PULMONARY BLOOD VOLUME AND PULMONARY EXTRAVASCULAR WATER VOLUME IN MEN

Michio Arakawa, M.D., Yo Yasuda, M.D., Kenjiro Kambara, M.D.
Junpei Inuma, M.D., Hidetaka Miyazaki, M.D., Masato Yamaguchi, M.D.
Tadatake Takaya, M.D., Toshihiko Nagano, M.D., Masahiro Goto, M.D.
Takahiko Suzuki, M.D., Tsutomo Tanaka, M.D., Hiromichi Miyamoto, M.D.
and Senri Hirakawa, M.D.

In order to estimate the pulmonary blood volume between the pulmonary artery trunk and the left atrium (PBV_{PAT-LA}), simultaneously with the pulmonary extravascular water volume (PEWV) in the chronically stable cardiac patients, we employed the double indicator dilution method using heat as a diffusable indicator and indocyanine green as a non-diffusible indicator. The PEWV was obtained as the extravascular lung thermal volume estimated in the aortic root (LTV_{AO}).

In the group of hemodynamically normal patients, in spite of ischemic heart disease (G-N, n = 22), the mean pulmonary artery wedge (PAW) pressure was 9.3 ± 3.9 mmHg (mean ± SD), PBV_{PAT-LA} was 8.95 ± 1.71 ml/kg, LTV_{AO} was 5.71 ± 1.37 ml/kg and PBV_{PAT-LA}/LTV_{AO} ratio was 1.64 ± 0.44. In the group of hemodynamically slightly compromised patients with mitral stenosis (G-MS, n = 13), the mean PAW pressure was 14.2 ± 2.6 mmHg, PBV_{PAT-LA} was 11.12 ± 2.86 ml/kg, LTV_{AO} was 5.68 ± 1.41 ml/kg and PBV_{PAT-LA}/LTV_{AO} ratio was 2.02 ± 0.58. Between the two groups, LTV_{AO} was not statistically significant, whereas the mean PAW pressure, PBV_{PAT-LA} and PBV_{PAT-LA}/LTV_{AO} ratio were all significantly increased in G-MS (p < 0.05). Neither PBV_{PAT-LA} nor LTV_{AO} correlated with the mean PAW pressure in both groups.

From PBV_{PAT-LA}/LTV_{AO} ratio, fluid volume in the intravascular space was greater than that in the extravascular space in both groups. From LTV_{AO}, PEWV in G-MS was identical with that in G-N, in spite of the elevated mean PAW pressure. Therefore, even in the patients with mitral stenosis, the interstitium in the lung is kept “dry” under conditions of the mean PAW pressure below 20 mmHg. The safety factors that prevent pulmonary edema, as evidenced in animal studies, seem to operate effectively in man.

Key Words:
Extravascular lung thermal volume
Pulmonary blood volume
Left ventricular volume
Critical pressure
Plasma colloid osmotic pressure

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The Second Department of Internal Medicine, Gifu University School of Medicine, Gifu, Japan
Mailing address: Michio Arakawa, M.D., The Second Department of Internal Medicine, Gifu University School of Medicine, 40 Tsukasa-machi, Gifu 500, Japan

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extensively studied in animals\textsuperscript{1–10}. In a clinical setting of pulmonary congestion or edema, one should realize the intricate relations among the pulmonary extravascular water volume, the pulmonary blood volume and the pulmonary capillary pressure.

In this study, applying a modification of this method to humans, we aimed to provide factual information on the following subjects. Firstly, the possible loss of the indicators during the passage through the pulmonary circuit was studied partly to investigate the validity of this method. Secondly, the pulmonary blood volume from the pulmonary artery trunk to the left atrium (PBV\textsubscript{PAT-LA}) and the extravascular lung thermal volume in the aortic root (LTV\textsubscript{Ao}) were simultaneously estimated. Thirdly, PBV\textsubscript{PAT-LA}/LTV\textsubscript{Ao} ratio, i.e., the pulmonary intravascular-extravascular ratio of fluid volume was calculated and finally, the relationships between PBV\textsubscript{PAT-LA} or LTV\textsubscript{Ao} and the mean pulmonary artery wedge (PAW) pressure, and the relationships between LTV\textsubscript{Ao} and the intravascularly generated driving pressure (difference in pressure between the plasma colloid osmotic pressure and mean PAW pressure) were studied.

**MATERIALS AND METHODS**

*Materials*

We studied patients who were considered hemodynamically normal in spite of the presence

![Diagram](https://example.com/diagram.png)

**Fig.1.** A scheme of the double indicator dilution method with ICG and heat for measuring the pulmonary blood volume and extravascular lung thermal volume. Theoretically, ICG as a non-diffusible indicator remains in the intravascular space, whereas heat, a diffusible indicator, equilibrates with solids and water in the extravascular space as well as the intravascular space during pulmonary circulation. A mixture of indicators is delivered to the right atrium through Swan-Ganz catheter and subsequent thermodilution curve in the pulmonary artery trunk (PAT) and the thermodilution and dye dilution curves in the aortic root (Ao) are simultaneously obtained.

**GLOSSARY OF TERMS:**

Ao = aortic root; CBVPAT-Ao = central blood volume between the pulmonary artery trunk and the aortic root; CO = cardiac output; G-MS = group of hemodynamically slightly compromised patients with mitral stenosis; G-N = group of hemodynamically normal patients in spite of the presence of ischemic heart disease; LTV\textsubscript{Ao} = extravascular lung thermal volume measured from the dilution curves in the aortic root, indicating the pulmonary extravascular water volume estimated in the aortic root; "LVV" = arithmetic mean left ventricular volume; LAV = integral mean left atrial volume; PAT = pulmonary artery trunk; PAW pressure = pulmonary artery wedge pressure; PCOP = plasma colloid osmotic pressure; PBV\textsubscript{PAT-LA} = pulmonary blood volume between the pulmonary artery trunk and the left atrium; PBVPAT-PV = pulmonary blood volume between the pulmonary artery trunk and the pulmonary vein not including the left atrium; PEWV = pulmonary extravascular water volume; PBV\textsubscript{PAT-LA}/LTV\textsubscript{Ao} ratio and PBV\textsubscript{PAT-PV}/LTV\textsubscript{Ao} ratio = pulmonary intravascular-extravascular ratio of fluid volume; $\dot{Q}$ = blood flow or cardiac output x 1/60
of ischemic heart disease (n = 22, 21 men and 1 woman), abbreviated hereafter as G-N, and those who were slightly hemodynamically compromised with mitral stenosis (n = 13, 4 men and 9 women), abbreviated hereafter as G-MS. All were chronically stable. The patients with valvular regurgitation were excluded from the study, and all patients included showed no clinical signs of overt heart failure at the time of the catheterization.

**Methods**

1) Experimental procedures

As shown in Fig. 1, a Swan-Ganz catheter (93A-131-7F, Edwards Laboratories Inc.) with a thermistor and a hole at the tip, and with another hole, 15 cm proximal to the tip, was used. A tip of one Swan-Ganz (S-G₁) catheter was positioned in the pulmonary artery trunk (PAT) to record the thermodilution curve. The proximal port of this catheter was in the right atrium (RA) to inject the indicators. A tip of another Swan-Ganz (S-G₂) catheter was placed in the aortic root (Ao) to record the thermodilution and dye dilution curves.

The dye dilution curves were obtained by a
densitometer with a cuvette (EN 80, Erma Optical Works, Ltd.), through which blood was withdrawn by a constant withdrawal pump (SU 105, Erma Optical Works, Ltd.) at a rate of 0.6 ml/sec. The thermodilution curves were obtained by cardiac output computers (Model 9520, 9520A, American Edwards Laboratories).

The mean pulmonary artery wedge (PAW) pressure was measured by a strain gauge pressure transducer (Statham P23ID) with the zero level for pressure measurements at the mid-thoracic level. These signals were connected to the polygraph recorder (Model RM 85, Nihon Kohden Kogyo Co., Ltd. or VR 12, Electronics for Medicine).

The typical record was shown in Fig. 2.

The plasma colloid osmotic pressure (PCOP) was determined prior to the catheterization. The total protein concentration was measured by the biuret method (Model 726, Hitachi Co.) and the protein composition by electrophoresis (Model AES, Olympus Co.).

Although the theory and procedures are described in detail elsewhere? a brief description is as follows: employing a single injection and double sampling technique, a mixture of indocyanine green (ICG, 2.5 mg) and ice-cold 5% glucose solution (5 ml) was brought instantaneously into RA by a bolus injection. Simultaneously, the thermodilution curve was recorded from PAT, and the thermodilution curve and the dye dilution curve were recorded from Ao.

2) Calculations

Cardiac output (CO) was determined manually by the Stewart-Hamilton principle.

As shown in the bottom in Fig. 2, the extravascular lung thermal volume in the aortic root (LTVAo) was calculated as the product of the dye dilution flow, \( Q \), namely, \( CO \times 1/60 \) and the difference in the "mean transit time" \( (t_m) \) between the thermal and dye dilution curves in Ao. An alternative method was occasionally used for estimating the mean transit time, namely MTT.

Initially, \( t_m \) was calculated following the Stewart-Hamilton principle. The sum of the appearance time (from the injection to the first appearance of the dilution curve) and \( t_m \) equals MTT by our definition. The \( t_m \) of the dye dilution curve and \( t_m \) of the thermodilution curve in Ao were expressed as \( t_mAo(IGC) \) and \( t_mAo(heat) \). A practical equation is:

\[
\text{LTV}_{Ao} = CO \times 1/60 \times (t_mAo(IGC) - t_mAo(heat)) \times 0.9 
\]

In addition, traditional computation of MTT following the Stewart-Hamilton principle, was done manually. Namely, \( \text{MTT}_{RAi-Aos(heat)} \) indicates the mean transit time of the thermodilution curve obtained by injecting the indicators into RA (abbreviated as RAi) and sampling heat from Ao (abbreviated as Aos), while \( \text{MTT}_{RAi-Aos(IGC)} \) indicates the mean transit time of the dye dilution curve obtained by injecting the indicators into RA and sampling ICG from Ao. An another equation is:

\[
\text{LTV}_{Ao} = CO \times 1/60 \times (\text{MTT}_{RAi-Aos(heat)} - \text{MTT}_{RAi-Aos(IGC)}) \times 0.9
\]

The time of delay through the dead space of the catheter in the dye-cuvette system had been determined previously \( (2.0 \pm 0.1 \text{ sec}, \ n = 10, \ \text{unpublished observation}) \), and this delay time was checked in every recording and subtracted from the each mean transit time in the case of measuring LTVAo by equation (2) and CBVPAT-Ao by equation (3). Elings et al.\(^4\) and Lewis et al.\(^5\) showed that the appearance time of the thermal and dye indicators in the aorta after pulmonary circulation was identical. The differences in the response times of thermistor system and catheter-cuvette-dye densitometer system were considered negligible, and were not corrected. As shown in equations (1) and (2),

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<th>No.</th>
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<th>BSA (m²)</th>
<th>PAW (mmHg)</th>
<th>PCOP (L/min)</th>
<th>CBV&lt;sub&gt;PAT-Ao&lt;/sub&gt; (ml)</th>
<th>LV&lt;sup&gt;eff&lt;/sup&gt;/EDV, ESV (ml)</th>
<th>PV&lt;sub&gt;PAT-LA&lt;/sub&gt; (ml)</th>
<th>LTV&lt;sub&gt;Ao&lt;/sub&gt; (ml)</th>
<th>PBV&lt;sub&gt;PAT-LA&lt;/sub&gt; (ml)</th>
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<td>817</td>
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Mean: 9.3 4.90 4.90 641.6 112.6 529.2 324.5 8.95 335.0 206.0 5.71 1.64
SD: 3.9 1.30 1.30 120.8 36.9 117.2 65.1 1.71 78.5 46.9 1.37 0.44

**Table: Clinical Findings and Hemodynamic Parameters Collected from the Group of Hemodynamically Normal Patients in Spite of the Presence of Ischemic Heart Disease (G-N)**

**Abbreviations:**
- **PAW** = mean pulmonary artery wedge pressure
- **PCOP** = plasma colloid osmotic pressure
- **CO** = cardiac output
- **CBV<sub>PAT-Ao</sub>** = central blood volume between the pulmonary artery trunk and the aortic root
- **LV<sup>eff</sup>/EDV, ESV** = mean left ventricular volume (EDV = end-diastolic volume; ESV = end-systolic volume)
- **PV<sub>PAT-LA** = pulmonary blood volume between the pulmonary artery trunk and the left atrium
- **LTV<sub>Ao** = extravascular lung thermal volume measured in the aortic root

Pulmonary Blood Volume and Lung Thermal Volume
### TABLE II CLINICAL FINDINGS AND HEMODYNAMIC PARAMETERS COLLECTED FROM THE GROUP OF HEMODYNAMICALLY SLIGHTLY COMPROMISED PATIENTS WITH MITRAL STENOSIS (G-MS)

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<th>Name</th>
<th>BW (kg)</th>
<th>BSA (m²)</th>
<th>PAW (mmHg)</th>
<th>PCOP (mmHg)</th>
<th>CO (L/min)</th>
<th>CBV_PAT-Ao (ml)</th>
<th>&quot;LTV(^{3})&quot;/(EDV, ESV) (ml)</th>
<th>PBV_PAT-LA (ml)</th>
<th>PBV_PAT-LA (ml/kg)</th>
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<th>LTV_Ao (ml/kg)</th>
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<td>133</td>
<td>4.2</td>
</tr>
<tr>
<td>34</td>
<td>E.T.</td>
<td>51.6</td>
<td>1.50</td>
<td>12</td>
<td>26.7</td>
<td>5.88</td>
<td>774</td>
<td>120/(191, 48)</td>
<td>654</td>
<td>436</td>
<td>12.7</td>
<td>300</td>
<td>200</td>
<td>5.8</td>
</tr>
<tr>
<td>35</td>
<td>A.I.</td>
<td>53.0</td>
<td>1.45</td>
<td>17</td>
<td>29.7</td>
<td>4.17</td>
<td>834</td>
<td>95/(136, 54)</td>
<td>739</td>
<td>510</td>
<td>13.9</td>
<td>369</td>
<td>214</td>
<td>7.0</td>
</tr>
</tbody>
</table>

|        | mean | 14.2* | 25.00 | 3.70* | 661.5 | 98.1 | 563.5 | 379.6 | 11.12* | 286.5 | 190.1 | 5.68 | 2.02* |
|        | ± SD  | 2.6   | 2.33  | 1.12  | 185.5 | 17.5 | 172.1 | 105.0 | 2.86  | 77.7  | 45.9  | 1.44 | 0.58 |

Abbreviations are the same as in Table I. Dash indicates datum not obtained. Values are significantly different between G-MS and G-N by unpaired t test; * = p < 0.05

### TABLE III SUMMARY OF PULMONARY INTRAVASCULAR-EXTRAVASCULAR RATIO OF FLUID VOLUME DERIVED FROM THE LEFT ATRIAL ANGIOGRAPHY

<table>
<thead>
<tr>
<th></th>
<th>PBV_PAT-LA (ml/m²)</th>
<th>LAV (ml/m²)</th>
<th>PBV_PAT-PV (ml/m²)</th>
<th>LTV_Ao (ml)</th>
<th>PBV_PAT-PV (ml/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-N</td>
<td>325 ± 58</td>
<td>9.1 ± 1.6</td>
<td>12 ± 3.3</td>
<td>40 ± 10</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>G-MS</td>
<td>405 ± 49</td>
<td>11.2 ± 1.9</td>
<td>126 ± 8.1</td>
<td>126 ± 8.1</td>
<td>3.5 ± 2.3</td>
</tr>
</tbody>
</table>

|        | 292 ± 61            | 7.8 ± 1.6   | 217 ± 55            | 6.0 ± 1.6    | 1.37 ± 0.38         |
|        | 279 ± 77            | 7.7 ± 2.5   | 192 ± 13            | 5.3 ± 0.6    | 1.45 ± 0.38         |

Abbreviations: G-N = group of hemodynamically normal patients in spite of the presence of ischemic heart disease; G-MS = group of hemodynamically slightly compromised patients with mitral stenosis; PBV_PAT-LA = pulmonary blood volume between the pulmonary artery trunk and the left atrium; LAV = mean left atrial volume; PBV_PAT-PV = pulmonary blood volume between the pulmonary artery trunk and the pulmonary vein not including the left atrium; LTV_Ao = extravascular lung thermal volume measured in the aortic root. Values are means ± SD.
LTV$_{Ao}$ was further corrected by multiplying LTV$_{Ao}$ by 0.9 for the difference between the water volume and the blood volume in agreement with Staub. For the analysis, the duplicate determinations were usually done at intervals of about 5 minutes.

As shown in Fig. 1 and Fig. 2, the blood volume between PAT and Ao was defined as the central blood volume (CBV$_{PAT-Ao}$) and it was calculated as the product of the dye dilution flow, Q, namely, CO x 1/60 and the differences in two MTTs i.e., MTT$_{RAI-Aos(ICG)}$ and MTT$_{RAI-PATs(heat)}$. An equation is:

$$CBV_{PAT-Ao} = CO \times \frac{1}{60} \times (MTT_{RAI-Aos(ICG)} - MTT_{RAI-PATs(heat)}) \ldots (3)$$

The former indicates MTT of the curve obtained by injecting a mixture of ICG and negative heat into RA and sampling ICG from Ao, and the latter indicates MTT of the curve obtained by injecting a mixture of ICG and negative heat into RA and sampling heat from PAT. In this connection, MTT$_{RAI-PATs(heat)}$ is defined as identical to ideal MTT of the dye dilution curve in that place, namely MTT$_{RAI-PATs(ICG)}$. That is, the thermal equilibrium with the right heart wall is regarded as negligible. Next, in order to obtain the pulmonary blood volume between PAT and the left atrium (LA) (PBVPAT-LA), the arithmetic mean left ventricular volume ("LVV") was subtracted from CBV$_{PAT-Ao}$. Namely;

$$PBV_{PAT-LA} = CBV_{PAT-Ao} - \text{"LVV"} \ldots (4)$$

The arithmetic mean left ventricular volume ("LVV") was determined by averaging the left ventricular end-diastolic volume (EDV) and the left ventricular end-systolic volume (ESV), which
were measured independently during catheterization in each case, by an area-length method from a conventional single-plane cineangiogram (50 frames a second) in RAO projection (30 degrees). The PCOP was calculated following an equation proposed by Nitta et al.  

3) Statistics
Student’s t test for independent samples and paired samples was done. All values were reported as mean ± one standard deviation. For all tests, p < 0.05 was accepted as significant.

RESULTS

1. Potential loss of indicators during passage through pulmonary circuit
Possible events of indicator loss during the passage in pulmonary circulation were investigated by comparing cardiac outputs (CO), simultaneously determined from the thermodilution curves and the dye dilution curves, recorded in the pulmonary artery trunk (PAT) and the aortic root (Ao). In Fig. 3, cardiac outputs from the thermodilution curves in Ao (CO_{Ao,heat}) were plotted against those from the thermodilution curves in PAT (CO_{PAT,heat}). The regression equation was:

\[ CO_{Ao,heat} = 0.90 \times CO_{PAT,heat} + 0.39 \]

(L/min), n = 60,

\[ (r = 0.92, p < 0.001) \]

\[ CO_{Ao,heat} = 4.17 \pm 1.04 \text{ L/min} \]

The differences between CO_{Ao,heat} and CO_{PAT,heat} were not significant (p > 0.25).

The relations between cardiac outputs from the dye dilution curves in Ao (CO_{Ao,ICG}) and those from the thermodilution curves in PAT (CO_{PAT,heat}) was:

\[ CO_{Ao,ICG} = 1.16 \times CO_{PAT,heat} - 0.69 \]

(L/min), n = 27,

\[ (r = 0.95, p < 0.001) \]

\[ CO_{Ao,ICG} = 4.18 \pm 1.46 \text{ L/min} \]

The differences between CO_{Ao,ICG} and CO_{PAT,heat} were not significant (p > 0.5).

These facts demonstrate the virtually complete conservation of the indicators, both heat and ICG.

2. Reproducibilities of central blood volume and extravascular lung thermal volume
The duplicate determinations of the central blood volume from PAT to Ao (CBV\textsubscript{PAT-Ao}) and the extravascular lung thermal volume in Ao (LTV\textsubscript{Ao}) were performed at intervals of about 5 minutes. The excellent reproducibilities were demonstrated. The regression equations were:

\[ Y = 1.0X + 0.1 \text{ (ml/kg)} \text{ for CBV}_{PAT-Ao} \]

\[ n = 10, (r = 0.92, p < 0.001) \]

\[ Y = 0.8X + 1.3 \text{ (ml/kg)} \text{ for LTV}_{Ao} \]

\[ n = 10, (r = 0.94, p < 0.001) \]

The differences between the first measurements (X) and second measurements (Y) for CBV\textsubscript{PAT-Ao} and LTV\textsubscript{Ao} were not significant (p > 0.5 for LTV\textsubscript{Ao}, p > 0.5 for CBV\textsubscript{PAT-Ao}).

3. Pulmonary blood volume
As shown in Tables I and II, PBV\textsubscript{PAT-LA} was 324.5 ± 65.1 ml/m\textsuperscript{2} BSA, or 8.95 ± 1.71 ml/kg in G-N and, 379.6 ± 105.0 ml/m\textsuperscript{2} BSA, or 11.12 ± 2.86 ml/kg in G-MS. On an average, G-MS had larger PBV\textsubscript{PAT-LA} than G-N. There was a statistically significant difference only in volumes normalized to body weight between G-N and G-MS (0.01 < p < 0.02).

4. Extravascular lung thermal volume
As shown in Tables I and II, the extravascular lung thermal volume in Ao (LTV\textsubscript{Ao}) averaged 5.71 ± 1.37 ml/kg in G-N, and 5.68 ± 1.41 ml/kg in G-MS. The differences in LTV\textsubscript{Ao} between the two groups were not statistically significant.

In patients No.3, No.8, No.22 in G-N, both the left ventricular end-diastolic volume and the left ventricular end-diastolic volume index were large, i.e., 149, 143 and 148 ml/m\textsuperscript{2} BSA, respectively. However, their LTV\textsubscript{Ao} averaged 5.9 ml/kg, not differing from a grand average of 5.71 ± 1.37 ml/kg.

5. Pulmonary intravascular-extravascular ratio of fluid volume
The pulmonary intravascular-extravascular ratio of fluid volume was investigated by observing the ratio of PBV\textsubscript{PAT-LA} which represented the pulmonary intravascular blood volume to LTV\textsubscript{Ao} which represented the pulmonary extravascular water volume. The PBV\textsubscript{PAT-LA}/LTV\textsubscript{Ao} ratio was 1.64 ± 0.44 in G-N, and 2.02 ± 0.58 in G-MS as shown in Tables I and II. From this viewpoint, the fluid volume in the intravascular space was greater than in the extravascular space in the lung in both groups. The differences between the two groups were statistically significant (p < 0.05). Since LTV\textsubscript{Ao} in G-MS is identical with that in G-N, this significance in differences appears to arise from the

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fact that the pulmonary blood volume in G-MS is larger than in G-N.

6. Relationship of pulmonary blood volume, pulmonary extravascular water volume and pulmonary intravascular-extravascular ratio of fluid volume to pulmonary intravascular pressure

In a system of pulmonary circulation, $PBV_{PAT-LA}$ and $LTV_{Ao}$ were evaluated in relation to the mean pulmonary artery wedge (PAW) pressure, reflecting the pulmonary capillary pressure.

As shown in Fig. 4-(A), in both groups, $LTV_{Ao}$ remained unchanged at around 6 ml/kg over the range of 5–21 mmHg in the mean PAW pressure and no correlation was noted, while $PBV_{PAT-LA}$ increased weakly but insignificantly along with the pressure elevation over the range of 5–21 mmHg in the mean PAW pressure, as shown in Fig. 4-(B).

The pulmonary intravascular-extravascular ratio of fluid volume as a function of the mean PAW pressure was not correlated in both groups (Fig. 4-(C)).

As presented in Fig. 5, the intravascularly generated driving force, namely, the differences in pressure between the plasma colloid osmotic pressure (PCOP) and the mean PAW pressure (PCOP-mean PAW pressure gradient) showed no correlation with $LTV_{Ao}$ over the range of 2–24 mmHg.

DISCUSSION

1. Potential loss of heat during passage through pulmonary circuit

There are several animal studies$^{9,14,15}$ that demonstrate the virtual thermal conservation during pulmonary circulation, but in human studies, only a few workers$^{5,16}$ reported that an average of 5–10% of the injected thermal indicator was lost, and in these studies the statistical significance was unspecified. To our knowledge, the present study (Fig. 3) is the first report dealing with the precise simultaneous comparison of cardiac outputs during pulmonary circulation between the pulmonary artery trunk and the aortic root in humans. Our results constitute probable evidence that the thermal conservation is also substantially complete in humans.

2. Pulmonary blood volume

2-A) Validity of method for estimating $LVV$

In a preliminary study, we obtained the left ventricular volume-time curve for one cardiac cycle in three patients, computing the left ventricular volume at intervals of 20 msec, and calculated the integral mean left ventricular volume. In patient No.35 in G-MS (heart rate (HR) = 82), patient No.16 (HR = 68) and patient No.17 (HR = 67) in G-N, the integral mean left ventricular volumes were 94 ml, 122 ml and 126 ml respectively. Arithmetic means of the end-diastolic and end-systolic volume, $LVV$, were 95 ml, 117 ml and 131 ml respectively. The difference was apparently negligible. This suggests that $LVV$ can be used, in practice, instead of the true integral mean left ventricular volume.

2-B) Pulmonary blood volume

The reported mean values of the pulmonary blood volume were 246 ml/m$^2$ $^{171}$ 295 ml/m$^2$ $^{18}$ 271 ml/m$^2$ $^{19}$ in normal patients and 362 ml/m$^2$ $^{20}$ 335 ml/m$^2$ $^{171}$ 238 ml/m$^2$ $^{19}$ in the patients with mitral stenosis. The values of the pulmonary blood volume in this study ($PBV_{PAT-LA}$) were larger than those reported above, probably because the left atrial volume was entirely incorporated into $PBV_{PAT-LA}$.

Table III shows the results of preliminary studies for assessing the magnitude of the left atrial volume, in connection with $PBV_{PAT-LA}$. The integral mean left atrial volume (LAV) was obtained, from the biplane cineangiogram (50 frames a second) with a standard area-length method.$^{21}$ From these we obtained the pulmonary blood volume from the pulmonary artery trunk to the pulmonary vein (PV) up to the entry of the left atrium, namely $PBV_{PAT-PV}$.

$PBV_{PAT-PV}$ was $292 \pm 61$ ml/m$^2$, $7.8 \pm 1.6$
ml/kg in G-N and 279 ± 77 ml/m², 7.7 ± 2.5 ml/kg in G-MS. Apparently, the corrected pulmonary blood volume obtained by eliminating the left atrial volume (PBV_{PAT.PV}) was about the same as previous reports. However, the number is too small to analyze further the significance of this parameter.

3. Extravascular lung thermal volume

In previous studies, extravascular pulmonary water volume was determined by the double indicator dilution method using heat as a diffusible indicator.

Mihr et al. confirmed an excellent agreement between the thermal-dye technique and the direct destructive method in human organ transplant donors.

In many other reputed studies, the reported normal values (in the range of 5.4—7.3 ml/kg) of the extravascular lung thermal volume (LTV) are generally agreeable with our data.

As to the patients with mitral stenosis, Oonishi et al. found a relatively large amount of LTV, 11.6 ± 3.9 ml/kg (n = 7), for the mean PAW pressure, ranging from about 20 to 30 mmHg. However, interestingly enough, we found that LTV_{A0} in G-MS was 5.68 ± 1.41 ml/kg (n = 13) for the mean PAW pressure, ranging from 10 to 19 mmHg, which was essentially the same as that in G-N (5.71 ± 1.37 ml/kg, n = 22). This discrepancy would result from the difference in the subjects with varying degrees of the cardiac disorders and will be explored in detail later in discussion 5-b).

4. Pulmonary intravascular-extravascular ratio of fluid volume

As shown in Tables I and II, PBV_{PAT.LA}/LTV_{A0} ratio in G-N and G-MS were 1.64 ± 0.44 and 2.02 ± 0.58 respectively. If one prefers PBV_{PAT.PV} to PBV_{PAT.LA}, the ratios of PBV_{PAT.PV}/LTV_{A0} were 1.37 ± 0.38 in G-N and 1.45 ± 0.38 in G-MS, as in Table III. The PBV_{PAT.PV}/LTV_{A0} ratio between the two groups lost the statistical significance of the difference, although the statistical significance of the difference between the two groups was noted in the case of PBV_{PAT.LA}/LTV_{A0} ratio.

In other words, the pulmonary intravascular-extravascular ratio of fluid volume in G-MS may be spuriously larger than in G-N. On the basis of this observation, we may extend the speculation that the lungs are relatively "dry".

5. Relationship of pulmonary blood volume and pulmonary extravascular water volume to pulmonary intravascular pressure

5-a) Pulmonary blood volume as a function of pulmonary intravascular pressure

The pulmonary blood volume (PBV_{PAT.LA}) was poorly correlated with the mean PAW pressure in this study. The change in the pulmonary blood volume in mitral stenosis seems to be modified by a period of time and the extent of the elevation of the intravascular pressure. Even when considering the previously reported values, the relationship between the pulmonary blood volume and the pulmonary intravascular pressure in humans of chronically adapted state remains unclear.

5-b) Pulmonary extravascular water volume as a function of pulmonary intravascular pressure

The change of the pulmonary extravascular water volume (PEWV) was investigated primarily as a function of the pulmonary intravascular pressure. The relationships between LTV_{A0} and the mean pulmonary artery wedge (PAW) pressure, a fair approximation of the pulmonary capillary pressure, are shown in Fig. 4(A). The LTV_{A0} appears to stay constant and uncorrelated with the mean PAW pressure in the range of 5—21 mmHg. This finding is consistent with comparisons of acute animal experiments.

It is well known that the safety factors such as increased lymph drainage and colloid osmotic pressure gradient are effective in opposing the development of pulmonary edema when the pulmonary capillary pressure is below the critical pressure. For instance, Guyton et al. found by creating the left atrial pressure elevation by means of partial constriction of the aorta in dogs with normal plasma protein concentrations, that the critical left atrial pressure point was in the range of 20—25 mmHg below which the lungs were maintained in a persistently dry state. Likewise, Gaar et al. discovered that in isolated perfused dog lung preparation with blood composed of the normal plasma concentration, the definite critical pulmonary capillary pressure was 28 mmHg. From the work of Erdmann et al. who produced the left atrial hypertension in sheep by means of the inflation of the balloon for 4 hours, we can speculate that the pulmonary extravascular water volume remains at normal control value until the pulmonary microvascular pressure arrives at about 26 mmHg.

On the other hand, in our preliminary study...
on dogs, LTVAo remained unchanged over the low range of 3 to 17 mmHg in the pulmonary artery end-diastolic pressure (PAEDP) in the control state. Nevertheless, when we acutely loaded dogs with 6% dextran 70 (Macrodex), covering the high range from 3 to 52 mmHg in PAEDP, LTVAo increased and gained positive curvilinear correlations with PAEDP.

Only a few papers are available on the behavior of PEWV in the patients with mitral stenosis. As previously described, Oonishi et al.16 clearly demonstrated an increased PEWV in the range of 20 to 30 mmHg in the mean PAW pressure. Cross et al.32 reported that the development of pulmonary edema in patients with combined mild mitral stenosis and pneumonia may occur due to lung lymphatic insufficiency even a lower level of the mean PAW pressure (11 mmHg). In contrast, Rabin et al.33 achieved a chronic elevation of the left atrial pressure by producing mitral stenosis and maintained that state for up to 10 months in dogs, ranging from 10 to 23 mmHg. They observed neither pulmonary edema nor congestion.

Consequently, the lack of correlation between LTVAo and the mean PAW pressure in the present study, especially in mitral stenosis, may be attributed partly to the low range of the mean PAW pressure below the critical pressure. This may be also attributed partly to the action of chronically accomplished protective mechanisms against pulmonary edema, such as the increased lymph flow.34

Next, we investigated the lung fluid balance from the standpoint of the net intravascularly generated driving force. As presented in Fig. 5, the differences in pressure between PCOP and the mean PAW pressure (PCOP – mean PAW pressure gradient) showed no correlation with LTVAo over the range of 2–24 mmHg.

The finding seems compatible with the results published from Gabel et al.35 who demonstrated in sheep that the pulmonary extravascular water volume was not significantly increased when the pulmonary capillary pressure was below (PCOP + 5) mmHg.

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