Heart Failure With a Normal Ejection Fraction
Is Measurement of Diastolic Function Necessary to Make the Diagnosis of Diastolic Heart Failure?

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Background—The diagnosis of diastolic heart failure is generally made in patients who have the signs and symptoms of heart failure and a normal left ventricular (LV) ejection fraction. Whether the diagnosis also requires an objective measurement of parameters that reflect the diastolic properties of the ventricle has not been established.

Methods and Results—We hypothesized that the vast majority of patients with heart failure and a normal ejection fraction exhibit abnormal LV diastolic function. We tested this hypothesis by prospectively identifying 63 patients with a history of heart failure and an echocardiogram suggesting LV hypertrophy and a normal ejection fraction; we then assessed LV diastolic function during cardiac catheterization. All 63 patients had standard hemodynamic measurements; 47 underwent detailed micromanometer and echocardiographic-Doppler studies. The LV end-diastolic pressure was $>16$ mm Hg in 58 of the 63 patients; thus, 92% had elevated end-diastolic pressure (average, $24\pm8$ mm Hg). The time constant of LV relaxation (average, $51\pm15$ ms) was abnormal in 79% of the patients. The E/A ratio was abnormal in 48% of the patients. The E-wave deceleration time (average, $349\pm140$ ms) was abnormal in 64% of the patients. One or more of the indexes of diastolic function were abnormal in every patient.

Conclusions—Objective measurement of LV diastolic function serves to confirm rather than establish the diagnosis of diastolic heart failure. The diagnosis of diastolic heart failure can be made without the measurement of parameters that reflect LV diastolic function. (Circulation. 2001;104:779-782.)

Key Words: heart failure • diastole • hemodynamics • hypertrophy

The prognosis of patients with heart failure has improved substantially in recent years, largely as a consequence of therapies developed in multicenter, randomized, placebo-controlled trials. Virtually all of the clinical trial data were developed in patients with depressed left ventricular (LV) systolic function. The results of these studies do not necessarily apply to patients with heart failure and a normal LV ejection fraction; such patients constitute a significant fraction of the total heart failure population. Treatment of this group remains empirical and based largely on anecdotal information. Certainly, there is a need for research that provides evidence-based management strategies for patients with heart failure and a normal LV ejection fraction.

Heart failure in patients with a normal ejection fraction is generally referred to as heart failure caused by LV diastolic dysfunction (ie, diastolic failure). Such a clinical definition of diastolic failure requires (1) the presence of signs and symptoms of heart failure and (2) a normal LV ejection fraction. Whether the diagnosis requires an objective measurement of parameters that reflect the diastolic properties of the ventricle has not been established and remains controversial. Thus, it has been suggested that the clinical definition lacks sensitivity and specificity and that an accurate diagnosis of diastolic failure requires a demonstrable abnormality in the diastolic properties of the ventricle as assessed through measurement of LV passive stiffness constants and/or indexes of active relaxation. Others have argued on experimental and conceptual grounds that measurement of relaxation rates is of doubtful diagnostic value. Recognizing the difficulties inherent in the measurement and analyses of such data and the fact that many if not most clinicians do not utilize such measurements, we sought to evaluate the accuracy of the clinical diagnosis of diastolic heart failure. Accordingly, we hypothesized that most patients with a history of heart failure and normal ejection fraction do indeed have measurable abnormalities in diastolic function. We tested this hypothesis by identifying a group of patients with heart failure and an echocardiogram suggesting at least borderline or mild LV hypertrophy with normal LV ejection fraction and subsequently evaluating the diastolic properties of the ventricle during cardiac catheterization.
Methods
This was a prospective hemodynamic and echocardiographic study of patients with clinically defined diastolic heart failure. Patients who were scheduled for diagnostic cardiac catheterization were screened, and those who met specific inclusion and exclusion criteria were invited to participate in the study. Recordings made during catheterization were later sent to core laboratories for measurement.

Patient Population
The screening criteria included a history of heart failure and normal LV ejection fraction. Patients who met these criteria and had been scheduled for diagnostic cardiac catheterization were then evaluated for participation in the study. Those who met the Framingham criteria for congestive heart failure were potential candidates. A contemporary echocardiogram was then performed; enrollment required evidence of a normal LV chamber dimension (<55 mm), combined with LV wall thickness ≥11 mm, relative wall thickness ≥0.45, or LV mass ≥125 g/m². Thus, stable patients with heart failure and echocardiographic evidence suggesting LV hypertrophy with an ejection fraction exceeding 50% were invited to participate in the study. It should be emphasized that echocardiographic indexes of diastolic function were not used as inclusion criteria.

Patients were not included in the study if they had a poor-quality echocardiogram or if they were unable or unwilling to give informed consent. Specific exclusion criteria included concurrent severe systemic disease, evidence of coronary heart disease (including LV asynergy or a history of previous coronary bypass surgery), significant congenital or valvular disease, or known cardiomyopathy. We also excluded patients with recent hemodynamic instability; those who had been treated with dopamine, dobutamine, or other positive inotropic agent within 48 hours; and those with clinically significant atrial or ventricular arrhythmia, electronic pacemakers, or implantable cardiac defibrillators.

Sixty-three patients provided written informed consent and participated in this study. All 63 were hemodynamically stable at the time of cardiac catheterization. There were 41 men and 22 women; their average age was 58±14 years. Sixteen patients had LV pressure measured with fluid-filled catheters, whereas 47 underwent combined echocardiographic-hemodynamic (micromanometers) studies. Data are presented as mean±SD. Relationships between 2 variables were tested by linear regression analysis. A value of P<0.05 was considered statistically significant.

Cardiac Catheterization
Cardiac catheterizations were performed with standard techniques. To provide conscious sedation during the procedure, all patients were treated with benzodiazepines. Other medications were withheld, and patients fasted for 12 hours before catheterization. A high-fidelity micromanometer pigtail catheter was placed into the LV under fluoroscopic guidance. Before insertion, the micromanometer catheter was precalibrated in warm saline. After insertion, calibration was confirmed, and the catheter was recalibrated if necessary. Then, Doppler and LV echocardiographic recordings were obtained at the same time as the acquisition of LV pressure data. We measured LV systolic pressure, diastolic pressures, and the time constant of isovolumic pressure decline. LV early diastolic pressure was defined as the lowest pressure after mitral valve opening; LV pre-A-wave pressure was defined as the LV pressure midway through diastole; LV end-diastolic pressure (LVEDP) was defined as the pressure after atrial contraction just before LV systolic pressure rise. An LVEDP ≥16 mm Hg was considered abnormal; in the setting of a normal LV chamber size, a pressure >16 mm Hg can be taken as a major indicator of LV diastolic dysfunction. LV pressure data were digitalized at 5-ms intervals, and the relaxation time constant was calculated with the method of Weiss et al. The vast majority of normal human beings exhibit a time constant <44 ms; we also used a more conservative limit of 48 ms as an indication of abnormal LV relaxation.

<table>
<thead>
<tr>
<th>Diastolic Function in Patients With Heart Failure and a Normal Ejection Fraction</th>
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<tr>
<td><strong>Average±SD</strong></td>
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<td><strong>LV pressure</strong></td>
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<td>EDP, mm Hg</td>
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<td>IVRT, ms</td>
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<tr>
<td>E, mm/s</td>
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<td>DT, ms</td>
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<tr>
<td>A, mm/s</td>
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<td>E/A ratio</td>
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r indicates relaxation time constant; E, peak E velocity; DT, deceleration time; and A, peak A velocity.

Echocardiography
Echocardiographic data were obtained after placement of the LV catheter. We used standard 2.5- to 3.5-MHz transducers and standard equipment with settings adjusted to optimize visualization of the ventricular endocardial contours while avoiding excessive gain artifact. LV dimensions and wall thickness were measured according to the recommendations of the American Society of Echocardiography by use of the leading edge convention, and calculations were made with previously published methods. Pulsed Doppler examination of mitral inflow was accomplished with the sample volume between the tips of the mitral leaflets in the 4-chamber view with the use of 1- to 2-mm sample volume aligned with color inflow. Images were recorded on super VHS tape and recording paper (100 mm) for measurement. A normal peak E-wave velocity falls in the range of 70 to 100 cm/s; a normal A wave ranges from 45 to 70 cm/s. An E/A ratio <1.0 or >1.5 and an E-wave deceleration time <160 or >280 ms were considered abnormal. Pulsed Doppler overlapping both aortic outflow tract and transmirtal velocities was used to derive isovolumic relaxation time (IVRT) as the time from the end of aortic ejection to the onset of mitral inflow. An IVRT <60 or >105 ms was considered abnormal.

Results
The major results are presented in the Table. These average data indicate that the LV pressure parameters are more frequently abnormal than the echocardiographic indexes of diastolic function. Catheterization and/or echocardiographic measures of LV diastolic function were abnormal in the vast majority of our patients.

The major indicator of diastolic dysfunction (ie, an LVEDP ≥16 mm Hg) was present in 58 of the 63 patients. Thus, 92% of the patients with clinically defined diastolic heart failure were found to have an abnormal LVEDP. The mean LVEDP was 24±8 mm Hg. The mean values for early and mid diastolic pressures were also elevated (12±8 and 16±2 mm Hg, respectively). LV systolic pressure was 160±40 mm Hg. The time constant of relaxation was >44 ms in 44 of the 47 patients (93%) and ≥48 ms in 37 (79%); the mean value for the group was 59±15 ms. There was a significant positive correlation between the time constant and LVEDP (r=0.62, P<0.001), with 1 or both of these parameters in the abnormal range in 94% of our patients.

The duration of IVRT ranged from 55 to 153 ms and exceeded the upper limits of normal (105 ms) in 17 patients (38%); the IVRT was short (<60 ms) in only 1 patient. The E and A velocities also exhibited wide variation. The E velocities
ranged from 32 to 131 cm/s; the E-wave velocity was <70 cm/s in 42% and >100 cm/s in 11%. Thus, the E-wave velocity fell outside the normal range in 51% of the patients. The A velocities ranged from 36 to 138 cm/s; the A-wave velocity was >70 cm/s in 50% and <45 cm/s in 7%. The E/A ratio ranged from 0.4 to 2.5; the ratio was <1.0 in 21 patients (48%) and >1.5 in 4 (9%). Thus, the E/A ratio was abnormal in 58% of the patients. The deceleration time ranged from 101 to 622 ms; it was >250 ms in 37 patients and was markedly prolonged (>280 ms) in 64%. The deceleration time was abnormally short (<160 ms) in only 4 patients.

Of the 47 patients who participated in the echocardiographic-catheterization studies, ≥1 of the parameters reflecting LV diastolic function were abnormal in every patient. Thus, the 3 patients with normal LV EDP had abnormal deceleration time and/or abnormal E- or A-wave velocity. Of the 16 patients who did not undergo echocardiographic-catheterization studies, 14 had an abnormal LV EDP. Therefore, virtually all patients who met our clinical definition of diastolic heart failure had objective evidence of LV diastolic dysfunction.

Discussion
Diastolic heart failure is relatively common and carries an ominous prognosis, but specific criteria for the diagnosis are incompletely defined. The need to develop precise guidelines for the diagnosis, a Canadian consensus group, a European study group, and others have published recommendations for the assessment of LV diastolic function and the diagnosis of diastolic heart failure. It is generally agreed that the diagnosis requires evidence of congestive heart failure in the presence of a normal ejection fraction. However, the European study group also requires "evidence of abnormal LV relaxation, filling, diastolic distensibility, or diastolic stiffness." This latter recommendation was made in spite of the well-recognized difficulties in assessing LV diastolic function. Thus, the load dependence of the indexes of relaxation and the changing functional patterns over time limit their interpretation. For these and other reasons, many if not most clinicians make the clinical diagnosis of diastolic dysfunction or failure if a patient simply has heart failure in the presence of a normal ejection fraction. However, the European study group also requires "evidence of abnormal LV relaxation, filling, diastolic distensibility, or diastolic stiffness." This latter recommendation was made in spite of the well-recognized difficulties in assessing LV diastolic function. Thus, the load dependence of the indexes of relaxation and the changing functional patterns over time limit their interpretation. For these and other reasons, many if not most clinicians make the clinical diagnosis of diastolic dysfunction or failure if a patient simply has heart failure in the presence of a normal ejection fraction.

Vasan and Levy refined these concepts and suggested specific criteria for the diagnosis, probable, and possible diastolic heart failure. All 3 categories require definitive evidence of heart failure and a normal LV ejection fraction; the definite and probable categories require that the ejection fraction be measured within 3 days of the episode of heart failure. Objective evidence of diastolic dysfunction (ie, abnormal LV relaxation, filling, or distensibility indexes measured during cardiac catheterization) is required for the diagnosis of definite but not for the diagnosis of probable or possible diastolic heart failure. These standardized diagnostic criteria, especially the addition of probable and possible categories, provide a major advancement in our ability to classify patients with heart failure. As emphasized by Vasan and Levy, their definitions require prospective validation. Our study provides some such validation.

The major finding in our study is that objective measures of abnormal LV diastolic function are present in the overwhelming majority of our patients. Thus, >90% of the patients who met our clinical definition of diastolic heart failure exhibited an abnormal LV EDP and increased early and mid-diastolic pressures. Such high filling pressures in the setting of a normal chamber size indicate an abnormality in the physical properties of the ventricle (ie, increased LV diastolic stiffness). A prolonged time constant of relaxation was also present in most patients, indicating a reduced or slowed LV relaxation rate. The positive correlation between LV EDP and the time constant likely reflects a close relationship between both parameters and the severity of diastolic dysfunction; it does not necessarily imply cause and effect.

The duration of LV IVRT and the indexes of auxotonic relaxation derived from the echocardiographic-Doppler studies were also frequently abnormal, but in contrast to the catheterization data, these parameters exhibited considerable variability. This is likely due to the sensitivity of the echocardiographic-Doppler parameters to changes in hemodynamic conditions and heart rate. For example, it is well recognized that the duration of IVRT may be normal or even shortened despite slow relaxation and a prolonged time constant if the left atrial pressure is elevated and the mitral valve opens early. Likewise, elevated filling pressures can produce a “pseudonormalization” of early diastolic events, whereas treatment of a congestive state can transform a restrictive or pseudonormal pattern into a picture of delayed relaxation. Despite these potential limitations of the echocardiographic-Doppler methods, our data indicate that ≥1 of the noninvasive indexes of diastolic function were abnormal in virtually all of the patients who met our clinical definition of diastolic heart failure.

We targeted patients with LV hypertrophy because of the high prevalence and morbidity of hypertension and hypertensive heart disease, because of the likelihood that LV hypertrophy plays a major role in many if not most patients with diastolic dysfunction, and because small therapeutic trials have emphasized patients with hypertension. However, LV mass did not exceed 125 g/m2 in more than half of our patients; strictly speaking, therefore, many did not have LV hypertrophy. In contrast, >90% of the patients did exhibit an absolute wall thickness ≥11 mm and/or a relative wall thickness ≥0.45, a value indicating hypertrophic remodeling. Regardless of whether or not hypertrophy was present, virtually all of our patients exhibited abnormal indexes of diastolic function.

Although our results likely apply to most patients with heart failure and a normal ejection fraction, our specific inclusion/exclusion criteria should be considered before application in future research or therapeutic trials. Because a major purpose of our study was to identify a population that might be appropriate to study in a therapeutic trial, we did not include patients with obvious coronary disease. Certainly, many such coronary patients manifest signs and symptoms of heart failure despite a normal LV ejection fraction, but we think that they are potential candidates for revascularization procedures and that therapeutic trials should emphasize patients who do not have overt coronary heart disease. A second consideration is related to our requirement of a normal LV chamber size. Although LV enlargement would not necessar-
ily rule out diastolic heart failure, most such patients have a strain-dependent cause, not a primary disturbance of diastolic function. Finally, it should be mentioned that patients with valvular heart disease, known infiltrative cardiomyopathy, or constrictive pericarditis were not included in our study; such patients should not be included in therapeutic trials of patients with heart failure and a normal ejection fraction.

The current management of patients with heart failure caused by LV systolic dysfunction is based largely on measurement of the LV ejection fraction. Thus, patients with an ejection fraction <35% to 40% are candidates for medical therapies, regardless of whether they are symptomatic or asymptomatic. Ongoing and planned studies that examine new treatment strategies for patients with systolic dysfunction also depend heavily on determination of the ejection fraction. Unfortunately, there is no single index of diastolic function that is as useful and widely applicable as ejection fraction in patients with systolic dysfunction. Indeed, after decades of study, there is little agreement as to the utility of the echocardiographic-Doppler indexes of LV diastolic function in the diagnosis of diastolic heart failure. Although measurement of diastolic function may be useful in specific areas of clinical research, our data indicate that patients who meet the clinical definition of diastolic heart failure do indeed have abnormal diastolic function. We therefore conclude that objective evidence of abnormal LV relaxation, filling, or distensibility is not necessary to make the diagnosis of diastolic heart failure.

Appendix

Study site, principal investigator, associate investigators, and nurse coordinators are listed here: Medical University of South Carolina and the Ralph H. Johnson Veterans Affairs Medical Center: Michael R. Zile, MD, Christopher D. Nelson, MD, Melia Knotts, RN, Joan Zile, RN, and Leslie Harrell, RN; Lahey Clinic Medical Center: William H. Gaasch, MD, and Robin Sgroso; University of Colorado Health Sciences Center: John D. Carroll, MD, JoAnn Lindenfeld, MD, Kathy Kioussopoulos, RN, and Keith Himmel; University of Texas Health Science Center San Antonio: Marc D. Feldman, MD, John Erikson, MD, PhD, Teresa Huber, RN, and Mary Alice Garcia, RDCS; University of Massachusetts Medical Center: Gerard R. Aurigemma, MD, Theo E. Meyer, MD, PhD, Eugene S. Chung, MD, and Kathy Coleman, RN; Rush Medical College, Rush-Presbyterian-St Luke’s Medical Center: Joseph Parrillo, MD, Gary L. Schauer, MD, R. Jeffrey Snell, MD, Clifford Kavinsky, MD, Carolyn Ault, RN, Tony Turvey, MPH, Philip R. Liebson, MD, and Joanne Sandelski, RDMS; Cardiac Centers of Louisiana, LLC: Jalal Ghali, MD, Tommy Brown, MD, James Smith, MD, and Lela Parks, RN; and Mitsubishi Chemical America: David Katz, PhD, and Connie Colonnese, RN.

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References

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