Independent and Incremental Prognostic Value of Doppler-Derived Mitral Deceleration Time of Early Filling in Both Symptomatic and Asymptomatic Patients With Left Ventricular Dysfunction

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Objectives. **This study sought to investigate the relative and incremental prognostic value of demographic, historical, clinical, echocardiographic and mitral Doppler variables in patients with left ventricular systolic dysfunction.**

Background. **The prognostic value of diastolic abnormalities as assessed by mitral Doppler echocardiography has yet to be defined.**

Method. **A total of 508 patients with left ventricular ejection fraction ≤35% were followed up for a mean (±SD) period of 29 ± 11 months.**

Results. **During the follow-up period, 148 patients (29.1%) were admitted to the hospital for congestive heart failure, and 100 patients (19.7%) died. By Cox model analysis, Doppler-derived mitral deceleration time of early filling ≤125 ms (relative risk [RR] 1.93, 95% confidence interval [CI] 1.4 to 3.7), New York Heart Association functional class III or IV (RR 1.49, 95% CI 1.4 to 2.3), ejection fraction ≤25% (RR 1.85, 95% CI 1.6 to 2.9), third heart sound (RR 2.06, 95% CI 1.8 to 3.2), age >60 years (RR 1.95, 95% CI 1.8 to 3.1) and left atrial area >18 cm^2 (RR 1.73, 95% CI 1.6 to 2.7) were all found to be independent and additional predictors of all-cause mortality, and deceleration time was the single best predictor (chi-square 37.80). When all these significant variables were analyzed in hierarchic order, after age, functional class, third sound, ejection fraction and left atrial area, deceleration time still added significant prognostic information (global chi-square from 9.2 to 104.7). Also, deceleration time was the strongest independent predictor of hospital admission for congestive heart failure (RR 4.88, 95% CI 3.7 to 6.9) and cumulative events (congestive heart failure or all-cause mortality, or both; RR 2.44, 95% CI 2.0 to 3.8) in both symptomatic and asymptomatic patients.**

Conclusions. **Deceleration time of early filling is a powerful independent predictor of poor prognosis in patients with left ventricular systolic dysfunction, whether symptomatic or asymptomatic. A short (≤125 ms) deceleration time by mitral Doppler echocardiography adds important prognostic information compared with other clinical, functional and echocardiographic variables.**

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During the past decade, several indicators have been established to predict poor prognosis in patients with left ventricular dysfunction and chronic heart failure, including age, etiology, left ventricular ejection fraction, functional class, exercise capacity, pulmonary arterial pressures and cardiac output (1–4). It has also been demonstrated that left ventricular diastolic dysfunction may contribute to signs and symptoms of several cardiovascular disorders, particularly during periods of clinical deterioration (5).

Doppler echocardiography has provided a rapid, repeatable, noninvasive method of assessing left ventricular filling in various cardiac diseases in which diastolic abnormalities have been observed, both with and without systolic dysfunction (6–9). Recently, the pathophysiology and clinical importance of the transmitral flow velocity pattern as assessed by Doppler echocardiography have been extensively investigated (6–16). It has been observed that the so-called restrictive transmitral flow pattern, characterized by a shortened isovolumic relaxation time and deceleration time of early filling, minimal filling during atrial systole and increased ratio of peak flow velocity in early to late diastole, is a common finding in more symptomatic patients with elevated filling pressure and may be related to advanced New York Heart Association functional class and poor exercise capacity (7–11,14–16). More recent studies have also indicated that Doppler-derived diastolic filling variables, specifically the restrictive filling pattern, may play an important role in predicting cardiac mortality in patients with cardiac amyloidosis (17), dilated cardiomyopathy (18–20) and conges-

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tive heart failure (21). However, there are some limitations concerning the available prognostic studies with mitral Doppler echocardiography that have so far blunted the clinical impact of these findings, for instance, the relatively small sample size of published studies and the highly selected nature of the patient populations. To date, a large-scale study based on a sample size sufficient to enable a conclusive definition of the prognostic value of diastolic abnormalities as assessed by Doppler echocardiography has not been performed. Furthermore, the incremental prognostic value of abnormal filling patterns has never been investigated.

Accordingly, the present study was designed to evaluate the capability of mitral Doppler echocardiography in the prognostic stratification of either symptomatic or asymptomatic patients with left ventricular systolic dysfunction. The relative and incremental prognostic value of demographic, historic, clinical, echocardiographic and mitral Doppler variables was also assessed.

Methods

Subjects. Study patients were consecutively enrolled from the Heart Failure Unit at the Cardiology Department of Veruno Medical Center between January 1989 and March 1993. Patients with either symptomatic or asymptomatic left ventricular systolic dysfunction as defined by resting echocardiographic ejection fraction ≤35% were eligible for the study. Patients were ineligible if they were >80 years old or had any of the following: atrial fibrillation, echocardiographic images and mitral Doppler tracings of insufficient quality for analysis, hemodynamically serious valvular disease requiring operation, echocardiographic findings indicative of restrictive cardiomyopathy, unstable angina pectoris, angina or myocardial ischemia thought to be severe enough to require revascularization procedures, myocardial infarction during the previous 3 months, severe pulmonary disease, coronary artery bypass surgery during the previous 6 months, significant chronic renal failure (serum creatinine level >2 mg/dl), cancer or other systemic disease that might substantially shorten survival.

Five hundred eight patients met the entry criteria for the study. All patients provided written informed consent to perform the protocol and to participate in this prospective study, which had been approved by the Science and Ethics Committee of our institution.

Study protocol. The study consisted of two parts: noninvasive evaluation at entry and follow-up. Entry evaluation included historic data collection, physical examination, functional classification and Doppler echocardiography. Patients' symptoms were assessed according to functional classification. Asymptomatic patients were assigned to functional class I, mildly symptomatic patients to class II, those moderately symptomatic to class III and those very symptomatic with minimal activity or at rest to class IV.

Echocardiography. Complete M-mode and two-dimensional echocardiography and Doppler ultrasound examination were performed in all patients at the time of the entry visit in the standard manner using commercially available equipment (Hewlett-Packard imaging system, model 77729-A or 77622-A). Diastolic flow velocity at the left ventricular inflow tract was recorded with pulsed wave Doppler echocardiography using a 2.5-MHz transducer, as previously described (9,15). In the apical four-chamber view, the Doppler sample volume was placed in the middle of the left ventricular inflow tract, ~1 cm below the plane of the mitral annulus between the tips of the mitral leaflets, where maximal flow velocity in early diastole was recorded. Care was taken to obtain the smallest possible angle between the presumed direction of the diastolic blood flow and the orientation of the ultrasound beam. Color Doppler measurements were also performed in all patients to assess the degree of both mitral and tricuspid regurgitation. Images were stored on a professional videotape (Panasonic AG-7330E) for further analysis.

Measurements. Left ventricular volume was calculated from orthogonal apical views of the two-dimensional echocardiogram using the biplane area-length method (10). Ejection fraction was derived from the standard equation. Maximal atrial area and right ventricular end-diastolic diameter 1 cm below the tricuspid annulus were also measured from the apical four-chamber view. For the mitral Doppler echocardiographic variables, traces of five to eight consecutive cardiac cycles were analyzed using a microcomputer-based digitizing system (Leading Edge), and the following variables were measured: peak flow velocity in early diastole (E), peak flow velocity at atrial contraction (A), peak E/A wave velocity ratio and deceleration time of early filling. To avoid the influence of heart rate, deceleration time was calculated as the time between peak E wave and the upper deceleration slope extrapolated to the zero baseline (10,15). Cardiac cycles with nonlinear deceleration slopes and fusion of early and late mitral flow velocity were excluded from the analysis. The restrictive filling pattern was defined as an E/A ratio ≥2 or by the combination of an E/A ratio between 1 and 2 with a deceleration time ≤140 ms. The nonrestrictive pattern was defined as E/A ratio ≤1 or E/A ratio between 1 and 2 with deceleration time >140 ms (21). Mitral and tricuspid regurgitation were evaluated by color Doppler flow imaging and graded as none, mild, moderate or severe, according to previously reported criteria (22).

Follow-up data. After entry evaluation, patients were seen in our outpatient clinic at regular intervals (every 6 months). The follow-up of patients who did not attend the scheduled appointments was obtained by personal communication with the patient's physician and review of the patient's chart, telephone interview with the patient conducted by trained personnel or review of the patient's hospital record. Follow-up data were obtained in all patients. The outcome events were all-cause mortality (death from all causes), hospitalization for congestive heart failure and total events (death or hospitalization for congestive heart failure). Only one event was considered in each patient, and any event occurring after the initial event was not considered.

Statistical analysis. Kaplan-Meier life table estimates of survival, hospital admission for congestive heart failure-free survival and of all-event-free survival were used to summarize the follow-up experience in these patients and to clarify presentation. The individual effect of certain variables on event-free survival was evaluated with the use of the Cox regression model (BMDP2L, Department of Biomathematics, University of California at Los Angeles, revised 1987). All variables analyzed in this study were first assessed by univariate analysis. Differences between patients with events and event-free survivors were also compared by unpaired *t* testing and frequency of parameters and events by the chi-square test with Yates correction. Those variables that showed a significant association with the outcome ($p < 0.1$) were included in the multivariate Cox model in stepwise fashion.

Two different multivariate analyses were carried out with the Cox proportional hazards model procedure. The first analysis was performed according to the unmodified forward selection stepwise procedure. In this analysis, variables were entered into or removed from the model on the basis of a computed significance probability (maximized partial likelihood ratio). The p values to enter and remove variables were 0.1 and 0.15, respectively. In order to clarify the incremental information from the addition of the historic, clinical, echocardiographic and mitral-Doppler variables, we also analyzed the data according to a modified stepwise procedure in which the significant individual factors were included in the model in the same order in which they are actually considered in clinical practice (demographic or historic data first, clinical data second, echocardiographic variables third and mitral-Doppler variables last). Increment in information of the model at each step was considered significant when the difference in log-likelihood associated with each model (adjusted for differences in degrees of freedom) corresponded to $p < 0.05$.

The demographic and historic variables selected for examination were age (continuous values), gender, etiology of idiopathic dilated cardiomyopathy, history of previous myocardial infarction, previous coronary artery bypass surgery and overt heart failure (yes/no for all). Clinical variables included functional class (I to IV) and presence of third heart sound and pulmonary rales (yes/no) on physical examination. For the echocardiographic data, the variables selected were left ventricular volumes and ejection fraction, right ventricular end-diastolic dimension, right and left atrial area (continuous values for all), and both mitral and tricuspid regurgitation (graded as absent, mild, moderate or severe). Finally, the mitral Doppler variables selected were peak E and peak A velocity, E/A ratio, deceleration time of early filling (continuous values for all) and the presence of a restrictive filling pattern (yes/no). A p value <0.05 was considered statistically significant.

Results

The study group consisted of 508 consecutive patients (451 men, 57 women; mean age 59 ± 10 years). The etiology of left ventricular dysfunction in these patients was coronary artery disease (history of previous myocardial infarction or coronary artery bypass surgery) in 94% and idiopathic dilated cardiomyopathy in the remaining 6%. Patients were taking a variety of medications including digitalis (197 patients), diuretic agents (308 patients), angiotensin-converting enzyme inhibitors (303 patients) and nitrates (388 patients). At entry, 137 patients had symptomatic left ventricular dysfunction as defined by a previous unequivocal episode of clinical heart failure, and 107 patients were in functional class III or IV. Mean left ventricular ejection fraction was 26 ± 5% (10% to 35%).

Prognostic data. Patients were followed up for a period of 29 ± 11 months (range 6 to 58). During the follow-up period, 148 patients (29.1%) were admitted to the hospital for congestive heart failure, and 100 patients (19.7%) died. In more detail, there were 87 (17.1%) cardiac and 13 (2.6%) noncardiac-related deaths. Of the 87 patients with cardiac deaths, 48 died of refractory congestive heart failure, 24 of sudden death and 15 of fatal myocardial infarction. The 1-year and 4-year cumulative mortality rates were 13% and 28%, respectively. Overall, there were 190 (37%) hard events (all-cause mortality or hospitalization for congestive heart failure).

At univariate analysis, except for gender and etiology, all baseline clinical features and all echocardiographic (including left ventricular volumes and ejection fraction, atrial size, right ventricular dimension and regurgitations) and mitral Doppler variables were found to be predictive of fatal outcome. Clinical, echocardiographic and mitral Doppler data in survivors and nonsurvivors are summarized in Table 1. Nonsurvivors were significantly older, in a higher functional class and more frequently had a history of clinical heart failure or showed third heart sound and pulmonary rales on physical examination. Nonsurvivors also had larger left ventricular volumes and larger left and right atrial size, a larger right ventricle, more depressed left ventricular systolic function, and they more frequently showed significant mitral and tricuspid regurgitation. In addition, analysis of mitral Doppler curves revealed in nonsurvivors (compared with survivors) a significantly higher peak E velocity, lower peak A velocity, higher E/A ratio and a shorter deceleration time of early filling. Digitalis and diuretic drugs were more frequently administered in nonsurvivors, but patients who received angiotensin-converting enzyme inhibitors and nitrates were equally distributed in the two groups.

However, when multivariate analysis in a forward stepwise regression procedure was performed (including in the model all significant baseline clinical characteristics, echocardiographic and mitral Doppler variables, and the use of digitalis, diuretics, angiotensin-converting enzyme inhibitors and other vasodilators), only deceleration time ≤125 ms, functional class III or IV, ejection fraction ≤25%, presence of third heart sound, age >60 years and left atrial area >18 cm^2 emerged as independent and additional predictors of subsequent death (Table 2). Deceleration time proved the single best predictor (chi-square 37.80). When these six significant variables were entered into the model in hierarchic order according to a

Table 1. Baseline Clinical Echocardiographic and Mitral-Doppler Characteristics of Survivors and Nonsurvivors

	All Patients (n = 508)	Survivors (n = 408)	Nonsurvivors (n = 100)	p Value
Clinical data				
Age (yr)	59 ± 9	57 ± 8	61 ± 9	0.0040
Overt CHF	137 (27%)	86 (21%)	51 (51%)	0.0000
NYHA III or IV	107 (81%)	63 (15%)	44 (44%)	0.0000
Third heart sound	59 (12%)	31 (7.5%)	28 (28%)	0.0000
Pulmonary rales	57 (11%)	31 (7.5%)	26 (26%)	0.0000
Echocardiographic data				
LVEDVI (ml/m^2)	106 ± 32	101 ± 25	124 ± 46	0.0000
LVESVI (ml/m^2)	77 ± 29	72 ± 23	96 ± 42	0.0000
LVEF (%)	26 ± 5	28 ± 5	23 ± 6	0.0009
Left atrial area (cm^2)	17 ± 5	16 ± 4	19 ± 6	0.0002
Right atrial area (cm^2)	13 ± 4	12 ± 3	14 ± 4	0.0002
RVEDD (mm)	29 ± 5.6	28 ± 5.4	31 ± 6.2	0.0001
MR mild–severe	143 (28%)	90 (22%)	53 (53%)	0.0000
TR mild–severe	33 (6%)	14 (3%)	19 (19%)	0.0000
Mitral Doppler data				
Peak E velocity (cm/s)	67 ± 25	64 ± 24	78 ± 26	0.0000
Peak A velocity (cm/s)	56 ± 24	59 ± 23	46 ± 25	0.0000
E/A ratio	1.64 ± 1.42	1.43 ± 1.2	2.5 ± 1.9	0.0000
Dec time (ms)	144 ± 43	151 ± 42	119 ± 41	0.0000
Restrictive filling pattern	211 (42%)	143 (35%)	68 (68%)	0.0000
Medication				
Digitalis	197 (39%)	139 (34%)	58 (58%)	0.0000
Diuretic drugs	308 (61%)	233 (57%)	75 (75%)	0.0010
ACE inhibitors	303 (60%)	244 (60%)	59 (59%)	NS
Nitrates	388 (76%)	313 (77%)	75 (75%)	NS

Data presented are mean value ± SD or number (%) of patients. A = atrial contraction; ACE = angiotensin-converting enzyme; CHF = congestive heart failure; Dec time = deceleration time of early filling; E = early diastole; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; MR = mitral regurgitation; NYHA = New York Heart Association functional class; RVEDD = right ventricular end-diastolic diameter; TR = tricuspid regurgitation.

realistic interactive clinical approach, after considering age (demographic data, step 1), functional class and third heart sound (clinical data, step 2), left ventricular ejection fraction and left atrial area (echocardiographic data, step 3), it was found that deceleration time (step 4) still added significant prognostic information. Global chi-square value, as an index of the predictive power of the significant variables that emerged from the four major categories, improved from 9.2 to 104.7 (Table 3). Survival according to the deceleration time is reported in the curves in Figure 1A. The cumulative 4-year mortality rate was 45% in patients with a deceleration time ≤125 ms and 13% in those with a deceleration time >125 ms ($p < 0.0001$). Mean deceleration time in patients who died secondary to refractory heart failure was significantly ($p < 0.001$) shorter (98 ± 29 ms) than that in patients who had a sudden death (121 ± 36 ms) or a fatal myocardial infarction (167 ± 39 ms). Similarly, the proportion of patients with a short (≤125 ms) deceleration time was significantly ($p < 0.001$) higher among those who died of refractory heart failure (91%) than in those with sudden death (65%) or fatal myocardial infarction (14%). Of note, patients who died of congestive heart failure and those who died suddenly had a similar ejection fraction (23 ± 7% and 25 ± 6%, respectively), which was lower than that observed in patients who died from myocardial infarction (28 ± 7%), though the difference was statistically significant ($p < 0.05$) only with the heart failure group.

Table 2. Ranked Independent Predictors of All-Cause Mortality in Study Cohort by Cox Model According to Forward Stepwise Procedure

Variable	Chi-Square	p Value	Relative Risk	95% CI
Dec time ≤125 ms	37.80	0.000	1.93	1.4–3.7
NYHA III or IV	19.54	0.000	1.49	1.4–2.3
LVEF ≤25%	10.20	0.001	1.85	1.6–2.9
3rd heart sound	8.20	0.004	2.06	1.8–3.2
Age >60 yr	6.10	0.014	1.95	1.8–3.1
Left atrial area >18 cm^2	5.79	0.016	1.73	1.6–2.7

Each chi-square and p value is a measure of the improvement that each selected variable makes in a model containing all other significant variables. The relative risk is the independent risk of a cardiac event that is associated with a variable. The total risk is the product of the risks associated with each variable when present. CI = confidence interval; other abbreviations as in Table 1.

Furthermore, when survival without hospital admission for congestive heart failure and survival without any events (hospital admission for heart failure or all-cause mortality, or both) were analyzed, deceleration time emerged as the most powerful independent predictor of adverse outcome (Tables 4 and 5). Again, when the incremental prognostic value of the significant variables was assessed in hierarchic order, deceleration time added prognostic information after demographic, clinical and echocardiographic data. The addition of clinical (functional class and pulmonary rales) and historic (overt heart failure) data to age improved the global chi-square value from 9.2 to 125.5; the addition of echocardiographic data (left ventricular end-systolic volume, ejection fraction and left atrial area) to age and clinical data improved the value to 174.1. Finally, the addition of mitral deceleration time to demo-

Table 3. Significant Predictors of Death According to an Interactive Stepwise Procedure: Incremental Prognostic Value of Models Developed at Four Steps in Hierarchic Order

		Global Chi-Square	p Value
Step 1.	Demographic data: age	9.2	0.002
Step 2.	Demographic and clinical data: age, NYHA class, 3rd heart sound	70.1	0.000
Step 3.	Demographic, clinical and echocardiographic data: age, NYHA class, 3rd heart sound, LVEF, left atrial area	97.4	0.000
Step 4.	Demographic, clinical, echocardiographic and mitral Doppler data: age, NYHA class, 3rd heart sound, LVEF, left atrial area, Dec time	104.7	0.000

Abbreviations as in Table 1.

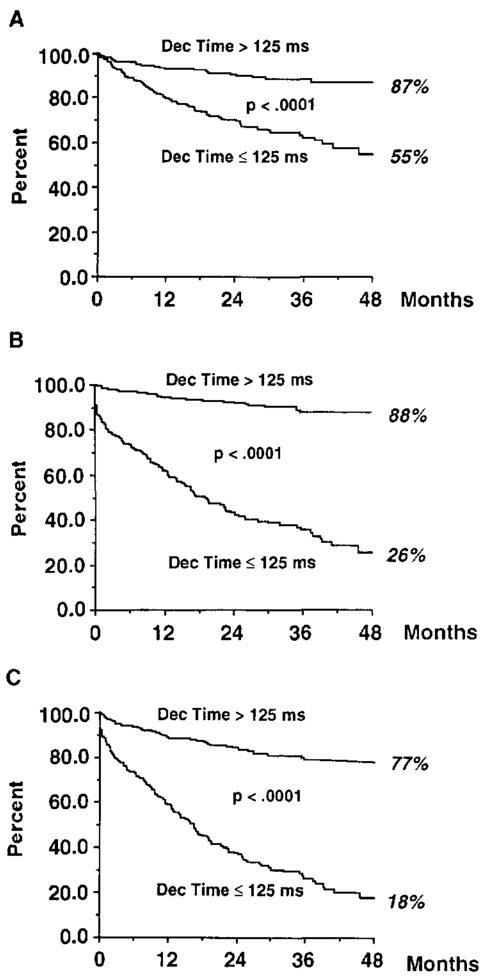

Figure 1. **A,** Cumulative survival rates considering all-cause mortality as an event. **B,** Cumulative survival rates free of hospital admission for congestive heart failure. **C,** Cumulative survival rates free of all events (including death and hospital admission for congestive heart failure) in the study cohort of 508 patients with ≤35% ejection fraction, according to the value of deceleration time (Dec Time) of early filling.

graphic, clinical and echocardiographic data further improved the chi-square value to 232.5. Survival without congestive heart failure and survival without any events according to the value of deceleration time are reported in the curves in Figure 1, B and C. The cumulative 4-year incidence rate of all hard events was 82% in patients with a deceleration time ≤125 ms and 23% in those with a deceleration time >125 ms ($p < 0.0001$).

Prognostic data in symptomatic and asymptomatic patients. The study group was further analyzed on the basis of history of overt heart failure at the time of the entry evaluation. At entry, 137 patients had symptomatic left ventricular dysfunction as defined by a previous unequivocal episode of clinical heart failure, and the remaining 371 patients with no history of overt heart failure were considered asymptomatic. Most symptomatic patients (78%) were in functional class III or IV, and all asymptomatic patients were in functional class I or II. Furthermore, all symptomatic patients were receiving digitalis and diuretics; in contrast, only 16% of asymptomatic patients were taking digitalis, and 46% diuretic drugs ($p < 0.001$). Similarly, angiotensin-converting enzyme inhibitors were more frequently administered in symptomatic than in asymptomatic patients (80% vs. 52%, $p < 0.01$). Symptomatic, compared to asymptomatic, patients also had a greater end-diastolic volume (122 ± 45 vs. 99 ± 26 ml/m^2, $p < 0.0001$) and end-systolic volume (95 ± 38 vs. 70 ± 21 ml/m^2, $p < 0.0001$), a lower ejection fraction (24 ± 7 vs. 29 ± 5%, $p < 0.0001$), a higher E/A ratio (2.5 ± 1.8 vs. 1.3 ± 1, $p < 0.0001$) and a shorter deceleration time (120 ± 42 vs. 154 ± 41 ms, $p < 0.0001$). The cumulative 4-year event rate was significantly higher in symptomatic than in asymptomatic patients (84% vs. 44%, $p < 0.0001$). In both groups, deceleration time remained the strongest independent predictor of all events (chi-square value 21.15 and 58.5, respectively). The proportion of patients with a short (≤125 ms) deceleration time was significantly higher in symptomatic than in asymptomatic patients (69% vs. 28%, $p < 0.0001$). Survival without events according to the value of deceleration time is shown in Figure 2. The cumulative 4-year event rates in symptomatic and asymptomatic patients with a deceleration time ≤125 ms were 95% and 67%,

Table 4. Ranked Independent Predictors of Hospital Admission for Congestive Heart Failure in Study Cohort by Cox Model According to Forward Stepwise Procedure

Variable	Chi-Square	p Value	Relative Risk	95% CI
Dec time ≤125 ms	153.21	0.000	4.88	3.7–6.9
Overt CHF	46.25	0.000	2.01	1.7–3.1
NYHA III or IV	11.33	0.001	1.98	1.6–3.0
Left atrial area >18 cm^2	7.03	0.008	1.69	1.5–2.6
LVESVI >75 ml/m^2	3.72	0.054	1.42	1.4–2.1

Each chi-square and p value is a measure of the improvement that each selected variable makes in a model containing all other significant variables. The relative risk is the independent risk of a cardiac event that is associated with a variable. The total risk is the product of the risks associated with each variable when present. Abbreviations as in Tables 1 and 2.

Table 5. Ranked Independent Predictors of All Events (death and congestive heart failure) in Study Cohort by Cox Model According to Forward Stepwise Procedure

Variable	Chi-Square	p Value	Relative Risk	95% CI
Dec time ≤125 ms	126.25	0.000	2.44	2.0–3.8
Overt CHF	34.50	0.000	1.63	1.5–2.5
LVEF ≤25%	10.61	0.001	1.52	1.4–2.3
Left atrial area >18 cm^2	9.25	0.002	1.76	1.5–2.6
Age >60 yr	4.98	0.026	1.42	1.4–2.1
Restrictive vs. nonrestrictive	3.36	0.067	2.00	1.8–3.2
Pulmonary rales	2.81	0.093	1.40	1.4–2.1

Each chi-square and p value is a measure of the improvement that each selected variable makes in a model containing all other significant variables. The relative risk is the independent risk of a cardiac event that is associated with a variable. The total risk is the product of the risks associated with each variable when present. Abbreviations as in Tables 1 and 2.

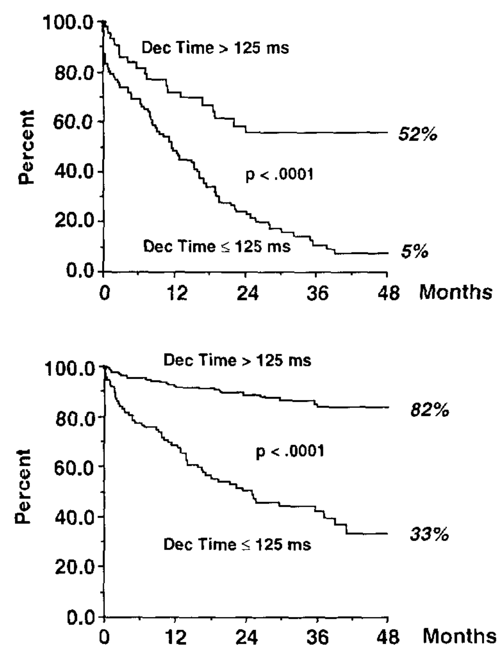

Figure 2. Top, Cumulative event-free survival rates, including all events, such as death and hospital admission for congestive heart failure, in 137 symptomatic patients with ejection fraction ≤35% and overt heart failure, according to the value of deceleration time (Dec Time) of early filling. **Bottom,** Cumulative survival rates free of total events (death and congestive heart failure) in 371 asymptomatic patients with ejection fraction ≤35%, according to the value of deceleration time of early filling.

respectively, and the event rates in patients with a deceleration time >125 ms were 48% and 18%, respectively ($p < 0.001$).

Discussion

Patients with ventricular dysfunction and congestive heart failure generally have poor prognosis (1–4,23–26). Although there are no univocal data on the prognostic value of the various variables that have been considered, some factors, such as functional status, left ventricular dimension and function, and hemodynamic variables, have emerged as significant and useful prognostic indicators (2–4,25,26). Recently, it has become increasingly apparent that left ventricular diastolic dysfunction rather than systolic functional impairment may contribute to signs and symptoms in cardiac patients with various underlying diseases who present with congestive heart failure (5). However, the long-term prognostic significance of abnormal left ventricular diastolic filling in patients with systolic dysfunction has still to be clearly defined.

Prognostic value of transmitral Doppler echocardiography. The assessment of diastolic function by noninvasive Doppler echocardiographic analysis of the transmitral flow has revealed a close relation among Doppler parameters of left ventricular filling, the severity of clinical symptoms and filling pressure (7–12,15). Preliminary data in selected patients have also indicated that Doppler-derived diastolic filling variables, in particular the restrictive filling pattern, could play an important role in predicting cardiac mortality in patients with dilated cardiomyopathy and congestive heart failure (18–21). The present study carried out on a large series of patients with severe left ventricular systolic dysfunction (with or without clinical heart failure) clearly demonstrates that Doppler-derived mitral deceleration time of early filling is the most powerful independent predictor of future events (all-cause mortality and hospitalization for congestive heart failure) among demographic, historic, clinical, echocardiographic and mitral Doppler variables. In addition, our results indicate that patients at higher risk for fatal outcome can be identified by a group of noninvasive variables including a short (≤125 ms) deceleration time of early filling, advanced functional class, left ventricular ejection fraction <25%, the presence of third heart sound, age >60 years and left atrial area >18 cm^2. All of these parameters are independent and additional prognostic indicators, deceleration time being the single best predictor of all-cause mortality. Over a 4-year follow-up period mortality occurred in 45% of patients with ≤125 ms deceleration time as compared with 13% of patients with >125 ms deceleration time.

Comparison with previous studies. Previous data by Pinamonti et al. (19) and Werner et al. (20) indicated the prognostic value of a short deceleration time of early filling as an index of restrictive physiology in small groups of patients with idiopathic dilated cardiomyopathy. Other studies found that the combination of E/A ratio and deceleration time was a better predictor of cardiac mortality than individual Doppler echocardiography measurements in patients with cardiac amyloidosis (17), dilated cardiomyopathy and congestive heart failure (18,21). For this reason, in the present study we used as a definition of restrictive filling pattern by Doppler echocardiography an E/A ratio ≥2 or the combination of an E/A ratio between 1 and 2 and a deceleration time ≤140 ms (21). The "nonrestrictive pattern" was defined as E/A ratio ≤1 or E/A ratio 1 to 2 with deceleration time >140 ms. Therefore, patients who may have had a "pseudonormal" transmitral flow pattern (E/A ratio 1 to 2) were further classified into restrictive and nonrestrictive groups on the basis of deceleration time measurement. Although at univariate analysis such a restrictive filling pattern was significantly associated with a worse outcome, at multivariate analysis it did not prove to be an independent predictor of mortality. On the contrary, a short (≤125 ms) deceleration time (which was associated with an E/A ratio <2 in 38% of patients), irrespective of the filling pattern, was found to be the single most powerful indicator of poor prognosis. Importantly, when the prognostic value of the significant predictors was analyzed in hierarchic order after taking account of age, functional class, third heart sound, left ventricular ejection fraction and left atrial area, Doppler-derived mitral deceleration time of early filling still added significant prognostic information. Furthermore, deceleration time of early filling remained the most important prognostic factor when patients were stratified according to the presence or absence of overt heart failure at the time of entry evaluation: in either symptomatic or asymptomatic patients with left ventricular systolic dysfunction, a short deceleration time resulted in the most powerful independent predictor of poor prognosis.

Mechanism. In patients with chronic heart failure, in addition to the influence of systolic impairment on survival, a relation was also observed between survival and hemodynamic indexes of congestion (i.e., increased left ventricular filling pressure, pulmonary artery pressure and pulmonary capillary wedge pressure) (2,25,26). This could explain the observed association between Doppler parameters of diastolic filling, particularly deceleration time, and prognosis. Indeed, in patients with severe left ventricular systolic dysfunction, we recently demonstrated a close negative correlation between deceleration time of early filling and pulmonary capillary wedge pressure (9,15). As filling pressure increases, the nondistensible ventricle may induce a more rapid increase in diastolic pressure with a faster equilibration of left atrial and left ventricular pressure, resulting in premature cessation of mitral flow and a short deceleration time of early filling. In our experience, irrespective of the filling pattern as expressed by the E/A ratio, a very short deceleration time (≤120 ms) reliably predicted a markedly elevated (≥20 mm Hg) pulmonary wedge pressure, and this was also the case in some asymptomatic patients with severe left ventricular dysfunction in functional class I or II (15). In line with this observation, the results of the present study also demonstrate that a short deceleration time, as an expression of a more pronounced restrictive physiology and more severe hemodynamic features (markedly elevated filling pressure), gives important and incremental prognostic information in both symptomatic and asymptomatic patients. A short deceleration time as an index of abnormal filling is clearly superior to the traditional variables of left ventricular systolic function (ejection fraction, end-systolic volume) in the noninvasive prognostication of patients with significant impairment of systolic function. Notably, the majority (91%) of patients who died from refractory heart failure had a short deceleration time, which was also found in a significantly high proportion (65%) of patients who had a sudden death (both groups exhibiting similar ejection fraction). These data underline the important contribution of abnormal filling and diastolic dysfunction in the clinical deterioration and prognosis of patients with comparable left ventricular systolic dysfunction.

Finally, although restrictive filling is a common finding in patients with clinical heart failure, a sizable number (28%) of asymptomatic patients in our study had a short deceleration time (often associated with an apparently normal filling pattern: E/A ratio <2 in 44% of this subset of patients), indicating that a significant hemodynamic impairment may also be present in the absence of clinical heart failure, before the manifestation of symptoms. Importantly, our data demonstrate that even asymptomatic patients with systolic dysfunction at higher risk for adverse outcome may be potentially identified by a short deceleration time.

Study limitations. In the present study, we did not consider the pulmonary venous flow velocity pattern, which, as suggested in a recent report, correlates with left ventricular diastolic pressure and may be more accurate than mitral Doppler studies in detecting abnormal hemodynamic variables (27). We evaluated only the transmitral flow velocity signal (obtained with the sample volume placed between the leaflets at the point where the highest early flow velocity is recorded) because it is more standardized, easy to obtain in all patients and extensively used in the noninvasive assessment of left ventricular filling abnormalities. However, it should be noted that because deceleration time appears to be such a useful variable, the sample volume position is critical: different locations (too medial, too far into the left ventricle or at the annulus) influencing the flow velocity curve could give different results.

Left ventricular filling by mitral Doppler echocardiography may be partially affected by several physiologic factors, including age, heart rate, valvular regurgitation and loading conditions (13,14). In our series of patients, age was an independent predictor of prognosis, and no correlation was found between age and deceleration time. Tachycardia may increase A wave velocity, but it does not seem to influence early deceleration time, which is independent of velocity and heart rate (10,15). Similarly, although mitral regurgitation may influence E velocity, it was not found to be independently correlated with deceleration time and prognosis. Digitalis and diuretics were more frequently administered in nonsurvivors (as they were more symptomatic) than in survivors, and angiotensin-converting enzyme inhibitors and nitrates were equally distributed over the two groups. However, at multivariate analysis, the use of these drugs was not independently related to survival. Therefore, loading conditions and medical treatment were not likely to have influenced our results. Finally, the use of a single Doppler echocardiographic examination to assess prognosis has some limitations because the transmitral flow pattern may change during the follow-up period (20,21). In spite of the dynamic nature of diastolic filling, our data indicate that patients with left ventricular systolic dysfunction should be considered at higher risk for adverse outcome whenever a short deceleration time of early filling is documented. Serial Doppler echocardiographic follow-up studies are needed to provide further insights into the complex diastolic filling dynamics and to investigate whether a reversible restrictive physiology (prolongation of an initially short deceleration time) with long-term medical therapy may predict (or be associated with) a more favorable prognosis.

Conclusions. Doppler-derived mitral deceleration time of early filling is a powerful independent predictor of poor prognosis in both symptomatic and asymptomatic patients with left ventricular dysfunction. The presence of a short (≤125 ms) deceleration time by mitral Doppler echocardiography as an index of abnormal filling and diastolic dysfunction adds important prognostic information compared with other clinical, demographic and echocardiographic data (including traditional variables of left ventricular systolic function), and it identifies patients at very high risk of subsequent death and/or hospitalization for congestive heart failure.

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