EFFECT OF CARDIAC OUTPUT ON PULMONARY SHUNT

BY

Takeshi Sawa, Hiromichi Yamauchi, Teruo Kumazawa,
and Etsutaro Ikezono[*1]

Abstract

The effect of cardiac output on pulmonary shunt was studied in living lungs of human patients and dogs which had alveoli and blood vessels, and also in artificial lung (bubble-type oxygenator) which had no such structural factors. In spite of such a structural difference, quite similar results were observed in both living and artificial lungs, and this suggests that some common factors other than the change in blood vessels result in the change in pulmonary shunt. It was observed that pulmonary shunt increased as the saturation of mixed venous blood became higher. It was clarified that the oxygen-receiving capacity of blood decreased as the oxygen saturation became higher, i.e., the amount of reduced hemoglobin became less. The reduction in oxygen-receiving capacity of blood results in the reduction in oxygen-transfer efficiency from alveoli to blood and hence pulmonary shunt increases, and this can be regarded as a kind of shunt-like effect. It can be concluded that the change in pulmonary shunt by cardiac output is not due to the change in the lung function but is caused by the change in the oxygen-receiving capacity of the mixed venous blood.

Introduction

The effect of cardiac output on pulmonary shunt has been reported and discussed by many investigators for the past ten years. They reported that pulmonary shunt changed proportionally to cardiac output in patients and also in dogs. To explain this, the mechanisms such as the redistribution of the pulmonary blood flow and the lack of transit time have been suggested. However, since the experimental proofs have not been obtained, all proposed mechanisms are merely conjectures.

To clarify this mechanism, we analyzed the data reported by other investigators in living lungs of human patients and dogs, and also made experiments with a bubble-type artificial lung (oxygenator). Special symbols shown in Table 1 were used in this paper.

Materials and Methods

I. Analysis on living lungs of patients and dogs:

Concerning the study on living lungs of patients[1–6] and dogs,[7–14] we did not make experiments but made analysis of the data reported by other investigators. We inspected the data before using and found that those data were accurate enough for the purpose of our study. The changes in PaO, $P\bar{v}O_2$, CaO_2, $C\bar{v}O_2$, ć-a O_2 content difference, ć-$\bar{v}$ O_2 content difference and pulmonary shunt (Qs/Qt) were analyzed for the change in cardiac output.

[*1] 沢　桓，山内紘通，熊沢光生，池園悦太郎：Department of Anesthesiology (Chief: Prof. E. Ikezono), Faculty of Medicine, Tokyo Medical and Dental University (Tokyo Ika Shika Daigaku).

Table 1. List of special symbols

$\dot{c}-aCO_2$:	$C\dot{c}O_2-CaO_2$, numerator of shunt equation
$\dot{c}-\bar{v}CO_2$:	$C\dot{c}O_2-C\bar{v}O_2$, denominator of shunt equation
$a-\bar{v}CO_2$:	$CaO_2-C\bar{v}O_2$
red·Hb:	reduced hemoglobin

II. Experiment with an artificial lung:

We had an idea that the change in pulmonary shunt by cardiac output might not be due to the change in pulmonary blood vessels and redistribution of pulmonary blood flow. Therefore we planned to examine whether a similar change in pulmonary shunt as in the living lungs could also occur in the artificial lung (oxygenator) which had no pulmonary blood vessels.

Two bubble-type oxygenators (Temptrol, Infant Q-130, Bentley Lab., California, U.S.A.) and one roller pump were used to build up the experimental respiratory and circulatory system as shown in Fig. 1. The circuit was filled with about 1,200 ml of ACD blood and acid-base balance was adjusted by adding bicarbonate and CO_2. O_2 and CO_2 were bubbled through one of the artificial lungs which was to be used as the lung in this experiment. N_2 and CO_2 were bubbled through the other artificial lung and this was used as a deoxygenator by which the oxygen consumption in the whole body was simulated. Blood was fed from the oxygenator to the deoxygenator by means of the roller pump and returned from the deoxygenator to the oxygenator by gravity. Blood flow, i.e., cardiac output, was measured with a magnetic flow-meter and blood temperature was monitored with a thermister-type thermometer. Blood temperature was maintained between 36° and 38°C by circulating water of 40°C through the warmers of both artificial lungs. CO_2 concentration in the gas flowing through the oxygenator was $3.8\pm1.0\%$ (mean±S.D.) and that of the deoxygenator was $11.9\pm8.3\%$. Blood
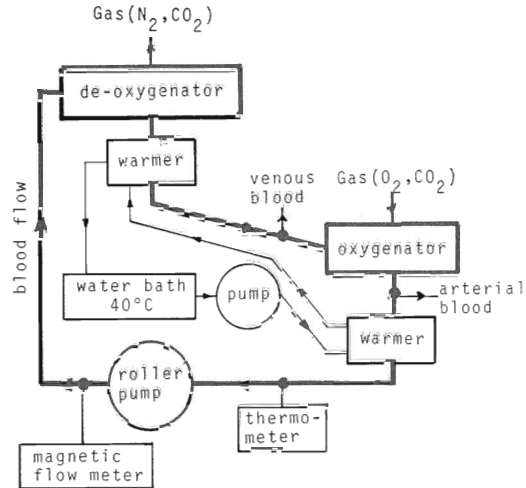

Fig. 1. Experimental respiratory and circulatory system built up with artificial lungs (oxygenators) and a roller pump.

samples were taken from the inlet and outlet of the oxygenator and PO_2, PCO_2, pH, and bicarbonate were determined with an IL-meter (type 213) at 37°C. Oxygen saturation was calculated by using the nomogram by Kelman and Nunn.[15] Hb content was measured with a Hb-meter (Type 10-101D, American Optical Co.). P_AO_2 was estimated using the alveolar air equation, and pulmonary shunt of the artificial lung was calculated with shunt equation.

While the gas flow through the deoxygenator was maintained at a constant rate, cardiac output was altered from 0.1 to 2.0 L/min in random order.

Results

I. Relationship between cardiac output and pulmonary shunt:

Fig. 2 shows the relationship between

(PATIENT)

M :Michenfelder('66)(O_2)
H :Hedley-Whyte('66)(O_2)
F :Fordham('68)(air)
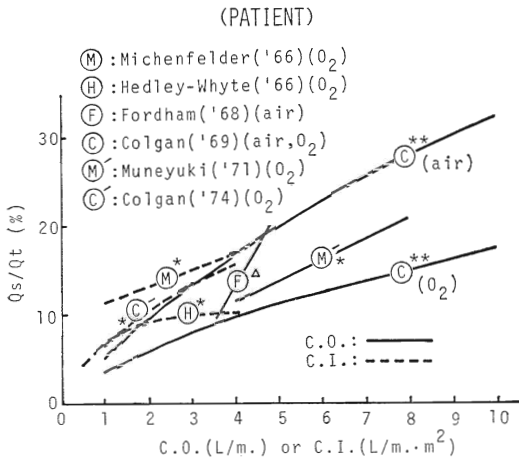C :Colgan('69)(air,O_2)
M' :Muneyuki('71)(O_2)
C' :Colgan('74)(O_2)

Fig. 2. Relationship between cardiac output and pulmonary shunt in patients. *(p <0.05) and **(p<0.01) show statistical significance of their correlations, and △ shows that significance could not be tested.
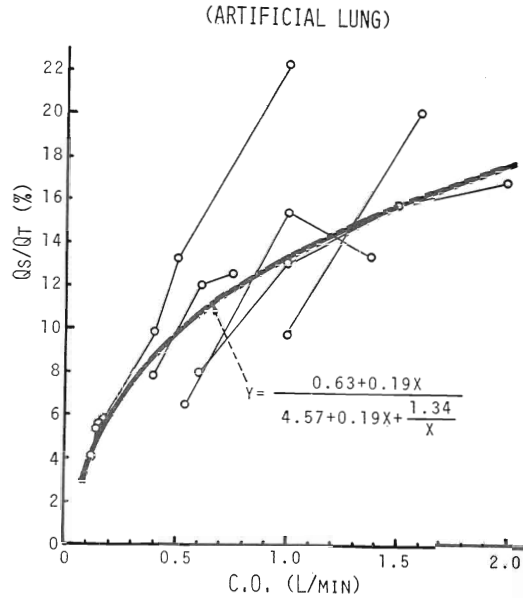
(DOG)

G :Gerst('59)(air)
K :Kaito('68)(O_2)
W :Watanabe('69)(air,O_2)
W' :Wahrenbrock('70)(O_2)
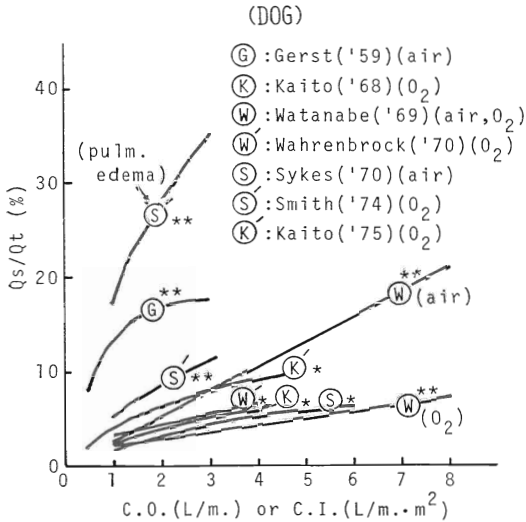S :Sykes('70)(air)
S' :Smith('74)(O_2)
K' :Kaito('75)(O_2)

Fig. 3. Relationship between cardiac output and pulmonary shunt in dogs. *(p< 0.05) and **(p<0.01) show the statistical significance.

cardiac output and pulmonary shunt measured in human patients. The curves (see appendix) and regression lines were obtained from statistical treatment of the data. Pulmonary shunt increased proportionally

(ARTIFICIAL LUNG)

$$Y = \frac{0.63 + 0.19X}{4.57 + 0.19X + \frac{1.34}{X}}$$

Fig. 4. Relationship between cardiac output and pulmonary shunt in artificial lung.

to cardiac output. Fig. 3 shows the relationship in dogs. This relationship in dogs is quite similar to that in human patients. Fig. 4 shows the relationship in artificial lung. Pulmonary shunt changed proportionally to cardiac output as in the living lungs of patients and dogs. In all cases (Figs. 2, 3, and 4), the change in pulmonary shunt to cardiac output was steeper in the range of lower cardiac output and became flatter with the increase in cardiac output.

II. Relationships between cardiac output and $\acute{c}$-aCO_2, $\acute{c}$-$\bar{v}CO_2$:

Pulmonary shunt is calculated with the shunt equation as follows:

$$\frac{Qs}{Qt} = \frac{C\acute{c}O_2 - CaO_2}{C\acute{c}O_2 - C\bar{v}O_2} = \frac{\acute{c}\text{-a}CO_2}{\acute{c}\text{-}\bar{v}CO_2}$$

(1)

Therefore, the magnitude of pulmonary shunt can be altered either by the change in $\acute{c}$-aCO_2 (numerator of the shunt equation) or $\acute{c}$-$\bar{v}CO_2$ (denominator). We analyzed the change in $\acute{c}$-aCO_2 and $\acute{c}$-$\bar{v}CO_2$ due to the
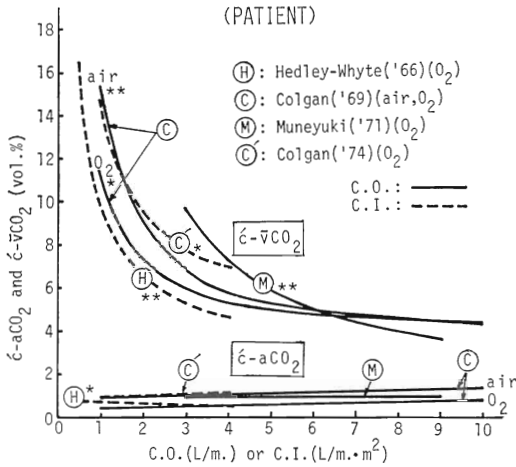
Fig. 5. Relationships between cardiac output and $\acute{c}-\bar{v}CO_2$, $\acute{c}-aCO_2$ in human patients. *($p<0.05$) and **($p<0.01$) show statistical significance.
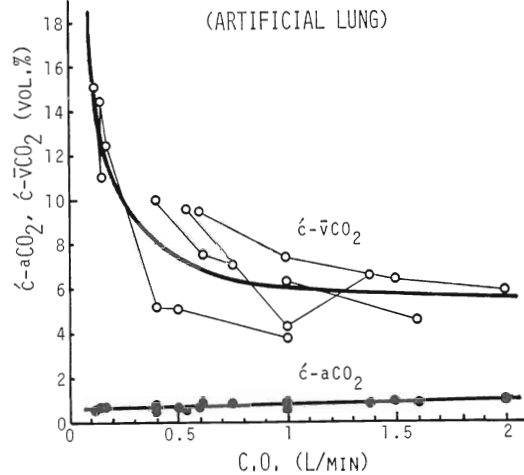

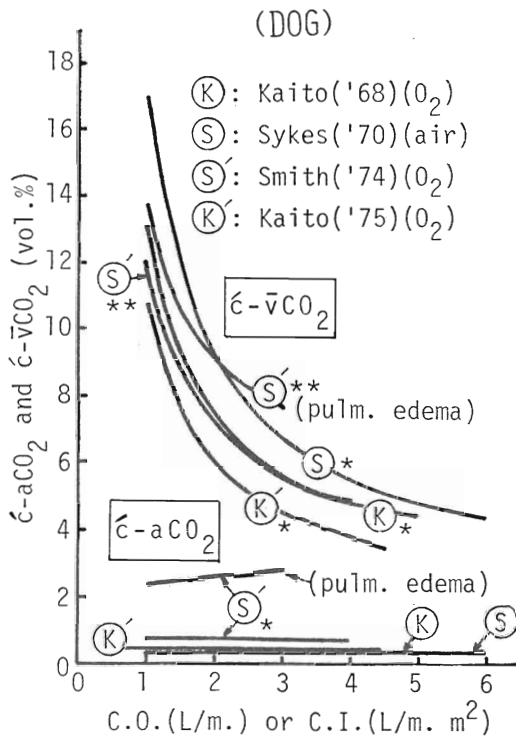Fig. 7. Relationship between cardiac output and $\acute{c}-\bar{v}CO_2$, $\acute{c}-aCO_2$ in artificial lung.

Fig. 6. Relationships between cardiac output and $\acute{c}-\bar{v}CO_2$, $\acute{c}-aCO_2$ in dogs. *($p<0.05$) and **($p<0.01$) show statistical significance.

change in cardiac output. Fig. 5 shows the relationship between cardiac output and $\acute{c}-aCO_2$, $\acute{c}-\bar{v}CO_2$ in human patients. When cardiac output changed, $\acute{c}-\bar{v}CO_2$ (denominator) changed remarkably drawing hyperbolic curve but $\acute{c}-aCO_2$ (numerator) showed only a very small change. Fig. 6 shows the relationship in dogs. Changes were similar as in human patients. Fig. 7 shows the relationship measured in artificial lung. This result was also quite similar as in the living lungs of patients and dogs.

III. Relationships between cardiac out- and $C\bar{v}O_2$, CaO_2:

It was clarified that the magnitude of pulmonary shunt was altered by the change in the denominator ($C\acute{c}O_2-C\bar{v}O_2$) of shunt equation when cardiac output changed. The denominator can be altered by the change in $C\acute{c}O_2$ or $C\bar{v}O_2$. Under the condition of the present study, the inspired oxygen concentration was constant (air or 100% O_2), so that $C\acute{c}O_2$ remained almost unchanged. Therefore, it is obvious that the change in $C\acute{c}O_2-C\bar{v}O_2$ was caused only by the change in $C\bar{v}O_2$.
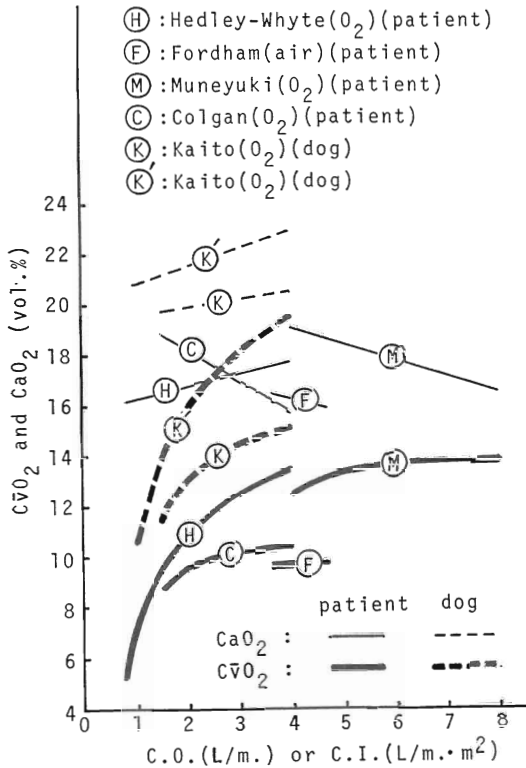
Fig. 8. Relationships between cardiac output and CaO_2, $C\bar{v}O_2$ in patients and dogs.

Fig. 9. Relationships between cardiac output and CaO_2, $C\bar{v}O_2$ in artificial lung.

Fig. 8 shows the relationships between cardiac output and $C\bar{v}O_2$, CaO_2 in human patients or dogs. $C\bar{v}O_2$ increased consistently according to the increase in cardiac output while CaO_2 increased in three cases (H, K, K') and decreased in other three cases (C, F, M). Fig. 9 shows the relationship in artificial lung. The change in $C\bar{v}O_2$ was remarkably large but CaO_2 showed only a slight decrease according to the increase in cardiac output. In both Figs. 8 and 9, the change in $C\bar{v}O_2$ was very steep in the range of lower cardiac output and became flatter as cardiac output increased.

IV. Summary of the results:

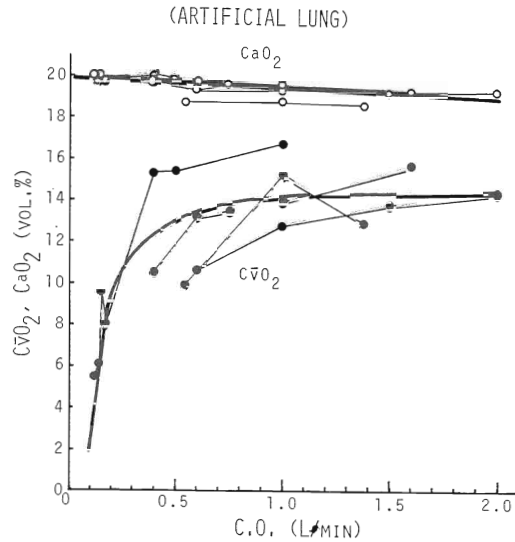In the living lungs of human patients and dogs, and also in the artificial lung, the change in cardiac output appeared first as a remarkable change in the mixed venous oxygen level, $C\bar{v}O_2$ (Figs. 8 and 9). This change in $C\bar{v}O_2$ resulted in the change in the denominator of the shunt equation ($C\dot{c}O_2$-$C\bar{v}O_2$) (Figs. 5 to 7), and this change in $C\dot{c}O_2$-$C\bar{v}O_2$ resulted in the change in pulmonary shunt (Figs. 2 to 4). Thus the following causal relationship can be obtained.

$$\text{C.O.}\uparrow—C\bar{v}O_2\uparrow—\dot{c}\text{-}\bar{v}CO_2\downarrow—Qs/Qt\uparrow \tag{2}$$

$$\text{C.O.}\downarrow—C\bar{v}O_2\downarrow—\dot{c}\text{-}\bar{v}CO_2\uparrow—Qs/Qt\downarrow \tag{3}$$

The change in pulmonary shunt was steeper in the range of lower cardiac output and became flatter with the increase in cardiac output. This change in pulmonary shunt (Figs. 2 to 4) corresponded well to the change in $C\bar{v}O_2$ (Figs. 8 and 9).

DISCUSSION

I. Mechanisms suggested by other investigators:

For explaining the cause of the change in pulmonary shunt due to cardiac output

several mechanisms have been suggested by many investigators. These mechanisms can be summarized as follows:

(1) Changes in cardiac output and/or mixed venous oxygen level cause vasoconstriction or vasodilatation at the non- or under-ventilated area in the lung, regionally and selectively, and redistribution of the pulmonary blood flow occurs.

(2) The transit time for the saturation of hemoglobin becomes insufficient as cardiac output increases.

The mechanism (1) was suggested to make the cause of change in pulmonary shunt consistent to the conventional "two-compartment model". As a proof of vasoconstriction or vasodilatation many investigators measured the total pulmonary vascular resistance. However, it seems impossible to find the regional vascular change in non- or under-ventilated area separately from the change in total pulmonary vascular resistance. Up to the present time, the pulmonary shunt and its change have always been interpreted by the "two-compartment model". This, therefore, has led all investigators to suggest such mechanisms as redistribution of pulmonary blood flow or alveolar collapse.

If the mechanism (2), transit time, is valid, increment in pulmonary shunt must become larger according with the increase in cardiac output, i.e., as the transit time becomes shorter. As seen in Figs. 2 to 4, the change in pulmonary shunt was rather steeper in the range of lower cardiac output and became flatter as the cardiac output increased. Therefore, the mechanism of transit time may be unlikely.

As a result, it can be said that the experimental proofs of the change in pulmonary shunt by cardiac output have not been obtained yet and thus all proposed mechanisms are merely conjectures.

II. Similarity of the data of artificial lung and those of living lungs:

Differing from the living lungs of human patients and dogs, the artificial lung (bubble-type oxygenator) has no alveoli or blood vessels. Therefore, the change in pulmonary shunt of the artificial lung cannot be attributed to the change in alveoli or blood vessels. In spite of such a difference between the artificial lung and the living lungs, the data of the artificial lung were quite similar to those of the living lungs as seen in Figs. 2 to 9. This means that there might be some common causes for the changes in pulmonary shunt in living lungs and artificial lung. We had an idea that true cause of the change in pulmonary shunt might be found by analysing the change in these common factors existing in both living lungs and artificial lung. We also thought that the change in pulmonary shunt of the living lungs might not be caused by the change in alveoli or pulmonary blood vessels but by the change in some other factors.

III. The role of hemoglobin in the oxygen transfer efficiency in the lung:

It was clarified that the change in pulmonary shunt (Figs. 2 to 4) was closely related to the change in $C\bar{v}O_2$ (Figs. 8 and 9). Here, $C\bar{v}O_2$ can be regarded as representing the "oxygen level of blood" returning to the lung. Therefore, the above close relationship between pulmonary shunt and $C\bar{v}O_2$ suggests that the oxygen level in the blood returning to the lung might alter the magnitude of pulmonary shunt.

Up to the present time, the following three factors have always been thought to be the cause of pulmonary shunt. They are (a) true shunt such as anatomical shunt or atelectasis, (b) V/Q inequality, and (c) diffusion impairment. These three factors have

been considered to represent the actual pathological situation in the lung and have been illustrated with the "two-compartment shunt model" for the purpose of simplifying the situation. The situation which is represented by the shunt model is called "venous admixture," and venous admixture has been thought to be one of the most important concepts in the oxygen transfer in the lung.

However, Nunn[16] stated that, "venous admixture is a convenient index of lung function but does not define the anatomical pathway of shunt, and also it will be clear that venous admixture reduces the overall efficiency of gas exchange". This is another important definition of pulmonary shunt which stresses the meaning as the efficiency of oxygen transfer in the lung.

It is well known that oxygen transfer from alveoli to blood is performed not by mere physical diffusion but by "physicochemical diffusing process" which is affected by the chemical reaction between hemoglobin and oxygen. Therefore, if the oxygen saturation of mixed venous blood is higher the amount of reduced hemoglobin (red·Hb) becomes less and then the increment in oxygen content, $\Delta(Hb·O_2)$, which blood can receive while it passes through the lung, becomes less:

$$(red·Hb)\downarrow + O_2 \rightarrow \Delta(Hb·O_2)\downarrow \qquad (4)$$
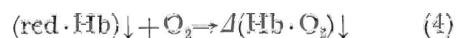
On the other hand, if the oxygen saturation of mixed venous blood becomes lower the increment in oxygen content of blood might become larger.

Baumberger[17] described this fact clearly as follows: "Since oxygen delivery rate increases as the blood is reduced, it may be assumed that O_2 is transferred more effectively when the un-oxygenated hemoglobin fraction is large."

It is, therefore, concluded that the common factor which affected the pulmonary shunt in both living lungs and artificial lung might be the change in the oxygen level in mixed venous blood due to the change in cardiac output because the change in the oxygen level in mixed venous blood altered the efficiency of oxygen transfer in the lung as Baumberger stated as above and thus the "inefficiency of oxygen transfer,"[18] i.e., pulmonary shunt, was altered.

IV. Mechanism of the change in pulmonary shunt due to cardiac output:

As a result of the above discussion, following mechanism is suggested;

When cardiac output increases the mixed venous oxygen saturation becomes higher and the amount of reduced hemoglobin, i.e., the "oxygen-receiving capacity of blood", is reduced. As the ventilatory condition is unchanged, the oxygen tension in the gas supplied from alveoli to blood does not change, and then the efficiency of oxygen transfer from alveoli to blood is reduced according to the decrease in the oxygen-receiving capacity of blood and, as a result, pulmonary shunt increases.

On the contrary, when cardiac output decreases, the mixed venous oxygen saturation is reduced and the oxygen-receiving capacity of blood is increased. This increase in oxygen-receiving capacity of blood facilitates the oxygen transfer from alveoli to blood and thus pulmonary shunt decreases.

V. Two major factors affecting the oxygen transfer efficiency in the lung:

Up to the present, it has been thought that the pulmonary shunt and its change are always caused by some changes in the lung, i.e., "intrapulmonary factors". However, as shown above, it has become evident that pulmonary shunt can be altered by the factors other than the lung function such as the oxygen-receiving capacity of the blood, i.e.,
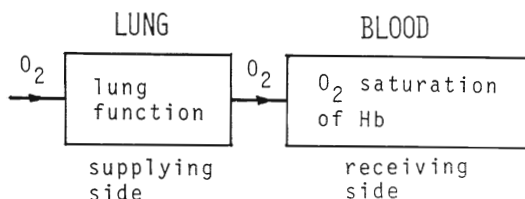
LUNG   BLOOD

Fig. 10. A model which shows two major factors
          affecting oxygen transfer efficiency in
          the lung.

"extrapulmonary factor". Fig. 10 shows the
two major factors affecting the oxygen trans-
fer efficiency in the lung. One of these
factors is the so-called "lung function" which
is a most important factor clinically. This is
a factor for the supplying side of oxygen.
Up to the present time, the pulmonary shunt
or its change has always been attributed to
this factor alone. Another factor is the
"oxygen-receiving capacity of blood" which
was proposed newly in this paper. This is
a factor for the receiving side of oxygen.
This factor has not been noted until now be-
cause pulmonary shunt has always been
interpreted by the two-compartment shunt
model and the qualitative contribution of
the chemical property of hemoglobin to the
oxygen transfer in the lung has always been
ignored.

This oxygen-receiving capacity of blood
affects the oxygen transfer efficiency from
alveoli to blood like the change in lung func-
tion, and therefore it can be regarded as "a
kind of shunt-like effect" due to the extra-
pulmonary factor. Although the effect of
oxygen-receiving capacity of blood is less
important clinically, it must not be ignored
because it relates to the change in pulmo-
nary shunt due to changes not only in cardi-
ac output but also in inspired oxygen con-
centration, body temperature, etc. (unpub-
lished observations).

Finally, as the increase in pulmonary
shunt due to cardiac output is not caused by
the impairment of the lung function but by
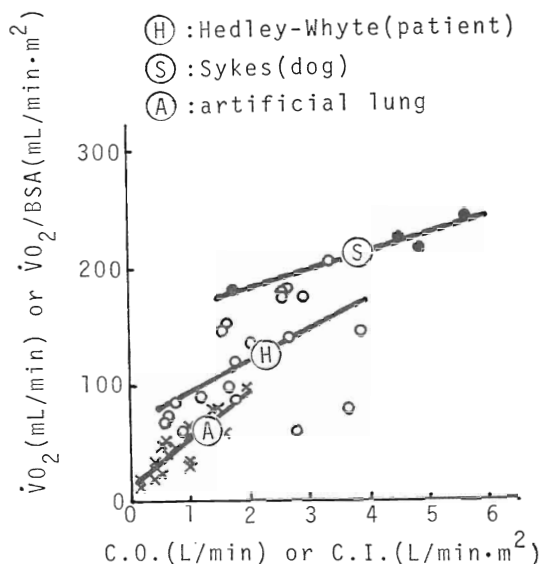

Fig. 11. Relationship between cardiac output
          and oxygen consumption in human
          patients, dogs, and artificial lung.

an extrapulmonary factor, it can be said that
this increase in pulmonary shunt due to
cardiac output is little worth the considera-
tion clinically.

Appendix

Derivation of experimental equations:

The curves shown in Figs. 2 to 9 were
drawn by using the experimental equations
which were derived as follows:

Oxygen consumption increased propor-
tionally according to the increase in cardiac
output in all cases of human patient, dog,
and artificial lung as shown in Fig. 11. From
this relationship, the following regression
line was obtained:

$$\dot{V}O_2 = A + (B \times C.O.) \qquad (5)$$

where A and B are constants.
Next, a-$\bar{v}$ oxygen content difference, a-$\bar{v}CO_2$
can be obtained by dividing $\dot{V}O_2$ by the
cardiac output.

$$a\text{-}\bar{v}CO_2 = \frac{\dot{V}O_2}{C.O.} = B + \frac{A}{C.O.} \qquad (6)$$
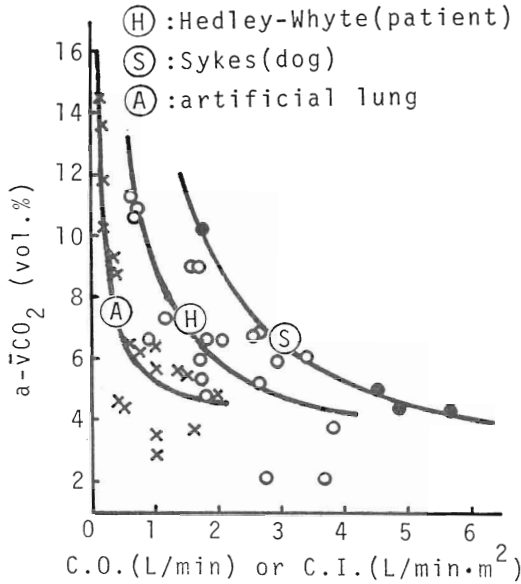
Fig. 12. Relationship between cardiac output and a–$\bar{v}CO_2$ in human patients, dogs, and artificial lung.

Fig. 12 shows this relationship between cardiac output and a-$\bar{v}CO_2$. As seen in Figs. 5 to 7, $\acute{c}$-aCO_2 (the numerator of the shunt equation) changed slightly linearly according to the change in cardiac output. Then, their relationship can be shown as follows:

$$\acute{c}\text{-a}CO_2 = C + (D \times \text{C.O.}) \qquad (7)$$

where C and D are constants.
The denominator of the shunt equation, $\acute{c}$-$\bar{v}CO_2$ can be obtained as the sum of $\acute{c}$-aCO_2 (Eq. 7) and a-$\bar{v}CO_2$ (Eq. 6),

$$\begin{aligned}
\acute{c}\text{-}\bar{v}CO_2 &= (\acute{c}\text{-a}CO_2) + (\text{a-}\bar{v}CO_2)\\
&= C + (D \times \text{C.O.}) + B + A/\text{C.O.}\\
&= (B + C) + (D \times \text{C.O.}) + A/\text{C.O.}
\end{aligned}$$
$$(8)$$

As a result, the relation of cardiac output to pulmonary shunt can be shown by the following experimental equation;

$$\begin{aligned}
\frac{Qs}{Qt} &= \frac{\acute{c}\text{-a}CO_2}{\acute{c}\text{-}\bar{v}CO_2}\\
&= \frac{C + (D \times \text{C.O.})}{(B + C) + (D \times \text{C.O.}) + A/\text{C.O.}}
\end{aligned}$$
$$(9)$$

The curves of pulmonary shunt shown in Figs. 2 to 4 were drawn by using this Eq. (9). These equations (5) to (9) are all experimental equations but they can be regarded as theoretical equations because they were derived from the physiological relationship shown in Fig. 11.

REFERENCES

1) Michenfelder, J. D., Fowler, W. S., and Theye, R. A.: CO₂ levels and pulmonary shunting in anesthetized man. J. Appl. Physiol., 21: 1471–1476, 1966.
2) Hedley-Whyte, J., Pontoppidan, M., and Morris, M. J.: The response of patients with respiratory failure and cardio-pulmonary disease to different levels of constant volume ventilation. J. Clin. Invest., 45: 1543–1554, 1966.
3) Fordham, R. M. M., and Resnekov, L.: Arterial hypoxemia, A side-effect of intravenous isoprenaline used after cardiac surgery. Thorax, 23: 19–23, 1968.
4) Colgan, F. J., and Mahoney, P. D.: The effects of major surgery on cardiac output and shunting. Anesthesiology, 31: 213–221, 1969.
5) Muneyuki, M., Urabe, N., Kato ,H., Shirai, K., Ueda, Y., and Inamoto, A.: The effects of catecholamines in arterial oxygen tension and pulmonary shunting during the post-operative period in man. Anesthesiology, 34: 356–364, 1971.
6) Colgan, F. J., Nichols, F. A., and Deweese, J. A.: Positive end-expiratory pressure, oxygen transport, and the low-output state. Anesth. Analg. (Cleveland), 53: 538–543, 1974.
7) Gerst, P. H., Rattenborg, C., and Holaday, D. A.: The effects of hemorrhage in pulmonary circulation and respiratory gas exchange. J. Clin. Invest., 38: 524–538, 1959.
8) Kaito, K.: Effect of cardiac output on the physiologic shunt during general anesthesia in dogs. Masui, 17: 849–859, 1968.
9) Yamamura, H., Kaito, K., Ikeda, K., Nakajima, M., and Okada, K.: The relationship between physiologic shunt and cardiac output in dogs under general anesthesia. Anesthesiology, 30: 406–413, 1969.
10) Watanabe, S.: The effect of the cardiac output on the pulmonary physiologic shunt ratio. Kokyu-to-Junkan, 17: 319–325, 1969.
11) Wahrenbrock, E. A., Carrico, C. J., Amundsen, D. A., Trummer, M. J., and Severinghaus, J. W.: Increased atelectatic pulmonary shunt

during hemorrhagic shock in dogs. J. Appl. Physiol., 29: 615–621, 1970.

12) Sykes, M. K., Adams, A. P., Finlay, W. E. I., Wightman, A. E., and Munroe, J. P.: The cardiorespiratory effects of hemorrhage and overtransfusion in dogs. Br. J. Anaesth., 42: 573–584, 1970.

13) Smith, G., Cheney, F. W. Jr., and Winter, P. M.: The effect of change in cardiac output on intrapulmonary shunting. Br. J. Anaesth., 46: 337–342, 1974.

14) Kaito, K., Yokoyama, M., Nakajima, M., Asahara, H., and Yamamura, H.: The effects of hemorrhagic shock on pulmonary circulation in

dogs. Rinshô Seiri, 5: 63–72, 1975.

15) Nunn, J. F.: "Applied Respiratory Physiology, with Special Reference to Anaethesia." 1st Ed. Butterworth, London, 1969, pp. 355.

16) Nunn, J. F.: "Applied Respiratory Physiology, with Special Reference to Anaesthesia." 1st Ed. Butterworth, London, 1969, pp. 243–255.

17) Baumberger, J. P., Leong, H. C., and Neville, J. R.: Oxygen delivery rate of human blood. J. Appl. Physiol., 23: 40–46, 1967.

18) Gray, T. C., and Nunn, J. F.: "General Anaesthesia." 3rd Ed. Butterworth, London, 1971, pp. 103 (Bendixen and Suwa).