The Role of Vasodilators in Patients with Progressive Systemic Sclerosis*

Interstitial Lung Disease and Pulmonary Hypertension


The use of systemic vasodilator drugs in reducing pulmonary artery pressures in patients with pulmonary hypertension is controversial. The effect of hydralazine in four patients with pulmonary hypertension resulting from interstitial lung disease (group 1) and nifedipine in four patients with pulmonary hypertension secondary to progressive systemic sclerosis (group 2) was investigated. Hydralazine blunted exercise induced elevations in pulmonary arterial pressures in individual group 1 patients; nifedipine failed to effect significant salutary hemodynamic changes in any group 2 patients.

Most studies investigating the role of systemic vasodilators in the treatment of pulmonary hypertension have concerned themselves with patients with primary pulmonary hypertension or cor pulmonale secondary to obstructive lung disease. A spectrum of responses, varying from an increase in cardiac output with a decrease in pulmonary artery pressures to simultaneous increases in pulmonary artery pressures and cardiac outputs, has been observed. Which patients will respond to vasodilators cannot be determined without invasive monitoring of systemic and pulmonary vascular pressures and cardiac outputs. Less commonly studied are those patients with secondary pulmonary hypertension from such entities as far-advanced interstitial lung disease (ILD) and progressive systemic sclerosis (PSS). Pulmonary hypertension occurs in from 35 to 80 percent of patients with PSS. The etiology of this hypertension is complex; in addition to hypoxia and loss of capillary units, there is probably some degree of reactive pulmonary vasoconstriction, the so-called Ravnauld's phenomenon of the pulmonary vascular tree. Whether these patients will respond to vasodilators has not been studied in detail. This investigation determined the hemodynamic effect of various vasodilators in patients with far advanced ILD and PSS.

Materials and Methods

Pulmonary hypertension is defined as a mean resting pulmonary artery pressure (PAP) greater than 20 mm Hg or an exercise PAP greater than 30 mm Hg.

Two groups of patients were studied:

Group 1: Hydralazine treatment.—Three patients with severe sarcoidosis and one patient with mixed connective tissue disease.

Group 2: Nifedipine treatment.—Four patients with PSS.

After determining that the patients met our criteria for entry into the study, a balloon-tipped right heart catheter was inserted via a brachial or internal jugular vein into the right heart. The following baseline measurements were determined: systemic blood pressure (SBP), systolic and diastolic pulmonary artery pressures, PAP (mean), cardiac output (CO), systemic and pulmonary vascular resistance (SVR and PVR). The patients exercised on a bicycle ergometer at 75-100 watts for three to nine minutes, until they achieved a steady-state PAP.

Following this baseline period, hydralazine (group 1) or nifedipine orally (group 2) was administered. The dose of drug was the amount which caused the resting SVR to fall by 20 to 40 percent from baseline (predrug) values. To attain this new SVR level usually required 25 to 50 mg of hydralazine or 20 to 50 mg of nifedipine. The above studies were repeated after 30 to 60 minutes.

Table 1—Hemodynamics Before and After Hydralazine in Group 1 Patients*

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*Control; e = exercise; t = p < 0.05 pre- vs postdrug PAP, FVR, SVR, CO = L/min; SBF = mm Hg.

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Analysis of variance was employed for intragroup comparisons. When a significant difference was found, a modified, paired t test was used (± SD).

RESULTS

Group 1 (Table 1)

Patients 1 to 3 had sarcoidosis and patient 4 mixed connective tissue disease. All had moderate restrictive disease (FVC 60 ± 19 percent of predicted) and exercise-induced hypoxemia (58 ± 16 mm Hg). Resting PAP (predrug administration) was 26 ± 7.6 mm Hg. With exercise, PAP increased significantly to 48.5 ± 9.7 mm Hg (p < 0.01). CO also increased significantly from rest to exercise while the SVR fell. There was no significant change in any other parameter measured from rest to exercise.

After hydralazine administration there was no significant change in resting PAP, but there was a significant fall in resting SVR and an increase in CO (p < 0.05). With exercise (postdrug) PAP increased to a value not significantly different from the predrug exercise PAP. There was no significant change from rest to exercise in any other parameters except CO.

Group 2 (Table 2)

The four patients with PSS had moderate to severe restrictive lung disease (FVC 49 ± 13 percent of predicted). Mean resting PAP prior to nifedipine administration was 22 ± 5.7 mm Hg. PAP increased with exercise to 39 ± 6.7 mm Hg. There was no other significant change in any other parameter from rest to exercise. Following nifedipine administration, there was no significant change in any resting parameter except SVR compared to predrug levels. With exercise, postdrug PAP increased to 39 ± 9 mm Hg, which was not significantly different from baseline predrug exercise values. There was no other significant difference in any other parameter compared to predrug exercise levels.

Two patients had unusual hemodynamic reactions. One patient (who did not have pulmonary hypertension at rest or with exercise and therefore was not included in the study) had a dramatic increase in PAP (from 26/12 to 90/22 mm Hg) immediately following the injection of iced (0°C) saline solution for CO determinations. The PAP slowly returned to normal over ten minutes during this time. The patient experienced systemic hypotension (BP 60/0 mm Hg), which responded to IV fluid administration and leg raising.

During insertion of an arterial cannula, another patient complained of upper extremity pain (Raynaud's phenomenon). The BP increased to 160/100 mm Hg, with a concomitant rise in the PWP from 8 to 32 mm Hg. PAP rose from 24/10 to 60/33 mm Hg. These changes reversed within ten minutes as the Raynaud's phenomenon abated.

DISCUSSION

Our results indicate that pulmonary hypertension at rest or with exercise is relatively common in patients with far-advanced ILD (group 1) and PSS (group 2). In group 1 treatment with hydralazine, an arterial vasodilator drug caused a minimal but nonsignificant decrease in exercising PAP; a significant decrease in resting SVR, and an increase in resting CO. Individual patients had some blunting of the exercise-induced pulmonary hypertension, although the biggest fall was 18 percent compared to predrug baseline exercise values.

In group 2 patients, although there was a significant decrease in resting SVR following nifedipine treatment, there was no decrease in PAP at rest or with exercise compared to predrug levels. In two patients who were followed up during long-term nifedipine therapy, there was no evidence for further improvement in these parameters.

Two patients with PSS had marked elevations in their PAP during our study; one patient had what could be interpreted as a Raynaud's phenomenon of the pulmonary artery and the other had PAP elevations secondary to either transient left ventricular failure or a decrease in left ventricular compliance.

In conclusion: (1) the role for nifedipine in the therapy of patients with PSS remains unclear. Patients with a vasoconstrictive component to their pulmonary hypertension may be helped; (2) in selected patients with far-advanced ILD, hydralazine may blunt the exercise-induced pulmonary hypertension; and (3) elevation in PAP may be induced by invasive procedures or the injection of iced saline solution in patients with PSS.

REFERENCES


DISCUSSION

The question was raised as to the mechanisms responsible for pulmonary hypertension in the interstitial lung diseases and scleroderma. It is not clear to what extent vasoconstriction, intravascular obstruction, or the loss of vessels is responsible for the observed pulmonary hypertension. While in the interstitial lung diseases a marked reduction in vital capacity (<50 percent of expected) correlates with the
presence of pulmonary hypertension at rest, there is no morphologic study measuring the extent of vascular disease or the severity of interstitial disease in relation to pulmonary hypertension. The poor response of the patients with interstitial disease to hydralazine was comparable to the observations of another group, which had also used vasodilators in similar patients. The lack of response may indicate that vasconstriction plays a relatively small part in the mechanism of the pulmonary hypertension. The use of bleomycin to produce an interstitial lung disease in animals may permit study of the mechanisms underlying the development of pulmonary hypertension.

The question was asked, how important is pulmonary hypertension in the prognosis of patients with interstitial lung disease? While no data specifically address the role of pulmonary hypertension in patients with severe sarcoid, these patients have a high mortality and frequently develop right heart failure. Similarly, in COPD poor survival has been reported to be correlated with the presence of pulmonary hypertension.

With regard to scleroderma, it was pointed out that there may be patchy fibrosis in both arteries and veins, medial hypertrophy, and even plexogenic lesions. There is no other disease which can give rise to such a variety of vascular abnormalities. The presence of plexogenic lesions in some patients raises the possibility of an overlap with primary pulmonary hypertension.

The reactivity of the pulmonary vascular bed in some patients is illustrated by the severe pulmonary hypertensive response of the patient given iced saline solution during cardiac output measurement. That the pulmonary hypertensive response to cold also applied to environmental cold has been demonstrated in calves and included the observation of pulmonary vasoconstriction. The mechanisms raised as possibly being responsible for the pulmonary hypertension included increased renin release, augmented sympathetic tone, myocardial ischemia, and pulmonary venospasm. The rise in right atrial pressure was considered to be unprecedented and unexplained.

### Does Pulmonary Vasoconstriction Play an Important Role in Patients with Primary Pulmonary Hypertension?*

**A Skeptic's View of Vasodilator Therapy**

*Milton Packer, M.D.†*

Despite isolated reports of dramatic hemodynamic and clinical improvement over the past 30 years, most patients with primary pulmonary hypertension fail to benefit from treatment with vasodilator drugs and many develop serious adverse reactions. The failure of this approach strongly suggests that pulmonary vasoconstriction does not play an important role in the pathogenesis of this disorder.

Because vasodilator drugs have proved to be a useful approach to the management of patients with systemic hypertension and left ventricular failure,† there has been great interest in their application in the treatment of patients with primary pulmonary hypertension. This therapeutic approach makes a number of assumptions that need to be critically evaluated: (1) pulmonary vasoconstriction plays an important role in a significant number of patients with primary pulmonary hypertension; (2) pulmonary vasoconstriction is pharmacologically responsive to drug therapy; (3) drugs can be developed that selectively antagonize this vasoconstrictor response; and (4) the benefits of drug therapy can be sustained for long periods with few adverse reactions.

Most of the evidence that pulmonary vasoconstriction plays an important role in the pathogenesis of pulmonary hypertensive states is derived from the study of patients with hypoxic pulmonary hypertension and reactive pulmonary hypertension associated with mitral valve disease, in whom a dramatic reduction of pulmonary artery pressures follows specific therapeutic interventions, such as oxygen therapy and mitral valve surgery.‡ Unfortunately, there is little evidence that pulmonary vasoconstriction contributes to the clinical state of patients with primary pulmonary hypertension. Although the presence of medial hypertrophy in the pulmonary arterioles of affected patients.§ and the association of primary pulmonary hypertension with disorders of known vasospastic origin¶ suggest that pulmonary vasoconstriction is important in patients with primary pulmonary hypertension, the ultimate test of this hypothesis is the demonstration that hemodynamic and clinical improvement follows the administration of pulmonary vasodilator drugs to patients with this disorder. Unfortunately, our personal experience suggests that a successful therapeutic outcome following the use of currently available drugs is distinctly uncommon. It remains unclear, however, whether our unfavorable experience is due to the fact that the importance of pulmonary vasoconstriction has been overstated or that currently available drugs are seriously flawed in their ability to achieve this goal.

### Early Experience with Vasodilator Drugs

Initial attempts to dilate the pulmonary vasculature pharmacologically in patients with primary pulmonary hypertension were cautiously conducted with drugs that were administered directly into the pulmonary artery and had a brief