extraction as a major way of increasing the oxygen supplied to the tissues. This should improve the arterial PO₂ at any given level of work, since the PO₂ will be higher. On the other hand, vasodilation may increase the degree of V/Q inequality, worsening the efficiency of pulmonary gas exchange. Further studies will be necessary before any definitive statements can be made, although preliminary results suggest that successful vasodilation does not often lead to marked worsening of exercise hypoxemia. 5,10

REFERENCES

DISCUSSION
Discussion developed about the relationship between

Calcium Channel Blockers in Primary Pulmonary Hypertension*

Lewis J. Rubin, M.D., F.C.C.P.

The demonstration that the calcium channel blockers reduce pulmonary vaso dimerate activity in experimental models of pulmonary hypertension has served as the rationale for their use in the management of primary pulmonary hypertension. The three currently available agents, verapamil, nifedipine, and diltiazem, have varying degrees of pulmonary vasoactivity. Experience with their use is reviewed.

Primary pulmonary hypertension (PPH) is characterized by extreme elevations in pulmonary artery pressure and pulmonary vascular resistance and usually progresses inexorably to right ventricular failure and death. The pathologic demonstration of pulmonary arteriolar muscular hypertrophy as one of the earliest and most consistent features of this disease suggests that vasoconstriction in varying degrees may be responsible, at least in part, for the elevation in right ventricular afterload. A variety of vasodilating drugs, including hydralazine,5,6 phen tolamine,4 diazoxide,6 nitroglycerin,7 and prostacycline,6 have been used to treat PPH patients, with mixed results.8,11

The calcium channel blockers are a relatively new class of drugs which exert varying effects on the conduction system.
of the heart and vascular smooth muscle. Several studies have suggested that these agents may exert a pulmonary vasodilator effect in experimental animals with enhanced pulmonary vascular tone induced by hypoxic ventilation or the infusion of prostaglandin E₁. It is not surprising, therefore, that clinical studies evaluating the effects of these agents in patients with pulmonary vascular disease have been undertaken in the search for more effective pulmonary vasodilator drugs.

NIFEDIPINE

Of the three calcium channel blockers currently available, nifedipine has been the most extensively evaluated in patients with PPH. Camerini et al.⁶ reported the case of a 34-year-old woman with severe pulmonary hypertension (mean pulmonary artery pressure 63 mm Hg and total pulmonary resistance 2,255 dynes·sec·cm⁻⁴) who displayed a 54 percent fall in pulmonary resistance and a 14 percent decrease in pulmonary artery pressure in response to nifedipine, 20 mg, administered sublingually. Long-term treatment with nifedipine was associated with symptomatic improvement and diminished signs of right heart failure. Subsequently, McLeod and colleagues⁷ reported similar beneficial hemodynamic effects using nifedipine in three patients with PPH, and also noted improved exercise performance using treadmill testing. Wise⁸ reported that treatment with nifedipine, 10 mg orally four times daily for four months, resulted in a marked reduction in rest and exercise pulmonary resistance and increases in cardiac output.

Rubin and colleagues⁹ reported the short- and long-term effects of nifedipine in nine patients. Nifedipine treatment increased cardiac output from 3.6±1.7 to 5.3±2.8 L/min (p<0.001) and decreased total pulmonary resistance from 1,605±787 to 1,025±540 dynes·cm⁻⁵ (p<0.005) without substantially changing mean pulmonary artery pressure. Right ventricular volumes, estimated by radionuclide angiocardiography, were decreased and ejection fraction increased by 18 percent (Fig 1). Additionally, increases in right ventricular ejection fraction correlated with reductions in total pulmonary resistance (Fig 2), suggesting that the responses to nifedipine might be followed noninvasively. Persistent hemodynamic and symptomatic improvement were observed in five of the six patients who were given long-term oral nifedipine in doses of 40 to 120 mg/day for four to 14 months. Saito et al.⁴ found a similar response in their patient with severe PPH. Olivari and colleagues⁹ found persistent hemodynamic and symptomatic improvement and prolonged exercise tolerance with long-term nifedipine therapy in seven patients with PPH.

Not unexpectedly, the effects of nifedipine have not been consistently beneficial. Berkenboom and associates⁴ noted no response to 20 mg of nifedipine administered sublingually.

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21493/)

**FIGURE 1.** Scintigraphic evaluation of right ventricular (RV) end-systolic and end-diastolic volumes and ejection fraction before (C) and after sublingual nifedipine (N) treatment in eight patients with primary pulmonary hypertension. (From reference 17, with permission.)

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21493/)

**FIGURE 2.** Correlation between changes in right ventricular ejection fraction (RVEF) and total pulmonary resistance (TPR) after sublingual nifedipine in eight patients with primary pulmonary hypertension. (Drawn from data presented in reference 17.)
to a 36-year-old woman with PPH, and Rubin et al\textsuperscript{17} reported a paradoxical increase in pulmonary artery pressure, concomitant with an increased cardiac output, in one patient. Furthermore, initial responses may not be sustained chronically, due either to the development of tolerance to the drug or to progression of the underlying disease.\textsuperscript{17}

**VERAPAMIL**

The other calcium channel blockers have not been as extensively investigated. Landmark et al\textsuperscript{15} evaluated the effects of intrapulmonary injection of verapamil, 0.15 mg/kg, in 12 patients with pulmonary hypertension, nine of whom had PPH, and found small decreases in pulmonary artery pressure which were accompanied by reductions in cardiac output and systemic artery pressure. Because of this apparent negative inotropic effect, the authors advised caution in using verapamil in PPH patients.

**DILTAZEM**

Kambara et al\textsuperscript{12} reported a woman with PPH who had a dramatic response to diltiazem, 10 mg administered intravenously (IV). Eleven months after instituting oral diltiazem therapy, 30 mg three times daily, the patient was asymptomatic, and right ventricular strain was no longer present on ECG. Crevey et al\textsuperscript{18} evaluated the effects of diltiazem 0.25 mg/kg IV on rest and exercise hemodynamics and gas exchange. They found small reductions in total pulmonary resistance during exercise and no significant change in the overall distribution of ventilation and perfusion.

**NEWER AGENTS**

Armman and associates\textsuperscript{14} recently reported that felodipine, a new and more "selective" calcium channel blocker, produced improvement in two patients with PPH.

**THE FUTURE**

The ideal vasodilator for use in PPH would be one with selective, or even preferential, effects on the pulmonary circulation. While it appears unlikely from experience to date that a calcium channel blocker will meet these criteria, the development of newer agents with more selective cardiac pharmacologic effects could lead to more effective and better tolerated drugs for use in patients with hypertensive pulmonary vascular disease.

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**DISCUSSION**

The subject of the validity of control measurements of pulmonary arterial pressure was raised. Pulmonary arterial pressure has been noted to fluctuate over time during catheterization in some patients. This is especially marked in young children. Consequently, to be considered significant, a vasodilator should decrease pulmonary vascular resistance by 20 to 30 percent. One discussant felt that patients who respond to one vasodilator often respond to others as well. However, the corollary is not necessarily true. Another discussant suggested that in children a short history of
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. Prostaglandin 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, psychologic, 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...