The Kingdom of the Near-Dead
The Shortened Unnatural Life History of Primary Pulmonary Hypertension

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Hippocrates is supposed to have stated that "desperate diseases demand desperate measures." Burckhardt, the father of the ill-fated therapy of psychosurgery for schizophrenia, did say "better a dangerous treatment than no treatment at all."

The concept is widely held that patients who are about to die (the "near-dead") or those with dreadful diseases may (should) be managed in a highly aggressive or even dangerous way; however, suppose that the generally accepted view of the natural life history of a given disease is wrong. Suppose a significant subpopulation of patients turns out to have a substantially better prognosis than assigned to it by conventional wisdom. As a result, these patients may be exposed to needless risks based on a fundamental misconception. The fact of early death may turn out to be a self-fulfilling prophecy because of the interaction of the disease and aggressive management. These abstract and somewhat philosophical ramblings can be translated into reality using recent developments in the understanding and management of primary pulmonary hypertension (PPH).

LENGTH OF SURVIVAL

Primary pulmonary hypertension has generally been regarded as an inextricably progressive disease which is rapidly fatal within a few years. Once the diagnosis is established, these patients enter the kingdom of the near-dead.

Most large series describe rare individual patients surviving 5, 10, or 20 years after diagnosis. Such patients have been regarded as statistical aberrations or outliers.

The viewpoint that PPH is rapidly fatal in the overwhelming majority of patients is no longer tenable. In a study of 90 patients with PPH, we observed that tolling the time between significant symptoms and death was almost six years and tolling the time between a definite diagnosis and death was about three and one half years. More significantly, by actuarial analysis, 37 percent (33) of the group lived for five years and 15 percent (14) for ten years following diagnoses.

Patients surviving over two to three years have an excellent chance of surviving for five to 15 years. When physicians are confronted with these data for the first time, they, not unusually, ask the names of the magic drugs which are responsible for long survival. The best available answer may be two uncommon potions: diagnostic restraint and therapeutic restraint.

A similar but smaller experience was accumulated in England and commented upon editorially in Lancet. Of a group of 34 patients, 18 died within five years of presentation to the hospital, 12 survived more than five years, and four improved and lived for more than five years.

There is no doubt that the mean length of survival following a diagnosis of PPH is significantly longer than previously believed, and prolonged survival without treatment is not unusual. In fact, the data fit a bimodal distribution. One mode consists of patients with an accelerated course, with death occurring within months. In terms of outcome, this group may be considered to have "malignant" PPH. (The term, malignant, merely characterizes outcome. Actuarial analysis is not a sufficiently accurate method to resolve pathogenetic issues. Malignant pulmonary hypertension has a different connotation than malignant systemic hypertension, which has highly specific features.)

The other mode consists of patients with a slow evolution of disease, with death occurring years after diagnosis. In this context, this latter group cannot be described as having a benign disease (in contrast to malignant). They have a significant mortality and an
impaired quality of life. On the other hand, they are not part of the near-dead, and the conservation of years and lives should be a major objective. A similar model of a bimodal distribution of survival times was extrapolated from isolated case reports by Packwood and Yu.20 Unfortunately, they had no quantitative estimate of the size of the long-surviving group.

Is the course of PPH inexorably progressive? Apparently not. There have been well-documented reports of spontaneous improvement or regression.6,9,18 In one retrospective series of 38 patients, four patients improved during careful observation. Given the possibility of spontaneous improvement, evaluation of therapy becomes more difficult without a well-designed clinical trial.

The failure to recognize the less malignant group has had its “amusing” side. A prestigious journal publishes a single case report of a notable patient who showed improvement for three years despite progressive disease because of treatment with isoproterenol.13 Perhaps the patient might have thrived for 20 years without the treatment. Less amusing is the fact that numerous patients were undoubtedly treated with a drug whose safety and efficacy was and is unknown.

Whatever bias of selection may have been present in our study, the bottom line remains: substantial numbers of patients with PPH survive for relatively long periods. It might be useful to discuss the impact of previous estimates of a very short natural life history of PPH on three forms of management and, in turn, to consider the impact of these forms of management on the length of survival in PPH.

PULMONARY VASODILATORS

The original report which suggested efficacy for hydralazine in the treatment of PPH did not show any improvement in mortality, nor was there evidence of an improved quality of life.14 Hydralazine did result in a significant reduction in mean pulmonary arterial pressure. This surrogate criterion may have little or nothing to do with improved outcome in patients. Three of seven patients with pulmonary hypertension secondary to chronic obstructive pulmonary disease died in months following the onset of potent pulmonary vasodilator therapy. The drug shows an impressive hemodynamic effect, but the patients do not survive.16 One is reminded of the old cynicism, “The drug was successful, but the patient died.”

The adventuresome physician now has some 16 drugs available (which I shall lump as pulmonary vasodilators), including captopril, diazoxide, epoprostenol, hydralazine, isoproterenol, nifedipine, nitrendipine, nitroglycerin, nitroprusside, minoxidil, phentolamine, phenoxybenzamine, prazosin, terbutaline, tolazoline, and verapamil, with which to treat PPH. The use of none of these has been documented as effective for improving outcome. Statements in the literature, such as “vasodilators provide an effective treatment in selected cases,” even if true, do not have a scientific basis.

No reports have dealt quantitatively with the mortality associated with the use of pulmonary vasodilators in PPH. There are two forms of iatrogenic death. There have been a number of immediate deaths which occur during cardiac catheterization as the patient is “titrated” with a vasodilator or combination of vasodilators. Knowledge of this form of mortality is sufficiently widespread so that the number of patients dying during catheterization is probably not insignificant. There has not been a mechanism for collecting these data; and, of course, there has been the feeling that even without a drug titration, the patient was doomed (c’est la mort).

There is almost certainly another form of mortality associated with pulmonary vasodilator therapy: that occurring during long-term use. Given a high and fixed pulmonary vascular resistance, a reduction in systemic vascular resistance must result in decreased cardiac output. It is therefore almost inconceivable that no long-term deaths have occurred.

The question arises: how many patients have died during long-term treatment? It is not possible to make an accurate estimate. Death occurring under these circumstances would usually be attributed to death from PPH and not from its treatment.

Is there a mechanism for estimating the incidence of drug-related mortality? A randomized, controlled prospective clinical trial would provide this information (as well as critically important data about efficacy). Excess deaths related to drug use would equal total deaths (control plus treated) minus deaths in controls. Such an approach has already been used for estimating the excess number of abortions caused by amniocentesis.16

The other question is whether pulmonary vasodilators improve the quality of life. Undoubtedly, individual patients have shown an improved functional status during treatment; however, given the possibility of spontaneous improvement or regression, it is not possible to attribute improvement to the use of vasodilators. As mere opinion, the use of the drugs seldom is associated with an obvious improvement in the quality of life.

Despite their use for over a decade, no adequate trials have been performed. Attention has been focused on other issues, such as the pragmatic use of vasodilators in other forms of pulmonary hypertension,19 the development of better and perhaps safer pulmonary vasodilators, and the use of agents like epoprostenol (prostacyclin) to identify a reversible component in PPH.17 No doubt these are interesting tangents, but they cast little or no light on the safety and efficacy of pulmonary vasodilators.
A troublesome question is whether the widespread use of pulmonary vasodilators has resulted in a sufficient number of deaths among potentially long-term survivors to shorten unnaturally the natural life history of PPH. Only a well-designed and well-executed clinical trial will provide an answer, and the case for such a trial has been argued persuasively by others.†.

**Heart-Lung Transplantation**

Human heart-lung transplantation has been used in the treatment of pulmonary hypertension at Stanford Medical School for approximately five years. The conceptual basis for its use was based on a highly successful program of cardiac transplantation. Actuarial analysis of candidates for heart transplantation showed that 90 percent of potential candidates not receiving a transplanted heart were dead within a year. Mean survival in patients receiving a transplant is in the order of years, and striking improvements in the quality of life occur in the majority of surviving patients.† The difference in outcome between the two groups was obvious and striking. This experience was grafted onto the problem of heart-lung transplantation with PPH. It was considered (by some, myself included) that patients with PPH shared an equally grim prognosis with patients suffering from advanced myocardial disease. Offering heart-lung transplantation to patients with pulmonary hypertension seemed like an obvious and desirable extension of the heart transplant program.

The benefit side is clear. Approximately two thirds of the patients survive the perioperative period. As surgical experience has accumulated and with more rational selection of cases, perioperative mortality has tended to fall further. Early in the program, an important long-term complication of lung transplantation became obvious—obliterative bronchiolitis. Although one third of the first group of patients developed this chronic complication. As experience accumulated, it became reasonable to attribute obliterative bronchiolitis to lung rejection. In any case, early obliterative bronchiolitis seems to be manageable by early treatment with steroids or antirejection regimens. In addition to obliterative bronchiolitis, there are a number of other complications with a low incidence, but surviving patients can usually look forward to marked improvements in the quality of life.

When contrasted with an assumed mortality of 90 percent for PPH within a year or two, a favorable risk-benefit balance seemed obvious. Given a five-year survival rate without surgery, the status of the risk-benefit balance is not as clear.

†I am personally involved in the heart-lung transplant program, and the readers should be warned that I may be unconsciously biased in my evaluation of that program.

To resolve the risk-benefit status of heart-lung transplantation would obviously require a controlled prospective randomized trial. Such a trial would present a number of unique difficulties. Theoretically, a well-designed clinical trial would be feasible; however, whether such a trial will be organized depends upon a number of technical as well as conceptual problems.

In general, appropriate clinical trials of surgical procedures have not been as vigorously pursued as those involving medical procedures. There are notable exceptions. An international trial which demonstrated that extracranial-intracranial anastomosis for strokes resulted in a 15 percent increase in mortality and strokes is a milestone example.

Prospective candidates for heart-lung transplants are provided rigorously honest informed choices about the procedure. They are specifically informed of the uncertain nature of the risk-benefit balance; but no matter, without the data provided by a clinical trial, truly informed consent cannot be provided, and the therapeutic value of heart-lung transplantation cannot be rigorously established. Based on quality-of-life considerations, I believe that such a trial would show a favorable risk-benefit balance, but that is mere opinion. If so, then the natural life history of PPH would be unnaturally lengthened.

**PPH Registry**

The establishment of a PPH registry, with a major objective to determine the natural life history of PPH, was a laudable and worthwhile idea. The word, "registry," meaning a mechanism for recording information or data, has a benign and passive connotation. This registry has developed partially as an interventionist project, and three of the interventions are capable of modifying the natural life history of PPH.

**Open Lung Biopsy**

Obtaining an open lung biopsy is not an official prerequisite for registering patients; however, it has been strongly suggested, so strongly that the PPH registry believed it necessary to clear up confusion by disavowing the procedure as a mandated procedure. In any case, it appears that open lung biopsy has been performed on some 10 to 15 percent of patients. There has been at least one death in a patient associated with (more bluntly, because of) open lung biopsy. From the standpoint of outcome for the patients, it must be said that open lung biopsy is seldom, if ever, justified, even with the vaguest of hopes that the information will prove useful in changing the outcome.

In the context of the present discussion, open lung biopsy is not acceptable for a registry which is attempting to outline the natural life history of PPH. Whatever their longevity, these patients are fragile, and death from lung biopsy is a misadventure which is not a
natural consequence of the disease. It is not clear whether a patient dying of open lung biopsy is included in the registry.

Are there less risky alternatives to the use of open lung biopsy? One would be to restrict the histologic examination to postmortem material; or if postmortem material is considered to be skewed by specimens which come largely from the sickest group of patients, Stanford has appropriate material from approximately 25 patients who underwent transplantation who were not preterminal. The American medical system should be collegial enough to furnish this material to the registry. At the very least, it is hoped that the mortality and morbidity associated with open lung biopsy will be emphasized in the final report of the registry.

CATHETERIZATION AND REPEAT CATHETERIZATION

It is mandated that each patient in the registry have a recent right-sided catheterization for entry. The mortality of a single right-sided catheterization in PPH extracted from the literature is about 5 percent. My understanding is that no fatalities have occurred as a result of repeat catheterization alone in the registry’s patients, but there have been deaths during catheterization during the testing of pulmonary vasodilators. It is not clear whether patients dying during catheterization are eligible for entry into the registry.

The registry has encouraged the testing of various pulmonary vasodilators in patients entering the registry. The short-term and long-term risks inherent in such testing have been described previously. There should not be any illusions that this information will settle issues of safety and efficacy. More likely, this information will confuse these issues. This form of gathering data is no substitute for an acceptable clinical trial. Moreover, a smorgasbord of 16 drugs is available and used in various ways, in various combinations, in various patients. What this addition to the registry’s protocol will do, predictably, is to modify the natural life history of PPH unfavorably.

One hopes that the registry will supply an accurate estimate of deaths during drug testing under the auspices of the registry to alert physicians to the hazards.

In a general way, then, the interventionist components of the registry have introduced a variant of the Heisenberg uncertainty principle. A series of observations have made it impossible to determine the true natural state of the phenomenon being investigated.

Some of the major problems associated with PPH are related to basic problems; PPH is not a disease but a wastebasket. It would be more accurate to call the nosologic entity, pulmonary hypertension of unknown etiology. Being a diagnosis of exclusion, it is not surprising that its features are not homogeneous. One of the most heterogeneous characteristics has previously not been emphasized. The prognosis varies widely from patient to patient. Ascribing a short and invariably fatal course to the disease has not been in the best interests of patients, and spontaneous regression does occur in some patients.

The actual history of PPH will not be accurately determined until a noninvasive approach to the measurement of mean pulmonary arterial pressure becomes available. If that occurs, we may be surprised. Perhaps a substantial segment of the population may have elevated mean pulmonary arterial pressures without symptoms and without progression. Whether or not such an outcome is found, there is much to recommend a substantially less aggressive and invasive approach to patients than currently seems to be the style in medical centers.

Given the nature of this column, it is expected that it will evoke strong differences in opinion. I invite readers to provide contrary views.

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