Prognostic Value of Pulmonary Venous Flow Doppler Signal in Left Ventricular Dysfunction
Contribution of the Difference in Duration of Pulmonary Venous and Mitral Flow at Atrial Contraction

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OBJECTIVES We assessed the contribution of difference in duration of pulmonary venous and mitral flow at atrial contraction (ARd-Ad) for prognostic stratification of patients with left ventricular (LV) systolic dysfunction.

BACKGROUND Although pulmonary venous flow (PVF) variables may supplement mitral flow patterns in evaluating left ventricular (LV) diastolic function, their value to the prognostic stratification of patients has not been investigated.

METHODS Pulsed wave Doppler mitral and PVF velocity curves were recorded in 145 patients (mean age: 70 years) with LV systolic dysfunction secondary to ischemic or nonischemic cardiomyopathy who were followed for 15 ± 8 months. In 38% of patients, PVF signal was enhanced by the intravenous (IV) administration of a galactose-based echo-contrast agent. Based on E-wave deceleration time $\leq$ or $>130$ ms and ARd-Ad, patients were grouped into restrictive (group 1, $n = 40$), nonrestrictive with ARd-Ad $\geq 30$ ms (group 2, $n = 55$) and nonrestrictive with ARd-Ad $<30$ ms (group 3, $n = 50$).

RESULTS During follow-up, 29 patients died from cardiac causes and 28 were hospitalized for worsening heart failure (HF). On multivariate Cox model, ARd-Ad $<30$ ms provided important prognostic information with regard to cardiac mortality and emerged as the single best predictor of cardiac events (cardiac mortality, hospitalization). The 24-month cardiac event-free survival was best (86.3%) for group 3; it was intermediate (37.9%) for group 2; and it was worst (22.9%) for group 1 ($p < 0.0002$ group 1 vs. 3; $p < 0.0005$ group 2 vs. 3; $p < 0.0003$ group 1 vs. group 2).

CONCLUSIONS Assessment of ARd-Ad exhibited an independent value in the prognostic evaluation of patients with LV systolic dysfunction. Moreover, it contributed to identify patients at low, intermediate and high risk of cardiac events. (J Am Coll Cardiol 2000;36:1295–302) © 2000 by the American College of Cardiology

It is well known that restrictive left ventricular (LV) filling, as assessed by pulsed wave Doppler of the mitral flow, usually identifies advanced heart disease associated with a poor prognosis (1–3). However, because many patients with LV systolic dysfunction display a nonrestrictive mitral flow pattern (4–7), it would be desirable to identify other indices able to stratify them in groups with different degree of risk for cardiac death or hospitalization for worsening heart failure (HF). In this respect, assessment of the difference in duration of pulmonary venous and mitral flow at atrial contraction (ARd-Ad) may provide valid information complementary to that of mitral flow recordings. This study was designed to determine the value of measuring ARd-Ad in the prognostic stratification of patients with LV systolic dysfunction.

METHODS Patient selection. The study involved 145 consecutive patients, prospectively examined owing to either ischemic or nonischemic cardiomyopathies, undergoing echocardiography for clinical purposes. Inclusion criteria were LV systolic dysfunction, as defined by an ejection fraction (EF) $\leq 45\%$ and sinus rhythm. Excluded from the study were patients with aortic or mitral organic valve disease, severe functional mitral regurgitation according to the method of Helmcke et al. (8), atrial fibrillation, postcardioversion atrial mechanical failure, heart rate (HR) >100 beats/min, and those with undetectable pulmonary venous flow (PVF) throughout the cardiac cycle or absent PVF reversal wave.

Doppler echocardiographic examination. A complete M-mode, two-dimensional and Doppler echocardiographic study was carried out with an Acuson 128 XP-10 sector scanner operating at 2.5 MHz. The same operator (F.L.D.) performed all the examinations. Recordings were made with the patient in left lateral decubitus during quiet respiration. Continuous single-lead electrocardiogram (ECG) monitoring was maintained during the study. The LV volumes and EF were calculated from apical two- and four-chamber views using the modified Simpson’s rule. The LV volume
mitral early wave deceleration time (EDT) in 1) restrictive and 2) nonrestrictive study groups. Contrast-enhanced-Doppler echocardiographic examinations. A different observer who reviewed the tapes of both unenhanced and contrast-enhanced study performed the echocardiographic study and by an independent, blinded observer. Interobserver variability was assessed in 70 randomly selected patients with pulmonary venous flow (PVF) as prognostic indicators, nonrestrictive patients were subdivided into two groups on the basis of mitral and PVF velocity patterns. First, they were grouped based on ARd-Ad (≥30 ms or <30 ms). Next, they were separated according to mitral early-to-atrial (E/A) wave ratio: E/A >1 (normalized) and E/A ≤1 (impaired relaxation).

Follow-up data. The patients were followed from 1 to 24 months (mean 15 ± 8 months; median 16 months) after the index Doppler echocardiogram. End points were cardiac mortality, cardiac events (including cardiac mortality plus hospitalization for worsening HF) and HF events (cardiac events excluding sudden death). Deaths due to end-stage HF were defined as those occurring in hospital as a result of refractory progressive HF. Only one event was counted in each patient. If a patient died after being previously hospitalized and regularly discharged, the event was considered as death. The follow-up data were obtained monthly by regular visits, through telephone calls, from local authority registry, and from hospital records.

Statistical analyses. Data were expressed as mean values ± 1 SD. Comparisons among clinical, instrumental and Doppler echocardiographic variables were analyzed with chi-square test for categorical variables and one-way analysis of variance (ANOVA) for numerical variables (multiple comparisons were performed according to Bonferroni test in case of significant F value). To calculate survival and event rates in the patient population, life tables of survival were obtained by using the Kaplan-Meier method (Product-Limit Estimate). In assessing the impact of HF events, sudden cardiac death was treated as censored observation. Differences of survival curves were tested with Mantel-Cox statistic log-rank analysis. The impact of demographics, New York Heart Association (NYHA) functional class, LV EF, LV mass, left atrial dimension, pulmonary artery systolic pressure and selected mitral and PVF variables were all analyzed by Cox proportional-hazards regression analysis (BMDP 2L, Department of Biomathematics, University of California, Los Angeles, revised 1990). Multivariate Cox proportional-hazards regression analysis (toward stepwise procedure) was used to investigate whether the following variables were independent predictors of survival and event rates: age, gender, NYHA functional class, LV EF, LV mass, mitral regurgitation, restrictive mitral filling pattern, E/A wave ratio >1, systolic-to-diastolic PVF wave ratio, ARd-Ad and pulmonary artery systolic pressure. The above variables were treated as dichotomous variables. Interobserver variability was tested by the Bland and Altman method (13).

RESULTS

Patient characteristics. Mean age of the study population was 70 years (range 42 to 86; median 71 years). Coronary artery disease was the etiology of LV systolic dysfunction in 70% of patients as assessed by coronary angiography or by a
history of prior myocardial infarction. Mean LV EF was 31 ± 7%. Forty-six patients (32%) were in NYHA functional class I, 48 (33%) in class II, 38 (26%) in class III and 13 (9%) in class IV (Table 1).

Enhancement of pulmonary venous flow. Out of 145 patients, well-defined PVF Doppler tracings of antegrade and reversal wave were obtained in 110 (76%) and 90 (62%) of patients, respectively. In 55 patients (38%), Levovist was administered to enhance poor PVF Doppler signals. After contrast, all patients had enhancement of PVF Doppler signals. Optimal or near optimal envelope tracings were achieved for antegrade and retrograde waves in 142 (98%) and 140 (97%) patients, respectively (Fig. 1). In patients with poorly defined envelope recordings after contrast enhancement, PVF wave velocities and the duration of reversal A-wave were obtained by consensus. The interobserver variability in patients not submitted to contrast enhancement and in those who received the medium is shown in Table 2.

Table 1. Doppler Echocardiographic Variables in Patients Grouped According to Pulmonary Venous and Mitral Flow Indices

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n = 40)</th>
<th>Group 2 (n = 55)</th>
<th>Group 3 (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>67 ± 10</td>
<td>73 ± 9‡</td>
<td>69 ± 10</td>
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<tr>
<td>% Women</td>
<td>28</td>
<td>31</td>
<td>36</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>58</td>
<td>65</td>
<td>64</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>88 ± 8</td>
<td>74 ± 12‡</td>
<td>71 ± 12**</td>
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<tr>
<td>NYHA functional class III–IV (%)</td>
<td>75</td>
<td>74 ± 12‡</td>
<td>12**</td>
</tr>
<tr>
<td>LVEDVi (ml/m²)</td>
<td>140 ± 39</td>
<td>118 ± 36‡</td>
<td>122 ± 28*</td>
</tr>
<tr>
<td>LVESVi (ml/m²)</td>
<td>106 ± 33</td>
<td>81 ± 27‡</td>
<td>80 ± 23**</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>25 ± 7</td>
<td>32 ± 6‡</td>
<td>35 ± 6*</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>164 ± 40</td>
<td>159 ± 32</td>
<td>149 ± 30</td>
</tr>
<tr>
<td>LAi (mm/m²)</td>
<td>28.6 ± 2.5</td>
<td>26.4 ± 3.1‡</td>
<td>25.5 ± 2.7**</td>
</tr>
<tr>
<td>Mitral regurgitation &gt;1+ (%)</td>
<td>40</td>
<td>13‡</td>
<td>17**</td>
</tr>
<tr>
<td>E wave (cm/s)</td>
<td>110 ± 18</td>
<td>82 ± 22‡</td>
<td>66 ± 20**§</td>
</tr>
<tr>
<td>A wave (cm/s)</td>
<td>46 ± 19</td>
<td>86 ± 23‡</td>
<td>85 ± 21**</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>2.9 ± 1.5</td>
<td>1 ± 0.4‡</td>
<td>0.8 ± 0.4**</td>
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<td>EDT (ms)</td>
<td>115 ± 12</td>
<td>198 ± 41‡</td>
<td>217 ± 35**†</td>
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<tr>
<td>Ad (ms)</td>
<td>112 ± 12</td>
<td>130 ± 15‡</td>
<td>148 ± 14**§</td>
</tr>
<tr>
<td>AR wave (cm/s)</td>
<td>36 ± 11</td>
<td>33 ± 7</td>
<td>29 ± 8</td>
</tr>
<tr>
<td>ARd (ms)</td>
<td>176 ± 20</td>
<td>171 ± 18</td>
<td>158 ± 18**§</td>
</tr>
<tr>
<td>S wave (cm/s)</td>
<td>37 ± 14</td>
<td>56 ± 14‡</td>
<td>58 ± 10**</td>
</tr>
<tr>
<td>D wave (cm/s)</td>
<td>67 ± 13</td>
<td>51 ± 15‡</td>
<td>41 ± 12**</td>
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<tr>
<td>S/D ratio</td>
<td>0.6 ± 0.2</td>
<td>1.2 ± 0.4‡</td>
<td>1.5 ± 0.4**§</td>
</tr>
<tr>
<td>SFvti (%)</td>
<td>38 ± 7</td>
<td>56 ± 11‡</td>
<td>60 ± 10**†</td>
</tr>
<tr>
<td>ARd-Ad (ms)</td>
<td>63 ± 19</td>
<td>43 ± 12‡</td>
<td>10 ± 15**‡</td>
</tr>
<tr>
<td>PASP (mm Hg)</td>
<td>59 ± 11</td>
<td>43 ± 12‡</td>
<td>39 ± 15**</td>
</tr>
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</table>

Group 1: restrictive; Group 2: nonrestrictive with ARd-Ad ≥30 ms; Group 3: nonrestrictive with ARd-Ad <30 ms.

*p < 0.05 Group 3 vs. Group 1; **p < 0.01 Group 3 vs. Group 1; †p < 0.05 Group 3 vs. Group 2; §p < 0.01 Group 3 vs. Group 2; ‡p < 0.01 Group 3 vs. Group 2; ‡‡p < 0.001 Group 3 vs. Group 1.

LVEDVi = LV end-diastolic volume index; LVESVi = LV end-systolic volume index; LAi = left atrial index; S wave = systolic wave peak velocity; D wave = diastolic wave peak velocity; SFvti = systolic fraction of time-velocity integrals; PASP = pulmonary artery systolic pressure.

Figure 1. Pulsed Doppler mitral flow velocity (left panel) and contrast-enhanced pulmonary venous flow velocity (right panel) in a patient with LV systolic dysfunction. Mitral A-wave duration (measured from the start of flow until flow ceases) was 125 ms. Pulmonary vein atrial reversal duration (from onset to the cessation of reversed flow) was 175 ms. The difference was 50 ms. Assessment of pulmonary venous flow variables was accomplished after venous contrast administration.
Outcome study. During follow-up, 30 patients (21%) died, and 28 (19%) were hospitalized for worsening HF and were discharged alive. One patient died of a noncardiac cause. Of the 29 cardiac deaths, 11 occurred suddenly (38%) and 18 (62%) were due to progressive HF. In the entire study group, sensitivity and specificity of restrictive mitral flow, ARd-Ad $30$ ms and E/A $1$ in predicting clinical events are illustrated in Figure 2.

Seven variables were predictors of cardiac death on univariate analysis. In descending order of power, they were NYHA class III–IV; ARd-Ad $30$ ms; age $>70$ years; more than mild mitral regurgitation; LV EF $<25$%; pulmonary artery systolic pressure $>50$ mm Hg; and restrictive mitral pattern. By univariate analysis, an increased ARd-Ad was the most powerful predictor of cardiac death or hospitalization for worsening HF (Table 3), whereas restrictive mitral pattern was associated with an increased risk of HF events, followed by NYHA functional class III–IV; ARd-Ad $30$ ms; pulmonary artery systolic pressure $>50$ mm Hg; PVF systolic-to-diastolic velocity ratio $>1$; LV EF $<25$%; HR $>80$ beats/min; more than mild mitral regurgitation; E/A ratio $>1$; increased left atrial dimension; and increased LV mass.

On multivariate analysis, increased ARd-Ad was among predictors of cardiac mortality, along with age $>70$ years, LV EF $<25$%, and advanced NYHA functional class. An ARd-Ad $30$ ms proved to be the best predictor of fatal outcome or hospitalization for worsening HF, followed by LV mass $>125$ g/m$^2$, older age, rapid HR, and NYHA functional class III–IV. When freedom from HF events was analyzed, several Doppler and echocardiographic variables (i.e., increased ARd-Ad; restrictive mitral flow; E/A ratio $>1$; and increased LV mass) were found to be predictive of adverse outcome (Table 4).

Study group analyses. Characteristics of the study patients in the restrictive and nonrestrictive groups, classified according to ARd-Ad $\geq 30$ ms or $<30$ ms, are displayed in Table 1. The rates of survival free from cardiac mortality, event-free survival and freedom from HF events in the three groups are illustrated in Figure 3. Of note, the three Kaplan–Meier curves were clearly discernible and exhibited statistically significant differences at Mantel-Cox analysis for both cardiac event–free survival and freedom from HF events.

When patients were stratified according to restrictive, nonrestrictive with E/A $>1$, and nonrestrictive with E/A $\leq 1$ patterns, statistical significance for survival free from cardiac mortality was reached only in the comparison between restrictive and nonrestrictive groups ($p < 0.05$),
whereas no statistical difference was found between nonrestrictive patients with E/A ≥1.

For cardiac event-free survival and freedom from HF events, the nonrestrictive group with E/A ≥1 and that with E/A <1 showed broadly overlapped curves, while the two curves were clearly discernible and statistically different (p < 0.0001) from that of the restrictive group. Accordingly, no significant differences emerged between nonrestrictive groups for both cardiac event-free survival and freedom from HF events.

**DISCUSSION**

This study showed that increased ARd-Ad may be clinically relevant to patients with LV systolic dysfunction. Although less specific than the restrictive pattern, this abnormality exhibited a higher sensitivity in predicting clinical events. On multivariate analysis, ARd-Ad ≥30 ms was independently associated with both cardiac mortality and HF events, and it was the most powerful predictor of cardiac events. Additionally, the association of a nonrestrictive physiology with ARd-Ad ≥30 ms allowed us to identify a group with a prognostic outcome intermediate between patients with restriction and those with nonrestrictive pattern without increased ARd-Ad.

**Prognostic significance of LV diastolic parameters.** The clinical interest of the abnormalities in diastolic function has been recognized as they are linked to both the symptom status and the outcome of patients with LV systolic dysfunction (2,14). In particular, several studies have shown that Doppler-derived mitral flow variables are important indicators of cardiac mortality and worsening HF in various cardiac diseases (13,15–24). In the majority of previous studies carried out in patients with LV systolic dysfunction secondary to either ischemic or idiopathic dilated cardiomyopathy, restrictive mitral flow was independently associated with a poor outcome. Moreover, the restrictive pattern identified a subset of patients with higher mortality (13,18,20–24).

Recently, novel approaches have been developed to improve Doppler assessment of LV diastolic function (2). Similarly to E/A >1 in LV dysfunction, a PVF reversal wave exceeding mitral A-wave duration at atrial contraction was associated with elevated LV filling pressure (25–29). However, ARd-Ad has the advantage of being less affected by factors such as age, load and the degree of mitral regurgitation with little overlap of its values between patients with and without elevated LV filling pressures (29–33). Therefore, consideration of this parameter may provide clinically relevant information that supplements information obtained from mitral flow velocity tracings. In this study, the high sensitivity of ARd-Ad ≥30 ms in predicting adverse outcome is probably related to its ability to pick up a wide range of patients—either restrictive or nonrestrictive—more prone to the occurrence of clinical events at follow-up.

Although the nonrestrictive LV filling was associated with better NYHA functional class and LV EF than was the restrictive pattern, at variance from other studies (18,20–23), a sizable number of patients in this category (30%) had adverse events at follow-up. This probably derives from the characteristics of our study population, mainly elderly patients with ischemic cardiomyopathy. Indeed, the age difference between our group (70 years) and those of previous studies (with a mean age ranging between 39 and 61 years) may help explain the large number of events among patients in the nonrestrictive category (13,18–23).

Finally, in addition to the influence of clinical, LV
systolic and diastolic parameters, an independent association was observed between increased LV mass and outcome. Although this may also partly account for the large number of events in the nonrestrictive subset, further investigations are needed to better assess its role as predictor of adverse outcome in LV systolic dysfunction.

**Subgrouping of nonrestrictive patients.** Because many patients with LV systolic dysfunction exhibited a nonrestrictive mitral flow pattern, it was interesting to classify them further in groups with intermediate and low risk. Accordingly, a useful categorization was accomplished using a cutoff of 30 ms in ARd-Ad (26,29). Our results provide evidence that it is possible to classify nonrestrictive patients into two groups significantly different from a prognostic standpoint. Despite similar degree of systolic dysfunction and functional class, nonrestrictive patients with ARd-Ad ≥30 ms showed a higher frequency of events at follow-up as opposed to those with nonrestrictive filling without that difference.

The observation of a nonrestrictive group with an intermediate risk of clinical events is in line with that made by Pozzoli et al. (13), who found that in a population with nonrestrictive flow a change in mitral flow pattern toward restriction during dynamic preload variations was associated with a worse prognosis compared to those with stable nonrestrictive flow. Results from the same study and those of a recent one (34) confirm a limited value of mitral E/A ratio in the prognostic assessment of nonrestrictive patients with LV dysfunction. Indeed, when E/A ≤1 and E/A >1 were employed to categorize our series nonrestrictive patients, the resulting two groups were not significantly different for occurrence of both cardiac events and HF events at follow-up. The high dependence of mitral flow velocity patterns to varying patient conditions, such as load, age and heart rate, may contribute to justify this observation (2,35–37). Moreover, severely impaired LV relaxation may account for blunting of early mitral flow with E/A ≥1 despite increased LV filling pressure (38).

The mechanism whereby nonrestrictive patients with increased ARd-Ad were associated with a large number of events at follow-up is not clear. Of interest, the number of sudden deaths (presumably arrhythmic) in our series was rather elevated in patients with this pattern. Hence, coexisting intrinsic myocardial abnormalities (e.g., myocardial fibrosis, responsible for either the elevation of LV diastolic pressure or the propensity to fatal arrhythmias) may be the substrate of this finding.

**Study limitations.** The major limitation of the study is the lack of simultaneous hemodynamic measurement with Doppler examination. However, the data from previous investigations are strong enough to support the association between elevated LV end-diastolic pressure and increased ARd-Ad; this may allow us to categorize patients according to this index (25,26). Although the deceleration time of early mitral flow was significantly different in the two groups of nonrestrictive patients, cutoff values based on the relative duration of atrial flow at pulmonary veins and mitral valve seem preferable as they are associated with clear-cut hemodynamic reference values regardless of the pattern.

Another limitation is that Doppler echocardiography was not used to perform quantitative assessment of mitral regurgitant jets (39). Even if this could have reduced the potential value of mitral regurgitation as a predictor of adverse events, methods to evaluate the regurgitant orifice area are not yet routine practice in our busy echocardiographic laboratory. Measurement of ventricular volumes by two-dimensional echocardiography has also been criticized. Although LV volume measurements were obtained by the biplane Simpson’s rule, detection of LV myocardial contours without tissue harmonic imaging or contrast-enhancement limited the image acquisition and accuracy of volume determination. Finally, because not all patients

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**Figure 3.** Twenty-four-month estimates of survival and event rates after index Doppler echocardiogram by Kaplan-Meier analysis. Groups were stratified according to restrictive mitral flow (group 1), nonrestrictive mitral flow with an ARd-Ad ≥30 ms (group 2) and nonrestrictive mitral flow with ARd-Ad <30 ms (group 3). (A) Rates of survival free from cardiac mortality. (B) Rates of cardiac event-free survival. (C) Rates of freedom from heart failure.
returned to our laboratory for a follow-up Doppler echocardiographic study, the evolution of mitral and PVF patterns and their modifications by medical therapy were not considered.

Conclusions. The major finding of the study is that an increased ARd-Ad ≥30 ms has an additive value in predicting prognosis of patients with LV systolic dysfunction. Particularly, this measure in asymptomatic nonrestrictive patients with LV dysfunction can aid clinical decision making by separating patients into those with different risk of clinical events at follow-up.

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REFERENCES

