Acute Effects of Increase in Pulmonary Vascular Distending Pressures on Pulmonary Blood Volume and Pulmonary Extravascular Fluid Volume in Man

STEPHEN M. Austin, M.D., BERNARD F. Schreiner, M.D., PRAVIN M. Shah, M.D., AND PAUL N. Yu, M.D.

SUMMARY The acute hemodynamic effects of supine leg exercise or atrial pacing were studied in 114 patients undergoing right and either transseptal (87 cases) or retrograde (27 cases) left heart catheterization. Seventy-one patients — 15 with coronary artery disease, 22 with aortic valve disease, and 34 with mitral valve disease — performed exercise on a bicycle ergometer. Forty-three patients, of whom 22 had coronary artery disease, nine aortic valve disease and 12 mitral valve disease, were studied during rapid atrial pacing. Cardiac index (CI), pulmonary artery mean (PAM), and left atrial mean (LAM) pressure, pulmonary blood volume (PBV) and pulmonary extravascular volume (PEV) were measured during the control state and during acute intervention. Both exercise and pacing resulted in significant elevations in PAM (range 37-65%) and LAM (range 36-43%) mean pressures in all patients. Cardiac index rose between 34 and 58% in the exercise groups, but did not change in those who were paced. During intervention both PBV and PEV increased significantly in all but the nine patients with aortic valve disease who were paced. Although volume increases occurred, they did not achieve the 5% significance level. For all patients the mean increment in PBV ranged between 37 and 123 ml/m² over control, while PEV rose between 15 and 35 ml/m². In each group the increases in PEV and PBV were proportionate, so that the ratio of PEV/PBV did not change significantly between the control and intervention states. Thus PEV and PBV increases occurred with elevations in pulmonary vascular pressures whether or not blood flow increased. Our data in patients with normal pulmonary vascular beds (i.e., coronary artery disease and aortic valve disease) strongly support the hypothesis that recruitment of vascular channels accounts for the acute changes in PEV and PBV and that the changes in PEV over a brief period of time do not necessarily reflect a “true” increase in extravascular fluid water. Although pressures are higher in the lungs of patients with mitral valve disease, the data also suggest that recruitment is likely to be the mechanism for the observed proportionate increase in pulmonary extravascular volume and pulmonary blood volume.

PREVIOUS STUDIES from this and other laboratories have examined the relationships of pulmonary blood volume (PBV) and pulmonary extravascular fluid volume (PEV) to clinical and hemodynamic parameters among patients with cardiac disease.1, 4 Studies in subjects with normal hemodynamics and in patients with valvular or myocardial heart disease have indicated that the PBV tends to increase above the normal range among American Heart Association functional Class III patients as left atrial mean and/or left ventricular end-diastolic pressures rise.1, 4 However among Class IV patients with chronic left atrial hypertension of either myocardial or valvular etiology, the PBV tends to be normal or even subnormal.2, 5 Since pressures in the pulmonary artery and left atrium are greatly elevated, pulmonary vascular compliance is severely reduced in comparison to less incapacitated patients.

In contrast there is a progressive rise in PEV in patients with increasing degrees of left atrial hypertension, functional impairment and radiologic evidence of pulmonary “vascular” congestion.3, 5 Such the ratio of PEV/PBV increases, suggesting that the PEV is more sensitive than the PBV to pressure elevations within the pulmonary circulation.3, 5 In patients with left atrial hypertension secondary to acute myocardial infarction, elevations in PEV have been found to correlate directly with clinical and radiologic manifestations of congestive heart failure.4

The purpose of this study is to investigate the changes in PEV and PBV during acute interventions in which pulmonary vascular pressures and flow increase concomitantly (supine exercise) and in which only pulmonary vascular pressures increase (atrial pacing) in patients with valvular or coronary artery disease.

Materials and Methods

One hundred and fourteen adult patients undergoing diagnostic cardiac catheterization were investigated. The study was approved by the Clinical Investigation Committee of this University and informed consent was obtained from each patient. Although the patients do not represent a consecutive series, only two criteria were used for exclusion: 1) cardiovascular compromise deemed too advanced to permit safe hemodynamic intervention; and 2) valvular regurgitation causing significant distortion of indicator dilution curves.

Thirty-seven patients had coronary artery disease. Of these 15 were exercised and 22 were paced. Among the 31 patients with aortic valve disease all of the nine who were paced had predominant aortic stenosis. Twenty-two patients were exercised, of whom nine had aortic stenosis, ten aortic regurgitation, and three mixed lesions. Forty-six patients had mitral valve disease. Exercise was performed by 34 patients of whom 27 had pure or predominant mitral stenosis. In none of the latter group did the left atrial mean pressure exceed 18 mm Hg during the control state. Six patients had nonrheumatic mitral regurgitation and one was a postoperative patient who had a Starr-Edward’s mitral valve prosthesis for predominant mitral stenosis. The 12

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patients who were paced had advanced mitral stenosis and were in sinus rhythm. No patient with critical aortic stenosis or severe mitral stenosis was exercised.

All patients underwent simultaneous right and either transseptal (87 patients) or retrograde (27 patients) left heart catheterizations. Cardiac output and PBV (in those patients with transseptal left heart catheterization) were determined at least in duplicate at rest by the indicator dilution technique, as reported previously from this laboratory.4 Pulmonary blood volume was not calculated in the patients who had retrograde left heart procedures. Indocyanine green was injected sequentially into the main pulmonary artery (PA) and left atrium (LA) with sampling of dye from a brachial artery cannula. The data were analyzed by an XDS Sigma 3 computer for determination of cardiac output and mean transit time of each curve using a program incorporating the Stewart-Hamilton equation.2

Pulmonary blood volume, defined as that volume in the pulmonary arteries, pulmonary capillaries, pulmonary veins and an indeterminate portion of the left atrium, was calculated from the equation:

\[
PBV = CI \times (TM_{PA-BA} - TM_{LA-BA})
\]

where PBV = pulmonary blood volume (ml/m\(^2\))
CI = mean cardiac index (ml/m\(^2\)/sec)
\(TM_{PA-BA}\) = mean transit time of indocyanine green from pulmonary artery to brachial artery (sec)
\(TM_{LA-BA}\) = mean transit time of indocyanine green from left atrium to brachial artery (sec)

Pulmonary extravascular fluid volume was measured by the simultaneous injection of a mixture of radioisotopes, radioiodinated serum albumin, and triturated water into the main pulmonary artery, as modified from Chinard and Enns.11 Sequential samples of 1.5 to 2.0 ml were collected from the brachial arterial cannula at two second intervals. Plasma aliquots were analyzed in a three channel Beckman LS 250 beta scintillation counter, as reported elsewhere.10

The mean transit time was determined for each indicator and PEV calculated by the equation:

\[
PEV = CI \times (TM_{THO-PA-BA} - TM_{RISA-PA-BA})
\]

where PEV = pulmonary extravascular fluid volume (ml/m\(^2\))
CI = mean cardiac index (ml/m\(^2\)/sec)
\(TM_{THO-PA-BA}\) = mean transit time of THO from pulmonary artery to brachial artery (sec)

The observed PEV was multiplied by a correction factor of 0.8, as suggested by Chinard et al12 and reported previously from this laboratory.10 In order to test the reproducibility of the method, duplicate measurements of PEV over a 15-20 min period were made in 16 patients not included in this series in whom no hemodynamic intervention was made. The mean value was 138 ml/m\(^2\) with a standard deviation of 15.6 ml/m\(^2\) (11.3% of the mean value) and a correlation coefficient of 0.96.

Duplicate PBV determinations at rest were made in all 87 patients who had transseptal left heart catheterizations (table 1). The mean values of the duplicates varied by only 3 ml/m\(^2\), and had a standard error of 2.6. This value compares to our previous study on the reproducibility of the method in 57 patients in whom the standard error of duplicate determinations of PBV was 2.1.1 During the interventions duplicate determinations of PBV were available in 28 patients who were paced and in 25 patients who were exercised. The standard errors of these duplicate measurements were 3.1 and 4.5 respectively.

Pressures were recorded by conventional methods using Statham P23DB transducers and a direct writing oscillograph (Brush Instruments, Model 480). Mean pressures were obtained by electronic integration.

During the control period patient composure, heart rate, and constancy of intravascular pressures were monitored over a 15 minute period. Initially two or three indicator dilution curves were inscribed in order to accustom the patient to the procedure and to adjust amplifier gain. Determinations of PBV were then carried out in duplicate and of cardiac index in quadruplicate. All blood sampled was collected aseptically in a syringe and reinfused into the patient. Because of the relatively large blood samples required for in vitro analysis, only one determination of PEV was made. The ratio of PEV/PBV was computed. Pulmonary artery, left atrial, and systemic artery mean pressures were recorded. During the intervention all parameters were repeated.

Supine leg exercise was performed on a bicycle ergometer with a load sufficient to increase oxygen consumption two to three times over the control value. Minute ventilation was monitored by a wet test meter and oxygen consumption was determined by analysis of oxygen content by the Scholander technique. Exercise was maintained for 10-15 min during which a steady state was achieved.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number</th>
<th>CI (ml/m(^2)/sec)</th>
<th>SEM CI</th>
<th>TM(_{PA-BA}) (sec)</th>
<th>SEM TM(_{PA-BA})</th>
<th>TM(_{LA-BA}) (sec)</th>
<th>SEM TM(_{LA-BA})</th>
<th>PBV (ml/m(^2))</th>
<th>SEM PBV</th>
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<tr>
<td>Rest</td>
<td>87</td>
<td>1) 3.04</td>
<td>0.02</td>
<td>12.8</td>
<td>0.10</td>
<td>6.7</td>
<td>0.07</td>
<td>312</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) 3.07</td>
<td></td>
<td>12.9</td>
<td>0.10</td>
<td>6.8</td>
<td>0.09</td>
<td>309</td>
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<tr>
<td>Pace</td>
<td>28</td>
<td>1) 2.91</td>
<td>0.04</td>
<td>15.6</td>
<td>0.12</td>
<td>7.8</td>
<td>0.10</td>
<td>369</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) 2.91</td>
<td></td>
<td>15.7</td>
<td>0.12</td>
<td>7.8</td>
<td>0.11</td>
<td>369</td>
<td>3.1</td>
</tr>
<tr>
<td>Exercise</td>
<td>25</td>
<td>1) 4.08</td>
<td>0.05</td>
<td>12.7</td>
<td>0.15</td>
<td>6.8</td>
<td>0.11</td>
<td>377</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) 4.15</td>
<td></td>
<td>12.5</td>
<td>0.15</td>
<td>6.9</td>
<td>0.11</td>
<td>372</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI = mean cardiac index (L/m\(^2\)/min); SEM = standard error of the mean difference; TM\(_{PA-BA}\) = mean transit time from main pulmonary artery to brachial artery (sec); TM\(_{LA-BA}\) = mean transit time from left atrium to brachial artery (sec); PBV = pulmonary blood volume (ml/m\(^2\)).
### Table 2. Summary of Hemodynamic Data for 37 Patients with Coronary Artery Disease Who Underwent Exercise or Atrial Pacing

<table>
<thead>
<tr>
<th>Group</th>
<th>CI (mL/min/m²)</th>
<th>HR (bpm)</th>
<th>PEV (mm Hg)</th>
<th>PBV (mm Hg)</th>
<th>SAmm (mL/m²/m²)</th>
<th>LAmm (mL/m²/m²)</th>
<th>Ratios</th>
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<tr>
<td>Exercise (N = 15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>2.89</td>
<td>79</td>
<td>15</td>
<td>7</td>
<td>112</td>
<td>129</td>
<td>0.44</td>
</tr>
<tr>
<td>(±SEM)</td>
<td>(0.13)</td>
<td>(3.4)</td>
<td>(1.2)</td>
<td>(1.1)</td>
<td>(6.6)</td>
<td>(8)</td>
<td>(0.02)</td>
</tr>
<tr>
<td>Exercise</td>
<td>4.05*</td>
<td>109*</td>
<td>23†</td>
<td>12§</td>
<td>130*</td>
<td>164*</td>
<td>0.45</td>
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<td>(±SEM)</td>
<td>(0.21)</td>
<td>(4.0)</td>
<td>(2.6)</td>
<td>(2.9)</td>
<td>(6.7)</td>
<td>(12)</td>
<td>(0.04)</td>
</tr>
<tr>
<td>Atrial pace (N = 22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>3.05</td>
<td>73</td>
<td>15</td>
<td>7</td>
<td>105</td>
<td>109</td>
<td>0.36</td>
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<tr>
<td>(±SEM)</td>
<td>(0.11)</td>
<td>(2.3)</td>
<td>(0.8)</td>
<td>(0.6)</td>
<td>(2.9)</td>
<td>(9)</td>
<td>(0.03)</td>
</tr>
<tr>
<td>Atrial pace</td>
<td>3.02</td>
<td>133*</td>
<td>24*</td>
<td>17*</td>
<td>125*</td>
<td>122†</td>
<td>0.57</td>
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<tr>
<td>(±SEM)</td>
<td>(0.12)</td>
<td>(3.9)</td>
<td>(2.5)</td>
<td>(2.7)</td>
<td>(4.2)</td>
<td>(11)</td>
<td>(0.03)</td>
</tr>
</tbody>
</table>

*P < 0.001 compared to control.
†P < 0.01 compared to control.
‡P = 0.02 compared to control.
§P = 0.06 compared to control.

Abbreviations: CI = cardiac index (mL/min/m²); HR = heart rate; PAm = pulmonary artery mean pressure; LAm = left atrial mean pressure; SAmm = systemic artery mean pressure; PEV = pulmonary extravascular fluid volume; PBV = pulmonary blood volume; N = number of patients in each group; ±SEM = standard error of the mean.

Atrial pacing was performed using a temporary bipolar pacing catheter positioned in the coronary sinus in order to achieve consistent capture. Patients with mitral stenosis were paced for 20-25 min before repeating blood flow, pressure and volume measurements. Pacing in patients with either coronary artery disease or aortic valve disease was performed to evaluate angina pectoris. Pacing rates were progressively increased by 15-20 beats/min until the development of angina or the attainment of a maximum heart rate of 150 beats/min. Pacing at each interval was maintained for 3 to 5 min. Prolongation of the P-R interval at rapid rates uniformly produced elevations of left atrial and pulmonary artery pressures because of the early occurrence of the left atrial "a" wave against a closed mitral valve. Thus in patients with coronary artery disease or aortic valve disease pressure elevations were maintained for 10-20 min before repeating hemodynamic measurements.

Statistical analysis was performed by the paired t-test, in which each patient served as his own control. Correlation coefficients and regression equations were calculated using standard methods.

### Results

#### Coronary Artery Disease (table 2)

Resting pulmonary artery mean (PAm) and left atrial mean (LAm) pressures were normal in this group. The 15 patients who were exercised had a 40% mean increase in cardiac index (CI) above the resting level (P < 0.001) while PAm pressures rose 53% (P < 0.01) and LAm pressures 71% (P = 0.06). Concomitant with the elevations in pressure, PEV increased from 129 to 164 mL/m² (P < 0.001) and PBV from 294 to 373 mL/m² (P < 0.001). The increments in PEV and PBV were proportionate so that the ratio of PEV/PBV remained constant with exercise.

Among the 22 patients who had atrial pacing, CI was unchanged (3.0 L/min/m²), while PAm and LAm rose 60 and 143%, respectively (P < 0.001). During pacing PEV increased from 109 to 124 mL/m² (P = 0.02) and PBV rose from 302 to 339 mL/m² (P < 0.01). The ratio of PEV/PBV again remained constant.

The entire group of patients with coronary artery disease who had either exercise or pacing also demonstrated a constant relationship between PEV and PBV in the resting and intervention states. As shown in figure 1 the ratio of PEV/PBV cluster along a line of identity and have a strong correlation, with an r value of 0.753. The slope of the line was unity and its y intercept did not differ significantly from zero (fig. 2). Table 3 indicates that the PEV did not correlate well with LAm pressure at rest, but the relationship was somewhat stronger with hemodynamic intervention but was still too weak to have predictive use.

#### Aortic Valve Disease (table 4)

In the 22 patients who were exercised CI rose 58% (P < 0.001) over the resting state. Pulmonary artery mean and LAm pressures were normal in the control period but increased during exertion by 65% and 64% respectively (P < 0.001). With exercise PEV rose from 107 to 126 mL/m² (P < 0.02) and PBV from 323 to 446 mL/m² (P < 0.001). The increments in PEV and PBV were proportionate, so that the ratio of PEV/PBV remained unchanged.

Among the nine patients who were paced the normal resting PAm and LAm pressures rose 33% (P < 0.001) and 90% (P < 0.01), respectively, whereas CI was unchanged at 2.7 L/min. Despite pressure elevations comparable to those observed in the exercise group smaller increments in PEV and PBV occurred which did not achieve the 5% significance level. Again the ratio of PEV/PBV did not change.

Combining all patients with aortic valve disease who were either paced or exercised, a correlation was observed between the ratio of PEV/PBV in the resting and intervention states (r = 0.63) (fig. 1). Regression analysis revealed that the y intercept did not differ significantly from zero nor was the slope significantly different from identity (fig. 2). These data coincided with those obtained in patients with coronary artery disease.

Pulmonary extravascular volume and LAm pressures were weakly related at rest (r = 0.48) but this relationship was not maintained during hemodynamic intervention (table 3).

#### Mitral Valve Disease (table 5)

In the 34 patients who were exercised, CI increased 34% over the control level (P < 0.001). Pulmonary artery mean and LAm pressures rose by 52% and 57%, respectively, during exercise (P < 0.001), pulmonary extravascular volume
increased from 133 to 155 ml/m² and PBV from 350 to 422 ml/m². The increases in both volume measurements were highly significant ($P < 0.001$). During exercise the increments in PEV and PBV were proportionate, so that the ratio of PEV/PBV remained essentially unchanged (0.38 at rest and 0.35 with exercise).

All 12 patients who underwent atrial pacing had advanced mitral stenosis. Their resting PAm and LAm pressures of 35 and 22 mm Hg, respectively, were substantially higher than those of the exercise group. With pacing PAm and LAm pressures increased by 37% and 36%, respectively, ($P < 0.001$) but their CI remained unchanged at 2.7 L/min. Despite the lack of change in cardiac index, PEV rose from 171 to 206 ml/m² ($P < 0.01$) and PBV from 344 to 417 ml/m² ($P < 0.001$). These increments were proportionate. The mean PEV/PBV ratio of 0.48 during pacing was lower than the control value of 0.54 but was not of statistical significance.

Considering all patients with mitral valve disease who had either protocol a constant relationship was found between the ratio of PEV/PBV at rest and during intervention. Figure 1 shows a correlation coefficient of $r = 0.75$. However, linear regression analysis of the data revealed a $y$ intercept of 0.20 which was significantly different from zero ($P < 0.01$) and from the identity line which described the PEV/PBV for patients with coronary artery disease and aortic valve disease (fig. 2). When the patients with mitral valve disease who were examined were compared to those who were paced, the resting PAm, LAm, and PEV, but not the PBV, were significantly greater in the latter group. Furthermore the ratio of PEV/PBV was also significantly higher in those patients who were paced.

For all patients with mitral valve disease an association

<table>
<thead>
<tr>
<th>Group</th>
<th>Regression equation</th>
<th>$r$</th>
<th>SEE</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td>C PEV = 1.82 (LAm) + 103.58 0.15 38.6 NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I PEV = 1.41 (LAm) + 118.70 0.32 49.8 NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVD</td>
<td>C PEV = 4.73 (LAm) + 59.05 0.48 32.4 &lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I PEV = 1.01 (LAm) + 108.52 0.19 45.8 NS</td>
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</tr>
<tr>
<td>MVD</td>
<td>C PEV = 3.79 (LAm) + 76.30 0.46 46.1 &lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I PEV = 4.40 (LAm) + 54.06 0.55 52.0 &lt;0.001</td>
<td></td>
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<tr>
<td>All patients</td>
<td>C PEV = 3.34 (LAm) + 83.78 0.48 40.6 &lt;0.001</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>I PEV = 2.40 (LAm) + 99.00 0.44 51.5 &lt;0.001</td>
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</tr>
</tbody>
</table>

$r =$ correlation coefficient; SEE = standard error of the estimate; CAD = coronary artery disease; AoVD = aortic valve disease; MVD = mitral valve disease; C = control; I = intervention.

FIGURE 1 The ratio of pulmonary extravascular volume (PEV) to pulmonary blood volume (PBV) are plotted at rest (abcissa) and during both pacing and exercise intervention for the three groups of patients studied. The right lower panel indicates all data for the 114 patients.
been suggested that the excellent reproducibility of duplicate determination of PBV at rest may not extend to interventions; especially those in which changes in blood flow occur. The data in the present study do not support this contention since the reproducibility of PBV both with pacing and with exercise was good in the 53 patients in whom duplicate determinations were made (table 1). It would therefore appear that single determination of PBV in the remaining patients are reliable and that the observed increases in PBV are valid.

In the determination of PEV potential error may be related to the subtracted values of the tritiated water (THO) and radiiodinated serum albumin (RISA) mean transit times. The results of the duplicate resting PEV determination in our 16 patients showed close agreement ($r = 0.96$). Since the cardiac index remained unchanged, the subtracted mean transit times of THO and RISA indicator had to agree closely. Furthermore, even though there may be a significant potential error in a given patient, it should not be a systematic error. In examining a large group of patients, such as those in this study, any subtraction error between mean transit times would be random and would cancel out.

The results of the duplicate PEV determinations in our series of 16 patients are similar to those reported by others. McCredie reported duplicate resting PEV in 13 patients in which the standard deviation was 15.2 ml/m$^2$ or 11.2% of the mean value. Similar studies by Luepker et al. in seven patients had a standard deviation of 21 ml or 10% of the mean. Animal studies in 13 dogs in which 37 duplicate measurements were made had a mean percentile deviation of 15%. Thus despite potential sources of error duplicate PEV values generally fall within $\pm 10\%$ of one another in man and approximately $\pm 15\%$ in dogs.

In patients with valvular and coronary artery disease both PBV and PEV were observed to increase during the stress of either exercise or atrial pacing. Increases in pulmonary artery and left atrial pressures and increases in both PBV and PEV occurred regardless of whether or not resting pressures were normal or elevated. Furthermore, the increases in PBV and PEV were independent of changes in blood flow since cardiac output did not change with atrial pacing. It may be concluded that pressure elevations were responsible for the observed increases in both PBV and

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**Table 4. Summary of Hemodynamic Data for 31 Patients with Aortic Valve Disease who Underwent Exercise or Atrial Pacing**

<table>
<thead>
<tr>
<th>Group</th>
<th>CI</th>
<th>HR</th>
<th>PAm (mm Hg)</th>
<th>LAm (mm Hg)</th>
<th>SAm (mm Hg)</th>
<th>PEV (ml/m²)</th>
<th>PBV (ml/m²)</th>
<th>Ratio PEV/PBV</th>
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<tbody>
<tr>
<td><strong>Exercise</strong> (N = 22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Control</td>
<td>3.01</td>
<td>71</td>
<td>17</td>
<td>11</td>
<td>104</td>
<td>107</td>
<td>323</td>
<td>0.32</td>
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<tr>
<td>(SEM)</td>
<td>(0.13)</td>
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<td>(1.2)</td>
<td>(0.8)</td>
<td>(2.0)</td>
<td>(7)</td>
<td>(19)</td>
<td>(0.02)</td>
</tr>
<tr>
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<td>28*</td>
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<td>126*</td>
<td>446*</td>
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<td>(0.26)</td>
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<td>(2.5)</td>
<td>(2.0)</td>
<td>(4.3)</td>
<td>(10)</td>
<td>(27)</td>
<td>(0.04)</td>
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<tr>
<td>Atrial pace (N = 9)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>2.71</td>
<td>75</td>
<td>16</td>
<td>10</td>
<td>101</td>
<td>118</td>
<td>328</td>
<td>0.36</td>
</tr>
<tr>
<td>(SEM)</td>
<td>(0.08)</td>
<td>(4.1)</td>
<td>(0.9)</td>
<td>(1.2)</td>
<td>(5.5)</td>
<td>(16)</td>
<td>(23)</td>
<td>(0.04)</td>
</tr>
<tr>
<td>Pace</td>
<td>2.72</td>
<td>143*</td>
<td>24*</td>
<td>19*</td>
<td>111†</td>
<td>123</td>
<td>375</td>
<td>0.34</td>
</tr>
<tr>
<td>(SEM)</td>
<td>(0.16)</td>
<td>(4.0)</td>
<td>(1.7)</td>
<td>(2.0)</td>
<td>(7.31)</td>
<td>(16)</td>
<td>(47)</td>
<td>(0.04)</td>
</tr>
</tbody>
</table>

*P < 0.001 compared to control.
†P < 0.01 compared to control.
Abbreviations: Same as for Table 2.
Table 5. Summary of Hemodynamic Data for 46 Patients with Mitral Valve Disease Who Underwent Exercise or Atrial Pacing

<table>
<thead>
<tr>
<th>Group</th>
<th>CI (mm Hg)</th>
<th>HR</th>
<th>PEV (ml/m²)</th>
<th>PBV (ml/m²)</th>
<th>PEV/PBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise (N = 34)</td>
<td>2.83 (0.10)</td>
<td>77 (2.2)</td>
<td>25 (1.6)</td>
<td>15 (1.0)</td>
<td>96 (2.4)</td>
</tr>
<tr>
<td>Atrial pace (N = 12)</td>
<td>2.72 (0.18)</td>
<td>83 (2.4)</td>
<td>35 (3.7)</td>
<td>22 (1.7)</td>
<td>90 (2.8)</td>
</tr>
</tbody>
</table>

*P < 0.001 compared to control.
+P < 0.01 compared to control.
For abbreviations, see table 2.

PEV. To our knowledge no other similar observations have been previously made in man.

On the basis of acute dog experiments, Maseri and associates have suggested that recruitment of previously closed channels rather than distensibility changes in the pulmonary vascular bed is the major determinant of changes in pulmonary vascular volume under conditions of altered inflow pressure.14, 16 If indeed volume changes in the pulmonary circulation occur primarily through changes in the number of vessels perfused (i.e. recruitment and re-recruit-

ment), then acute changes in PBV must necessarily be accompanied by changes in PEV measured by the double isotope indicator dilution technique. Each vessel recruited not only contributes to the augmented PBV but also to the measured PEV, even if no real increases in extravascular lung water were to occur. Thus a valuable marker of the significance of changes in PEV could be obtained by examining the ratio of PEV/PBV in the control and intervention states.17 Furthermore it has been shown in dogs that increments in PEV are time dependent, with little increase in PEV/PBV occurring over the first 30 min after the attainment of an average transcapillary gradient of 25 mmHg.14, 18 Increases in PEV only occurred during the second half hour when the PEV/PBV had risen from a control of 0.20 to 0.39.14

Both animal studies support our over-all observations in man. Failure of the PEV/PBV ratio to rise during either intervention suggests recruitment of additional vascular channels. If the ratio increased over the control value a real increase in lung extravascular water volume would be implied. In addition our observations were made for shorter periods of time and at lower transcapillary gradients than the animal studies of Levine and associates.18

Our findings in 68 patients with coronary artery disease or aortic valve disease in whom the pulmonary vasculature is presumably normal or nearly so are entirely in keeping with the recruitment hypothesis. In both groups of patients resting pulmonary artery and left atrial pressures were normal during the control period and the pressure elevations at both sites, whether caused by exercise or pacing, resulted in a proportionate increase in PBV and PEV. In all of the studies the stimulus to pressure elevation was applied for less than 30 min, suggesting that the Starling hypothesis of fluid transudation is time dependent as well as determined by the magnitude of elevation of pulmonary capillary pressure.14, 18

Otherwise the PEV/PBV would rise during our period of observation signifying a "true" increase in lung water.

The recruitment concept is also supported by pulmonary function studies in which carbon monoxide diffusing capacity (DLCO) and capillary blood volume (Vc) were measured during changes in position,19, 20 during inflation of antigravity suits21, 22 and during exercise23, 24 in normal subjects. Assumption of the supine position, augmentation of venous return by peripheral venous compression, and exercise each produced an increase in DLCO and Vc which varied from 14 to 90% above control. The increases in Vc with exercise varied depending upon the lung volume. At functional residual capacity the increase averaged 15% compared to 90% at total lung capacity.24 In all of these studies recruitment of previously closed vascular beds or limited dilatation of already open capillaries were suggested mechanisms. The present study would support the former mechanism as playing a dominant role. McCreddie and Chia25 examined the relationship between PEV and indirect left atrial mean pressure in a group of patients who were exercised for more than five minutes. They demonstrated a weak correlation between PEV and LAm pressures during exercise (r = 0.40), as well as a correlation between these variables both at rest and with exercise in subjects who had a resting PEV above 150 ml/m². On the basis of these data it was suggested that the PEV may be a useful index of left ventricular failure in ischemic heart disease. They did not, however, determine PBV. Based upon observations made in our laboratory, we believe that the elevation of PEV after five minutes of exercise probably reflects increases in PBV due to recruitment of vascular channels, and not true increases in the water content of the lungs. Thus the implication that an elevated PEV, particularly during an intervention, is a useful index of left ventricular failure is probably not warranted.

Whether or not the recruitment-de-recruitment hypothesis applied to patients with normal lungs and normal PAm and LAm pressures can be equally applied to those with mitral valve disease is probably less certain. The hemodynamics in the latter patients formed a continuum, from those with mild left atrial and pulmonary hypertension to those patients with moderately severe left atrial hypertension (LAm = 22 mm Hg) who were paced. The more severe the hemodynamic pressure abnormality, the greater the mean PEV and the higher the PEV/PBV ratio.
These findings are similar to those reported previously. It may be suggested that in some of our patients in whom LAm pressure exceeded 20 mm Hg at rest that all vascular channels would be open because critical closing pressures were exceeded. With further pressure elevations during either intervention, recruitment of additional vascular channels would not be possible. However, since the pulmonary vasculature in mitral valve disease is characterized by structural changes in the pulmonary arteries, capillaries and veins as well as by functional vasconstriction affecting both arteries and veins, the pressure volume characteristics are likely to be severely altered.

Thus some capillary networks might not be perfused despite the presence of significant left atrial hypertension because of altered pressure-volume relationships in the lung with decreased pulmonary vascular compliance. These vessels would be operating on the steep portion of the pressure-volume curve. Despite their relative resistance to volume elevations, they are not necessarily impervious to pressure changes. Increases in PBV and PEV could then occur in response to further elevation in left atrial pressure.

Corroborative evidence of an increased pulmonary capillary bed in mitral valve disease is conflicting. Previous studies from this laboratory have indicated that Vc was normal in 56 patients with mitral valve disease (Functional Class II and III) but reduced in 13 Class IV patients. Palmer et al. studied Vc in 30 patients of whom 27 had predominant mitral stenosis. The mean Vc in their group I to II (which were approximately comparable to the American Heart Association functional classification by class) increased with exercise from approximately 100 ml (Group I) to 160 ml (Group III), but the range varied from 70 to 300 ml. In contrast, exercise in Group IV patients resulted in an average increase in Vc of only 45 ml (range: 35 to 70 ml). The latter mean was significantly lower than the average values for Groups I to III. The resting average pulmonary artery systolic and diastolic pressures for these four groups varied as follows: Group I: 34/12; Group II: 53/23; Group III: 58/34; Group IV: 80/45. In the same laboratory the mean value for Vc in normal exercising subjects was 143 ml at an average oxygen consumption of 1.2 L/min.

These data lend support to our contention that the number of perfused pulmonary capillaries can be increased in patients with mitral valve disease even though considerable left atrial and pulmonary hypertension are present at rest. It would appear that our exercised patients are comparable mainly to patients in Groups I and II studied by Palmer et al.

since resting PAm averaged 25 mm Hg and LAm averaged 16 mm Hg. (It is reasonable to assume that the pulmonary diastolic pressures and left atrial mean pressures were comparable.) The paced patients had a resting PAm of 35 mm Hg with an average LAm of 22 mm Hg (comparable to Group II and possibly Group III). Thus it could be assumed that elevation of pressures in our exercising or paced patients would result in an appreciable increase in Vc even though this parameter was not measured in the present study.

The more extensive disease of the pulmonary circulation and the altered pressure-volume relationships in patients with mitral valve disease is further emphasized by the regression line formed by the PEV/PBV at rest and during intervention (fig. 2). The y intercept is positive and the slope is significantly flatter than the lines of the other two groups studied. The higher resting PEV/PBV ratios have been documented by Luepker and associates as well as ourselves. Although the data of Luepker et al. demonstrates a proportionate increase in both PEV and PBV and an apparent linear relationship between PEV at rest and during exercise our linear regression analysis of their data has a positive y intercept and a flattened slope when compared to identity \( y = 0.245 + 0.528x \). Our data are essentially similar.

While none of our data contradict the recruitment hypothesis we admit that in mitral valve disease it is conceivable that the constancy of the PEV/PBV is a resultant of two opposing mechanisms, i.e., capillary distension tending to increase the ratio, and pulmonary artery and venous distension tending to decrease the ratio.

To summarize, in patients with coronary artery disease or aortic valve disease we have found increases in PEV and PBV accompanying elevations in PAm and LAm pressures during supine leg exercise or atrial pacing. The increases in PEV and PBV were proportionate so that the ratio of PEV/PBV remained almost constant and they were observed in the absence of changes in cardiac index during rapid atrial pacing as well as during exercise. These observations support the hypothesis that recruitment of vascular channels accounts for the acute changes in PEV and PBV and that the changes in PEV over a brief period of time do not necessarily reflect a real increase in pulmonary extravascular water.

Similar changes in PEV, PBV, PAm and LAm pressures were observed in patients with mitral valve disease during either intervention. However the recruitment hypothesis is less easily substantiated in the presence of already elevated PAm and LAm pressure. Nonetheless evidence is presented which suggests that a similar recruitment phenomenon is likely to be present in these patients as well.

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