

Public Lecture by Dr. Lewis J. Rubin, M.D.
Pulmonary Artery Hypertension: From Bench to Bedside
June 20, 2001 at 6:00 p.m. in the Garren Auditorium, Basic Science Building
Sponsored by the Sam & Rose Stein Institute for Research on Aging, UCSD

Primary pulmonary hypertension (PPH) is a rare and progressive disease in which an increased pulmonary arterial pressure usually leads to right heart failure and death within 2-3 years. Although the majority of PPH cases are sporadic, a familial association occurs in approximately 10% of cases, implying a genetic predisposition for disease development in at least some patients. A number of other conditions also appear to be associated with an increased PPH in those conditions of ~ 1-3%. The use of diet-suppressant agents, particularly fenfluramine and its isomer dexfenfluramine is also associated with an increased risk of PPH which appears to be related, at least in part, to the duration of their use. Taken together, these observations suggest that a susceptibility to PPH may exist in some individuals, which results in the disease development in response to exposure to one or more triggers. There is no cure for PPH; the primary therapeutic approaches consist of oral calcium channel blocking drugs for patients with demonstrable reversible pulmonary vasoconstriction, and continuous intravenous prostacyclin or transplantation in those without reversible vasoreactivity.

There are no *a priori* characteristics that identify individuals who are likely to develop PPH in the background of predisposing conditions or exposures, nor are there baseline clinical or hemodynamic patterns that identify those with reversible vasoreactivity. Patients who manifest a 20% or greater fall in pulmonary artery pressure in response to acute testing with a short-acting vasodilator such as inhaled nitric oxide (NO), intravenous prostacyclin or adenosine can be successfully treated chronically with oral calcium channel blockers (CCB) with sustained benefit and markedly improved survival. In contrast, nonresponders to acute vasodilator challenge are treated with prostacyclin (flolan), which has been shown to improve exercise tolerance and prolonged survival. Although the mechanism responsible to the beneficial effects of prostacyclin in these patients is unclear, it likely is due to properties of the drug other than vasodilatation such as inhibition of platelet aggregation and antiproliferative effects. Only 20-25% of PPH patients are responders to vasodilators; thus, the majority must be treated with more complex and expensive modalities which also have a substantially less dramatic impact on the course of the disease.

Our laboratory is interested in understanding:

1. The molecular basis for the development of PPH.
2. The molecular determinants of responsiveness to oral vasodilators and intravenous prostacyclin.
3. The mechanisms responsible for the beneficial remodeling of the pulmonary vessels that is produced by prostacyclin treatment.

The overall goal of our research is to gain a more complete understanding of the mechanisms responsible for the development of pulmonary vascular disease and to apply this knowledge to develop newer and more effective treatments.