Different Vasoactive Mechanisms of Various Pulmonary Vasodilators

To the Editor:

We read with appreciation and interest the ACCP Consensus Statement “Primary Pulmonary Hypertension” by Rubin,1 which appeared in the July 1993 issue of Chest. In the section of therapy, the author states that many vasodilators such as prostacyclin, calcium channel blockers, nitrates, and others are currently available for treatment of primary pulmonary hypertension. About a fourth of patients, however, are felt to have “fixed” vascular disease, and vasodilator therapy is contraindicated. He also mentioned the advantage of prostacyclin to determine the potential and magnitude of vasoactivity and the use of prostaglandin E1 (PGE1) as an alternative in this setting. It is a comprehensive and useful guideline. Nevertheless, the vasoactive mechanisms of these various agents on pulmonary arteries (PA) are not discussed. Are they all acting on the same site and through the same mechanism? Or do they cause the same degree of vasodilation?

Recently, we have conducted a series of investigations to study the direct vasoactive effects of various agents on isolated rabbit PAs.2,3 We used vessel rings precontracted with either norepinephrine or potassium chloride to determine the vasodilatory mechanism. Is it the result of the effect of Ca++ flux across the cellular membrane or release/reuptake of Ca++ from the sarcoplasmic reticulum (SR)? At the concentration of 10-6 M, norepinephrine-precontracted PA rings, PGE1 caused about 26 percent relaxation, nitroprusside (NTP) 70 percent, diltiazem (DTZ) 12 percent, and verapamil (VPM) 4 percent. On KCl-precontracted vessels, PGE1 produced 3 percent relaxation, NTP 20 percent, DTZ 55 percent, and VPM 22 percent. In summary, we have found that PGE1 and NTP act more on inhibiting Ca++ release from SR whereas DTZ and VPM on blocking Ca++ influx as expected. They cause different magnitude of vasodilation, which may be affected by the baseline sympathetic tone.

Is there any advantage in combined therapy? Should we base on prostacyclin only to determine the vasoactivity? Before we can effectively and comfortably treat pulmonary hypertension, we need more information about the pharmacology of these pulmonary vasodilators.

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To the Editor:

Dr. Lee’s letter raises several important issues relating to the management of patients with primary pulmonary hypertension which warrant elaboration.

Although the mechanisms responsible for the vasodilator actions of the agents currently used to treat pulmonary hypertension are of great importance, the committee thought that a detailed discussion of this subject was beyond the scope of this clinical concensus statement. It is generally agreed, however, that the vasodilators that are commonly used to treat pulmonary hypertension do not work either at the same site or through a common mechanism, nor do they produce the same degree of vasodilation in the clinical setting. While the calcium channel blockers are generally regarded as first line vasodilator therapy for primary pulmonary hypertension both because of the convenience of oral administration and the sustained hemodynamic and symptomatic benefit manifested by responsive patients, Dr. Lee is correct in his statement that only a minority of patients will experience these optimal responses. Recent experience suggests that continuous intravenous infusion of prostacyclin may produce hemodynamic and symptomatic improvement even in patients who are unresponsive or intolerant of calcium channel blocker therapy.1,2 Additionally, the absence of a vasodilator response to prostacyclin administered acutely does not preclude the possibility of a beneficial response to chronic therapy.3 This raises the possibility that the chronic effects of continuous infusion prostacyclin may have less to do with its vasodilator properties than with other effects, such as altering the remodeling process in the pulmonary vascular bed. Combined therapy with oral vasodilator agents and continuous infusion prostacyclin has been used,1 and this approach may be beneficial for some patients.

Studies such as the one by Lee et al (Crit Care Med 1993; 21:S209, S203) have provided us with a greater understanding of the cellular mechanisms of calcium handling and vasoactivity in pulmonary vascular smooth muscle cells. We agree that the optimal approach to medical therapy of primary pulmonary hypertension, however, will await the clarification of the cellular mechanisms responsible for the pathogenesis of this disease. Nevertheless, clinical investigation in this area has yielded several useful treatment options for patients with this heretofore untreatable disease; these treatment options are available at the present time to the majority of patients with primary pulmonary hypertension, and we need not wait until the pathogenesis is clarified to treat patients with this disease.

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