Pulmonary Hypertension in the Interstitial Lung Diseases*

The interstitial lung diseases, like many chronic lung diseases, may lead to the development of pulmonary hypertension and cor pulmonale. The prevalence of pulmonary hypertension in these diseases is unknown, however. Current data suggest that prevalence varies with the type of interstitial disease.1,2 In a group of patients with either idiopathic pulmonary fibrosis or interstitial lung disease associated with a collagen vascular disorder, 70 percent had auscultatory findings consistent with pulmonary hypertension.2 These data are in agreement with those of Stack et al,4 who found that 68 percent of patients with terminal fibrosing alveolitis died with advanced fibrotic lung disease and cor pulmonale. Although considerable data are available on the pathogenesis of pulmonary hypertension in the interstitial lung diseases, the exact pathogenetic mechanism remains unknown. Current data suggest that the etiology of pulmonary hypertension in the interstitial diseases is multifactorial and involves the following: 1) primary lesions of the pulmonary vessels (eg, vasculitis in sarcoidosis),1,3 2) compression and/or destruction of pulmonary vessels by the interstitial process,5,6 and 3) vasoconstriction of vessels mediated by hypoxia, acidosis, or autacoids.5,7,8 Additional factors that may modulate pulmonary artery pressure include pulmonary blood volume, pulmonary artery compliance, lung water, temperature, and left ventricular function.5,9,10 The contribution of each of these factors to the genesis of pulmonary hypertension in patients with interstitial lung disease is speculative, but quite likely varies with the type of interstitial disease, course of the disease, and individual susceptibility.

Treatment of pulmonary hypertension secondary to chronic pulmonary disease poses a difficult problem for the clinician. Clearly, the major therapeutic emphasis should be directed toward the underlying lung disease. For example, in patients with chronic obstructive lung disease, treatment with bronchodilators and antimicrobials may result in lowering pulmonary artery pressure.5 In patients with alveolar hypoaxia, supplemental O2 has also been shown to improve pulmonary hemodynamics. Despite optimal treatment of the underlying chronic pulmonary disease, however, symptomatic pulmonary hypertension with cor pulmonale often persists.

Widespread use of vasodilating agents in systemic hypertension and in the management of left ventricular failure has encouraged a similar approach in patients with pulmonary hypertension. Both primary pulmonary hypertension and pulmonary hypertension secondary to chronic lung disease have been studied. Several potent vasodilator agents including hydralazine,12 diazoxide,14 phentolamine,15 captopril,16 nifedipine,17 acetylcholine,18 tolazoline,19,20 sodium nitroprusside,21 isoproterenol,22 verapamil,23 nitroglycerin,24 prostaglandin E1,25 and prostacyclin26 have been used. While improvement in pulmonary hemodynamics and cardiac output has been reported with virtually all of these agents, no selective pulmonary artery vasodilators are available for chronic use. Additionally, serious adverse responses have been observed in both primary pulmonary hypertension and in pulmonary hypertension secondary to chronic lung disease.27-30 Systemic hypotension with subsequent cardiac arrest remains the most feared response, although arrhythmias, heart failure, and hypoxemia may limit the usefulness of these agents.27

Despite the large number of studies of vasodilator therapy in primary pulmonary hypertension and in pulmonary hypertension associated with chronic airways disease, there are scant data on treating pulmonary hypertension secondary to chronic interstitial lung disease. In the current issue of Chest (see page 564), Lupi-Herrera and colleagues studied a small group of patients with chronic interstitial lung disease and pulmonary hypertension and cor pulmonale. Hydralazine was used, and both the immediate and short-term effects on pulmonary and systemic hemodynamics at rest and during exercise was evaluated. Open lung biopsies were performed in all patients and suggested that most were early to mid-course in their disease. All had active alveolitis, and in none was the severity of the fibrosis predominant over the inflammation. The Heath and Edwards classification was used to assess the degree of vascular lesions. Five were grade 1 (medial hypertrophy in arteries and arterioles), and eight were grade 2 (medial hypertrophy and intimal proliferation in the smallest muscular arteries and arterioles). After intravenous hydralazine at rest, there was an increase in cardiac index, arterial oxygen tension (PaO2), and mixed venous saturation (SvO2). Pulmonary vascular resistance decreased but pulmonary artery pressure did not change. During exercise, PaO2, SvO2 and cardiac index increased so that pulmonary vascular resistance was further reduced. The improved hemodynamic effects of hydralazine were still evident in most patients after seven days of oral hydralazine. The data of Lupi-Herrera support those of others suggesting that patients more likely to benefit from vasodilators are those with early disease and active pulmonary vasoconstriction.30,31 Correlative functional-pathologic data suggest that muscular hyperplasia and medial hypertrophy (grade 1 and 2 disease) are associated with active vasoconstriction.31 These data and those of others suggest that there exists a subset of patients who may benefit from vasodilator therapy. Patients with early disease characterized by active vasoconstriction have the best hemodynamic...
response. While Lupi-Herrera found a correlation between resting levels of pulmonary artery pressure and the reduction in pulmonary vascular resistance, the mean pulmonary artery pressure in their patients was 26.8 mm Hg. Previous studies suggest that there is a level of pulmonary artery pressure beyond which vasodilators are not helpful; patients with primary pulmonary hypertension or advanced airways disease associated with advanced fixed vascular disease do not respond to vasodilator drugs.3

The article by Lupi-Herrera et al raises an important question regarding the effects of vasodilator therapy in the presence of hypoxia. Their patients were hypoxic while breathing ambient air at an elevation of 2,240 meters. In a similar study, marked improvement in pulmonary hemodynamics resulted after administration of supplemental O₂.34 Thus, it seems possible that the effect of hydralazine in the present study was due to reversal of hypoxia-induced vasoconstriction. Clearly, both clinical and basic research data suggest that some vasodilator drugs may reverse hypoxic pulmonary vasoconstriction.35-36 Whether hydralazine would provide a beneficial effect beyond that of supplemental O₂ is not reported. Would vasodilator therapy be a useful adjunct to supplemental O₂ in the treatment of pulmonary hypertension associated with the interstitial lung diseases? Other important questions regarding the role of vasodilator therapy in the treatment of pulmonary hypertension remain to be answered. Is a reduction of pulmonary vascular resistance and an associated increase in cardiac index of any benefit in the absence of a change in pulmonary artery pressure? More importantly, will long-term vasodilator therapy for pulmonary hypertension improve morbidity and mortality? The work of Lupi-Herrera and colleagues provides new information and points to new avenues for investigation of this important subject.

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Digital Angiography
The Physician's Love Affair with the Computer

The dawn of the computer age of electronic information is clearly upon us. Even fearless physicians find themselves increasingly entangled in data bases and electronic worksheets or hounded by pixelization, deconvolution algorithms, and gigabytes. To better understand this process, let us review one particular phase of the application of computers in medicine, i.e., digital cardiac angiography.

An x-ray picture of the heart can be converted into a computer format that consists of a large series of numbers in the same way that satellite pictures of Saturn are formatted before transmission. The reason for changing photographic images into a computer format is that images, when reduced to a matrix of numbers, can be manipulated for specific advantages. During the experimental development phase of radiologic imaging computers, intense effort was made to make the computers fast, reliable, and capable of providing image quality that was comparable to film-based images. These basic requirements have now been met by the imaging computer industry working in conjunction with academic medical laboratories.

Initial clinical studies with digital imaging explored the possibility that angiograms could be obtained less invasively. These studies demonstrated that computers can enhance iodine contrast about fourfold to permit visualization of aortic, carotid, renal or femoral arteries following intravenous administration of contrast media. For cardiac imaging, digital acquisition can be used to obtain first-pass right and left ventriculo-gram following intravenous injections. Analysis of these images is relatively easy because the images are already in a computerized format and are readily available for quantitative analysis without the laborious techniques that are required for analyzing film-based images.

Subsequent studies have indicated that a more attractive application of digital angiography is to use the computer-processed images as an adjunct to standard intra-arterial catheterization, thereby allowing images to be obtained with less contrast media. The paper by Mancini et al in this issue of Chest (see page 598) corroborates work by other investigators and demonstrates the ease with which complicated quantitative analysis of left ventricular function can be performed from low dose ventriculograms through the use of imaging computers. Such low dose left ventriculograms are clinically important because they make it possible to obtain multiple images of the heart without using an excessive contrast media load. Thus, it becomes feasible at the time of routine cardiac catheterization to perform interventional studies such as atrial pacing in order to assess the functional significance of specific coronary stenoses.

Computerized images also can be manipulated with simple (for a computer) mathematical processes such as mask mode subtraction, edge enhancement, and picture magnification in order to improve coronary artery visualization. For example, there are a variety of analyses that can be used to quantitate the severity of coronary stenoses such as operator or automatic edge detection, and videodensitometry. The latter process assesses the relative volume of contrast media in the narrowed and nonnarrowed coronary segments and has the advantage of being relatively independent of any irregular geometry of the stenosis. Other researchers are attempting to use digital coronary angiograms to assess myocardial perfusion by measuring the density of contrast media throughout the capillary system. An alternate approach uses the computer to look at the relative time of arrival of a contrast bolus in order to determine the functional significance of coronary stenoses.

Another direct application of digital angiography is the ability to obtain aortic root angiograms with relatively low amounts of contrast media. These images are immediately available within the catheterization laboratory (since there is no film to develop) and can be reviewed for the presence of atherosclerotic stenoses of the left main and proximal coronary arteries. Such information may allow coronary angiography to be performed more safely because the greatest risk from this procedure occurs when one cannulates the coronary arteries for selective injection in patients who have disease of the left main coronary artery.

One of the more exciting applications of digital...