Perfusion Lung Scans Provide a Guide to Which Patients With Apparent Primary Pulmonary Hypertension Merit Angiography

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There is hesitancy, based on the perceived risk, to do pulmonary angiography in patients believed to have primary pulmonary hypertension. Yet pulmonary hypertension due to major-vessel, chronic thromboembolism mimics primary pulmonary hypertension clinically and on standard laboratory tests. Because thromboembolic pulmonary hypertension is potentially remediable by thromboendarterectomy and primary pulmonary hypertension is not, differentiating between these disorders is essential. Angiography is required in patients with thromboembolic pulmonary hypertension to define the anatomic location of the thrombi. In evaluating perfusion lung scans of 110 patients with pulmonary hypertension to determine whether the scan might provide a guide to selecting those patients who merit angiography, no segmental-size perfusion defects were noted on the scans of 64 patients with primary pulmonary hypertension, whereas all 46 patients with thromboembolic hypertension had one or more defects that were segmental in size or larger. These data indicate that a perfusion lung scan should be done in patients with pulmonary hypertension of uncertain cause and that those with one or more segmental or larger defects merit pulmonary angiography before being diagnosed as having primary pulmonary hypertension.

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Primary pulmonary hypertension remains enigmatic in pathogenesis, is nominally responsive to therapy, and has a poor prognosis.[1-4] On the other hand, pulmonary hypertension due to chronic thromboembolic obstruction of major (main, lobar, segmental) pulmonary arteries is of a known cause and is potentially correctable by thromboendarterectomy.[5-9] Therefore, differentiating between these two disorders is essential, but it may be difficult. The history, physical examination, and standard laboratory tests—chest x-ray films, electrocardiogram (ECG)—and right heart catheterization may provide no differential clues.[5,9,10] Indeed, only the results of pulmonary angiography can unequivocally make the diagnosis. Yet, there is reluctance to do angiography in all patients with apparent primary pulmonary hypertension because of the perceived risk.[1,11,12]

Limited prior experience at our institution and others has suggested that the perfusion lung scan might assist in the decision to do pulmonary angiography in patients with severe, unexplained pulmonary hypertension.[13-15] To determine whether this suggestion could be validated in a large series, we have reviewed perfusion lung scans and collateral data in 110 patients: 64 who had primary pulmonary hypertension and 46 who had pulmonary hypertension due to major-vessel thromboembolism. The data confirm that the perfusion scan provides a highly reliable guide to selecting patients who merit pulmonary angiography.

Patients and Methods

The 64 patients with primary pulmonary hypertension were referred to various centers, including the University of California, San Diego (UCSD), that are participating in the National Heart, Lung, and Blood Institute's Primary Pulmonary Hypertension Registry; after evaluation, the patients met the criteria for registry inclusion.[16] The entry criteria include compatible findings on a history, physical examination, and chest radiograph; a right heart catheterization confirming pulmonary hypertension in the absence of a left-to-right cardiac shunt, or an elevated pulmonary capillary ("wedge") pressure; and pulmonary spirometric tests excluding significant restrictive or obstructive abnormalities. While pulmonary angiography or a lung biopsy are not required for entry in the registry, 57 (89%) of these 64 patients did have pulmonary angiographic (44 patients), lung biopsy (6 patients), or autopsy (7 patients) confirmation of the diagnosis of primary pulmonary hypertension. This is a substantially higher rate of angiographic-biopsy-autopsy confirmation than exists among the approximately 300 patients admitted to the registry thus far.

The 46 patients with chronic thromboembolic pulmonary hypertension were all evaluated at the UCSD Medical Center, and 38 of them ultimately underwent thromboendarterectomy between 1970 and 1985. All were referred for evaluation of pulmonary hypertension of an uncertain cause. All

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ABBREVIATIONS USED IN TEXT
ECG = electrocardiogram
UCSD = University of California, San Diego

had pulmonary angiography. (Angiography also disclosed that 16 patients referred during this period had primary pulmonary hypertension, and these are included in the series of registry patients.)

All 110 patients had perfusion scans, including at least four views (anterior, posterior, and both laterals). Most (92 patients) also had either ventilation scans using xenon Xe 133 or inhalation scans using technetium Tc 99m-labeled pentetic acid (sodium zinc diethylenetriaminepentaacetate, DTPA). The scans from all patients, with all identifiers removed, were intermixed in a random fashion and submitted to two reviewers experienced in interpreting scans. They were asked, first, to classify the perfusion scans into two categories: those with one or more segmental or larger defects and those without defects of this size. They were also asked to subclassify those in the second category as to whether the distribution of radioactivity was inhomogeneous—specifically, to classify those with no or equivocal inhomogeneity as normal and those with unequivocal differences in regional radioactivity as inhomogeneous. Finally, the reviewers were asked to note the presence of any subsegmental defects or defects due to cardiac or other vascular structures.

Results

Analysis of the scan classification according to the presence or absence of segmental or larger defects disclosed no disagreement between the two reviewers. Furthermore, none of the 64 patients with primary pulmonary hypertension had such defects, whereas all 46 patients with pulmonary hypertension due to chronic, major-vessel thromboembolism had one or more defects that involved one or more segments. Thus, there was no overlap in classification between the two groups.

Among the 46 patients with thromboembolic pulmonary hypertension, all ventilation scans were classified as normal—that is, these defects showed a ventilation-perfusion "mismatch" (Figure 1).

The reviewers also agreed on the subclassification among 60 of the 64 patients without segmental defects. Of the 60 patients, 41 were classified as showing either no or minimal inhomogeneity; 6 of these also showed one subsegmental defect (Figure 2). In 19, the reviewers agreed that the distribution was inhomogeneous (Figure 3); of these, 2 also had subsegmental defects. In four patients, there was disagreement as to whether more than minimal inhomogeneity was present.

Two other types of abnormalities were seen in some patients with both forms of pulmonary hypertension. One type was due to the pronounced cardiomegaly present in some patients (Figures 4 and 5). On the anterior scan view, cardiomegaly widened the "cardiac space" normally seen and encroached on the left lower lobe. On the posterior view, it diminished scan perfusion to the left lower lobe, and, often, on one or both lateral views, cardiomegaly was reflected as diminished to absent perfusion to the lower anterior lung zones.

The second common scan abnormality was due to increased size of the central pulmonary arteries (Figures 2, 4, and 5). Decreases in perfusion to areas corresponding to these arteries were often seen in anterior, posterior, and lateral views.

Discussion

The pathogenesis of "primary" pulmonary hypertension is uncertain. The World Health Organization has recom-

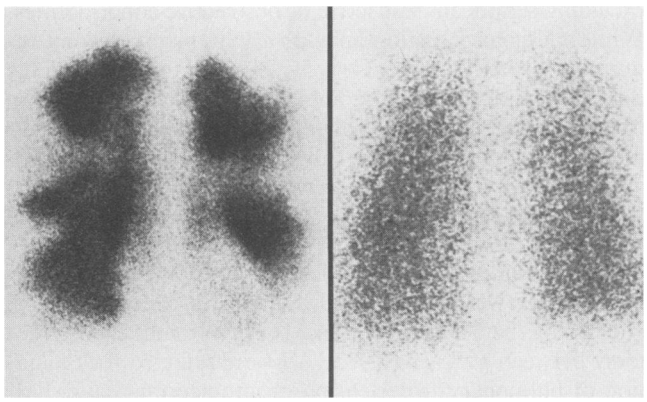

Figure 1.—Left, A perfusion scan is shown of a patient with pulmonary hypertension due to chronic obstructing thromboembolism who subsequently underwent thromboendarterectomy. Many segmental defects are present in both lungs. **Right,** The ventilation scan was normal during wash-in of xenon Xe 133 (shown) and during wash-out.

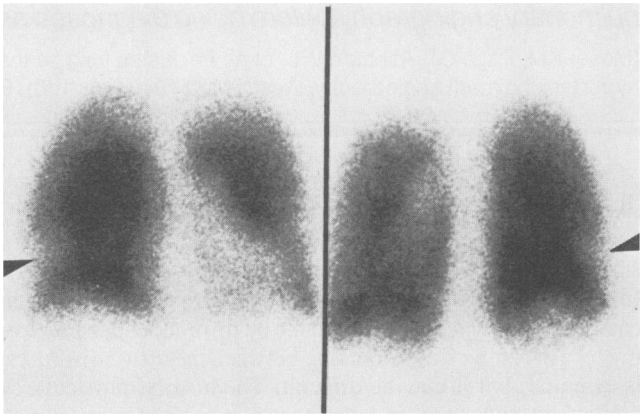

Figure 2.—Perfusion scans are normal in a patient with primary pulmonary hypertension except for a subsegmental defect **(arrow)** on anterior **(left)** and posterior **(right)** views. A left pulmonary artery imprint is seen on the posterior view. The patient's pulmonary angiogram disclosed no embolic obstruction.

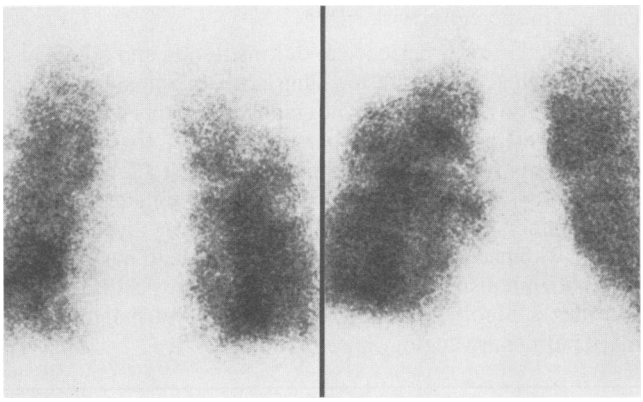

Figure 3.—A perfusion scan in a patient with primary pulmonary hypertension shows an inhomogeneous distribution of radioactivity on anterior **(left)** and posterior **(right)** views.

mended separating primary pulmonary hypertension into three categories on the basis of histologic findings, namely, plexogenic pulmonary arteriopathy, microthrombotic pulmonary hypertension, and pulmonary veno-occlusive disease.[17] Whether these three conditions are pathogenetically distinct remains uncertain. There is a fourth disorder, however—chronic, major-vessel thrombotic pulmonary hypertension—that differs from those comprising "primary" pulmonary hypertension in important ways. Indeed, it might be clarifying to describe primary pulmonary hypertension as "small-vessel obliterative pulmonary hypertension" to distinguish it from the major-vessel form in which the obstruction involves main, lobar, and segmental pulmonary arteries. The distinction is more than anatomic; it conditions therapeutic options. Small-vessel obliterative pulmonary hypertension is not subject to correction by surgical thromboendarterectomy, whereas the disorder due to major-vessel thromboembolism is.[5-10]

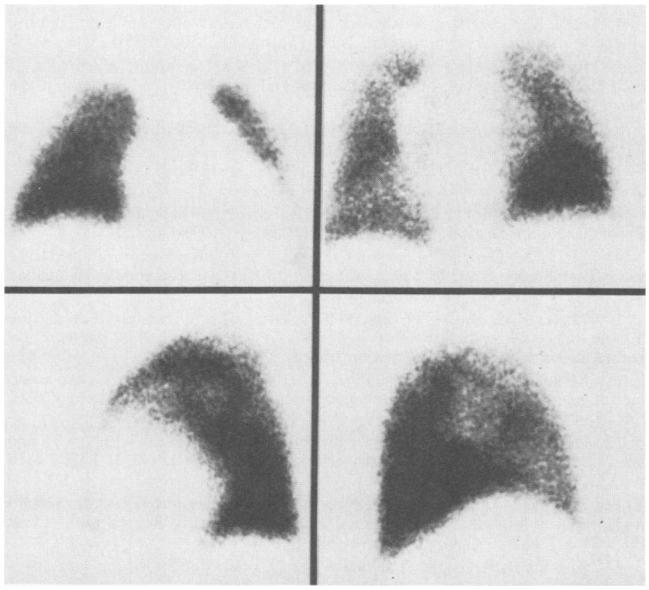

Figure 4.—A perfusion scan done in a patient with primary pulmonary hypertension and marked cardiomegaly shows substantial widening of the cardiac space, with particular encroachment on the left lower lobe in anterior **(upper left)** and posterior **(upper right)** views. The left lateral view **(lower left)** shows a large anterior cardiac imprint. Pulmonary artery imprints are seen well on posterior and right lateral **(lower right)** views.

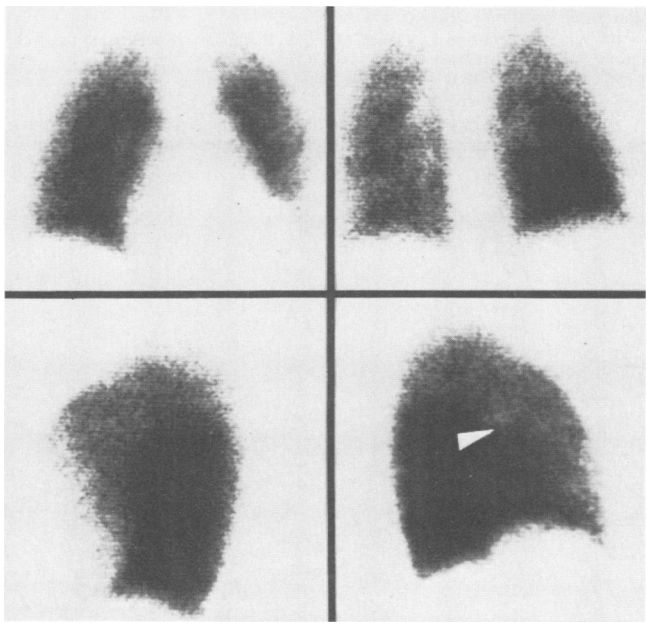

Figure 5.—Left and right pulmonary arteries in a patient with primary pulmonary hypertension cause imprints on the posterior view **(upper right)** and the right lateral view **(lower right, arrow).** Cardiomegaly also is present.

Despite the importance of this differential diagnosis, we and others have found that many patients with thromboembolic pulmonary hypertension have been labeled, for varying periods of time, as having primary pulmonary hypertension.[5-10] This is understandable because the two conditions closely mimic each other with regard to clinical findings and the results of standard laboratory tests, such as ECG, chest radiography, pulmonary function, and right heart catheterization findings.[9,10] Yet, the diagnostic delay in making this distinction may be unfortunate for several reasons. First, the patients with thromboembolic pulmonary hypertension have been told of the rather grim prognostic outlook for the primary form. Second, and more important, misdiagnosis as primary pulmonary hypertension often has delayed the consideration of a thromboendarterectomy for months to years. This delay has, in a number of instances, led to a deterioration in right ventricular function and a patient's overall status, factors that increase the risk of surgical thromboendarterectomy.[9,10] Furthermore, there is evidence that a delay in doing a thromboendarterectomy may be associated with progressive injury to the pulmonary arterial vessels,[5,18] a development that also may increase the surgical risk and may moderate and delay post-operative pulmonary hemodynamic improvement.[9,10]

Often the diagnostic delay has been based on a reluctance to do pulmonary angiography in patients diagnosed as having primary pulmonary hypertension because of prior reports that this procedure entails substantial risk.[11,12] While more recent reports indicate that modern methods for angiography pose substantially less risk in patients with pulmonary hypertension,[19,20] it would be useful if a safe, noninvasive technique were available to guide selection of those who merit angiography.

Previous reports of small series of patients have suggested that perfusion lung scanning might fill this role.[13-15] The present report of a large series confirms the reliability of the perfusion scan in differentiating primary pulmonary hypertension from potentially operable thromboembolic pulmonary hypertension. Using the simple criterion of the presence or absence of one (or more) perfusion defects that are the size of a lung segment or greater, there was no overlap between patients with the primary type and those with the thromboembolic type of hypertension. In the 46 patients in whom perfusion defects were found involving one or more segments, pulmonary angiography confirmed chronic thrombotic occlusion of one or more lobar or segmental arteries. We would suggest, therefore, that before a patient is characterized as having primary pulmonary hypertension on the basis of clinical and laboratory studies—including right heart catheterization—lung scanning should be done. If this procedure discloses one or more segmental or larger "mismatched" perfusion defects, pulmonary angiography is warranted.

The question could be raised as to the need for angiography even among patients with thromboembolic pulmonary hypertension, if the scan is so definitive. The answer lies in the

fact that locating the thrombi precisely is an essential antecedent to surgical treatment.[10] In patients with thrombi limited to segmental or subsegmental arteries, a thromboendarterectomy may be difficult or impossible to do.[5,9] A lung scan cannot distinguish whether segmental or larger defects are due to one proximal obstruction or several more distal obstructions. Only angiography can provide such anatomic information. The decision for thromboendarterectomy is, of course, not based exclusively on detecting scan or angiographic abnormalities, as we have described elsewhere.[10] For example, we require a pulmonary vascular resistance above 300 dynes·sec·cm^{-5} before surgical treatment is recommended.

It is also reasonable to consider whether the excellent perfusion scan separation between primary pulmonary hypertension and major-vessel thromboembolic hypertension may, in part, reflect some bias in patient selection in the present series. For example, it is theoretically possible that there are patients with major-vessel thromboembolic pulmonary hypertension in whom segmental or larger mismatched defects may be absent. This would require critical placement of partially obstructing thrombi—for example, in both main pulmonary arteries. While we have seen such an occurrence in animals, this has not yet been reported in humans.

On the other hand, may there not be patients with primary pulmonary hypertension in whom the scan will show segmental or larger defects? In our own experience, in which all patients with pulmonary hypertension of an uncertain cause have undergone angiography, this has not yet occurred. Nor are we aware of a patient studied elsewhere in whom such a scan-angiographic disparity has occurred. Thrombosis does occur in the *distal* pulmonary arteries in some patients with primary pulmonary hypertension.[13] In a recent report, this was suggested as the basis for the inhomogeneous lung scan pattern, whereas a homogeneous pattern may reflect plexogenic pulmonary arteriopathy[21]; but no segmental-sized defects have been reported in such patients.

In summary, the extensive experience reported here indicates that perfusion lung scanning provides an excellent noninvasive low-risk tool for distinguishing between pulmonary hypertension due to potentially operable large-vessel chronic thromboembolism and obliterative, small-vessel pulmonary hypertension ("primary"). This experience suggests that patients with one or more segmental or larger perfusion defects who are considered candidates for correction by surgical thromboendarterectomy should undergo arteriography. Continued study of scan-angiographic relationships is warranted to determine whether exceptions to the findings reported here may occur.

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