Primary Pulmonary Hypertension
The Risk and Benefit of Lung Biopsy

Pascal Nicod, MD, and Kenneth M. Moser, MD

Among the many enigmas in cardiopulmonary medicine, primary pulmonary hypertension (PPH) holds a prominent place. Such prominence derives from the disquieting yet challenging recognition that its pathogenesis remains unknown; it usually eludes diagnosis for several years; no satisfactory therapy exists; and its prognosis in the individual patient is uncertain.\textsuperscript{1-3}

See pp 1198 and 1207

In an effort to resolve some of these questions, the National Heart, Lung, and Blood Institute established a registry of patients with PPH, using strict criteria for entry and obtaining extensive initial and follow-up characterization. The data published so far have provided some insights into this disorder, but much remains unknown.\textsuperscript{3} One unsettled issue is the value of open lung biopsy in PPH. This is a potentially hazardous procedure, and one that may compromise subsequent selection for transplantation. Therefore, establishment of its risk and benefit is of substantial importance.

There are at least four potential benefits of open lung biopsy: insights into pathogenesis, guidance of therapy, confirmation (or refutation) of the diagnosis, and establishment of prognosis. In this issue of \textit{Circulation}, two reports deal with the value of lung histopathology in addressing these questions.\textsuperscript{4,5}

With respect to pathogenetic insights, previous reports have suggested that so-called “plexogenic (plexiform) lesions” and concentric intimal thickening point to pulmonary vasoconstriction as the dominant mechanism, whereas microthrombotic lesions and eccentric intimal thickening indicate in situ thrombosis as the major underlying basis for small vessel obstruction.\textsuperscript{6-9} In the latter instance, some confusion has resulted from use of the term thromboembolic pulmonary hypertension, even though no evidence exists for an embolic source.

Furthermore, previous reports and the one by Pietra et al\textsuperscript{4} in this issue of \textit{Circulation} cast doubt on the pathogenetic differentiation implied by these histopathologic findings. It is clear that a great degree of histologic heterogeneity is found among patients with PPH. As noted by Pietra et al,\textsuperscript{4} patients with plexiform lesions also have microthrombotic lesions and eccentric intimal fibrosis. Interestingly, they found that biopsies more often demonstrated microthrombotic lesions, whereas autopsy-pneumonectomy specimens more often revealed plexogenic lesions. This raises a sampling issue because the finding of one plexogenic lesion leads to placement in that subgroup, regardless of other findings. Plexogenic lesions are rarely numerous and, therefore, may escape detection on lung biopsy.

Furthermore, none of the lesions is pathognomonic of PPH. They are seen in patients with “Eisenmenger” pathophysiology.\textsuperscript{10,11} In addition, these lesions occur in pulmonary hypertension due to chronic, major vessel thromboembolism, a disorder that is clearly embolic in origin and potentially correctable by thromboendarterectomy.\textsuperscript{12} Finally, in the familial form of PPH, in which a common pathogenetic mechanism presumably is operative, both thrombotic and plexiform lesions are present.\textsuperscript{13} Thus, in terms of providing pathogenetic insights, vascular histopathology does not appear to be very useful. Indeed, the accumulated evidence suggests to us that these histopathologic changes are the “footprints” of pulmonary endothelial cell injury and dysfunction induced by unknown agents. True pathogenetic insights appear, therefore, more likely to arise from study of endothelial cell pathophysiology than from histopathology.

Can histopathology guide therapy? The therapies now available are vasodilators, anticoagulant drugs, and lung or heart-lung transplantation. With respect to predicting the response to vasodilator drugs, the answer appears to be negative. As Palevsky et al\textsuperscript{15} report in this issue of the journal, only a minority of these patients respond to such drugs. The vasodilator response when observed was not seen more often in any of their subsets of hypertensive pulmonary arteriopathy. Thus, even with a lung biopsy in hand, drug testing is required to identify individual responders because there is no uniformity of response to a given vasodilator or to a given dose of

The opinions expressed in this editorial comment are not necessarily those of the editors or of the American Heart Association.

From the Divisions of Cardiology and Pulmonary Critical Care Medicine, University of California San Diego School of Medicine, San Diego.

Address for correspondence: Pascal Nicod, MD, Division of Cardiology, UCSD Medical Center, H-811-A, 225 Dickinson Street, San Diego, CA 92103.

Received August 4, 1989; revision accepted August 7, 1989.
these agents. The complexity of such appraisal has been emphasized.14 There is hope that intravenous infusion of prostacyclin (or synthetic analogues) may prove useful in differentiating responders from non-responders and that oral vasodilators need only be applied to responders.15–17 Studies are still underway to confirm this simpler decision-making pathway.

With respect to anticoagulant therapy, biopsy provides no guidance. Microthrombotic lesions are common. No well-designed trial has demonstrated that long-term anticoagulation is of benefit, although this approach has been advocated based on limited retrospective data.18,19 Until an appropriate trial is done, the value of long-term anticoagulation will remain uncertain.

Can lung biopsy aid in confirming the diagnosis? The answer seems to be only to a minor degree and with a pitfall involved. The occurrence of the same lesions in other forms of pulmonary hypertension is the pitfall. This pitfall is a deep one in the case of chronic, large vessel thromboembolic hypertension in which a PPH biopsy may deflect the physician from performing angiography20 and considering potential corrective surgery.12,21 The small gains provided by biopsy would include the identification of pulmonary venoocclusive disease (for which no medical therapy exists),22 of vasculitis, and of unsuspected interstitial fibrotic disease. The last, however, should be detectable by methods other than open lung biopsy.

The potential value of tissue to define prognosis is suggested by the two reports in this issue4,5 and by previous reports.3,7,8,18 Plexiform lesions and intimal thickening appear to predict shorter survival from the time of biopsy. However, perhaps such lesions reflect a longer prediagnosis duration of PPH because the onset of PPH usually is difficult to define with any precision. Whatever the case, wide individual variability in prognosis exists despite the presence or absence of plexiform and other lesions.

Thus, viewed in broad context, the clinical impact of open lung biopsy is quite limited, even when expert vascular pathologists review the slides. In the individual patient, the information to be gained must be carefully weighed against the risks. There are two risks: the morbidity and mortality of the procedure itself and the effect of open biopsy on future transplantation decisions. While the immediate risks appear modest, they exist,4 and the procedure should certainly not be undertaken lightly. More critical, perhaps, is the fact that a previous thoracotomy is considered a relative contraindication to lung or heart-lung transplantation because of the pleural scarring induced. With the growing consideration of transplantation in patients with PPH who fail medical therapy—and long current waiting lists—this concern must condition biopsy decisions.23

Given the current situation, then, the risk-to-benefit ratio of open lung biopsy in PPH remains quite uncertain. If it is undertaken, the indications should be clear, the risks discussed, and the biopsy reviewed by highly experienced eyes.

References


(Circulation 1989;80:1486–1488)
Primary pulmonary hypertension. The risk and benefit of lung biopsy.
P Nicod and K M Moser

Circulation. 1989;80:1486-1488
doi: 10.1161/01.CIR.80.5.1486

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