

Epoprostenol (Prostacyclin) and Pulmonary Hypertension

Pulmonary hypertension is a prevalent disorder, and the list of its causes is long and varied. Included in the list, which is densely populated by so-called secondary types of pulmonary hypertension, is the category of unexplained (primary) pulmonary hypertension, presumably the final common pathway for multiple unidentified causes. For those concerned with the pathogenesis of the more common and diverse pulmonary hypertensive disorders that make up the category of secondary pulmonary hypertension, interest in primary pulmonary hypertension is high because it represents a model of “pure” intrinsic pulmonary vascular disease, uncomplicated by concomitant disease of the heart or lungs. Those concerned with therapy continue to direct their attention at relief of pulmonary vasoconstriction, which seems to be involved in the pathogenesis of primary pulmonary hypertension (1).

Before epoprostenol (prostacyclin) became available for clinical use, primary pulmonary hypertension was a calamitous disorder, destined to pursue a relentlessly downhill course that ended in right ventricular failure within 2 to 3 years. All sorts of systemic vasodilators were tried as pulmonary vasodilators, with largely inconsistent or futile results. The advent of prostacyclin introduced the most potent vasodilator known; other useful attributes of this agent are antiplatelet aggregation and adhesion inhibition of smooth-muscle proliferation. It marked the end of inevitability of early death and the beginning of a brighter outlook for quality of life in primary pulmonary hypertension.

The first applications of prostacyclin were diagnostic. They led to the recognition of prostacyclin as the “gold standard” for testing the ability of the hypertensive pulmonary circulation to undergo vasodilation (2). The pulmonary hypertension centers that were established by the National Heart, Lung, and Blood Institute as part of the National Registry on Primary Pulmonary Hypertension played an important role in the recruitment of sufficient numbers of patients with primary pulmonary hypertension. The collective experience indicated that prostacyclin elicited pulmonary vasodilation in only about one third of patients with primary pulmonary hypertension. Although these results were somewhat disap-

pointing, identification of such responders was subsequently turned to an advantage by the demonstration that disease in responders could be managed successfully with oral calcium-channel blockers instead of more demanding routes, such as continuous intravenous infusion of prostacyclin (3, 4).

The role of prostacyclin in the management of primary pulmonary hypertension began to switch from diagnosis to treatment when continuous intravenous administration of prostacyclin was shown to serve as a life-saving bridge to lung transplantation (5). An even greater role followed the disclosure that patients with primary pulmonary hypertension who did not respond to acute testing with prostacyclin would improve hemodynamically and clinically with continuous intravenous administration of prostacyclin (6, 7). How continuous administration of prostacyclin decreased pulmonary vascular resistance was, and still is, enigmatic. Because the decrease in pulmonary vascular resistance could not readily be ascribed to vasodilation, consensus emerged that structural changes, so-called remodeling, were involved. How prostacyclin managed this remodeling is still speculative.

A logical extension of this gratifying experience with prostacyclin in primary pulmonary hypertension was to apply the same treatment to patients with secondary pulmonary hypertension in which the pulmonary vascular lesions are histologically indistinguishable from those of primary pulmonary hypertension (8). The scleroderma spectrum of disease seemed to fit the bill for several reasons. First, pulmonary hypertension is a common complication, and often a cause of death, in diffuse scleroderma, particularly the CREST syndrome (calcinosis cutis, the Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) (9). Second, the pulmonary vascular lesions of scleroderma resemble those of primary pulmonary hypertension. Third, recent reports have suggested that the clinical and hemodynamic improvements produced by prostacyclin in primary pulmonary hypertension can be replicated in pulmonary hypertension resulting from the scleroderma spectrum of disease (4, 10–12). Finally, the Raynaud phenomenon, which occurs in primary pulmonary hypertension as well as in

scleroderma, has been reported to improve with prostacyclin or its analogues (13).

Against this background, Badesch and colleagues (9) undertook a 12-week unblinded, randomized, multicenter, controlled trial of intravenous prostacyclin for moderate to severe pulmonary hypertension in patients with scleroderma. They found that prostacyclin relieved symptoms and improved both exercise capacity and cardiopulmonary hemodynamics. In contrast, controls who received conventional therapy deteriorated. The reason why survival was the same in both the test and control groups requires future study in a larger sample. In addition, the study did not address the question of whether acute testing for pulmonary vasoresponsiveness would have identified a subgroup of responders that could have been treated successfully with a less demanding vasodilator program, such as calcium-channel blockers taken orally (4).

Unfortunately, despite the favorable outcomes, continuous intravenous prostacyclin is far from ideal as treatment of pulmonary hypertension: The agent is available in only limited supply; it is very costly; and optimal management requires that the intravenous therapy with prostacyclin be started in specialized centers that have become familiar with the technique, equipment, and dose ranging, although ongoing care can be delivered by physicians briefed by and in continuing contact with the centers. Moreover, continuous intravenous administration of prostacyclin exacts a high, albeit usually tolerable, price in discomfort and disability. Jaw pain, nausea, and anorexia are common, and the patient is continually under the hanging sword of complications from prolonged catheterization and breakdowns in the delivery system. Moreover, mistaking pulmonary veno-occlusive disease for the more usual precapillary type of primary pulmonary hypertension creates the risk that prostacyclin will precipitate life-threatening pulmonary edema (14).

The salutary effects of continuous intravenous vasodilator therapy have encouraged trials of other agents delivered by different routes. Agents currently under study include antivasoconstrictors, such as antiendothelins, and vasodilators, such as analogues of prostacyclin, adenosine, and nitric oxide. UT-15, an analogue of prostacyclin, is being administered by subcutaneous injection. Inhalation is an alternate route that has been tried for prostacyclin and for iloprost, its more stable and accessible analogue, as well as for nitric oxide. Olschewski and associates put this approach to the test (15). Extending the results of their previous studies of patients with primary or secondary pulmonary hypertension, researchers at six centers in Germany undertook "rescue attempts" with inhaled iloprost or nitric oxide in 19 patients with severe pulmonary

hypertension who were in or were verging on right-heart failure. At 3 months, 12 of the 19 patients had clinical and hemodynamic improvement; 7 could continue using this regimen for 1 year or longer. Iloprost seemed to work better than nitric oxide.

This uncontrolled trial leaves several unanswered questions that stem from the relatively small number of patients, the different causes of the pulmonary hypertension, and uncertainties about the severity of the pulmonary hypertension in individual patients. Most desirable but difficult to achieve would be a controlled clinical trial to compare the effectiveness of inhaled prostacyclin with that of continuous intravenous prostacyclin over months to years. Although the inhalation route has attractive features, the practicality of a standard regimen for delivery of inhalants, such as iloprost or nitric oxide, to outpatients for years remains to be shown. Moreover, whether agents other than prostacyclin, such as nitric oxide, can accomplish long-term remodeling is unknown.

Both studies in this issue can be viewed as pioneering efforts in different stages of evolution. Badesch and colleagues' study (9) is the first randomized trial of treatment for secondary pulmonary hypertension. The article by Olschewski and associates (15) is a harbinger of new trials in the search for novel routes and agents that will improve on the success of continuous intravenous infusion of prostacyclin (16).

Until now, almost all of the advances in the management of primary pulmonary hypertension and intrinsic pulmonary vascular pathology have been directed at relieving pulmonary vasoconstriction. The use of prostacyclin and other vasodilators is now being extended beyond primary pulmonary hypertension and the scleroderma spectrum of pulmonary hypertension to subsets of secondary pulmonary hypertension, such as congenital heart disease, in which the pulmonary vascular histopathology is similar (17). On the immediate list of targets for trial with pulmonary vasodilators are causes of pulmonary hypertension such as HIV, anorectic agents, and familial pulmonary hypertension. In the meantime, the feasibility and effectiveness of long-term therapy with inhalants continue to be evaluated (18, 19).

Preoccupation with vasodilators in managing pulmonary hypertension should not obscure the fact that vasodilation seems to be only one effect of prostacyclin. The purported remodeling induced by continuous infusion of prostacyclin has raised the possibility of medically arresting or reversing the factors involved in proliferative and occlusive pulmonary vascular disease (20). Whether agents other than prostacyclin share this potential is under investigation.

In addition to the possibility of reversing the proliferative vascular changes and remodeling the pulmonary hypertensive circulation, other bright prospects for dealing with pulmonary hypertension seem to be in the offing. High on the list is the likelihood that the genetic bases for primary pulmonary hypertension will soon be defined, along with a better understanding of inherited predisposition to pulmonary hypertension. Should these promises live up to expectations, the treatment of pulmonary hypertension will shift from the current empirical management of abnormal hemodynamics and clinical manifestations to the prevention and treatment of pulmonary hypertensive disorders on the basis of a firm grasp of etiology, individual susceptibility, and pathogenetic mechanisms.

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