DIASTOLIC HEART FAILURE: NOMENCLATURE AND PATHOPHYSIOLOGY

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INTRODUCTION

With the advent of cardiac angiography over 40 years ago, ejection fraction (EF) emerged as the preferred index of left ventricular (LV) systolic performance. Despite its limitations, LVEF has stood the test of time as an indicator of the LV pumping function and allows separation of patients with myocardial dysfunction into grades of severity that predict different clinical outcomes. As echocardiography and radionuclide angiography became widely available, LVEF became the single most commonly used indicator of cardiac performance.

In 1971, I was a cardiology fellow working at Baylor College of Medicine with Dr. William Gaasch, who was interested in the evaluation of cardiac function and LV compliance. Practicing in a county hospital, we saw a good number of patients with chronic pressure overload lesions such as hypertension and aortic stenosis who presented with a congestive state (dyspnea, high PCWP) but with normal LV dimensions and fractional shortening by echocardiography. This prompted us to do a series of studies evaluating the LV pressure-volume properties in these patients and compare them to patients with dilated cardiomyopathy.1 Our studies were subsequently followed by a large volume of clinical and basic investigations that clearly demonstrated the presence of abnormalities (relaxation, LV diastolic stiffness) in patients presenting with the clinical syndrome of "heart failure" and normal LVEF. In 1988, Kessler introduced the term "diastolic heart failure" to describe a group of patients with a congestive state characterized by normal or near-normal LVEF and absence of progressive LV dilatation.2 By contrast, "systolic heart failure" referred to heart failure associated with dilated left ventricles and depressed EF. This review will cover the issues concerning the use of this terminology and discuss some of the pathophysiologic mechanisms currently in vogue to explain the occurrence of heart failure in the presence of normal systolic pump function.

HEART FAILURE NOMENCLATURE

The terms *diastolic* and *systolic* heart failure have been routinely used in clinical practice to establish categories of heart failure. This nomenclature, although practical, limited our thinking about the pathoph$_{y s}$iology of these disorders and often created a simplified view of what is now recognized to be a more complex disease. It may have also delayed the development of effective therapies for heart failure. For years, we looked for an ideal inotropic agent that would improve contractile performance in systolic heart failure and later learned that this approach lead to an adverse impact on patient survival. Likewise, in an attempt to find an ideal therapy for diastolic heart failure (DHF), researchers searched for a lusitropic agent to improve LV relaxation, thus missing the opportunity to look for innovative approaches that are currently under investigation.

On February 28, 2004, a group of heart failure experts met for two days in Woodstock. Vermont to discuss the current nomenclature for heart failure, whether or not it should be changed and, if so, how. Despite their diverse opinions, the group agreed that no single term could completely describe the various forms of heart failure - given the multiplicity of mechanisms involved in its pathogenesis - and that the terms "systolic heart failure" and "diastolic heart failure," while imperfect, had become an integral part of our daily practice. They recommended that these terms be equated with the descriptive features characterizing each group with a dear understanding that they do not necessarily imply pathophysiologic mechanisms.[3] In the recently revised ACC-AHA guidelines for the diagnosis and management of HF, the term "heart failure with preserved ejection fraction" was used as a substitute for DHF.[4] Currently, both terms are used interchangeably in the literature.

PATHOPHYSIOLOGY OF DHF

The pathoph$_{y s}$iology of DHF is not completely understood, and there is disagreement among experts as to whether or not the heart (versus extracardiac factors) is the primary culprit. Even so, evidence suggests that both cardiac and extracardiac factors play important roles in the precipitation of heart failure symptoms. Excluding genetic causes such as hypertrophic cardiomyopathy and infiltrative disorders such as amyloidosis, a majority of patients with

Common Clinical	Characteristics Common Physiologic Abnormalities
· Advanced age	· Concentric LVH or LV remodeling
· Female gender	· Abnormal LV relaxation
· Hypertension	· Increased LV stiffness
· Atrial fi brillation	· Impaired coronary reserve-myocardial ischemia
· Although CAD may be present, previous MI is uncommon	· Interstitial fibrosis
· Common comorbidities associated with clinical heart failure	· Subtle abnormalities of systolic myocardial performances
· Obesity	· Impaired systolic reserve
· Diabetes	· Increased vascular stiffness
· Anemia	
· Renal failure	

Table 1. Common clinical characteristics and physiologic abnormalities of DHF patients.

DHF share several clinical characteristics and physiologic abnormalities that serve to postulate potential pachophysiologic mechanisms (Table 1).

A significant proportion of patients with DHF are women of advanced age (>70 years), and many of them have systolic hypertension with a wide pulse pressure.' They frequently but not always have evidence of concentric LV hypertrophy or remodeling (normal mass with increased wall thickness to cavity radius), and there generally is no evidence of prior myocardial infarction, though th$_{ey}$ may have coronary artery disease with or without symptoms. Certain comorbidities such as atrial fibrillation, obesity with or without diabetes, anemia, and renal failure are common and contribute to the acute exacerbation of heart failure.

Patients with DHF have normal or near-normal end-diastolic volumes with demonstrable abnormalities of diastolic function, mainly impaired LV relaxation and an upward shift of the diastolic pressure-volume relation implying increased chamber stiffness (Figure l).I.[6] It is important to remember that relaxation is an active process that is altered by many factors including aging, increased afterload, pathologic hypertrophy, and ischemia. LV stiffness is primarily influenced by myocardial stiffness, which in itself is altered by interstitial fibrosis, wall thickness, and incomplete relaxation; LV geometry; biventricular interactions; and pericardia) constraint. Neurohormonal factors such as the renin-angiotensin system are also known co modulate ventricular stiffness (interstitial fibrosis and hypertrophy) and relaxation.- Consequently, abnormalities of relaxation and stiffness are commonly present in hypertensive and/or elderly patients without clinical manifestations of heart failure (point A in Figure 1). Their presence makes these patients susceptible to the effect of volume loading (moving from point A to point B in Figure 1) and partially explains the influence of anemia, obesity, and renal failure as precipitants of DHF. An acute upward shift in the diastolic pressure-volume curve (point A to C in Figure I) can occur secondary co changes in relaxation/$_{myo}$cardial stiffness, such as with ischemia, rapid atrial fibrillation, or due to pericardia! constraint during right heart loading. A chronic upward shift in the diastolic pressure-volume curve is often induced by interstitial fibrosis or severe hypertrophy and can also occur with myocardial infiltration, as in amyloidosis, and pericardia! constriction.

Myocardial ischemia may occur in patients with DHF even in the absence of significant obstructive coronary artery disease and contribute co worsening of their symptoms. Pathologic hypertrophy, in contrast to physiologic hypertrophy, is associated with increased collagen deposition in the extracellular matrix and around the intramyocardial coronary arteries.,s The resulting interstitial and perivascular fibrosis have been linked to impaired coronary reserve and increased LV stiffness. Elevated LV diastolic pressure in the presence of concentric LV hypertrophy may act over intramyocardial capillaries and small resistance coronary vessels, disrupting their ability to vasodilate and further worsening coronary reserve.[9] In addition, elevated right atrial pressure may lead to coronary venous engorgement and increased myocardial turgor with further worsening of myocardial stiffness.[10]

Although DHF is characterized by a normal or near-normal LVEF, even during episodes of acute decompensation,[11] systolic myocardial performance may nor be completely normal. Reduced stress-velocity relations and myocardial systolic velocities have been documented in hypertensive patients with concentric LV hypertrophy with and without clinical signs of heart failure.[12,13] The role chis subclinical systolic dysfunction plays in the pathogenesis of DHF is still uncertain.

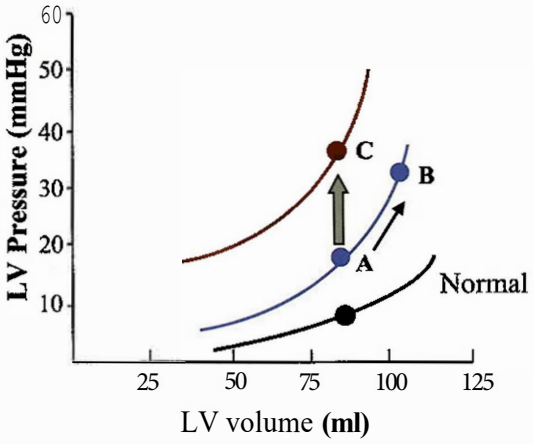

Figure 1. Examples of three LV diastolic pressure-volume relations are illustrated. In a normal ventricle, end-diastolic pressure (EDP) remains normal (<15 mmHg) throughout a range of end-diastolic volumes (EDV). In patients with early diastolic dysfunction (blue curve), the pressure-volume relation is shifted upward and to the left so that at a normal EDV of 90 ml, LVEDP is mildly elevated at around 15 mmHg (point A). These ventricles operate in a steeper slope of their pressure-volume relation so that with volume loading, EDP increases (point B) to a level that can induce pulmonary congestion. With severe diastolic dysfunction or acute changes in stiffness (red curve), the diastolic pressure-volume relation can shift further up so that EDP reaches very high levels with minimal changes in EDV (point C). See text for further details.

Patients with DHF often have normal or even small end-systolic volumes with steep end-systolic pressure-volume relationships (Figure 2, panel B). This increased "systolic stiffness" limits the ventricle's ability to eject ω a smaller end-systolic volume and precludes rhe augmentation of stroke volume during exercise (i.e., abnormal systolic reserve).[14] To compensate, during exercise the cardiovascular system shifts volume redistribution by increasing venous return ω the right heart in order to increase preload reserve. However, increased LV diastolic stiffness and impaired relaxation limits utilization of the Frank-Starling mechanism, further reducing systolic reserve. The inability of the left ventricle to accommodate the increased venous return induces acute changes in the diastolic pressure-volume curve (Figure 2, panel B), resulting in elevations ofleft atrial pressures and dyspnea during exercise.

The vascular compartment plays an important role in the pathophysiology of DHF. Reduced distensibility of the aorta is common in the elderly and in patients with DHF.[14,15] The increased vascular stiffness leads to systolic hypertension with wide pulse pressure and imposes a higher afterload on the left ventricle. This contributes to the worsening of relaxation, systolic stiffness, and reduced systolic reserve seen in these patients. Together with the other mechanisms discussed above, increased vascular stiffness is an important contributor to exercised-induced dyspnea and may play a key role in precipitating acute pulmonary edema during hypertensive episodes.[14]

SUMMARY

We have reviewed several cardiac and extracardiac mechanisms that are invoked in the pathophysiology of DHF and discussed why no current terminology is perfect in describing this fascinating syndrome. Boch diastolic heart failure and heart failure with

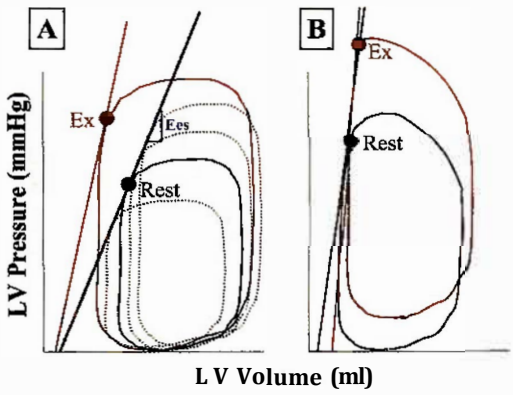

Figure 2. Illustrative examples of LV pressure-volume loops at rest (black) and during exercise (red) in a normal heart (panel A) and in an elderly hypertensive patient with vascular stiffness and diastolic dysfunction (panel B). The tangential lines depict the end-systolic elastance (Ees), the slope of the end-systolic pressure-volume relation occurring with changing afterload (dotted loops in panel A). The normal heart during exercise shifts to a new pressure-volume loop, decreasing end-systolic volume despite higher afterload (i.e., enhanced contractility) and increasing end-diastolic volume through an increased venous return (preload reserve). The end result is a significant improvement in stroke volume. In contrast, the curves in panel B show a marked increase in systolic pressure with exercise but an inability to further reduce end-systolic volume (i.e., systolic stiffness). The mild enhancement in end-diastolic volume occurs at the expense of a marked shift in the diastolic pressure-volume relation and high filling pressures. Also note that in a healthy person, the ejection phase of the pressure-volume loop is relatively flat, while in the patient this segment shows a continuing increase in pressure. This reflects the increased arterial pulse pressure related to a decrease in arterial compliance.

preserved LVEF are acceptable terminologies. Although abnormal diastolic function (impaired relaxation/increased stiffness) is seen at the time of clinical presentation, diastolic dysfunction may be induced or worsened by intrinsic (e.g., ischemia, interstitial fibrosis) and extrinsic (e.g., vascular stiffness, volume load) factors. It is also likely that genes, neurohormonal regulation (such as the renin-angiotensin system that modulates ventricular stiffness and relaxation), and environmental factors (diet, sodium consumption, sedentary versus active lifestyle) influence many of these mechanisms and explain in part why, for instance, not every elderly patient with hypertension has DHF.[16] At the early stages these mechanisms result only in exercise-induced symptoms of dyspnea and fatigue, but at some point they intensify, inducing significant elevation of filling pressures at rest wirh the resulting signs and symptoms of acute heart failure. The remaining articles in this issue will review the clinical and laboratory evaluation of these patients and current therapeutic options.

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