± 0.20	NS
Medications				
Angiotensin converting enzyme inhibitors/angiotensin receptor blockers	43%	45%	32%	NS
β-blocker	41%	42%	38%	NS
Calcium blocker	32%	34%	20%	NS
Statin	58%	56%	79%	<0.05
Antiplatelet agents	81%	80%	92%	NS
Number of coronary arteries narrowed‡				NS
0	25%	26%	12%	
1	26%	24%	40%	
>1	49%	49%	48%	
Heart rate, beat/min	68 ± 12	68 ± 12	65 ± 12	NS
Systolic aortic pressure, mmHg	139 ± 25	139 ± 25	140 ± 21	NS
Diastolic aortic pressure, mmHg	68 ± 11	69 ± 11	65 ± 11	NS
Left ventricular end-diastolic pressure, mmHg	14.4 ± 5.4	14.3 ± 5.2	15.0 ± 5.9	NS
Relaxation time constant (Tau), ms	46.4 ± 9.1	46.0 ± 9.1	49.5 ± 8.4	0.06
Left ventricular end-diastolic volume index, mL/m^2	85.2 ± 21.0	84.5 ± 21.4	90.1 ± 22.7	NS
Left ventricular end-systolic volume index, mL/m^2	34.0 ± 19.2	33.5 ± 19.4	37.6 ± 18.0	NS
Ejection fraction	62 ± 13%	62 ± 13%	60 ± 11%	NS
Echocardiographic indices				
E/A	0.84 ± 0.41	0.84 ± 0.42	0.82 ± 0.34	NS
Deceleration time, ms	211 ± 50	213 ± 51	200 ± 45	NS
e' cm/s	7.0 ± 2.0	7.1 ± 2.1	6.4 ± 1.7	0.06
E/e'	9.6 ± 3.3	9.5 ± 3.4	10.0 ± 2.8	NS
Left ventricular mass index, g/m^2¶	108.6 ± 27.6	107.2 ± 26.9	121.6 ± 30.9	0.05

Data are expressed as the mean ± standard deviation or frequency.
*Outcomes were defined as cardiac death (acute myocardial infarction, heart failure, and sudden cardiac death) or unscheduled admission for cardiovascular causes.
†Outcomes yes versus no.
‡Narrowed coronary artery was defined as major epicardial artery with ≥75% stenosis on angiogram.
¶Left ventricular mass was available in 152 patients.

in Table 1. Compared with patients who survived without cardiovascular hospitalization during the followup, those who died or were hospitalized due to cardiovascular causes were more likely to be older, to be prescribed statins, and to have higher levels of Tau and lower levels of e' and were less likely to have hypertension.

Based on receiver-operating characteristic analyses for the prediction of death or cardiovascular hospitalization, the best cut-off points for e' and E/e' were determined as 5.8 cm/s (sensitivity 56%, specificity 73%, likelihood ratio 2.06) and 13.2 (sensitivity 20%, specificity 88%, likelihood ratio 1.69), respectively. Among LV function indices, significant univariate predictors for death or cardiovascular hospitalization included Tau > 48 ms (HR [95% CI] = 2.57 [1.13–5.81], $P < 0.05$) and $e' < 5.8$ cm/s (3.47 [1.57–7.70], $P < 0.01$). In contrast, no significant predictive value was

Table 2: Clinical and hemodynamic features of patient subgroups stratified by left ventricular relaxation time constant (Tau) and peak early diastolic mitral annular velocity (e').

	Tau			e'		
	≤48 ms ($n = 127$)	>48 ms ($n = 95$)	P Value	≥5.8 cm/s ($n = 153$)	<5.8 cm/s ($n = 69$)	P value
Age, year	67 ± 8	67 ± 9	NS	65 ± 8	70 ± 6	<0.001
Men	76%	82%	NS	80%	75%	NS
Body mass index, kg/m^2	23.8 ± 3.1	24.5 ± 3.3	NS	23.9 ± 3.3	24.6 ± 3.0	NS
Hypertension	47%	53%	NS	52%	49%	NS
Diabetes	40%	41%	NS	35%	53%	<0.05
Dyslipidemia	80%	94%	<0.01	83%	91%	NS
Previous myocardial infarction	48%	76%	<0.001	53%	75%	<0.01
Previous coronary revascularization	42%	53%	NS	44%	52%	NS
Coronary revascularization after the index cardiac catheterization	18%	31%	<0.05	19%	33%	<0.05
Serum creatinine, mg/dL	0.83 ± 0.19	0.85 ± 0.21	NS	0.83 ± 0.19	0.87 ± 0.20	NS
Medications						
Angiotensin converting enzyme inhibitors/angiotensin receptor blockers	39%	48%	NS	38%	55%	<0.05
β-blocker	30%	56%	<0.001	41%	41%	NS
Calcium blocker	35%	29%	NS	37%	23%	<0.05
Statins	52%	66%	NS	58%	60%	NS
Antiplatelet agents	77%	87%	<0.05	81%	82%	NS
Number of coronary arteries narrowed			<0.01			<0.01
0	32%	15%		31%	12%	
1	26%	26%		26%	26%	
>1	42%	59%		43%	62%	
Heart rate, beat/min	71 ± 12	64 ± 10	<0.001	68 ± 12	69 ± 11	NS
Systolic aortic pressure, mmHg	142 ± 27	134 ± 21	<0.05	137 ± 24	143 ± 27	0.07
Diastolic aortic pressure, mmHg	69 ± 11	67 ± 11	NS	68 ± 10	68 ± 12	NS
Left ventricular end-diastolic pressure, mmHg	12.3 ± 3.8	17.2 ± 5.7	<0.001	14.2 ± 5.2	14.8 ± 5.4	NS
Relaxation time constant (Tau), ms	40.2 ± 5.1	54.6 ± 6.1	<0.001	45.2 ± 9.3	48.9 ± 8.1	<0.01
Left ventricular end-diastolic volume index, mL/m^2	77.0 ± 16.3	96.1 ± 23.1	<0.001	80.3 ± 17.4	95.9 ± 25.8	<0.001
Left ventricular end-systolic volume index, mL/m^2	26.6 ± 12.2	43.9 ± 22.3	<0.001	29.2 ± 15.0	44.5 ± 23.1	<0.001
Ejection fraction, %	66 ± 10	56 ± 14	<0.001	65 ± 12	56 ± 14	<0.001

observed in EDP > 16 mmHg (HR [95% CI] = 1.36 [0.61–3.0], $P = 0.4$), EF < 50% (0.83 [0.29–2.4], $P = 0.7$), or $E/e' >$ 13.2 (2.02 [0.76–5.42], $P = 0.2$). Survival curves of patients stratified by Tau and e' are shown in Figure 1. Among other variables listed in Table 1, significant predictors for death or cardiovascular hospitalization included age (HR [95% CI] = 2.21 [1.31–3.71] per 1-SD increment, $P < 0.01$).

Clinical features of patients stratified by Tau and e' are shown in Table 2. Compared with patients with Tau ≤ 48 ms, those with Tau > 48 ms were more likely to have dyslipidemia and history of myocardial infarction, to be prescribed β-blockers, and to undergo coronary revascularization after the index cardiac catheterization. Compared with patients with $e' \geq 5.8$ cm/s, those with $e' < 5.8$ cm/s were more likely to be older, to have diabetes and history of myocardial infarction, to be prescribed angiotensin converting enzyme inhibitors/angiotensin receptor blockers, and to undergo coronary revascularization after the index cardiac catheterization and were less likely to be prescribed calcium blockers.

Hemodynamic and echocardiographic features of patients stratified by Tau and e' are also shown in Tables 2 and 3. Compared with patients with Tau ≤ 48 ms, those with Tau > 48 ms were more likely to have greater number of coronary arteries narrowed and higher levels of heart rate,

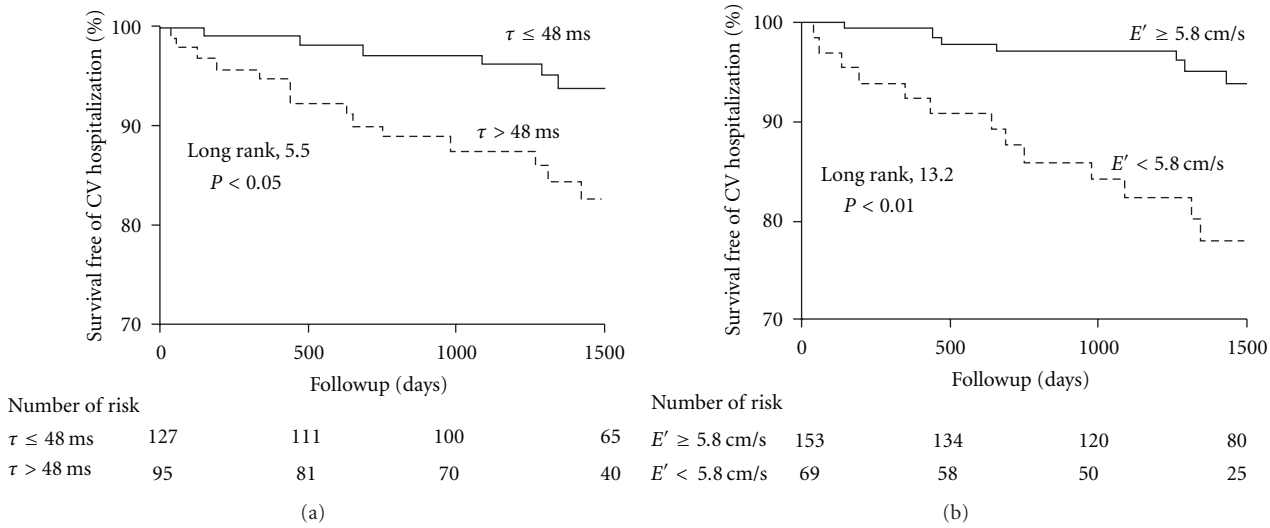

Figure 1: Kaplan-Meier survival curves of patients stratified by left ventricular relaxation time constant (Tau) and early diastolic mitral annular velocity (e'). CV indicates cardiovascular.

Table 3: Echocardiographic feature of patient subgroups stratified by left ventricular relaxation time constant (Tau) and peak early diastolic mitral annular velocity (e').

	Tau			e'		
	≤48 ms ($n = 127$)	>48 ms ($n = 95$)	P value	≥5.8 cm/s ($n = 153$)	<5.8 cm/s ($n = 69$)	P value
Echocardiographic indices						
E/A	0.79 ± 0.23	0.90 ± 0.55	0.05	0.87 ± 0.33	0.77 ± 0.54	NS
Deceleration time, ms	218 ± 48	201 ± 52	NS	210 ± 51	214 ± 49	NS
e' cm/s	7.5 ± 2.0	6.4 ± 1.9	<0.001	8.0 ± 1.6	4.8 ± 0.8	<0.001
E/e'	8.8 ± 2.8	10.6 ± 3.7	<0.001	8.3 ± 2.3	12.4 ± 3.6	<0.001
Left ventricular mass index, g/m^2	99.8 ± 24.5	120.7 ± 26.9	<0.001	101.5 ± 25.4	122.9 ± 26.5	<0.001

EDP, and LV volumes and lower levels of systolic aortic pressure and EF. Compared with patients with $e' \geq 5.8$ cm/s, those with $e' < 5.8$ cm/s were more likely to have greater number of coronary arteries narrowed and higher levels of Tau, EDP, and LV volumes and lower levels of EF.

Patients who were diagnosed to have abnormal LV relaxation by both cardiac catheterization and Doppler echocardiography (Tau > 48 ms and $e' < 5.8$ cm/s ($n = 41$)) were more likely to be older, to have history of myocardial infarction, to be higher in serum creatinine levels, LV volume, and LV mass index, and to be lower in EF, compared with those who were diagnosed to have abnormal LV relaxation by only one modality ($n = 82$).

After adjustment for potential confounders (traditional cardiovascular risk factors, the severity of CAD, and cardiovascular medications, coronary revascularization after the index cardiac catheterization), the predictive value of Tau > 48 ms continued to be significant (Table 4). Similar adjustment revealed the independent predictive value of $e' < 5.8$ cm/s (Table 4).

Modest but significant correlations were observed between LV diastolic function indices determined by cardiac catheterization and those by Doppler echocardiography; Tau correlated with e' ($r = -0.26$, $P < 0.001$) and E/e' ($r = 0.26$, $P < 0.001$) and EDP correlated with E/e' ($r = 0.23$, $P < 0.001$) but not with $e\prime$ ($r = -0.08$, $P = 0.3$).

4. Discussion

In the present study, we found that Tau > 48 ms and $e' < 5.8$ cm/s were each associated with an increased risk for cardiac death or subsequent cardiovascular hospitalization in patients undergoing cardiac catheterization for CAD. In contrast, no prognostic value was observed in EDP, E/e', or EF.

Although studies have reported that LV diastolic abnormalities assessed by Doppler echocardiography are predictive of cardiac mortality and morbidity in patients with myocardial infarction [5], those with heart failure with preserved EF [7], those with reduced EF [8], and hypertensive subjects [6, 9], only a few studies have examined the predictive value of invasively-determined diastolic dysfunction. Specifically, Liang et al. examined the prognostic value of EDP as well as Doppler echocardiographic diastolic measures in patients undergoing cardiac catheterization for CAD [16]. They

Table 4: Unadjusted and adjusted hazard ratios of left ventricular relaxation time constant (Tau) > 48 ms and peak early diastolic mitral annular velocity (e') < 5.8 cm/s by Cox proportional hazards regression analysis.

	Unadjusted	Adjusted		
		Model 1*	Model 2†	Model 3‡
Tau > 48 ms	2.57 (1.13–5.81)¶	2.45 (1.04–5.82)¶	3.12 (1.16–8.37)¶	3.23 (1.31–7.97)¶
e' < 5.8 cm/s	3.47 (1.57–7.70)#	2.38 (1.03–5.52)¶	4.09 (1.75–9.57)#	3.81 (1.65–8.81)#

Data are represented as hazard ratio (95% CI).
*Adjusted for age, sex, hypertension, dyslipidemia, diabetes, and coronary revascularization after the index cardiac catheterization.
†Adjusted for previous history of myocardial infarction, the number of coronary arteries narrowed, ejection fraction, systolic aortic pressure, and heart rate.
‡Adjusted for use of β-blocker, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, calcium blocker, statin, and antiplatelet agents.
¶$P < 0.05$.
#$P < 0.01$.

found that EDP > 20 mmHg and $E/e' \geq 15$ were each predictive of future heart failure events. In contrast, in our study, no prognostic value was observed in EDP or E/e'. Compared with a cohort of Liang et al., our patients had lower EDP (18.2 ± 7.3 versus 14.4 ± 5.4 mmHg) and E/e' (12.5 ± 5.6 versus 9.6 ± 3.3) levels, due probably to that patients with congestive heart failure were not included in our study. Thus, EDP or E/e' may not be predictive of adverse prognosis in a cohort of patients without congestive heart failure in which the majority have normal or slightly elevated EDP and E/e'.

The strength of the present study is that LV hemodynamic variables were obtained with the use of a micromanometer catheter but not a fluid-filled catheter. Although a fluid-filled catheter accurately measures late diastolic LV pressures, it cannot precisely determine rapidly changing pressures as occur during LV isovolumetric relaxation [17]. Use of a micromanometer catheter enabled us to determine Tau, an index of LV relaxation. Although LV relaxation can be estimated from e' on Doppler echocardiography, e' quantitates the peak velocity of early diastolic longitudinal motion of the mitral annulus [18] and measurement of e' only provides best-available noninvasive assessment of LV relaxation. Our study is significant in showing for the first time the prognostic value of abnormal LV relaxation determined by cardiac catheterization in patients with known or suspected CAD.

Although the present study does not provide direct mechanisms underlying the association between abnormal LV relaxation and adverse prognosis in patients with known or suspected CAD, there are possible explanations. The most common cause of cardiac death or cardiovascular hospitalization in our study was ischemic myocardial events. It is well-established that the presence of myocardial ischemia impairs LV relaxation [19]. In fact, we observed that patients with impaired LV relaxation had more severe CAD (Table 2). Thus, the prognostic association of impaired LV relaxation may be mediated at least in part by CAD severity. We observed, however, that after adjustment for the index coronary angiographic findings, the predictive value of impaired LV relaxation remained significant (Table 4, Model 2). Thus, a part of the prognostic association of impaired LV relaxation may be due to inducible myocardial ischemia regardless of the stenoses of epicardial coronary arteries. Consistent with this explanation, studies have shown that impaired LV relaxation diminishes early diastolic coronary flow [20, 21] and may thereby further exaggerate myocardial ischemia particularly when accompanied by tachycardia (such as tachyarrhythmia and during exertion).

Another possible explanation for our observed association of impaired LV relaxation with adverse prognosis is that LV diastolic abnormalities may coexist with other disorders that may adversely impact on prognosis. Specifically, Lee et al. reported that altered LV diastolic function assessed by Doppler echocardiography was independently associated with endothelial dysfunction and hemostatic abnormalities [22], both of which have been reported to be predictive of the development of atherosclerotic diseases and ischemic myocardial events in patients with CAD [23, 24].

There are several limitations in the present study. First, LV mass was available in the limited number of the patients (68%), which could have influenced our results [25]. Furthermore, estimation of LV mass by M-mode echocardiography in the presence of altered LV geometry such as myocardial infarction may be inappropriate [15]. Second, we did not measure left atrial volume index, a powerful predictor for left atrial pressure and clinical outcomes [14, 26]. Third, the time difference between cardiac catheterization and Doppler echocardiographic examination is not small (about one day). This may explain our observed modest correlations of diastolic function indices obtained from cardiac catheterization with those from Doppler echocardiography and may also possibly explain the lack of prognostic value of E/e'. Forth, our study patients were composed of stable known or suspected CAD patients without congestive heart failure who were referred for cardiac catheterization for assessment of CAD. Our findings cannot be extended to other populations. Finally, our study is not large enough to permit us to evaluate the association of LV diastolic dysfunction with specific causes of death or hospitalization.

Our study suggests that measurement of e' by Doppler echocardiography may provide useful information for risk stratification in known or suspected CAD patients without congestive heart failure. The cut-off point of e' used in the present study, however, is higher than that previously reported. Specifically, Wang et al. reported that $e' < 3$ cm/s was a powerful predictor for cardiac death in patients with reduced (<50%) EF [8]. Similarly, the same group reported the predictive value of $e' < 3.5$ cm/s for cardiac death in hypertensive subjects with LV hypertrophy [9]. These results

suggest that the best cut-off point of e' for the prediction of adverse prognosis may be variable depending on population studied. Further studies are necessary for determining the optimal cut-off points of e' for identifying high-risk patients in various populations.

Our findings suggest that patients with impaired LV relaxation may need more aggressive treatment of CAD. A recent study has reported that altered LV relaxation assessed by Doppler echocardiography is improved after coronary revascularization in patients with ischemic cardiomyopathy [27]. The prognostic impact of improved LV relaxation after coronary revascularization in CAD patients merits future research.

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