Vasodilators and Primary Pulmonary Hypertension

Variability of Long-term Response

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Long-term response to vasodilator therapy was assessed in six patients with PPH. Following an acute trial, each patient was restudied after (1) two months of drug administration, (2) one month of abstinence from therapy, and (3) an additional two months of therapy. Three of six patients had no long-term reduction of PVR after treatment; one showed a progressive increase. Of the three patients whose PVR was still reduced at the end of the second therapy period none showed a return of PVR to baseline during the abstinence phase, which may suggest that long-term reduction of pulmonary vascular tone may modify the vasoconstrictive component of this disease. The heterogeneous response of this small number of patients to sequential drug administration and withdrawal demonstrates the difficulty of interpreting previously reported clinical trials and underscores the need for a well-designed controlled study of vasodilator administration in these patients.

(Chest 1989; 95:1185-8)

PVR = pulmonary vascular resistance; PPH = primary pulmonary hypertension; SVR = systemic vascular resistance; NYHA = New York Heart Association

Primary pulmonary hypertension is a lethal disease with an estimated two-year survival of 57 percent and five-year survival of 28 percent (from the Patient Registry for Characterization of Primary Pulmonary Hypertension, personal communication, Paul S. Levy). The only definitive therapy is heart-lung transplantation, but this is presently an option for only a few individuals because of the expense and the scarcity of available organs. Since vasoconstriction is thought to contribute to the increased PVR, vasodilators have been considered a possible alternative to transplantation or at least a way of maintaining patients until transplantation is feasible.

The efficacy of this form of therapy has been variable, at best, and a healthy skepticism remains as to its usefulness or even its ability to effect a sustainable reduction in PVR. In addition, there is a clearly demonstrated potential for serious side effects when these agents are used in this setting. This is a particular problem when reductions in SVR predominate or far exceed changes in PVR.

Clearly, the best method for evaluating the usefulness of any drug regimen is to study it in a double-blind, placebo-controlled trial. This has not been done with vasodilators in the setting of PPH because of the lethality of the disease (and thus the difficulty of denying treatment to a patient who shows some "beneficial" response) as well as the problems of blinding in a setting where the drugs have so many side effects and the population is so fragile. Because of this we attempted to study the question of long-term efficacy using a protocol which interspersed two treatment periods around a shorter period of no drug therapy.

Methods

Six patients with PPH were recruited to participate after the protocol was fully explained and consent was obtained according to the regulations of the Committee for the Protection of Human Subjects of the University of Texas Health Science Center at Houston. The PPH was diagnosed as the presence of pulmonary hypertension in the absence of any clear-cut etiology. Specifically there was no evidence of primary lung disease as defined by chest x-ray film and pulmonary function studies. Valvular heart disease, intracardiac shunt and left ventricular failure were ruled out during cardiac catheterization and connective tissue disease was eliminated by the absence of characteristic clinical and laboratory findings. Pulmonary embolic hypertension was ruled out by the finding of a normal or very low probability ventilation-perfusion lung scan.

Measurements

Invasive measurements were done in the University Clinical Research Center and the cardiac catheterization laboratory in the Hermann Hospital. For each study period, a right heart catheterization was done using a No. 7 French thermistor catheter introduced through the right internal jugular or femoral vein. A radial artery was cannulated with a short polyethylene catheter.

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Pulmonary and systemic vascular pressures as well as the ECG were continuously monitored and recorded on a multi-channel strip chart recorder. Cardiac outputs represent the average of three measurements. Pulmonary vascular resistance and SVR were calculated from the mean pressure across the vascular bed divided by the cardiac output. All measurements were obtained with the patient in the supine position, and repeat catheterizations were done at the same time of day and under similar environmental conditions.

**Drug Administration**

On the initial visit, catheters were inserted in the catheterization laboratory and then the patients were moved to the clinical research center where they were tested with three different vasodilators: intravenous nitroglycerine and hydralazine and sublingual nifedipine. The drugs were administered with either 4 h, as in the case of nitroglycerine, or 6 h, as in the case of nifedipine and hydralazine, allowed between drugs to prevent overlapping of drug events. Nifedipine was given as a 20-mg sublingual dose and measurements were made after 15, 30, 45 and 60 min. Hydralazine was administered as a 0.25 mg/kg intravenous infusion over 10 min with measurements taken after 20 and 40 min. Nitroglycerine was infused intravenously starting at 5 μg/min and the dose was increased by 5 μg/min every 3 min until mean systemic blood pressure decreased by 20 percent or heart rate increased by 20 beats per minute. Measurements were made during the highest dose tolerated. Patients were then placed on nifedipine, 20 mg by mouth four times a day, unless one of the other drugs was clearly superior at reducing the PVR.

**Study Phases**

There were three phases to the study. In the first phase, patients were maintained on the vasodilator for two months and then brought back for repeat catheterization in the cardiac catheterization laboratory. The measurements were made 2 h after the last dose of medication. Following this, the medication was stopped during phase 2 and the patient was followed up for one month while not taking any vasodilators. A third catheterization was done and the patient was restarted on the initial drug at the same dose for the additional two months of phase 3 wherein a fourth catheterization was done 2 h after the last dose.

Because of the heterogeneity of the response and the small number of patients who could be recruited into this type of drug trial, it was decided not to interpret group statistics. For this reason, a significant change in PVR, cardiac index and mean pulmonary artery pressure was assessed by confidence limits for a drug effect in one patient, which we had determined in a previously reported study of spontaneous hemodynamic variability in PPH. The 95 percent confidence limits for a significant change in cardiac output, pulmonary artery pressure and total pulmonary resistance are 29, 22 and 36 percent, respectively.

**RESULTS**

The characteristics of the six patients are summarized in Table 1. There were five women and one man with an age range of 22 to 54 years. Their functional status according to the NYHA classification was predominantly class 2 with one patient in class 3 and they had had their symptoms for 1 to 12 years. Five of six patients were treated chronically with nifedipine (20 mg every 6 h) and the sixth with isosorbide dinitrate (20 mg every 8 h). All six patients completed the three phases of the study and the four catheterizations.

The acute response to the drug chosen for long-term administration for each patient is shown in Figure 1 and Table 2. All but one patient (No. 2) had a greater than 20 percent reduction in PVR. However, using

<table>
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<th>Patient</th>
<th>Age (yr)</th>
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<th>NYHA Class</th>
<th>Years of Symptoms</th>
<th>Drug Regimen</th>
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<td>4</td>
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<tr>
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<td>34</td>
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Table 1—Characteristics of Six Patients with PPH

<table>
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<th>Baseline</th>
<th>Drug</th>
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<td>1.6</td>
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<td>2.0</td>
<td>2.3</td>
<td>17.1</td>
<td>11.6</td>
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</tbody>
</table>

Table 2—Hemodynamic Response to Acute Vasodilator Administration

**FIGURE 1.** The acute response of selected cardiovascular parameters to the administration of a pulmonary vasodilator expressed as a percentage of the control value. In all but patient 5 the data shown are in response to sublingual nifedipine. For patient 5 the data are in response to intravenous nitroglycerine. The dotted lines represent the 95 percent confidence limits for a significant change as previously determined (see Rich et al).
the 95 percent confidence limits for a significant response, previously determined based on the intrinsic variability of the hemodynamic measurements in patients with PPH, only patient No. 5 would have qualified as having a significant improvement. Acute increases in cardiac index and reductions in mean pulmonary artery pressure were more variable. Using the same criteria as for PVR, only one patient (No. 5) had a significant reduction in pulmonary pressure and another (No. 4), a significant increase in cardiac output.

The chronic response to the three phases of the study is shown in Table 3 and Figure 2. The heterogeneity of the long-term response of PVR to treatment is obvious. No patient demonstrated the expected alternating changes coincident with initiation and cessation of drug therapy. Three patients (No. 1, 4, and 6) had a significant reduction of PVR at the end of the third phase of the study. While there was a tendency for some increase of PVR during the one month of drug cessation in patients 4 and 6, all three of these maintained a reduced PVR during the abstinent phase of the study. Two patients had no apparent response to drug therapy. The only patient with a significant acute reduction of PVR (No. 5) failed to maintain it through the initial chronic phase of therapy and, in fact, showed a progression of the pulmonary hypertension apparently uninfluenced by the presence of the vasodilator.

The changes in cardiac output followed the course of drug therapy with more consistency in that cardiac output fell when the vasodilator was stopped and rose on reintroduction of treatment in each case. The changes in mean pulmonary artery pressure showed no apparent relationship to the manipulation of drug therapy. Subjectively, all six patients felt better when they were on their medication despite the marked variability in their hemodynamic measurements.

**DISCUSSION**

There are a large number of clinical studies which have documented the effect of acute and chronic vasodilator therapy on pulmonary hemodynamics in patients with PPH. Estimates of the total number of patients likely to respond in a favorable manner to an acute vasodilator trial range from 15 to 50 percent. As many as 50 percent of these acute responders have been reported as sustaining the reduction of PVR months to even years after the initiation of the therapy.

Many of these reports have suffered from the use of subjective feelings on the part of the patient as a parameter of improvement. Others have taken an arbitrary change in hemodynamic variables as an index of success. None has compared the response to a proximate control group. We attempted to improve upon previous studies by using each patient as his own control during the non-treatment period of observation. Unfortunately, this study design, in retrospect, had many of its own faults which make it difficult to come to any firm conclusions. In particular, its complexity precluded a large enough patient enrollment to allow for direct statistical analysis of the data.

Reeves et al suggested that the acute response to a vasodilator may be used to predict a long-term improvement. In their review of multiple drug trials reported in the literature, only 6 percent of patients sustaining an acute reduction of PVR of less than 30 percent had a long-term benefit in contrast to 62 percent of those whose acute reduction was greater than 30 percent. We have previously suggested that in an individual patient, a reduction of PVR of greater than 39 percent was necessary to be certain that the response was due to the drug and not to spontaneous variability. In the small group of patients reported here, the more lenient limit (PVR decrease by 30 percent or greater) would have picked out two of the three long-term responders while the more restrictive one (greater than 39 percent) would have selected none. The best acute response was seen in the one patient whose PVR continued to increase during chronic therapy with isorbidine dinitrate (Isordil), emphasizing the difficulty in predicting long-term success in any individual patient with this type of acute trial. However, it is also possible that this discordance was due to differing potency of the intravenous and oral

**Table 3—Hemodynamic Response to Chronic Vasodilator Administration**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mean Pulmonary Artery Pressure (mm Hg)</th>
<th>Cardiac Index (L/min/m²)</th>
<th>PVR (L/min/mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base line</td>
<td>1st Drug Period</td>
<td>Off Drug</td>
</tr>
<tr>
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<td>40</td>
<td>37</td>
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</tr>
<tr>
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</tr>
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<td>62</td>
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nitrate preparations.

The acute changes in cardiac index and pulmonary pressure were equally inaccurate in predicting eventual long-term responders. The one patient with a significant drop in mean pulmonary artery pressure was the one who progressed during the chronic phase. Only one of three long-term responders had a significant acute increase in cardiac index.

One of the goals of this study was to demonstrate a reversible and reproducible change in hemodynamics as a result of pharmacologic intervention. The only variable which demonstrated the expected reciprocal change was cardiac index, which increased during the period of drug treatment and fell during the abstinence phase. Mean pulmonary artery pressure did not change much throughout the study period and showed no tendency to fall in response to drug therapy.

The three patients whose PVR was significantly improved at the end of the second drug period compared with baseline showed a persistence of the improvement achieved with the first two months of therapy during the abstinence phase and then into the second drug phase. The persistent reduction in PVR during the period of time that no drug was administered was unexpected and is difficult to explain. One possible explanation is that we were seeing an extreme example of spontaneous variability in the hemodynamic measurements. However, in at least two patients (No. 1 and 6), the reduction of PVR exceeded the 95 percent confidence limits for spontaneous variability expected in these patients, although it should be noted that these limits were derived from the variability measured over hours and not days and thus may underestimate the variability possible over the longer length of this study. A second possibility is that these patients underwent spontaneous remission during the study. The natural history of this disease, unmodified either in a beneficial or detrimental manner by attempts at treatment, has never been clearly defined. While it is the general impression that this disease is one of progressive deterioration, albeit at differing rates in different patients, examples of apparent spontaneous improvement have been reported. These have been quite rare, however, and it would seem unlikely that three such patients would be included in this small a cohort.

An intriguing possibility is that the initial two months of vasodilatation in some way modified the vasoconstrictive component of the pulmonary hypertension. Vascular smooth muscle is known to respond to increases in wall stress by increasing intrinsic tone. This may be due to a myogenic reflex where an increase in excitation-contraction is elicited or to the effect of prolonged muscle elongation induced by an alteration in the actin and myosin crosslinking. A myogenic response has been suggested as an amplification mechanism in pulmonary hypertension and thus a reduction in tone secondary to vasodilator therapy could have had a prolonged effect by a reversal
of this mechanism. Alternatively, Laks et al10 have described a neurogenic reflex in which proximal
distention of the main pulmonary artery leads to distal
increases in PVR. Reductions in tone could reverse
any contribution from this mechanism.

Recently it has been pointed out by Robin1 that
little is known about the true natural history of PPH
or whether or not vasodilators have any impact,
positive or negative. The data reported here unfortu-
nately may be most useful only to emphasize this sad
state of affairs and point out the need for a carefully
done truly controlled trial of vasodilator therapy in
this difficult patient population.

REFERENCES
1 Robin ED. The kingdom of the near dead: the shortened
unnatural life history of primary pulmonary hypertension. Chest
1987; 92:330-34
2 Packer M, Greenberg B, Massie B, Dash H. Deleterious effects
of hydralazine in patients with pulmonary hypertension. N Engl
J Med 1982; 306:1326-31
3 Rich S, D’Alonzo GE, Dantzker DR, Levy PS. Magnitude and
implications of spontaneous hemodynamic variability in primary
pulmonary hypertension. Am J Cardiol 1985; 55:159-63
4 Packer M. Vasodilator therapy for primary pulmonary hyperten-
sion. Ann Intern Med 1985; 103:258-70
5 Reeves JT, Groves BM, Turkevich D. The case for treatment of
selected patients with primary pulmonary hypertension. Am
Rev Respir Dis 1986; 134:342-46
6 Rozkovec A, Montanes F, Oakley CM. Factors that influence
the outcome of primary pulmonary hypertension. Br Heart J
1986; 55:449-56
7 Bourdillon PDV, Oakley CM. Regression of primary pulmonary
hypertension. Br Heart J 1976; 38:264-70
8 Johnson PG. The myogenic response. In Bohr DF, Somlyo AE
Sparks HV, eds. The cardiovascular system. Bethesda, MD:
American Physiological Society, 1980:409-42
9 Harris P, Heath D. The human pulmonary circulation Edin-
10 Laks MM, Juratsch CE, Garner D, Benzell J, Criley JM. Acute
pulmonary artery hypertension produced by distention of the
main pulmonary artery in the conscious dog. Chest 1975; 68:807-
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