INVITED REVIEW

Future strategies for the treatment of diastolic heart failure

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Abstract

It is estimated that 30% to 50% of heart failure patients have preserved systolic left ventricular (LV) function, often referred to as diastolic heart failure (DHF). Mortality is high in this patient population, and morbidity and rate of hospitalization are similar to those of patients with systolic heart failure. The management of patients with diastolic heart failure is essentially empirical, limited, and disappointing. New drugs, devices, and gene therapy based treatment options are currently under investigation. In this review, future strategies for the treatment of diastolic heart failure are discussed.

Key Words: Diastolic heart failure, diastolic dysfunction, device, gene therapy, cell therapy

Introduction

The term diastolic heart failure (DHF) generally refers to the clinical syndrome of heart failure associated with a preserved left ventricular ejection fraction (EF), in the absence of major valvular disease (1). Forty percent of incident CHF cases and 50–60% of prevalent CHF cases occur in the setting of preserved systolic function (2). Mortality rate among patients with DHF is considered lower than in systolic heart failure (3). Some challenge this notion, showing that the natural history of patients with DHF may not be different from that of patients with systolic heart failure (2,4). The morbidity and rate of hospitalization are similar to those of patients with systolic heart failure (3,4). Due to its higher prevalence in the elderly population, the incidence of DHF is expected to rise with the increased aging of the western world population.

The fundamental problem in diastolic heart failure is the inability of the left ventricle to accommodate blood volume during diastole at normal filling pressures (5,6). Two basic types of diastolic abnormalities may be present: impaired ventricular relaxation (which primarily affects early diastole), and increased myocardial stiffness (which primarily affects late diastole) (7–9). The rate and extent of the active relaxation may influence LV suction during the early filling phase (10). Both abnormalities lead to elevation of diastolic pressures. In DHF patients, a relatively small increase in central blood volume or an increase in venous tone, arterial stiffness, or both, can cause a substantial increase in left atrial and pulmonary venous pressures and may result in exercise intolerance (11,12) and acute pulmonary edema (13,14).

The mechanisms underlying abnormalities in diastolic function can be divided into factors intrinsic to the myocardium itself and factors that are extrinsic to the myocardium (15). Myocardial factors can additionally be divided to cellular and extracellular. Cellular factors include impaired calcium homeostasis leading to abnormalities in both active relaxation and passive stiffness, changes in sarcomeric proteins isotypes, such as titin, which acts as a viscoelastic spring that gains potential energy during systole and provides a recoiling force to restore the myocardium to its resting length during diastole (16). Since relaxation is an energy-consuming process, any abnormalities in cellular energy supply and utilization can lead to impaired relaxation (15). Extracellular factors include changes in structures and quantity of the extracellular matrix, i.e. fibrosis, that lead to increased myocardial stiffness (17). There is limited data on neurohumoral markers in DHF patients other than natriuretic peptides (NPs). This probably reflects the fact that DHF has only recently been

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recognized as an important clinical problem (18). Certain neurohumoral pathways such as the renin-angiotensin-aldosterone system and sympathetic nervous system are likely to play a detrimental pathophysiological role in DHF. Benedict et al. (19) found a small but statistically significant increase in arginine vasopressin (AVP) and plasma renin activity in patients with radiologically proven pulmonary edema and EF > 45% compared to control subjects but this was to a lesser extent than patients with pulmonary edema and EF < 45% in all parameters (i.e. neuropeptide, plasma rennin, and ANP) except AVP. The use of diuretics and angiotensin converting enzyme inhibitors (ACE-I) in this patient population may have been the cause for these differences. However, Kitzman et al. (20) demonstrated significant increase in plasma norepinephrine and BNP concentrations compared to control subjects, norepinephrine values were similar to those of patients with systolic heart failure. Another study, comparing patients with DHF who had been stable for at least 1 year after an emergency presentation with acute pulmonary edema to patients with hypertension, did not reveal significant differences in plasma renin activity and plasma concentrations of norepinephrine and aldosterone (21). Therefore, the evidence that these pathways are chronically activated in stable DHF patients is not conclusive.

The management of diastolic heart failure is mostly empirical (13,22–24). Current treatment recommendations according to the ACC/AHA Practice Guidelines (25), which refer to DHF are more often based on expert opinion and common medical practice rather than evidence-based. These recommendations include control of diastolic and systolic hypertension, control of ventricular rate in patients with atrial fibrillation, and use of diuretics to control pulmonary congestion and peripheral edema (class I). Less conclusive recommendations are coronary revascularization in patients with coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is judged to have an adverse effect on cardiac function (class IIa), and restoration and maintenance of sinus rhythm in patients with atrial fibrillation (class IIb). The use of beta-adrenergic blocking agents, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, or calcium antagonists in patients with controlled hypertension is regarded as potentially effective to minimize symptoms of heart failure (class IIb), use of digitalis is viewed as less well established (class IIIb).

In this review, potential future strategies for the treatment of diastolic heart failure are discussed.

Medications

The role of agents that improve left ventricular relaxation and of medications currently used for the treatment of systolic heart failure has not been studied comprehensively in DHF patients. However, several studies are currently on the way. Potential medications under extensive research include Renin-Angiotensin-Aldosterone System (RAAS) modulators: Angiotensin Receptor Blocker (ARB), Angiotensin Converting Enzyme Inhibitors (ACE-I), and aldosterone receptor blockers. Other compounds currently under clinical investigation for the treatment of DHF are ALT-711 (alagebrium) and MCC-135 (caldaret).

Renin-Angiotensin-Aldosterone System modulators

**Angiotensin receptor blockers.** The widespread role of the RAAS in cardiovascular disease, particularly in systolic heart failure, has led to investigation of RAAS inhibitors in DHF patients. A single, large, randomized clinical trial of patients with heart failure and a preserved left ventricular ejection fraction (> 0.40) was recently published (CHARM-Preserved trial) (26). This study showed that treatment with candesartan (an angiotensin receptor blocker) did not affect cardiovascular death, but significantly less patients in the candesartan group were admitted to hospital for CHF. The I-PRESERVE trial is a randomized placebo controlled trial designed to further test and provide definite results regarding the efficacy of ARB, specifically irbesartan, enrolling 4100 DHF patients (27).

**Angiotensin converting enzyme inhibitors.** There is limited and conflicting evidence for the benefit of ACE inhibitors in patients with CHF and preserved systolic function. The CONSENSUS study (28) suggested no benefit, but this sub-group probably comprised only 50 patients. The V-HeFT-II study (29) suggested a mortality benefit in the subgroup of approximately 250 patients with EF > 40%. The ACE inhibitor Perindopril was demonstrated to improve arterial compliance in large arteries, restore the structure of small resistance arteries, cause regression of left ventricular hypertrophy, restore flow-mediated coronary vasodilation in hypertensive patients, and reverse endothelial dysfunction in patients with heart failure (30–35). Based on these studies a multi-center, double-blind, randomized, parallel-group, placebo-controlled trial (PEP-CHF trial (36)) was designed, aiming to assess the potential benefits of the ACE inhibitor perindopril to treat chronic heart failure in elderly people, in the absence of any major left ventricular systolic dysfunction, enrolling 1000 patients.

**Aldosterone receptor antagonists.** There is increasing evidence regarding the potentially favorable effect of aldosterone receptor antagonists in DHF patients.
Spironolactone was demonstrated to prevent myocardial fibrosis in a rat model of renovascular hypertension and in aldosterone models of acquired arterial hypertension (37). A recent prospective, double-blind, randomized, placebo-controlled trial that enrolled 30 patients aged 60–83 years with isolated diastolic dysfunction demonstrated significant improvement in mitral E/A ratio and deceleration time following four months of treatment with 25 mg/day of spironolactone (38). A randomized, double-blinded, placebo-controlled trial using the aldosterone antagonist eplerenone in 4500 patient with CHF and preserved EF (TOPCAT), sponsored by the National Heart, Lung, and Blood institute (NHLBI), is expected to begin recruitment in January 2006.

**Beta blockers.** The addition of Carvedilol, a non-selective β-receptor blocker and selective vasodilating α1-receptor blocker, to conventional therapy (diuretics and/or ACE-inhibitors and/or digoxin) was evaluated in a prospective, randomized, double-blind, placebo-controlled, multi-centre study including 97 patients suffering from DHF in the Swedish Doppler-echocardiographic study (SWEDIC) (39). The maximal dose of Carvedilol was 25 mg b.i.d. or 50 mg b.i.d., achieved by 82% of the treatment group at the end of the six-month study period. The primary endpoint of the study was regression of diastolic LV dysfunction measured by Doppler echocardiography, and was not significantly affected, although a trend towards a better effect in carvedilol treated patients was noticed in patients with heart rates above 71 beats per minute. Additionally, a statistically significant improvement in age-adjusted E:A ratio was found in the carvedilol treated group. Carvedilol was also studied as an addition to conventional therapy on 19 patients randomly selected from 40 patients suffering from heart failure with preserved ejection fraction, referred to a heart failure outpatient clinic (40). After a 12-month period plasma concentrations of BNP decreased significantly in patients receiving carvedilol but not in those receiving conventional therapy. NYHA functional class and exercise capacity significantly improved in the carvedilol group compared to the control group.

**Digitalis.** The effect of digitalis on patients with heart failure and preserved systolic function was evaluated in an ancillary trial of the DIG study, a randomized, double-blind clinical trial by the Digitalis Investigation Group (41). The study included 492 heart failure patients with ejection fractions greater than 0.45 in the digoxin treatment group and 496 patients in the placebo group. Mortality was similar in the two groups and the combined outcome of death or hospitalization due to worsening heart failure was markedly reduced (risk ratio, 0.82; 95% confidence interval, 0.63–1.07).

**Furosemide.** The effect of Furosemide withdrawal on functional status and orthostatic blood pressure homeostasis was studied in a placebo-controlled pilot trial for a three-month follow-up period (42). Thirty-two elderly heart failure patients with preserved LV ejection fraction were randomized at a 2:1 ratio to withdrawal and continuation groups in this double-blinded placebo-controlled study. Heart failure score, blood pressure, heart rate, spirometry, exercise tolerance, and functional status were similar between the two groups. Doppler E:A ratio increased (potentially reflecting an increase in left atrial pressure), while blood pressure response on active standing improved after successful withdrawal from furosemide.

ALT-711 (alteon) is the first drug in a new class of therapeutic agents that break established AGE cross-links between proteins (44). In animal models, ALT-711 was found to be effective in reducing large artery stiffness (as measured by systemic arterial compliance, aortic impedance, and carotid artery compliance and distensibility), slowing pulse-wave velocity, enhancing cardiac output, and improving left ventricular diastolic distensibility. Additionally, in a diabetes animal model, treatment reduced left ventricular mass and cardiac expression of brain natriuretic peptide (22,45–47).

The Distensibility Improvement and Remodeling in Diastolic Heart Failure (DIAMOND) trial, was conducted to investigate the effects of ALT-711 on diastolic heart failure (48). Twenty-three male and female patients over 60 years old, with stable heart failure symptoms, New York Heart Association (NYHA) class II or III, and ejection fraction > 50%, participated in this open label study and were treated with the compound for a period of 16 weeks, while maintaining previous therapy. Fourteen of the 21 patients who completed the study showed an improvement in NYHA class. Additionally, LV mass was reduced and LV diastolic filling improved. Treatment with ALT-711 also had a positive effect on three key quality-of-life measurements, as determined by the Minnesota Living with Heart Failure (MLHF) questionnaire: the MLHF total score, physical score, and mental score. Blood
pressure, exercise tolerance (peak exercise VO2), and aortic distensibility remained unchanged.

**MCC-135 (caldaret).** Myocardial relaxation is induced by the uptake of Ca\(^{2+}\) into the sarcoplasmic reticulum (SR). Reduction of the SR Ca\(^{2+}\) uptake activity may be one of the mechanisms underlying prolonged relaxation and a new compound, MCC-135 (Mitsubishi Pharma Corporation) was shown to improve SR Ca\(^{2+}\) uptake and reduce Ca\(^{2+}\) leakage from the SR in rats with diabetic cardiomyopathy (49). A clinical study aiming to test the safety, tolerability, and efficacy of MCC-135 in patients with mild to moderate CHF, the MCC-135 GO1 study, has completed patient follow up during February 2003 (50). This was a phase II, multi-center, randomized double-blind study that recruited over 500 patients divided into two cohorts, one with an ejection fraction under 40% and the second with an ejection fraction over 40%. Results of the study were yet to be published.

**Devices**

The use of devices for the treatment of heart failure is emerging as a potential new paradigm; some devices are already in clinical use for systolic heart failure, such as left ventricular assist devices (LVAD) (51) and biventricular pacing devices (Cardiac Resynchronization Therapy) (52). Passive restraining devices, such as the Corcap (Acorn Cardiovascular Inc.) and Myosplint (Myocor Inc.), are in advanced stages of clinical research (53). These devices are aimed at improving cardiac systolic function. The following section describes two preclinical stage device concepts with a potential future role in the treatment of DHF patients.

**Levram VAD**

A cardiac assist device was developed by Landesberg et al. (54), which utilizes a single cannula inserted through the apex of a beating left ventricle and is synchronized with the heart-beat. Blood is withdrawn from the LV and into the assist device during diastole, to be injected back into the LV during systole through the single connecting cannula. This mechanism is different from most other mechanical ventricular assist devices, which support the failing left ventricle by rerouting the blood from the ventricle into the aorta. The authors propose that the Levram VAD may augment both systolic and diastolic LV function. Systolic LV function is improved by adding external work during the ejection phase, thus increasing the stroke work. Diastolic LV function is improved by actively unloading the LV only during diastole, thus improving LV filling. Diastolic unloading by the device begins immediately after aortic valve closure, causing the LV volume to reduce during the physiological isovolumic relaxation phase, and continues after mitral valve opening. The device was acutely studied on a sheep model of chronic heart failure (n=5) with dilated LV and reduced ejection fraction, induced by repetitive injections of polystyrene microspheres into the coronary arteries (54). The authors present an increase in LV stroke volume, cardiac output, systolic pressure, and stroke work, and a decrease in left atrial pressure, LV end diastolic volume and heart rate. This device might have a potential role in the treatment of patients with severe DHF by relieving high filling pressures.

**Passive diastolic assist device**

An alternative approach for treating diastolic heart failure may be the transfer of energy from systolic contraction to diastolic filling, by an elastic self-expanding device (CorAssist Cardiovascular Limited) which is attached to the epimyocardial surface of the left ventricle. The device exerts radial outward forces on the left ventricle, which may potentially reduce ventricular filling pressures, without compromising ventricular systolic function. The concept is directed towards reducing chamber stiffness, an important pathophysiological component of diastolic dysfunction. Since the device is directly attached to the epimyocardial surface, it stores potential energy during ventricular contraction—essentially being loaded in systole like a spring—and releases the energy during diastole. Thus, the device provides a recoiling force to restore the myocardium to its resting length during diastole.

Since diastolic LV pressure is much lower than systolic LV pressure, the transfer of a small percentage of the force developed by the LV in systole may be sufficient to reduce LV filling pressures substantially.

The feasibility of this concept was evaluated by our group on a healthy sheep, using a stainless steel device (Figure 1). The device was comprised of two separate stainless steel wires that were bent into a series of v-shaped sections, and the apex of each v-shaped section was twisted around its longitudinal axis, to form a loop. The two wires were connected to one another by a central connecting-element (Figure 1a). The connecting element enabled gradual elongation of the spring, thus allowing in vivo adjustment of the force applied by the device to the left ventricular wall. During each contraction of the ventricle, the device was constricted, thus causing a force directed towards reversing the contraction, and expanding the ventricle during diastole.

The device was attached, in a loaded state, to the epimyocardium of the beating left ventricle, by spiral
coils that were screwed into the LV wall. Device loading was accomplished by constricting sutures between adjacent spring loops, following the release of which, the device would apply expansion forces on the LV wall.

Figure 1(c) presents left ventricular pressure over time curves averaged from 180 consecutive cardiac cycles. A baseline measurement, taken before device deployment, revealed end diastolic pressure (EDP) of 8.1 mmHg and minimal pressure (MP) of 4.1 mmHg. Following implantation of the loaded device EDP was elevated to 12.6 mmHg and MP was elevated to 7 mmHg. Following release of the loading sutures, allowing the device to exert an outward force on the ventricular wall, EDP decreased to 8 mmHg and MP decreased to 3.1 mmHg. The device was then modulated to exert stronger outward radial force and another set of pressure measurements was taken, demonstrating a more significant reduction of pressures to an EDP of 5.8 mmHg and MP of 0.4 mmHg, suggesting a dose–effect response.

Further evaluation of this concept, using a silicon lattice device attached to the LV through the epicardial surface, was performed following this proof of concept (submitted to publication).

Gene and cell therapy

The possibility of treating various disorders by over expression of a gene encoding a specific protein to enhance or replace a malfunctioning one has emerged in the past four decades as a promising approach. However, clinical trials to date have been widely unsuccessful and have led many physicians and scientists to doubt the potential of the modality. Problems occurred in the delivery, long-term efficacy, and safety of the procedure. Despite the setbacks and limited success in the field, gene therapy is one of the most active research fields in medicine, and improvement of vectors, better delivery techniques, and advanced understanding of the safety issues may lead to more successful treatment modalities using gene therapy.

Impaired calcium homeostasis can lead to abnormalities in both active relaxation and passive stiffness. Alterations in expression or function of the Ca\(^{2+}\)-ATPase (SERCA2a), phospholamban (PLB) (55–58), SR–Ca\(^{2+}\) release channel, FK-506 binding protein 12.6 (FKBP12.6), and NCX may hamper calcium homeostasis, and are associated with delayed relaxation.

Based on the fact that SERCA2a expression is reduced in heart failure (59) Miyamoto et al tested the effect of SERCA2a overexpression in a rat heart failure model that was induced by aortic banding (60). The rats received adenovirus carrying the SERCA2a gene (Ad.SERCA2a) or β-galactosidase. They demonstrated in the Ad.SERCA2a group significant improvement in maximal rate of decline of LV pressure and the time course of pressure decline Tau; however, no significant reduction in diastolic
pressure was measured. Schmidt et al demonstrated on Senescent rats restoration of Tau, and minimum first derivative of LV pressure (min LV dP/dt) in rats infected with the Ad.SERCA2a (61).

Hoshijima et al. used recombinant adeno associated virus (rAAV) to express a pseudophosphorylated mutant of human phospholamban (S16EPLN), a key regulator of SERCA2a, in BIO14.6 cardiomyopathic hamsters. This group also demonstrated significant improvement in the min LV dP/dt and Tau at 28–30 weeks after the rAAV/ S16EPLN delivery. Moreover, diastolic wall stress estimated by LVEDD/LVPWT was significantly lower than that in the control group, and wall thickness (LVPWT) was preserved over 28–30 weeks in rAAV/S16EPLN-treated animals (62).

Recently, over expression of parvalbumin in aged rats myocardium was demonstrated to improve diastolic function. Reduction of diastolic pressure as well as min LV dP/dt was demonstrated. Over expression of parvalbumin also improved the force frequency relationship in the senescent rats (63).

In the past decade cell therapy has emerged as a potential treatment for CHF. Cell sources were embryonic stem cells, skeletal myoblasts, fetal cardiomyocytes, and dermal fibroblasts. Both myoblasts and fibroblasts transplantation were associated with improvement in diastolic indices (64).

While both strategies, cell and gene therapy, demonstrated improvement in diastolic indices, none demonstrated reduction of left ventricular end diastolic pressure or minimal pressure, and none were tested on a diastolic heart failure model.

Discussion

The current and future treatment modalities for DHF can be divided into preventive measures, medications that delay progression and remodeling at the early disease state, and methods aiming to reverse the disease and prevent symptoms at an advanced disease stage. Preventive measures focus on treatment of underlying causes such as hypertension, diabetes, and ischemic heart disease. Delaying progression and remodeling may be achieved by medications such as RAAS modulators, ALT-711 and MCC-135. Reversing the disease state and improvement of symptoms may be achieved by medical devices and gene therapy that are more likely to be used in advanced stages of the disease.

Figure 2 summarizes a selected group of future strategies that may have a potential role in the treatment of DHF. Currently, the prognosis of DHF patients is poor and associated with high morbidity and mortality, however, the increasing recognition of this patient population among those suffering from CHF in the past decade has contributed to significant advances in understanding the mechanisms underlying DHF and the development of multiple strategies, which will ultimately lead to better management of DHF patients.

Disclosure

This research was supported by CorAssist Cardiovascular Limited. Ehud Schwammenthal, and Amir Elami, are medical consultants of CorAssist Cardiovascular Limited. The device was invented by Yair Feld, who is a shareholder in CorAssist Cardiovascular Limited. Shay Dubi and Yotam Riesner are also shareholders in CorAssist Cardiovascular Limited.

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