Long-term Clinical Trials in Pulmonary Hypertension
Long Overdue

The clinical consequences of primary and the second- 
dary forms of pulmonary hypertension have been long known and 
were believed to be related to the degree of impairment of the 
pulmonary circulation. Over the years, the poor prognosis associated 
with pulmonary hypertension was ascribed, to a large extent, to the 
lack of effective therapy. Thus, the 
possibility of successful therapeutic regimens for all 
forms of pulmonary hypertension was based on the 
development of agents with the capacity to reduce 
pulmonary vascular resistance.

Ideally, effective therapy for all forms of disease, let 
alone pulmonary hypertension, should improve the 
quality as well as extend the duration of life. Although 

it still seems logical to focus on the pulmonary circulation 
in order to acquire a favorable outcome in pulmonary 

hypertension, it still remains unknown if improvement of hemodynamic responses (ie, to drugs) correlates with improved and extended life. This would be especially true in secondary pulmonary hypertension.

The development and successful application of 
vasodilating pharmacologic agents in systemic hypertension and in severe left ventricular failure led to the use of vasodilators in both primary and secondary forms of pulmonary hypertension. As a general rule, these agents were used in a number of short-term studies which primarily assessed the hemodynamic responses in small numbers of patients without long-term follow-up, and without well-designed attempts to correlate clinical outcome with the hemodynamic responses. These hemodynamic responses are well described and will not be detailed herein. Although most agents improved pulmonary hemodynamics, as judged by a fall in pulmonary vascular resistance and an increase in cardiac output, none acted primarily on the pulmonary circulation alone. Often, there appeared to be more significant effects on the systemic circulation with the mean pulmonary arterial pressure remaining unaltered. Major adverse effects also occurred, with systemic hypotension and cardiac arrest being the most feared, as well as arrhythmias, heart failure, and hypoxemia. The argument could be made that a large number of patients with pulmonary hypertension were treated with vasodilators as a result of these studies and were exposed to a situation where therapy had a significant factor of risk without any proven long-term benefit. An equally important, and unanswered, question is whether or not they were subjected to greater harm?

In the current issue of Chest (see page 141), the report by Rubin and Moser further emphasizes some of the key questions being raised in this commentary. In the context of studies evaluating the use of vasodilators in pulmonary hypertension, their report represents an advance over previous ones and yet, at the same time, has some of the same limitations.

Rubin and Moser report rather impressive hemodynamic data obtained with the use of nitrendipine (calcium-channel blocker) in eight patients with severe chronic obstructive pulmonary disease (COPD) and cor pulmonale who were also receiving supplemental oxygen. Nitrendipine appeared to exert its vasodilating effect primarily on the pulmonary circulation, which was sustained over the course of six weeks of therapy, as documented by catheterization. The advances here, over previous studies, are the documentation of the response for a period of six weeks and the rather impressive hemodynamic effects of this agent without adverse reactions. It should be noted that similar results have been reported by Burke et al using captopril in a similar group of patients who were also receiving supplemental oxygen; however, their study was short-term, with no long-term follow-up measurements.

Despite the excellent hemodynamic responses documented with nitrendipine, long-term follow-up revealed that three of seven patients died at eight, nine, and ten months, respectively, following the onset of continuous nitrendipine therapy. Regardless of the cause of death, these results further emphasize the disparity between hemodynamic and survival data at present. In this regard and in view of the small number of patients studied, Rubin and Moser stressed the preliminary nature of their results and the need for further studies.

The time is past due when well-designed long-term clinical trials are needed to determine the efficacy of vasodilator therapy in all forms of pulmonary hypertension. These studies should require adequate numbers of patients with a comparable control population, long-term follow-up, comparison of hemodynamic responses with clinical course, and real attempts to determine the "bottom line" with respect to the quality and duration of life. These kinds of studies are definitely needed to make certain that more benefit, rather than harm, is being derived from therapy in patients.

With respect to cor pulmonale with COPD, additional therapeutic facets should be assessed. Based on the studies reported herein and previously, is there a greater benefit derived from combined vasodilator and long-term oxygen therapy in COPD over that derived from each agent individually? Which is safer? What are the clinical differences in long-term outcome?

There is no doubt that increasing numbers of new
therapeutic agents will be generated for use in pulmonary hypertension in the future. This in itself should further hasten the process for determining the long-term effects of vasodilator therapy on outcome in all forms of pulmonary hypertension.

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References

Thoughts on the Swan-Ganz Catheter

Since the introduction of the pulmonary artery catheter 15 years ago, there have been reports of its role in the diagnosis and management of patients with cardiopulmonary disorders as well as severe multi-system disease. Furthermore, it has been instrumental in facilitating the application of vasodilator therapy and new inotropic agents. More than two million catheters have been inserted at a cost of over two billion dollars. A literature search has revealed that almost one fourth of the more than 350 papers published about the catheter have focused on complications. Chest has published over 15 papers describing the morbidity of the catheter. During the past year, continued reports of morbidity and mortality have appeared.

Compounding these reports is the disturbing reality that no paper has demonstrated, in a controlled fashion, that the catheter reduces mortality. Appropriately, over the last five years, several editorials have cautioned against indiscriminate use of this catheter based upon the apparent failure to improve survival rates. What are the benefits and limitations of the pulmonary artery catheter, and where do we go in 1985?

The catheter has been reported to be useful in diagnosis and management, but we believe too much has been expected of this catheter and anticipating improved survival rates may be unrealistic. The technique is, after all, merely an elaborate extension of our monitoring ability. Moreover, its probable that with the more critically ill patient, the catheter becomes a less reliable monitor. The pulmonary wedge pressure may not reflect left ventricular end-diastolic volume, which actually determines the preload of the Starling curve. This inaccurate correlation results from abnormalities of left ventricular compliance in the critically ill. Furthermore, unless the catheter is in West's zone 3, inaccurate pulmonary wedge pressures which do not reflect the left atrial pressure may be expected. This discrepancy occurs in particular when positive end-expiratory pressure (PEEP) is used. Chronic obstructive pulmonary disease and hemorrhagic shock may also limit the accuracy of the catheter readings, especially if the catheter is not positioned in the appropriate zone. All of these clinical situations, coupled with technical problems in the measurement of pressures, normal fluctuations in pressures, and changes related to the position of the patient, further complicate the reliability of the catheter recordings.

We believe it unlikely that any monitoring system alone can improve survival in critically ill patients. Unfortunately, there have never been any controlled clinical trials looking at the effect that the insertion of the pulmonary artery catheter itself has in altering the status of the patient. Five years ago, it was suggested that Killip class I patients be randomized for management with and without right heart catheterization. Regrettably, such a study was never undertaken and would be unethical today because of the known hazards of the procedure.

Given the present limitations, we believe that there are clearly useful applications of the catheter. The catheter can be used to diagnose and differentiate acute ventricular septal defect, acute mitral insufficiency, cardiac tamponade, restrictive/constrictive heart disease, and cardiac vs noncardiac pulmonary edema. In addition, it is of value in the management of right ventricular infarction and the adult respiratory distress syndrome (ARDS) with co-existent left ventricular dysfunction. Despite the lack of controlled trials, the catheter is shown to have a major effect on therapeutic interventions in the critically ill. Unfortunately, the patient mortality remains high. We do not feel that the routine use of the catheter is justified in patients with ARDS, myocardial infarction and coronary artery bypass surgery, if there are no complications.

We believe that management may be altered with the pulmonary artery catheter and that these changes in therapy are noteworthy. However, a better understanding of the pathophysiology of diseases, coupled with better pharmacologic agents, may lead to improved survival—not the catheter itself. It appears