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EFFECT OF UNILATERAL HYPOXIA ON THE DISTRIBUTION  
OF PULMONARY BLOOD FLOW IN MAN

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It is a well established fact that acute hypoxia gives rise to pulmonary arterial pressure rise in both experimental animals and human subjects. According to Aviado et al.<sup>1), 2), 3)</sup>, the pressure rise in acute hypoxia can be explained by pulmonary vasoreflex mediated through chemoreceptors as well as increased pulmonary blood flow produced by stimulation of carotid and aortic chemoreceptors and the heart itself.

On the other hand, Euler and Liljestrand<sup>4)</sup> suggested the presence of pulmonary vasoconstriction through which regional pulmonary blood flow is regulated. Nisel<sup>5), 6)</sup> confirmed the presence of pulmonary vascular local reflex where neither nervous nor neurohumoral factors are involved, demonstrating the pulmonary vascular pressor response to hypoxia with isolated perfusion of the animal lung.

In the present study, we attempted to show the presence of this local reflex caused by regional hypoxia in man, since this reflex is quite important in regulating pulmonary blood flow in various pathologic situations of the lung. We induced unilateral lung hypoxia on healthy volunteers using Carlens double lumen tube without causing severe systemic hypoxia to demonstrate local effect of hypoxia and observed blood flow shift using the lung scanning method.

## METHODS

The experimental procedures were carried out with 15 normal subjects on supine position breathing room air on the first experimental run (control stage).

After the subjects who showed no abnormalities of both roentgenological and cardiopulmonary functional examinations were given 150—200 $\mu$ c I<sup>131</sup> macro-aggregated serum albumin (I<sup>131</sup> MAA) intravenously, we performed scanning of the chest using a scintillation scanner (Shimazu)<sup>7)</sup>. In order to determine distribution ratio of pulmonary blood flow between right and left lungs, we measured gamma radiation of the injected I<sup>131</sup> MAA (density of scanning spots) on 6 pairs of spots located at the first to sixth intercostal space on bilateral midclavicular lines as shown in Figure 1, using one-inch porthole type photometer (Shimazu).

We set another day for the second experimental run for same subjects (experimental stage) more than one week after the first run where I<sup>131</sup> MAA injected could be expected to be excreted completely. After administration of 10 mg morphine and 0.3 mg atropine 30 min. prior to the study for premedication, we introduced a Carlens tube into the subject's trachea under local anesthesia spraying 4% Xylocaine into pharynx and trachea. Through the double lumen tube, each lung could breathe a different gas mixture i.e. 100% O<sub>2</sub> in one lung constantly (control side) and various gas mixtures on the other (experimental side). The gas mixtures were composed of 6 different hypoxic, normoxic and hyperoxic ones, i.e. 100% N<sub>2</sub>, 7.4%, 10.3% and 13.4% O<sub>2</sub> in N<sub>2</sub>, room air and 100% O<sub>2</sub>. We devised a tubing system so as to prevent rebreathing of the gas mixtures.

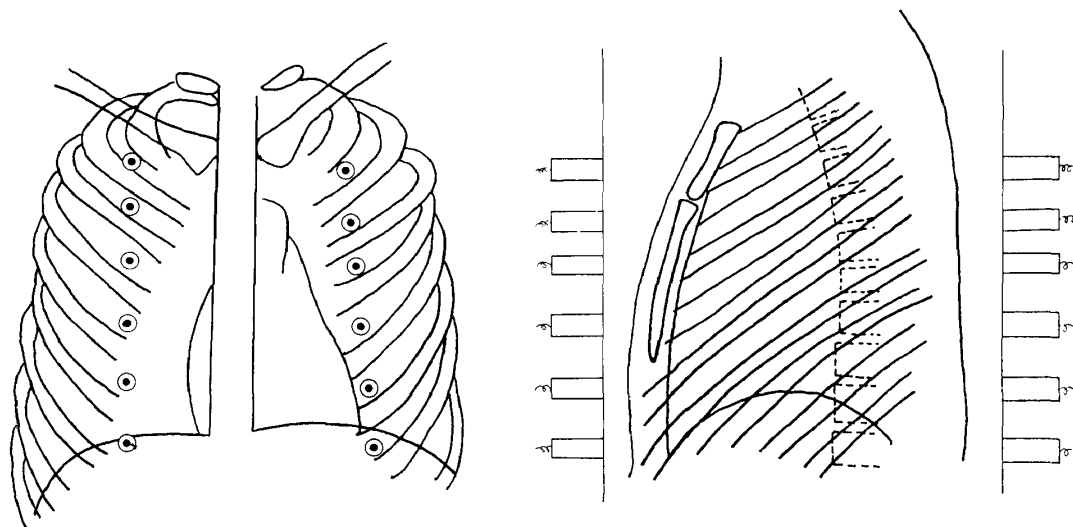


Fig. 1. Diagram illustrating the placing of the detector to measure the radioactivity of each lung from the lung scan.

For the purpose of determining the equilibration time for alveolar gas composition in each subject, we utilized a nitrogen washout curve obtained from the subject just before each run of study. We could keep all subjects in good relaxation throughout the whole study by application of enough local anesthetics. After completion of equilibration of the subject's alveolar gas with the gas mixture, we injected 150–200 $\mu$ c I<sup>131</sup> MAA intravenously.

We took the ratio of flow through one lung against total lung flow in a subject without divided ventilation as a control and calculated out the ratio of change (or per cent decrease) of the ration in the same subject with divided ventilation as follows:

$\%Q = \frac{Q}{Q_T} \times 100$ : Ratio of flow through experimental side of lung against total lung flow in control stage.

$\%Q' = \frac{Q'}{Q'_T} \times 100$ : Ratio of flow through experimental side of lung against total lung flow in experimental stage.

Where  $Q_T$  is total pulmonary blood flow in control stage estimated from total gamma radiation of injected I<sup>131</sup> MAA,  $Q$  is pulmonary blood flow through experimental side in control stage estimated from gamma radiation on that side,  $Q'_T$  is total blood flow in experimental stage estimated from total gamma radiation of I<sup>131</sup> MAA; and  $Q'$  is blood flow through experimental side in control stage estimated from gamma radiation on that side.

Ratio of change:  $\frac{\%Q'}{\%Q}$

Per cent decrease:  $\frac{\%Q - \%Q'}{\%Q} \times 100$

While the chest scanning was proceeding, we drew blood samples from the pulmonary artery through as intracardiac catheter and from femoral artery through a Cournand needle. We measured arterial, mixed venous and endtidal  $P_{O_2}$  and  $P_{CO_2}$  using I.L. meter, and the Rahn-Otis method was used for collection of endtidal gas sample. We also made a bronchospriometric observation such as ventilation, vital capacity and  $O_2$  uptake of each lung, using bellows type dual spirometer (Fukuda). For the assessment of validity of right to left ratio of ventilation, we always tried to compare this value with right to left ratio of  $O_2$  uptake.

## RESULTS

From the results shown in Fig. 2, it can be said that the 6th individual densities of each lung field on scan are in good accordance with the distribution of pulmonary blood flow in 10 normal subjects in supine position. The results could be explained by the fact that the evenness of flow is maintained quite well in normal

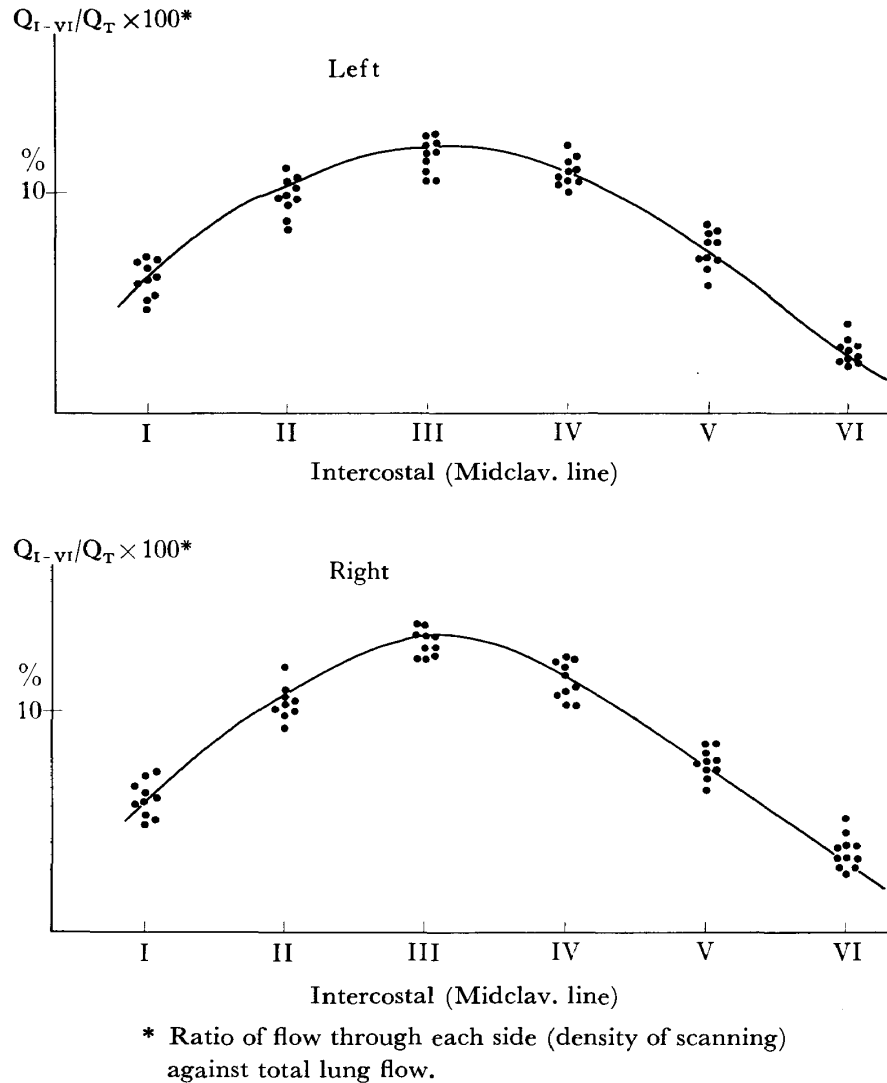


Fig. 2. Distribution of pulmonary blood flow in 10 normal cases.

subjects in supine position as Wagner, et al., suggested. The ratio of pulmonary blood flow between right and left lung was 55%: 45% which agrees with observations reported by other authors.

While the ratio of blood flow and that of vital capacity between right and left lung showed good accord in normal subjects, we could not find similar relationship

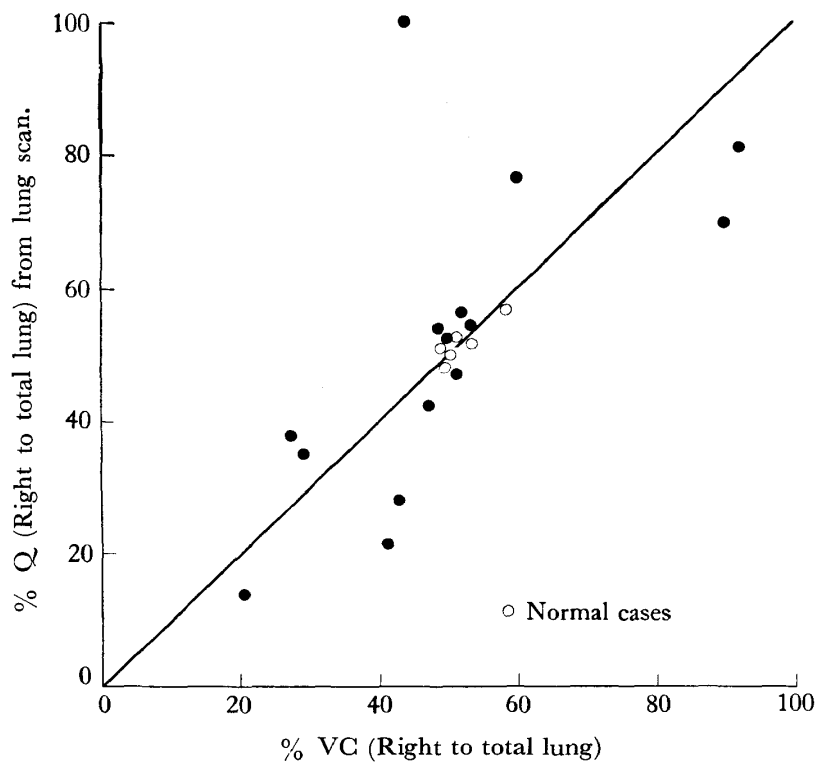


Fig. 3. Correlation between Q and VC.

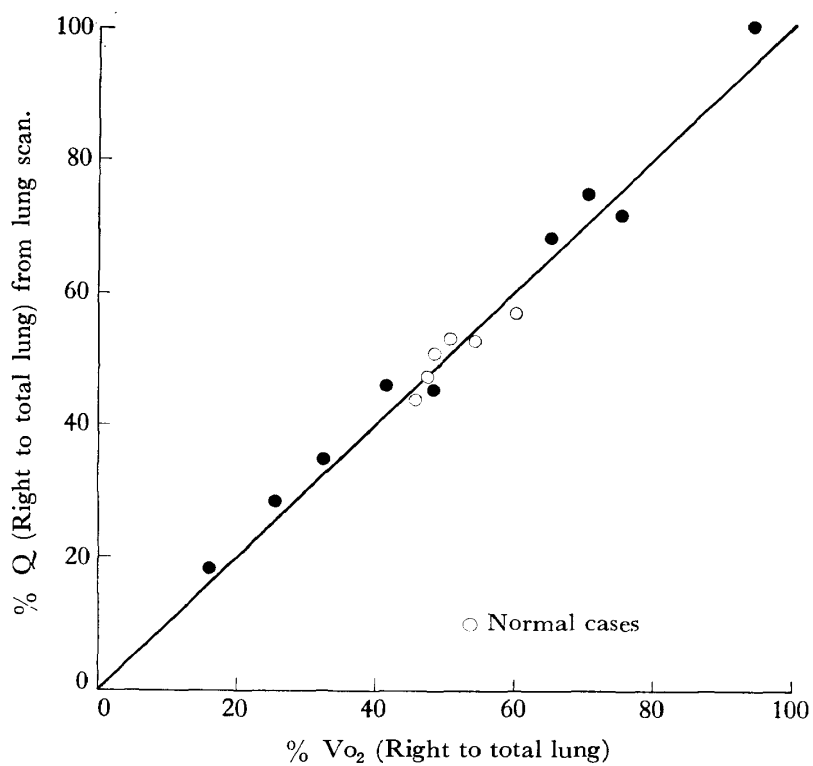


Fig. 4. Correlation between Q and Vo<sub>2</sub>.

in patients with various lung diseases such as pulmonary tuberculosis, obstructive emphysema, bronchiectasis and lung tumor, as shown in Fig. 3.

The results shown in Fig. 4 indicate again good correlation between right and left ratio of flow and O<sub>2</sub> uptake. In short, we could demonstrate that the proportions of pulmonary blood flow, vital capacity and O<sub>2</sub> uptake between right and left lung are identical in 10 normal subjects. In order to examine the effect of unilateral breathing of gas mixtures with various O<sub>2</sub> levels on the subjects while contralateral lung was breathing 100% O<sub>2</sub>, we measured Pa<sub>O<sub>2</sub></sub>, Pa<sub>CO<sub>2</sub></sub> and ventilation on each lung. Table 1 shows the results. Pa<sub>O<sub>2</sub></sub> showed over 100 mmHg even with extreme unilateral hypoxia, indicating that no severe systemic hypoxia occurred during experimental stage. Pa<sub>CO<sub>2</sub></sub> with normal range also indicate that neither

Table 1. Pa<sub>O<sub>2</sub></sub>, Pa<sub>CO<sub>2</sub></sub> and partition of ventilation (two lungs) during divided ventilation studies.

Exp. No.	Divided ventilation		Pa <sub>O<sub>2</sub></sub> (mm.Hg)	Pa <sub>CO<sub>2</sub></sub> (mm.Hg)	$\frac{\dot{V}_E}{\dot{V}_{E_T}} \times 100$ (%)
	Right	Left			
1	100% O <sub>2</sub>	100% N <sub>2</sub>	112	41	45% (Control) <sup>1)</sup> 44% (Experi.) <sup>2)</sup>
2	100% O <sub>2</sub>	100% N <sub>2</sub>	121	38	48% (Control) 48% (Experi.)
3	100% N <sub>2</sub>	100% O <sub>2</sub>	134	42	58% (Control) 59% (Experi.)
5	100% O <sub>2</sub>	7.4% O <sub>2</sub>	220	38	57% (Control) 58% (Experi.)
6	100% O <sub>2</sub>	7.4% O <sub>2</sub>	195	41	45% (Control) 43% (Experi.)
7	100% O <sub>2</sub>	10.3% O <sub>2</sub>	225	39	47% (Control) 47% (Experi.)
9	10.3% O <sub>2</sub>	100% O <sub>2</sub>	220	40	50% (Control) 53% (Experi.)
10	100% O <sub>2</sub>	13.4% O <sub>2</sub>	250	42	46% (Control) 45% (Experi.)
12	100% O <sub>2</sub>	Room air	232	42	50% (Control) 50% (Experi.)
15	100% O <sub>2</sub>	100% O <sub>2</sub>	580	41	49% (Control) 46% (Experi.)

- 1): Ratio of ventilation in experimental side of lung against total ventilation in control stage. (100% O<sub>2</sub> breathing to both lungs)  
2): Ratio of ventilation in experimental side of lung against total ventilation in experimental stage.

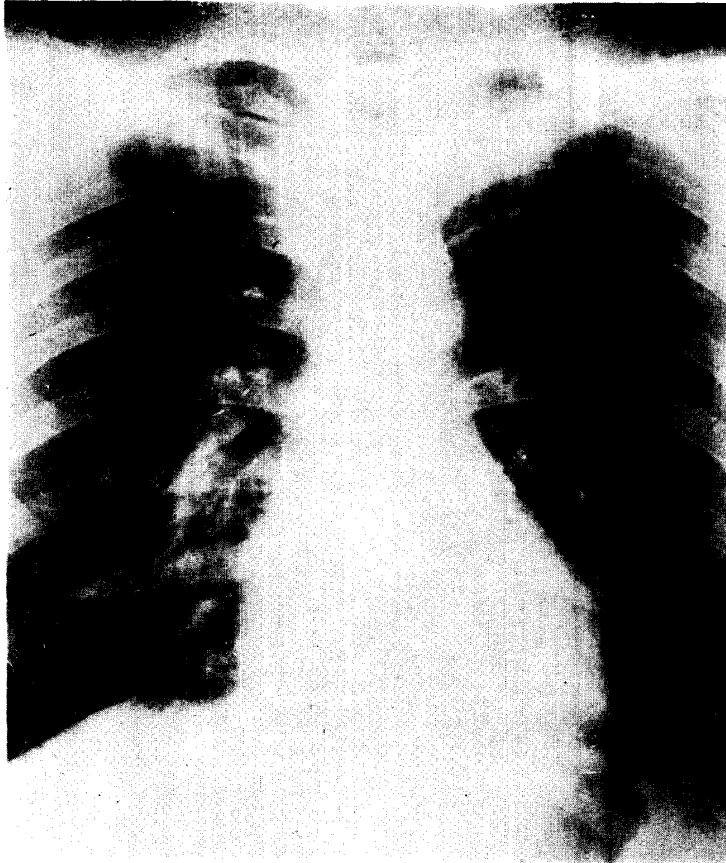


Fig. 5. Chest radiograph of subject No. 4.

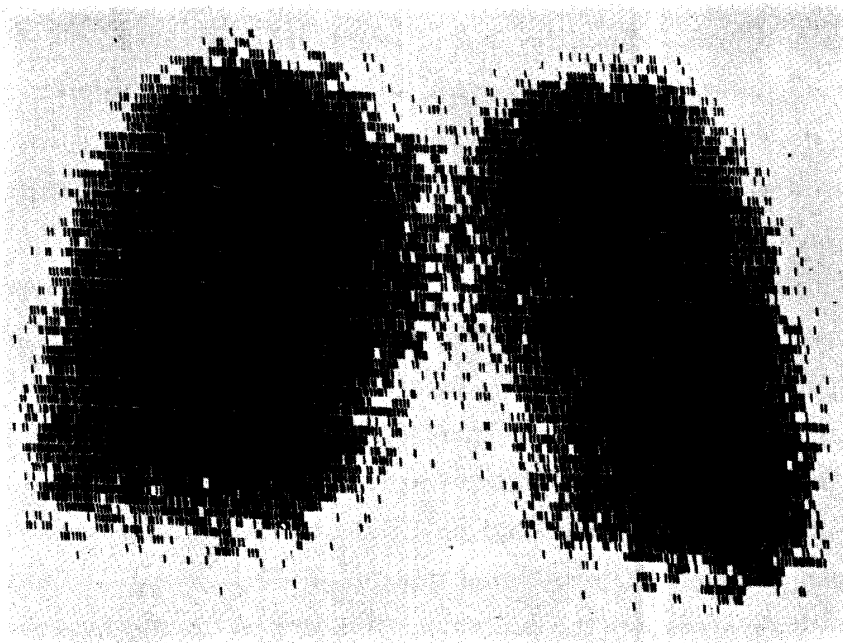


Fig. 6. Control lung scan of same subject during room air breathing.



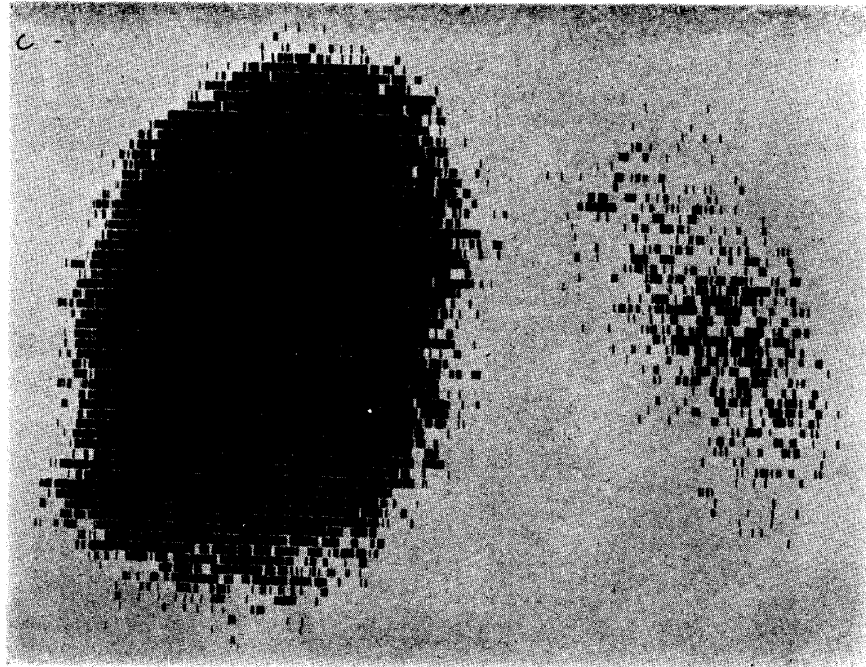


Fig. 7. Lung scan of same subject during unilateral hypoxia. (7.4% O<sub>2</sub> to the left lung).

hyperventilation nor hypoventilation occurred during experimental stage. No remarkable change in proportion of ventilation between the two lungs could be observed during experimental stage compared with control stage in all subjects.

Figures 5, 6 and 7 show the typical results from study of one subject. The chest roentgenogram and scan in control stage of this subject showed normal distribution of flow and aeration. Following unilateral hypoxia with 7.4% O<sub>2</sub> in left lung for the duration of 4'.30", the lung scan showed marked decrease in pulmonary blood flow on that side.

Table 2 shows the results obtained from a series of unilateral hypoxia studies performed on two experimental groups. Each group was composed of 3 subjects who breathed unilaterally 100% N<sub>2</sub> and 7.4% O<sub>2</sub> in N<sub>2</sub> respectively. Mean per cent decrease in pulmonary blood flow on hypoxic side calculated from the 6 results was 30. No essential difference was found between responses in two groups. However, we could not demonstrate flow reduction with mild unilateral hypoxia using hypoxic gas mixtures containing more than 10.3% O<sub>2</sub>. We also could not demonstrate an increase in the pulmonary blood flow to the hyperoxic lung, as shown in the same Table.

Table 2. Partition of pulmonary blood flow between the two lungs during the control and divided ventilation studies.

Exp. No.	Divided ventilation (Experimental stage)		Time of exposure (Min.)	$\frac{Q}{Q_T} \times 100$ (Control)*	$\frac{Q'}{Q_T} \times 100$ (Experi.)	$\frac{\%Q'}{\%Q} \left( \frac{\%Q - \%Q'}{\%Q} \times 100 \right)$
	Right	Left				
1	100% O <sub>2</sub>	100% N <sub>2</sub>	5.00	50%	36%	0.72 (28%)
2	100% O <sub>2</sub>	100% N <sub>2</sub>	4.30	47%	31%	0.67 (34%)
3	100% N <sub>2</sub>	100% O <sub>2</sub>	4.30	52%	36%	0.69 (31%)
4	100% O <sub>2</sub>	7.4% O <sub>2</sub>	4.30	48%	34%	0.71 (29%)
5	100% O <sub>2</sub>	7.4% O <sub>2</sub>	4.30	55%	40%	0.73 (27%)
6	7.4% O <sub>2</sub>	100% O <sub>2</sub>	5.00	45%	32%	0.71 (29%)
7	100% O <sub>2</sub>	10.3% O <sub>2</sub>	5.00	47%	51%	1.08
8	100% O <sub>2</sub>	10.3% O <sub>2</sub>	4.30	48%	46%	0.96
9	100% O <sub>2</sub>	10.3% O <sub>2</sub>	4.30	45%	44%	0.98
10	100% O <sub>2</sub>	13.4% O <sub>2</sub>	4.30	47%	48%	1.02
11	100% O <sub>2</sub>	13.4% O <sub>2</sub>	5.00	46%	46%	1.00
12	100% O <sub>2</sub>	Room air	4.30	44%	44%	1.00
13	Room air	100% O <sub>2</sub>	4.30	56%	56%	1.00
14	100% O <sub>2</sub>	100% O <sub>2</sub>	4.30	52% (Right)	52% (Right)	1.00
15	100% O <sub>2</sub>	100% O <sub>2</sub>	5.00	46% (Left)	45% (Left)	0.98

\* Room air breathing to both lungs.

Fig. 8 shows one of typical responses in hypoxic study where the flow reduction could be seen occurring evenly within the lung.

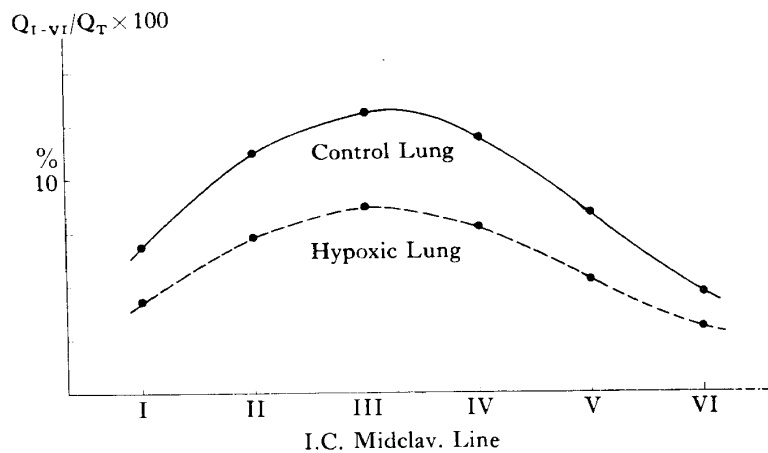


Fig. 8. Correlation between control lung scan and lung scan during unilateral hypoxia in 6 normal cases.

Fig. 9 shows findings obtained from right cardiac catheterization. There was no remarkable change in pulmonary arterial pressure throughout the whole study.

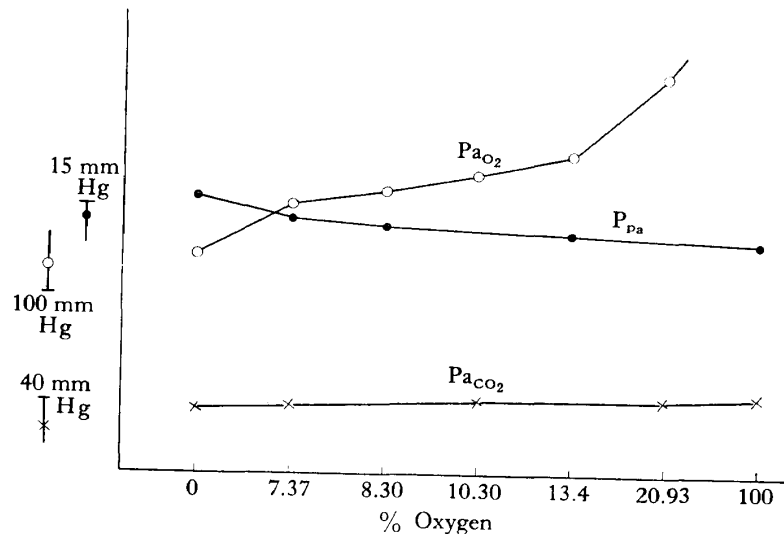


Fig. 9. Pulm. art. pressure, PaO<sub>2</sub>, PaCO<sub>2</sub>.  
during unilateral hypoxia.

## DISCUSSION

In order to detect the presence of local reflex regulating pulmonary circulation in acute hypoxia in man, we proposed to observe changes in distribution of pulmonary blood flow during unilateral hypoxia using lung scanning method by injecting I<sup>131</sup> MAA into normal subjects intravenously. The results showed the presence of a local reflex to hypoxic stimulus which gives rise to regional flow reduction without pulmonary arterial pressure rise.

As for the response to hypoxic stimulus of pulmonary vascular bed both in man and experimental animals, extensive studies have been carried out by a large number of workers. According to Fishman<sup>8)</sup>, change in pulmonary blood flow could not be demonstrated in unilateral hypoxic lung as far as flow distribution was measured based on the Fick principle. Himmelstein et al<sup>9)</sup>, Defares et al.<sup>10)</sup> and Blakemore et al.<sup>11)</sup> reported separately flow reduction in the human hypoxic lung. Peters et al.<sup>12)</sup> succeeded in showing the flow decrease with cat lung using Fick principle and estimated the decrease as approximately 40% 10 to 30 min. after breathing of hypoxic gas. This is comparable to average 30% decrease 4–5 min. after hypoxic gas breathing in our study.

It is probable that the decrease in pulmonary blood flow is the result of pulmonary vasoconstriction. As for the site of constriction, Nisell<sup>5), 6), 7)</sup> suggested

venous side of the pulmonary vascular bed and postulated dilatation of arterial side. On the other hand, Duke<sup>14)-16)</sup> emphasized the role of pulmonary capillary and small pulmonary vein in the constrictive response.

In previous studies<sup>22)</sup> we made a series of observations using guinea pigs. We ventilated each lung of the animal separately, rapidly froze the lungs using liquid nitrogen<sup>17)</sup> and observed the pulmonary vascular bed morphometrically. The results showed marked constriction mainly of small pulmonary artery with 100–200 $\mu$  diameter accompanying terminal bronchiole. No evidence of constriction was found of capillary or pulmonary vein.

The flow shift that we observed in the present study is considered due to this regional vasoconstriction. One of remarkable findings we obtained in the present study is that no flow shift occurred with hypoxic gas mixtures containing more than 10% O<sub>2</sub>, suggesting that no constrictive response occurred where P<sub>A</sub>O<sub>2</sub> (alveolar O<sub>2</sub> tension) was higher than P<sub>v</sub>O<sub>2</sub> (mixed venous O<sub>2</sub> tension). This led us to conceive

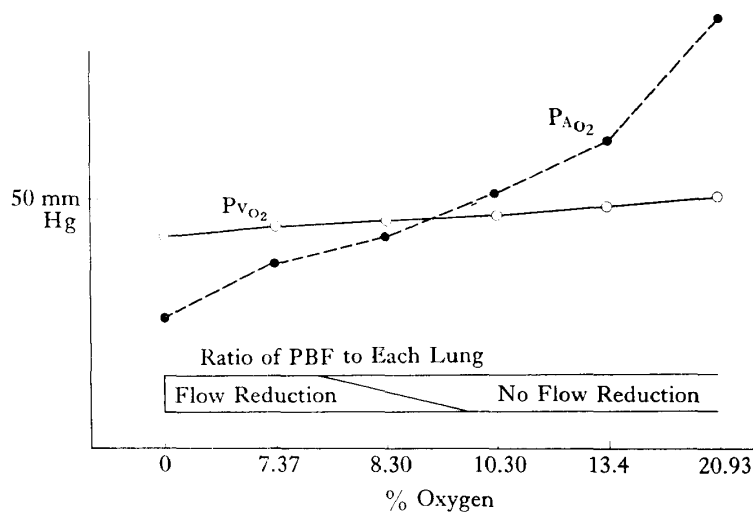


Fig. 10. Alveolar O<sub>2</sub> tension, mixed venous O<sub>2</sub> tension, during unilateral hypoxia.

that P<sub>v</sub>O<sub>2</sub> always plays a dominant role in hypoxic constrictive response, where P<sub>A</sub>O<sub>2</sub> is higher than P<sub>v</sub>O<sub>2</sub>, Bergofsky et al.<sup>18), 19)</sup> suggested that P<sub>v</sub>O<sub>2</sub> could affect pulmonary arterial pressure response. We could also demonstrate in a previous study<sup>22)</sup> pulmonary arterial constriction of one lobe perfused with hypoxic blood in the guinea pig. However, as far as the present study is concerned, constrictive response seems to occur only when P<sub>A</sub>O<sub>2</sub> is lower than P<sub>v</sub>O<sub>2</sub> as shown in Fig. 10.

Therefore, the mechanisms by which the hypoxic constrictive response occurred in the present study could be explained by direct diffusion of hypoxic alveolar gas into small pulmonary arterial wall as Staub and Jameson<sup>20), 21)</sup> suggested.

### SUMMARY

1) We induced unilateral pulmonary hypoxia in human subjects by means of divided ventilation using Carlens tube. Decrease in pulmonary blood flow in hypoxic lung was demonstrated by lung scanning method using  $I^{131}$  MAA.

2) The response occurred without accompanying systemic hypoxia or pulmonary arterial pressure rise.

3) The response occurred only when  $PA_{O_2}$  is lower than  $Pv_{O_2}$ .

4) The flow reduction is the result of pulmonary blood flow shift from hypoxic to hyperoxic lung area due to regional vasoconstriction in hypoxic lung area.

### ACKNOWLEDGEMENTS

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