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DIASTOLIC DYSFUNCTION: A LINK BETWEEN HYPERTENSION AND HEART FAILURE

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Summary

Diastolic heart failure is characterized by the symptoms and signs of heart failure, a preserved ejection fraction and abnormal left ventricular (LV) diastolic function caused by a decreased LV compliance and relaxation. The signs and symptoms of diastolic heart failure are indistinguishable from those of heart failure related to systolic dysfunction; therefore, the diagnosis of diastolic heart failure is often one of exclusion. The majority of patients with heart failure and preserved ejection fraction have a history of hypertension. Hypertension induces a compensatory thickening of the ventricular wall in an attempt to normalize wall stress, which results in LV concentric hypertrophy, which in turn decreases LV compliance and LV diastolic filling. There is an abnormal accumulation of fibrillar collagen accompanying the hypertension-induced LV hypertrophy, which is also associated with decreased compliance and LV diastolic dysfunction. There are no specific guidelines for treating diastolic heart failure, but pharmacological treatment should be directed at normalizing blood pressure, promoting regression of LV hypertrophy, preventing tachycardia and treating symptoms of congestion. Preventive strategies directed toward an early and aggressive blood pressure control are likely to offer the greatest promise for reducing the incidence of diastolic heart failure.

Introduction

Heart failure is a complex clinical syndrome arising from any structural or functional cardiac condition that impairs left ventricular (LV) filling or ejection (1). The principal symptoms of heart failure are dyspnea, fatigue and fluid retention, which may lead to pulmonary congestion and peripheral edema (1). In the United States, approximately 5 million patients have heart failure, and over 550,000 individuals are newly diagnosed with heart failure each year (2). The estimated total direct and indirect cost of heart failure in the United States is close to 30 billion dollars per year (2,3).

Hypertension is the most common risk factor and the principal precursor of heart failure (4). The risk for developing heart failure in hypertensive compared with normotensive individuals is about twofold in men and threefold in women (4). The 20-year follow-up of the Framingham Heart Study and the Framingham Offspring Study revealed 392 new cases of heart failure representing 7.6% of the studied population (4). For 91% of these patients with heart failure, hypertension antedated the development of the disease (5). At age 40, the lifetime risk for congestive heart failure was 11.4% for men and 15.4% for women (6). Lifetime risk doubles for subjects with blood pressure $\geq 160/100$ versus $< 140/90$ mmHg (6).

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Diastolic heart failure

Diastolic heart failure is a clinical syndrome characterized by the symptoms and signs of heart failure, a preserved ejection fraction and abnormal diastolic function (7). Diastolic heart failure occurs when the left ventricle is unable to accept an adequate volume of blood at normal diastolic pressures. Diastolic heart failure is also referred to as heart failure with normal ejection fraction or heart failure with preserved ejection fraction. Depending on the criteria used to delineate heart failure and the accepted threshold defining preserved ejection fraction, it is estimated that as many as 20–60% of patients with heart failure have a preserved ejection fraction, with an equal or greater prevalence of diastolic dysfunction in men than women (1, 8–10).

A normal LV diastolic pressure-volume curve allows increases in LV filling in the normal physiological range without significant changes in LV end-diastolic pressure. With decreased LV compliance, as is the case in diastolic heart failure, there is a shift of the curve upwards and to the left, indicating that a higher pressure is necessary to fill the left ventricle to the same volume, possibly due to LV hypertrophy or alterations in the collagen network (11) (Fig. 1). It is the transmission of this higher LV pressure to the pulmonary circulation that eventually leads to pulmonary congestion, dyspnea and other symptoms of heart failure (12).

Diastolic dysfunction may also be caused by changes in the rate and degree of LV relaxation (13). Relaxation of the ventricles involves the active transport of calcium ions into the sarcoplasmic reticulum, which allows the dissociation of myosin-actin crossbridges (12). Slow or incomplete relaxation due to changes in calcium homeostasis decreases the atrioventricular pressure gradient in early diastole, which decreases LV filling (14).

The morbidity and mortality associated with diastolic heart failure may be nearly as profound as that with low ejection fraction, as it is associated with frequent and repeated hospitalizations (8,15,16). The annual mortality rate for isolated diastolic heart failure is approximately 2–3% (17). However, it is believed that patients with heart failure and preserved ejection fraction have a better prognosis than those with systolic heart failure, at least over the first three to four years of follow-up (8,9,13).

Diagnosis of diastolic heart failure

The signs and symptoms of diastolic heart failure are indistinguishable from those of heart failure related to systolic dysfunction (13). Therefore, the diagnosis of diastolic heart failure is often one of exclusion as the distinction between systolic and diastolic heart failure cannot be made on the basis of history, physical examination, ECG or chest radiograph alone (7). According to the European Study Group on Diastolic Heart Failure, diagnosis of diastolic heart failure requires three obligatory conditions: presence of signs and symptoms of congestive heart failure, presence of normal or only mildly abnormal LV systolic function, and evidence of abnormal LV relaxation, filling, diastolic distensibility or stiffness (7). Following criticisms regarding specificity, sensitivity and accuracy as well as the technical difficulty of LV diastolic measurement associated with this classification, Vasan and Levy (9) proposed a classification of definite, probable and possible diastolic heart failure depending on the presence of three conditions: definite evidence of heart failure, objective evidence of normal LV systolic function measured within 72 hours of heart failure event, and objective evidence of LV diastolic dysfunction by cardiac catheterization. When all three conditions are present, there is definite diastolic heart failure. If only the first two are present, the diagnosis of diastolic heart failure is probable. If only the first condition is present or only partial evidence of the second condition is present, the diagnosis of heart failure is considered possible.

The serum level of brain natriuretic peptide (BNP) is secreted in response to ventricular after-load and is also an accurate tool for establishing the diagnosis of heart failure (18). However, the test cannot distinguish diastolic from systolic heart failure, although it has been suggested that the secretion of natriuretic peptides is more closely associated with impairments of LV diastolic filling than with the deterioration of LV systolic function, suggesting that diastolic rather than systolic dysfunction is the main stimulus for this type of neurohumoral activation (12,19).

LV diastolic dysfunction

LV diastolic function can be evaluated by observing the pattern of mitral inflow of the left ventricle (20,21). A normal transmitral filling pattern is biphasic and represents LV early filling upon mitral valve opening and atrial or late filling occurring during atrial contraction (21). The peak early flow velocity and the peak atrial flow velocity are defined as E and A, respectively.

Impairments in diastolic function are characterized by a progression of three different LV filling patterns representing changes in transmitral blood inflow over time of disease evolution (Fig. 2). Impaired relaxation occurs when the rate of relaxation is slower and LV pressure decreases less rapidly and is characterized by a reversed E/A ratio. Consequent to the impaired relaxation, there is often a compensatory elevation in left atrial pressure to re-establish a normal atrioventricular pressure gradient and return early diastolic filling velocities to normal (20, 22). This results in a pseudonormal filling pattern representing abnormalities of both LV relaxation and compliance with an apparently normal E/A ratio. Patients with pseudonormal filling pattern typically experience shortness of breath during exertion and have moderate functional impairment. Finally, a restrictive filling pattern is observed in patients with severe decrease in LV compliance causing an increased E/A ratio, which reflects an even higher left atrial pressure and severe decrease in LV relaxation and compliance. The result is a dramatically increased E/A ratio often accompanied by symptoms of heart failure (23,24).

Factors affecting LV filling pattern

LV filling pattern depends on factors governing atrioventricular pressure gradient (7). Ventricles that have impaired early filling because of altered chamber compliance are more dependent on atrial contraction for complete filling (13). Therefore, the loss of atrial contraction during atrial fibrillation can potentially lead to significant underfilling of the left ventricle and a decreased stroke volume. Slowed or prolonged LV relaxation is also associated with a decrease in early filling (25).

LV filling pattern is also affected by age and other diseases like type 2 diabetes. Indeed, LV diastolic function is commonly impaired in type 2 diabetic patients and with healthy aging as observed through a reduced E/A ratio (26–31). Elderly patients with borderline systolic hypertension have shown signs of diastolic dysfunction without any impairment of systolic function, partly because of a decreased LV compliance (32). On the other hand, impairments in LV diastolic filling are common in type 2 diabetes and might be the primary abnormality, as impairments in diastolic function are repetitively observed in the presence of normal systolic function (33–38).

Measurement of LV diastolic function

Because cardiac catheterization provides direct measurement of LV diastolic pressure, it is the gold standard to determine impairments in LV diastolic filling. However, the invasive nature of this measurement makes it an inconvenient tool. On the other hand, Doppler echocardiography is commonly used to evaluate LV diastolic function as it is quick, relatively inexpensive and noninvasive. However, there are several limiting factors to Doppler

echocardiography since measurements of LV filling are influenced by age and fitness level, as well as by changes in preload, afterload and heart rate (39). Therefore, it is desirable to have additional variables, like tissue Doppler imaging or measurements of pulmonary vein velocity, to complement mitral inflow velocity when evaluating LV diastolic function (21). Tissue Doppler imaging (TDI) measures the velocity of mitral annular motion, which reflects the shortening and lengthening of the myocardial fibers in the long-axis dimension (20,21). TDI has the theoretic advantage of being less affected by preload manipulation than Doppler echocardiography (21,40). Lately, magnetic resonance imaging (MRI) has also been used to determine LV diastolic filling pattern (41). Unlike Doppler echocardiography or TDI, MRI is a true three-dimensional method that is not affected by preload conditions, geometric assumptions or the position or orientation of the images section (42–44). However, MRI is a very expensive tool requiring highly skilled operators; therefore, Doppler echocardiography remains the best noninvasive tool to confirm the diagnosis of diastolic heart failure.

Mechanisms causing diastolic heart failure

The majority of patients with heart failure and preserved ejection have a history of hypertension. Laplace's law dictates that afterload-induced increases in systolic wall stress are offset by increases in wall thickness (45). Therefore, hypertension induces a compensatory thickening of the ventricular wall in an attempt to normalize wall stress (45). The resulting increase in LV mass is termed "concentric hypertrophy" and is defined by an increased relative wall thickness without changes in LV dimension (45). Many of the patients with heart failure and preserved ejection fraction have evidence of LV hypertrophy on echocardiography (1). LV hypertrophy affects the passive portion of the pressure-volume relationship, reducing the atrioventricular pressure gradient and reducing LV filling (45). Left ventricular hypertrophy is also a marker for increased risk of developing chronic heart failure (6).

In the LV hypertrophy that accompanies hypertension, the extracellular space is frequently the site of an abnormal accumulation of fibrillar collagen (46). Development of hypertensive heart disease includes the transition of cardiac fibroblasts to myofibroblasts, which produces a different extracellular matrix and modifies the balance of matrix metalloproteinases and their inhibitors to promote fibrosis (47). Pressure overload is capable of activating systemic local renin-angiotensin systems resulting in cardiac fibroblast growth (48,49). Chronic activation of the renin-angiotensin-aldosterone system has been shown to increase extracellular matrix fibrillar collagen and to be associated with decreased compliance, LV diastolic dysfunction and heart failure (4,14,46). Therapies targeting the expression, synthesis or activation of the enzymes responsible for extracellular matrix homeostasis might represent novel opportunities to modify the natural progression of hypertensive heart disease.

Hypertension may lead to severe heart failure in one patient, whereas it may be without any perceivable effects on cardiac function in another patient (50). Thus, it has been hypothesized that genetic factors may modulate the manifestation or progression of cardiac remodeling. Angiotensin-converting enzyme (ACE) levels were threefold greater in patients with heart failure compared to healthy individuals, and an insertion/deletion (I/D) polymorphism has been reported to be responsible for approximately 50% of the interindividual variability in serum ACE levels (51–53). Therefore, the role of the I/D polymorphism in the development of heart failure was examined, and hypertensive subjects did not have a significantly increased risk of heart failure compared to normotensive subjects unless they carried one or two copies of the D allele (50).

The increase in afterload observed in patients with heart failure and preserved ejection fraction also induces a prolonged LV relaxation resulting in a decreased atrioventricular pressure gradient, which in turn reduces early filling and stroke volume (54). Indeed, there is an inverse

linear relationship between stroke volume and afterload (55) (Fig. 3). More recent analyses using animal models and human failing heart samples suggest that alterations in sarcoplasmic reticulum function, which regulates free calcium concentration and plays a central role in LV relaxation, may be primarily due to alterations in the expression level of mRNAs encoding key sarcoplasmic reticulum calcium transport proteins (7,56).

Treatment for diastolic heart failure

There are no specific recommendations for treating diastolic heart failure, but general suggestions should target symptom reduction, pathological causes and underlying mechanisms that are altered by the disease processes (14). Therefore, pharmacological treatment of diastolic heart failure is directed at normalizing blood pressure, promoting regression of LV hypertrophy, preventing tachycardia, treating symptoms of congestion and maintaining atrial contraction.

Blood pressure control

Preventive strategies directed toward an early and aggressive blood pressure control are likely to offer the greatest promise for reducing the incidence of heart failure (4). Since the majority of patients with heart failure and preserved ejection fraction have hypertension, ACE inhibitors or angiotensin II receptor blockers should be part of the treatment regimen (57). Clinical trials have demonstrated approximately 50% reductions in heart failure incidence with active treatment of hypertension in older individuals (58,59). In older persons with isolated systolic hypertension, treatment based on a low dose of a diuretic exerted a strong protective effect in preventing heart failure (58). Moreover, the lowering of blood pressure over a three- to five-year period of time is effective in preventing severe disease, LV hypertrophy and congestive heart failure (59). Pulmonary congestion and systolic pressures can also be decreased by reducing total blood volume through fluid and sodium restriction or diuretics, and by decreasing central blood volume with nitrates (14,60).

Regression of LV hypertrophy

Hypertrophy is associated with activation of the renin-angiotensin-aldosterone system (46). Therefore, treatment for diastolic heart failure might include agents such as ACE inhibitors, angiotensin II receptor antagonists and aldosterone antagonists. The Candesartan in Heart Failure–Assessment of Mortality and Morbidity (CHARM) three-year program found no difference in cardiovascular mortality but a small decrease in hospitalization for worsening heart failure among patients taking candesartan compared with individuals taking placebo (57). There was also an improvement in the New York Heart Association functional score in patients treated with candesartan. ACE inhibitors and angiotensin II receptor antagonists directly affect myocardial relaxation and compliance by inhibiting production or blocking angiotensin II receptors, thereby reducing interstitial collagen deposition and fibrosis (61,62). Indeed, a randomized double-blind trial showed that in patients with hypertensive heart disease ACE inhibitors can regress myocardial fibrosis, irrespective of LV hypertrophy regression, and improve LV diastolic function as observed by an increase in E and A as well as a shortened isovolumic relaxation time (63).

Beta-blockers and calcium channel blockers

In diastolic heart failure, beta-blockers are used to decrease blood pressure, increase the duration of diastole and modify the hemodynamic response to exercise, and cause regression of LV hypertrophy (12). Beta-blockers have been independently associated with improved survival in patients with diastolic heart failure (64). Moreover, beta blockers reduced heart rate, levels of atrial natriuretic peptide and BNP mRNA expression, as well as atrial natriuretic peptide concentration, and increased survival of patients with heart failure (65).

Calcium channel blockers have been shown to improve diastolic function directly by decreasing cytoplasmic calcium concentration and causing myocardial relaxation or indirectly by reducing blood pressure, reducing or preventing myocardial ischemia, promoting regression of LV hypertrophy and by slowing heart rate (66). Moreover, calcium channel blockers are the only agents shown to improve symptoms and exercise tolerance in clinical trials of diastolic heart failure (5). An ongoing study is targeting intracellular calcium homeostasis using an intracellular calcium-handling modulator that is proposed to improve sarcoplasmic reticulum calcium reuptake (67). Finally, overexpression of sarcoplasmic reticulum Ca^{2+} -ATPase 2a (SERCA2a) in human ventricular myocytes from patients with end-stage heart failure resulted in an increase in both protein expression and pump activity and induced an enhanced relaxation velocity (68). These results support the premise that gene-based therapies and targeting of specific pathways in human heart failure may offer a new modality for the treatment of the disease.

Exercise response in patients with diastolic heart failure

At rest, patients with diastolic heart failure have similar end-diastolic and stroke volumes as healthy individuals. However, due to the decreased LV compliance in this population, the increase in LV filling pressure induced by exercise is not accompanied by increases in end-diastolic volume due to an inability to use the Frank-Starling mechanism (11,69). Moreover, an abnormal relaxation–heart rate relationship prevents augmentation of relaxation velocity as heart rate increases during exercise in patients with diastolic heart failure. Surprisingly, exercise limitations in patients with heart failure cannot always be attributed to diastolic abnormalities, as exercise capacity was observed to correlate with changes in cardiac output, heart rate and vascular resistance but not end-diastolic or stroke volume (70). A small trial showed that angiotensin II receptor antagonists improve exercise tolerance in patients with diastolic dysfunction and a hypertensive response to exercise (71).

Patients with LV diastolic dysfunction often present with unexplained exertional dyspnea, and it has been suggested that cardiac-induced alterations in the pulmonary system may contribute to the reduced exercise tolerance. Indeed, there is a correlation between left atrial volume and exercise capacity as well as with breathing pattern and gas exchange measures in this population (72). Patients with isolated LV diastolic dysfunction had greater submaximal ventilatory equivalents for carbon dioxide ($V_E/V\text{CO}_2$) than patients with LV systolic dysfunction and control subjects; this appeared to be related primarily to hyperventilation rather than ventilation-perfusion abnormalities (Fig. 4). Thus, symptoms during exercise and the resultant gas exchange abnormalities may be quite similar to those reported in patients with more classic systolic dysfunction

Novel contributors to LV diastolic dysfunction

The prevalence of obstructive sleep apnea is 10–37% in patients with heart failure and may be associated with nocturnal hypoxia (73). In addition, central sleep apnea was observed in more than half of patients with asymptomatic LV dysfunction (74). The chronic dips in arterial partial pressures of oxygen along with potentially marked changes in intrathoracic pressure associated with obstruction could also contribute to the degree of LV diastolic dysfunction. Previous studies have suggested that inspired hypoxia in healthy adults may induce an increase in the ratio of early filling to early myocardial relaxation, a marker of LV filling pressure, and prolong isovolumic relaxation time (75). In addition, large negative swings in intrathoracic pressure during obstruction decreased LV end-diastolic length, stroke volume and cardiac output in pigs with congestive heart failure (76). The chronic intermittent hypoxia may also increase sympathetic drive and contribute to systemic hypertension further aggravating the development of diastolic heart failure (77).

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Fig. 1.

The filling phase of the cardiac cycle moves along the end-diastolic pressure-volume relationship or passive filling curve of the ventricle. A shift of the curve from A to B indicates that a higher LV pressure is required to distend the left ventricle to a similar volume, in this case from 100 to 120 ml. Modified with permission from Little, W.C., Downes, T.R. *Clinical evaluation of left ventricular diastolic performance*. Prog Cardiovasc Dis 1990, 32(4): 273–90. Copyright 1990 Elsevier Ltd. All rights reserved.

Fig. 2. Doppler measurement of mitral inflow velocity of A) impaired, B) pseudonormal and C) restrictive filling patterns. Modified with permission from Sohn, D.W., Chai, I.H., Lee, D.J. et al. *Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function*. J Am Coll Cardiol 1997, 30(2). 474–80. Copyright 1997 Elsevier Ltd. All rights reserved.

Fig. 3.

For any given LV filling pressure (end-diastolic pressure: EDP), the greater the afterload, the less the stroke volume. As filling pressure is raised, the flow and volume displaced from the chamber increases for any given ejection pressures. With permission from Weber, K.T., Janicki, J.S., Hunter, W.C., Shroff, S., Pearlman, E.S., Fishman, A.P. *The contractile behavior of the heart and its functional coupling to the circulation*. Prog Cardiovasc Dis 1982, 24(5): 375–400. Copyright 1982 Elsevier Ltd. All rights reserved.

Fig. 4.

Gas exchange during exercise in patients with primarily systolic dysfunction (SysD), isolated diastolic dysfunction (DiaD) and in healthy normals (NL). Patients with DiaD and SysD had an elevated V_E/VCO_2 at rest and during exercise relative to NL subjects ($P < 0.05$), while patients with DiaD only had elevated values at rest and light exercise relative to patients with SysD ($P < 0.05$). With permission from Arruda, A.L., Pellikka, P.A., Olson, T.P., Johnson, B.D. *Exercise capacity, breathing pattern, and gas exchange during exercise for patients with isolated diastolic dysfunction*. J Am Soc Echocardiogr 2007, 20(7): 838–46. Copyright 2007 Elsevier Ltd. All rights reserved.