The Pulmonary Capillary Bed in Various Forms of Pulmonary Hypertension


In a previous study of the pulmonary capillary bed in mitral valve disease, the mean value for pulmonary diffusing capacity for carbon monoxide (Dl) was found to be significantly lower than normal, in agreement with several other reports. This was due mainly to impairment of the membrane diffusing capacity (Dm). Reduction in pulmonary capillary blood volume (Vc) was found only in patients with higher pulmonary vascular pressures and resistances. It was suggested that reduction of Vc was due to constriction or partial obliteration of the pulmonary capillary bed and that this may be an important contributing factor in the elevation of pulmonary vascular resistance found in mitral valve disease.

This study has now been extended to a larger number of patients with mitral valve disease and other conditions associated with pulmonary hypertension, before and after surgery, to find out (1) if similar changes in the pulmonary capillary bed occurred in aortic valve disease, primary myocardial disease, and idiopathic pulmonary hypertension, (2) if changes in the pulmonary capillary bed were related in any way to functional disability or to the results of cardiac surgery, and (3) if Dl, Dm, or Vc changed after cardiac surgery.

Methods

Forty-four patients were studied by right and left heart catheterization, using standard procedures, after premedication with papaveretum, B.P.C. (opium concentration).

Steady-state measurements of pulmonary diffusing capacity for carbon monoxide (Dl), using an end-tidal sampling method, have been described in detail elsewhere. The diffusing capacity of the alveolar-capillary membrane (Dm) and the pulmonary capillary blood volume (Vc) were derived from measurements of Dl at two different levels of alveolar oxygen tension, following the methods of Forster, Roughton and associates. Gas chromatography was used for the analysis of respired air samples and for the estimation of the carbon monoxide content of arterial blood. This method is accurate to within less than ±2% for both blood and air samples. No premedication was given for the diffusion studies; otherwise they were done under the same conditions as, and within 4 days of, cardiac catheterization.

As Dl, Dm, and Vc in normal subjects have been shown to be related to body surface area, Dl and Dm were expressed in milliliters of carbon dioxide per minute per mm Hg per square meter and Vc in milliliters per square meter. Pulmonary vascular resistance (PVR) was expressed in "resistance units" also related to body surface area (RU · m²); it was obtained by dividing the gradient from mean pulmonary arterial pressure (PmA) to mean left atrial pressure (PLx) in mm Hg by the cardiac index in liters per minute per square meter. The patients were grouped arbitrarily according to the level of PVR which was considered normal when the level was less than 3 RU · m², moderately raised if 3 to 10 RU · m², severely raised if 10 to 20 RU · m², and extreme if more than 20 RU · m². Functional disability at the same time of the study was classified I to IV by standard criteria.

The patients were also grouped according to diagnosis: (1) mitral valve disease, 31 patients, including 18 previously reported on, of whom 26 had pure mitral stenosis and five had dominant mitral incompetence; there were 15 males and 16 females, and ages ranged from 20 to 59 years, with a mean of 41 years; (2) aortic valve disease, six male patients, two with pure aortic stenosis and four with dominant incompetence, with ages ranging from 13 to 53 years, with a mean of 33 years; (3) primary myocardial disease, five patients including three with idiopathic hypertrophic

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*Beckman GC2 Gas Chromatograph, Beckman Instruments, South Pasadena, California.
Table 1

Estimates of $D_L$, $D_M$, and $V_c$ in Normal Subjects and in Patients with Heart Disease

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
<th>$D_L$, ml CO/min/mm Hg/m²</th>
<th>$D_M$, ml CO/min/mm Hg/m²</th>
<th>$V_c$, ml/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td>18</td>
<td>15.0 ± 0.59</td>
<td>30 ± 2.45</td>
<td>52 ± 3.51</td>
</tr>
<tr>
<td>Mitral valve disease</td>
<td>31</td>
<td>(P &lt; 0.001)</td>
<td>(P &lt; 0.001)</td>
<td>(N.S.)</td>
</tr>
<tr>
<td>Aortic valve disease</td>
<td>6</td>
<td>12.1 ± 1.06</td>
<td>21 ± 1.55</td>
<td>53 ± 9.72</td>
</tr>
<tr>
<td>Primary myocardal disease</td>
<td>5</td>
<td>9.2 ± 0.89</td>
<td>13 ± 1.25</td>
<td>55 ± 10.01</td>
</tr>
<tr>
<td>Idiopathic pulmonary</td>
<td>2</td>
<td>10.5, 9.4</td>
<td>14, 12</td>
<td>44, 61</td>
</tr>
</tbody>
</table>

$D_L$ and $D_M$ are the diffusing capacities of the lung and of the alveolar-capillary membrane; $V_c$ is the pulmonary capillary blood volume. Values are mean ± 1 standard error; level of significance of difference of means from normal values indicated in brackets; N.S., not significant.

subaortic stenosis and two with left ventricular failure of unknown etiology; there were three males and two females with ages ranging from 10 to 46 years, with a mean of 25 years; and (4) idiopathic pulmonary hypertension, two patients, both male, aged 31 and 33 years.

A control group of 18 normal subjects, whose data appeared in a previous report,1 were used for comparison. Included were 15 males and three females; their ages ranged from 8 to 46 years, with a mean of 29 years.

Twenty-seven of these patients underwent cardiac surgery: 22 for mitral valve disease, four for aortic valve disease, and one for subaortic obstruction. Four died at operation. The symptomatic result 3 months or more after operation was judged to be excellent if the functional disability of the patient was class I, good if class II, and poor if class III or worse.

In 11 of these patients who underwent mitral valvotomy, measurements of $D_L$, $D_M$, and $V_c$ were repeated 2 weeks to 8 months after surgery.

Results

Values for $D_L$, $D_M$, and $V_c$ in normal subjects and in the diagnostic groups are shown in table 1. Although a few patients had $V_c$ above or below the normal range, the means for each group lay within normal limits, and there were no differences between the four groups. Mean $D_L$ and $D_M$ were significantly reduced in all groups.

The relationships of functional disability to determinations of $D_L$, $D_M$, and $V_c$ are shown in figure 1. Mean $D_L$ was lower than normal at all grades of disability ($P < 0.001$ in all), and significantly more so in class IV patients ($P < 0.01$). Mean $D_M$ was also lower than normal in all grades ($P < 0.001$ in all), but there were no differences between the four grades. Mean $V_c$ for patients in classes I, II, and III did not differ significantly from normal.

![Figure 1](http://circ.ahajournals.org/) Relationships of $D_L$, $D_M$, and $V_c$ to functional classification. Closed circles and bars represent mean ± 2 SE for each group.

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but it was significantly lower in class IV patients ($P < 0.01$).

The relationships of $D_L$, $D_M$, and $V_e$ to pulmonary vascular resistance, irrespective of diagnosis, are shown in figure 2. Twenty-three patients had normal pulmonary vascular resistance (less than 3 RU·m²); 10 had moderate elevation (3 to 10 RU·m²), and five had severe elevation (10 to 20 RU·m²). In these three groups, there was a progressive reduction in $V_e$ with increasing resistance. Six patients, four with mitral stenosis and two with idiopathic pulmonary hypertension, had extreme elevation of PVR (over 20 RU·m²). Mean $V_e$ for this group was 53 ml/m² (range 24 to 102 ml/m²), and this was within normal limits and significantly higher than group 3. No such relationship existed between $D_L$ or $D_M$ and pulmonary vascular resistance.

### Results of Surgery

Symptomatic relief was excellent in nine of the 27 patients undergoing cardiac surgery, good in nine, and poor in five. Four patients died postoperatively: two after aortic valve repair, one after mitral valve replacement, and one after closed mitral valvotomy.

These results are related in figure 3 to the preoperative measurements of pulmonary capillary blood volume and pulmonary vascular resistance. Those with smaller $V_e$ fared less well after surgery. The relationship between pulmonary vascular resistance and clinical state after surgery was poor, mainly because three of the four patients with extreme elevation of PVR had good or excellent clinical results.

The effects of surgery for mitral stenosis on $D_L$, $D_M$, and $V_e$ in 11 patients (table 2) are illustrated in figure 4. The majority of patients showed no significant changes. From previous estimates¹ of the variability of these measurements (SD ± 1.12 and ± 9.32 ml CO per minute per mm Hg per m² for $D_L$ and $D_M$ respectively, and ± 5.66 ml per m² for $V_e$), $D_L$ fell significantly, that is by more than 2 SD, in only one (case 7) after operation and rose after an initial fall in another (case 4). There were no significant changes in $D_M$. Three cases showed significant falls in $V_e$ after operation (cases 2, 5, and 6), including the only two in this group in whom the initial $V_e$ was above the normal range, and one (case 10) showed a small but significant rise. These changes in $D_L$, $D_M$, and $V_e$ were not related to the degree of symptomatic relief after surgery.

### Discussion

A number of factors may influence these estimates of $D_L$, $D_M$, and $V_e$, such as uneven distribution of alveolar ventilation⁵⁻⁸ or of $V_e$,¹²,¹⁹ or possible changes in $V_e$ when breathing 100% oxygen.¹²,²⁰ Although errors from these sources cannot be excluded entirely, there was no evidence of a systematic error affecting the present results. These factors

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**Figure 2**

Relationships of $D_L$, $D_M$, and $V_e$ to pulmonary vascular resistance. Closed circles and bars represent mean ±2 SE for each group.
PULMONARY HYPERTENSION

Results of surgery in 27 patients related to preoperative measurements: (A) Pulmonary capillary blood volume ($V_c$); (B) Pulmonary vascular resistance (PVR). Each dot represents one patient; the four marked with crosses are patients with extreme elevation of PVR ($>20$ RU $\cdot m^2$) all in group 4 of figure 2 (see text). Solid and broken lines represent mean $\pm 2$ SE for each group.

Figure 3

Results of surgery in 27 patients related to preoperative measurements: (A) Pulmonary capillary blood volume ($V_c$); (B) Pulmonary vascular resistance (PVR). Each dot represents one patient; the four marked with crosses are patients with extreme elevation of PVR ($>20$ RU $\cdot m^2$) all in group 4 of figure 2 (see text). Solid and broken lines represent mean $\pm 2$ SE for each group.

have been discussed previously in detail in relation to the pulmonary capillary bed in mitral valve disease.\(^1\)

In each diagnostic group, there was a significant reduction in mean $D_M$, attributable mainly to reduction in membrane diffusion, as mean $V_c$ in each group was within normal limits (table 1). This reduction in $D_M$ may reflect decreased permeability due to fibrosis or thickening of the alveolar walls, as described by Parker and Weiss\(^2\) in mitral valve disease, and the same changes probably occur in other conditions with left heart dysfunction and pulmonary venous congestion. The impairment of $D_M$ found here in two patients with idiopathic pulmonary hypertension suggests some functional involvement, at least, in this condition also.

The relationship of $V_c$ to clinical disability (fig. 1) is similar to the finding of Palmer and associates\(^6\) that $V_c$ in mitral stenosis was reduced in class IV patients. Total diffusing capacity of the lungs ($D_{L}$) was reduced in all, mainly due to reduction in $D_M$, but was still further reduced in class IV patients because these patients also have a reduced $V_c$. This combination of reduced $D_M$ and $V_c$ found in the most disabled patients may well contribute to their incapacity.

The volume of a normally distensible pulmonary capillary bed will increase with rise in transmural pressure until a plateau is reached corresponding to maximum distention. This has been demonstrated in animal lung preparations,\(^22,23\) and in man.\(^24\) Figure 5 presents a hypothetical pressure-volume curve for a normal lung, the shape of the normal curve being based on data from the isolated dog lung\(^23\);
the three curves with progressively lower plateaus would represent the effects of progressive reduction in maximum $V_c$. From such a diagram it can be seen (1) that a substantial lowering of transmural pressure could occur in the more restricted capillary beds without any significant change in $V_c$, and (2) that $V_c$ must be on or near the steep portion of the curve for any marked change to occur with lowering of transmural pressure. The results shown in figure 4 may be explained on this basis. After successful mitral valvotomy, the only three patients who showed a fall in $V_c$ had increased or high normal $V_c$ preoperatively and were presumably on, or close to, the steep part of their pressure-volume curve. The fact that all but one of those with low normal or reduced $V_c$ showed no significant change over a period up to 8 months (fig. 4) suggests that this reduction in $V_c$ is usually irreversible. Neither was there any significant improvement in $D_l$ or $D_M$ in the group over the same period.

If reduction in $V_c$ in the presence of high intravascular pressure reflects a decrease in cross-sectional area of the capillary bed, it may contribute an important part of the total increase in PVR.\(^1\) Reduction in $V_c$ also appears to be related to poorer symptomatic results from surgery (fig. 3). But of the six patients with extreme elevation of PVR, $V_c$ was not reduced in five; the only one in whom it was reduced (24 ml/m\(^2\)) died 1 week after mitral valve replacement. Three had much better symptomatic results from mitral valvotomy than might have been expected from their initial levels of PVR, and the other two had idiopathic pulmonary hypertension which may not involve the capillary bed histologically.\(^{25-27}\)

High or normal $V_c$ in these patients with extreme elevation of PVR could be related
to the dilatation lesions described by Heath and Edwards. Although these dilatation lesions are not structurally capillaries, it is possible that they take some part in gas exchange in the lungs and, therefore, would be included in the estimate of $V_c$. But it is doubtful that these lesions would be sufficiently numerous to account for the present results.

If, however, the pulmonary capillary bed is relatively less affected by disease in these patients, the increase in pulmonary vascular resistance must be almost entirely due to precapillary obstruction. Recently Aber and Campbell compared $D_L$ measurements in 79 patients with mitral stenosis with results of histological examination of lingular biopsies taken at operation. They found that reduction in $D_L$ was associated with intimal changes in small lung vessels and with increasing pulmonary vascular resistance. In four patients with the highest resistances, however, $D_L$ was not reduced, and the histological change was confined to medial thickening.
of the muscular arteries without intimal damage. If these patients with very high resistance but relatively normal $D_L$ (and by inference $V_c$) exist as a distinct group, with vascular changes suggesting muscular constriction rather than intraluminal obstruction, perhaps the patients with high or normal $V_c$ despite extreme elevation of resistance belong to the same group. I do not have any histological comparisons, but possibly, in a few patients with mitral stenosis, intense precapillary vasoconstriction really does protect the pulmonary capillary bed.

Summary

Pulmonary diffusing capacity for CO ($D_L$), membrane diffusing capacity ($D_M$), and pulmonary capillary blood volume ($V_c$) were measured in 44 patients with various forms and severity of pulmonary vascular disease, and these measurements were compared with hemodynamic data obtained at cardiac catheterization, with clinical disability, and, in 27 patients, with the results of corrective cardiac surgery. In 11 of these patients, $D_L$, $D_M$, and $V_c$ were remeasured up to 8 months after cardiac surgery.

In general, the diffusing characteristics and pressure-volume relationships in this larger group confirmed the previously reported findings in mitral valve disease. $D_M$ was impaired in almost all cases regardless of etiology or severity. Most of the 11 patients restudied showed no change in $D_L$, $D_M$, or $V_c$ up to 8 months after surgery. Reduction in $V_c$ correlated well both with clinical disability and with surgical results.

Two patients with primary pulmonary hypertension and three of the four patients with equally severe pulmonary hypertension due to mitral valve disease had high $V_c$ relative to pulmonary vascular resistance. If the measurements of $V_c$ are not falsely high, then it appears that the capillary bed makes relatively and absolutely less contribution to the total rise in pulmonary vascular resistance in these patients. This could be explained by intense precapillary vasoconstriction in the presence of a relatively normal pulmonary capillary bed.

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References

PULMONARY HYPERTENSION


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