Echocardiographic Predictors of an Adverse Response to a Nifedipine Trial in Primary Pulmonary Hypertension*

Diminished Left Ventricular Size and Leftward Ventricular Septal Bowing

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Background: The clinical course in primary pulmonary hypertension (PPH) is improved by calcium channel blocker therapy in those with a favorable hemodynamic response during a trial of high-dose oral nifedipine. Although trials of nifedipine are performed only in patients who demonstrate pulmonary vasodilator reserve to short-acting agents, this response does not predict the safety of nifedipine treatment, which can result in severe first-dose hypotension and death.

Study objectives: To identify echocardiographic parameters that predict first-dose nifedipine-induced hypotension in patients with PPH.

Methods: The pretrial echocardiograms of 23 consecutive PPH patients (mean age, 42.3 ± 13 years; 77% female) undergoing evaluation of pulmonary vasodilator reserve with nifedipine were analyzed. Patients were classified as those who suffered first-dose nifedipine hypotension (group 1) and those who did not (group 2). Echocardiographic measures of chamber size and septal geometry in the two groups were compared.

Results: Five measures reflecting diminished left ventricular (LV) size and leftward ventricular septal bowing were found to be associated with nifedipine hypotension: LV transverse diameter in systole (LVDs; p = 0.007), LV transverse diameter in diastole (LVDd; p = 0.05), LV area in systole (LVAs; p = 0.009), LV area in diastole (LVAd; p = 0.03), the ratio of RV to LVAs (p = 0.02), and leftward ventricular septal bowing (p = 0.01). The LV dimensions found to best predict nifedipine-induced hypotension were LVDs < 2.7 cm, LVDd < 4.0 cm, LVAs < 15.5 cm², and LVAd < 20.0 cm².

Conclusions: Readily available echocardiographic parameters in patients with PPH are predictive of nifedipine-induced hypotension, and can be used to select patients in whom a trial of nifedipine should be avoided.

Key words: echocardiography; hypotension; nifedipine; primary pulmonary hypertension

Abbreviations: CO = cardiac output; LA = left atrium/left atrial; LV = left ventricle/left ventricular; LVAd = left ventricular area in diastole; LVAs = left ventricular area in systole; LVDd = left ventricular transverse diameter in diastole; LVDs = left ventricular transverse diameter in systole; LVSB = leftward ventricular septal bowing; mPA = mean pulmonary artery pressure; mRA = mean right atrial pressure; NYHA = New York Heart Association; PPH = primary pulmonary hypertension; PVR = pulmonary vascular resistance; RA = right atrium/right atrial; RV = right ventricle/right ventricular; RVSP = right ventricular systolic pressure

Primary pulmonary hypertension (PPH) is a rapidly progressive fatal disease primarily affecting young women. High-dose calcium channel–blocking drugs and continuous-infusion epoprostenol (Flolan; Glaxo Wellcome; Research Triangle Park, NC), and lung transplantation are the predominant treatment options, and the choice depends on functional class, severity of disease, and pulmonary vascular response to a vasodilator trial. The clinical course and prognosis in PPH is improved by long-term calcium channel blockade in approximately 25% of patients, those who demonstrate pulmonary vasodil-
Vasodilator trials in severe pulmonary hypertension, particularly with nifedipine, are not without added risk and expense. Oral nifedipine trials may be associated with first-dose severe systemic hypotension and death.\textsuperscript{11,12} Hypotension is generally considered the consequence of nonselective vasodilation affecting the systemic circulation and negative inotropy on the right ventricle (RV). A retrospective multicenter survey of nifedipine trials found an increased risk associated with high right atrial (RA) and pulmonary artery pressures and low cardiac output (CO), but no clinical or noninvasive hemodynamic parameters are predictive of nifedipine first-dose hypotension.\textsuperscript{11}

Although echocardiography can be used as a predictor of clinical outcome and survival in PPH,\textsuperscript{13–15} criteria predictive of an adverse response to nifedipine have not been reported. Several echocardiographic observations in severe pulmonary hypertension correlate with structural and hemodynamic changes that could cause or contribute to hypotension following administration of nonselective vasodilators. Louie et al\textsuperscript{16} and others\textsuperscript{17–20} have shown RV pressure overload to be associated with late systolic and early diastolic septal flattening, which impairs left ventricular (LV) filling. The alteration in septal configuration can also result in LV outflow tract obstruction simulating hypertrophic cardiomyopathy.\textsuperscript{21,22} We hypothesized that echocardiographic measures of impaired LV filling and LV outflow tract obstruction would identify PPH patients likely to develop first-dose nifedipine-induced hypotension.

**Materials and Methods**

**Hemodynamic Assessment**

Transthoracic echocardiograms were obtained in 23 consecutive PPH patients referred to the University of Michigan Pulmonary Hypertension Service for hemodynamic assessment and a vasodilator trial with high-dose oral nifedipine. Twenty of the 23 subjects underwent an acute trial with inhaled nitric oxide and/or IV prostacyclin,\textsuperscript{6} adenosine,\textsuperscript{7,8} and inhaled nitric oxide.\textsuperscript{9,10}

Echocardiograms were obtained using a standard protocol by one of three experienced technicians within 1 week preceding the nifedipine trial. Each study was recorded on standard VHS-format videotape. Standard and nontraditional measurements were performed by one of the investigators and confirmed by an experienced cardiologist without knowledge of the patient. In addition to conventional parameters of chamber size and wall thickness, the following were derived: apical four-chamber RA and left atrial (LA) area; diastolic and systolic RV and LV transverse diameter, longitudinal diameter, and area in the parasternal short-axis and apical four-chamber views; the ratio of apical four-chamber RA/LA area; the ratio of RV/LV diameter and area in the parasternal short-axis and apical four-chamber views (Fig 1); Doppler echocardiographic estimate of tricuspid regurgitation severity; RV systolic pressure (RVSP) estimate, and the presence of leftward ventricular septal bowing (LVS). End-diastole was defined at the R wave on simultaneous ECG recording. RVSP was defined as $4 \times (\text{peak tricuspid velocity})^2 + 14 \text{ mm Hg}$.\textsuperscript{23,24} Cavity dimensions of area and diameter were derived off-line by tracing the chamber endocardium from images digitized from videotape using commercially available graphics software (Tomtec P-90 echo review station; Boulder, CO). LVS was defined as systolic and diastolic reversal of the normal septal curvature with convex deformity of the septum into the LV.

**Statistical Analysis**

Statistical methods include the Student’s t test, univariate and multivariate analysis, and logistic regression analysis. Significance was inferred at $p < 0.05$ for nonparametric data. Because of the number of measured and derived observations for normally distributed variables, we consider $p < 0.001$ highly significant, $p \leq 0.01$ significant, and $p \leq 0.05$ likely significant.

**Results**

**Patient Population**

The patients were predominantly female, moderately to severely limited, and had a 70 ± 20% 1-year
survival based on the National Institutes of Health database (Table 1). Patients were classified into group 1 (hypotension) and group 2 (no hypotension) based on the systemic pressure response to the first dose of nifedipine. Twenty-two of the 23 patients received one or more doses of nifedipine. In one patient, nifedipine was considered contraindicated based on initial hemodynamic findings of markedly elevated right heart pressures and very low CO (mean right atrial pressure [mRA], 22 mm Hg; mean pulmonary artery pressure, [mPa], 64 mm Hg; and CO, 2.1 L/min). Because the primary goal of the study was to determine if echocardiographic parameters could identify a high-risk group, this patient was included in group 1.

Baseline Assessment

The six patients in group 1 had significantly different and generally worse baseline hemodynamics than those who tolerated nifedipine. Group 1 had higher mRA, mPA, mean systemic BPs, and pulmonary vascular resistance (PVR), but comparable CO (Table 2). Conventional Doppler echocardiographic findings in groups 1 and 2 are presented in Table 3. The LA and LV diameter (particularly the LV internal diameter in systole, p = 0.007) were less in group 1, and LVSB was detected in 3 of 6 group 1 patients (50%) vs 1 of 18 group 2 patients (p = 0.01). RV enlargement and RV hypertrophy was present in all patients.

<table>
<thead>
<tr>
<th>Table 1—Patient Demographics*</th>
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<tr>
<td>Patients, No.</td>
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<tr>
<td>Mean age, yr</td>
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<tr>
<td>Female, %</td>
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<tr>
<td>NYHA class (range)</td>
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<tr>
<td>Predicted 1-yr survival25, %</td>
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*Data are presented as mean ± 1 SD, unless otherwise indicated.

<table>
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<tr>
<th>Table 2—Baseline Hemodynamic Parameters*</th>
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<tr>
<td>Variables</td>
</tr>
<tr>
<td>RA, mm Hg</td>
</tr>
<tr>
<td>mPA, mm Hg</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
</tr>
<tr>
<td>CO, L/min</td>
</tr>
<tr>
<td>PAR, Wood units</td>
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<tr>
<td>mBA, mm Hg</td>
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</table>

*Data are presented as mean ± 1 SD; RA = right atrial pressure; PCWP = pulmonary capillary wedge pressure; PAR = pulmonary arteriolar resistance (mPA–PCWP/CO); mBA = mean arterial blood pressure. CO determined by thermodilution.
†Group 1, hypotension with nifedipine.
‡Group 2, no hypotension.

<table>
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<th>Table 3—Findings on Standard Doppler Echocardiography*</th>
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<tr>
<td>Parameters</td>
</tr>
<tr>
<td>LA, cm</td>
</tr>
<tr>
<td>LVDDd, cm</td>
</tr>
<tr>
<td>LVDDs, cm</td>
</tr>
<tr>
<td>IVS, cm</td>
</tr>
<tr>
<td>LVPW, cm</td>
</tr>
<tr>
<td>E : A ratio</td>
</tr>
<tr>
<td>TR</td>
</tr>
<tr>
<td>RVSP, mm Hg</td>
</tr>
<tr>
<td>LVSB, No.</td>
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<tr>
<td>RVE, No.</td>
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<tr>
<td>RVH, No.</td>
</tr>
</tbody>
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*Data are presented as mean ± 1 SD, unless otherwise indicated; LA = left atrial size; LVDDd = LV internal diameter in diastole; LVDDs = LV internal diameter in systole; IVS = interventricular septal thickness; LVPW = LV posterior wall thickness; E : A = mitral valve Doppler echocardiography to A wave ratio; TR = tricuspid regurgitation severity (range, 0 to 3+); BVE = RV enlargement (not routinely quantified); RVH = RV hypertrophy (not routinely quantified); NS = not significant. All patients had normal LV systolic function.

Univariate Analysis

We analyzed a total of 42 measured and derived variables. Those found to be significantly associated with nifedipine hypotension by univariate analysis are presented in Table 4. Five measures in the apical four-chamber view, reflecting diminished LV size and the presence of LVSB, were found to be significant or highly significant: LV transverse diameter in systole (LVDs, p = 0.007), LV transverse diameter in diastole (LVDDd, p = 0.05), the ratio of RV to LV area in systole (p = 0.02), LV area in systole (LVAs, p = 0.009), LV area in diastole (LVAd, p = 0.03), and LVSB (p = 0.01). Representative examples of short-axis, parasternal long-axis and apical four-chamber views from patients in group 1 are shown in Figures 2-4. The LV dimensions best discriminating...
the two groups are LVDs < 2.7 cm, LVDd < 4.0 cm, LVAs < 15.5 cm², and LVAd < 20.0 cm² (Table 5).

**Multivariate Analysis**

The six parameters were subjected to multivariate analysis to determine which, if any, were independent. As anticipated, because each measure is a function of LV size, none were independently associated with nifedipine hypotension.

**Logistic Regression Analysis**

To determine whether the measures of LV and RV diameter and area were simply a function of the severity of pulmonary hypertension, logistic regression analysis was performed controlling for noninvasive (Doppler echocardiography RVSP) and invasive hemodynamic parameters (mRA, mPA, CO, pulmonary artery resistance). All six variables remained significantly associated with nifedipine hypotension independent of pulmonary artery pressure as estimated by RVSP and the invasive measures of mRA, mPA and CO. The association between these six echocardiographic variables and nifedipine hypotension was diminished significantly when controlling for pulmonary artery resistance.

**DISCUSSION**

The rapid clinical progression and poor prognosis in patients with PPH warrants a multidisciplinary effort on the part of experienced cardiologists, pulmonologists, and lung transplant surgeons to determine appropriate treatment options. The parameters used to select treatment options include functional impairment and the response to a carefully performed pulmonary arterial vasodilator trial with inhaled nitric oxide, IV adenosine, or IV

**Table 5—LV Size Discriminators for Nifedipine Hypotension**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Diastole</th>
<th>p Value</th>
<th>Systole</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV diameter, cm</td>
<td>&lt; 4.0</td>
<td>0.02</td>
<td>&lt; 2.7</td>
<td>0.007</td>
</tr>
<tr>
<td>LV area, cm²</td>
<td>&lt; 20.0</td>
<td>0.04</td>
<td>&lt; 15.5</td>
<td>0.04</td>
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*Apical four-chamber transverse diameter and area measures below which there is a strong association with nifedipine hypotension.
epoprostenol. Standard adjunctive treatments generally include digoxin, anticoagulation with sodium warfarin, diuretics, and oxygen as necessary. Patients aged < 60 years (50 years in some centers) are referred for lung transplant evaluation. Those New York Heart Association (NYHA) class II and III patients with a ≥ 20% reduction in mPA or PVR, a cardiac index of ≥ 2 L/min/m² and without evidence of severe right heart failure (RA pressure > 12 to 14 mm Hg) may be candidates for oral calcium channel-blocking drugs. While continuous IV epoprostenol has been very useful in PPH patients with advanced symptoms, there remains a sizable number who may benefit from calcium channel blockers such as nifedipine and diltiazem.2 This group includes those with functional class I and II symptoms (for which epoprostenol is not approved by the US Food and Drug Administration), and the approximate 25% of NYHA class III patients with pulmonary vascular vasodilator reserve as determined by the acute vasodilator trial.26 Careful dose titration of oral calcium channel-blocking drugs with hemodynamic monitoring as described by Rich et al.3 is the preferred method, but these trials may be associated with first-dose severe systemic hypotension and death.11,12 While a decrease in pulmonary artery pressure and resistance following IV adenosine and prostacyclin is predictive of a similar response to high-dose nifedipine, these agents have not been shown to predict the safety of such a trial. Schrader et al.7 reported that 2 of 12 patients with a favorable response to adenosine later had nifedipine-induced hypotension, highlighting the importance of identifying those at risk for nifedipine hypotension independent of the acute screening vasodilator response.

We have identified readily available echocardiographic parameters useful for selecting patients in whom a trial of oral nifedipine would impose excessive risk. Each of the six patients in group 1 (26% of those tested) had diminished LV size and/or LVSB. Systolic dimensions were more strongly associated with nifedipine hypotension than diastolic dimensions. These associations were independent of pulmonary artery pressure elevation severity as estimated by RVSP, as well as the invasive measures of mRA, mPA, and CO. Interestingly, when controlling for pulmonary artery resistance, the association between the six echocardiographic variables and adverse nifedipine hypotension was diminished. This may reflect a strong direct relationship between PVR and the echocardiographic measures (i.e., the effect of increased PVR may be the most important determinant of the effect of pulmonary hypertension on the RV and therefore ventricular septum and LV).

### Mechanism of Nifedipine Hypotension

Severe RV pressure overload in PPH causes dramatic changes in the size and function of not only the RV, but also the LV. In the PPH registry of the National Institutes of Health, the degree of pulmonary hypertension as determined by pulmonary arterial resistance was inversely related to LV internal dimension.27 Several echocardiographic studies have reported that the reversal of the normal ventricular septal curvature in pulmonary hypertension results in impaired LV filling.26 The demonstration of a pattern consistent with hypertrophic cardiomyopathy and subaortic pseudo-obstruction of the LV outflow tract is of particular interest and importance.21,22 This anatomic substrate may contribute to the systemic hypotension associated with nifedipine. The lower LV pressure associated with systemic vasodilation is worsened by the LVSB and diminution of LV size that limit LV filling and stroke volume. The combination of nifedipine-induced systemic vasodilation and negative inotropy introduced to a ventricle with already impaired LV filling and outflow tract obstruction may explain the severity and refractoriness seen in those with first-dose nifedipine hypotension. It may also explain why acute arterial vasoconstriction is more effective than inotropic support for reversing the hypotension seen in this setting.

### Limitations

The number of subjects included in this report is relatively small. However, considering the strength of the results and the risk of death, we would be reluctant to perform nifedipine trials in PPH patients with an LVDd of < 4 cm, an LVDs < 2.7 cm, or significant LVSB. Because our study does not address whether a trial with a lower dose of nifedipine in high-risk patients is safe, we cannot conclude that these echocardiographic parameters should prescribe such a trial. In practice, however, we and others have witnessed severe systemic hypotension with a 10-mg test dose in the high-risk patient.

### Conclusion

Readily available echocardiographic parameters in patients with PPH are highly predictive of nifedipine-induced hypotension. The absence of these findings should not be construed to predict nifedipine efficacy or safety. When used in conjunction with clinical status, however, these parameters can assist in the selection of patients for whom a trial of nifedipine would impose increased risk.

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