Echocardiographic Determinants of Mortality in Patients >67 Years of Age With Chronic Heart Failure

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This study sought to assess the prognostic significance of echocardiographic measurements of left and right ventricular dimensions and function in patients >67 years of age with chronic congestive heart failure (CHF). This is a retrospective follow-up of elderly patients who underwent an echocardiography in the tertiary cardiac center. A total of 185 patients (131 men) aged ≥68 years (mean ± SD 75 ± 5) with CHF were enrolled into the study. After undergoing a detailed echocardiographic examination, all patients were followed-up for a median of 20 months (interquartile range 9 to 36). During the follow-up period 54 patients (29%) died. Left ventricular (LV) M-mode isovolumic relaxation time (IVRT), end-diastolic and end-systolic diameters, fractional shortening and mass, transmitral E:A ratio, and left atrial dimension, as well as New York Heart Association class and the age were found by Cox proportional-hazards univariate analyses to predict the outcome in these patients (all p <0.05). In multivariate analyses including these measurements, LV IVRT (p <0.04), age (p <0.03), and New York Heart Association class (p <0.001) were found to be the independent predictors of outcome. In the Kaplan-Meier analysis, patients with LV IVRT >30 ms had a better prognosis at 3 years (cumulative survival 78% [95% confidence interval 65% to 91%]) than those with LV IVRT ≤30 ms [survival 52% [95% confidence interval 37% to 68%]]. Measurements of LV performance, especially those obtained during diastole, are significantly related to prognosis in patients >67 years of age with CHF. LV M-mode IVRT is among the most important independent predictors of outcome in this population. ©2000 by Excerpta Medica, Inc.

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Although most cardiac diseases can affect left and right ventricles and left ventricular (LV) failure may secondarily impair right ventricular (RV) diastolic performance,1 there is little information about how RV abnormalities relate to prognosis in elderly patients with chronic congestive heart failure (CHF). This investigation assesses the prognostic value of echocardiographic measurements of LV and RV dimensions and function in patients >67 years of age with CHF, with emphasis on diastolic variables obtained by M-mode and Doppler echocardiography.

METHODS

Patients: The target population for this study was all elderly patients with CHF referred for echocardiographic examination as part of their routine assessment at the Royal Brompton Hospital between 1988 and 1998. A total of 185 consecutive patients were studied with no exclusions. We studied elderly patients from the age of ≥68 years, consistent with the definition of aging thresholds of the population.2,3 The diagnosis of heart failure was based on history, examination, electrocardiogram, chest radiograph, and echocardiographic findings. We took the European Society of Cardiology guidelines definition that the diagnosis of heart failure would be made if both of the following were present: symptoms compatible with a diagnosis of heart failure, mainly exertional breathlessness, and evidence of substantial impairment of LV systolic function or LV filling on Doppler echocardiography.4

Patient characteristics are listed in Table I. They ranged in age from 68 to 87 years (mean 75 ± 5). Twenty-eight patients were in New York Heart Association (NYHA) functional class I, 83 in class II, 51 in class III, and the remaining 23 were in class IV. Heart failure was of ischemic origin in 116 patients and of nonischemic origin in 69 patients. The presence of ischemic heart disease was shown by coronary arteriography or documented myocardial infarction. No patient had significant primary valvular disease, 149 patients were in sinus rhythm, and 52 patients had either left or right bundle branch block. The medical regimens of all the enrolled patients were optimized according to standard practice at the time of enrollment into the study and all were symptomatically stable. Standardized medications included digoxin, an angiotensin-converting enzyme inhibitor, diuretics,
calcium antagonists, nitrates, \( \beta \) blockers, and aspirin or warfarin in varying combinations (Table I).

**Study design:** This is a retrospective study of 185 elderly patients with CHF who had undergone a routine Doppler echocardiographic examination. The patients were followed up for a median of 20 months (interquartile range 9 to 36) in the heart failure outpatient clinic at the Royal Brompton Hospital, London. If follow-up did not occur in the hospital, survival information was obtained from the general practitioner or the patient’s local hospital. The study end point was all-cause mortality.

**Procedures:** Simultaneous Doppler and M-mode echocardiograms and phonocardiograms were recorded along with standard lead II of the electrocardiogram with the patient supine and in the left semi-lateral position. All patients were studied at rest and in quiet respiration.

Echocardiograms were recorded using a Hewlett-Packard Sonos 1500 echocardiograph (Andover, Massachusetts) with a 2.5-MHz transducer. The pattern of LV wall motion was assessed from standard left parasternal and apical views. Systolic and diastolic LV dimensions and septal and posterior wall thicknesses were measured from the M-mode echocardiograms of the LV minor axis obtained with the cursor by the tips of mitral valve leaflets using leading-edge methods. End-diastole was taken as the onset of the Q wave of the simultaneously recorded electrocardiogram, and end-systole as the onset of the aortic component of the second heart sound (A2) on the phonocardiogram. All echocardiographic recordings were obtained at a paper speed of 100 mm/s. LV mass was calculated using the Penn convention: LV mass = 1.04 \times (1.04 \times (EDD + PWT + VSTD) – EDD) – 13.6 g, where EDD = end-diastolic dimension; PWT = posterior wall thickness in diastole, and VSTD = ventricular septal thickness in diastole.

LV fractional shortening was estimated as the percent decrease in dimension during ejection with respect to end-diastolic dimension. LV M-mode isovolumic relaxation time (IVRT) was measured as the time interval from the A2 to the onset of mitral cusp separation on the mitral echogram. RV IVRT was measured as the time interval between P2 (the pulmonary component of the second heart sound) and onset of Doppler tricuspid forward flow. From the trans-mitral and transtricuspid pulsed-Doppler traces, peak early (E) and late (A) diastolic filling velocities were measured and the E/A ratio calculated. Mitral and tricuspid E-wave deceleration times were measured from the peaks of the E waves to their end.

Phonocardiograms were recorded from the right or left sternal edge, using the Cambridge Instrument Company microphone (Cambridge, United Kingdom), in the position where A2 was most obvious. The identity of A2 itself was checked against aortic valve closure artifact on pulsed Doppler, and its timing was taken as that of the onset of the first high-frequency component.

**Statistical analysis:** Univariate and multivariate Cox proportional-hazards regression analysis was used to identify variables predictive of outcomes. Survival curves were constructed using the Kaplan-Meier product limit survival curve method when patients were dichotomized by the median value of LV IVRT. For all tests, a p value <0.05 was considered statistically significant. Descriptive values are expressed as mean ± SD. Statistical analysis was performed using a standard statistical program package (StatView, version 4.5, Abacus Concepts Inc., Berkeley, California).

**RESULTS**

Table II summarizes the main echocardiographic measurements for all 185 patients with CHF at the time of enrollment. As shown, in the patient population as a whole, the left ventricle was modestly dilated (as indicated by end-diastolic diameter of 59 ± 13 mm and end-systolic diameter of 45 ± 16 mm), LV mass was increased (400 ± 200 g), and LV systolic function was slightly impaired, indicated by mean LV fractional shortening of 24 ± 14%. At the same time, 42 patients had a normal LV cavity size (i.e., the
The left atrium in the patient group as a whole was increased (46 mm) compared with the upper limit of the normal range of 42 mm in the slightly enlarged (46 mm) and normal systolic dimensions, as well as the age and NYHA class were found by Cox proportional-hazards univariate analyses to be significant predictors of the outcome in these patients (all p <0.05). In multivariate analysis (Table IV) including the age, NYHA class, left atrial dimension, and 6 LV echocardiographic measurements—namely end-diastolic and end-systolic dimensions, mass and fractional shortening, M-mode IVRT and E/A ratio—the NYHA class (p <0.001), age (p <0.03), and the LV M-mode IVRT (p <0.04) were found to be the most important independent predictors of outcome.

Technically satisfactory measurements of the LV M-mode IVRT were available in 144 patients; it ranged from 0 to 80 ms. Its duration was related neither to the presence of a complete left or right bundle branch block nor to the presence of a QRS complex on the electrocardiogram (r = -0.03, p = 0.75). Figure 1 shows survival Kaplan-Meier curves when the patients studied were dichotomized by the median value of LV IVRT of 30 ms. Patients with LV IVRT >30 ms (n = 65) had a better prognosis at 3 years (cumulative survival 78% [95% confidence interval 65% to 91%]) than those with LV IVRT ≤30 ms (n = 79, cumulative survival 52% [95% confidence interval 37% to 68%]).

**DISCUSSION**

Our main observation was to demonstrate that in addition to age and NYHA class, the most discriminating measurement in determining prognosis in older patients with CHF was LV M-mode IVRT. Other diastolic measurements, such as A-wave velocity, E-wave deceleration time, and E/A ratio had prognostic significance, but in the proportional-hazards regression model, these variables were no longer significant once the effects of IVRT had been allowed. Indeed, the same applied to end-diastolic and end-systolic dimensions, with only fractional shortening achieving borderline significance.

It is well established that measurements of LV diastolic function are age related. In particular, in normal patients, there is progressive prolongation of IVRT, and the proportion of the stroke volume entering the ventricle during early diastole decreases during atrial systole increases. Like many other diastolic measurements, IVRT is sensitive both to disturbances of diastolic function and to ventricular filling pressure. Abnormal prolongation of IVRT is evidence of abnormal relaxation, whereas values lower than normal are consistently seen when LV filling pressure is increased. The mean value of IVRT of 30 ms in the present study, compared with a normal of 70 to 80 ms is thus clear evidence that left atrial diastolic diameter was <55 mm) and normal systolic function (i.e., fractional shortening >29%).

Measurements of left- and right-sided filling and relaxation velocities in the entire group of patients indicated moderate LV and RV diastolic dysfunction in terms of a restrictive pattern: increased peak E-wave velocities (0.7 ± 0.3 for mitral and 0.4 ± 0.2 for tricuspid flow), and short left and right E-wave deceleration time (61 ± 21 and 60 ± 15 ms, respectively). The left atrium in the patient group as a whole was slightly enlarged (46 ± 9 mm) compared with the upper limit of the normal range of 42 mm in the elderly control population.6,7

During the median 20-month follow-up (interquartile range 9 to 36 months), 54 patients (29%) died. Of the 42 patients with normal LV cavity size and normal systolic function, 4 (10%) died. Of the remaining 143 patients, 50 (35%) died. The results of univariate Cox proportional-hazards regression analysis of studied echocardiographic variables, age, and NYHA class are presented in Table III. The values of LV end-diastolic and end-systolic dimensions, mass and fractional shortening, LV and RV IVRT, transmitral peak A-wave velocity, E/A ratio and E-wave deceleration time, and left atrial dimension, as well as the age and NYHA class were found by Cox proportional-hazards univariate analyses to be significant predictors of the outcome in these patients (all p <0.05). In multivariate analysis (Table IV) including the age, NYHA class, left atrial dimension, and 6 LV echocardiographic measurements—namely end-diastolic and end-systolic dimensions, mass and fractional shortening, M-mode IVRT and E/A ratio—the NYHA class (p <0.001), age (p <0.03), and the LV M-mode IVRT (p <0.04) were found to be the most important independent predictors of outcome.

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pressure was raised throughout the group, in line with the clinical diagnosis of heart failure. The limited prognosis of the patients' value of IVRT below the median value of 30 ms is thus likely to be related to a significantly raised ventricular filling pressure persisting despite standard medical treatment. The duration of IVRT has also been shown to have a powerful predictive effect of subsequent diastolic events, so that when it is short, E-wave velocity is likely to be increased, and E/A ratio high.\textsuperscript{11,12} Our results are thus in accord with previous results demonstrating that a restrictive ventricular filling pattern persisting with medical treatment is also a marker of poor prognosis\textsuperscript{13–15}, when directly compared with these measurements based on filling pattern, a short IVRT appears more discriminating.

Our measurements of IVRT were based on the interval from the onset of A2 on the phonocardiogram and confirmed by its coincidence with the aortic closure artifact on the Doppler, and with mitral cusp separation on the M-mode echocardiogram. This definition is in line with the original one by Wiggers.\textsuperscript{16} Importantly, there are significant discrepancies in timing between the timing of mitral cusp separation on the M-mode and that of the onset of transmitial flow from the Doppler.\textsuperscript{17} In normal subjects, the onset of transmitial flow at the level of the tips of the mitral cusps follows cusp separation by 20 to 30 ms, but in patients with dilated cardiomyopathy and functional mitral regurgitation, the discrepancy may amount to >100 ms.\textsuperscript{18} Because it is now recognized that the timing of the onset of flow is sensitive to the level of the sample volume within the ventricle,\textsuperscript{19} we elected to use the M-mode definition. It does not necessarily follow that estimates of IVRT based on Doppler will demonstrate the same discriminating value as those based on M mode.

**Clinical significance:** M-mode IVRT thus provides a simple measurement that is closely related to prognosis in elderly patients, more discriminating than measurements based on diastolic inflow patterns or activation disturbances. It is also independent of ventricular dimensions or shortening fraction, and so our results apply to patients with the combination of heart failure and normal cavity size. There is no general agreement as to whether this combination does, in fact, constitute a discrete clinical entity. Our results would suggest that this combination would have prognostic significance only when IVRT is short (i.e., in patients with increased filling pressures, and a dominant E wave on transmitral Doppler). Such patients thus conform to the clinical diagnosis of restrictive cardiomyopathy. By contrast, patients with normal cavity size, with IVRT prolonged, E-wave suppressed, and A-wave accentuated abnormally for age (i.e., those to whom the diagnosis of “diastolic heart failure” is usually applied) would seem to have a particularly good prognosis. However, our results do not indicate whether this combination can be the direct cause of significant limitation of exercise tolerance.