ORIGINAL ARTICLE

Diastolic Heart Failure — Abnormalities in Active Relaxation and Passive Stiffness of the Left Ventricle

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ABSTRACT

BACKGROUND

Patients with signs and symptoms of heart failure and a normal left ventricular ejection fraction are said to have diastolic heart failure. It has traditionally been thought that the pathophysiological cause of heart failure in these patients is an abnormality in the diastolic properties of the left ventricle; however, this hypothesis remains largely unproven.

METHODS

We prospectively identified 47 patients who met the diagnostic criteria for definite diastolic heart failure; all the patients had signs and symptoms of heart failure, a normal ejection fraction, and an increased left ventricular end-diastolic pressure. Ten patients who had no evidence of cardiovascular disease served as controls. Left ventricular diastolic function was assessed by means of cardiac catheterization and echocardiography.

RESULTS

The patients with diastolic heart failure had abnormal left ventricular relaxation and increased left ventricular chamber stiffness. The mean (±SD) time constant for the isovolumic-pressure decline (τ) was longer in the group with diastolic heart failure than in the control group (59±14 msec vs. 35±10 msec, P = 0.01). The diastolic pressure–volume relation was shifted up and to the left in the patients with diastolic heart failure as compared with the controls. The corrected left ventricular passive-stiffness constant was significantly higher in the group with diastolic heart failure than in the control group (0.03±0.01 vs. 0.01±0.01, P<0.001).

CONCLUSIONS

Patients with heart failure and a normal ejection fraction have significant abnormalities in active relaxation and passive stiffness. In these patients, the pathophysiological cause of elevated diastolic pressures and heart failure is abnormal diastolic function.

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HEART FAILURE IS A COMMON CAUSE OF cardiovascular disease and death and may occur in the presence of either a normal or an abnormal left ventricular ejection fraction.[1-3] Patients with heart failure who have a normal ejection fraction differ substantially from those with heart failure and a decreased ejection fraction in several ways, including demographic characteristics, ventricular remodeling, ventricular function, the mortality rate, underlying causal mechanisms, and pathophysiological mechanisms.[4-14] It is widely accepted that the pathophysiology of heart failure in patients with a decreased ejection fraction involves a predominant (though not isolated) decrease in systolic function; this association has justified the use of the term "systolic heart failure."[1,15,16] In contrast, the underlying pathophysiology in patients with heart failure and a normal ejection fraction involves a predominant (though not isolated) abnormality in diastolic function, justifying the use of the term "diastolic heart failure."[4,5,10,14,17,18] However, a recent editorial questioned this conventional wisdom and concluded that "there exists no consistent abnormality of intrinsic diastolic properties that can explain the occurrence of heart failure" in these patients.[19]

We performed a prospective clinical study in which we analyzed measurements of both active relaxation and passive stiffness in patients with heart failure and a normal ejection fraction. All patients in the study met the criteria of Vasan and Levy for definite diastolic heart failure.[20] Thus, we tested the hypothesis that patients with heart failure and a normal ejection fraction have abnormalities in active relaxation and an increase in passive stiffness — changes that are sufficient to explain their increased left ventricular diastolic pressures and their signs and symptoms of heart failure.

METHODS

In this multicenter, prospective study, we used left ventricular pressure and Doppler echocardiographic data to assess the diastolic properties of the left ventricle in 47 patients who had diastolic heart failure and 10 normal controls who had no evidence of heart disease. The research protocol used in this study was reviewed and approved by the institutional review board of each participating center. All the patients were enrolled after written informed consent had been obtained.

PATIENTS

Patients with a history of heart failure and a normal left ventricular ejection fraction (>50 percent) who had been scheduled for diagnostic cardiac catheterization were evaluated for participation in the study. All the patients met the Framingham criteria for congestive heart failure.[20] Patients with pulmonary disease, renal disease, heart-valve disease, atrial fibrillation, or evidence of hypertrophic cardiomyopathy were excluded. Echocardiographic indexes of diastolic function were not used as inclusion criteria. Forty-seven patients met the inclusion criteria and underwent combined catheterization and echocardiographic studies. Data on the left ventricular end-diastolic pressure and left ventricular filling dynamics in these 47 patients have been reported previously.[21] However, data on these patients' left ventricular volume and passive stiffness (the relation between diastolic pressure and volume) have not been previously published. All 47 patients met the criteria of Vasan and Levy for definite diastolic heart failure. There were 31 men and 16 women; their mean (±SD) age was 59±12 years.

The 10 controls had a mean age of 58±16 years. They underwent cardiac catheterization for the evaluation of symptoms of chest pain. They had no history of cardiovascular disease, and all 10 had angiographically normal epicardial coronary arteries and normal left ventricular volume, ejection fraction, and wall motion.

CARDIAC CATHETERIZATION

Cardiac catheterization was performed with the use of standard techniques. A high-fidelity micromanometer catheter was placed in the left ventricle, Doppler echocardiographic recordings were obtained, and left ventricular pressures and the time constant of the isovolumic-pressure decline (τ) were measured. The left ventricular minimal diastolic pressure was defined as the lowest pressure after the opening of the mitral valve, the left ventricular diastolic pre–A-wave pressure was defined as the diastolic pressure before atrial contraction, and the left ventricular end-diastolic pressure was defined as the pressure after atrial contraction, just before the rise in left ventricular systolic pressure. Pressure data were digitized at intervals of 5 msec, and τ was calculated by the method of Weiss et al.[22] Analysis of the pressure data was performed in a core laboratory.[21]

ECHOCARDIOGRAPHY

The dimensions and wall thickness of the left ventricle were measured according to the recommendations of the American Society of Echocardiography. Calculations of left ventricular volume and mass were made with standard published methods.[23] Analysis of the echocardiographic data was performed in a core laboratory.[21]

Total stroke volume was calculated on the basis of the echocardiographic measurements. The increment in left ventricular diastolic volume that occurred between the opening of the mitral valve and the point of minimal diastolic pressure was calculated first by determining, with the use of Doppler echocardiographic techniques, the fraction of the total left ventricular inflow velocity integral that occurred during this period. Next, the total stroke volume was multiplied by this fraction and added to the end-systolic volume. The result was the volume at the time of minimal diastolic pressure. A similar technique was used to calculate the volume at the point of pre–A-wave pressure.

CALCULATION OF PASSIVE DIASTOLIC STIFFNESS

Diastolic stiffness was assessed with the use of three left ventricular diastolic pressure–volume coordinates: end-diastolic pressure and volume, pre–A diastolic pressure and volume, and pressure and volume at the time of minimal diastolic pressure. The diastolic pressure–volume relation can be described by an exponential equation, $P = Ae^{\beta V}$, where P is the left ventricular diastolic pressure, V is the left ventricular diastolic volume, and A and β are curve-fitting constants used to quantify passive stiffness.[4]

We reasoned that the abnormally slow rate of ventricular relaxation in our patients with diastolic heart failure would preclude full relaxation of the myocardium in early diastole. Thus, incomplete relaxation at the point of left ventricular minimal diastolic pressure might cause the latter value to be higher than it would be if it reflected the purely passive stiffness of the ventricle. Therefore, a corrected value of left ventricular minimal diastolic pressure was obtained by subtracting the contribution to pressure of slow (or incomplete) relaxation from the measured pressure value. This corrected pressure was used to calculate a corrected passive-stiffness constant.

The method used to make this correction, illustrated in Figure 1, is based on standard engineering concepts and published experimental data.[24-28] In brief, the time course of the decline in left ventricular pressure was plotted from the point of aortic-valve closure to the time that the left ventricular pressure would approach zero if relaxation proceeded in the absence of filling. This approach was based on the concept that relaxation is essentially complete after a time interval equal to 3.5τ.[24-28] Then the time from the closure of the aortic valve to the point of left ventricular minimal diastolic pressure was measured, and the pressure at this time was determined from the plot of the natural log of pressure versus time. This contribution of slowed relaxation to pressure represents the extent to which the left ventricular minimal diastolic pressure exceeds the purely passive pressure. By subtracting the pressure contribution of slowed relaxation from the measured value of the left ventricular minimal diastolic pressure, we
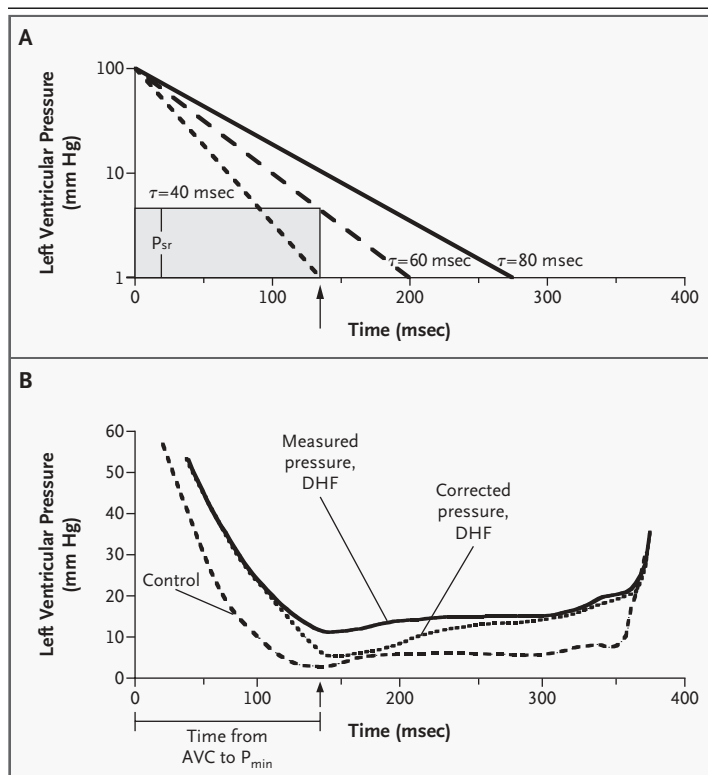
Figure 1. Diagram of the Method Used to Correct the Measured Value of Left Ventricular Minimal Diastolic Pressure for Slow Relaxation Rate.

In Panel A, the decline in left ventricular pressure is illustrated for three values of the relaxation time constant (τ). For example, if τ equals 60 msec and the minimal early diastolic pressure (P_{min}) occurs 130 msec after aortic-valve closure (indicated by the vertical arrow), the contribution of slowed relaxation to pressure (P_{sr}) is 7 mm Hg. In Panel B, measured and corrected pressure tracings in a patient with diastolic heart failure are shown in relation to a normal (control) pressure tracing. AVC denotes aortic-valve closure, and DHF diastolic heart failure.

Table 1. Left Ventricular Pressure, Volume, Relaxation, and Passive Stiffness.*

Variable	Patients with Diastolic Heart Failure (N=47)	Controls (N=10)	P Value
Body-surface area (m²)	2.2±0.25	2.1±0.18	0.31
Heart rate (beats/min)	71±11	73±13	0.81
Volume at P_{min} (ml)	51±13	55±7	0.31
Volume at P_{preA} (ml)	75±15	88±8	0.03
End-diastolic volume (ml)	103±22	115±9	0.01
P_{min} (mm Hg)	12±6	4±1	<0.001
P_{preA} (mm Hg)	16±5	6±2	<0.001
End-diastolic pressure (mm Hg)	25±6	8±2	<0.001
τ (msec)	59±14	35±10	0.01
P_{sr} (mm Hg)	7±5	0	<0.001
Corrected minimal diastolic pressure (mm Hg)	5±2	4±1	0.10
Measured stiffness			
Curve-fitting constant	6.5±4.3	2.3±0.8	0.003
Stiffness constant	0.02±0.01	0.01±0.01	0.01
Corrected stiffness			
Curve-fitting constant	1.5±1.1	2.3±0.8	0.03
Stiffness constant	0.03±0.01	0.01±0.01	<0.001

* Plus–minus values are means ±SD. P_{min} denotes the minimal left ventricular diastolic pressure, P_{preA} the left ventricular diastolic pressure just before atrial contraction, τ the time constant for the isovolumic-pressure decline, and P_{sr} the pressure contribution of slowed relaxation.

obtained a corrected left ventricular minimal diastolic pressure. This corrected pressure was used to calculate the corrected passive-stiffness constant.

STATISTICAL ANALYSIS

The 47 patients with definite diastolic heart failure had participated in a previous clinical trial[21]; the 10 controls had not participated in that trial. The sample size for the control group was based on the hypothesis that the mean value for the corrected stiffness constant in the group with diastolic heart failure would be two times as high as that of the control group. Therefore, using a sample size of 47 patients with diastolic heart failure and 10 controls would yield 80 percent power to detect a twofold difference in the corrected stiffness constant with the use of a conservative standard deviation of 0.01 and a two-sided alpha level of 0.05. Differences between the group with diastolic heart failure and the control group were examined with the use of an unpaired t-test. A P value of less than 0.05 was considered to indicate statistical significance. All reported P values are two-sided. Data were collected at each of the seven study sites and analyzed in the two core laboratories. Additional data analysis was

performed and the manuscript was written by the authors.

RESULTS
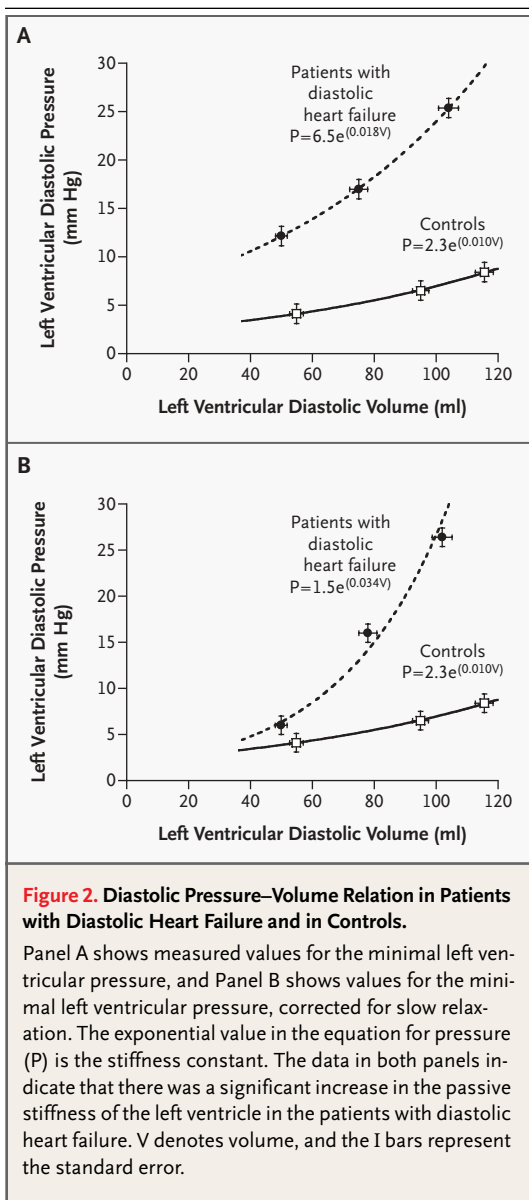
LEFT VENTRICULAR ACTIVE RELAXATION

In the patients with diastolic heart failure, τ was abnormal, the left ventricular early minimal diastolic pressure was increased, and there was a positive correlation between τ and the minimal diastolic pressure ($R^2=0.77$). In these patients, the left ventricular minimal diastolic pressure occurred a mean of 138±5 msec after closure of the aortic valve, which occurred before 3.5τ (i.e., before 218±5 msec). Thus, relaxation was incomplete at the time of left ventricular minimal diastolic pressure in all the patients with diastolic heart failure; incomplete relaxation accounted for 7±1 mm Hg of the measured value of this pressure. By contrast, relaxation was complete at the time of left ventricular minimal diastolic pressure in all the controls.

LEFT VENTRICULAR PASSIVE STIFFNESS

The end-diastolic pressure was higher and the end-diastolic volume was lower in the group of patients with diastolic heart failure than in the control group (Table 1). These data alone suggest the presence of increased chamber stiffness in the patients with diastolic heart failure. As shown in Figure 2A, the entire diastolic pressure–volume relation was displaced up and to the left in the patients with diastolic heart failure as compared with the controls. The left ventricular chamber-stiffness constant and curve-fitting constant, when calculated on the basis of measured values, were higher in the patients with diastolic heart failure than in the controls. When the corrected values for left ventricular minimal diastolic pressure were used to calculate the chamber stiffness (Fig. 2B), the difference in passive stiffness was even more pronounced. As shown in Figure 3, the chamber-stiffness constant was higher in the patients with diastolic heart failure than in the controls.
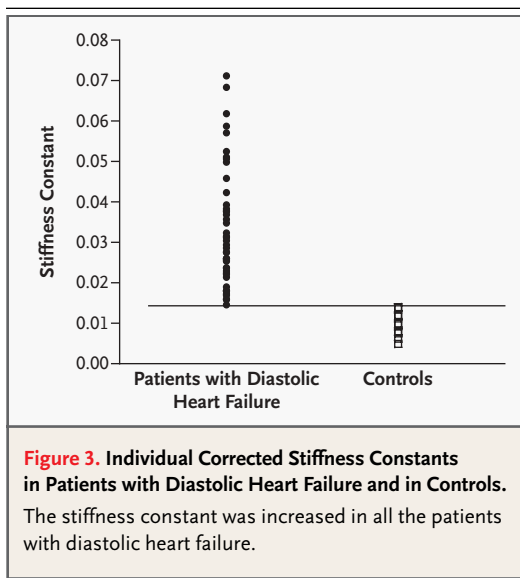
DISCUSSION

This study provides evidence that patients with heart failure and a normal ejection fraction have abnormalities in the diastolic properties of the left ventricle that are sufficient to explain the patients' hemodynamic abnormalities and occurrence of heart failure. The patients in this study who had clinical evidence of heart failure with a normal ejection

Figure 2. Diastolic Pressure–Volume Relation in Patients with Diastolic Heart Failure and in Controls.

Panel A shows measured values for the minimal left ventricular pressure, and Panel B shows values for the minimal left ventricular pressure, corrected for slow relaxation. The exponential value in the equation for pressure (P) is the stiffness constant. The data in both panels indicate that there was a significant increase in the passive stiffness of the left ventricle in the patients with diastolic heart failure. V denotes volume, and the I bars represent the standard error.

Figure 3. Individual Corrected Stiffness Constants in Patients with Diastolic Heart Failure and in Controls.

The stiffness constant was increased in all the patients with diastolic heart failure.

fraction and who met the criteria of Vasan and Levy for definite diastolic heart failure had abnormal active relaxation and increased passive stiffness.[20] These results support the hypothesis that the presence of increased diastolic pressures and signs and symptoms of heart failure in patients with a normal ejection fraction are characterized, if not caused, by abnormalities in the diastolic properties of the left ventricle. Therefore, the term "diastolic heart failure" can be appropriately used to describe the abnormalities in such patients.

Cardiogenic pulmonary edema in patients with diastolic heart failure is often the result of sodium retention and expansion of the central blood volume.[7] Neurohormonally mediated increases in venous tone and systemic arterial pressure may contribute to a shifting of the blood to the central circulation and thereby cause a substantial increase in left ventricular diastolic pressure in such patients.[29] Alterations in arterial stiffness may also contribute by exacerbating the underlying abnormalities in active relaxation and passive stiffness. However, none of these individual factors (sodium retention, neurohormonal activation, increased venous tone, or increased arterial stiffness) cause heart failure in patients with normal left ventricular structure and function. It is the increased left ventricular stiffness in patients with diastolic heart failure that makes them especially vulnerable to the development of pulmonary edema. Increased passive stiffness of the left ventricle dictates the association of very small changes in volume with large changes in left ventricular diastolic pressure.[4,5] Indeed, significant changes in pressure may be seen even with little or no detectable change in ventricular volume.[29,30] Thus, pulmonary edema in patients with diastolic heart failure is the direct consequence of increased passive chamber stiffness; the ventricle is unable to accept venous return adequately without high diastolic pressures. Such high filling pressures result in decreased lung compliance, which increases the work of breathing and contributes to dyspnea.

The mechanisms responsible for chronic exercise intolerance (particularly dyspnea and fatigue with effort) in patients with left ventricular diastolic dysfunction are less well understood. However, at least two mechanisms play a role, and both are de-

pendent on abnormalities in diastolic function.[31] First, patients with diastolic dysfunction (even those with little or no elevation in left ventricular filling pressure at rest) have a substantial increase in left ventricular diastolic pressures and pulmonary venous pressures during exercise and a significant limitation in exercise tolerance.[30] This mechanism is similar to the mechanism that underlies dyspnea in patients with pulmonary edema.[29] Second, the noncompliant stiff ventricle has a limited ability to use the Frank–Starling mechanism.[30,31] As a result, patients with diastolic dysfunction have little or no increase in stroke volume during exercise, a finding that correlates positively with symptoms of exercise intolerance.[30,31] Therefore, during exercise, the small, stiff ventricle in patients with diastolic dysfunction is unable to fill optimally, and despite an increased filling pressure, the cardiac output cannot increase. Thus, the exercise intolerance in patients with diastolic heart failure is the direct consequence of abnormal left ventricular diastolic function.

A number of methods have been used to evaluate left ventricular diastolic stiffness.[24,32-34] Pak et al. showed that there is agreement between measurements of passive chamber stiffness obtained with "single-beat analysis" (i.e., multiple pressure–volume coordinates from a single beat) and those obtained with "multiple-beat analysis" (i.e., end-diastolic pressure–volume coordinates from multiple beats) in patients with hypertensive heart disease, the disease process that most often leads to diastolic heart failure.[33] For this reason, and because the multiple-beat method is difficult to apply in large clinical studies, we used a single-beat method of analysis. However, the accuracy of the curve-fitting constants derived from the pressure and volume data is dependent on a number of factors, including the number of data points used in the calculation. In addition, the effects of slow or prolonged relaxation on early diastolic pressure can limit the accuracy of the single-beat method. In the current study, we avoided this problem by correcting the early diastolic pressures for delayed relaxation. In the patients with diastolic heart failure, such a correction yielded substantially higher passive-stiffness constants than those obtained with the traditional, uncorrected method.

Many, but not all, of the structural, functional, and demographic features of the patients in the current study are shared by the patients examined in recently reported epidemiologic community studies of patients with diastolic heart failure.[7-12] For example, more than 75 percent of the patients in both the current and the previous studies had hypertension. Thirty-eight percent of the patients in the current study had left ventricular hypertrophy (defined as a left ventricular mass that exceeded 125 g per square meter of body-surface area). These findings are consonant with data from the studies by Chen et al.[7] and Kitzman et al.,[10] in which 43 percent and 35 percent of patients with diastolic heart failure, respectively, had left ventricular hypertrophy. Therefore, left ventricular hypertrophy is a common finding in patients with diastolic heart failure; its presence supports but is not required for a diagnosis of diastolic heart failure.[20,21] Patients with diastolic heart failure generally have normal or even small left ventricular chamber volumes.[10,13,35] Echocardiographic studies have shown that the left ventricular end-diastolic volume is 103±20 ml (where the normalized value indexed to body-surface area is 56±10 ml per square meter) in normal persons but 90±18 ml (where the normalized value indexed to body-surface area is 47±5 ml per square meter) in patients with diastolic heart failure.[10,13,35-40] Data from the current study also indicate that left ventricular volumes are normal or decreased in patients with diastolic heart failure.

Despite these many similarities, there are some differences between the current study and previous studies.[6-12] For example, the patients in the current study were younger than those in the previous studies, and a higher proportion of them were men. However, each of the patients examined in the current study fulfilled the criteria of Vasan and Levy for definite diastolic heart failure — a requirement the epidemiologic studies were not designed to meet. Therefore, we believe that the conclusions made in the current study are applicable to a wider population of patients, such as those described in the previous studies.[6-12]

Patients who meet the criteria for definite diastolic heart failure have abnormal active relaxation and increased passive stiffness. The predominant pathophysiological cause of heart failure in these patients is abnormal diastolic function. Therefore, it is appropriate to use the term "diastolic heart failure" to describe the abnormalities in these patients.

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