A STUDY ON THE PULMONARY FUNCTIONS AND THE PULMONARY CIRCULATION IN CARDIO-PULMONARY DISEASES

(I) Pulmonary Diffusing Capacity in Cardio-Pulmonary Diseases

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Pulmonary diffusing capacity ($D_{LCO}$), alveolar membrane diffusing capacity ($D_{MCO}$), and pulmonary capillary blood volume ($V_C$) were determined with CO single breath method in (i) healthy subjects and, (ii) patients with cardio-pulmonary diseases. In the latter right heart catheterization was also performed. Values obtained were compared between healthy subjects and patients with cardio-pulmonary diseases. They were also compared with those reported by other workers. Relationships between $D_{LCO}$, $D_{MCO}$ or $V_C$ and hemodynamic parameters of pulmonary circulation were examined.

Gas exchange, an essential function of the lung as a respiratory organ, is carried out through a physical process of gas diffusion between the alveolar space and the pulmonary capillary blood through the intervening alveolar capillary membrane. If the diffusion process in the lung is impaired, it will lead to anoxemia or dyspnea. Therefore, the quantitative evaluation of the diffusing capacity of the lung has a great significance both in respiratory physiology and clinical diagnostics.

Forster, in 1955, modified Krogh's method and developed the single breath method using carbon monoxide, which made the quantitative measurement of the lung diffusing capacity in clinical practice comparatively easy. With the introduction in 1957 of the separate determination of the two components of the lung diffusing capacity ($D_L$), i.e. the alveolar membrane diffusing capacity ($D_M$) and the capillary blood volume ($V_C$), it has become possible to correlate the lung diffusing capacity with the pulmonary circulation.

In the present study, pulmonary diffusing capacity and pulmonary capillary blood volume have been measured in healthy subjects and in patients with cardio-pulmonary diseases and the relationship between these parameters and hemodynamic parameters of the pulmonary circulation has been examined.

Subjects Studied

Thirty healthy male subjects ranging from 19 to 63 years of age and 90 patients were included in the study.

Seventy patients were those with cardiac diseases on whom right heart catheterization was performed (28 mitral stenosis, 19 mitral insufficiency or mitral steno-insufficiency, 9 aortic insufficiency or aortic steno-insufficiency, and 14 atrial or ventricular septal defect).

Twenty patients were those with chronic pulmonary diseases (14 pulmonary emphysema and 6 pulmonary fibrosis).

Methods

Measurement of pulmonary diffusing capacity was performed in supine position.

In those patients on whom right heart cathet-
erization was performed, pulmonary diffusing capacity measurement was made within one week prior to or after the catheterization.

The single breath method by Forster\(^1\) using CO and He was employed. Three measurements were made for \(D_{L\text{CO}}\) with five minute interval, and the mean value of the two closer values of the three was employed as \(D_{L\text{CO}}\) value.

\(D_{L\text{CO}}\) (in ml/min/mmHg) was calculated using the following Formula (1) of Roughton and Forster\(^3\)

\[
D_{L\text{CO}} = \frac{V_A \times 60}{(B - 47) \times t} \ln \left[ \frac{F_{ACO}}{F_{ECO}} \right] \tag{1}
\]

where:

\(F_{ACO} = (F_{EHe}/F_{IHe})F_{ICO}\)

\(V_A\): alveolar volume (STPD) (ml)

\(B\): atmospheric pressure (mmHg)

\(t\): breath holding time (sec)

\(\ln\): Natural logarithm

\(F_{ACO}\): CO concentration in alveolar gas before being absorbed in the pulmonary capillary blood

\(F_{ECO}\): CO concentration in alveolar gas at the end of 10 sec breath holding interval

\(F_{IHe}\): CO concentration in inspired gas

\(F_{EHe}\): CO concentration in expired gas

Alveolar membrane diffusing capacity (\(D_{M\text{CO}}\)) and pulmonary capillary blood volume (\(V_C\)) were determined by measuring \(D_{L\text{CO}}\) values under two different alveolar oxygen tensions, which were induced by inhaling two different gases (0.3% CO and 10% He in air; and 0.3% CO and 10% He in \(O_2\)) and using the Formulae (1) and (2).

\[
\frac{1}{D_L} = \frac{1}{D_M} + \frac{1}{\theta V_C} \tag{2}
\]

\(\theta\): the rate at which 1 ml of blood combines with CO (ml/min-mmHg/ml)

As \(\theta\), the value reported by Roughton and Forster\(^3\) (assuming that \(\lambda = 2.5\)) was employed.

For analyzing the alveolar gas sample for CO, He and \(O_2\), a gas chromatograph (Hitachi KGL-2A) was used.

The functional residual capacity (FRC) was determined by the helium closed circuit method using a Pulmonet (Godart). The gas analysis of the arterial blood was performed using a physiological gas analyzer (Toshiba-Beckman Type 160) and a Van Slyke-Neill manometer.

### RESULTS

1) \(D_{L\text{CO}}, D_{M\text{CO}}\) and \(V_C\)

Table I shows \(D_{L\text{CO}}, D_{M\text{CO}}\) and \(V_C\) measured in 30 healthy male subjects ranging from 19 to 63 years of age. The mean \(D_{L\text{CO}}\) was 18.1 ± 3.0 ml/min/mmHg/M\(^2\) (30.6 ± 5.6 ml/min/mmHg). The mean \(D_{M\text{CO}}\) was 30.4 ± 7.3 ml/min/mmHg/M\(^2\) (51.4 ± 12.8 ml/min/mmHg). The mean \(V_C\) was 58.3 ± 16.3 ml/M\(^2\) (98.6 ± 23.9 ml).

Table I also shows \(D_{L\text{CO}}, D_{M\text{CO}}\) and \(V_C\) measured in patients with cardio-pulmonary diseases. As is shown in Table I, no significant difference was observed in \(D_{L\text{CO}}\) and \(D_{M\text{CO}}\) between healthy subjects and patients with cardiac diseases, whereas many patients with pulmonary diseases showed lower \(D_{L\text{CO}}\) and \(D_{M\text{CO}}\) than healthy subjects.

In regard to \(V_C\), patients with pulmonary diseases and patients with aortic valvular disease showed lower values than normal. Fig.1 shows the correlation of \(D_{L\text{CO}}, D_{M\text{CO}}\) and \(V_C\) versus the severity of cardiac diseases by the classification of the New York Heart Association. The patients with advanced cardiac diseases showed

### TABLE I ESTIMATES OF \(D_{L\text{CO}}, D_{M\text{CO}},\) AND \(V_C\) IN NORMAL SUBJECTS AND IN PATIENTS WITH CARDIAC OR PULMONARY DISEASES

<table>
<thead>
<tr>
<th>Cases</th>
<th>No. of case</th>
<th>(D_{L\text{CO}}) (ml/min/mmHg/M(^2))</th>
<th>(D_{M\text{CO}}) (ml/min/mmHg/M(^2))</th>
<th>(V_C) (ml/M(^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>30</td>
<td>18.1 ± 3.0</td>
<td>30.4 ± 12.8</td>
<td>58.3 ± 16.3</td>
</tr>
<tr>
<td>MS</td>
<td>28</td>
<td>17.7 ± 5.3</td>
<td>27.9 ± 11.6</td>
<td>73.5 ± 26.4</td>
</tr>
<tr>
<td>M1 &amp; MS1</td>
<td>19</td>
<td>16.8 ± 4.3</td>
<td>27.7 ± 8.0</td>
<td>65.5 ± 29.1</td>
</tr>
<tr>
<td>Aortic valvular disease</td>
<td>9</td>
<td>16.6 ± 5.4</td>
<td>34.5 ± 16.0</td>
<td>47.0 ± 14.2</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>14</td>
<td>18.6 ± 5.4</td>
<td>29.1 ± 10.3</td>
<td>73.7 ± 19.4</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>20</td>
<td>7.9 ± 3.4</td>
<td>15.7 ± 7.4</td>
<td>40.0 ± 14.8</td>
</tr>
</tbody>
</table>

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Fig.1. Relationship of $D_{LCO}$, $D_{MCO}$, and $V_c$ to functional classification.

<table>
<thead>
<tr>
<th>TABLE II</th>
<th>CORRELATION OF $D_{LCO}$, $D_{MCO}$, AND $V_c$ TO HEMODYNAMIC PARAMETERS AND ARTERIAL BLOOD GAS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$PAm$</td>
</tr>
<tr>
<td>$MS$</td>
<td>$D_{LCO}$</td>
</tr>
<tr>
<td>(28 cases)</td>
<td>$D_{MCO}$</td>
</tr>
<tr>
<td></td>
<td>$V_c$</td>
</tr>
<tr>
<td>Pulmonary disease</td>
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</tr>
<tr>
<td>(20 cases)</td>
<td>$D_{MCO}$</td>
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<tr>
<td></td>
<td>$V_c$</td>
</tr>
</tbody>
</table>

Thus, $PAm$ showed a significant negative correlation with $D_{LCO}$, $D_{MCO}$ or $V_c$ in mitral stenosis.

In patients with pulmonary emphysema or pulmonary fibrosis, $PAm$ showed a significant correlation with $D_{LCO}$ ($r = -0.48$, $p < 0.01$) and $V_c$ ($r = -0.48$, $p < 0.01$). However, no significant correlation was observed between $PAm$ and $D_{MCO}$ ($r = -0.30$, $p > 0.10$).

The mean pulmonary capillary pressure ($PCm$) showed a significant negative correlation with $D_{LCO}$ ($r = -0.59$, $p < 0.01$) in mitral stenosis, pulmonary emphysema, and pulmonary fibrosis. $PCm$ showed a significant negative correlation with $D_{MCO}$ both in mitral stenosis ($r = -0.51$, $p < 0.01$) and in pulmonary emphysema and pul-

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monary fibrosis ($r = -0.47$, $p<0.05$). With $V_C$, PCm showed a significant negative correlation in mitral stenosis ($r = -0.48$, $p<0.01$), but no significant correlation in pulmonary emphysema or pulmonary fibrosis ($r = -0.31$, $p>0.10$).

The pulmonary vascular resistance (PVR) showed a significant negative correlation with $D_{LCO}$ both in mitral stenosis ($r = -0.48$, $p<0.05$) and in pulmonary emphysema or pulmonary fibrosis ($r = -0.61$, $p<0.01$). With $D_{MCO}$, however, PVR showed an insignificant negative correlation in mitral stenosis ($r = -0.36$, $p<0.10$) and no correlation in pulmonary emphysema or pulmonary fibrosis. PVR showed a highly significant negative correlation with $V_C$ in pulmonary emphysema or fibrosis ($r = -0.72$, $p<0.001$) but no correlation in mitral stenosis.

The pulmonary arteriolar resistance (PAR) showed no correlation with $D_{LCO}$, $D_{MCO}$ or $V_C$ either in mitral stenosis or in pulmonary emphysema or fibrosis, except that it showed a highly significant correlation with $V_C$ in pulmonary emphysema or fibrosis ($r = -0.74$, $p<0.001$).

The cardiac output showed no correlation either with $D_{LCO}$, $D_{MCO}$ or $V_C$, either in mitral stenosis or in pulmonary emphysema or fibrosis. A significant correlation was observed between the oxygen saturation of the peripheral arterial blood ($\text{SaO}_2$) and $D_{MCO}$ in mitral stenosis ($r = 0.46$, $p<0.05$).

**Discussion**

Since Forster$^{1,4}$ first reported the single breath method using CO to measure the pulmonary diffusing capacity, there have been many reports on the diffusing capacity in healthy subjects. Values of the diffusing capacity vary depending on reporters, positions and methods of measurement employed. Most of these values reported were obtained in sitting position, and values obtained in recumbent position have been reported only rarely.

Table III shows the normal values of $D_{LCO}$, $D_{MCO}$ and $V_C$ obtained in recumbent position as reported by Flatley$^{5}$, Hamer$^{6}$, Daly$^{7}$ and McCredie$^{8,9}$.

If the fact$^{10,11}$ that the steady state method yields a lower value than the single breath method is taken into consideration, the normal values reported by McCredie$^{8,9}$ seem to be comparable with those obtained in the present study.

Johnson$^{12}$, Hamer$^{6}$, Daly$^{7}$ and McCredie$^{8,9}$ reported slightly lower $D_{LCO}$ and $D_{MCO}$ and slightly higher $V_C$ than normal in mitral and aortic valvular diseases. Bedell$^{13}$, Bucci$^{14}$, Flatley$^{5}$, Hamer$^{6}$ reported twice as high $D_{LCO}$ and $V_C$ as normal in atrial septal defect. Similar results were obtained in the present study by the author.

In pulmonary diseases, MacNamara$^{16}$ and Bedell$^{13}$ reported lower $D_{LCO}$ than normal, and Bates$^{17}$ reported a marked decrease in $D_{MCO}$ in pulmonary fibrosis. Lewis$^{15}$, Pecora$^{18}$ reported a marked decrease in $D_{LCO}$, $D_{MCO}$ and $V_C$ in advanced pulmonary emphysema. In the present study also, patients with pulmonary emphysema or fibrosis showed markedly decreased $D_{LCO}$, $D_{MCO}$ and $V_C$.

As is shown in Fig.1, many patients with advanced congestive heart failure showed decreased $D_{LCO}$, $D_{MCO}$, and $V_C$.

Flatley$^{5}$ showed that, in mitral stenosis, $D_{LCO}$ decreased but $V_C$ increased with the advancement of heart failure, the latter indicating the advancement of pulmonary congestion.

Burton$^{19}$ reported that the volume of the normal pulmonary vascular bed increased with the increase of intravascular pressure. Similar results were obtained with normal pulmonary vascular bed by Lewis$^{20,21}$, Ross$^{22,23}$ and Rosenberg$^{24}$.

Palmer$^{25}$ and McCredie$^{6,9}$ observed that, in mitral stenosis, $V_C$ increased when there was a
slight pulmonary hypertension, but with a severe pulmonary hypertension, \( V_C \) rather decreased.

These results suggest that with a slight pulmonary congestion, the reserve of the pulmonary vascular bed is opened, thus increasing \( V_C \), while, with advancement of heart failure and development of severe pulmonary congestion and sustained pulmonary hypertension, accumulation of the alveolar exudate, thickening of the alveolar wall, and obstruction of the pulmonary capillary vessels will develop, thus leading to the reduction of \( V_C \).

Regarding the relationship between the pulmonary diffusing capacity and the pulmonary arterial pressure, Flatley\(^5\) observed a positive correlation between pulmonary arterial pressure and \( DLCO \), and Hamer\(^6\) observed a positive correlation between pulmonary arterial pressure and \( V_C \). Burton\(^19\), Lewis\(^20,21\) and Rosenberg\(^24\) reported similar results. Auchincloss\(^27\) and Reid\(^26\) however, observed a negative correlation between pulmonary arterial pressure and \( DLCO \), and Mc Credie\(^8,9\) observed a negative correlation between pulmonary arterial pressure and \( V_C \). In the present study, pulmonary arterial pressure showed a negative correlation with \( DLCO \), \( DMCO \), and \( V_C \). This suggests that, with a persistent and severe pulmonary hypertension, an organic change is induced in alveolar membrane and pulmonary vascular bed, thus leading to the reduction of pulmonary diffusing capacity.

As regards the relationship between pulmonary diffusing capacity and pulmonary capillary pressure in mitral stenosis, Flatley\(^5\) and Hamer\(^6\) observed no correlation between the two. Mc Credie\(^8,9\) however, observed a negative correlation between pulmonary capillary pressure and \( V_C \).

In the present study, the pulmonary capillary pressure showed a negative correlation with \( DLCO \), \( DMCO \) and \( V_C \) in mitral stenosis.

This suggests that the degree of impairment of the pulmonary circulation in mitral stenosis can be estimated by the parameters of pulmonary diffusing capacity.

In this study, a negative correlation was observed in mitral stenosis between \( DLCO \) and PVR or between \( DMCO \) and PVR, whereas no correlation was observed in mitral stenosis between PAR and either \( DLCO \), \( DMCO \) or \( V_C \).

Hamer\(^6\) also observed a negative correlation between \( DLCO \) and PVR and between \( DMCO \) and PVR. He, however, did not refer to the correlation between \( V_C \) and PVR.

In contrast, McCredie\(^8,9\) observed a negative correlation between \( V_C \) and PVR in mitral stenosis, and attributed the increase in PVR to the reduction of the pulmonary capillary bed.

The lack of correlation between \( V_C \) and PVR and between \( V_C \) and PAR in mitral stenosis in this study may be explained by the fact, as has been already discussed, that \( V_C \) increases as slight pulmonary congestion develops but it decreases as pulmonary congestion becomes severe.

In addition, with the elevation of left atrial pressure in mitral stenosis, the pressure in the pulmonary artery also is elevated passively, thus keeping the pressure gradient across the pulmonary vascular system comparatively unchanged. This is another possible explanation for the lack of correlation between \( V_C \) and PVR or PAR in mitral stenosis.

In this study a negative correlation was observed between \( DMCO \) and PVR but no correlation was found between \( DMCO \) and PAR. The lack of correlation between \( DMCO \) and PAR can probably be explained by the fact, as Dexter\(^28\) postulated, that the constriction of the pulmonary arterioles does not occur unless the pulmonary capillary pressure exceeds a certain level and because, as Piiper\(^29\) pointed out, PAR accounts for a comparatively small portion of PVR.

In the present study, no correlation was observed at all between pulmonary diffusing capacities and cardiac output in mitral stenosis. A similar result was obtained by Aber\(^30\) while McCredie\(^8,9\) observed a positive correlation between \( V_C \) and cardiac output in mitral stenosis.

A positive correlation was observed between \( DMCO \) and \( SaO_2 \) in mitral stenosis. This suggests that, with the development of heart failure, sustained elevation of pulmonary arterial pressure and pulmonary capillary pressure develops and exudate accumulates in the interstitial space around pulmonary vessels and airways and also in the alveolar wall. This leads to the swelling of the alveolar wall and the increase in the distance of gas diffusion across the alveolar wall and the reduction in the area of gas diffusion. Thus the gas exchange will be markedly impaired and lead to the reduction of \( SaO_2 \).

There have been only few reports regarding the relationship between pulmonary diffusion and pulmonary circulation in pulmonary diseases. In the present study, \( DLCO \) showed a similar correlation with hemodynamic parameters of pulmonary circulation as in cardiac diseases. Miyamoto\(^31\) also observed a negative correlation.
between DLCO and pulmonary arterial pressure in pulmonary diseases.

In the present study DmCO showed no correlation with hemodynamic parameter of pulmonary circulation in pulmonary diseases, except that it showed a negative correlation with pulmonary capillary pressure. This is in contrast to the fact that in mitral stenosis DmCO showed a good correlation with many hemodynamic parameters of pulmonary circulation.

This suggests that in cardiac disease, pulmonary alveolar membrane is comparatively intact and DmCO varies with impairment of pulmonary circulation, whereas in pulmonary diseases, impairment of ventilatory function and organic change in alveolar membrane develop prior to the development of pulmonary circulation disturbance, and as the pulmonary disease advances, further obstructive pulmonary arteriitis, the thrombosis, and the reduction of the pulmonary vascular bed reserve develop.

The close negative correlation between pulmonary vascular resistance and VC in pulmonary diseases suggests that the increase in PVR subsequent to the reduction in pulmonary vascular bed leads to the impairment of the pulmonary circulation.

Close correlations between DmCO and hemodynamic parameters of pulmonary circulation in mitral stenosis and a close correlation between VC and PVR in pulmonary diseases suggest that DmCO in mitral stenosis and VC in pulmonary diseases can be regarded as an index of degree of impairment of the pulmonary circulation.

The lack of correlation between pulmonary diffusion and cardiac output either in mitral stenosis or in pulmonary diseases seems to be related with the effects on pulmonary diffusion of such various factors as contact time of the alveolar gas with red blood cell, intrapulmonary arteriovenous shunt and abnormal distribution of gas in the lung.

**Conclusion**

1. Pulmonary diffusing capacity and pulmonary capillary blood volume were determined by CO single breath method of Forster et al. in 30 healthy subjects, 70 patients with cardiac diseases on whom right heart catheterization was performed, and 20 patients with pulmonary diseases.

The mean values in healthy subjects were:

\[ DLCO = 18.1 \pm 3.0 \text{ ml/min/mmHg/M}^2 \]
\[ DmCO = 30.4 \pm 7.3 \text{ ml/min/mmHg/M}^2 \]

\[ V_C = 58.3 \pm 16.3 \text{ ml/M}^2 \]
\[ (98.6 \pm 23.9 \text{ ml}) \]

In cardiac diseases, DLCO and DmCO were almost similar to those obtained in healthy subjects. VC, however, showed a slightly higher value than normal. In pulmonary diseases, DLCO, DmCO and VC all showed markedly lower values than normal.

2. It was suggested that in cardiac diseases the severity of heart failure and impairment of the pulmonary diffusion were parallel.

3. It was suggested that, in mitral stenosis, reduction in DmCO, and in pulmonary diseases, reduction in VC, could be regarded as an index of degree of impairment of the pulmonary circulation.

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**REFERENCES**


