Mortality Rate in Patients With Diastolic Dysfunction and Normal Systolic Function

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Background: Diastolic dysfunction (DD) is known to be associated with increased mortality rate in the presence of impaired systolic function. However, few prognostic data exist regarding the effect of DD in patients with normal systolic function.

Methods: We reviewed clinical records and echocardiographic findings of consecutive patients who underwent an outpatient echocardiogram that revealed normal systolic function (ejection fraction, ≥55%) from January 1, 1996, through December 31, 2005. Diastolic function was graded using echocardiographic Doppler variables designated as normal, mild (grade I, ie, impaired relaxation pattern), moderate (grade II, ie, pseudonormal pattern), or severe (grade III, ie, restrictive filling pattern) dysfunction. Propensity analysis was performed to compare outcomes among the groups.

Results: A total of 36,261 patients were identified (mean [SD] age, 58.3 [15.4] years; 54.4% female) with a mean (SD) follow-up time of 6.2 (2.3) years. In 65.2% of the cohort, DD was present, with mild DD being the most prevalent type of dysfunction. A total of 5789 deaths occurred during the follow-up period. The unadjusted survival rate was worse according to the presence and degree of DD (P < .001). However, after propensity matching, only moderate and severe DD were associated with an increased mortality risk (hazard ratio, 1.58; 95% confidence interval, 1.20-2.08; and hazard ratio, 1.84; 1.29-2.62, respectively; P < .001 for each).

Conclusions: In this single-center study of patients with normal ejection fraction who presented for outpatient echocardiography, the presence of moderate or severe DD was an independent predictor of mortality. Mild DD, although prevalent, did not affect survival rate.

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See Invited Commentary at end of article.
assessed, or if severe mitral valve disease was present or prior mitral valve surgery had occurred. Inability to assess diastolic function was common in certain clinical scenarios such as in patients with tachycardia, patients with severe lung disease with limited acoustic windows for echocardiographic testing, and patients in whom echocardiographic testing was performed on an urgent basis. If a patient had undergone more than 1 study, only results from the first was included in the analysis.

During the study period, 36,261 patients were included from a total of 65,696 echocardiographic tests performed (Figure 1). The survival rate of patients who were excluded for reasons other than an unavailable US Social Security Number was not different from that of patients who were included (log-rank $P=.20$).

**Echocardiographic Methods**

Diastolic function was assessed in a standard manner at our institution in accordance with relevant guidelines by using a combination of echocardiographic variables, including transmural inflow pattern, pulmonary venous flow pattern, and, beginning in the late 1990s and almost uniformly after 2001, mitral annular velocities as assessed by tissue Doppler imaging. In patients with atrial fibrillation, diastolic stage was assessed when possible using a combination of variables, including transmural inflow pattern (ie, deceleration time of mitral $E$ wave velocity) and tissue Doppler imaging (ie, peak early mitral inflow velocity/diastolic early tissue velocity [E/e]).

With the use of these variables, function was deemed normal or abnormal in the study population. Then DD was graded in a standard manner as being mild (grade I, ie, impaired relaxation pattern), moderate (grade II, ie, pseudonormal pattern), or severe (grade III, ie, restrictive filling pattern) dysfunction, as previously described. Mild DD is typified by abnormal myocardial relaxation with normal left atrial pressures. In moderate and severe DD, increases in mean left atrial pressures occur in addition to impairment of left ventricular relaxation and compliance. Systolic function was assessed by a semiquantitative evaluation of ejection fraction by an experienced reader (among them, W.A.J. and J.D.T.), in accordance with published guidelines.

The interobserver agreement for reproducibility of DD classification extrapolated from our ongoing quality assurance effort was, on average, 83.0% and intraobserver agreement was 94.0%.

**Clinical Data**

Clinical data were obtained from review of electronic medical records recorded from a period starting 6 months before the echocardiographic testing date and ending 6 months afterward. The clinical diagnosis of conditions, including coronary artery disease, peripheral vascular disease, atrial fibrillation, diabetes mellitus, hypertension, congestive heart failure (CHF), dyslipidemia, chronic obstructive pulmonary disease, and chronic renal failure, was established by reviewing records documented by a providing physician in an electronic medical record system (EpicCare; Epic Systems Corporation, Madison, Wisconsin) that was then linked to relevant International Classification of Diseases, Ninth Revision (ICD-9) codes (eTable; http://www.archinternmed.com). All diagnoses (primary and nonprimary) and encounters (inpatient and outpatient) were considered, and only 1 code was required to fulfill the criteria for a given diagnosis. Individual all-cause mortality was obtained using the Social Security Death Index with a previously reported high degree of specificity. The censoring date was December 14, 2009. The study was conducted with the approval of the Cleveland Clinic institutional board review with waiver of consent.

**Statistical Analyses**

Continuous data are expressed as mean (SD), with median and 15th and 85th percentile values (comparable to 1 SD). Kruskal-Wallis tests were used to analyze group differences for the continuous data. Categorical data are displayed as frequencies and percentages, and comparisons are made using $\chi^2$ tests and Fisher exact tests if appropriate.

Several factors differentiated the patients in the 4 groups. To evaluate survival with more comparable patients among the diastolic stages, we used propensity matching. Multivariable logistic regression analyses were used to determine factors related to severe DD compared with each of the other groups. For continuous variables, investigations of transformations of scale were used (log, inverse, and exponential) to properly calibrate the effects with outcome. Because of imbalance in group sizes, a model was developed for each stage vs the 127 patients with severe DD. The logistic models yielded a propensity score for inclusion in the severe DD group. Using the propensity scores, many-to-1 matching was used to find the maximum number of matches of the 127 severe DD cases for each comparison group using greedy matching of closest matches within a maximum distance of 0.1.

After matching, data from patients were sorted based on propensity scores and divided into quintiles. Characteristics were evaluated to ensure balanced factors in the groups within similar propensity score ranges. Propensity matching was performed using the variables listed in Table 1. The propensity models incorporated each of the variables regardless of their significance.

Overall and stratified nonparametric survival estimates were obtained via the method created by Kaplan and Meier. A parametric method was used to resolve the number of phases of instantaneous risk for death (ie, hazard function) and to estimate the shaping variables.

The degree of DD as a single covariate was forced into the final parametric model for all patients and for the matched cohort of patients. Statistical analyses were performed using SAS statistical software, version 9 (SAS Institute Inc, Cary, North Carolina).
In 65.2% of the cohort, DD was present, with mild DD being the most prevalent type of dysfunction (60.0% mild DD, 4.8% moderate DD, and 0.4% severe DD). Patients with DD were more likely to be male, older than 65 years, and obese (body mass index [calculated as weight in kilograms divided by height in meters squared] > 30). They also were more likely to have cardiovascular risk factors and established cardiovascular disease (all P < .001) (Table 1). Although noncardiac chronic medical conditions such as chronic obstructive pulmonary disease and chronic renal failure were uncommon (3.1% and 1.5%, respectively), patients with these conditions also were more likely to have DD (P < .001 for each).

**MORTALITY AND DIASTOLIC FUNCTION**

During the follow-up period, 5789 deaths occurred: 842 in the normal diastolic function group (representing 7.0% of the patients with normal diastolic function), 4469 (21.0%) in the mild DD group, 429 (24.0%) in the moderate DD group, and 49 (39.0%) in the severe DD group. The unadjusted survival rate was worse in patients with DD, and this risk was greater with worsening degrees of DD (P < .001).

After propensity matching was performed, data from a resulting group of 1249 patients were used in subse-
quent analysis. Clinical characteristics of the matched patient population according to diastolic function stage are listed in Table 2.

Among the propensity-matched group, 379 deaths occurred during a mean (SD) follow-up of 6.2 (2.9) years. After matching, moderate and severe DD were associated with worse survival rate compared with normal diastolic function (log-rank \( P < .001 \)) (Figure 2), with 8-year survival estimates with normal diastolic function, mild DD, moderate DD, and severe DD of 78.0%, 72.0%, 68.0%, and 58.0%, respectively. The adjusted survival model is presented in Table 3. After matching, moderate and severe DD were associated with increased mortality (hazard ratio, 1.58; 95% confidence interval, 1.20-2.08; and hazard ratio, 1.84; 1.29-2.62, respectively; \( P < .001 \)). However, mild DD was not an independent predictor of mortality (hazard ratio, 1.11; 95% confidence interval, 0.85-1.47; \( P = .45 \)) (Table 3).
A high prevalence (65.0%) of DD was observed in our cohort with normal ejection fraction who presented for outpatient echocardiographic testing. Although DD was associated with the presence of cardiovascular risk factors and cardiovascular disease, the overall prevalence of established disease and particularly CHF was low. Unadjusted survival was worse according to the presence and degree of DD, but after propensity matching, only moderate and severe DD were independent predictors of mortality. For the first time, to our knowledge, moderate and severe DD have been shown to be independent predictors of mortality rate, although mild DD has not shown this characteristic after adjusting for common cardiovascular risk factors and existing comorbidities in a large cohort of outpatients with normal ejection fraction. This finding has important clinical implications, especially given the high prevalence of mild DD in the population studied.

Because the link between DD and mortality rate in impaired systolic function is well established, we sought to study the prevalence and outcome of DD specifically in a cohort with a normal ejection fraction. We chose to include patients with CHF because the precise underlying pathophysiologic cause of heart failure with preserved ejection fraction is still debated, and abnormalities in these patients include abnormal left ventricular systolic properties; ventricular-arterial coupling; left ventricular diastolic function, torsion, or twist; ventricular-ventricular interaction; pericardial constraint with impaired chronotropic vasodilator reserves; and pulmonary hypertension. Furthermore, in a recent study of patients with normal systolic function and moderate or severe DD, the rate of progression to clinical heart failure for 2 years was low, although a moderate rate of progression in the development of symptoms and cardiac hospitalizations occurred.

In fact, in our cohort, the prevalence of CHF and therefore of heart failure with preserved ejection fraction was low, as was the prevalence of other cardiac diseases. Therefore, because the overall prevalence of DD was high, most patients who presented for outpatient echocardiographic testing in our institution had, by definition, preclinical DD. Because the use of echocardiography as a clinical tool in the outpatient setting continues to increase, with an estimated 9 million echocardiographic tests performed in 2004 in the US Medicare system, our study provides the physician with a prognostic context when DD is reported, especially because most procedures are requested by noncardiologists.

Prior studies have demonstrated increased mortality from DD in patients with normal systolic function but have varied in characterizing the degree of risk according to the stage of DD. A large community cohort demonstrated increased mortality associated with mild, moderate, and severe DD independent of age, ejection fraction, and sex but without adjustment for other comorbidities. However, in a cohort of 3008 middle-aged or elderly American Indian men (ie, the second Strong Heart Study), although mild DD was associated with an increase in all-cause and cardiac mortality, this increase was not independent of other comorbidities. A recent cohort study of 735 patients with an ejection fraction greater than 45% found that severe DD was an independent predictor of mortality in addition to age, hyperlipidemia, and the presence of a comorbid illness. All these studies had a DD prevalence of less than 30%, in contrast to the current study. In addition, women were underrepresented in some studies. Our study overcame some of the limitations of preceding studies by including a large sex-balanced population with representation and targeted analysis of all stages of DD and a true normal ejection fraction (≥55%). In this setting, we identified moderate and severe DD as independent predictors of worse survival rate. Contrary to the largest study to date, mild DD was not associated with increased mortality rate.

The potential mechanisms by which moderate and severe DD independently confer mortality risk require further study to identify whether a targeted therapeutic approach directed at DD can be found. However, our results suggest that an increased awareness of the clinical significance of advanced DD may lead to earlier identification of those patients who are at risk, especially at a preclinical stage.

Limited data exist regarding the natural history of DD and specifically regarding whether progression among stages exists over time. One study has demonstrated that in patients with DD and ejection fractions greater than 45%, the condition of approximately half of patients remained stable, 21% displayed improvement, and 27% deteriorated clinically during a follow-up of 3.6 years. A mortality benefit was observed in those whose DD improved compared with those whose DD remained the same or had deteriorated clinically. Further investigation is warranted to understand the natural history of DD and the factors that affect progression.

Our study had several limitations. It is a retrospective study from a single institution. Also, the assessment of diastolic function using Doppler echocardiographic testing is performed in a standard manner in our institution, but the use of tissue Doppler to assess mitral annular velocities only began in the late 1990s. Individual patient histories were unmasked to the reader when interpreting the echocardiographic results. Systolic function was assessed using the ejection fraction, which is an imperfect but universally understood variable used in a manner consistent with those of prior studies of diastolic dysfunction. The outcome studied was all-cause mortality, which is clinically relevant, objective, and nonbiased compared with cardiac-specific causes of death, but we do not report clinical events before death.

We recorded clinical data from a period starting 6 months before the echocardiographic testing date and ending 6 months afterward, thus representing only a brief period. Therefore, relevant clinical diagnoses before or after the interval and subsequent changes in medical regimens were not captured. Furthermore, clinical data were obtained by review of electronic medical records and linking to relevant ICD-9 codes, which can have limited sensitivity. The propensity matching did not include certain unmeasured variables or unobserved variables, such
as history of cancer and severity of native valve disease; therefore, potential confounding by these variables cannot be excluded.

In a single-center cohort of patients with normal ejection fraction referred for outpatient echocardiographic testing for a variety of indications, DD, especially mild DD, was highly prevalent. After adjustment for a number of cardiac and noncardiac comorbidities, moderate and severe DD were independent predictors of mortality during follow-up but mild DD was not. Further studies are required to identify the precise mechanistic linkage between advanced DD and mortality rate.

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Online-Only Material: The Table is available at http://www.archinternmed.com.

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