REGIONAL LUNG FUNCTION IN PULMONARY HYPERTENSION

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Utilizing 133-xenon gas and a scintillation camera, we examined the distributional relation between ventilation (V) and perfusion (Q) in patients with pulmonary hypertension (PH) comprising mitral stenosis (MS) and left to right shunt disease (shunt). In the case of MS, Q decreased at the dependent part of lung in proportion to the degree of PH, but preserved normal V and resulted in high V/Q value at this region, which was estimated to cause the physiological dead space effect on the gas exchange function. In the case of shunt disease, even with a high degree of PH, reduction of Q at the dependent lung region was not observed with normal preservation of V, thus obviating any type of the V/Q imbalance. Since the washout of xenon gas by resting tidal volume ventilation was observed to be delayed from the dependent lung region, latent ventilatory impairment in this region due to small airway closure at tidal breathing was also suspected.

In order that the gas exchange units of the lung may remain persistently dry without a flooding of blood content, the pulmonary circulatory system should be in a low pressure state. Furthermore, this system is also designed to be housed in a negative pressure box, the thorax, which implements in and out ventilation, towards subatmospheric pressure, so as to obviate the collapse of the vessels of this low pressure system during these respiratory fluctuations. It is well known that the lung, so designed as a low-negative pressure system is necessarily under the effect of gravity due to the hydrostatic pressure of blood and the lung itself, causing a predilection for the dependent distribution of blood flow and ventilation at a normal state. On this basis, the hypertensive state of the pulmonary vascular system might axiomatically cause a disturbance of these distribution dominated by gravity, and precipitate a crisis of drowning, pulmonary edema, predominantly at the dependent region to be in a preparatory state for respiratory failure. Conventional spirographic test and blood gas findings, however, have often failed to demonstrate an expected respiratory failure consistent with this probable state of about to drown.

Since current availability of a scintillation camera and a computer, offers more detailed quantitative assessment of the regional lung function than ever as in a form of the functional

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imaging it appears worth while to examine the nature of the distributional change of the ventilation as well as the perfusion and the consequent ventilation/perfusion imbalance in patients with pulmonary hypertension using this facility and to correlate this distributional disturbance with physiological change.

**SUBJECTS AND METHOD**

Nine patients with or without pulmonary hypertension were studied. Four had a variety of disorders with an intracardiac left to right shunt disease and the remaining five had mitral stenosis. Two of those four with the shunt disease who underwent cardiac catheterization revealed a pulmonary hypertension and all showed a high flow state at the pulmonary vascular bed averaging 11.32 ± 2.87 L/min. One of the five with mitral stenosis proved not to have definite pulmonary hypertension and all cases showed a low flow state averaging 3.01 ± 0.74 L/min of the cardiac output. In all patients with shunt disease, a spirometric evaluation of pulmonary function and arterial blood gas findings revealed normal range, whereas, in some patients with mitral stenosis, we observed a slight or moderate decrease of maximum breathing capacity (MBC) which averaged 66 ± 10%, a slight reduction of Pco2 which averaged 35 ± 2 mm Hg, and an averaged pH of 7.43 ± 0.03, without any appreciable abnormalities in other determinations. (Table I).

A patient is in a sitting position with a scintillation camera viewing the entire field of bilateral lung from the back using a diverging collimator. Approximately 10 mCi of 133-xenon gas were given to the patient in a single inspiration from the level of the functional residual capacity (FRC) to the level of tidal volume (TV), which could be attained by inhaling about 500 ml of air containing the tracer gas in a rubber bag attached to a mouth-piece. While the patient held his breath, the ventilation distribution (V) of the camera recording was obtained. After rebreathing the gas within the closed circuit of a spirometer, the equilibrated distribution in the lung was considered to represent the volume distribution (V) of the lung. Seated in the same position, approximately 5 mCi of 133-xenon solution was injected intravenously and the initial distribution in the lung represented the perfusion distribution (Q) while holding breath. By breathing at a resting tidal ventilation out of the closed circuit,
the integrated activity of this washout process (A) was recorded and the disappearance rate constant (λ)\(^{16,18}\) which represents the regional ventilation rate was calculated.

Upon processing these images with each other, point by point, in the form of 40 x 40 digitized words matrix by a digital computer\(^{17,18}\) the ventilation per unit volume (V/V), the perfusion distribution per unit volume (Q/V) and the ratio of the ventilation to perfusion (V/Q) were processed to depict an isocontour image with ten levels as shown in the Fig. 1. In addition, image of the ventilation rate (λ) was derived from the ratio of the initial distribution Q to the subsequent integration of the washout process (Q/A), according to the height-over-area method proposed by Zierler\(^{18,19}\). Fig. 1 exemplifies these processed images of a normal subject in a sitting position. Five healthy subjects aged 21–24 without a history of tobacco smoking in a sitting position were selected for normal controls. Those subjects were averaged in the form of normalized value, with standard deviation in a vertical direction\(^{17}\). Namely, two or three arrays of the elemental matrix of horizontal slice at each unilateral lung region were lumped as a percentage value for the total amount of activities in the lung region. Elemental matrix corresponds to a square with a side of approximately one centimeter. Normalized values at the each slice of the patient with the pulmonary hypertension were plotted equidistantly from the base to the apex of the lung, as shown in Fig. 4 & 5, in order that a comparison with normal range could be made.

At each region with given range of V/Q ratio, normalized values of ventilation distribution V and perfusion distribution Q were numerated to obtain the fractional distribution of V or Q for each level of V/Q ratio, as shown in Figs 6 & 7. Using these quantitative relations of V versus V/Q and V versus Q, an estimated loss of gas exchange function was calculated by the computer. The computer processing consisted of a searching program along the V\(_{A}/Q\(_{S}\) line on the O\(_{2}\) – CO\(_{2}\) diagram\(^{20}\) and a program simulating a blood gas dissociation curve proposed by Kelman\(^{21,22}\). In seven cases, the cardiac output using the external counting method\(^{23}\) as well as the minute ventilation using the spirometer were
determined to give an absolute value for the \( V/Q \) ratio. Input of these values into the computer program, made possible the calculation of estimated A-aDO\(_2\) and A-aDCO\(_2\) as an index of gas exchange function.

RESULTS

Figs. 2 & 3 show two typical images. The former was case 6, a patient with mitral stenosis. In this case, the perfusion distribution (\( Q \)) shifted upwards, whereas the ventilation distribution (\( V \)) preserved a normal gravitated pattern, so that the dependent part of the lung showed a high value \( V/Q \) ratio, constituting a so-called physiological dead space effect. Fig. 3 represents case 2, a patient with ventricular septal defect. In this case, the perfusion distribution (\( Q \)) was homogenous without the effect of gravity as was clearly seen in the \( Q/V \) image, whereas the ventilation distribution (\( V \)) was observed to be a normal gravitated pattern, so that the \( V/Q \) images revealed a rather homogenous distribution.

In Figs. 4 and 5, all cases were plotted in the form of the vertical distribution from the base of the lung to the apex. The shaded range indicates the normal range of standard deviation. Bar lines in Fig. 4 indicates distribution in the right lung of case 6 shown in Fig. 2, whereas the same lines in Fig. 5 indicates distribution in the right lung of case 2.

Concerning the shunt group with high pulmonary blood flow, as shown in Fig. 4, the ventilation per unit volume revealed a rather normal gravitated pattern, whereas the perfusion per unit volume (\( Q/V \)) revealed the loss of gravity effect with a homogeneous distribution from the apex to the bottom of the lung, even with high degree of pulmonary hypertension of case 2 as indicated by the bar line. Consistent with this observation, in some patients the \( V/Q \) became homogeneous distribution with a slight tendency to constitute the physiological dead space effect at the base of lung. The regional ventilation rate (\( \lambda \)) derived from the washout disappearance rate
constant, however, showed an appreciable reduction at the dependent part of lung. This tendency was exaggerated when a high degree of pulmonary hypertension was present such as in case 2.

Concerning the group with mitral stenosis characterized by low flow with pulmonary hypertension, as is shown in Fig. 5, a normal preservation of V/Q was observed, whereas the upwards shift of Q/V was observed to be a characteristic feature. Consistent with this observation between ventilation and perfusion, an inverted distribution of V/Q was observed, suggesting the presence of the dead space effect at the base of the lung. Regarding the ventilation rate (\( \lambda \)), the downwards decrease was also noted to be more prominent than that observed in the shunt group.

As shown in Figs. 6 and 7, the quantitative relations between the spatial distribution of \( V \) or \( Q \) for ordinate and a specific level of V/Q in logarithmic scale for abscissa were examined, in order to estimate a consequent loss of gas exchange function in the lung. In these figures, dotted distributions represent ones approximated from the five normal controls. These distribution curves were approximated by a log-normal distribution function with slight dissociation between V versus V/Q and Q versus V/Q. This dissociation was calculated according to the computer program to result in the presence of A-aDO\(_2\) for 11.6 mmHg and A-aAD\(_{CO_2}\) for 0.6 mmHg, assuming that the overall ventilation/perfusion ratio is 0.85. Four cases with shunt were averaged for the minute ventilation to be 8.87 ± 1.14 L/min and for the perfusion to be 9.33 ± 0.93 L/min, whereas three cases with mitral stenosis were averaged for the ventilation to be 7.77 ± 0.81 L/min and for the perfusion to be 3.02 ± 0.14 L/min. Owing to this absolute dissociation between the ventilation and the perfusion in the group of mitral stenosis, distribution curves in Fig. 7 shifted towards the right side at a higher value of V/Q ratio, whereas those in the shunt group as shown in Fig. 6 did not show such a shift. These tendencies resulted in a high setting of arterial and expiratory gas PO\(_2\) (128 mmHg) and a low setting of the same of PCO\(_2\) (28 mmHg) to be estimated in the group.

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Fig. 4. Normalized distributions in a vertical direction in cases with left to right intracardiac shunt diseases.

Fig. 5. Normalized distributions in a vertical direction in cases with mitral stenosis.
Fig. 6. Distributions for $\dot{V}$ (upper panel) and $\dot{Q}$ (lower panel) at specific level of $V/Q$ ratio (Abscissa in a logarithmic scale) in cases of left to right shunt. Estimated partial gas pressure of overall expiratory output and arterial output are shown at each panel.

Fig. 7. Distributions for $\dot{V}$ and $\dot{Q}$ at specific level of $V/Q$ ratio and estimated partial gas pressure in the cases of mitral stenosis.
with mitral stenosis (Fig. 7); and normal setting of those of $P_{O_2}$ (105 mmHg) and $P_{CO_2}$ (39 mmHg) in the shunt group (Fig. 6), as one might except on the $O_2 - CO_2$ diagram. Concerning the dissociation between the V versus V/Q and Q versus V/Q curves which indicates V/Q imbalance, the former curves of the mitral stenosis dissociated more towards a high level of V/Q value and resulted in a significant magnification of a-AD$_{CO_2}$ (4 mmHg) as shown in Fig. 7; whereas in respect to the shunt in Fig. 6, Q versus V/Q curve was slightly deviated towards the lower value of the V/Q value, resulting in a moderate magnification of the A-aDO$_2$ (22 mmHg). These values were calculated on the computer program using averaged distribution curves as indicated by the shaded zones in Figs. 6 & 7, respectively.

In summary, the ventilation/perfusion imbalance may occur on two occasions; one being the overall V/Q imbalance which is seen in mitral stenosis with hyperventilation despite of a low flow; the other the regional V/Q imbalance seen also in this group and attributed to the wasted ventilation at the dependent part of lung. Such might explain the tendency of respiratory alcalosis seen in the mitral stenosis. Neither of these particular imbalances were observed to exist in the shunt group.

DISCUSSION

While the prime function of the lung is undoubtedly gas exchange, which depends on the relative distribution of ventilation and perfusion in the lung, the advent of a radioactive gas and an external detecting probe have proved this concept for the first time at a level of clinical medicine in a form of topographical mismatch between these distributions$^{4,5,13}$ However, since these distributions were averaged within several of detecting field of probe, range of this mismatch was likely to be an underestimate of the actual degree of ventilation-perfusion imbalance$^{24}$ Current availability of a scintillation camera together with digital storage and processing systems offers further possibilities to handle more detailed topographical information concerning the ventilation-perfusion relation$^{15,16}$ At present, however, most of clinical studies with this fascility have merely portrayed these distribution independently, localizing subjectively of regional mismatch between them to assume abnormal gas exchange function of the lung$^{25,26}$ We examined resolution capabilities with this facility in order to deduce the effect of regional ventilation-perfusion mismatch on the gas exchange function in the lung by comparing the result deduced from the actual blood gas data, and reasonable correlations were found if topographical relation between ventilation and perfusion was not so complex$^{17}$ As has been shown in this report, the ventilation-perfusion imbalance in the case with pulmonary hypertension appeared rather straightforward, as simply related with the distributional change of the gravity effect, present type of approach to investigate the regional lung function in pulmonary hypertension seems to be quite pertinent. The limit of spatial resolution and loss of detectability in a direction of depth might still obscure composite imbalance of a million of respiratory units in this type of presentation. However, despite these limitation, this presentation do provide a substantial measure of physiological concept by making the regional lung function more easily understood.

The inversion of the normal gravitated pattern of pulmonary blood flow was observed only in the case of mitral stenosis, where the pulmonary venous hypertension with a low flow is characteristic. On the contrary, patients with the left to right shunt, which is characteristic of a high pulmonary blood flow with an occasional pulmonary hypertension were seen to be free from this inverted distribution. The gravity effect on the pulmonary vascular bed has been explained on the basis of the relation between pulmonary arterial, alveolar and venous pressure as predicted from the influence of the hydrostatic gradient of the blood itself on the low pressure characteristics of the lung$^1$ Using an isolated dog lung where these three variables could be controlled, West et al. clearly reproduced the basal flow reduction due to perivascular edema in the presence of high venous pressure with a low arterial-venous pressure difference, however, a high arterial-venous pressure difference with an increasing flow eliminated this basal flow reduction$^5$ This animal flow model might simulate the different flow distribution between the case with the MS and the shunt of the present investigation.

In addition to the effect of these variables on the flow distribution, recent investigations$^{14,27,28}$ have suggested that the reduction of lung volume could also fascilitate the reduction of flow at dependent part of the lung with perivascular edema. Such has been explained to be a loss

of tethering effect of lung expansion on extraalveolar vessels so as to decrease their transmural pressure and reduced flow. The effect of perivascular edema on pulmonary vascular resistance are only apparent below a certain lung volume. Hence, it is probable that a relatively high lung volume may obscure changes associated with edema. In this connection, the present results, that the image obtained from equilibrated radioxenon did not indicate any appreciable loss of volume in the dependent lung region associated with wasted ventilation on the state of hyperventilation, might indicate the compensational mechanism to prevent further progression of the lung edema. Thus, the recent suggestion of a J-receptor seems plausible. These receptors are in a position to detect excess water in the perivascular space in cases of pulmonary edema, and to stimulate increased ventilatory activity which, in turn, promotes the removal of excess water from the lung via the lymphatics.

Since abnormal distribution of pulmonary blood flow in pulmonary hypertension is considered to be caused either by interstitial edema or decreased volume expansion in the lung, it is presumed that an airway in the lung is affected. In a prepared lung experiment where edema was induced, Iff et al. observed that the ventilation distribution by slow inspiration of a bolus of 133-xenon decreased in the dependent edematous lung, where little effect was noted in the case of rapid inspiration. According to Otis the distribution of tidal volume between two units in a parallel depends upon their time constants (Compliance × Resistance). For slow inspiration, the distribution of gas will depend largely on the compliance of different regions, whereas for a fast inspiration the distribution will in theory be resistance dominated. The more even distribution will in theory be resistance dominated. The more even distribution of the fast inspiration may be due to an earlier opening of the small airway, previously closed at lower lung volume at the base of lung, by the greater transpulmonary pressure required for the fast inspiration. The different patterns between V/V and λ distributions in our present series may be attributable to different manner of these inspirations. The V/V distribution represents the one dominated by resistance and the λ by compliance. Hence it is assumed that interstitial edema present in our patients did not significantly alter the total airway resistance of the edematous region, but, probably by closure of small airway, caues a reduction in ventilation to these regions during resting tidal ventilation. In vivo investigations using dogs substantiated that raising left arterial pressure resulted in increased small airway resistance mainly due to competition for space between arteries and small airways in the bronchovascular sheath followed by interstitial and alveolar edema. In this connection, we already substantiated that same type of the washout delay at dependent lung region under the normal V/V distribution were noted in elderly cases with smoking habits in whom increased "closing volume" were suspected.

The xenon gas, as a relatively insoluble innert gas, may be retained much in the dependent lung region with lower V/Q ratio and less in the upper lung region with higher V/Q ratio according to theoretical suggestion of Farhi. Hence elimination of this gas must be delayed thus to result much decreased value of the ventilation rate λ than those estimated by the single inhalation method, the V/V distribution. However, the present measurement underwent on an instant introduction of the radioxenon into pulmonary circulation, instead of steady state introduction, the recognizable retention of this gas at V/Q region due to recirculating radioxenon does not seems to be probable.

At any rate, this problem of the innert gas elimination with different solubility, the Ostward partition coefficient for that gas, is essential for accurate determination of ventilation-perfusion ratio, as proposed by other investigators. However, as a routine clinical test these methods is appeared to be tedious and impractical. Recent progress of nuclear medicine both in the field of instrumentation and radiopharmaceutical, such as construction of three dimensional imaging as well as on site use of variety of radioactive gas with an ultrashort half-life, might solve such defects as presented in this paper, namely, the non-invasive visualization of the ventilation-perfusion mismatch and be sure to satisfy the demand of severe respiratory physiologist.

In conclusion, regarding the ventilation-perfusion imbalance using present method it is said, that notable impairment of gas exchange function may not yet have occurred, at least to the extent where it was comparable to the case of hepatic cirrhosis, but could be compared to the case of myocardial infarction. Before coming to an overt respiratory failure, the pulmonary hypertension is counteracted by the concomitant impairment of blood flow, so as
not to cause the physiological shunt effect on blood gas oxygenation, but rather a physiological dead space effect. Together with the hyperventilation, the latter effect, appears more advantageous to promote fluid exchange in an edematous lung.

In summary, since the pulmonary vascular bed is characteristic with low pressure system housed in a subatmospheric environment, pressure disturbance such as pulmonary hypertension might sensitively be expressed in the form of distributional disturbance against gravity related to ventilation-perfusion imbalance. This approach would enable insight into the latent state of respiratory failure which is otherwise left undetermined, on the level of non-invasive clinical test.

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