Echo/Doppler and Hemodynamic Correlates of Vasodilator Responsiveness in Primary Pulmonary Hypertension*

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To determine correlates of acute vasodilator responsiveness in primary pulmonary hypertension, we retrospectively studied 25 patients, comparing 41 resting echo/Doppler and nine resting catheterization variables with the maximal reduction in pulmonary vascular resistance achieved during vasodilator trials. Twelve vasodilators were tested (mean, 5.6 drugs per patient; range, three to eight). Eight patients were vasodilator responsive, as defined by a reduction in pulmonary vascular resistance ≥30 percent in response to at least one agent. Univariate and multivariate analyses revealed only Doppler pulmonary peak flow velocity to be an independent correlate of responsiveness (p<0.05). Responders differed from nonresponders in having a higher Doppler pulmonary peak flow velocity (PV) (SD 81±24 vs 64±15 cm/s; p=0.05), lower mean right atrial pressure (RAP) (6±4 vs 13±7 mm Hg; p=0.04), and longer median survival (37 vs 5 months; p=0.03). Seven of eight responders had RAP ≤10 mm Hg, and all responders had PV >60 cm/s. Seven of ten patients with both RAP ≤10 and PV >60 and one of the 15 remaining patients were vasodilator responsive (p<0.001). Thus, echo/Doppler and invasive hemodynamic parameters correlate with acute vasodilator responsiveness in primary pulmonary hypertension. Patients with low PV and high RAP values were almost never vasodilator responsive. Doppler pulmonic peak velocity and mean RAP may be useful in identifying patients most likely to respond to acute vasodilator trials and those in whom testing is unlikely to yield positive results.

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PPH = primary pulmonary hypertension; PVR = pulmonary vascular resistance

Although pharmacologic therapy can improve resting pulmonary hemodynamics and alleviate symptoms in primary pulmonary hypertension (PPH), a beneficial response is neither universal nor predictable. With no clinical or noninvasive algorithm routinely available to identify patients likely to have a beneficial hemodynamic response to vasodilators, patients with PPH are often empirically subjected to expensive and invasive testing of multiple agents over several days, in the hope of finding one that reduces pulmonary vascular resistance (PVR) and increases cardiac output.

We and others have previously shown that both echo/Doppler and baseline catheterization parameters yield valuable prognostic information in patients with PPH. Since those patients who respond to vasodilator testing tend to live longer, we postulated that echo/Doppler and other characteristics identifying longevity will also identify vasodilator responsiveness. This is supported by the finding of Cooper et al that Doppler patterns are sensitive to pulmonary resistance and compliance. Thus, the purpose of this study was to determine retrospectively in our population of patients with PPH whether echo/Doppler assessments of cardiac function and baseline hemodynamic measurements correlated with acute vasodilator responsiveness. If so, initial catheterization and Doppler variables might be used to identify patients with PPH who are likely to respond to vasodilators acutely (i.e., those in whom drug testing would be worth the cost and morbidity) and to identify those unlikely to respond (i.e., those in whom testing and its attendant risks and costs might be avoided without compromise of care).

METHODS

Study Population

Twenty-five PPH patients with mean pulmonary artery pressures of SD 60±17 mm Hg who had undergone echocardiography within 1½ months of right heart catheterization formed the study population. The 17 female and eight male patients were aged 16 and 70 years (mean, 41 years). In all cases PPH was diagnosed on the basis of the criteria established by the National Heart, Lung, and Blood Institute for the PPH Registry. All echocardiograms were technically adequate. Sixteen echocardiograms were obtained within 2 days of catheterization (mean time between studies, 5.9 days). No patient was receiving anticoagulation or cardiac medications other than digoxin (n=5) at the time of study. Follow-up information was obtained from living patients and from physician records and/or autopsy reports for deceased patients. Six patients were alive at the time of follow-up (July 1990). Follow-up of survivors ranged from 25 to 69 months after evaluation.

Two-dimensional Echocardiography

Echocardiograms were obtained with commercially available

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ultrasonographic equipment. Standard views were used, and recordings were made when visualization of the endocardium and epicardium of each of the cardiac chambers was optimal. Using the apical four-chamber view, endocardial surfaces of each of the four chambers were traced on stop-frame images using a video screen and light pen interfaced with a computerized graphic analyzer. Right and left atrial and ventricular end-systolic (smallest ventricular cavity area) and end-diastolic (R-wave peak) cavity areas were digitized and averaged over three to five cardiac cycles. The percentage of change in right or left ventricular area was calculated as [diastolic area - systolic area/diastolic area] × 100. The percentage of change in right or left atrial area was calculated as ([systolic area - diastolic area/systolic area] × 100. Similarly, endocardial left ventricular area was digitized from the parasternal short-axis view at the high chorial level, and the percentage of change in left ventricular short-axis area was calculated. The interobserver reproducibility of these methods has previously been shown to be excellent in our laboratory (r = 0.96 to 0.98).  

Systolic and diastolic left ventricular eccentricity indices* were derived from the ratio of two short-axis diameters, each measured at end-systole and end-diastole. The diameter D2 was drawn parallel to the plane of the interventricular septum. The diameter D1 was drawn perpendicular to that plane, bisecting D2. The eccentricity index was defined as D2/D1. We chose to use only planar cavity areas, rather than calculating right and left ventricular and atrial volumes and ejection fractions, since such calculations would necessitate potentially erroneous geometric assumptions regarding chambers the shapes of which have been grossly distorted by the disease process under study. Further, even in normal subjects the right atrium and ventricle may be quite irregular.* In addition, the percentage of change in right ventricular area obtained from the apical four-chamber view has been closely correlated with scintigraphically and angiographically estimated ejection fractions in patients with right heart pressure overload.  

Two-dimensional echocardiographic variables included heart rate, severity of pericardial effusion, systolic and diastolic areas, and percentage of change in area for each of the four cardiac chambers. Additional left ventricular variables included systolic and diastolic eccentricity indices, systolic and diastolic short-axis endocardial areas, the ratio of short-axis diameter to long-axis left ventricular length, and the ratio of mean wall thickness to short-axis left ventricular radius.  

**Doppler Echocardiography**  
Two-dimensionally guided pulsed Doppler recordings were made with use of a commercially available ultrasonograph equipped with a strip-chart recorder. Mitral and tricuspid inflow velocities were recorded from the apical four-chamber view with the cursor positioned at the midpoint of each anulus, parallel to assumed flow. Pulmonary artery flow velocities were recorded from the parasternal short-axis view just above the level of the aortic valve with the cursor positioned at the midpoint of the pulmonic anulus in each patient. Three to six flow-velocity profiles were digitized and averaged for each valve. Measurements included peak velocities of left and right ventricular inflow in early diastole and accompanying atrial systole, their ratios, the areas under the early and atrial velocity curves, and total flow velocity area. Mean rates of acceleration and deceleration of rapid filling velocity were also determined. Pulmonic valve measurements included maximal pulmonic peak velocity; time from onset of flow to peak velocity, or acceleration time (AT); and right ventricular systolic time intervals, including duration of Doppler flow signal, or ejection time (ET); time from Q wave to onset of flow, or prejection period (PEP); and the ratios PEP/ET, AT/ET, and PEP/AT. The extent of tricuspid regurgitation was not considered a variable because all patients had severe regurgitation, as determined with pulsed Doppler flow mapping. In 11 patients, continuous-wave recordings of tricuspid regurgitant flow of sufficiently high quality were obtained from either the apical four-chamber or parasternal short-axis views, with three to five beats digitized for maximal systolic pressure gradient between the right ventricle and atrium. In the remaining 14 patients, either continuous-wave Doppler imaging was not available in our institution at the time of presentation or the study obtained was suboptimal.  

Interobserver variability of these Doppler methods was examined in a separate cohort of seven patients with pulmonary hypertension. Comparison of repeat studies performed by two observers showed the following correlations for peak right ventricular inflow velocities (r = 0.88, standard error of the estimate (SEE) = 8 cm/s) and peak left ventricular inflow velocities (r = 0.87, SEE = 11 cm/s). Repeated studies of right ventricular systolic time intervals derived from pulmonic flow velocity recordings were closely related (r = 0.94, SEE = 14 ms) with a slope of 1.08 and an intercept of 2.88.  

**Hemodynamic Studies**  
Right heart catheterization was performed in all patients with use of a balloon-flotation thermodilution catheter to record right heart, pulmonary arterial, and wedge pressures. All pressures were measured at end-expiration. Pulmonary vascular resistance (dynes/cm²) was calculated as [(PAP – PCWP)/CO] × 79.9, where PAP is mean pulmonary artery pressure (mm Hg), PCWP is mean wedge pressure (mm Hg), and CO is cardiac output (L/min). Cardiac output was determined with either the thermodilution method (in triple-cath) in patients without clinical findings of tricuspid regurgitation or the estimated Fick principle, whereby cardiac output equals nomographically predicted oxygen consumption divided by the arterial-venous oxygen content difference. Intracardiac shunting was excluded by assessment of oxygen saturations in the pulmonary artery and aorta. Hemodynamic variables included systolic, diastolic, and mean pulmonary arterial pressures; vascular resistance; right atrial pressure; systolic and diastolic systemic pressures; pulmonary wedge pressure; and cardiac index.  

**Vasodilator Studies**  
Systemic and pulmonary arterial pressures were recorded and cardiac output was repeatedly measured until reproducible baseline values were obtained. The number and sequence of vasodilators tested in each patient varied, as did the individual agents. On average, 5.6 drugs were tested in each patient (range, three to eight drugs), for a total of 140 trials. Agents studied included isoproterenol (22 patients), nitroprusside (21 patients), nitroglycerin (20 patients), nifedipine (18 patients), propranol (15 patients), acetylcholine (15 patients), phenolamine (12 patients), hydralazine (7 patients), verapamil (6 patients), diltiazem (2 patients), terbutaline (1 patient), and prazosin (1 patient). Each was given to the limits of patient tolerance, according to protocols previously published from our hospital. Briefly, the administration of any agent was discontinued if the blood pressure dropped below 95 mm Hg, if heart rate exceeded 120 beats per minute, or if the mean pulmonary artery pressure increased by more than 10 mm Hg over the baseline. A positive vasodilator response was defined as ≥50% reduction in PVR, a response pattern that has been associated with long-term therapeutic benefit.  

**Treatment Schedules**  
Subsequent vasodilator treatment was guided by the results of acute vasodilator testing and was monitored by a single physician (H.I.E.) in all cases. Maintenance vasodilator agents are shown in Table 1. Since it is not certain that the lack of an acute vasodilator response rules out the possibility of a response to chronic therapy, patients who did not meet criteria for acute responsiveness were nevertheless treated with the agent to which they were most
responsive. In patients in whom drug trials had resulted only in adverse effects, long-term therapy was not employed.

Statistical Analysis

Resting echo/Doppler and hemodynamic variables were compared with maximal changes in pulmonary vascular resistance by univariate and then multivariate linear regression. In patient subgroups stratified by vasodilator responsiveness, the unpaired t test was employed to determine significant differences between groups. Critical values for significant variables were selected by inspection of the distribution of the data; Fisher’s exact χ² analysis was performed to verify the significance of these values. Categorical variables thus created were then used to create a Doppler echocardiographic hemodynamic model. Kaplan-Meier survival curves for responders and nonresponders were compared using the nonparametric log-rank test.

RESULTS

Reductions in calculated PVR after vasodilator administration varied from 8 percent to 75 percent with a mean of 28 percent (median, 23 percent). Eight patients were responsive (change in PVR ≥30 percent) to at least one drug. Seven drugs resulted in a reduction in PVR ≥30% in at least one patient: nifedipine (5 of 18 patients studied responded), prostacyclin (4/15), nitroprusside (2/21), isoproterenol (2/22), hydralazine (1/7), phenolamine (1/12), and acetylcholine (1/15). One patient responded to four agents, 1 to three agents, 3 to two agents, and 3 to only one drug. Three patients had their maximal decreases in PVR to prostacyclin, 2 to nifedipine, and 1 each to phenolamine, nitroprusside, and isoproterenol.

Of all variables examined, only resting pulmonic...
peak flow velocity correlated with maximal percentage of change in PVR during drug testing ($r = -0.47$, $p = 0.01$) (Fig 1). No two-dimensional echocardiographic assessment of ventricular size or shape was significantly correlated with vascular responsiveness. Variables approaching significance ($p < 0.15$) were tricuspid peak velocity of atrial flow ($r = 0.37$, $p = 0.07$), mean right atrial pressure ($r = 0.36$, $p = 0.08$), the ratio of short-axis diameter to long-axis left ventricular length ($r = 0.34$, $p = 0.08$), the ratio of mean wall thickness to short-axis left ventricular radius ($r = 0.32$, $p = 0.12$), and the ratio of tricuspid atrial flow to total flow ($r = 0.30$, $p = 0.14$). With the use of multivariate analysis, these six variables were examined together, but only pulmonic peak flow velocity was independently significant ($r = 0.73$, $p = 0.04$). When compared with hemodynamic variables, pulmonic peak flow velocity correlated with cardiac index ($r = 0.39$, $p = 0.04$) and resting PVR ($r = -0.37$, $p = 0.07$) and was not related to pulmonary artery pressures.

A comparison of drug responders and nonresponders revealed significant differences in only three variables. Responders had longer median survival (37 vs 5 months) and mean survival (61 vs 11 months) ($p = 0.03$ by log-rank test). Kaplan-Meier survival curves are shown in Figure 2. Two-year Kaplan-Meier survival probabilities were 62 percent for responders and 17 percent for nonresponders (Table 2). Responders had lower mean right atrial pressures (6 vs 13 mm Hg, $p = 0.04$) (Fig 3). Responders had higher pulmonic peak flow velocity (81 vs 64 mm Hg, $p = 0.05$) (Fig 1).

Using optimal critical values of the baseline hemodynamic variables, we found that all responsive patients had a pulmonic peak flow velocity of $>60$ cm/s, and seven of eight responsive patients had a right atrial pressure of $\leq 10$ mm Hg. Seven of ten patients with both a right atrial pressure of $\leq 10$ mm Hg and a pulmonic peak flow velocity of $>60$ cm/s had a $\geq 30$ percent reduction in PVR produced by at least one agent, but only one of the remaining 15 was vasodilator responsive ($p < 0.001$).

The one patient who was vasodilator responsive with a right atrial pressure of $>10$ mm Hg (16 mm Hg) was unusual in that she lived only 12 days after treatment (the shortest survival in the responsive group). Of the three patients who were unresponsive to vasodilators, with a low right atrial pressure and high pulmonic peak flow velocity, two had lived for 15.5 and 7.5 months at the time of follow-up; the third patient died 2.8 months after study.

**Discussion**

Vasodilator therapy has been reported to be clinically beneficial in PPH patients, with responders having increased survival and long-term symptomatic benefit. Rich et al reported that a reduction in PVR of $>20$ percent in response to the short-term administration of nifedipine or hydralazine was predictive of longer survival. Reeves et al retrospectively reviewed 117 cases reported in the literature and found that 62% of PPH patients who achieved a $\geq 30$ percent reduction in PVR in response to short-term vasodilator testing had clinical or hemodynamic improvement for at least 3 months while receiving that agent, compared

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**Table 2—Kaplan-Meier Survival Probabilities for Responders and Nonresponders**

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<thead>
<tr>
<th>Interval (yr)</th>
<th>Responders</th>
<th>Nonresponders</th>
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<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>62</td>
<td>17</td>
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<td>3</td>
<td>47</td>
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with only 6 percent who experienced improvement while receiving medications that had acutely reduced PVR by <30 percent. Our finding of a survival benefit among patients who were drug responsive confirms the findings in these previous reports and supports the beneficial effects of vasodilator therapy in PPH.

Although other definitions of vasodilator responsiveness have been proposed, we employed the most rigorous published criteria in order to minimize confusion of spontaneous variability\(^\text{16}\) with drug responsiveness. The significant relationship found between decreased PVR and survival confirms the clinical usefulness of this definition.

The correlation between Doppler pulmonic peak flow velocity and maximal change in pulmonary vascular resistance found in this study is analogous to reports of a similar relationship between the aortic flow pattern and systemic vascular resistance in patients with congestive heart failure.\(^\text{17,18}\) In one study,\(^\text{17}\) patients who responded to a variety of drug treatments tended to have a higher peak acceleration and peak velocity of aortic flow than nonresponders. Elkayam et al\(^\text{19}\) found a correlation \((r = -0.89)\) between the percentage of change in Doppler aortic peak flow velocity and the percentage of change in systemic vascular resistance after vasodilator administration. Cooper et al\(^\text{20}\) studied children with pulmonary hypertension due to an interventricular communication and found that following successful vasodilator treatment mean pulmonary artery peak velocity increased in patients with vasodilator-responsive pulmonary hypertension.

Vasodilators may have substantial effects on pulmonary blood flow without marked changes in intravascular pressures.\(^\text{19}\) In general, Doppler pulmonic flow patterns should be affected by several factors, including the pressure difference between the right ventricle and the pulmonary artery, ventricular function, and the distensibility or compliance of the pulmonary circulation. Thus, the Doppler pulmonic flow pattern may be a better reflect of the physiologic parameters of the pulmonary circulation than are pulmonary artery pressures. We might therefore expect that as vascular compliance decreases and right ventricular systolic function worsens with advancing pulmonary hypertension, velocity of flow would decrease. That Doppler measures of pulmonic flow velocities do indeed provide insight into ventricular and vascular characteristics is supported by the closer relations we found between peak pulmonic velocity, cardiac index, and PVR as compared with pulmonary artery pressures.

High right atrial pressure in patients with PPH has been correlated with poor survival\(^\text{20,21}\) and may reflect use of preload reserve by the failing right ventricle\(^\text{22}\) to maintain systolic performance. If so, the correlation noted between low right atrial pressure and vasodilator responsiveness may indicate that those with better-compensated right ventricular systolic function are more likely to be drug responsive. This may reflect an earlier stage of pulmonary vascular disease. Alternatively, lower right atrial pressure may reflect better diastolic right ventricular function, a lesser degree of tricuspid regurgitation, higher right atrial compliance, or neurohumoral factors, each of which may also be markers of less advanced disease.

Gardin et al\(^\text{23}\) found that peak aortic flow velocity discriminated between normal subjects and patients with cardiomyopathy, in whom peak aortic flow velocities were markedly reduced with left ventricular systolic dysfunction. These data suggest that in patients with lower peak pulmonic velocity, more advanced disease and/or poorer right ventricular function may be reasons for their lack of vasodilator responsiveness.

**Limitations**

Data in this study were calculated in a nonsimultaneous, retrospective fashion (although in 64 percent of the patients echo/Doppler and hemodynamic data were obtained within a 2-day period). The lack of simultaneous data collection may have affected the relationships between pulmonic peak velocity and PVR or cardiac index. Furthermore, the true predictive value of these Doppler/hemodynamic predictors awaits confirmation in a prospective study.

Unfortunately, as in many other studies,\(^\text{1,2,13}\) our patients received a variety of vasodilator agents, and no single drug was tested in all patients. However, because of the large number of agents examined in each patient, it is unlikely that significant vasodilator responsiveness was missed, which could occur with more limited testing.\(^\text{13,14}\) Thus, our goal of assessing noninvasive indicators of responsiveness to any vasodilator appears to have been accomplished.

We chose to report only primary data directly obtained from our two-dimensional and Doppler analysis rather than possibly introducing artifacts by calculations of right ventricular volume, right atrial volume, or ejection fraction. However, it is possible that if validated methods were available, right atrial and ventricular volumes would prove to be significantly related to pulmonary vasodilator responsiveness. The lack of correlation between two-dimensional echo variables and the percentage of change in PVR after vasodilator administration suggests that aspects of cardiac size, shape, and ventricular function are less important in predicting vasodilator responsiveness than are variables reflecting pulmonary hemodynamics.

Although all vasodilator-responsive patients had a pulmonic peak flow velocity >60 cm/s, and the major-
ity of patients with a right atrial pressure ≤10 mm Hg and a pulmonic peak flow velocity >60 cm/s were vasodilator responsive, three patients who fit the "responsive" profile were unresponsive to vasodilator testing. Thus, vasodilator responsiveness is only partially described by these clinical parameters.

In summary, the occurrence together of right atrial pressure ≤10 mm Hg and pulmonic peak flow velocity >60 cm/s was associated with drug responsiveness in the majority of our patients. The converse is even more striking: low pulmonic peak velocity and high right atrial pressure were almost never seen in vasodilator-responsive patients. Since PPH patients who are responsive to vasodilator therapy have a better prognosis, our data suggest that a group of patients may be identified who are likely to benefit most from treatment and who therefore should undergo extensive vasodilator trials. Conversely, patients who are unlikely to benefit may also be identified. However, whether vasodilator testing should be omitted in PPH patients with right atrial pressure >10 mm Hg or pulmonic peak velocity <60 cm/s must await confirmation of the predictive value of these variables in a prospective study.

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