A NONINVASIVE method for detecting and quantifying pulmonary arterial hypertension would be useful in many investigational and clinical contexts. Several promising methods are being explored, but none has provided consistently useful results. We investigated the value of a method that relies on detecting the alteration in the apex-to-base distribution of pulmonary blood flow that occurs when patients move from the supine to the erect position.

The apex-to-base distribution of pulmonary blood flow is normally determined by the relationships among pulmonary arterial, pulmonary alveolar and pulmonary venous pressures. In the erect position with normal pulmonary arterial pressures, these relationships, modulated by gravitational hydrostatic effects, result in an increment in flow per unit lung volume from the apex to the base of the lung. In the supine position, the apex-to-base distribution is much more uniform because the longitudinal axis is perpendicular to the gravitational hydrostatic effects.

Under normal circumstances, a substantial shift in the distribution of pulmonary blood flow can be anticipated when a person moves from the supine to the erect position. If pulmonary arterial pressure is significantly elevated and pulmonary alveolar and venous pressure are not significantly altered, a different apex-to-base perfusion pattern might be anticipated. In patients with pulmonary arterial hypertension, the apex-to-base distribution should be substantially more uniform in the erect position, and its relative uniformity in the supine position should remain. Therefore, the shift in distribution from the supine to the erect position should be moderated. Further, the extent to which this shift is reduced may reflect the extent to which pulmonary arterial pressure has become elevated, i.e., the degree of pulmonary hypertension.

We evaluated this thesis in 12 normal subjects and 10 patients with precapillary pulmonary hypertension.

Methods

The study population included 12 normal volunteers and 10 patients with precapillary pulmonary hypertension, either primary pulmonary hypertension or thromboembolic disease. The normal subjects were 24–32 years old (mean 29 years) and the patients were 30–62 years old (mean 43 years). The normal subjects were nonsmokers, had no symptoms related to cardiorespiratory function, and had normal physical examinations and chest roentgenograms. The pulmonary hypertensive group had a variable smoking history and were usually being evaluated for symptoms of breathlessness. Initially, all patients underwent a complete history, physical examination, posteroanterior and lateral chest films, ECG and arterial blood gas analysis. Seven of the 10 patients underwent pulmonary function tests. Six of the 10 patients had had perfusion scans; four of these had one or more segmental or larger perfusion defects.

Cardiac Catheterization

After completion of the initial studies, the 10 patients underwent right-heart catheterization. While the patients were breathing room air, a balloon-tipped, flow-directed catheter was inserted into a median antecubital vein and advanced under pressure monitoring to a pulmonary arterial segment. The zero pressure
reference point was the midthoracic line. Right atrial, right ventricular, pulmonary arterial and pulmonary arterial wedge pressures were measured using a Statham P23Db gauge manometer and recorded on a DR12 Electronics for Medicine recorder. The anatomic location of the catheter was confirmed by examining the phasic contour of the pressure tracing. The mean pulmonary arterial pressure and mean wedge pressure were determined electronically. All other pressures were averaged over three respiratory cycles. The patients underwent radionuclide scanning within 6 hours after right-heart catheterization.

**Scintillation Camera Studies**

The radionuclide studies were performed with Searle Pho Gamma III scintillation camera with a diverging collimator to allow simultaneous counting of both lung fields. The camera was interfaced to a General Electric Med II digital data acquisition system. Data were stored on tape in the form of 64 × 64-word matrices for later off-line processing. A low-resistance spirometer circuit designed for delivery of xenon-133 was used for the ventilation studies. A light source system attached to the scintillation camera was used to ensure reproducibility of position between the patient and the detector for each study.9

For the initial study, the subjects were placed in the supine position for 1 minute, and human albumin microspheres labeled with 1 mCi of technetium-99m (99mTc) were injected intravenously while the subject performed sequential slow inspiratory capacity maneuvers from functional residual capacity to total lung capacity. After remaining in the supine position for 2 minutes, the subjects were seated with the camera facing the posterior thorax. Once the subject was properly positioned, the light source system was attached to the detector and the subject marked to ensure reproducibility of position. Data from the supine injection were then recorded for 2 minutes and stored (scan 1).

For the second study, the patients remained seated. A second injection microspheres labeled with 2 mCi of technetium-99m was administered during sequential slow inspiratory capacity maneuvers. After 2 minutes, the subjects were repositioned to the detector and data were recorded and stored (scan 2).

The subject was then connected to the xenon spirometer system and allowed to become accustomed to the mouthpiece and noseclip. The scintillation camera was set for the xenon window, and the subject was repositioned before the camera. Because 15–25% of the 99mTc activity injected for the perfusion scans is included in the xenon window, a 2-minute background scan was recorded and stored before the xenon-133 study (scan 3).

Finally, still positioned against the camera, the subject was switched into the spirometer system, which had been charged to an activity of 10 mCi of xenon per liter. The subject was instructed to breathe normally. At equilibrium with the spirometer, determined by a stable count rate over the lung fields for 30 seconds, the subject was again realigned to the detector and an equilibrium ventilation scan was recorded (scan 4) for 2 minutes and stored.

The above procedures thus produced four images: scan 1, supine blood flow; scan 2, upright and supine blood flow; scan 3, background 99mTc activity within the xenon window; and scan 4, ventilation equilibrium.

**Data Analysis**

The supine scan (scan 1) was recalled from computer memory and displayed in a 64 × 64-pixel format. A region of interest corresponding to the right lung was manually assigned. The supine scan was used in all cases to assign this region of interest because blood flow is more evenly distributed from apex to base in this position. The area assigned as the right lung remained constant during the processing of all remaining scans.

Next, the unprocessed scans were corrected for background. The upright blood flow (scan 2) contained information from both the initial supine injection and the second upright injection. Since both scans were recorded for 2 minutes, the supine scan (scan 1) was subtracted from the supine plus upright scan (scan 2) to yield the net upright blood flow distribution scan. A certain portion of the 99mTc activity injected for the two blood flow scans will be included in the xenon window. To correct for this, we subtracted scan 3 (background obtained by recording the 99mTc activity with the camera set for the xenon window) from scan 4. The data in each region of interest were then normalized to 100,000 counts.

Finally, the apex-to-base blood flow distribution was determined. The region of interest (right lung) was trisected along its long axis by the computer into three regions of equal longitudinal dimension (fig. 1). For the corrected and normalized supine, upright and equilibrium scans, the total counts in the apical (upper third) and basilar (lower third) regions were determined. The counts in these upper and lower regions of each blood flow scan were divided by the corresponding region of the equilibrium ventilation scan to yield values that represent blood flow per unit volume in the upper and lower regions, respectively. For example, the corrected blood flow per unit volume for the apical region of the supine scan is R1/R5 and for the upright scan R3/R5. The blood flow per unit volume for the basilar regions for the supine and upright scans are R2/R6 and R4/R6, respectively. The apex-to-base ratios of blood flow per unit volume are, therefore, (R1/R5)/(R2/R6) for the supine scan and (R3/R5)/(R4/R6) for the upright scan.

**Statistical Analysis**

For the 10 normal subjects, the blood flow per unit volume of lung in upper and lower thirds (U:L zone ratio) was calculated for the supine and upright positions, and the percent change in this ratio after assumption of upright posture also was determined. Seven normal subjects underwent studies several days later to assess the reproducibility of data obtained.
The percent change in the U:L zone ratio was calculated for the patients and compared with that in the normal subjects. The percent shift was also correlated with the pulmonary arterial mean, systolic and diastolic pressures, the pulmonary capillary wedge pressures and the pulmonary vascular resistance.

The significance of differences between the control group and the pulmonary hypertensive group was determined by two-tailed t-test. The t-test was also used to determine the significance of correlation coefficients.

**Results**

The results of arterial blood gas analysis and spirometry in the patients with precapillary pulmonary hypertension are summarized in table 1. Chest roentgenograms in all 10 patients were free of gross infiltrates.

Hemodynamic data are recorded in table 2. The mean pulmonary arterial pressure in the patient group was 50 ± 24.2 mm Hg (range 21–96 mm Hg). The pulmonary capillary wedge pressure averaged 9.1 ± 3.5 mm Hg, and only two patients had wedge pressures greater than 12 mm Hg; these two patients had minimally elevated values of 13 and 14 mm Hg, which did not increase with handgrip. Pulmonary vascular resistance was calculated in seven patients and averaged 1167.38 ± 783 dyn-sec-cm⁻².

In the 12 normal subjects, the U:L zone ratio averaged 0.70 ± 0.05 in the supine position and 0.20 ± 0.08 in the upright position (p < 0.0001). This represented a 70.7 ± 12.2% shift of flow as the subjects altered their body positions (table 3).

Seven of the normal subjects had repeat ventilation-perfusion studies within 5 days of the original scans. There was no difference in these results compared with those initially obtained (table 3).

The 10 patients with precapillary pulmonary hypertension had a supine U:L zone ratio of 1.11 ± 0.69. This differed significantly (p < 0.05) from the supine ratio in the control group. The upright U:L zone ratio averaged 0.90 ± 0.63, also significantly different from the upright ratio in normal subjects (p < 0.005).

The postural shift in the ratio was only 19.0 ± 17.4% in the patient group (p < 0.0001 vs normals) (fig. 2).

All normal subjects had a greater than 50% shift in U:L zone ratio after assuming an upright posture, while no patient had a shift of 50%. All patients with elevation of the pulmonary arterial mean pressure above 30 mm Hg had a postural change in the U:L zone ratio of less than 30%.

A statistically significant inverse correlation (fig. 3) existed between the postural change in the U:L zone ratio and the mean pulmonary arterial pressure (r = -0.84, p < 0.01). Similarly, the percent shift also correlated inversely with the pulmonary arterial systolic pressure (r = -0.83, p < 0.01) pulmonary arterial diastolic pressure (r = -0.72, p < 0.05), and pulmonary vascular resistance (r = -0.74, p < 0.02).

No significant correlation existed between the upright U:L zone ratio and the pulmonary arterial press-

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**TABLE 1. Pulmonary Function Test Results in Pulmonary Hypertensive Patients**

<table>
<thead>
<tr>
<th>Blood gases (n = 10)</th>
<th>Mean ± sd</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.47 ± 0.05</td>
<td>7.43–7.53</td>
</tr>
<tr>
<td>Pco₂ (mm Hg)</td>
<td>32.6 ± 4.1</td>
<td>28–39.5</td>
</tr>
<tr>
<td>Paco₂ (mm Hg)</td>
<td>63.9 ± 8.1</td>
<td>51–75</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Spirometry (n = 7)</th>
<th>Mean ± sd</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC*</td>
<td>76.0 ± 12.5</td>
<td>59–99</td>
</tr>
<tr>
<td>FRC*</td>
<td>81.9 ± 12.2</td>
<td>66–101</td>
</tr>
<tr>
<td>RV*</td>
<td>92 ± 21.4</td>
<td>54–105</td>
</tr>
<tr>
<td>TLC*</td>
<td>81.4 ± 12.9</td>
<td>67–105</td>
</tr>
<tr>
<td>FEF₂₅-₇₅%*</td>
<td>80.3 ± 25.0</td>
<td>64–88</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>79.3 ± 8.4</td>
<td>45–113</td>
</tr>
</tbody>
</table>

*Percent of predicted value.

Abbreviations: Paco₂ = partial pressure of carbon dioxide in arterial blood; Paco₂ = partial pressure of oxygen in arterial blood; VC = vital capacity; FRC = functional residual capacity; RV = residual volume; TLC = total lung capacity; FEF₂₅-₇₅% = forced expiratory flow from 25% to 75% of vital capacity; FEV₁/FVC = ratio of 1 second forced expiratory volume to forced vital capacity.
sures, wedge pressures, or pulmonary vascular resistance. Nor did the hemodynamic measurements correlate with spirometric or blood gas values.

**Discussion**

Right-heart catheterization permits reliable detection and quantification of pulmonary arterial pressure. This invasive procedure is not suitable for screening patients or for repetitive observations in patients with pulmonary hypertension in whom definition of the natural history of this process, or of the effect of therapy, is desired.

The potential use of the distribution of pulmonary arterial blood flow as an indicator of pulmonary arterial pressure has been explored by others. Investigators in the early 1960s, using radioactive gas techniques, demonstrated the presence and the determinants of the apex-to-base gradient in the distribution of pulmonary blood flow. The interplay among three pressures — pulmonary arterial, pulmonary venous and alveolar — was shown to underlie the increasing blood flow per unit volume that is present from apex to base in the erect position.

Clearly, when pulmonary arterial hypertension occurs, the relationships among these pressures are altered. As pulmonary arterial pressure increases, the hydrostatic decrement in the pressure above the hilum (which is constant and determined by the geometry of the upright lung) becomes less and less important. This hydrostatic decrement in pressure is the cause of the normal gradient of perfusion from apex to base, and is approximately 15 mm Hg in the average-sized adult. When the mean pulmonary arterial pressure is normal (i.e., 15 mm Hg), the perfusion pressure at the lung apex may decrease almost to zero. Should the pulmonary arterial pressure increase to high levels, the fixed

**Table 2. Catheterization Data in Pulmonary Hypertensive Patients**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>PAs (mm Hg)</th>
<th>PAd (mm Hg)</th>
<th>PA (mm Hg)</th>
<th>PAW (mm Hg)</th>
<th>PVR (dyne·sec·cm⁻²)</th>
<th>Upper/lower zone ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>BH</td>
<td>30</td>
<td>39</td>
<td>16</td>
<td>21</td>
<td>4</td>
<td>201</td>
<td>1.58</td>
</tr>
<tr>
<td>MF</td>
<td>45</td>
<td>40</td>
<td>20</td>
<td>25</td>
<td>4</td>
<td>450</td>
<td>0.83</td>
</tr>
<tr>
<td>LC</td>
<td>50</td>
<td>47</td>
<td>20</td>
<td>30</td>
<td>8</td>
<td>1.05</td>
<td>0.75</td>
</tr>
<tr>
<td>RW</td>
<td>62</td>
<td>49</td>
<td>25</td>
<td>33</td>
<td>6</td>
<td>1.07</td>
<td>0.78</td>
</tr>
<tr>
<td>TB</td>
<td>32</td>
<td>60</td>
<td>30</td>
<td>42</td>
<td>13</td>
<td>593</td>
<td>2.84</td>
</tr>
<tr>
<td>DP</td>
<td>42</td>
<td>74</td>
<td>40</td>
<td>50</td>
<td>14</td>
<td>886</td>
<td>0.61</td>
</tr>
<tr>
<td>BR</td>
<td>60</td>
<td>100</td>
<td>48</td>
<td>65</td>
<td>12</td>
<td>1834</td>
<td>1.16</td>
</tr>
<tr>
<td>EB</td>
<td>42</td>
<td>92</td>
<td>42</td>
<td>68</td>
<td>10</td>
<td>1378</td>
<td>0.42</td>
</tr>
<tr>
<td>DT</td>
<td>30</td>
<td>109</td>
<td>25</td>
<td>70</td>
<td>10</td>
<td>1468</td>
<td>0.82</td>
</tr>
<tr>
<td>Al</td>
<td>33</td>
<td>140</td>
<td>70</td>
<td>96</td>
<td>10</td>
<td>2529</td>
<td>0.76</td>
</tr>
<tr>
<td>Mean</td>
<td>42.6</td>
<td>75.0</td>
<td>54.3</td>
<td>50.4</td>
<td>9.1</td>
<td>1167</td>
<td>1.11</td>
</tr>
</tbody>
</table>

Abbreviations: PAs = pulmonary arterial systolic pressure; PAd = pulmonary arterial diastolic pressure; PA = mean pulmonary arterial pressure; PAW = mean pulmonary wedge pressure; PVR = pulmonary vascular resistance.

**Table 3. Upper/Lower Zone Ratio in Normal Subjects**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Supine</th>
<th>Upright</th>
<th>% change</th>
<th>Repeat studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS</td>
<td>32</td>
<td>0.75</td>
<td>0.18</td>
<td>68</td>
<td>0.68</td>
</tr>
<tr>
<td>RH</td>
<td>32</td>
<td>0.71</td>
<td>0.11</td>
<td>86</td>
<td>0.57</td>
</tr>
<tr>
<td>CF</td>
<td>28</td>
<td>0.76</td>
<td>0.06</td>
<td>92</td>
<td>0.53</td>
</tr>
<tr>
<td>AM</td>
<td>26</td>
<td>0.70</td>
<td>0.20</td>
<td>71</td>
<td>0.81</td>
</tr>
<tr>
<td>RL</td>
<td>30</td>
<td>0.73</td>
<td>0.10</td>
<td>86</td>
<td>0.80</td>
</tr>
<tr>
<td>JS</td>
<td>30</td>
<td>0.67</td>
<td>0.18</td>
<td>73</td>
<td>0.62</td>
</tr>
<tr>
<td>ES</td>
<td>24</td>
<td>0.61</td>
<td>0.25</td>
<td>59</td>
<td>0.62</td>
</tr>
<tr>
<td>RC</td>
<td>27</td>
<td>0.71</td>
<td>0.27</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>SB</td>
<td>29</td>
<td>0.76</td>
<td>0.33</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>JB</td>
<td>31</td>
<td>0.68</td>
<td>0.32</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>BB</td>
<td>32</td>
<td>0.70</td>
<td>0.22</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>JV</td>
<td>29</td>
<td>0.65</td>
<td>0.21</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>29.1</td>
<td>0.70</td>
<td>0.20</td>
<td>70.7</td>
<td>0.66*</td>
</tr>
</tbody>
</table>

*Difference from initial study not significant.
hydrostatic decrement exerts a proportionally smaller influence on the perfusion pressure, which decreases or abolishes the normal gradient in blood flow.

Several investigators have studied alterations in pulmonary perfusion distribution as an indicator of pulmonary arterial pressure.\textsuperscript{10-13} However, all of these prior investigations have relied upon U:L zone ratios obtained from single upright images. Technical and methodologic problems have compromised these attempts. Abnormalities of pulmonary parenchyma, pleural effusions, cardiomegaly and the wide range of U:L zone ratios among patients with similar pulmonary arterial pressures have obscured the relationship between single erect U:L ratios and pulmonary arterial pressure.

Also, within various clinical settings, the distribution of flow in the upright lung will have disparate physiologic determinants. For example, Friedman and Braunwald\textsuperscript{10} used macroaggregated albumin labeled with iodine-131 to measure the distribution of pulmonary blood flow in upright patients with mitral stenosis. They derived an index of perfusion by dividing the counts in the upper third of the lung by those in the lower third (U:L zone ratio). In upright normal subjects, this ratio averaged 0.43. Patients with mitral stenosis had an upright U:L zone ratio of 1.01, which correlated highly with mean left atrial pressure and less closely with mean pulmonary arterial pressure.

Giuntini et al.\textsuperscript{11} studied 99 patients with various types of valvular heart disease, using iodine-131 macroaggregated albumin and a single upright U:L zone ratio as the index of distribution of flow. Despite elaborate corrections for lung volume and detector sensitivity, and exclusion of several patients for technical reasons, a close correlation between the U:L zone ratio and hemodynamic variables could not be demonstrated. This was attributed to technical problems as well as to the combined influence of multiple physiologic variables on flow.

Relatively few studies have examined the usefulness of scanning techniques for the assessment of pulmonary hypertension in patients with primary lung disease. Steiner et al.\textsuperscript{13} used probe detectors and iodine-131 macroaggregated albumin to investigate the upright flow distribution in six persons with valvular heart disease and five with idiopathic pulmonary hypertension. They used the ratio of upper to middle zone counts as an index of relative perfusion, and concluded that their method could detect pulmonary hypertension, but not estimate its severity. Steiner et al. correctly pointed out that abnormalities of lung parenchyma or focal perfusion defects adversely affected their estimation of pulmonary hypertension.

Soin et al.\textsuperscript{13} studied 36 patients with pulmonary hypertension, including 29 with precapillary hypertension. Unfortunately, their technique was qualitative, and hemodynamic data were measured in only 10 of their 36 patients. No attempt to assess the severity of pulmonary hypertension could be made.

Two problems have hampered previous investigations of U:L zone ratios. First, patients with similar hemodynamic status may show a wide range of U:L zone ratios in the erect position, which leads to considerable overlap between normal subjects and patients

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Postural change in the apex/base blood flow ratio in the control subjects and in patients with primary pulmonary hypertension or thromboembolic pulmonary hypertension. Crossbars represent the mean value in each group.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Correlation between the postural change in the apex/base blood flow ratio and the mean pulmonary arterial (PA) pressure. The regression line represents the best fit to the data by the least-squares method.}
\end{figure}
with elevated pressures. Second, patients with cardiomegaly, pleural effusions, parenchymal defects or other causes for perfusion-scan defects have been excluded from some studies, 11, 18 or, when included, have contributed to the wide dispersion of data points. Few patients with suspected pulmonary hypertension secondary to parenchymal or vascular lung disease will have normal perfusion scans. Four of our 10 patients had one or more segmental or larger perfusion defects on scans before the study, and three additional patients had one or more subsegmental defects on the perfusion scans performed in this study.

We attempted to deal with the problem of defects in the scans by studying patients in the supine and erect positions. The patient thus act as their own 'controls' with respect to the presence of perfusion defects and variability in single erect ratios. Our technique attempts to use the shift in perfusion ratio with change in body position rather than a single erect ratio. By analyzing the distribution of flow in both the supine and upright positions, the effect of perfusion defects, which might alter a single value of the U:L zone ratio, have less impact. The shift in flow distribution can be used to assess the level of pulmonary arterial pressure because, at least in theory, it reflects only those areas of lung where perfusion obeys the hemodynamic principles that normally govern perfusion distribution.

This shift in perfusion clearly delineated the normal subjects from patients with precapillary pulmonary hypertension secondary to thromboembolic disease or idiopathic causes. All normal subjects had a shift of greater than 50% when posture was altered, whereas none of the patient group had a shift of 50%. The two patients with shifts of 43% and 49% had minimally elevated pulmonary mean pressures of 21 and 25 mm Hg, respectively. None of the patients with mean pressure of greater than 30 mm Hg had a shift of even 30%. The range of the upright U:L zone ratio in our patients varied from 0.35 to 2.6, which reflected focal abnormalities in the scans as well as differences in pulmonary arterial pressures. Mean pulmonary artery pressure correlated inversely \((r = -0.84, p < 0.01)\) with the shift in perfusion, but unlike previous studies in patients with mitral stenosis, the pressure did not correlate with the single upright U:L zone ratio.

We conclude that our method not only detects elevated pulmonary arterial pressure in patients with suspected primary pulmonary hypertension or thromboembolic disease, but allows some estimation of its severity. Our method requires one additional injection of microspheres over previous techniques, and the data processing is straightforward and rapid. The perfusion defects in these patients did not compromise the method. Whether this will prove to be the case in patients with perfusion defects due to other processes remains to be demonstrated. We are extending our assessment of this technique to patients with chronic obstructive pulmonary disease, bullae, pleural effusions and valvular heart disease, as well as to additional patients with idiopathic or thromboembolic pulmonary hypertension.

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