Prognostic Value of Doppler Echocardiographic Mitral Inflow Patterns: Implications for Risk Stratification in Patients With Chronic Congestive Heart Failure

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OBJECTIVES This prospective study tested whether transmitral flow patterns add incremental value to peak oxygen consumption (VO₂) in determining the prognosis of patients with chronic congestive heart failure (CHF) and systolic dysfunction.

BACKGROUND Peak VO₂ is an objective marker of functional capacity and is routinely used as a criterion to identify heart transplant candidates. Diastolic dysfunction limits functional capacity, but its prognostic importance relative to that of peak VO₂ is unknown.

METHODS Peak VO₂ and mitral inflow velocities were prospectively measured in 311 consecutive patients (mean age 54 years, 84% male) with impaired left ventricular function (ejection fraction, 40%; 88 patients with ischemic and 223 with dilated cardiomyopathy) who were evaluated for heart transplant candidacy.

RESULTS During a mean follow-up period of 512 ± 314 days, 65 patients died and 43 patients underwent heart transplantation. Diastolic filling patterns, peak VO₂ and left ventricular end-diastolic diameters were independent predictors of cardiac mortality. In patients with peak VO₂ ≤ 14 ml/min per kg body weight, the outcome was markedly poorer in the presence of restrictive filling patterns as compared with their absence (two-year survival rate 52% vs. 80%). Similarly, despite peak VO₂ levels > 14 ml/min per kg, the outcome was less favorable in the presence of restrictive filling patterns (two-year survival rate 80% vs. 94%). A risk-stratification model based on the identified independent noninvasive predictors separated groups into those with high (93%), intermediate (65%) and low (39%) two-year survival rates.

CONCLUSIONS Transmitral flow patterns add incremental value to peak VO₂ in determining the prognosis of patients with CHF and impaired systolic function. (J Am Coll Cardiol 2001;37:1049–55)

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Despite advances in the medical management of patients with chronic congestive heart failure (CHF), the mortality rate for this condition remains high, and heart transplantation is an important treatment option (1,2). Although a large number of patients on the waiting list die before transplantation, a significant proportion of listed patients remain in a compensated clinical condition (3,4). Because supply of donor organs does not meet clinical demands, risk stratification in individual patients is an important clinical task to guide patient management.

The New York Heart Association classification, the presence of malignant ventricular arrhythmias, neurohormonal derangements and impaired functional status, as assessed by cardiopulmonary exercise testing, have been proposed as important prognostic markers in patients with CHF (5–8). Of these factors, peak oxygen consumption (VO₂) has evolved as the most widely used clinical selection criterion to direct patients toward heart transplantation (1,8).

There is increasing evidence that abnormalities of left ventricular diastolic filling are intimately related to functional status and prognosis of patients with chronic CHF (9–11). Transmitral flow patterns characterized by short isovolumetric relaxation times and dominant early diastolic inflow velocities have been found in the presence of severely impaired left ventricular compliance and elevated end-diastolic filling pressures (12,13). This “restrictive” pattern of mitral inflow has been recognized as a strong predictor of mortality in advanced heart failure (10). Although diastolic dysfunction is known to reduce exercise capacity, its prognostic importance relative to that of peak VO₂ and left ventricular ejection fraction (LVEF) is unknown. Therefore, the purpose of this prospective study was to investigate whether mitral inflow patterns provide prognostic information incremental to that obtained from routine cardiopulmonary exercise testing in patients with impaired systolic function (ejection fraction < 40%). A risk-stratification model was developed based on noninvasive independent predictors identified by the Cox proportional hazards model.

METHODS

Study group. The study group consisted of 311 consecutive patients (mean age 54 years, 84% male) with chronic CHF...
Tracings were obtained by pulsed wave Doppler echocardiography. Measurements were performed in triplicate and averaged. All measurements were derived from apical two- and four-chamber views according to the modified Simpson rule (14). Left ventricular ejection fraction was measured from M-mode tracings of parasternal long-axis views. Left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic dimensions were measured from M-mode tracings of mitral inflow were recorded on videotapes and analyzed off-line by an independent observer using a computerized workstation (EchoCom Systems 2.4, Fulda, Germany) with a 2.5-MHz available sector scanner (Aloka SSD 2200, Aloka Deubchland GmbH, Duesseldorf, Germany) at a constant pedaling speed of 60 rpm, with work load increments of 15 W/min, as recently described (16), after excluding significant pulmonary disease by using pulmonary function tests. Patients in sinus rhythm were assigned to two groups according to the presence of restrictive and nonrestrictive diastolic filling patterns. Restrictive mitral inflow patterns were defined as an E/A ratio >2 or 1 to 2, but DT ≤140 ms. Accordingly, nonrestrictive filling patterns were characterized by an E/A ratio of either <1 or 1 to 2, with DT >140 ms.

In addition, the prognostic value of the presence of atrial fibrillation was estimated by calculating relative risk ratios that indicated the odds of dying for patients with restrictive and those with nonrestrictive filling patterns. This approach was chosen because patients in sinus rhythm comprised both groups with restrictive and nonrestrictive filling patterns.

Cardiac catheterization. Routine left and right heart catheterization, including selective coronary angiography, was performed from the standard femoral approach in all patients. Measurements of pulmonary artery and intracardiac pressures were performed using fluid-filled catheters connected to standard Statham transducers (Statham P23ID). Cardiac output was calculated according to the Fick principle.

Radionuclide angiography. Radionuclide left ventricular angiograms were obtained using standard equilibrium ECG-gated techniques, as previously reported (16). In brief, red blood cells were labeled in vivo by an antecubital intravenous injection of an unlabeled mixture of 4 mg stannous fluoride and 6.8 mg sodium medronate, followed by 20 to 25 mCi of technetium-99m 15 to 20 min later. The counts of the precordial area were collected by a small field-of-view Anger gamma camera (Siemens Orbiter ZLC 7500) equipped with a general-purpose, parallel-hole collimator oriented in a 45° or “best septal” left anterior oblique view. Global LVEFs were calculated from the raw time-activity curves after background subtraction, using a commercial computer system.

Cardiopulmonary exercise testing. Symptom-limited exercise testing with respiratory gas exchange analysis was performed on a bicycle ergometer (Oxycon alpha, Jaeger, Germany) at a constant pedaling speed of 60 rpm, with work load increments of 15 W/min, as recently described (16), after excluding significant pulmonary disease by using pulmonary function tests.

Statistical analysis. Cardiac death was used as the clinical outcome event. Descriptive data are expressed as the mean value ± SD. The distributions of continuous variables were assessed for normality. The Student t test, with assumption of unequal variance (normal distribution of variables), and the Wilcoxon rank-sum test (non-normal distribution of

Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>A</td>
<td>late diastolic filling velocity</td>
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<tr>
<td>CHF</td>
<td>congestive heart failure</td>
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<td>DT</td>
<td>deceleration time</td>
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<tr>
<td>E</td>
<td>early diastolic filling velocity</td>
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<tr>
<td>ECG</td>
<td>electrocardiogram</td>
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<tr>
<td>LVEDD</td>
<td>left ventricular end-diastolic diameter</td>
</tr>
<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
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<tr>
<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>$\dot{V}_O_2$</td>
<td>oxygen consumption</td>
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Variables were used for group-to-group comparisons of continuous variables.

Survival was analyzed by the Kaplan-Meier method, and survival curves were compared by the log-rank test. Univariate analysis was performed by using log-rank tests to identify significant prognostic variables. The Cox proportional hazards model was used for multivariate survival analysis to determine independent predictors. A stepwise selection procedure using the maximal partial likelihood ratio chi-square test to enter (p < 0.1) or to remove (p > 0.1) a covariate into the model was employed. The variables of prognostic importance, identified by the Cox procedure, were used to derive a prognostic index to classify the patients into different risk groups. A p value < 0.05 was considered statistically significant.

**RESULTS**

**Baseline characteristics of the study group.** The final study group consisted of 311 patients (84% men, mean age 54 ± 10 years). A total of 48 (13%) of 359 initially screened patients were excluded because they did not meet the entry criteria.

Baseline data are summarized for all patients as a group and separately for survivors and nonsurvivors (Table 1). During a mean follow-up period of 512 ± 314 days (range 15 to 1,509), 65 patients (21%) died and 43 (14%) underwent heart transplantation because of end-stage heart failure.

Drug therapy, except for digoxin and warfarin, was similar in both groups (Table 1). Compared with event-free survivors, those who died were more symptomatic and had lower blood pressures, lower LVEFs, larger LVEDDs, larger left atrial dimensions, higher E/A ratios and shorter DTs, on average.

**Independent predictors of survival.** On multivariate analysis (Table 2), restrictive filling patterns (odds ratio [OR] 3.2, chi-square 12.9, p = 0.0003) and LVEDD > 65 mm (OR 3.2, chi-square 12.9, p = 0.0003) were independent predictors of cardiac mortality. Patients with atrial fibrillation (n = 46) had a 2.5-fold higher mortality risk than patients with nonrestrictive filling patterns, but a similar risk as patients with restrictive filling patterns (Table 2).
Survival was significantly lower in patients with peak VO2 ≤14 ml/min per kg than in patients with peak VO2 >14 ml/min per kg, with a one-year survival rate of 76% versus 93% and a two-year survival rate of 59% versus 90%, respectively.

Prognostic value of Doppler echocardiographic transmitral flow patterns. In patients with a restrictive filling pattern, peak VO2 was lower (13.2 ± 4.2 ml/min per kg, n = 122) than in those without a restrictive filling pattern (16.6 ± 5.8 ml/min per kg, n = 143, p < 0.0001). In patients with peak VO2 ≤14 ml/min per kg, the presence of a restrictive filling pattern indicated a very poor prognosis (two-year survival rate 52% vs. 80% in those with a nonrestrictive filling pattern) (Fig. 1). Likewise, in those patients with peak VO2 >14 ml/min per kg, a restrictive filling pattern indicated less favorable survival than that in patients without a restrictive pattern (two-year survival rate 80% vs. 94%) (Fig. 1).

As a group, patients with restrictive filling patterns were more symptomatic and had more extensive left ventricular dilation and a lower LVEF as compared with patients without restrictive filling patterns (Table 3). The frequencies of cardiac deaths and heart transplantations in relation to categoric grouping of patients according to their mitral filling pattern and peak VO2 are shown in Table 4.

Construction of a noninvasive risk score. To better define cardiac risk for individual patients in clinical practice, a noninvasive predictive model was developed based on the independent risk factors identified by multivariate analysis: peak VO2 ≤14 ml/min per kg, atrial fibrillation, restrictive mitral inflow patterns and LVEDD ≥65 mm. Low, medium and high risk groups were identified by the presence of ≤1, 2 or 3 risk factors with survival rates at two years of 93%, 65% and 39%, respectively (Fig. 2).

**DISCUSSION**

The results of this study show that Doppler mitral inflow patterns provide prognostic information that is independent of peak VO2 in patients with chronic CHF and impaired systolic function. An increase in chamber stiffness due to extensive scarring and structural changes of myocardial tissue, accompanied by an increase in left ventricular filling pressures and left atrial pressures, is the most likely underlying mechanism of this redistribution of flow to early diastole (19).
reduced ejection fractions may have a markedly different clinical course, contributing to the uncertainty in judging the prognosis of an individual patient (6). Peak V\(\dot{O}_2\) is the only prognostic factor that is widely used in routine clinical practice as a selection criterion in patients with CHF (1). Levels of peak V\(\dot{O}_2\) ≤14 ml/kg per min are usually considered to indicate the need for heart transplantation. However, a single cut-off value appears unlikely to unequivocally predict the need for transplantation and neglects other routinely obtained prognostic factors, such as clinical signs and symptoms of heart failure or the presence of malignant ventricular arrhythmias (5–7). The present study shows that although restrictive filling patterns have prognostic value, there is substantial overlap of filling indexes between survivors and nonsurvivors. Thus, for the patient groups as a whole, Doppler-derived information on diastolic function may have important prognostic information, but may not be applicable to an individual patient.

Therefore, there is a clear need for noninvasive predictive models to better define individual risk. Several studies have shown that a combination of predictive factors more accurately predict survival, but involved either small patient groups or neglected peak V\(\dot{O}_2\) or did not evaluate diastolic function (20–22). Notably, the models including invasive variables did not perform better than the noninvasive models (21).

In the present study, a predictive model was constructed on the basis of independent risk factors identified by multivariate analysis (peak V\(\dot{O}_2\) ≤14 ml/min per kg, restrictive mitral inflow pattern, atrial fibrillation and LVEDD). A combination of these predictive variables increased diagnostic accuracy. Low, medium and high risk groups were defined by the presence of ≤1, 2 or 3 risk factors, with two-year survival rates of 93%, 65% and 39%, respectively. The predictive power of this model was clearly superior to that of peak V\(\dot{O}_2\) alone and compared favorably with the results of previous investigations (20–22). The major advantage of this risk-stratification model is that the prognostic noninvasive variables evaluated in this study are readily available in routine clinical practice and are cost-effective, giving access to repeat evaluations of cardiac status and function in the clinical setting. However, it should be considered that the risk score proposed in this study needs to be tested in a prospective study of an independent patient population.

**Study limitations.** Several potential limitations should be considered when interpreting the results of this study. We investigated patients with chronic CHF due to either ischemic or nonischemic dilated cardiomyopathy and a mean LVEF of 22%. Thus, the results cannot be generalized to other patients with impaired diastolic function and less compromised or even preserved left ventricular systolic function.

The model is further complicated by its static nature; it uses only variables obtained at the time of initial enrollment after medical therapy for at least eight weeks and does not account for potential later changes in cardiac status.

Furthermore, survival analysis was limited to data routinely collected during the study period. Other potentially important predictors of survival, such as serologic markers, were not considered because of their currently limited availability as routine clinical variables.

### Table 3. Patient Characteristics According to Their Transmitial Filling Patterns

<table>
<thead>
<tr>
<th></th>
<th>Non-RFP (n = 143)</th>
<th>RFP (n = 122)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA functional class</td>
<td>2.1 ± 0.7</td>
<td>2.6 ± 0.7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HR at rest (beats/min)</td>
<td>80 ± 18</td>
<td>83 ± 15</td>
<td>0.07</td>
</tr>
<tr>
<td>SBP at rest (mm Hg)</td>
<td>122 ± 18</td>
<td>112 ± 15</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Peak V(\dot{O}_2) (ml/min per kg)</td>
<td>16.6 ± 5.8</td>
<td>13.2 ± 4.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PA resistance (dynes · cm(^{-5}))</td>
<td>164 ± 93</td>
<td>205 ± 99</td>
<td>0.007</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>15 ± 8</td>
<td>21 ± 8</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>RNA LVEF (%)</td>
<td>26 ± 12</td>
<td>19 ± 9</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>66 ± 11</td>
<td>70 ± 10</td>
<td>0.01</td>
</tr>
<tr>
<td>Echocardiographic LVEF (%)</td>
<td>27 ± 12</td>
<td>20 ± 10</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*\(p < 0.05\) was considered significant. Data are expressed as the mean value ± SD.

HR = heart rate; RFP = restrictive filling pattern; other abbreviations as in table 1.

### Table 4. Frequency of Death and Heart Transplantation in Relation to Mitral Inflow Patterns and Maximal Oxygen Uptake

<table>
<thead>
<tr>
<th></th>
<th>RFP</th>
<th>Non-RFP</th>
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<tbody>
<tr>
<td>Peak V(\dot{O}_2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤14 ml/min per kg</td>
<td>79</td>
<td>61</td>
</tr>
<tr>
<td>&gt;14 ml/min per kg</td>
<td>43</td>
<td>82</td>
</tr>
<tr>
<td>Deaths</td>
<td>31</td>
<td>10</td>
</tr>
<tr>
<td>HTX</td>
<td>19</td>
<td>7</td>
</tr>
</tbody>
</table>

Data are presented as the number of patients.

HTX = heart transplantation; RFP = restrictive filling pattern; V\(\dot{O}_2\) = oxygen consumption.
Another limitation is that mitral inflow patterns may not necessarily reflect left ventricular diastolic dysfunction. Diastolic filling patterns can be influenced by age, heart rate and loading conditions (23,24). Age is unlikely to have significantly influenced our results, because it could not be shown to have prognostic value for survival. Heart rate was significantly higher in nonsurvivors than in survivors, potentially leading to overestimation of late diastolic velocities, and thus supporting our results even more. The loading conditions of patients were not characterized in this study, but might have been influenced by the patients’ medications. However, diuretic agents and angiotensin-converting enzyme inhibitors were equally distributed among the groups.

Interpretation of transmitral flow patterns may also be confounded by factors, such as pericardial restraint, left atrial pressure and compliance, right and left ventricular interplay, coronary turgor and intrinsic properties of left atrial and left ventricular muscle (25). It must also be kept in mind that flow velocity-derived indices of diastolic filling are only indirect measures of diastolic function and do not directly assess ventricular relaxation and compliance and are subject to interobserver and intraobserver variations (26).

Clinical implications. The present study clearly shows that restrictive filling patterns indicating diastolic dysfunction provide prognostic value that is incremental to that derived from cardiopulmonary exercise testing. Implementation of Doppler filling patterns can add important information to the process of clinical decision making on the basis of peak VO₂. Although the proposed risk-stratification model based on the data of this study needs to be prospectively validated in a separate patient group, the patients presenting with a combination of identified risk factors are more likely to benefit most from early heart transplantation. This predictive model carries the potential to facilitate identification of high risk patients in routine clinical practice and offers the specific advantage of allowing repetitive evaluations when an update of the patient’s status is warranted. However, one should also consider that any such predictions should be integrated with other clinical impressions and not to make critical decisions based on computational models alone. A potential future advantage of using Doppler echocardiography to identify diastolic dysfunction in patients with CHF may be to identify patients amenable to new pharmacologic approaches, such as the use of nitric oxide donors or drugs that enhance nitric oxide release (27).

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