Studies on the Peripheral Pulmonary Circulation Time in COPD

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SUMMARY

The pulmonary circulation time was assessed by measuring the parameter "\( \tau_p \)" which had been developed and reported elsewhere, for detecting the disturbances of pulmonary blood flow in patients with respiratory diseases. The materials were thirteen normal subjects, seven cases of slight COPD (group I), nine cases of severe COPD (group II), and three cases of old tuberculosis with restrictive ventilatory impairment (group III). The mean \( \tau_p \) value were 1.78±0.48 in normal subjects, 1.55±0.39 in group I, 2.0±1.13 in group II, and 1.60±0.46 in group III.

The mean \( \tau_p \) value was increased in severe COPD patients compared with that in normal subjects or in slight COPD patients, but the difference between them was not significant. This is because the \( \tau_p \) values of some severe COPD cases were increased but others were not. Meanwhile the computer simulation showed that \( \tau_p \) values were the sensitive parameter to assess the circulatory disturbances in the lung, by detecting the uneven distribution of Q/\( \dot{Q} \) in addition to delay and stagnation of the blood flow. These findings showed that the circulatory impairment would not increase in parallel with the ventilatory impairment and would be brought about at the critical advanced emphysematous stage in this type of COPD patients.

INTRODUCTION

Disturbances of pulmonary blood flow in patients with respiratory diseases, such as COPD, has been assessed mainly from the pulmonary arterial side, using right heart catheterization, and increases of pulmonary arterial mean pressure, pulmonary arterial wedge pressure and pulmonary vascular resistance, decrease of cardiac output and so forth have been reported. Comparing these findings with histological studies of the operatively resected lungs, Wright et al showed thickened pulmonary small muscular arterial walls in patients with minimal emphysema and to a greater degree in patients with more severe emphysema. Also a significant reduction in the diameter of 2, 3, 4 orders of branching of the pulmonary artery (diameters ...

2–7 mm) were shown by Horsfield et al.9) using PA angiography. Brachii et al.4) reviewed the
microangiographic studies and described a reduction in the number and size of intralobular arterial
branches, loss of capillary back ground displacement and distortion of vessels and the presence
of A-V anastomosis. From these studies, as the cause of disturbances of pulmonary blood flow,
destruction of lung capillary bed, narrowing of the muscular small pulmonary arteries, hypoxic
vasoconstriction, polycythemia due to hypoxia and constriction of vessels by increased alveolar
pressure due to airway obstruction have been suggested and generally accepted.5) On the other
hand pulmonary scintigrams, using radioisotopes, showed the existence of the uneven distribution
of pulmonary blood flow in COPD patients, these perfusion-unevenness has been discussed
comparing it with ventilation-unevenness.6)

Although numerous studies on hemodymanics of pulmonary blood flow have been reported
and compared with anatomical changes as mentioned above, to our knowledge, there are limited
data available about the time factor of pulmonary blood flow in the lung, because there had been
no proper method for measuring merely the pulmonary circulation time independently.
Recently a method for measuring the time constant of wash out curve in the lung, which could
be the parameter indicating the circulation time in the lung was reported by Kuno, one of our
coworkers,1) and it was designated as "\( \tau_p \)".

In this paper, with the use of this method, \( \tau_p \) of COPD patients were measured and reported.
And the factors which might increase the \( \tau_p \) value in this disease was studied using computer
simulation and comparing it with that of normal subjects, tuberculosis and congestive heart
failure.

MATERIALS AND METHODS

MATERIALS

The materials were thirteen normal candidates and nineteen patients of respiratory
diseases in the Respiratory Department of Tsukaguchi Hospital. The patients were divided
into four groups on the basis of diseases: Group I; slightly affected COPD patients (mainly
bronchial asthma) whose FEV 1.0% was 50 or more during the non-attack period, six cases.
Group II; severe COPD whose FEV 1.0% was less than 50, nine cases. Group III; old
pulmonary tuberculosis with severe respiratory impairment, three cases.

METHODS

The method used in this study for assessing the circulation time in the peripheral lung field
was the same as the one reported by Kuno.1) Briefly followings: As shown in Fig. 1, precordial
radio-activity of isotopes which were injected via the cubital vein as the bolus was detected by a
Seale Radiographic PHO/Gamma LEOV camera and recorded on videotapes. Playing back
these data, the time activity curves of each ROIs (1. whole heart, 2. right heart, 3. right lung
field, 4. superial vena cava) were acquired for thirty seconds, and transferred to the magnetic
tape in 0.1 second intervals up to a total of 300 data, and were analysed by an off-line HP 1000
computer system. These measurements were performed in supine position.

As shown in Fig. 2, theoretical formulations were made using the serial two-compartment
open dilution model whose first compartment was the right heart and the second compartment the lung. Radioactivity curves of ROI of the right heart \((C_R(t))\) and right lung field \((C_P(t))\) were expressed as follows:

\[
C_R(t) = \frac{\alpha}{Q_R} e^{-t/\tau_R}
\]

\[
C_P(t) = K(e^{-t/\tau_R} - e^{-t/\tau_P})
\]

Where \(C_R(t)\) and \(C_P(t)\) were concentrations of radioisotopes, \(Q_R\) and \(Q_P\) were blood volumes and \(\tau_R\) and \(\tau_P\) are time constants, \(R\) and \(P\) meant right heart and lung respectively. \(\dot{Q}\) is the blood flow of the right heart and lung, \(K\) was the proportion constant.

\(\tau_R\) could be calculated from the slope of the regression line of \(C_R(t)\)-time curve which was plotted on a semilogarithmic scale. The value of \(\tau_P\) was selected to minimize the sum of squares of difference between measured PVDC and simulated PVDC. Simulations of PVDC were performed using equation (2) in which \(\tau_R\) was calculated as described above, \(K\) and \(T(0)\) were calculated from the height and time of maximum point of the measured PVDC. The sum of square was calculated at each \(\tau_P\) : 1.0, 1.1, 1.2, 1.3, ... 10.0, and compared to find the minimum value. The Flow-Chart of the computer processing is shown in Fig. 3.

The effect of intrapulmonary uneven perfusion upon the \(\tau_P\) value was studied using computer simulation, assuming that the pulmonary circulation system was composed of \(n\) (=120) parallel compartments, and each had a different \(Q_i/\dot{Q}\), the following differential equations could be formulated.

\[
\frac{d}{dt} C_R(t) = -\dot{Q}_R C_R(t)
\]

\[
\frac{d}{dt} C_i(t) = \dot{Q}_i C_R(t) - \dot{Q}_i C_i(t)
\]

where \(Q_R\), \(Q_i\) and \(\dot{Q}_i\) and \(C_R(t)\), \(C_i(t)\) were blood volume, blood flow and concentration of radioisotopes respectively, symbol \(R\) meant right ventricle and \(i\) meant compartment \(i\) of
Fig. 2. Theoretical formulation of the hemodynamic behavior in the right ventricle and in the pulmonary vascular system assuming that they are serial two compartment open dilution system.

Solving these differential equations, by assuming that the initial condition was $C_i(0)=0$ and the total injected radioisotope was $a$.

$$C_R(t) = \frac{a}{Q_R} e^{-\frac{Q_R}{Q_P}t}$$

$$C_i(t) = \frac{Q_i}{Q_R Q_i - Q_R Q_i} \left( e^{-\frac{Q_R}{Q_P}t} - e^{-\frac{Q_i}{Q_i}t} \right)$$

Radioactivity of compartment "$i$" was expressed as follows
Fig. 3. The flow chart of computer programming for assessment of $\tau_p$.

\[ G_i(t) = K Q_i C_i(t) \]
\[ = \frac{K \alpha Q_i \hat{Q}_i}{Q_R Q_i} (e^{-\hat{Q}_R/Q_R} - e^{-\hat{Q}_i/Q_i} t) \]  
\[ (1) \]

Assuming that $\hat{Q}_R = \hat{Q}_Q$ was distributed to the compartment of $\hat{Q}_i/Q_i (= X_i)$ according to the distribution function $f(X_i)$.

\[ \hat{Q}_i = f(X_i) \hat{Q}_R \]  
\[ (2) \]

from

\[ Q_i = (Q_i/\hat{Q}_i) \hat{Q}_i = X_i \hat{Q}_i \]  
\[ (3) \]

from equation (1) (2) and (3)

\[ G_i(t) = K \alpha \frac{X_i f(X_i)}{R - X_i} (e^{-t/R} - e^{-t/X_i}) \]  
\[ (4) \]

where $R = Q_R/\hat{Q_R}$

Therefore the total radioactivity was expressed as follows

\[ G(t) = K \alpha \sum_{i=1}^{n} \frac{X_i f(X_i)}{R - X_i} (e^{-t/R} - e^{-t/X_i}) \]
Using this equation, radioactivity-time curves of various distribution function \( f(X_i) \) were formulated and compared.

Simulation models were set as follows:
1. Distribution function \( f(X_i) \) was log normal distribution (normal distribution against \( \log X_i \)).
\[
f(X_i) = \frac{\log e}{\sqrt{2\pi} (\log \sigma_i)} e^{\frac{(\log X_i - \log \mu_i)^2}{2(\log \sigma_i)^2}}
\]
2. (Total blood volume)/(Total blood flow) \( = \frac{\sum Q_i}{\sum \dot{Q}_i} \) was constant \( (=3.0) \)
3. \( r_B(=Q_B/\dot{Q}_B) \) was constant \( (=2.0) \)

RESULT

CONVENTIONAL PULMONARY FUNCTION

The mean value of \( %VC \) in group I was 100.9 ± 14.0, \( %VC \) value of all cases was over 80, there was no restrictive ventilatory impairment in this group. The mean value of FEV1.0\% of this group was 59.4 ± 5.32, three cases out of six were under 60, the values of FEV1.0\% in five cases ranged from 55.0 to 62.2, therefore the ventilatory impairment of this group was classified as moderate obstructive, MMF was decreased to 0.89 ± 0.36 L/sec, \( Rr \) was increased to 5.48 ± 1.39 cmH\(_2\)O/L/sec. The arterial gas tensions were not measured in most cases in this group, because they had no symptom of respiratory insufficiency. \( PaO_2, PaCO_2 \) of measured case was in normal limit.

The mean value of \( %VC \) in group II was slightly decreased, 68.9 ± 19.8, two cases out of nine was within normal limit (over 80) and two cases under 50, this group had wide variety of \( %VC \), either normal or severe restrictive ventilatory impairment. The mean value of FEV1.0\% was 39.6 ± 5.34 in this group, six out of nine was under 40, relatively severe obstructive ventilatory impairment was seen. MMF was also decreased to 0.38 ± 0.15 L/sec. \( Rr \) was increased to 6.81 ± 3.82 cmH\(_2\)O/L/sec. The mean value of \( PaO_2 \) was 71.6 ± 13.0 mmHg, among them established hypoxic respiratory insufficiency was only one case (T. N. \( PaO_2 \) 54.3 mmHg), subclinical hypoxia (60–79 mmHg) was seen in two cases (62.1 mmHg Ta. O., 62.6 mmHg K. K.) two cases of hypercapnea were seen (57.6 mmHg T. N., 48.0 mmHg K. K.), other four measured cases were within normal limit.

Marked decreases of \( %VC \) were seen in group III, mean value was 41.5 ± 15.2, all cases of this group had severe to moderate restrictive ventilatory impairement. Marked obstructive ventilatory impairements were also seen except one case, mean FEV1.0\% was 58.4 ± 31.1 (36.8, 44.4 and 94.0). All cases of this group were under the condition of respiratory insufficiency, mean value of \( PaO_2 \) was 51.6 ± 4.3 mmHg, all of them showed increased \( PaCO_2 \), its mean value was 57.7 ± 1.2 mmHg.

THE VALUES OF \( \tau_R \) AND \( \tau_P \)

The mean value of \( \tau_P \) of 12 normal candidates was 1.89 and the standard deviation was 0.70, as shown in table 1. However \( \tau_P \) of one case (M. Mu) was 3.50, it was larger than the mean
The theoretical radioactivity-time curves of the ROI in the lung in which the blood flow distributed to the multiparaller compartment each has different Q/Q were presented by the computer simulation as shown in Fig. 7-a.

The simulated distribution of blood flow against Q/Q were shown in Fig. 7-b (frequency-Q/Q) and Fig. 7-c (frequency-log Q/Q). The blood flow was suposed to distribute as the normal distribution against log Q/Q, therefore the curves shown in Fig. 7-c would be the normal distribution curve, and when the scale of x-axis changed to linear, the shape of curve changed as shown in Fig. 7-b. The height of the curve in this figure were standarized to show the deformation of the curve more instinctively.

**Table 1.** \( \tau_F \) of 12 normal candidates

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>( \tau_R )</th>
<th>( \tau_F )</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. Mu.</td>
<td>24</td>
<td>male</td>
<td>1.88</td>
<td>(3.50)</td>
</tr>
<tr>
<td>K. Ka.</td>
<td>24</td>
<td>male</td>
<td>3.49</td>
<td>1.10</td>
</tr>
<tr>
<td>A. O.</td>
<td>24</td>
<td>male</td>
<td>2.20</td>
<td>2.30</td>
</tr>
<tr>
<td>M. Hi.</td>
<td>25</td>
<td>male</td>
<td>3.88</td>
<td>1.20</td>
</tr>
<tr>
<td>K. U.</td>
<td>27</td>
<td>male</td>
<td>2.61</td>
<td>2.50</td>
</tr>
<tr>
<td>J. Mu.</td>
<td>29</td>
<td>male</td>
<td>3.94</td>
<td>2.30</td>
</tr>
<tr>
<td>M. Na.</td>
<td>30</td>
<td>male</td>
<td>2.70</td>
<td>2.10</td>
</tr>
<tr>
<td>S. O.</td>
<td>30</td>
<td>male</td>
<td>2.57</td>
<td>1.80</td>
</tr>
<tr>
<td>M. Mi.</td>
<td>32</td>
<td>male</td>
<td>2.38</td>
<td>1.60</td>
</tr>
<tr>
<td>M. I.</td>
<td>37</td>
<td>male</td>
<td>1.54</td>
<td>1.10</td>
</tr>
<tr>
<td>K. I.</td>
<td>44</td>
<td>male</td>
<td>2.62</td>
<td>1.50</td>
</tr>
<tr>
<td>S. Ka.</td>
<td>57</td>
<td>male</td>
<td>2.41</td>
<td>1.70</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>mean</th>
<th>SD</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \tau_F ) of M. Mu. was excluded because its value was greater than mean + 2SD. (total mean = 1.89, SD = 0.50)</td>
<td>2.69</td>
<td>0.74</td>
<td>12</td>
</tr>
</tbody>
</table>

\( \tau_F \) of M. Mu. was excluded because its value was greater than mean + 2SD.

\( +2SD \ (3.29) \), and we decided to exclude this case. Therefore as the normal value of \( \tau_F \), 1.25–2.25 was taken (mean; 1.75, SD; 0.50). The mean value of \( \tau_R \) of these normal subjects was 2.69 ± 0.74.

In patients of group I, the \( \tau_F \) values were within normal limit and the average value was 1.55 ± 0.39 (mean SD). The mean value of \( \tau_R \) was 2.17 ± 1.03, also was in normal limit.

The average \( \tau_F \) value of group II was 2.00 ± 1.13 which was larger than the value of group I or normal candidates. Although the difference between them was not statistically significant, a marked increase in \( \tau_F \) was seen in three cases out of nine, they were 2.90, 4.30, 2.50. The average \( \tau_R \) value was 2.46 ± 1.05, slightly larger than the value of group I but within normal limit.

As for the group III, the old tuberculosis with severe ventilatory impairment, the \( \tau_F \) value was within normal limits even in the cases with obstructive ventilatory impairment (cases M. Y. and K. O.), the mean value was 1.60 ± 0.46. The \( \tau_R \) value was slightly increased in this group, and the mean value was 3.20 ± 0.99.

**COMPUTER SIMULATION**

The theoretical radioactivity-time curves of the ROI in the lung in which the blood flow distributed to the multiparaller compartment each has different Q/Q were presented by the computer simulation as shown in Fig. 7-a.
The even distribution means all compartment has one Q/\dot{Q}, therefore the unevenness would be expressed as the increase of the standard deviation of the curve of Fig. 7-c. When the value of log SD increase from 0.1 to 1.0, 2.0, 3.0, the shape of the distribution curve becoming flatter and the maximum point (Mode) is shifting to the left as shown in Fig. 7-c. The radioactivity curve at each distribution was shown in Fig. 7a, the peak value was dwindling and the slope of the curve was becoming gentler as the standard deviation was increasing from 0.1 to 1.0, 2.0, 3.0. In this figure the height of the curve was standardized to show the change of the shape of the curve precisely.

**DISCUSSION**

Reported normal values of mean pulmonary transit time are as followings; 5.8 seconds and 6.6 seconds by Shipley et al.,7 the former was measured by peak to peak time and the latter by mean transit time of the radiocardiogram, 5.8 seconds by Giuntini,8 4.0 seconds by Segre et al.,9 6.6 seconds by Jones.10 All of them are much larger than our \( \tau_p = 1.75 \pm 0.50 \). This is because all these reported values were measured by radiocardiogram and include the dilution time of the right heart and left heart, also include the transit time of right atrium, main pulmonary artery and main pulmonary vein. On the other hand our \( \tau_p \) includes only the circulation time of the peripheral lung field.

There are not many data available about the mean pulmonary transit time in COPD patients, Giuntini et al.8 reported the data, which suggest that the pulmonary transit time of COPD patients is increased compared with normal subjects; the average value of mean pulmonary transit time of seven cases of chronic bronchitis and chronic obstructive emphysema was 7.4\pm1.2, meanwhile that of 17 cases of normal candidates was 5.8\pm0.9, although Giuntini makes no remarks about it. However, in our studies, the \( \tau_p \) values in slight COPD, whose FEV1.0\% was 55-70, were within normal limits. In severe COPD, whose FEV1.0\% was under 55, three cases which had increased \( \tau_p \) were recognized out of nine cases. These findings show that \( \tau_p \) does not increase in slight COPD and may increase in some probably emphysematous cases of advanced severe COPD.

The relationship between \( \tau_p \) and ventilatory functions such as FEV1.0\%, \%VC, MMF, was very poor as shown in Figure 4. It suggests that ventilatory impairment and circulatory disturbances are not parallel. The relationship between \( \tau_p \) and arterial gas pressure, such as \( \text{PaO}_2 \), \( \text{PaCO}_2 \), A-aDO\_2 was also very small as shown in Figure 5. But as shown in Figure 6, the correlation between \( \tau_p \) and C. I. was significant \((R=0.457)\) which might be reasonable because theoretically \( \tau_p \) was defined as \( Q_S/\dot{Q} \). This was also supported by the fact that \( \tau_p \) was increased to 3.40 in the patient who was 67 year old male with ischemic heart disease, his ventilatory function was as followings; \%VC 98.2, FEV1.0\% 65.7, MMF 1.16 L/sec, arterial gas tension were \( \text{PaO}_2 \) 80.2 mmHg, \( \text{PaCO}_2 \) 36.3 mmHg, and A-aDO\_2 34.5 mmHg. His cardiac index was decreased to 1.56. Therefore the increase of \( \tau_p \) in this case might be explained by decreased \( \dot{Q} \). As for \( Q_p \), it might be possible that the decrease of \%VC decreased the pulmonary blood volume \( (Q_p) \) and consequently decreased the \( \tau_p \) value which offset the increase of \( \tau_p \) due to obstructive ventilatory impairment in group III patients. This might explain the fact that the \( \tau_p \) value of
<table>
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<tr>
<th>Group</th>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Disease</th>
<th>$\tau_R$</th>
<th>$\tau_p$</th>
<th>C.I.</th>
<th>%VC</th>
<th>FEV1.0%</th>
<th>MMF</th>
<th>RR</th>
<th>$\text{Pao}_2$</th>
<th>$\text{Paco}_2$</th>
<th>$\text{AaDo}_2$</th>
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<td>I</td>
<td>F. K.</td>
<td>66</td>
<td>♂</td>
<td>br. asthma</td>
<td>1.17</td>
<td>1.40</td>
<td>—</td>
<td>87.4</td>
<td>54.0</td>
<td>0.7</td>
<td>6.0</td>
<td>—</td>
<td>—</td>
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<td>E. F.</td>
<td>71</td>
<td>♂</td>
<td>br. asthma</td>
<td>3.43</td>
<td>1.50</td>
<td>—</td>
<td>108.5</td>
<td>61.8</td>
<td>—</td>
<td>3.6</td>
<td>—</td>
<td>—</td>
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<td>♂</td>
<td>br. asthma</td>
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<td>1.80</td>
<td>3.42</td>
<td>123.5</td>
<td>55.0</td>
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<td>59</td>
<td>♂</td>
<td>br. asthma</td>
<td>1.28</td>
<td>1.10</td>
<td>—</td>
<td>95.2</td>
<td>67.6</td>
<td>0.88</td>
<td>7.0</td>
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<td>N. A.</td>
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<td>♂</td>
<td>br. asthma</td>
<td>2.06</td>
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<td>4.14</td>
<td>87.0</td>
<td>55.9</td>
<td>0.55</td>
<td>6.3</td>
<td>—</td>
<td>—</td>
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<td>M. O.</td>
<td>70</td>
<td>♂</td>
<td>br. asthma</td>
<td>3.44</td>
<td>2.20</td>
<td>2.18</td>
<td>103.6</td>
<td>62.2</td>
<td>0.81</td>
<td>4.5</td>
<td>93.0</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>2.17</td>
<td>1.55</td>
<td>3.25</td>
<td>100.9</td>
<td>59.4</td>
<td>0.89</td>
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<td>93.0</td>
<td>38.0</td>
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<tr>
<td></td>
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<td>0.39</td>
<td>0.99</td>
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<td>♂</td>
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<td>4.36</td>
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<td>1.90</td>
<td>2.30</td>
<td>73.0</td>
<td>42.9</td>
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<td>br. asthma with chr. emphysema</td>
<td>1.86</td>
<td>2.90</td>
<td>—</td>
<td>104.1</td>
<td>48.5</td>
<td>0.71</td>
<td>3.7</td>
<td>62.1</td>
<td>36.1</td>
<td>42.5</td>
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<td></td>
<td>T. N.</td>
<td>57</td>
<td>♂</td>
<td>br. asthma with chr. emphysema</td>
<td>2.00</td>
<td>4.30</td>
<td>2.05</td>
<td>47.2</td>
<td>40.0</td>
<td>0.23</td>
<td>6.5</td>
<td>54.6</td>
<td>57.6</td>
<td>23.4</td>
</tr>
<tr>
<td></td>
<td>H. T.</td>
<td>63</td>
<td>♂</td>
<td>br. asthma with chr. emphysema</td>
<td>3.53</td>
<td>1.40</td>
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<td>0.90</td>
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<td>45.5</td>
<td>0.38</td>
<td>4.0</td>
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<td>chr. bronchitis</td>
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<td>88.0</td>
<td>38.0</td>
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<td></td>
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<td>2.00</td>
<td>3.09</td>
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<td>1.20</td>
<td>3.53</td>
<td>30.8</td>
<td>94.0</td>
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<td>6.0</td>
<td>46.8</td>
<td>58.8</td>
<td>29.7</td>
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<td>1.50</td>
<td>3.39</td>
<td>58.9</td>
<td>36.8</td>
<td>0.24</td>
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<td>55.1</td>
<td>56.4</td>
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<td>old Tbc</td>
<td>3.20</td>
<td>2.10</td>
<td>2.18</td>
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<td>44.4</td>
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<tr>
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<td>6.0</td>
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<td>—</td>
<td>4.28</td>
<td>1.2</td>
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this group was not increased. Although in the patients of group I and II, there were three cases whose $\tau_P$ increased, two of them had normal C. I. (K. K. 3.88 and T. M. 2.91). The increased $\tau_P$ in these two cases could hardly be explained by $Q/\dot{Q}$ because our patients, including these two cases, were not in the terminal stage or in a congested stage, and it is generally accepted that the pulmonary blood volume is not increased in COPD patients unless there is congestion.8,11) Therefore, there should be some important factor for increasing the $\tau_P$, other than $Q$ and $\dot{Q}$. This is why we studied theoretically the effect of an uneven blood volume blood flow ratio in the lungs on the PVDC by computer simulation.

The result of the computer simulation showed that the slope of the simulated PVDC would become gentler as the standard deviation increases, as shown in Figure 7-a. Therefore if the $\tau_P$ value which is measured and calculated as a single compartment from this gently sloped curve,
would be larger than $\frac{\Sigma Q_i}{\Sigma Q}$ ($=3.0$ in this simulation). Then it may be safely said that the increased unevenness causes the apparently increased $\tau_P$.

It is possible, theoretically, to calculate the standard deviation of the distribution of $\tau_P$ against log ($Q/\dot{Q}$) in addition to the $\tau_P$ itself from measured PVDC by least square method using a computer but we failed to calculate them because of the too gentle upslope curve of PVDC, probably due to incomplete bolus inflow to the right heart or the dilution effect in the main pulmonary artery.

Histologically, Horsfield et al.\textsuperscript{3}) pointed out the stricture of pulmonary small arteries as the main lesion of the pulmonary vascular system in COPD. If that stricture in the pulmonary arterial system occurs unevenly, the vascular resistance should increase in this constricted region and the blood flow decreases in this part, consequently $\tau_P$ ($=Q/\dot{Q}$) may increase if the blood volume of the pulmonary vascular bed does not change. Adding the redistributed blood flow, $\dot{Q}$ may increase in the remaining part of the lung and therefore the $\tau_P$ of this remaining part will

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**Fig. 5.** Correlation between $\tau_P$ and arterial gas pressures.

**Fig. 6.** Correlation between $\tau_P$ and cardiac index. $R$: correlation efficient.
Fig. 7. The effect of uneven blood volume blood flow ratio in the lung upon the PVDC. (by the computer simulation) Assumption: (total $Q$)/(total $\dot{Q}$) = 3.0, $\tau_R = 2.0$, $\dot{Q}$ is normally distributed against log $(Q/\dot{Q})$ at SD of 0.1, 1.0, 2.0, 3.0 respectively.

7-a: Simulated PVDC. 7-b: Distribution function of $\dot{Q}$ against $Q/\dot{Q}$. 7-c: Distribution function of $\dot{Q}$ against log $(Q/\dot{Q})$. 
Table 3. \(\tau_R\), \(\tau_P\) and ECG findings

<table>
<thead>
<tr>
<th>Name</th>
<th>(\tau_R)</th>
<th>(\tau_P)</th>
<th>right axis deviation &gt;90°</th>
<th>(R&gt;S) in V1</th>
<th>(R&gt;S) in aVR</th>
<th>(R&gt;S) in V5</th>
<th>P &gt; 2.5 mm</th>
<th>inverted T in V1,2,3</th>
<th>ST depression in II, III, aVF</th>
</tr>
</thead>
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<tr>
<td>Y. M.</td>
<td>1.22</td>
<td>2.10</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>K. Sa.</td>
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<td>1.90</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>T. Ao.</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>T. N.</td>
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<td>4.30</td>
<td>+</td>
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<td>+</td>
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</tr>
<tr>
<td>H. T.</td>
<td>3.53</td>
<td>1.40</td>
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<td>-</td>
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<td>+</td>
<td>-</td>
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<td>+</td>
</tr>
<tr>
<td>K. K.</td>
<td>1.83</td>
<td>2.50</td>
<td>-</td>
<td>-</td>
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<td>T. Am.</td>
<td>4.69</td>
<td>0.70</td>
<td>-</td>
<td>-</td>
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<td>-</td>
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<td>O. Y.</td>
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decrease. Thus the unevenness of distribution of \(\tau_P\) would be made up in COPD patients. Other factors may also have an influence on the \(\tau_P\), for example, A-V shunt such as described by Brachii\(^3\) may decrease the \(\tau_P\), and pooling of the blood in the lung or constriction of the pulmonary venous system may increase the \(\tau_P\). There is also the possibility that the reserve of the pulmonary blood volume may be called in, this will increase the effective Q value and subsequently increase the \(\tau_P\) value.

Since the \(\tau_P\) is a parameter directly indicating the state of the pulmonary vascular system, as mentioned above, then it is more direct and may be more sensitive parameter for detecting the pulmonary vascular lesion in COPD than that of ECG. It is shown in Table 3 that two cases of increased \(\tau_R\) and three cases of increased \(\tau_P\) were detected with this method, in the meantime there were two cases of abnormal ECG.

However in some cases it was impossible to get the bolus inflow into the right heart which was needed to measure the \(\tau_P\), probably due to anatomical factors of the vein, in this study the measurement of \(\tau_P\) was unable in 6 cases out 37 (16.2%).

Meanwhile, since the value of \(\tau_R\) was defined theoretically as \(Q_R/Q\) (right heart volume/cardiac output), increase of \(\tau_R\) suggest the increased right heart ventricular volume or decreased cardiac output. Therefore \(\tau_R\) indicate the performance status of right ventricle. In our cases the \(\tau_R\) value of group III was increased to 3.20 ± 0.99, this might be relevant to the increased \(Q_R\) due to right heart strain, for the \(Q\) (C. I.) of these cases was within normal limit. The \(\tau_R\) value of group II (2.46 ± 1.05) was larger than that of group I (2.17 ± 1.03) but they were within normal limit. This is explained by the fact that there were only a little cases of right heart strain in this group as shown in the data of ECG (Fig. 8).

In conclusion, the pulmonary circulation time in peripheral lung field (\(\tau_P\)) which was assumed, to be the sensitive parameter for assessing the circulation disturbances by the computer simulation, was increased in some cases of severe emphysematous COPD but not increased in moderate COPD or respiratory insufficiency due to old tuberculosis. These increase of \(\tau_P\) was not correlated with conventional ventilatory functions or arterial gas tensions. These findings showed that the circulatory disturbances would not increase side by side with the ventilatory function, but it would be brought about at the critical advanced emphysematous stage.
in COPD.

The increase of $\tau_R$ was suggested to be brought about by the increased right heart ventricular volume or decreased cardiac output. Meanwhile the decrease of pulmonary blood volume (accompanied by decrease of lung volume) and the increase of blood flow or A-V shunt were suggested as the cause of decreased $\tau_F$. As the causes of increase of $\tau_F$, uneven distribution of $Q/Q$ was suggested in addition to the decreased blood flow, increased blood volume and the localized stagnation of blood flow in the lung.

REFERENCES