symptoms tended to be associated with a greater pulmonary vascular responsiveness to vasodilators. It is not clear that this is also correct in adults. One patient was mentioned with an extremely responsive pulmonary vasculature, who died within ten months of diagnosis despite vasodilator therapy. Patients who show no response to prostacyclin are unlikely to respond to other vasodilators. If such patients are severely compromised, both hemodynamically and symptomatically, they may be candidates for heart-lung transplantation.

Probably prostacyclin is the best agent, both in terms of efficacy and safety, to assess the potential for pulmonary vasodilation acutely. Prostacyclin is not widely available. Prostacyclin E, may have similar characteristics. One discussant indicated that IV diltiazem, on the other hand, may be unsafe and recommended that the effects of oral administration of diltiazem be assessed hemodynamically after a week to avoid IV use.

Use of Calcium Channel Blockers in Hypoxic Lung Disease*

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COPD patients who are hypoxic develop pulmonary hypertension primarily because alveolar hypoxia induces muscular hypertrophy of pulmonary arteries. This muscular hypertrophy will regress in animals if they receive continuous oxygen therapy. Since many COPD patients refuse to use oxygen continuously, calcium channel blockers, which inhibit hypoxic pulmonary vasoconstriction, may be effective adjuvant therapy. Nifedipine lowers pulmonary vascular resistance during rest and exercise in hypoxic COPD patients.

The rationale for considering the combined use of vasodilators and low-flow oxygen in patients with COPD and hypoxemia is based on five hypotheses. The extent to which these hypotheses are correct will likely determine the long-term usefulness of vasodilators in these patients.

1. Hypoxic pulmonary vasoconstriction and hypoxia-induced vascular smooth muscle hypertrophy play key roles in the pathogenesis of pulmonary hypertension in patients with COPD.
2. The changes caused by alveolar hypoxia—hypertrophy of vascular smooth muscle, pulmonary hypertension, and right ventricular hypertrophy—are potentially reversible.
3. Even short periods of hypoxia on a chronic basis will cause arterial smooth muscle hypertrophy, pulmonary hypertension, and right ventricular hypertrophy.
4. Low-flow oxygen therapy may not, in portions of the lung, eliminate alveolar hypoxia, especially during exercise. Consequently, low-flow oxygen may be insufficient therapy to cause regression of the hypoxia-induced pathologic changes.
5. Long-term therapy with vasodilator drugs may augment the beneficial hemodynamic effects of low-flow oxygen therapy.

Although polycythemia and destruction of the pulmonary vascular bed by emphysema may contribute to the development of pulmonary hypertension in patients with COPD, the clinical and pathologic evidence available indicates that alveolar hypoxia is probably the major mechanism. Ample evidence exists in laboratory animals that the pathologic changes caused by hypoxia will reverse. Although little clinical data exist, the study of Sime et al clearly demonstrates the potential for reversibility in man. They found that high-altitude natives with hypoxic pulmonary hypertension had remarkable regression of their pulmonary hypertension after living at sea level for two years. Intermittent exposure to hypoxia is a potent stimulus for the development of the physiologic and pathologic changes caused by hypoxia. In fact, a recent report suggests that two hours per day of hypoxia may be sufficient to produce these pathologic changes. Intermittent periods of hypoxia will also maintain the pathologic changes caused by hypoxia, whereas continuous relief of hypoxia will promote regression of these changes.

**LOW-FLOW OXYGEN**

Low-flow oxygen therapy improves mortality in patients with COPD and hypoxemia. Although long-term low-flow oxygen therapy slows the rate at which pulmonary vascular resistance increases in these patients, it does not lead to a dramatic reduction in pulmonary vascular resistance. If continuous inhibition of hypoxia is required for regression of the pathologic changes, part of the lack of dramatic improvement in pulmonary vascular resistance may be the intermittent use of oxygen by patients. Most patients, because of social, psychological, or financial reasons, refuse to use oxygen continuously. Additionally, low-flow oxygen therapy may not completely eliminate focal areas of alveolar hypoxia in these patients, especially during exercise. The further reduction in pulmonary vascular resistance produced when nifedipine is added to low-flow oxygen therapy supports the concept that focal areas of hypoxic pulmonary vasoconstriction persist despite low-flow oxygen therapy.

**CALCIUM CHANNEL BLOCKERS**

The effects of a variety of calcium channel blockers have been assessed in patients with COPD and hypoxemia. We have been most interested in the possible role of calcium channel blockers because these compounds inhibit hypoxic pulmonary vasoconstriction. In 1976 McMurtry et al reported that verapamil inhibited hypoxic pulmonary vasoconstriction in rats. Subsequent studies have shown that nifedipine will inhibit acute hypoxic pulmonary vasoconstriction in...
laboratory animals. Although few studies have compared the effectiveness of different calcium channel blockers, Young et al. found that nifedipine was more effective in inhibiting the acute hypoxic pressor response in dogs than were verapamil or diltiazem.

A number of investigators have also addressed the question of whether chronic therapy with calcium channel blockers will attenuate the physiologic and pathologic changes produced in a rat model of hypoxic pulmonary hypertension. Overall, these studies demonstrate that verapamil or nifedipine therapy will attenuate the development of these pathologic changes in the rat. Stanbrook et al. recently published an article comparing the acute and chronic effects of verapamil, hydralazine, and nifedipine in hypoxic rats. Although all three vasodilator drugs prevented acute hypoxic pulmonary vasoconstriction in the rat, only long-term therapy with nifedipine significantly reduced the pulmonary vascular remodeling and right ventricular hypertrophy caused by chronic hypoxia. Stanbrook et al. also found that nifedipine promoted the regression of the pulmonary vascular changes in rats with hypoxic pulmonary hypertension despite their continued exposure to intermittent hypoxia. Thus, studies in laboratory animals clearly demonstrate that calcium channel blockers will inhibit hypoxic pulmonary vasoconstriction and, more importantly, attenuate the pathologic changes caused by alveolar hypoxia.

Calcium channel blockers have also been studied in patients with COPD and hypoxemia. Simonneau et al. studied the acute effect of nifedipine in 13 COPD patients with acute respiratory failure. They found that nifedipine acutely inhibited hypoxic pulmonary vasoconstriction, reducing pulmonary artery pressure and pulmonary vascular resistance. All measurements were made at rest in these critically ill patients. They also found that nifedipine did not further lower pulmonary vascular resistance when combined with high-flow oxygen therapy (average PaO₂ 277 mm Hg). Brown et al. studied the acute effect of intravenous verapamil during rest and exercise in stable COPD patients who were not hypoxic on room air. They failed to find any significant pulmonary hemodynamic effects of verapamil in this subset of COPD patients. Our group undertook a double-blind, controlled trial in clinically stable COPD patients with cor pulmonale and hypoxemia. Our objective was to determine whether nifedipine would acutely inhibit hypoxic pulmonary vasoconstriction during rest and exercise in these patients. We also sought to quantify the acute hemodynamic effects of nifedipine and determine whether nifedipine would augment the hemodynamic effects produced by low-flow oxygen.

**Results**

Nifedipine therapy completely inhibited hypoxic pulmonary vasoconstriction in these patients. We have subsequently evaluated the acute effect of nifedipine in 12 patients with COPD and hypoxemia. The results in this larger group of patients confirm our published findings (Fig I). While the patients breathed room air, nifedipine significantly reduced pulmonary vascular resistance index (PVRI) by 26 percent during rest and by 46 percent during exercise. Nifedipine did not reduce mean pulmonary artery pressure during rest, but dramatically reduced it during exercise (45 ± 3 vs 55 ± 3 mm Hg, p<0.001). Nifedipine significantly increased cardiac output during rest and exercise. Nifedipine did not affect right ventricular stroke work index (RVSWI) during rest, but significantly reduced RVSWI during exercise by 28 percent. Concomitant with its inhibition of hypoxic pulmonary vasoconstriction nifedipine reduced PaO₂ during rest by 7 ± 2 mm Hg. Mixed venous O₂ tension was unchanged by nifedipine therapy. Nifedipine increased O₂ delivery at rest by 10 percent and during exercise by 8 percent.

When combined with low-flow oxygen therapy, nifedipine further reduced PVRI at rest by 15 percent and during exercise by 32 percent compared to oxygen alone. Pulmonary artery pressure was unaffected by nifedipine during rest, but nifedipine significantly reduced pulmonary artery pressure during exercise when combined with low-flow oxygen by 11 ± 2 mm Hg. Nifedipine did not significantly lower PaO₂ during rest or exercise when combined with low-flow oxygen therapy. The O₂ delivery was increased by the combined therapy.

**Conclusions**

Thus, in patients with COPD and hypoxemia, nifedipine consistently reduces pulmonary vascular resistance and improves oxygen delivery while patients are breathing room air or low-flow oxygen. The acute beneficial effects of nifedipine are most marked during exercise, when nifedipine dramatically lowers pulmonary artery pressure and reduces right ventricular stroke work index.

In an uncontrolled study Sturani et al. found that nifedipine therapy for two months continued to produce significant pulmonary vasodilation at rest in patients with COPD and hypoxemia. They found, however, that the acute hemodynamic response in a given patient did not correlate with the chronic response observed. A controlled, double-blind study is currently in progress at our institution to determine whether the acute hemodynamic effects of nifedipine persist, are lessened, or are augmented after three months of therapy.

In summary, studies in laboratory animals demonstrate...
that calcium channel blockers can attenuate the development of the pathologic changes caused by hypoxia. Initial clinical studies demonstrate that acute administration of nifedipine inhibits hypoxic pulmonary vasoconstriction and augments the pulmonary vasodilation produced by low-flow oxygen. Controlled studies are needed to evaluate the long-term hemodynamic effects of nifedipine therapy. Presently, the use of these drugs as adjuvant therapy for hypoxic pulmonary hypertension is investigational. Oxygen therapy remains the treatment of choice.

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DISCUSSION

The discussion began by considering the conditions under which the measurements were made. They were made at rest and during supine bicycle exercise (25 watts/sec) before and after nifedipine administration (40 mg given orally over one hour). Serial measurements of cardiac output indicated a steady state after four to five minutes. Patients who could not exercise were excluded, and thus the results do not apply to patients with end-stage disease.

The question was raised as to the value of lowering pulmonary arterial pressure. Even if hemodynamic values can be improved, how does one measure benefit to the patient? The ensuing discussion indicated that exercise tolerance, sensed dyspnea, right ventricular function, and longevity should be evaluated by those assessing long-term vasodilator therapy. Extensive discussion considered each of these "yardsticks" as well as the hemodynamic evaluation.

Dyspnea, particularly with exertion, is a particularly distressing symptom and one difficult to measure. Methods of objective documentation such as measurement of ventilation per unit of work should be sought. Also, careful evaluation of the subjective sensation should be done.

The assessment of exercise tolerance, particularly in terms of endurance, is planned. One discussant indicated that leg fatigue rather than dyspnea limited exercise in some COPD patients. Thus, evaluation of exercise tolerance should take account of systemic oxygen transport.

Measurement of right ventricular stroke work is fraught with difficulty. Measurement of right ventricular O2 consumption is not possible. Dilatation of the right heart and increasing wall thickness will increase right ventricular oxygen consumption, but at present we cannot take these variables into account. Tricuspid insufficiency is often covert.
and will add to the already numerous difficulties of measuring right ventricular ejection fraction. The possibility of using radioactive krypton with a very short half-life (13 seconds) was considered. First-pass measurements with repeated trials is thus possible both at rest and during exercise. Even if technical problems interfere with accuracy, the opportunity for repeated measurements should allow assessment of changes in ejection fraction.

The value of the wedge pressure in the presence of lung disease was considered. It was considered that variations in intrathoracic pressure (as measured by esophageal pressure) did not invalidate pressure measured through a catheter wedged in zone 3 of the lung. In fact, subtracting wedge pressure from pulmonary arterial pressure helped take account of the swings of intrathoracic pressure and was a valid measure of driving pressure for blood flow through the lung.

The question was raised as to whether hypoxic pulmonary vasoconstriction in COPD could account for all of the immediately reversible pulmonary hypertension. For example, when patients reported here were on low-flow oxygen, the addition of nifedipine caused a further reduction in pulmonary vascular resistance. However, it was pointed out that in other studies, where COPD patients were given high-flow oxygen to eliminate residual hypoxia in poorly ventilated segments of the lung, nifedipine had no additional effect. Presumably, with low-flow oxygen, parts of the lung may continue to be hypoxic.

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 who have 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 Rovana'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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*From the Department of Medicine, Medical College of Virginia/ McGuire, VAH, Richmond.

*<sup>c</sup> = control; <sup>e</sup> = exercise; <sup>t</sup> = p<0.05 pre- vs postdrug PAP, PVR, SVR = dynsec cm<sup>-2</sup>, CO = L/min; SBF = mm Hg.

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