Impact of Progression of Diastolic Dysfunction on Mortality in Patients With Normal Ejection Fraction

Wael AlJaroudi, MD; M. Chadi Alraies, MD; Carmel Halley, MD; Leonardo Rodriguez, MD; Richard A. Grimm, DO; James D. Thomas, MD; Wael A. Jaber, MD

Background—Diastolic dysfunction is an independent predictor of mortality in patients with normal left ventricular ejection fraction. There are limited data, however, on whether worsening of diastolic function is associated with worse prognosis.

Methods and Results—We reviewed clinical records and echocardiograms of consecutive patients who had baseline echocardiograms between January 1, 2005, and December 31, 2009, that showed left ventricular ejection fraction ≥55% and who subsequently had a follow-up echocardiogram within 6 to 24 months. Diastolic function was labeled as normal, mild, moderate, or severe dysfunction. All-cause mortality was determined by use of the Social Security Death Index. Kaplan-Meier survival analysis and Cox regression analysis with a proportional hazard model were performed to assess outcomes. A total of 1065 outpatients were identified (mean±SD age, 67.9±13.9 years; 58% male). Baseline diastolic dysfunction was present in 770 patients (72.3%), with mild being the most prevalent. On follow-up testing (mean±SD, 1.1±0.4 years), 783 patients (73%) had stable, 168 (16%) had worsening, and 114 (11%) had improved baseline diastolic function. Eighty-eight patients (8.3%) had a decrease in left ventricular ejection fraction to <55% and were more likely to have advanced diastolic dysfunction (P=0.002). After a mean±SD follow-up (from the second study) of 1.6±0.8 years, 142 patients (13%) died. On multivariate analysis, a decrease in left ventricular ejection fraction to <55% and any worsening of diastolic function were independently associated with increased risk of mortality (hazard ratio, 1.78; 95% confidence interval, 1.10–2.85; P=0.02; and hazard ratio, 1.78; 95% confidence interval, 1.21–2.59; P=0.003, respectively).

Conclusion—In patients with normal baseline left ventricular ejection fraction, worsening of diastolic function is an independent predictor of mortality. (Circulation. 2012;125:782-788.)

Key Words: mortality ■ outpatients ■ diastole ■ progression

The assessment of diastolic function is required for a full and detailed examination of the heart by echocardiography.1,2 Diastolic dysfunction (DD) is believed to be associated with congestive heart failure symptoms in patients with preserved left ventricular ejection fraction (LVEF)3,4 and has recently been shown in the largest single-center study (≈36 000 outpatients with normal LVEF) to be an independent predictor of all-cause mortality.5 When present, it is graded as mild (impaired relaxation), moderate (pseudonormal), or severe (restrictive filling).2 The more advanced the stage is, the higher the filling pressures are6–8 and the worse the outcomes are.5 Furthermore, these stages have been shown to vary dynamically with passage from 1 stage to the next on repeat echocardiogram (mean follow-up time ≥4 years)9,10 and were associated with the development of heart failure.10 There are limited data, however, on the association of progression of DD and mortality. The only study to date (n=184) showed that the improvement in diastolic function was associated with better survival (P=0.05) in a mixed cohort of inpatients and outpatients with normal or mild systolic dysfunction.9

Editorial see p 743
Clinical Perspective on p 788

The aim of this study was to evaluate whether the progression of diastolic function is associated with increased mortality in a large cohort of outpatients with normal baseline LVEF.

Methods

Study Design

The study cohort consisted of consecutive patients who underwent an outpatient echocardiogram test with LVEF ≥55% at the Cleveland Clinic or its satellite facilities between January 1, 2005, and December 31, 2009, and who had a follow-up outpatient echocardiogram 6 to 24 months after the first echocardiogram. We excluded...
patients with prior mitral valve surgery, severe valvular stenosis, or regurgitation; those who lacked a valid US Social Security Number; and those in whom diastolic function was not reported. The inability to assess diastolic function was common in certain clinical scenarios such as in patients with tachycardia, atrial fibrillation, or poor acoustic window and in limited echocardiograms performed on an urgent basis.

During the study period, 1065 patients were included from a total of 3223 patients who underwent 2 consecutive echocardiographic tests (Figure 1). The survival rate of patients who were excluded for reasons other than an unavailable Social Security Number was not different from that of patients included in the study (log-rank \( P = 0.09 \)).

**Echocardiographic Methods**

Patients were imaged in the left lateral decubitus position with commercially available systems (Philips Electronics, Andover, MA; Sequoia, Siemens, Mountain View, CA; GE Medical Systems, Milwaukee, WI). Diastolic function was assessed in our institution in a standardized method and in accordance with the published and relevant guidelines by use of a combination of echocardiographic variables (transmitral inflow pattern, mitral annular velocities with tissue Doppler imaging, and pulmonary venous flow pattern). In patients with atrial fibrillation, if diastolic function was assessed, it was based on deceleration time of mitral E-wave velocity and tissue Doppler imaging (ie, peak early mitral inflow velocity/diastolic early tissue velocity \( E/e' \)).

Diastolic function was then labeled as normal or abnormal (DD). DD was then categorized as mild (grade 1, impaired relaxation), moderate (grade 2, pseudonormal), or severe (grade 3, restrictive). There were only 2 patients with severe DD at baseline (0.2%) and 4 at follow-up (0.4%); therefore, patients with grade 2 and 3 were grouped together. LVEF was assessed by quantitative and/or visual endocardial border detection and end-systolic volume (if tissue Doppler imaging was used). Both DD and LVEF were interpreted by an experienced, board-certified reader in accordance with published and relevant guidelines by use of a combination of echocardiographic variables (transmitral inflow pattern, mitral annular velocities with tissue Doppler imaging, and pulmonary venous flow pattern). The interobserver agreement of reproducibility and DD classification was based on deceleration time of mitral E-wave velocity and tissue Doppler imaging, and pulmonary venous flow pattern. In patients with atrial fibrillation, if diastolic function was assessed, it was based on deceleration time of mitral E-wave velocity and tissue Doppler imaging (ie, peak early mitral inflow velocity/diastolic early tissue velocity \( E/e' \)).

Diastolic function was then labeled as normal or abnormal (DD). DD was then categorized as mild (grade 1, impaired relaxation), moderate (grade 2, pseudonormal), or severe (grade 3, restrictive). There were only 2 patients with severe DD at baseline (0.2%) and 4 at follow-up (0.4%); therefore, patients with grade 2 and 3 were grouped together. LVEF was assessed by quantitative and/or visual endocardial border detection and end-systolic volume (if tissue Doppler imaging was used). Both DD and LVEF were interpreted by an experienced, board-certified reader.

The interobserver agreement of reproducibility and DD classification extrapolated from our ongoing quality assurance effort was on average 83%, and the intraobserver agreement was 94%.

**Clinical Data**

Clinical data were obtained from review of the electronic medical records from a period starting 6 months before the first echocardiographic testing and ending 6 months after the second one. The clinical diagnosis of conditions, including coronary artery disease, peripheral vascular disease, diabetes mellitus, hypertension, atrial fibrillation, congestive heart failure, dyslipidemia, chronic obstructive pulmonary disease, and chronic renal insufficiency, was established by reviewing records documented by a healthcare provider in an electronic medical record system (EpicCare, Epic Systems Corp, Madison, WI) and was retrieved for analysis. All-cause mortality was obtained from the Social Security Death Index with previously reported high specificity. The censoring date was June 1, 2011. The study was approved by the Cleveland Clinic institutional review board with waiver of consent.

**Statistical Analysis**

Continuous variables were expressed as mean ± SD and compared by use of the unpaired Student \( t \) test or Wilcoxon rank test as appropriate. Categorical variables were expressed as percentages and compared by use of the Fisher exact test or \( \chi^2 \) test as appropriate. The indications for echocardiographic testing (baseline and follow-up) were compared by use of the Cohen \( \kappa \) statistics. Comparisons between categorical variables at examinations 1 and 2 were made with the McNemar test; continuous variables were compared by use of the Paired \( t \) test. For survival analyses, Kaplan-Meier curves were generated and compared by use of the log-rank test. Survival analyses treated the time of the second echocardiogram as time 0 and analyzed survival after the second echocardiogram. The effect of diastolic function and its progression on outcomes was investigated with Cox regression analysis with a proportional hazards model. The variables entered into the model were age, sex, race, diabetes mellitus, hypertension, dyslipidemia, smoking, atrial fibrillation, peripheral vascular disease, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, chronic renal insufficiency, and EF. Baseline diastolic function and its progression were forced into the final model. We also reran the model and used diastolic function at follow-up instead of baseline diastolic function. Variables with collinearity were entered into the model one at a time. Stepwise forward selection was used to create the final model. All statistical tests were 2 sided. A value of \( P < 0.05 \) was set a priori and considered statistically significant. All statistical analyses were performed with the Statistical Package for Social Sciences version 11.5 for Windows (SPSS, Chicago, IL).

**Results**

**Clinical Data**

A total of 1065 outpatients were identified (mean ± SD age, 67.9 ± 13.9 years; mean LVEF, 59%; 58% male). Clinical characteristics and medications are summarized in Tables 1 and 2. Established cardiovascular disease such as coronary artery disease, prior revascularization, and congestive heart failure symptoms were not uncommon, prevalent in 27%, 12%, and 15% of the cohort, respectively. The 3 most common indications for baseline testing included symptom evaluation (44%) and valvular (37%) and ventricular (14%) function. Similarly,
the indications for follow-up testing were comparable with a high agreement rate ($\kappa=0.99$).

**Diastolic Function at Baseline and Follow-Up**

The echocardiographic parameters at baseline and follow-up are presented in Table 3. Of the 290 patients who had normal diastolic function, 260 (88%) had no significant valvular disease and were labeled as having a normal echocardiogram. Baseline DD was present in 770 patients (72.3%), with mild being the most prevalent (64.9%) and moderate or severe DD in only 7.4%. DD was associated with increasing age and hypertension (Table 1). There was no significant change in medications at baseline and follow-up (Table 2). On follow-up echocardiographic testing (mean ± SD, 1.1 ± 0.4 years), 783 patients (73%) had stable, 168 (16%) had worsening, and 114 (11%) had improved baseline diastolic function (100 patients by 1 grade and 14 by 2 grades; Figure 2). The change in diastolic function did not differ by race ($P=0.3$) or sex ($P=0.4$). Furthermore, 88 patients (8.3%) had a decrease in LVEF to <55% (mean LVEF, 46%) on follow-up testing; of those patients, 60 had stable, 19 had worsening, and 9 had improved diastolic function ($P=0.3$). Patients with a decrease in LVEF to <55% were more likely to have advanced DD: 14 (5.3%) had normal diastolic function, 56 (8.1%) had mild DD, and 18 (16%) had moderate/severe DD ($P=0.002$).
Diastolic Dysfunction Progression and Mortality

### Table 3. Echocardiographic Parameters at Baseline and Follow-Up (n=1065)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Examination 1</th>
<th>Examination 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF ≥55%, n (%)</td>
<td>1065 (100)</td>
<td>977 (92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF, mean (SD), %</td>
<td>59.1 (4.3)</td>
<td>58.1 (5.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV dimensions*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDD/height, mean (SD), mm/m</td>
<td>26.3 (5.3)</td>
<td>26.5 (6.0)</td>
<td>0.10</td>
</tr>
<tr>
<td>LVESD/height, mean (SD), mm/m</td>
<td>16.7 (4.4)</td>
<td>17.1 (4.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>LVEDVI, mL/m²</td>
<td>60.3 (25)</td>
<td>60.5 (24)</td>
<td>0.10</td>
</tr>
<tr>
<td>LVESVI, mL/m²</td>
<td>24.2 (12)</td>
<td>25.7 (13)</td>
<td>0.0075</td>
</tr>
<tr>
<td>Left atrium area, cm²</td>
<td>18.8 (4.6)</td>
<td>19.0 (4.9)</td>
<td>0.11</td>
</tr>
<tr>
<td>Ventricular filling, mean (SD)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E, m/s</td>
<td>0.87 (0.31)</td>
<td>0.92 (0.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/A</td>
<td>1.05 (0.53)</td>
<td>1.19 (0.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deceleration time, ms</td>
<td>201 (43)</td>
<td>227 (56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>e', m/s</td>
<td>0.10 (0.06)</td>
<td>0.09 (0.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/e</td>
<td>8.8 (4.4)</td>
<td>10.2 (6.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estimated PASP, mm Hg</td>
<td>33.4 (10.8)</td>
<td>33.9 (12.6)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Valvular heart disease, n (%)‡

- Moderate mitral stenosis: 1 (0.09) vs 0 (0.00); 1.0
- Moderate mitral regurgitation: 60 (5.6) vs 54 (5.1); 0.26
- Moderate tricuspid regurgitation: 45 (4.2) vs 63 (5.9); 0.06
- Moderate aortic stenosis: 1 (0.09) vs 2 (0.18); 1.0
- Moderate aortic regurgitation: 41 (3.8) vs 42 (3.9); 1.0
- Moderate pulmonary insufficiency: 8 (0.75) vs 13 (1.2); 0.18

LV indicates left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; and PASP, pulmonary artery systolic pressure.

*Measured in 947 and 970 patients at examinations 1 and 2, respectively, for LVEDD/height and LVESD/height; in 767 and 771 for LVEDVI; in 663 and 669 for LVESVI; and in 976 and 955 for left atrial areas.

†Measured in 631 and 628 patients at examinations 1 and 2, respectively, for E and E/A; in 846 and 710 for deceleration time; in 320 and 636 for e'; in 317 and 625 for E/e'; and in 623 and 681 for PASP.

‡Patients with more than moderate stenosis or regurgitation were excluded from the study.

### Discussion

To the best of our knowledge, this is the largest study to assess the association of progression of diastolic function and mortality in outpatients with normal baseline LVEF. Worsening of diastolic function and a decrease in LVEF to <55% were independently associated with increased risk of mortality.

#### Prevalence and Progression of Diastolic Function

Our study shows that DD not only is quite prevalent among outpatients with normal LVEF, similar to recently published data, but also is dynamic. Although a recent study showed that 32% of patients had a change in diastolic function after a mean ± SD follow-up of 4 ± 0.3 years, the present study showed that similar changes in diastolic function occur much sooner (mean ± SD follow-up, 1.1 ± 0.4 years; Figure 2). Such progression of DD has recently been shown by Kane et al to be associated with an increase in cumulative heart failure incidence during 6.3 ± 2.3 years of follow-up after the second echocardiogram (2.6% for patients whose diastolic function remained normal or normalized, 7.8% for patients who had persistent or progression to mild DD, and 12.2% for patients with persistent or progression to moderate/severe DD; P < 0.001). However, in that article, a link between progression of DD and total mortality was not investigated. Another decrease in LVEF to <55% and any worsening of diastolic function were independently associated with increased risk of mortality (hazard ratio [HR], 1.78; 95% confidence interval [CI], 1.10–2.85; P = 0.02; and HR, 1.78; 95% CI, 1.21–2.59; P = 0.003, respectively). Similarly, worsening of diastolic function from normal to abnormal and from mild to moderate or severe DD was associated with an increase in mortality (HR, 3.58; 95% CI, 1.71–7.53; P = 0.001; and HR, 2.13; 95% CI, 1.19–3.83; P = 0.01, respectively; Table 4).

### Outcomes

After a mean ± SD follow-up (from the second study) of 1.6 ± 0.8 years, 142 patients (13%) died: 20 (7.6%) with normal diastolic function, 102 (14.8%) with mild (grade 1) DD, and 20 (17.9%) with at least moderate DD (unadjusted mortality; log-rank P = 0.01; Figure 3). Worsening of diastolic function was associated with increased mortality compared with those who had no change or an improvement in diastolic function (unadjusted mortality, 21% versus 12%; log-rank P = 0.001; Figure 4). Patients who had improved diastolic function had a mortality similar to that of patients without change (11.4% versus 11.8%; P = 0.88); however, those who had improvement in DD by ≥2 grades (n = 14) had lower mortality compared with those with 1 grade improvement (n = 100), but the difference was not statistically significant (7% versus 12%; P = 0.59). After multivariate analysis, a
study showed a higher progression rate of diastolic function (48% of patients) in a smaller cohort (n=184) and after a mean follow-up of 3.6 years. However, there were several important differences in and limitations of that study: (1) Patients with baseline normal diastolic function were excluded; (2) the study included echocardiograms performed on inpatients who might have different loading conditions every day and more aggressive day-to-day titration of medications, particularly those admitted with congestive heart failure, and that can influence diastolic function; (3) the cutoff EF was 45%, and many patients had mildly reduced systolic function, although the actual number or percentage of these patients was not disclosed; and most important (4) tissue Doppler imaging was not used to assess diastolic function.

In addition, our study shows that 11% of patients with baseline DD (84 of 770) return to normal diastolic function on follow-up echocardiogram (Figure 2). Although the reason is not well known, it could perhaps be related to medication, diuresis, and treatment of risk factors. Although Achong et al did not report any improvement in diastolic function back to normal, probably because that subgroup was excluded from the start, a recent study confirmed that diastolic function may indeed return to normal in up to 27% of patients (70 of 252) after a long follow-up period.

Furthermore, although previous articles focused on analyzing diastolic progression in predominantly white populations, our study was more reflective of the current demographic nature of the US population and had a large representation of blacks, Hispanics, and Asians.

Traditional risk factors such as age, hypertension, diabetes, obesity, and fluid overload with elevated filling pressures...
have been associated with worsening diastolic function.\textsuperscript{5,8} Hence, aggressive risk factor modification, particularly blood pressure control, weight loss, and exercise, and salt restriction, are important steps that might halt diastolic progression.

### Mortality

The presence of DD has been shown to be an independent predictor of all-cause mortality.\textsuperscript{5} In our study, 142 patients (13\%) died (7.6\% with normal diastolic function, 14.8\% with mild DD, 17.9\% with moderate or severe DD; \(P=0.01;\) Figure 3). All-cause mortality, however, was strikingly higher than previously reported in patients with normal LVEF (13\% and a follow-up time of 1.6±0.8 years versus 16\% and follow-up time of 6.2±2.3 years\textsuperscript{5}). Although both studies consisted of outpatients with normal LVEF, our cohort had patients with more prevalent cardiovascular risk factors and disease (Table 1).

In addition, 8.3\% of patients had a decrease in LVEF to <55\% and were more likely to have advanced DD (\(P=0.002\)), but there was no difference when stratified by the change in diastolic function (\(P=0.3\)). An abnormal LVEF on follow-up echocardiogram, however, was an independent predictor of mortality (HR, 1.78; 95\% CI, 1.10–2.85; \(P=0.02\)). Similarly, any worsening of diastolic function was also an independent predictor of death even after adjustment for change in EF and diastolic function (whether obtained at baseline or at follow-up; HR, 1.78; 95\% CI, 1.21–2.59; \(P=0.003;\) Table 4). Those with stable or improved diastolic function, however, had similar good outcomes (overlapping survival curves; Figure 3). In the only other study, Achong et al\textsuperscript{5} showed that improvement of diastolic function was associated with better outcome (\(P=0.05\)); however, HRs were not calculated, patients with normal baseline diastolic function were excluded, inpatients and those with mild systolic dysfunction were included, and tissue Doppler imaging was not used to assess DD.

### Limitations

The study has several limitations. It is a retrospective study from a single tertiary center. The readers were unblinded to the medical history of patients and had access to their previous echocardiograms. In addition, a normal systolic function and LVEF ≥55\% are not synonymous, although they are used interchangeably in clinical practice. There was no systematic review of the echocardiograms to reassess diastolic function; rather, the data were extracted from prior reads, which is comparable to what is done in clinical practice. There is always potential error in interpreting diastolic function, particularly in distinguishing normal and pseudonormal. Although left atrial indexed volumes are necessary for complete evaluation of diastolic function, the data were not available for most patients but rather only the left atrial area. However, tissue Doppler imaging was available at the time of the read and used in addition to other echocardiographic variables in most studies, hence minimizing potential error. In addition, there were only 2 patients (0.2\%) with severe DD at baseline; thus, they were grouped with those with moderate DD. This low percentage, however, is not unusual in this cohort of patients and was similarly found in another study (127 of 36 261, 0.35\%).\textsuperscript{5} Although all-cause mortality is an objective and nonbiased primary outcome in our study, other outcomes such as cardiac death or hospitalization for heart failure were not assessed. Furthermore, clinical data were recorded between 6 months before the first test and 6 months after the second test. Hence, relevant clinical information or changes beyond this time interval were not captured. Finally, other unmeasured or unobserved variables, including malignancy and adherence and compliance to medical therapy, were not accounted for.

### Conclusion

In outpatients with preserved LVEF at the baseline echocardiogram, worsening of diastolic function on a follow-up study is an independent predictor of all-cause mortality.

### Disclosures

None.

### References

Diastolic dysfunction is an independent predictor of mortality in patients with normal ejection fraction. Diastolic function, whether normal or abnormal (stage 1, 2, or 3), varies dynamically and can pass from 1 stage to the other and in either direction. Although worsening of diastolic function has been associated with the development of congestive heart failure, there have been limited data on mortality with this progression. The present study showed that worsening of diastolic function in outpatients with normal ejection fraction (n=1065; age, 69±13 years) was associated with increased risk of death (hazard ratio, 1.78; 95% confidence interval, 1.21–2.59; P=0.003) independently of baseline or current diastolic function. This hazard ratio was equivalent to that from worsening of systolic function in the same population. Furthermore, progression from normal to abnormal diastolic function and from stage 1 to 2 or 3 diastolic dysfunction was associated with increased mortality (hazard ratio, 3.58; 95% confidence interval, 1.71–7.53; P=0.0001; and hazard ratio, 2.13; 95% confidence interval, 1.19–3.83; P=0.01, respectively). Given the present findings, it is important for clinicians not only to recognize the importance of progression of diastolic function for their patients but also to promote aggressive risk factor modifications, particularly blood pressure control, weight loss, exercise, and salt restriction; these risk factors have traditionally been associated with worsening of diastolic function.
Impact of Progression of Diastolic Dysfunction on Mortality in Patients With Normal Ejection Fraction

Wael AlJaroudi, M. Chadi Alraies, Carmel Halley, Leonardo Rodriguez, Richard A. Grimm, James D. Thomas and Wael A. Jaber

_Circulation_. 2012;125:782-788; originally published online January 18, 2012; doi: 10.1161/CIRCULATIONAHA.111.066423

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/125/6/782