Editorial:
Unexplained Pulmonary Hypertension

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PRIMARY PULMONARY HYPERTENSION is so uncommon that most reports of the effects of therapy are anecdotal. Thus, the preceding report by Lupi-Herrera et al. of 12 patients is bound to stimulate interest. Because this report appears while the search for optimal pulmonary vasodilators is in full swing, readers will scrutinize it to see if the case for hydralazine as the pulmonary vasodilator of choice is convincing.\(^1\)

Regardless of the final decision about hydralazine, the report by Lupi-Herrera et al. warrants careful reading because it illustrates how much is known and how much remains to be learned about primary pulmonary hypertension and its management.

The Name as a Reflection of the State of Understanding

Primary pulmonary hypertension is the familiar name for pulmonary arterial hypertension of unknown cause. A working group of the World Health Organization, seeking to dispel the ambiguity of “primary,” chose “unexplained pulmonary hypertension.”\(^2\) Herrera et al., possibly aware of the recent inclination to include pulmonary veno-occlusive disease under the same rubric, have chosen to spell it all out: “pulmonary arterial hypertension of unknown cause.” I prefer the designation “unexplained pulmonary hypertension,” because pulmonary veno-occlusive disease is a distinct entity clinically, pathologically and presumably pathogenetically, and because “unexplained pulmonary hypertension” conveys its message succinctly and precisely.

Having settled on the name, one might expect that it would be simple to list the criteria for diagnosis. Unfortunately, the same designation, primary or unexplained, is used by clinicians and pathologists but with different pictures in mind. Should the designation be based on clinical or pathologic grounds or both? Ideally, a sifting of both the clinical and pathologic evidence is appropriate. However, because enough tissue for histologic diagnosis is difficult to obtain, the diagnosis is generally made on clinical criteria alone, after systematic exclusion of identifiable causes of pulmonary arterial hypertension. It is not surprising that some patients in whom the etiology of pulmonary hypertension is clinically obscure are found to have an identifiable cause at biopsy or autopsy.\(^3\) Often, the mystery in one clinic is dispelled by more penetrating inquiry in another.

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Selection of Candidates for Pulmonary Vasodilator Therapy

It seems reasonable to anticipate that pulmonary vasodilation in a patient with pulmonary hypertension signifies relaxation of smooth muscle in the small muscular arteries and arterioles. The expedient approach to detecting pulmonary vasodilation is by demonstrating a decrease in calculated pulmonary vascular resistance that cannot be attributed to the opening of unused parts of the pulmonary circulation or to shunts. Although such interpretations can be misleading if the drug simultaneously changes the pressures and flow in the pulmonary circulation, most of the drugs in use leave either the pulmonary vascular pressures or the cardiac output unchanged, so that a change in calculated pulmonary vascular resistance can be translated, with reasonable assurance, into a change in tone of the pulmonary arterial tree.\(^4\)

Although considerable attention has been paid to plexiform lesions and angiomyoid transformations in unexplained pulmonary hypertension,\(^5\) little is known about the nature, extent and distribution of the anatomic changes in pulmonary vascular smooth muscle and how these changes relate to the response to vasodilator drugs. Thus, a lung biopsy is performed in our clinic whenever practical before starting pulmonary vasodilator therapy.\(^6\) Lupi-Herrera et al. did obtain a lung biopsy in one patient (case 2) with moderate pulmonary hypertension and in whom hydralazine elicited a modest decrease in pulmonary arterial pressure, both at rest and during exercise in the face of increasing pulmonary blood flow. Unfortunately, no comparison is offered between the nature and extent of the pulmonary vascular lesions and the pulmonary vascular response.

The population of patients used by Lupi-Herrera et al. was chosen on the basis of so-called classic clinical criteria and the hemodynamic response to the acute intravenous injection of hydralazine was used as the basis for continuing vasodilator therapy. Patients with moderate pulmonary hypertension (pulmonary arterial pressure no greater than a mean of 50–60 mm Hg) did manifest a pulmonary vasodilator response, whereas those with higher pressures did not. They continued the responsive group on hydralazine by mouth (200 mg/day in divided doses) for as long as 8 months and were gratified with the symptomatic relief that this therapy provided.

The selection of patients with unexplained pulmonary hypertension for chronic vasodilator therapy on the basis of the hemodynamic response to the acute administration of a pulmonary vasodilator agent has been tried, but is not always reliable. Moreover, the study by Lupi-Herrera et al. has not eliminated the possibility that the nonresponders to acute testing
(group B) would improve if vasodilators were continued by mouth for weeks to months.

The criterion for improvement is clinical: relief of dyspnea and chest pain and an increase in exercise tolerance. These manifestations are attributable to the increase in cardiac output, the most consistent hemodynamic response observed by Lupi-Herrera et al. Clearly, the use of hydralazine in these patients improved the quality of their lives. However, it is not clear what the effect will be on the duration of life, because both pulmonary arterial pressure and cardiac output are high, i.e., the work of the right ventricle is either unchanged or increased. It is difficult to imagine that this increase in the load on the right ventricle could improve the long-term prognosis.

Why Hydralazine?

In a recent report of four patients, Rubin and Peter described hydralazine as a very effective pulmonary vasodilator in unexplained pulmonary hypertension. The oral dosage was the same as that in the study of Lupi-Herrera et al., and the striking relief of dyspnea and improvement in exercise tolerance persisted during the 6 months of observation. The drug was well tolerated and no evidence of toxicity was encountered. However, the response to hydralazine is not always so benign. Some patients develop systemic hypotension, dizziness, anorexia, nausea, headaches and sweating at smaller doses of hydralazine than those used in these studies. At levels of 200 mg/day, chronic administration of hydralazine can elicit a lupus-like syndrome. Moreover, the use of this dose makes no distinction between slow-acetylators and rapid-acetylators who achieve different concentrations of hydralazine in plasma on the same oral dosage schedule. These reservations are only a reminder that the consequences of prolonged usage of hydralazine in primary pulmonary hypertension are not established with respect to either complications or long-term prognosis. Also, whether, as in the management of systemic hypertension, the use of hydralazine can be optimized by concurrent administration of a \( \beta \)-adrenergic blocking agent, such as propranolol, is not known.

Other Vasodilators

Other agents have been tried and advocated in the treatment of unexplained pulmonary hypertension. None has been consistently successful after acute administration; sometimes, one (e.g., phentolamine) has worked after another (e.g., hydralazine) has proved ineffective. This inconsistency is not surprising, in the light of the different mechanisms of action of the various vasodilators. Some, such as nitroprusside, diazoxide, hydralazine and isoproterenol, relax vascular smooth muscle directly; others, such as phentolamine, are \( \alpha \)-adrenergic blocking agents; and recently trials have begun with calcium-entry blockers, particularly verapamil and nifedipine. Inevitably, some will be used in combination. How does one choose among these?

The contemporary approach to treating unexplained pulmonary hypertension using vasodilator agents is described in the recent Request for Proposal For a Pulmonary Hypertension Registry, issued by the Lung Division of the National Heart, Lung, and Blood Institute. This registry is intended to collect information about, rather than to prescribe therapeutic approaches to, unexplained pulmonary hypertension. It distinguishes between short- and long-term effects of the various pulmonary vasodilators and envisages, as a reasonable progression, that assessment of vasodilator potential starts with agents that vasodilate by direct effects on vascular smooth muscle, continue to those that involve \( \alpha \)-adrenergic blockade or \( \beta \)-adrenergic enhancement, and finally reach calcium-entry blocking agents that are still categorized as experimental. Probably the greatest lesson from this prospectus is that the choice of a pulmonary vasodilator agent (or agents) is still largely based on trial and error.

Vasodilators in Secondary Pulmonary Hypertension

It is natural for interest in the vasodilator therapy of pulmonary hypertension to extend from the unexplained type, an uncommon disorder, to the much more prevalent secondary types. Two types of anatomic disturbances will shape the outcome of the trials using vasodilator agents in secondary pulmonary hypertension: the nature of the underlying process, e.g., predominantly irreversible fibrosis or reversible inflammatory process, and the degree of medial hypertrophy in the pulmonary arterial type. For example, in pulmonary hypertension secondary to multiple pulmonary emboli, the elevated pulmonary arterial pressures could evoke medial hypertrophy; in turn, the hypertrophied vascular smooth muscle can aggravate the pulmonary hypertension by adding the effects of increased vascular tone to those of the widespread vascular occlusion produced by the organized clots in the pulmonary arteries. In this circumstance, just as oxygen therapy relieves hypoxic pulmonary vasoconstriction, pulmonary vasodilators can interrupt a secondary but perpetuating and aggravating cycle of pulmonary hypertension. Similar considerations apply to other types of secondary hypertension.

References
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