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Diastolic and Systolic Heart Failure — Similarities and Differences – Part 2

By KANU CHATTERJEE, MB, FRCP, FCCP, FACC, MACP

Diastolic and systolic heart failure are the two clinical subsets of the syndrome of heart failure (HF). There are considerable similarities, as well as differences, between the two entities. Part 1, in the last issue of *Cardiology Rounds*, presented the definition and diagnosis, incidence and prevalence, and prognosis and natural history of diastolic and systolic HF. Part 1 also introduced a section describing the changes in ventricular function, hemodynamics, and remodeling. Part 2, in this issue of *Cardiology Rounds*, continues this discussion and also presents an overview of the therapeutic options available for heart failure.

Changes in ventricular function, hemodynamics, and remodeling

The principal functional derangement in primary diastolic heart failure (HF) is impaired relaxation and increased passive stiffness.¹ The diastolic pressure volume relation shifts upwards and to the left (Figure 1). As a result, there is a substantially greater increase in diastolic pressure for any increase in volume.^{2,3} Left ventricular (LV) diastolic and end-systolic volumes are usually smaller than those in normal controls. LV ejection fraction is normal or higher than normal and LV mass and mass/volume ratio is substantially increased in patients with diastolic HF.

Kitzman et al assessed LV volumes, mass, and ejection fraction by echocardiography in patients with systolic and diastolic HF and in normal controls, and the results confirm these morphologic and functional characteristics (Table 1). LV wall thickness is significantly increased and, as ventricular volume decreases,⁴ wall stress is reduced. Decreased wall stress is the mechanism for the normal or even increased ejection fraction in patients with diastolic HF. Ventricular shape usually remains unchanged and significant secondary mitral regurgitation is uncommon. Mechanical dyssynchrony is also uncommon, even in the presence of conduction disturbance.

Systemic hemodynamics may be similar in systolic and diastolic HF. In primary systolic HF, the principal functional derangement is reduced ejection fraction, which results in a reduction in stroke volume and cardiac output. Increased LV volume and, frequently, associated abnormal diastolic filling, results in increased LV diastolic pressure, a passive increase in left atrial and pulmonary venous pressure, and post-capillary pulmonary arterial hypertension. Post-capillary pulmonary hypertension may cause right ventricular failure and systemic venous hypertension and, often, secondary tricuspid regurgitation.

In primary diastolic HF, the principal functional derangement is decreased LV diastolic compliance, which is associated with increased LV diastolic pressure. This causes similar pulmonary and right heart hemodynamic changes as those observed in primary systolic HF. In primary diastolic HF, LV stroke volume and, therefore, cardiac output, may decline because of decreased end-diastolic volume (preload-dependent) and also, not infrequently, due to depressed myocardial contractile function, particularly in elderly patients.⁵ In both systolic and diastolic HF, chronic elevation of pulmonary venous pressure may be associated with increased pulmonary vascular resistance, probably due to pulmonary vasoconstriction.

In both systolic and diastolic HF, ventricular remodeling is an important pathophysiologic mechanism for initiation and progression of HF. The characteristics of the remodeling features, however, are different in the two types of heart failure – which has important therapeutic implications. Concentric hypertrophy is characteristic of diastolic HF, whereas eccentric hypertrophy is more frequent in



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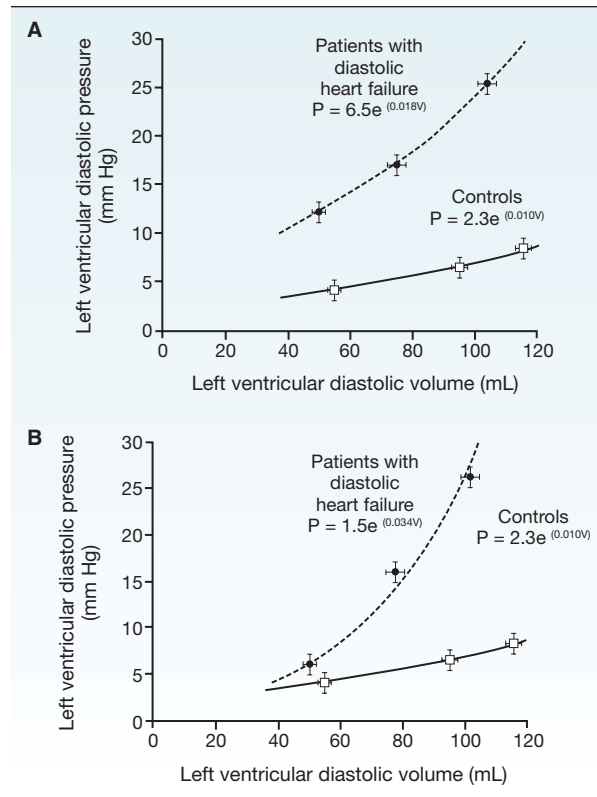
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Figure 1: The diastolic pressure-volume relation in patients with overt diastolic HF shifts upwards and to the left¹



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systolic HF. Eccentric hypertrophy is associated with increased myocyte length/ width ratio and the sarcomeres are deposited in series, allowing the myocytes to lengthen.⁶ In concentric hypertrophy, myocyte width is increased more than the length and the sarcomeres are deposited in parallel, allowing the increase in wall thickness. In concentric hypertrophy, increased myocyte protein synthesis has been documented. It has been hypothesized that decreased degradation of myocyte protein is more likely to occur in eccentric hypertrophy.⁶

The changes in the extracellular matrix and the abnormalities of collagen synthesis and degradation occur in both types of HF (Table 2). However, the matrix architectural changes are likely to be different since, despite fibrosis, progressive LV dilatation occurs in systolic HF, and LV dilatation is uncommon in diastolic HF (Figure 2).⁷ The abnormalities of activation of the matrix metalloproteinases (MMPs) and their endogenous tissue inhibitors (TIMPs) have been identified in both types of HF. Over-expression of several isoforms of metalloproteinases in the myocardium of the experimental post-infarction animal models has been observed.⁸ Remodeling following myocardial infarction (MI) occurs both in the infarct zone and in the remote non-infarct zone. Extracellular collagen matrix degradation in the infarct zone is associated with infarct expansion and, in the non-infarct zone, with global LV dilatation. Increased MMPs/TIMPs ratio with increased MMPs or decreased TIMPs favors adverse remodeling.⁹ There is upregulation of myocardial MMPs associated

Table 1: Echocardiographic LV morphologic and functional characteristics in primary systolic and diastolic HF compared to controls¹

	Controls	Systolic HF	Diastolic HF
LVEDV mL	102 ± 12	192 ± 10*	87 ± 10
LVESV mL	46 ± 11	137 ± 9*	37 ± 9
LVEF %	54 ± 2	31 ± 2*	60 ± 2 ⁺
LV Mass gm	125 ± 12	232 ± 9*	160 ± 9 ⁺
LV mass/ volume	1.49 ± 0.17	1.22 ± 0.14	2.12 ± 0.14 ⁺⁺
NE pg/ml	169	287	306 P = .007
BNP pg/ml	3	28	56 P = .02

LVED = Left ventricular end-diastolic volume

LVESV = Left ventricular end-systolic volume

LVEF = Left ventricular ejection fraction

LV = Left ventricle

* = Systolic heart failure vs controls P < .001

+ = Diastolic heart failure vs controls P < .001

++ = Diastolic heart failure vs controls P < .002

± = Mean (SE)

NE = Norepinephrine

BNP = B-type natriuretic peptide

with decreased fibrillar collagen cross-link formation, not only following acute MI, but also in patients with chronic systolic HF with cardiomyopathic ventricles.¹⁰ In addition to upregulation of soluble MMPs, certain membrane type MMPs appear to be increased in the myocardium of patients with systolic HF. This may be associated with the loss of myocyte connection with the extracellular collagen matrix and impaired sarcomere shortening.⁹

Increased plasma levels of MMPs are associated with severe systolic HF and probably reflect progressive remodeling.¹⁰ Plasma levels of TIMPs are inversely related to systolic function and echocardiographic measures of LV hypertrophy.¹¹ Circulating levels of amino-terminal propeptide of Type III procollagen (PIIINP), which reflect myocardial remodeling, are elevated in patients with dilated cardiomyopathy.¹² The extracellular matrix glycoprotein levels, (eg, tenascin-C), may be elevated in patients with systolic HF.¹³ The extracellular matrix remodeling is promoted by neurohormonal activation and activation of proinflammatory cytokines.^{9,14}

Table 2: Diastolic and systolic HF remodeling: myocyte and matrix changes

	Systolic HF	Diastolic HF
Myocyte		
Hypertrophy	+	+
Apoptosis	+	+
Necrosis	+	+
Myocardial fibrosis	+	+
Calcium regulation	-	-
MMPs/TIMPs	+	-
Collagen crosslinks	-	+

+ = Increased

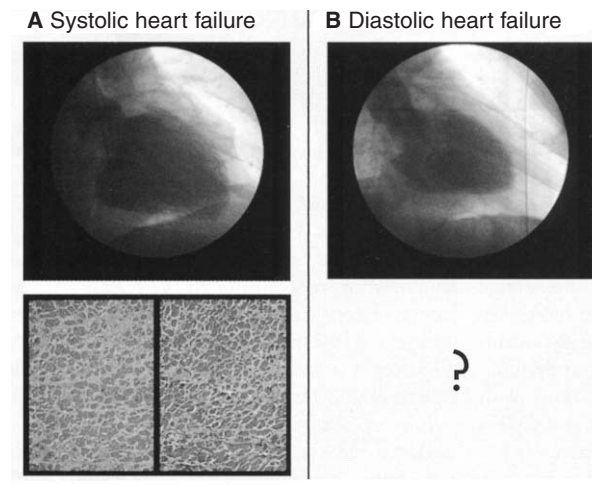
- = Decreased or Impaired

MMPs = Matrix metalloproteinases

TIMPs = Tissue inhibitors of metalloproteinases

Figure 2: In patients with systolic HF, the left ventricle is dilated, while in patients with diastolic HF, the left ventricular size remains normal⁷

Upper panels: (contrast ventriculography).
Lower panel: histopathology of the myocardium in systolic HF. In addition to myocyte hypertrophy, diffuse fibrosis is evident.



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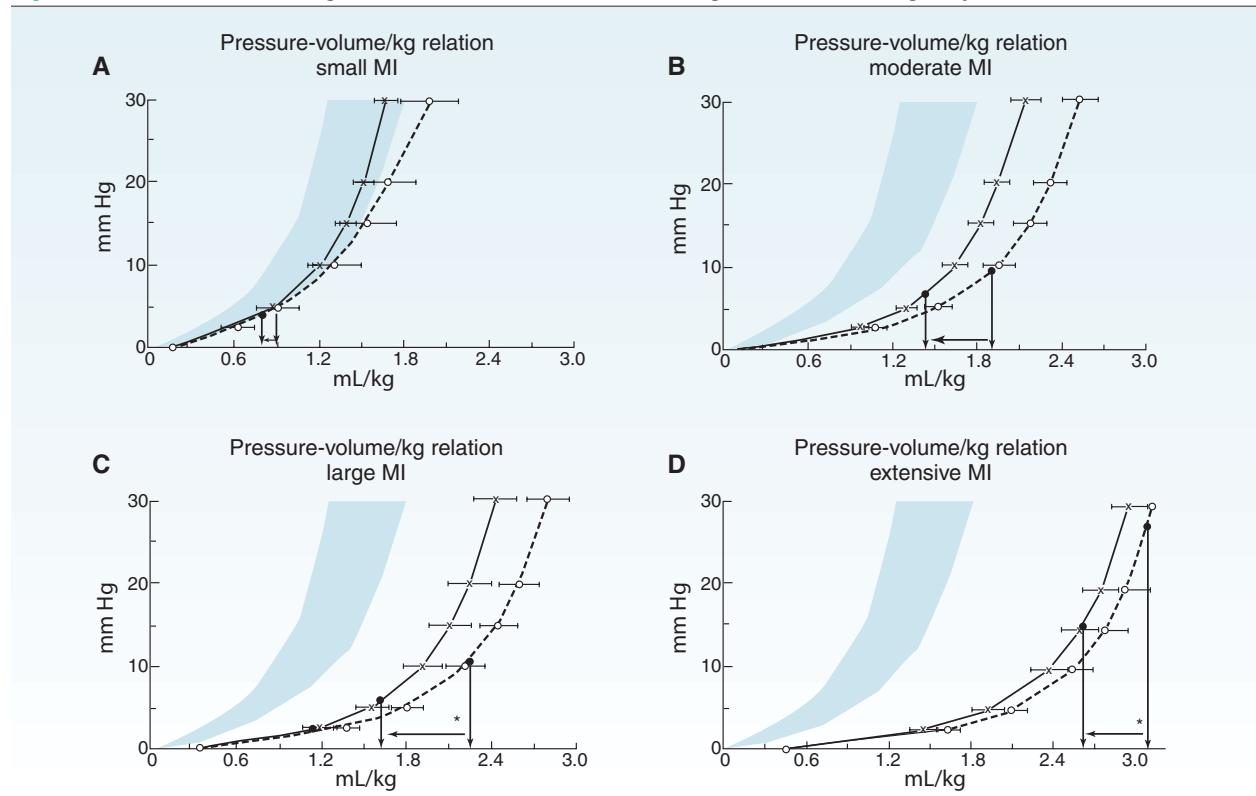
The changes in the extracellular matrix in primary diastolic HF have not been as extensively studied. In response to pressure overload, myocardial concentric hypertrophy is associated with increased myocardial fibrosis and altered structure

and composition of the extracellular matrix. In untreated hypertensive patients, collagen synthesis is upregulated with a decrease in plasma MMPs levels.¹⁵ Acute changes in pressure overload are associated with dynamic changes in TIMPs and MMPs. With an acute increase in pressure overload, myocardial TIMP activity tends to increase and MMP activity decrease.¹⁶ Whether similar changes occur in primary diastolic HF remains unclear. With pressure overload, activation of the renin-angiotensin-aldosterone system appears to contribute to extracellular matrix remodeling.

The precise stimuli for ventricular remodeling in primary systolic and diastolic HF have not been clearly delineated. In systolic HF, particularly in post-infarction patients, the extent of myocardial injury and the degree of depression of LV systolic function appear to be the major determinants for the initiation and progression of remodeling. A relatively small extent of myocardial damage is not associated with progressive ventricular dilatation¹⁷ (Figure 3). In patients with recent MI, reduced ejection fraction, despite recanalization of the infarct-related artery, is associated with remodeling. However, in patients with preserved ejection fraction, LV remodeling is attenuated.¹⁸ It is also likely that, even in patients with non-ischemic dilated cardiomyopathy, the extent of myocardial systolic dysfunction is an important determinant of progressive ventricular remodeling.

In patients with primary diastolic HF, the stimuli for ventricular remodeling remain unclear. The present or past pressure overload (hypertension) is very likely to be an important contributing factor. LV dilatation and, therefore, mechanical

Figure 3: Ventricular remodeling is attenuated with treatment with angiotensin-converting enzyme inhibitors¹⁷



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stress-induced remodeling is uncommon in the absence of an incident of myocardial injury, such as an MI.¹⁹ Neurohormonal activation, such as activation of the renin-angiotensin-aldosterone and adrenergic systems have been known to be important contributing factors in remodeling in systolic HF.²⁰ However, the same neuroendocrine abnormalities also occur in patients with HF and preserved ejection fraction.⁴ It is possible, however, that although the same neuroendocrine stimuli are present in both types of HF, different responses in primary systolic and diastolic HF occur during remodeling.

Myocyte loss, either by ischemic necrosis or enhanced programmed cell death (apoptosis), occurs in both types of HF.²⁰ However, the precise mechanisms of myocyte loss and the magnitude of myocyte loss in patients with primary systolic or diastolic HF have not been studied.

Therapeutic options (Table 3)

There have been considerable advances in the treatment of systolic HF, but very little progress has been made in the management of diastolic HF. For the relief of congestive symptoms, diuretics remain the principal therapy in both systolic and diastolic HF. In patients with acutely decompensated systolic HF, symptom relief and improvement in hemodynamics can occur with intravenous sodium nitroprusside, nitroglycerine and exogenous B-type natriuretic peptide (nesiritide) infusion.²¹ The role of such therapies in acutely decompensated diastolic HF remains unclear.

Angiotensin-receptor blocking agents (ARBs) and angiotensin-converting enzyme (ACE) inhibitors can reverse remodeling.²² In patients with chronic systolic HF, it has long been established that long-term treatment with ACE inhibitors, ARBs, and their combinations, and adrenergic antagonists, can cause sustained relief of symptoms and improvement in the quality of life.²³⁻²⁸ In patients with severe systolic HF, aldosterone antagonists can also improve symptoms and quality of life.²⁹ These therapeutic agents also substantially decrease mortality of patients with systolic HF. Furthermore, even in patients with asymptomatic systolic dysfunction, these pharmacologic agents have been shown to decrease the risk of development of overt heart failure.³⁰⁻³³ These beneficial effects have been linked to attenuation of progressive ventricular remodeling. Nitric oxide enhancing agents, such as the combination of hydralazine and isosorbide dinitrate, have been reported to improve prognosis in Black patients with systolic HF, even when added to background treatment with angiotensin and adrenergic inhibition therapy.³⁴

In patients with primary diastolic HF, however, only ARBs have been reported to decrease morbidity and, probably, mortality.³⁵ Statin therapy has been reported to decrease mortality in patients with primary diastolic HF.^{34,36} The mechanism for this potential beneficial effect with statins in diastolic HF remains unclear. Preliminary studies have also reported lower mortality with statin therapy in patients with systolic HF.³⁷ Prospective con-

Table 3: Diastolic and systolic HF: Management strategies

Diuretics are needed to relieve congestive symptoms in both systolic and diastolic HF

Digitalis may be effective in selected patients in both systolic and diastolic HF

Reduction in heart rate is beneficial in both systolic and diastolic HF

Angiotensin converting enzyme inhibitor

Decrease mortality and morbidity in systolic HF
Unproven benefit in diastolic HF

Angiotensin receptor blocking agent

Decrease mortality and morbidity in systolic HF
Decrease primarily morbidity in diastolic HF

Beta-blocker therapy

Decreases mortality and morbidity in systolic HF
Unproven benefit in diastolic HF

Hydralazine-nitrate

Decreases mortality and morbidity in systolic HF
Unproven benefit in diastolic HF

Aldosterone antagonists

Decreases mortality and morbidity in symptomatic patients with systolic HF
Unproven benefit in diastolic HF

Exogenous B-type natriuretic peptide

Decreases morbidity in decompensated systolic HF
Unproven benefit in diastolic HF

Chronic resynchronization therapy and/or implantable defibrillator

Decreases mortality and morbidity in systolic HF
Unproven benefit in diastolic HF

Implantable circulatory assist devices

May improve short-term survival in selected patients with refractory systolic HF
Unproven benefit in diastolic HF

Cardiac transplantation

May be of benefit in both systolic and diastolic HF

trolled studies will be required to evaluate the impact of statin therapy in improving the prognosis of patients with either systolic or diastolic HF. The role of aldosterone antagonist therapy in the management of patients with primary diastolic HF also remains uncertain.

Non-pharmacologic interventions, such as chronic resynchronization therapy, with or without, implantable cardioverter defibrillator, have been reported to improve prognosis of patients with refractory systolic HF.³⁹ LV assist devices that produce reverse remodeling have been of benefit in patients with systolic HF and may cause reverse remodeling by increasing collagen cross-linking and myocardial stiffness.⁴⁰ However, such therapies have not been shown as yet to be of benefit in patients with primary diastolic HF. Cardiac transplantation, however, is likely to be effective in both systolic and diastolic HF. It is apparent, therefore, that further research is necessary to understand the pathophysiologic mechanisms of primary systolic and diastolic HF and, therefore, to make further progress in the management of both types of heart failure.

Conclusion

Considerable differences exist in the pathophysiology and primary functional derangements between primary diastolic and systolic heart failure. However, hemodynamic consequences and neurohormonal activation may be remarkably similar. Although neurohormonal modulation is extremely effective therapy in systolic heart failure, such therapies, with the exception of angiotensin receptor blocking agents, have not been shown to improve morbidity-mortality in primary diastolic heart failure. Research must continue to further improve the prognosis of patients with heart failure, whether systolic or diastolic.

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