Heart Failure

Left Ventricular Systolic Performance, Function, and Contractility in Patients With Diastolic Heart Failure

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Background—Patients with diastolic heart failure (DHF) have significant abnormalities in left ventricular (LV) diastolic function, including slow and delayed relaxation and increased chamber stiffness. Whether and to what extent these abnormalities in diastolic function occur in association with abnormalities in LV systolic performance, function, and contractility has not been investigated thoroughly.

Methods and Results—The systolic properties of the LV were examined in 75 patients with heart failure and a normal ejection fraction (ie, DHF) and 75 normal control subjects with no evidence of cardiovascular disease. LV systolic properties were assessed with echocardiographic and cardiac catheterization data. Stroke work (an index of LV systolic performance), preload recruitable stroke work and ejection fraction (indices of LV systolic function), systolic stress-shortening relationship, end-systolic pressure-volume relationship, and peak (+) dP/dt (indices of LV contractility) were examined. The systolic properties of the LV were normal in patients with DHF. Stroke work was 8.4±2.3 in DHF versus 8.8±2.5 kg·cm in controls (P=0.26). Preload recruitable stroke work was 99±22 in DHF versus 109±18 g/cm² in controls (P=0.13). The relationship between stroke work and end-diastolic volume was similar in DHF and controls. Peak (+) dP/dt was 1596±362 in DHF versus 1664±305 mm Hg/s in controls (P=0.54). The end-systolic pressure-volume relationship was increased in DHF. The systolic stress versus endocardial fractional shortening relationship was similar in DHF and controls.

Conclusions—Patients with DHF had normal LV systolic performance, function, and contractility. The pathophysiology of DHF does not appear to be related to significant abnormalities in these systolic properties of the LV. (Circulation. 2005;111:2306-2312.)

Key Words: heart failure ■ systole ■ diastole ■ contractility

Patients with diastolic heart failure (DHF) are said to have detectable abnormalities in left ventricular (LV) systolic function despite the presence of a normal ejection fraction.1-7 Furthermore, it has been suggested that abnormalities of LV systolic properties constitute an important pathophysiological mechanism for the occurrence of heart failure in these patients.3,7 This notion is based on studies that examined the extent and velocity of LV long-axis shortening, mitral annular systolic velocity, myocardial strain, and strain rate.1,3,4,6 However, it is likely that these measurements, like all indices of LV systolic function, are affected by alterations in LV loading conditions and geometry, as well as changes in contractility.8,9 In addition, it is possible, if not likely, that some of these indices of LV systolic function reflect changes in ventricular remodeling independent of changes in contractility.10-12 Therefore, to determine whether and to what extent patients with DHF have abnormalities in the systolic properties of the LV, load and remodeling independent indices must be examined. Many such indices have been proposed, but there is no single, universally applicable index of systolic properties that is independent of load and remodeling.8 We hypothesized that if multiple indices are measured and if the results are in general agreement and viewed in aggregate, it should be possible to determine whether patients with DHF have significant abnormalities in the systolic properties of the LV. Accordingly, the purpose of this study was to measure indices of LV systolic performance, function, and contractility in a group of patients with DHF and to test the hypothesis that the systolic properties of the LV are normal.

Methods

Patient Population

Diastolic Heart Failure

Seventy-five patients with chronic heart failure and a normal ejection fraction underwent echocardiography and blood pressure measurement by sphygmomanometry. Forty-seven of these 75 patients underwent simultaneous cardiac catheterization to measure LV pressures. All patients had a history of heart failure (meeting the Framingham criteria for congestive heart failure13), a normal LV ejection fraction (>0.50), and LV end-diastolic pressure by cathe-

desired pressure by echocardiography.
graphic Doppler >16 mm Hg. Patients with pulmonary disease, renal disease, anemia, heart valve disease, atrial fibrillation, or evidence of hypertrophic cardiomyopathy were excluded. LV volume, mass, and diastolic function data from 47 of the 75 patients have been published previously15,16; however, none of the LV systolic performance, function, or contractility data reported in the present study have been published previously.

Normal Controls
Seventy-five normal subjects with no evidence of cardiovascular disease served as controls. Controls had normal LV volume, mass, ejection fraction, and wall motion by echocardiographic study. Sixty-five controls underwent echocardiography and blood pressure measurement by sphygmomanometry. Ten controls underwent simultaneous catheterization to measure LV pressures. Data documenting LV volume, mass, and diastolic function from 10 of 75 controls and midwall stress-shortening data (an index of myocardial contractility) from the remaining 65 control subjects have been published previously.16,17 None of the data on indices of LV systolic performance, function, or contractility from the 75 controls have been published previously.

The research protocol used in the present study was reviewed and approved by the institutional review board at the Medical University of South Carolina. Written informed consent was obtained from all patients.

Terminology
The systolic properties of the LV were assessed and evaluated by examination of indices that reflect LV performance, function, and contractility. The definitions and measurements used to determine these systolic properties are described below.

“Ventricular performance” describes the pumping properties of the ventricle. The performance of the ventricle as a pump can be assessed by measuring the pressure developed by the ventricle, the stroke volume ejected by the ventricle, or preferably, the stroke work generated by the ventricle. Stroke work gives credit to the ventricle for both pressure and shortening work in a single integrated index.

“Ventricular function” relates LV performance (stroke volume or work) to preload (end-diastolic pressure or volume). A classic ventricular function curve can be constructed by plotting coordinates of performance against preload. When contractility is increased, the stroke work versus preload relationship is shifted upward. When contractility is decreased, the stroke work versus preload relationship is shifted downward. Such a family of ventricular function curves credits the ventricle for pressure development and ejection, and it incorporates load and contractility. Thus, stroke work and end-diastolic volume (EDV) data allow construction of a Frank-Starling ventricular function curve or a preload recruitable stroke work relationship.

The term “ventricular function” has been expanded to include shortening parameters such as ejection fraction, long-axis shortening, myocardial systolic strain or strain rate, and mitral annular systolic velocity. Many of these indices have mistakenly been referred to as indices of ventricular contractility, but all of them are sensitive to changes in preload and afterload, as well as contractility and remodeling. If loading conditions and ventricular remodeling are considered or incorporated in the analysis, then these parameters of “function” may be used as indices of ventricular contractility.

“Ventricular contractility” refers to the contractile or inotropic state of the whole ventricle. Indices of ventricular contractility conventionally have been divided into isovolumic phase indices (peak positive dP/dt), ejection phase indices (systolic wall stress versus endocardial shortening), and those determined at the end of ejection (end-systolic elastance). The concept of ventricular contractility is similar to that of myocardial contractility, but the indices of ventricular contractility are not independent of loading conditions or ventricular remodeling. For example, (+) dP/dt may be altered by an acute change in preload, whereas end-systolic elastance (Ees) may be affected by chronic changes in LV volume and mass.

Myocardial contractility refers to a basic property of heart muscle that reflects the intensity of cross-bridge activity and as a result, the extent and velocity of force development and fiber shortening. Thus, the contractile or inotropic state of the myocardium represents a property that is independent of loading conditions and remodeling. Such measurements can be made in vitro in isolated cardiac muscle cells, muscle strips, or Langendorff-perfused hearts, but attempts to assess myocardial contractility in humans in vivo present a continuing challenge.

Measurements and Calculations
Cardiac catheterizations were performed by standard techniques. A high-fidelity micromanometer catheter was placed into the LV, and LV pressures were measured. Analysis of LV pressure data was performed in a core laboratory.15,16 Echocardiography was also performed by standard techniques. LV dimensions and wall thickness were measured according to the recommendations of the American Society of Echocardiography.19,20 Calculations of LV volume and mass were made by standard published methods.21 Analysis of the echocardiographic data was performed in a core laboratory.15,16

LV Systolic Performance
Stroke volume was calculated as the difference between EDV and end-systolic volume. Stroke work (SW) was calculated as the product of stroke volume and mean arterial blood pressure.22 In addition, in the subset of patients who had undergone simultaneous cardiac catheterization (47 DHF patients, 10 controls), SW was calculated as the LV pressure-volume area.22

LV Systolic Function
Ejection fraction, mean velocity of circumferential fiber shortening, and fractional shortening were calculated by standard formulas. The SW versus EDV coordinates were examined for all controls and DHF patients (Figure 1). Preload recruitable SW (PRSW) was determined by the single-beat method of Karunanithi and Feneley23 and Lee et al.24

LV Contractility
LV pressure was digitized at 5-ms intervals and the first derivative of LV pressure versus time (dP/dt) was calculated. The maximum value of (+) dP/dt max was used as an index of LV contractility. Ees was assessed as a simple ratio of end-systolic pressure versus end-systolic volume,25 and the slope of the end-systolic pressure–volume relationship was calculated by the single-beat method of Shishido et al.26
Effective arterial elastance (Ea) can be assessed as the ratio of end-systolic pressure versus stroke volume and can be used in the calculation of an arterial-ventricular coupling index, Ea/Ees. To assess LV function and contractility per gram of heart muscle, both the end-systolic pressure versus end-systolic volume ratio and Ees were divided by LV mass. These indices were also normalized by dividing by the LV mass/EDV ratio.

The relationship between endocardial fractional shortening and mean systolic stress was used as an index of LV contractility. Mean circumferential LV systolic stress was calculated with a cylindrical model. Data from the 75 controls were used to define the normal midwall systolic stress relationship. In Figure 3, the solid line shows the mean value of this normal relationship. The dashed lines show the 95% prediction intervals for the normal relationship. The individual stress versus endocardial shortening coordinates for DHF patients were plotted with reference to the normal mean±95% prediction interval data. DHF coordinates that fell within the 95% prediction intervals were considered to have normal contractility, and those that fell below the 95% prediction limit were considered to have decreased contractility.

Myocardial Contractility
The midwall fractional shortening versus systolic stress relationship was defined in normal controls and patients with DHF. Midwall shortening was calculated from the 2-shell cylindrical model. Data from the 75 normal controls were used to define the normal midwall fractional shortening versus mean midwall systolic stress relationship. In Figure 3, the solid line shows the mean value of this normal relationship. The dashed lines show the 95% prediction intervals for the normal relationship. The individual stress versus midwall shortening coordinates for DHF patients were plotted with reference to the normal mean±95% prediction interval data. DHF coordinates that fell within the 95% prediction intervals were considered to have normal myocardial contractility, and those that fell below the 95% prediction limit were considered to have decreased myocardial contractility.

Statistical Analysis
Data are presented as mean±SD in the text and Tables 1 and 2. Data are mean±SE in the figures. Differences between DHF patients and controls were examined with an unpaired t test. A probability value <0.05 was considered statistically significant. All reported probability values are 2-sided.

Results
Demographics, Hemodynamics, and Remodeling
Compared with normal controls, DHF patients had similar body surface area, age, and gender distribution (Table 1). As a group, patients with DHF had significantly higher blood pressure, lower EDV, greater LV mass, and greater relative wall thickness than the controls; however, neither LV hypertrophy nor concentric remodeling was a prerequisite inclusion criterion for patients with DHF. Sixty percent of the DHF patients had a relative wall thickness >0.45, and 40% had an LV mass >125 g/m². Thirty-four percent of the DHF patients...
had neither an increased relative wall thickness nor an increase in LV mass.

The remodeling present in the DHF patients was sufficient to normalize mean systolic stress in the presence of the increased arterial pressure. Thus, there were no significant differences in mean systolic stress between DHF patients and normal controls.

**LV Systolic Performance, Function, and Contractility**

Every index of LV systolic performance, function, and contractility examined in the present study was either normal or increased in the DHF patients compared with normal controls (Table 2). SW, calculated as the LV pressure-volume area, was 8.9±2.7 kg · cm in DHF patients and 8.4±1.3 kg · cm in controls (P=0.37). The SW/EDV ratio, end-systolic pressure/volume ratio, and Ees were increased in DHF patients compared with controls; however, when these indices were normalized to LV mass or the LV mass/EDV ratio, there were no significant differences between DHF patients and controls. Ees/(LV mass/EDV) was 1.2±0.4 in controls versus 1.1±0.6 mm Hg/g in DHF patients (P=0.56). Ea was increased in DHF patients (1.95±0.47) compared with controls (1.34±0.19, P<0.05), but the arterial-ventricular coupling index, Ea/Ees, was not different in DHF patients (0.72±0.17) than in controls (0.64±0.19, P=NS). In DHF patients, the SW versus EDV coordinates fell along a similar linear relationship as the control values (Figure 1). In the DHF patients, all of the endocardial fractional shortening versus mean systolic stress coordinates fell within the 95% prediction intervals for normal controls (Figure 2).

Presentation of mean values that demonstrate similarity between groups of patients does not rule out the possibility that some parameters in some patients may fall into an “abnormal” range. Therefore, all of the values for the SW/EDV ratio and PRSW for both DHF and controls are presented in Figure 3. There was complete overlap between the individual values for controls versus DHF. In none of the DHF patients did PRSW fall below the values for controls. In the present study, in all of the patients with DHF, measures of LV systolic performance, function, and contractility fell within the range of values for controls.

**Midwall Fractional Shortening Versus Mean Systolic Stress Relationship**

In both DHF and controls, there was an inverse relationship between midwall fractional shortening and mean systolic stress, with midwall fractional shortening decreasing as stress increased. In approximately one third of the DHF patients, this index of myocardial contractility fell below the 95% prediction intervals for normal controls, whereas the remaining two thirds fell within the normal range (Figure 4).

**Discussion**

The principal finding of the present study was that measurements of LV systolic performance (SW), function (ejection fraction and PRSW), and contractility (peak positive dP/dt, stress versus shortening, and Ees) were not significantly different in patients with DHF than in normal control subjects. To the best of our knowledge, this is the first time such a comprehensive evaluation of LV systolic properties has been made in patients with DHF. Because all of these LV systolic parameters were normal in patients with DHF, it appears reasonable to conclude that the underlying pathophysiology causing the symptoms and signs of heart failure is not based on abnormalities in these LV systolic properties.

The conclusions reported here differ from a number of published studies and editorials.1-3,4,6 These previous studies used measurements of long-axis shortening extent and velocity, mitral annular systolic velocity, systolic atrioventricular plane displacement, or myocardial systolic strain and strain rate as indices of LV contractility. These authors concluded that abnormalities of these shortening parameters contributed to the underlying pathophysiology in patients who had what traditionally has been called DHF. Although they did not...
A change in any measurement represents a specific change in fraction not the primary causal pathophysiology in these patients. There are a number of methodological differences (discussed below) between the present study and previous studies that may help to explain the discordance in conclusions between them. In the present study, all of the patients had an ejection fraction >0.50. In the studies mentioned above, a significant proportion of the patients with "heart failure and a preserved ejection fraction" in fact had an ejection fraction <0.50, some as low as 0.35. Importantly, it was those individuals with an ejection fraction <0.50 who were most likely to have abnormalities in long-axis shortening and systolic mitral annular motion. Furthermore, even when patients with an ejection fraction <0.50 in previous studies were excluded, there was a substantial overlap in values of long-axis shortening and systolic mitral annular motion between control patients and those with heart failure and a normal ejection fraction. Therefore, many of these patients (as many as half of the patients in some studies) actually had normal values of these shortening parameters. In the present study, in all of the patients with DHF, measures of LV systolic performance, function, and contractility fell within the distribution of normal values for the control population. All measurements that examine the extent or velocity of regional wall or mitral annulus motion, regardless of the method used to obtain them, can be altered by acute or chronic changes in preload, afterload, and contractility and influenced by remodeling. Therefore, to determine whether a change in any measurement represents a specific change in contractility, factors such as preload, afterload, and remodeling must either be held constant or be incorporated into the analysis. This was not the case in the studies discussed above. One study, however, did include data that examined systolic wall stress, an index of afterload. In the study by Yu et al, both midwall fractional shortening and systolic mitral annular motion were decreased and mean systolic stress was significantly increased in patients with DHF. If their stress versus midwall shortening data for the control group and the DHF patients were plotted on Figure 4 of the present study, all of their coordinates would fall within the normal 95% prediction intervals and lie very close to the average normal regression line of our data. Thus, in the case of the data from Yu et al, the observed decrease in midwall fractional shortening was likely the result of increased LV wall stress and not decreased contractility. By contrast, in the present study, approximately one third of the DHF patients had decreased midwall shortening at normal levels of LV wall stress. These data suggest that myocardial contractility may be decreased in at least some patients with DHF; however, a number of studies have shown that some patients with concentric hypertensive hypertrophy but no symptoms or signs of chronic heart failure also have decreased midwall shortening. These data suggest that the occurrence of DHF is not necessarily dependent on decreased midwall shortening.

It has recently been suggested that indices of systolic function, such as the extent and velocity of long-axis shortening, mitral annular systolic velocity, systolic atroventricular plane displacement, and myocardial systolic strain and strain rate, are less "load dependent" than other shortening parameters. Because all shortening or displacement indices are affected by hemodynamic loading conditions, it is difficult to imagine that any index of systolic function would be truly load-independent. For example, a recent study by Abraham et al showed that tissue Doppler-derived myocardial strain and strain rate fell as afterload was increased in normal myocardium. When the myocardium was injured by hypoxia, the slope of the inverse linear relationship between strain or strain rate and afterload decreased, so that a relatively large change in load caused a small change in strain or strain rate. These data do not necessarily indicate that tissue Doppler indices are independent of or insensitive to load, rather they indicate that the sensitivity to changes in load depends in part on the functional state of the ventricle. Despite the limitations discussed above, previous studies have documented (and future studies may confirm) abnormalities in some systolic measurements in some patients with DHF; however, the significance of such changes will depend on an understanding of 3 additional factors. First, whether changes in these systolic measurements reflect a change in hemodynamic load, LV remodeling, or an intrinsic property of the myocardium will need to be examined. Second, it should be necessary that these changes occur in at least the majority of the patients studied. Third, such "subtle" changes in systolic measurements should be examined in light of the pathophysiology underlying the development of diastolic dysfunction and the occurrence of DHF. In the present study, we measured systolic mitral annular velocity (Vsm) in 10 controls and 14 DHF patients. Vsm was lower in DHF...
patients (7.8±1.2 cm/s) than in controls (9.8±1.7 cm/s). Although this difference was statistically significant, there was considerable overlap between control and DHF data, and only one third of the DHF patients had values that were clearly in the abnormal range. There was an insufficient sample size to examine the relationship between changes in Vsm and systolic load. The presence of a decreased Vsm was not associated with abnormalities in the measurements of LV systolic performance, function, and contractility made in the present study. To fully understand the importance of these observations, further prospective studies should be performed to examine myocardial velocity, strain, and strain rate together with determinations of load and considerations of remodeling in patients with DHF.

The finding in the present study that LV systolic performance, function and contractility were normal in patients with DHF does not exclude the presence of cellular, extracellular, or molecular abnormalities at the myocardial, cardiomyocyte, or sarcomere level. Changes in molecular and biochemical properties in the cardiomyocyte and extracellular matrix are certainly present in these patients with DHF. For example, abnormalities in intracellular calcium handling, decreased sarcoplasmic reticulum calcium ATPase, increased phospholamban, and increased extracellular matrix proteins such as fibrillar collagen have been shown to be present in patients and animal models with DHF. These abnormalities have been associated with abnormalities in diastolic function but do not uniformly lead to abnormalities in the LV systolic properties examined in patients with DHF in the present study.

All of the indices of LV systolic performance, function, and contractility examined in the present study were measured under basal conditions. The ability to augment LV systolic performance and function during exercise or stress may be limited in some patients with DHF. It is not clear whether such a limited systolic reserve is caused by abnormalities in systolic function or diastolic function, or the combination of both systolic and diastolic dysfunction. This question will require further studies.

The present and previous studies add to our understanding of the pathophysiology of DHF and suggest targets for the treatment of patients with DHF. Given that there are profound differences in LV volume, mass, geometry, and systolic properties in patients with systolic heart failure and patients with DHF, long-term treatment will likely be fundamentally different. For example, it has become apparent that in patients with systolic heart failure, therapies that reverse eccentric remodeling by decreasing LV volume and restoring LV ejection fraction result in decreased morbidity and mortality. Therefore, the 2 important pathophysiological mechanisms present in systolic heart failure, namely, eccentric remodeling and abnormal systolic function, serve as appropriate targets for treatment. However, in DHF, there is no eccentric remodeling, LV volume is normal, and LV systolic properties are normal. Patients with DHF have concentric remodeling and predominant abnormalities in diastolic function. Therefore, the long-term treatment of DHF should be directed at reversing the cellular and extracellular mechanisms that lead to concentric remodeling, fibrosis, and abnormal diastolic function.

Conclusions

Measurements of LV systolic performance (SW), function (ejection fraction and PRSW), and LV contractility ([+]dP/dt, stress versus shortening, and Ees) were not significantly different in patients with DHF than in normal control subjects with no evidence of cardiovascular disease.

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References


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