Effect of local pulmonary blood flow control on gas exchange: theory

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GRANT, BRYDON J. B. *Effect of local pulmonary blood flow control on gas exchange: theory.* J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 53(5): 1100–1109, 1982.—The effect of local pulmonary blood flow control by local alveolar O_2 tension on steady-state pulmonary gas exchange is analyzed with techniques derived from control theory. In a single homogeneous lung unit with normal inspired and mixed venous blood gas composition, the homeostatic effect on local ventilation-perfusion ratios ($\dot{V}_A/\dot{Q}$) regulation occurs over a restricted range of $\dot{V}_A/\dot{Q}$. The homeostatic effect is maximal at a moderately low $\dot{V}_A/\dot{Q}$ (about 0.4) due to the slope of the O_2 dissociation curve. In a multicompartment lung with a lognormal distribution of $\dot{V}_A/\dot{Q}$, regulation of arterial O_2 tension varies with the extent of inhomogeneity. At mild degrees of inhomogeneity where local pulmonary blood flow ($\dot{Q}$) control acts predominantly on the lower $\dot{V}_A/\dot{Q}$ of the $\dot{Q}$ distribution, the regulatory effect is best. At severe degrees of inhomogeneity where local $\dot{Q}$ control acts mainly on the higher $\dot{V}_A/\dot{Q}$ of the $\dot{Q}$ distribution, the regulatory effect is worse, and positive-feedback behavior may occur. Local $\dot{Q}$ control has the potential of reducing the deleterious effects of lung disease on pulmonary gas exchange particularly when it operates in association with other regulatory mechanisms.

hypoxic pulmonary vasoconstriction; control theory; ventilation-perfusion ratio; parallel inhomogeneity

IT IS NOW THOUGHT that obstructive lung disease primarily affects small lung units and impairs gas exchange by increasing the dispersion of ventilation-perfusion ratios ($\dot{V}_A/\dot{Q}$). Von Euler and Liljestrand (3) have suggested that there is a local vascular response to alveolar gas tensions, and they have proposed that this response may reduce the extent of $\dot{V}_A/\dot{Q}$ mismatch. More recently, we confirmed experimentally that local alveolar O_2 tension ($P_{A_{O_2}}$) affects blood flow to small lung units that were less than 1% of the lung (6). Although we showed that local pulmonary blood flow ($\dot{Q}$) control by local $P_{A_{O_2}}$ can be considered as a mechanism controlling local $\dot{V}_A/\dot{Q}$, the effect of this controlling mechanism on gas exchange in a dispersion of $\dot{V}_A/\dot{Q}$ has not been analyzed.

This report describes a theoretical analysis of the conditions that influence the effect of local blood flow control on gas exchange in homogeneous lung units and in the inhomogeneous lung. The analysis proceeds in the following manner. First, it is shown that the ability of hypoxic pulmonary vasoconstriction to control the $\dot{V}_A/\dot{Q}$ of single lung units is maximal in units with moderately low $\dot{V}_A/\dot{Q}$. Since this finding is of importance for understanding the effect of local $\dot{Q}$ control in the presence of $\dot{V}_A/\dot{Q}$ mismatch, the reasons for this phenomenon are analyzed in detail. Second, the effect of inhomogeneity on the ability of hypoxic pulmonary vasoconstriction to control arterial O_2 tension ($P_{a_{O_2}}$) in response to changes of overall ventilation or the distribution of ventilation by causing a redistribution of $\dot{Q}$ is estimated in a multicompartment lung with mixed venous blood gas composition held constant. Third, the efficiency of hypoxic pulmonary vasoconstriction at controlling both arterial and mixed venous blood gas tensions to changes of ventilation distribution is analyzed under more realistic conditions with overall O_2 uptake ($\dot{V}_{O_2}$) and CO_2 output ($\dot{V}_{CO_2}$) held constant. In addition, I estimate the changes of the blood gas tensions that occur when the lung is subjected to increasing levels of $\dot{V}_A/\dot{Q}$ inequality in the absence and presence of local $\dot{Q}$ control and control of overall ventilation and of cardiac output. Some of these findings have been reported elsewhere in brief (4, 5).

METHODS

Local blood flow control is considered as a negative-feedback system that operates within each homogeneous lung compartment. Figure 1 shows a block diagram of the system. The controller represents the active effect of local $P_{A_{O_2}}$ changes on local $\dot{Q}$. The magnitude of this effect can only be determined by experiment. The controlled process represents the passive effect of local $\dot{Q}$ changes on local $P_{A_{O_2}}$. The magnitude of this effect can be determined from the steady-state gas exchange relationships. The disturbing input to the feedback system is a change of alveolar ventilation ($\dot{V}_A$), and the output (or controlled variable) is the local $\dot{V}_A/\dot{Q}$. The choice of local $\dot{V}_A/\dot{Q}$ as the controlled variable is arbitrary but reasonable because it is the local $\dot{V}_A/\dot{Q}$ that directly determines the local alveolar and end-capillary gas tensions. In a lung with many compartments, each feedback loop operates within each compartment. Therefore, in a multicompartment lung, the effect of local blood flow control on gas exchange is the resultant action of a multiloop system.

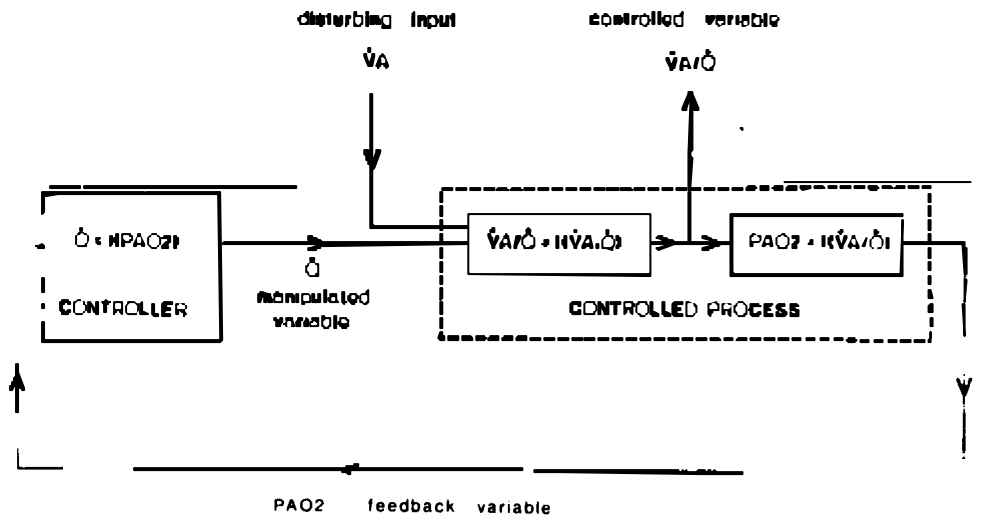

FIG. 1. A block diagram of feedback loop operating in a single homogeneous lung compartment. A change of local alveolar ventilation ($\dot{V}_A$) is disturbing input. For example, a fall of local $\dot{V}_A$ decreases the ventilation-perfusion ratios ($\dot{V}_A/\dot{Q}$) that in turn decrease alveolar O_2 tension ($P_{A_{O_2}}$) (feedback variable). A decrease of $P_{A_{O_2}}$ provokes a decrease of pulmonary blood flow ($\dot{Q}$) (manipulated variable). This decrease causes the $\dot{V}_A/\dot{Q}$ to return toward its initial value. System acts as a negative-feedback loop. Controller describes local $\dot{Q}$ response to $P_{A_{O_2}}$; controlled process describes how a change of $\dot{Q}$ alters $\dot{V}_A/\dot{Q}$ and in turn $P_{A_{O_2}}$.

Assessment of Local Blood Flow Control on Pulmonary Gas Exchange

To assess the effect of a feedback loop, the usual technique is to compare the result of stressing the system when feedback is operating (closed loop) with the result of stressing the system when feedback is not operating (open loop). Control theory has utilized both these results and expresses the results as a single number: open-loop gain (OLG). OLG can be calculated from the negative product of the first derivatives of the steady-state relationships around the feedback loop (12). For a single lung unit, the equation is as follows.

$$\mathrm{OLG} = -\frac{d\dot{Q}}{dP_{A_{O_2}}} \cdot \frac{\partial(\dot{V}_A/\dot{Q})}{\partial\dot{Q}} \cdot \frac{\partial P_{A_{O_2}}}{\partial(\dot{V}_A/\dot{Q})} \qquad (1)$$

Since the derivatives $\partial(\dot{V}_A/\dot{Q})/\partial\dot{Q}$ and $\partial P_{A_{O_2}}/\partial(\dot{V}_A/\dot{Q})$ are both obtained from the controlled process, their product can be expressed as $\partial P_{A_{O_2}}/\partial\dot{Q}$. Therefore, *Eq. 1* becomes

$$\mathrm{OLG} = -\frac{d\dot{Q}}{dP_{A_{O_2}}} \cdot \frac{\partial P_{A_{O_2}}}{\partial\dot{Q}} \qquad (2)$$

OLG is not defined further in this text because its use is limited to estimating the homeostatic ability of a single feedback loop.

As long as the system is stressed by small changes of the disturbing input, OLG can be used to assess a nonlinear feedback system (8). Large changes of the disturbing input in a nonlinear system would alter the values of the derivatives. Therefore, the estimated value of OLG only applies to small changes of disturbing input about a given set of initial conditions, i.e., the particular values of inspired and mixed venous blood gas compositions and $\dot{V}_A/\dot{Q}$ from which the system is perturbed by disturbing input.

OLG cannot be used to describe the behavior of a multiloop system such as a multicompartment lung that has a distribution of $\dot{V}_A/\dot{Q}$. In this circumstance, the disturbing input may be a change of overall $\dot{V}_A$ or the distribution of $\dot{V}_A$. The gas exchange variable of interest is not the overall $\dot{V}_A/\dot{Q}$ but the blood gas tensions, since these values depend not only on the overall $\dot{V}_A/\dot{Q}$ but also on the distribution of $\dot{V}_A/\dot{Q}$ that may be modified by local $\dot{Q}$ control. To overcome this problem, Riggs (8) developed a more general expression, gain due to feedback (Gfb).

$$\mathrm{Gfb} = \pm[(dy/dx)_{\mathrm{open}}/(dy/dx)_{\mathrm{closed}} - 1 \qquad (3)$$

where Gfb is a dimensionless ratio greater or equal to zero, y is the controlled variable, and x is the disturbing input. The subscript open refers to open-loop conditions when the effect of local Pa_{O_2} on local $\dot{Q}$ is excluded. The subscript closed refers to closed-loop conditions when the effect of the active mechanism is included. Gfb is calculated so that its sign is always positive. Gfb is identical to OLG when Gfb is used to calculate the effectiveness of a single feedback loop (see APPENDIX).

An alternative expression of feedback behavior is the ratio of derivatives (RD_x).

$$RD_x = (dy/dx)_{\mathrm{closed}}/(dy/dx)_{\mathrm{open}} \qquad (4)$$

This ratio gives the extent to which feedback has modified the change of the output variable for a given disturbing input. When RD_x is unity, there is no effective feedback. Values of RD_x between unity and zero indicate negative feedback. RD_x of zero indicates perfect homeostasis because a change of the output variable that occurs in response to a disturbance is completely avoided by the effect of feedback. Values of RD_x greater than unity indicate positive feedback and the extent to which feedback has magnified the change of the output variable for a given disturbing input.

The advantages of expressing the effect of feedback control in terms of Gfb is that Gfb increases numerically with increasing effect of feedback. The advantage of expressing the effect of feedback control in terms of RD_x is that RD_x provides a measure of the extent that feedback control has modified the response of the system to a disturbance. Although it is apparent from *Eqs. 3* and *4* that Gfb and RD_x are closely related to each other, both forms have advantages. Therefore, I have elected to present results in terms of Gfb and RD_x.

Calculation of Results

All results are calculated under steady-state conditions. Because of the interdependence of the O_2 and CO_2 dissociation curves, it is necessary to use a computer program to calculate most of the results obtained in this study. The major portion of this program comprises of subroutines developed by West and Wagner (10). Their report gives listings of these subroutines and explains how they can be used to estimate gas exchange variables in a single lung unit and in a multicompartment lung with a lognormal distribution of $\dot{V}_A/\dot{Q}$. In view of this detailed publication, this report describes only how their programs are utilized for this study. These subroutines can be used in three ways. First, given values of inspired and mixed venous blood gas composition, the alveolar and end-capillary blood gas tensions can be determined in a single lung unit of any given $\dot{V}_A/\dot{Q}$. Second, a lung with multiple compartments in a parallel arrangement of ventilation and perfusion can be used with each compartment having a different $\dot{V}_A/\dot{Q}$. The dispersion of $\dot{V}_A/\dot{Q}$ has a lognormal distribution. By increasing the lognormal standard deviation (σ), the degree of $\dot{V}_A/\dot{Q}$ mismatch is increased. With constant values of inspired and mixed venous blood gas composition, the alveolar and end-capillary blood gas composition for each compartment is calculated. From the blood flow weighted mean of end-capillary blood gas contents of the compartments, mixed arterial blood gas composition can be determined. Since mixed venous blood gas composition is constant, increasing degrees of $\dot{V}_A/\dot{Q}$ inequality impairs both $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ under these conditions. Third, the mixed venous blood gas composition is adjusted to maintain $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ constant regardless of the degree of inhomogeneity in the multicompartment lung.

In all calculations, the following parameters are held constant. The inspired gas is always air, barometric pressure is 760 Torr, body temperature is 37°C, hemoglobin concentration is 14.8 g/100 ml, hematocrit is 45%, O_2 half-saturation pressure (P_{50}) is 26.8 Torr, and there is no metabolic acid-base abnormality.

To express the effect of feedback in terms of Gfb and RD_∞ it is necessary to evaluate derivatives. An algebraic approach is always preferable to a numerical method. The algebraic method is possible to an extent for the single lung unit, but it is impractical in the multicompartment lung.

Single lung unit. Since Gfb of a negative-feedback loop is identical with OLG, Gfb for a single lung unit is calculated from *Eq. 2*. Algebraic methods can be used to evaluate $d\dot{Q}/dP_{A_{O_2}}$ because the controller can be defined by a simple equation (Fig. 2*A*). However, a numerical method of differentiation is required to calculate $\partial P_{A_{O_2}}/\partial\dot{Q}$. This calculation is achieved in the following manner. First, a computer program is set up from subroutines similar to those described by West and Wagner (10) that are capable of determining the alveolar gas tensions at a particular $\dot{V}_A/\dot{Q}$, the $P_{A_{O_2}}$ is calculated, and $\dot{Q}$ is considered to be unity. $\dot{Q}$ is increased and then decreased from its initial value by 10%. On both occasions, the $\dot{V}_A/\dot{Q}$ is altered and the corresponding values of $P_{A_{O_2}}$ are found. With the three pairs of values for the independent variable $\dot{Q}$ and the dependent variable $P_{A_{O_2}}$, a second-degree Lagrangian polynomial can be calculated. The derivative of the polynomial can be estimated at the initial $\dot{V}_A/\dot{Q}$ by using a standard library subroutine (SSP Library, DDGT 3). $d\dot{Q}/dP_{A_{O_2}}$ is calculated algebraically from equations describing local $\dot{Q}$ changes with local $P_{A_{O_2}}$. For each set of initial conditions, $d\dot{Q}/dP_{A_{O_2}}$ is calculated in terms of fractional changes of $\dot{Q}$ at the calculated $P_{A_{O_2}}$ for that particular $\dot{V}_A/\dot{Q}$.

Multicompartment lung. For the multicompartment lung, there is a choice of disturbing inputs and controlled variables to be considered, as mentioned earlier. Furthermore, Gfb can no longer be considered to be identical to OLG. Therefore, *Eqs. 3* and *4* are used to calculate Gfb and RD_∞, respectively. For simplicity, the mixed venous blood gas composition is held constant and only

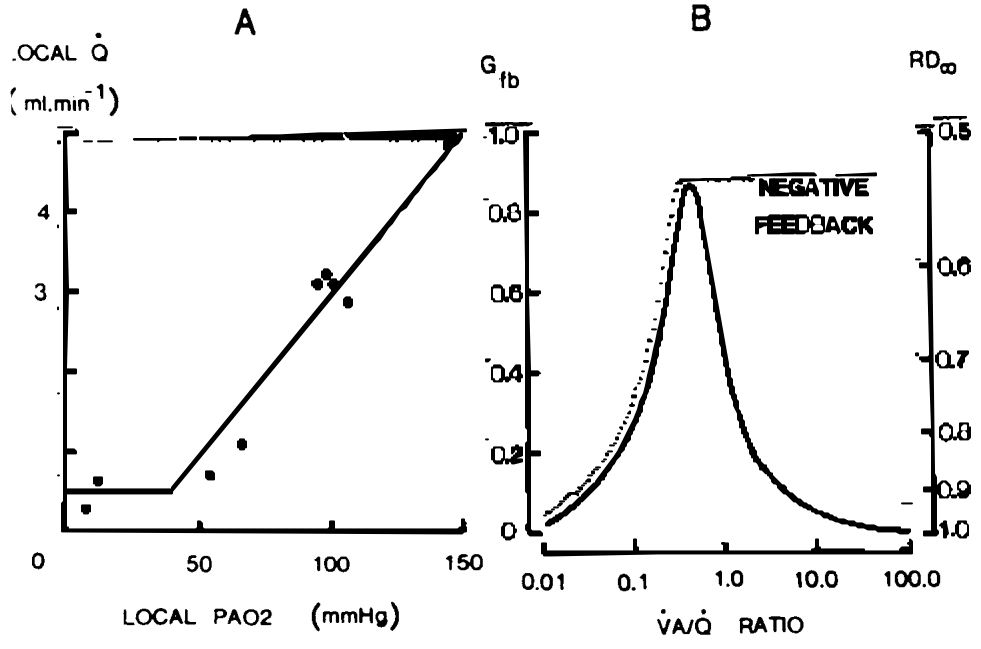

FIG. 2. *A*: local blood flow ($\dot{Q}$, ml·min^{-1}, *ordinate*) response curve to changes of local alveolar O_2 tension ($P_{A_{O_2}}$, Torr, *abscissa*) based on experimental results (6). Data points (*solid circles*) were approximated by 2 linear relationships: $\dot{Q}$ = 0.5 ml·min^{-1} for $P_{A_{O_2}}$ less than 40 Torr and $\dot{Q}$ = 0.04091·$P_{A_{O_2}}$ − 1.1364 for $P_{A_{O_2}}$ between 40 and 150 Torr. *B*: regulatory effect of local $\dot{Q}$ control on local ventilation-perfusion ratios ($\dot{V}_A/\dot{Q}$). Regulatory effect is expressed as gain due to feedback (Gfb on *left-hand ordinate*) with corresponding values of ratio of derivatives (RD_∞ on *right-hand ordinates*) at different $\dot{V}_A/\dot{Q}$ (*abscissa*, on log scale) in a single homogeneous lung unit (Gfb and RD_∞ are dimensionless ratios). Inspired gas was air. Mixed venous blood gas tensions were 41 and 46 Torr for O_2 and CO_2, respectively.

one controlled variable is examined, Pa_{O_2}, to compare the effect of using changes of overall ventilation as the disturbing input with the effect of using changes of the distribution of ventilation as the disturbing input.

To calculate the open-loop derivatives, the computer program is set up with subroutines described by West and Wagner (10) for a multicompartment lung with a hundred compartments. Input parameters are specified as mentioned above, and overall $\dot{V}_A/\dot{Q}$ is set at 0.85 (overall $\dot{V}_A$ of 5.1 and overall $\dot{Q}$ of 6 $l \cdot min^{-1}$) and a given degree of $\dot{V}_A/\dot{Q}$ inequality specified by the lognormal standard deviation of ventilation distribution (σ). The resulting values of Pa_{O_2}, arterial CO_2 tension (Pa_{CO_2}), $\dot{V}o_2$, and $\dot{V}co_2$ are then calculated. The value of Pa_{O_2} and the disturbing input (either $\dot{V}_A$ or σ) is then stored. The disturbing input is then increased by 10%, and the gas exchange variables are recalculated. The new values of Pa_{O_2} and the disturbing input are stored. This procedure is then repeated with a 10% decrease of the disturbing input from its initial value. Therefore, three pairs of values of the dependent variable, Pa_{O_2}, and the independent variable either $\dot{V}_A$ or σ are obtained and the open-loop derivative can be obtained by numerical differentiation of the interpolating second-degree Lagrangian polynomial using the subroutine already mentioned.

To calculate the closed-loop derivatives, the program is modified to incorporate local $\dot{Q}$ control. In each compartment, local $\dot{Q}$ is varied with changes of local $P_{A_{O_2}}$ induced by changes of the disturbing input. Local $\dot{Q}$ is altered by local $P_{A_{O_2}}$ in proportion to the changes of local $\dot{Q}$ defined by the local $\dot{Q}$ response curve (Fig. 2*A*). This change of local $\dot{Q}$ alters the $\dot{V}_A/\dot{Q}$ of each compartment and, in turn, alters the local $P_{A_{O_2}}$. Therefore, local $\dot{Q}$ must be readjusted according to the local $\dot{Q}$ response curve. This procedure is repeated until successive values of $P_{A_{O_2}}$ in each compartment vary by less than 0.5%. With this modification of the program, the closed-loop derivatives can be calculated in a manner similar to the open-loop derivatives as described in the preceding paragraph. Gfb and RD_∞ for regulation of Pa_{O_2} are calculated from the open- and closed-loop derivations of $dPa_{O_2}/d\dot{V}_A$ where overall ventilation is disturbing input and from the open- and closed-loop derivatives of $dP_{A_{O_2}}/d\sigma$ where the distribution of ventilation is the disturbing input. Each result is obtained at various degrees of inhomogeneity ranging from σ of 0.001 to 4.0. Because the compartmental blood flows vary with the compartmental $P_{A_{O_2}}$, overall $\dot{Q}$ will alter under closed-loop conditions when the disturbing input deviates from its initial value. To isolate the extent of Pa_{O_2} regulation due to alterations of the distribution of blood flow rather than changes in overall $\dot{Q}$, overall $\dot{Q}$ can be constrained at its initial value by rescaling the compartmental blood flows. Therefore, regulation of Pa_{O_2} is evaluated at different levels of inhomogeneity under four circumstances: with overall ventilation as the disturbing input with and without constraining overall $\dot{Q}$, and with the distribution of ventilation as the disturbing input with and without constraining overall $\dot{Q}$.

A more realistic approach with the multicompartment lung is to maintain $\dot{V}co_2$ and $\dot{V}o_2$ constant at 240 and 300 $ml \cdot min^{-1}$, respectively, by allowing mixed venous blood gas composition to vary. The output variables the program calculates are Pa_{O_2}, Pa_{CO_2}, and mixed venous O_2 and CO_2 tension ($P\bar{v}_{O_2}$ and $P\bar{v}_{CO_2}$, respectively). Under these conditions Gfb and RD_∞ for Pa_{O_2}, Pa_{CO_2}, $P\bar{v}_{O_2}$, and $P\bar{v}_{CO_2}$ are evaluated with just one disturbing input, changes of the distribution of ventilation, with overall $\dot{Q}$ constrained at its initial value at 6 $l \cdot min^{-1}$. I used techniques similar to those that were used to evaluate regulation of Pa_{O_2} with mixed venous blood gas composition constant. However, the added complexity of allowing mixed venous blood gas composition to vary requires an additional step when calculating the closed-loop derivatives. When the overall $\dot{Q}$ is constrained by rescaling the compartment blood flows, mixed venous blood gas composition is altered to maintain $\dot{V}co_2$ and $\dot{V}o_2$ constant. The change of mixed venous blood gas composition, in turn, alters the $P_{A_{O_2}}$ in each compartment. Therefore, additional iterations are required until successive values of $\dot{V}co_2$ and $\dot{V}o_2$ vary by less than 1%.

Evaluation of local $\dot{Q}$ control with other regulatory mechanisms. So far the effect of local $\dot{Q}$ control has been expressed in terms of Gfb and RD_∞. To evaluate the effects of local $\dot{Q}$ control in the presence of other mechanisms that regulate gas exchange a different approach is used. Increasing degrees of $\dot{V}_A/\dot{Q}$ inequality are imposed on a homogeneous multicompartment lung with $\dot{V}co_2$ and $\dot{V}o_2$ held constant, and the changes of Pa_{O_2}, Pa_{CO_2}, $P\bar{v}_{O_2}$, and $P\bar{v}_{CO_2}$ are calculated under the following conditions. First, the arterial and mixed venous blood gas tensions are calculated at each level of inhomogeneity from σ of 0.001 to 2.0 without any control mechanisms operating. This procedure is similar to that described by West and Wagner (10). Second, the process is repeated with local $\dot{Q}$ control incorporated into the subroutines. At each level of inhomogeneity, the change of Pa_{O_2} in each compartment from its value when the lung had no $\dot{V}_A/\dot{Q}$ inequality is used to modify the blood flow to each compartment according to the local $\dot{Q}$ response curve (Fig. 2*A*) as described above. No attempt was made to constrain overall $\dot{Q}$. Third, local $\dot{Q}$ control was removed from the subroutines, and overall $\dot{Q}$ is modified by the arterial blood gas tensions using equations developed by Grodins et al. (7).

$$\dot{Q} = 15.64682 - 0.2885 \cdot Pa_{O_2} + 0.002924 \cdot (Pa_{O_2})^2 - 0.00001033 \cdot (Pa_{O_2})^3 + 0.3 \cdot (Pa_{CO_2} - 40.91) \quad (5)$$

where no additional increase of $\dot{Q}$ due to Pa_{CO_2} occurs when Pa_{CO_2} is greater than 60 Torr. *Equation 5* causes overall $\dot{Q}$ to increase as the Pa_{O_2} falls and Pa_{CO_2} rises with increasing levels of inhomogeneity. At each level of inhomogeneity, it is necessary to modify the mixed venous blood gas composition to maintain $\dot{V}co_2$ and $\dot{V}o_2$. At each level of inhomogeneity, the increase of overall $\dot{Q}$ leads to an increase of $\dot{V}co_2$ and $\dot{V}o_2$. Therefore, additional iterations are required to modify the mixed venous blood gas composition to maintain $\dot{V}co_2$ and $\dot{V}o_2$ constant. Fourth, both local $\dot{Q}$ control by local $P_{A_{O_2}}$ in each compartment and control of overall $\dot{Q}$ by Pa_{O_2} and Pa_{CO_2} are incorporated into the program. Finally, under each of these four conditions at a $\log_e$ SD of 1.75, overall ventilation is increased to reduce the Pa_{CO_2} to 40 Torr.

TABLE 1. *Summary of analysis*

Model	Conditions	Disturbing Input	Controlled Variable	Expression of Results
Single lung unit with mixed venous blood gas composition constant	Experimental local $\dot{Q}$-$P_{A_{O_2}}$ response	$\dot{V}_A$	$\dot{V}_A/\dot{Q}$	Gfb (identical to OLG) and RD_∞
	Hypothetical local $\dot{Q}$-$P_{A_{O_2}}$ response			
	No local $\dot{Q}$-$P_{A_{O_2}}$	$\dot{Q}$	$P_{A_{O_2}}$	$\partial P_{A_{O_2}}/\partial\dot{Q}$
Multicompartment lung with mixed venous blood gas composition constant	Overall $\dot{Q}$ unconstrained	$\dot{V}_A$	Pa_{O_2}	Gfb and RD_∞
		σ		
	Overall $\dot{Q}$ constrained	$\dot{V}_A$		
		σ		
Multicompartment lung with overall $\dot{V}o_2$ and $\dot{V}co_2$ constant	Overall $\dot{Q}$ constrained	σ	Pa_{O_2}, Pa_{CO_2}, $P\bar{v}_{O_2}$, $P\bar{v}_{CO_2}$	Gfb and RD_∞
	No local or overall $\dot{Q}$ response	σ	Pa_{O_2}, Pa_{CO_2}, $P\bar{v}_{O_2}$, $P\bar{v}_{CO_2}$	Pa_{O_2}, Pa_{CO_2}, $P\bar{v}_{O_2}$, $P\bar{v}_{CO_2}$ in response to increasing degrees of inhomogeneity
	Experimental local $\dot{Q}$-$P_{A_{O_2}}$ response			
	Overall $\dot{Q}$ controlled by Pa_{O_2} and Pa_{CO_2}			
	Both local and overall $\dot{Q}$ responses			

$\dot{Q}$, pulmonary blood flow; $P_{A_{O_2}}$, alveolar O_2 tension; Pa_{O_2} and Pa_{CO_2}, arterial O_2 and CO_2 tension, respectively; $\dot{V}_A$, alveolar ventilation; σ lognormal standard deviation; $P\bar{v}_{O_2}$ and $P\bar{v}_{CO_2}$, mixed venous O_2 and CO_2 tension, respectively; Gfb, gain due to feedback; OLG, open-loop gain RD_∞, ratio of derivatives.

Because of the large number of approaches required to analyze the effects of local $\dot{Q}$ control on pulmonary gas exchange, a summary is provided in Table 1 to clarify the RESULTS section. The results are presented graphically. Continuous plots are drawn rather than individual data points if there are more than nine points for each decade of $\dot{V}_A/\dot{Q}$.

RESULTS

Single Homogeneous Lung Unit

In a single homogeneous lung unit, changes of local $\dot{V}_A$ are the disturbing input. The effect of local blood flow control is to minimize the resultant changes of local $\dot{V}_A/\dot{Q}$. Homeostasis is maximal at a moderately low $\dot{V}_A/\dot{Q}$ of 0.4 where Gfb is 0.87 (Fig. 2*B*). The corresponding value of RD_∞ is 0.53, a value which indicates that the system is able to reduce the change of $\dot{V}_A/\dot{Q}$ to 53% of the change that occurs in the absence of local blood flow control. At extremes of $\dot{V}_A/\dot{Q}$, Gfb tends toward zero (and RD_∞ towards unity), a trend which indicates deterioration of homeostatic ability. Instead of local $\dot{V}_A/\dot{Q}$, the controlled variable can be considered to be the alveolar or end-capillary O_2 and CO_2 tensions or contents. In the homogeneous lung unit, the same results apply to any of these variables since they are directly determined by the local $\dot{V}_A/\dot{Q}$. The existence of a maximal effect is an important factor for determining how local $\dot{Q}$ control acts in a distribution of $\dot{V}_A/\dot{Q}$ (see below, *Effect of inhomogeneity*). Therefore, it is useful to understand why local $\dot{V}_A/\dot{Q}$ regulation is optimal at moderately low $\dot{V}_A/\dot{Q}$. Is it due to the controller or the controlled process?

Shape of the response curve. The importance of the controller in determining the maximal effect on local $\dot{V}_A/\dot{Q}$ regulation at moderately low $\dot{V}_A/\dot{Q}$ can be inferred by using hypothetical local $\dot{Q}$-$P_{A_{O_2}}$ response curves of various shapes (Fig. 3*A*). Despite considerable variation in the shape of these response curves, the maximal effect of local $\dot{V}_A/\dot{Q}$ regulation occurs at similar $\dot{V}_A/\dot{Q}$, although there are differences in the magnitude of the maximal regulatory effect. Therefore, it is the controlled process rather than the controller that causes the optimal effect of local $\dot{V}_A/\dot{Q}$ regulation to occur at moderately low $\dot{V}_A/\dot{Q}$.

Influence of the controlled process. The effect of the controlled process in determining the magnitude of local $\dot{V}_A/\dot{Q}$ regulation depends on the extent that $P_{A_{O_2}}$ increases as $\dot{Q}$ falls (Fig. 1). This change is defined by the partial derivative, $-(\partial P_{A_{O_2}}/\partial\dot{Q})$. Figure 4 (continuous lines) compares the values of $-(\partial P_{A_{O_2}}/\partial\dot{Q})$ with $(\partial P_{A_{CO_2}}/\partial\dot{Q})$ that are obtained with standard O_2 and CO_2 dissociation curves. The maximal value of $-(\partial P_{AO2}/\partial\dot{Q})$ is greater and occurs at a lower $\dot{V}_A/\dot{Q}$ than the maximal value of $(\partial P_{A_{CO_2}}/\partial\dot{Q})$. The reason for this difference can be explored by assuming a linear dissociation curve and assigning a value of λ^* (Ostwald's partial solubility coefficient multiplied by the inspired gas fraction of the carrier gas). Details of this analysis are provided in the APPENDIX. The maximal value of $-(\partial P_A/\partial\dot{Q})$ for a gas with a linear dissociation curve occurs at a $\dot{V}_A/\dot{Q}$ equal to λ^*

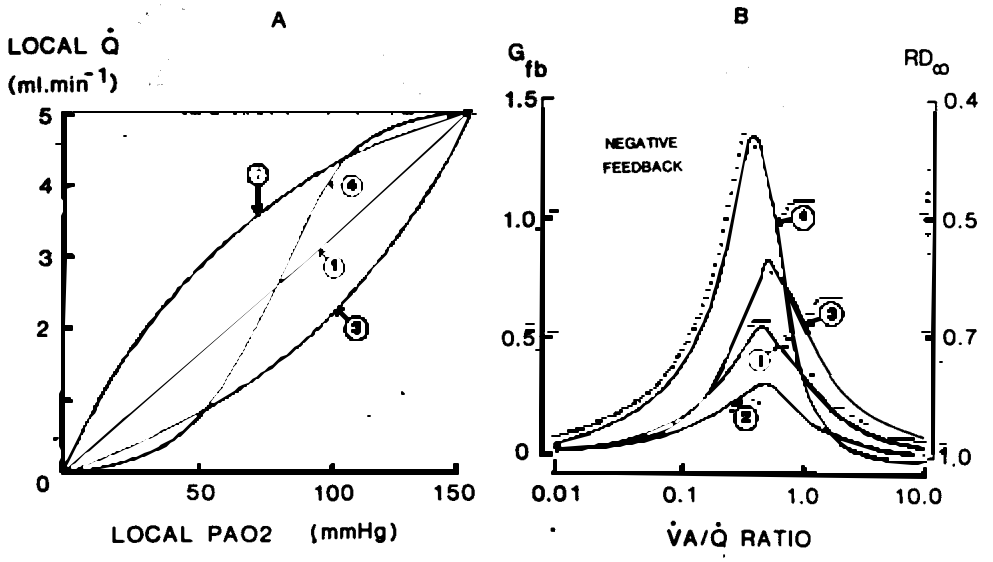

FIG. 3. *A*: hypothetical local pulmonary blood flow ($\dot{Q}$) response curves to changes of local alveolar O_2 tension ($P_{A_{O_2}}$). Axes are as described in Fig. 2*A*. Equations used to produce these curves are (*1*) $\dot{Q} = 0.033 \cdot P_{A_{O_2}}$, (*2*) $= 5.7383 [1 - \exp(-0.0133) \cdot P_{A_{O_2}}]$, (*3*) $\dot{Q} = \exp(0.0119 \cdot P_{A_{O_2}}) - 1$, and (*4*) $\dot{Q} = 5 \cdot \int_{-3}^{Z} [1/\sqrt{(2\pi)}] \cdot \exp(\bar{Z}^2/2)$ where $Z = (P_{A_{O_2}}/25) - 3$. *Equation 4* is based on a Gaussian continuous distribution function. *B*: regulatory effect of local $\dot{Q}$ control on local ventilation-perfusion ratios ($\dot{V}_A/\dot{Q}$) in a single homogeneous lung unit for hypothetical response curves in Fig. 3*A*. Axes and conditions imposed are as described in Fig. 2*B*.

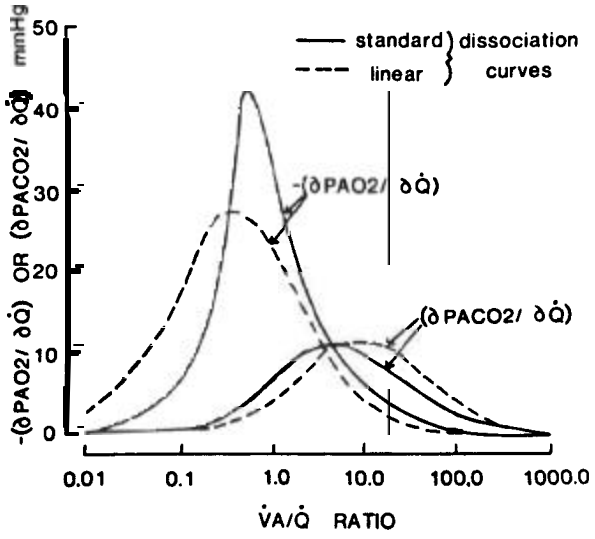

FIG. 4. Values of partial derivatives ($-\partial P_{A_{O_2}}/\partial \dot{Q}$ or $\partial P_{A_{CO_2}}/\partial \dot{Q}$, *ordinate*) at different ventilation-perfusion ratios ($\dot{V}_A/\dot{Q}$) (*abscissa* on log scale). Inspired and mixed venous blood gas tensions used are given in Fig. 2*B*. Units of partial derivatives are Torr because fractional changes of pulmonary blood flow ($\dot{Q}$) were used to calculate partial derivatives. *Solid lines* show values using standard dissociation curves, and *interrupted lines* show values using linear dissociation curves. $P_{A_{O_2}}$ and $P_{A_{CO_2}}$, alveolar O_2 and CO_2 tension, respectively.

and its value depends on the inspired-mixed venous blood gas tension difference. Figure 4 (interrupted lines) also plots the values of $(-\partial P_{A_{O_2}}/\partial \dot{Q})$ and $(\partial P_{A_{CO_2}}/\partial \dot{Q})$ calculated with linear approximations of the O_2 and CO_2 dissociation curves. Each curve is approximated by a linear relation over the working range, i.e., between 41 and 150 Torr for P_{O_2} and between 0.3 and 46 Torr for P_{CO_2}. The slope of each linear relation is used to calculate the values λ^* for O_2 and CO_2.

The maximal value of $-(\partial P_{A O_2}/\partial \dot{Q})$ for the linear O_2 dissociation curve occurs at a $\dot{V}_A/\dot{Q}$ of 0.36 compared with a $\dot{V}_A/\dot{Q}$ of 0.4 for the standard O_2 dissociation curve. This result suggests that the slope rather than the shape of the O_2 dissociation curve is the major reason why the maximal regulation of local $\dot{V}_A/\dot{Q}$ due to hypoxic pulmonary vasoconstriction occurs at moderately low $\dot{V}_A/\dot{Q}$. The major differences between the values of $-(\partial P_{A_{O_2}}/\partial \dot{Q})$ calculated with a standard rather than the linear O_2 dissociation curve occurs at $\dot{V}_A/\dot{Q}$ less than unity. Therefore, maximal value of $-(\partial P_{A_{O_2}}/\partial \dot{Q})$ depends not only on the difference between inspiratory O_2 tension ($P_{I_{O_2}}$) and $P\bar{v}_{O_2}$, but also on the shape of the O_2 dissociation curve. In contrast, the use of a linear CO_2 dissociation curve has little effect on the values of $\partial P_{A_{CO_2}}/\partial \dot{Q}$ (Fig. 4).

Inhomogeneous Lung with Fixed Mixed Venous Blood Gas Tensions

With an overall $\dot{V}_A/\dot{Q}$ of 0.85, the lung unit can be expanded from 1 to 100 compartments. When mixed venous blood gas composition is held constant, the changes of $P_{a_{CO_2}}$ due to $\dot{V}_A/\dot{Q}$ inequality are small, and only $P_{a_{O_2}}$ is used as the controlled variable. The magnitude of the effect of inhomogeneity depends on the disturbing input and on whether overall $\dot{Q}$ is constrained at its initial values (Fig. 5).

Effect of disturbing input. Results are shown for two disturbing inputs: changing of overall $\dot{V}_A$ (Fig. 5, open circles for overall $\dot{Q}$ unconstrained and solid circles for overall $\dot{Q}$ constrained) and changes of the distribution of $\dot{V}_A$ (Fig. 5, open triangles for overall $\dot{Q}$ unconstrained and solid triangles for overall $\dot{Q}$ constrained). If overall $\dot{Q}$ is constrained at its initial value, regulation of $P_{a_{O_2}}$ is greater when changes of the distribution of $\dot{V}_A$ are the disturbing input than when changes of overall $\dot{V}_A$ are the disturbing input. If overall $\dot{Q}$ is unconstrained, the same result occurs. These findings indicate that local $\dot{Q}$ control is more effective at regulating $P_{a_{O_2}}$ when the distribution of $\dot{V}_A$ is altered rather than overall $\dot{V}_A$.

Effect of constraining overall $\dot{Q}$. Any changes of overall $\dot{Q}$ may contribute to the regulation of $P_{a_{O_2}}$. When overall $\dot{Q}$ is constrained, the effect of local $\dot{Q}$ control on $P_{a_{O_2}}$ regulation is solely through the ability of local $\dot{Q}$ control to modify the distribution of $\dot{Q}$. Regulation of $P_{a_{O_2}}$ is only partially diminished by constraining overall $\dot{Q}$, when changes of $\dot{V}_A$ distribution are the disturbing input. On the other hand, regulation of $P_{a_{O_2}}$ is abolished by constraining overall $\dot{Q}$, when changes of overall $\dot{V}_A$ are the disturbing input. Therefore, with overall $\dot{Q}$ un-

constrained, regulation of Pa_{O_2} is mediated predominantly by changes of overall $\dot{Q}$, when the disturbing input is changes of overall $\dot{V}_A$; and by changes of both overall $\dot{Q}$ and its distribution, when changes of $\dot{V}_A$ distribution are the disturbing input.

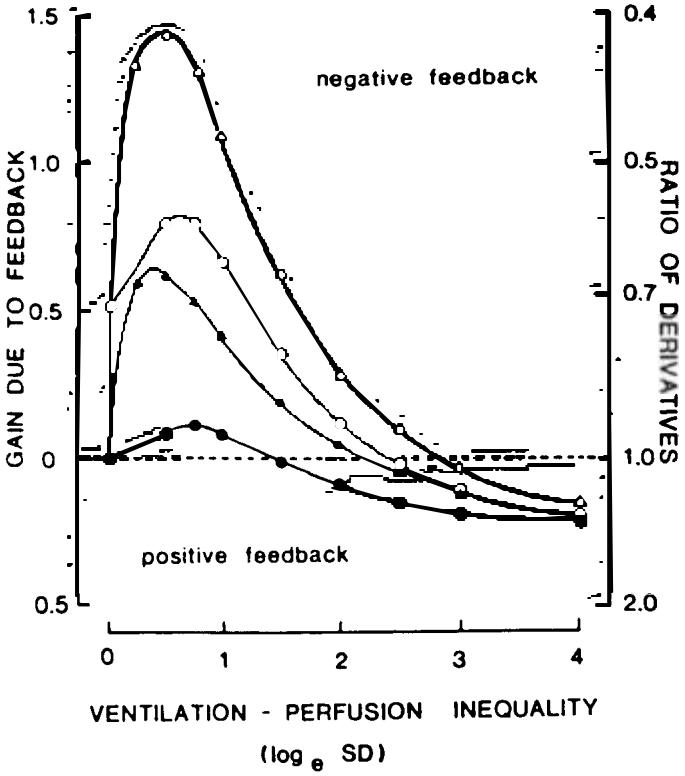

FIG. 5. Regulatory effect of local pulmonary blood flow ($\dot{Q}$) control on arterial P_{O_2} of an inhomogeneous lung breathing air with mixed venous blood gas composition (P_{O_2} = 41 and P_{CO_2} = 46 Torr) held constant, using local $\dot{Q}$ response curve (shown in Fig. 2*A*). Regulatory effect is expressed in terms of gain due to feedback (Gfb on *left-hand ordinate* and RD_∞ on *right-hand ordinate*) at various degrees of ventilation-perfusion ($\dot{V}_A/\dot{Q}$) inequality expressed as $\log_e$ SD on *abscissa*. Overall, $\dot{V}_A/\dot{Q}$ is 0.85. Disturbing inputs are small changes of overall ($\dot{V}_A$) with either overall $\dot{Q}$ allowed to vary (*open circles*) or constrained (*solid circles*) at its initial value, and small changes of $\dot{V}_A$ distribution with either overall $\dot{Q}$ allowed to vary (*open triangles*) or constrained (*solid triangles*) at its initial value.

Effect of inhomogeneity. Regardless of the various conditions imposed on the system, inhomogeneity has a striking effect on regulation of Pa_{O_2}. With minor degrees of $\dot{V}_A/\dot{Q}$ inequality, Gfb can exceed the homeostatic ability of a homogeneous lung unit of the same $\dot{V}_A/\dot{Q}$. At severe degrees of inhomogeneity, Pa_{O_2} regulation exhibits positive-feedback behavior, despite the fact that there is negative-feedback control of $\dot{V}_A/\dot{Q}$ within each compartment.

The reason for this effect of inhomogeneity on Pa_{O_2} regulation is explained with reference to Fig. 6 that compares the $\dot{Q}$ distribution at different levels of $\dot{V}_A/\dot{Q}$ inequality with the Gfb for $\dot{V}_A/\dot{Q}$ regulation in a single homogeneous lung unit. Gfb for $\dot{V}_A/\dot{Q}$ regulation in a single lung unit also reflects the fractional changes of compartmental $\dot{Q}$ for a given fractional change of local $\dot{V}_A$. This relationship can be shown algebraically (see APPENDIX).

The fractional change of $\dot{Q}$ for a given fractional change of $\dot{V}_A$ increases as Gfb increases. At a $\log_e$ SD of 0.0001 the entire $\dot{Q}$ is received by compartments with $\dot{V}_A/\dot{Q}$ close to 0.85. When the disturbing input is a change of overall $\dot{V}_A$ (Fig. 5, open circles) and overall $\dot{Q}$ is unconstrained, Gfb for Pa_{O_2} regulation is the same as that obtained for $\dot{V}_A/\dot{Q}$ regulation in a single homogeneous lung unit with a $\dot{V}_A/\dot{Q}$ of 0.85. Since there is virtually no $\dot{V}_A/\dot{Q}$ mismatch, the ability of local $\dot{Q}$ control to modify the distribution of $\dot{Q}$ is insignificant. Therefore, it is not surprising that there is no regulation of Pa_{O_2} (Gfb is 0 and RD_∞ is unity) when overall $\dot{Q}$ is constrained (Fig. 5, solid circles) or when the disturbing input is a change of $\dot{V}_A$ distribution (Fig. 5, open triangles and solid triangles). At $\log_e$ SD of 0.625, blood flow to the lower $\dot{V}_A/\dot{Q}$ of this distribution occurs close to where local $\dot{V}_A/\dot{Q}$ regulation is maximal. When overall $\dot{V}_A$ or $\dot{V}_A$ distribution is impaired, the redistribution effect of local $\dot{Q}$ control tends to shift blood flow away from the lower $\dot{V}_A/\dot{Q}$ toward higher $\dot{V}_A/\dot{Q}$ that receive the preponderance of blood flow; therefore, the distribution of $\dot{V}_A/\dot{Q}$ is improved and the fall of Pa_{O_2} is reduced (negative-feedback behavior). At a $\log_e$ SD of 2.75, the lower $\dot{V}_A/\dot{Q}$ of this distribution are barely affected by local $\dot{V}_A/\dot{Q}$ regulation. Local $\dot{Q}$

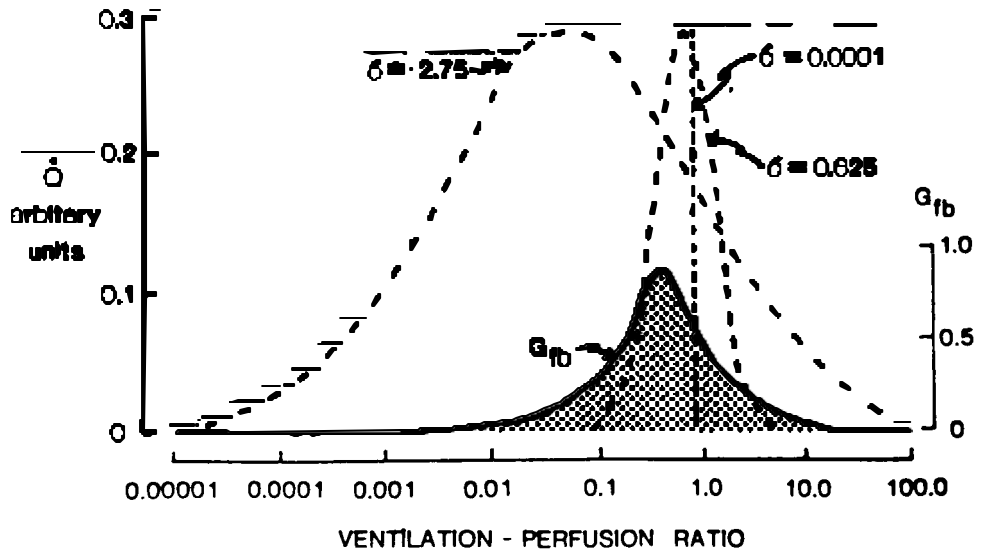

FIG. 6. Compartmental distribution of pulmonary blood flow ($\dot{Q}$) (*left-hand side*, arbitrary units) with respect to ventilation-perfusion ratios ($\dot{V}_A/\dot{Q}$) (*abscissa*, log scale) is compared with gain due to feedback for local $\dot{V}_A/\dot{Q}$ regulation in a single homogeneous lung compartment (*stippled area*). Individual compartmental values of $\dot{Q}$ are represented by an *interrupted line* for a $\log_e$ SD (σ) of 0.0001, 0.625, and 2.75. Gfb, gain due to feedback.

control operates on the higher $\dot{V}_A/\dot{Q}$ of this distribution. In contrast to $\log_e$ SD of 0.625, when overall $\dot{V}_A$ or $\dot{V}_A$ distribution is impaired, the redistribution effect tends to shift blood flow from the higher $\dot{V}_A/\dot{Q}$ that receive the preponderance of blood flow; therefore, the distribution of $\dot{V}_A/\dot{Q}$ is impaired further and the fall of Pa_{O_2} is magnified (positive-feedback behavior).

Inhomogeneous Lung with Fixed $\dot{V}co_2$ and $\dot{V}o_2$

The effect of local $\dot{Q}$ control on gas exchange is influenced by the presence of inhomogeneity, whether or not mixed venous blood gas composition is held constant. Figure 7 shows the regulatory effect on arterial and mixed venous blood gas tensions with overall $\dot{V}_A$, $\dot{Q}$, $\dot{V}o_2$, and $\dot{V}co_2$ held constant. The occurrence of positive-feedback behavior of Pa_{O_2} at a lower $\log_e$ SD is due to the decrease of $P\bar{v}O_2$ that occurs with increasing inhomogeneity. The decrease of $P\bar{v}O_2$ causes the low $\dot{V}_A/\dot{Q}$ compartments to operate on the flat part of the response curve (Fig. 2*A*). This exaggerates the effect of inhomogeneity described above.

Local $\dot{Q}$ Control and Other Regulatory Mechanisms

So far only small changes of $\dot{V}_A$ or the degree of $\dot{V}_A/\dot{Q}$ inequality have been used to assess the effects of local $\dot{Q}$ control on pulmonary gas exchange. This section examines the changes of blood gas tensions when a homogeneous lung is subjected to large changes of $\dot{V}_A/\dot{Q}$ inequality in order to obtain some idea of the way other regulatory mechanisms interact with local blood flow control.

For the purpose of comparison, the changes of blood gas tensions with increases of $\dot{V}_A/\dot{Q}$ inequality are shown without any controlling mechanisms (Fig. 8, interrupted lines). The maximum $\log_e$ SD that can be imposed on the lung can be determined by extrapolating the $P\bar{v}_{O_2}$ to zero. Without any controlling mechanisms, the maximum $\log_e$ SD is approximately 2.25. With local $\dot{Q}$ control (Fig. 8, open circles), the deterioration of arterial blood gas tensions is reduced. However, cardiac output is also reduced, which leads to a greater deterioration of $P\bar{v}_{O_2}$ as σ is increased so that the lung can only withstand a maximum $\log_e$ SD of 2.0. With overall $\dot{Q}$ control but without local $\dot{Q}$ control (Fig. 8, solid circles), the deterioration of $P\bar{v}_{O_2}$ is reduced so that the lung can withstand $\log_e$ SD of 2.7. There is also some improvement of arterial blood gas tensions compared with the case without any regulatory mechanisms. With both local and overall pulmonary $\dot{Q}$ control (Fig. 8, semisolid circles) there is marked improvement of both arterial and mixed venous gas tensions, and the lung can withstand a maximum $\log_e$ SD of approximately 3.5.

In addition, local $\dot{Q}$ control reduces the increase of overall $\dot{V}_A$ necessary to maintain an Pa_{CO_2} of 40 Torr. The increase of $\dot{V}_A$ required of a $\log_e$ SD of 1.75 to maintain normocapnia is 84 without $\dot{Q}$ control, 67 with local $\dot{Q}$ control, 48 with overall $\dot{Q}$ control, and 40% with both local and overall $\dot{Q}$ control.

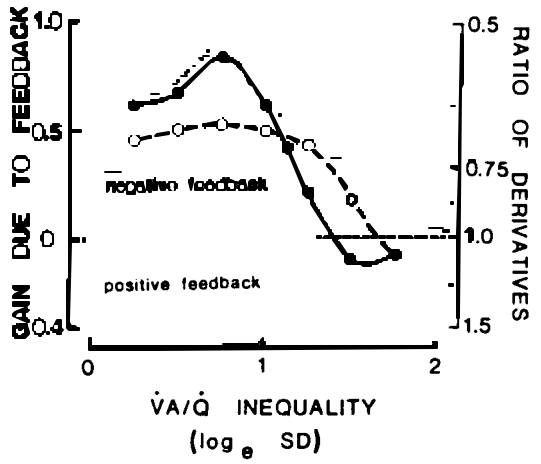

FIG. 7. Regulatory effect of local pulmonary blood flow ($\dot{Q}$) control on blood gas tensions (expressed in terms of gain due to feedback and ratio of derivatives) of an inhomogeneous lung at different degrees of ventilation-perfusion ($\dot{V}_A/\dot{Q}$) inequality with changes of $\dot{V}_A$ distribution as disturbing input. Axes are as described in Fig. 5. Overall alveolar ventilation ($\dot{V}_A$) of 5.1 l·min^{-1}, overall $\dot{Q}$ of 6.0 l·min^{-1}, O_2 uptake of 300 ml·min^{-1}, and CO_2 output of 240 ml·min^{-1} are held constant. Inspired gas is air. Regulatory effects of arterial and mixed venous P_{O_2} are similar to each other (*solid circles*), as are regulatory effects on arterial and mixed P_{CO_2} (*open circles*).

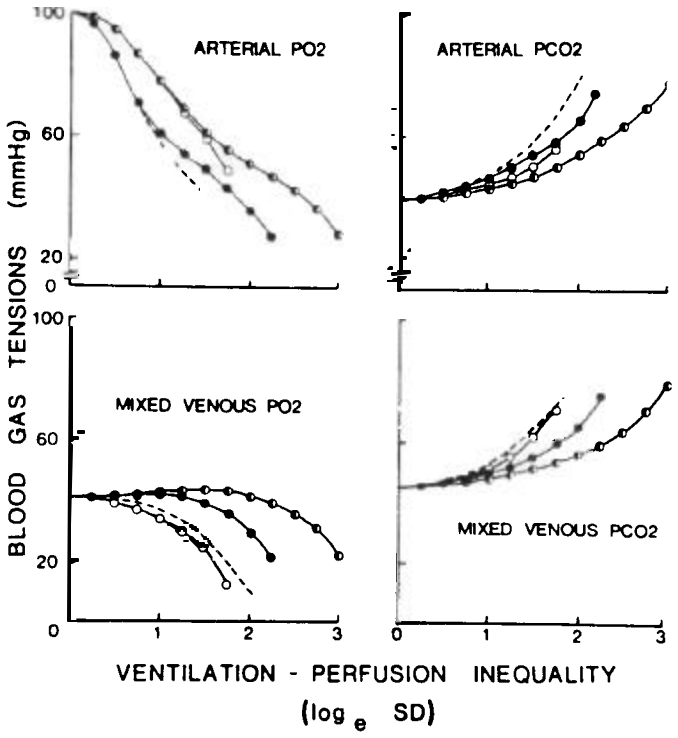

FIG. 8. Changes of blood gas tensions (Torr, *ordinate* on each panel) when a homogeneous lung is subjected to various degrees of ventilation-perfusion ($\dot{V}_A/\dot{Q}$) inequality ($\log_e$ SD, *abscissa*) under various conditions. *Interrupted lines* are results with no control mechanisms operating. *Continuous lines* are results with local pulmonary blood flow ($\dot{Q}$) control (with response curve in Fig. 2*A*) and overall $\dot{Q}$ is unconstrained (*open circles*), overall $\dot{Q}$ is controlled by arterial blood gas tensions (see text for details) but no local $\dot{Q}$ control (*solid circles*), or with both local and overall $\dot{Q}$ control operating simultaneously (*semisolid circles*).

DISCUSSION

The relevance of this study to understanding how the local vascular response to local $P_{A_{O_2}}$ affects gas exchange in lung disease depends on the extent a distribution of

$\dot{V}_A/\dot{Q}$ accounts for the gas exchange defect in lung disease. Experimental data suggest that $\dot{V}_A/\dot{Q}$ inequality is the major cause of gas exchange abnormalities in lung disease (9). Most of the assumptions made in this study are commonly used in the analysis of pulmonary gas exchange. Ventilation and perfusion are considered to be continuous flows without cyclical changes and supply lung units with no diffusion defect in a parallel arrangement. In addition, the effects of dead space and lung metabolism are ignored. Only lognormal distributions of $\dot{V}_A/\dot{Q}$ are used because their simplicity makes them readily amenable to analysis. The local pulmonary vascular response to P_{AO_2} is considered to be uniform throughout the lung, which may not be the case (6). However, these simplifications should not detract from the insight obtained into the effects of local blood flow control or gas exchange.

The effect of the local vascular response to $P_{A_{O_2}}$ on gas exchange in a single lung unit is significant over a narrow range of $\dot{V}_A/\dot{Q}$. The previously reported maximal effect at moderately low $\dot{V}_A/\dot{Q}$ (2, 6) can be attributed to the slope of the O_2 dissociation curve rather than its shape or the shape of the local vascular response curve.

The maximal regulation of local $\dot{V}_A/\dot{Q}$ at moderately low $\dot{V}_A/\dot{Q}$ is an important factor in determining how inhomogeneity modifies the effect of local $\dot{Q}$ control on gas exchange. In general, if the preponderance of $\dot{Q}$ occurs at $\dot{V}_A/\dot{Q}$ greater than where the maximal effect of local $\dot{V}_A/\dot{Q}$ regulation occurs, the regulatory effect on overall gas exchange is improved. If the preponderance of $\dot{Q}$ occurs at $\dot{V}_A/\dot{Q}$ less than where the maximal effect occurs, the regulatory effect on overall gas exchange is impaired.

The positive feedback behavior of arterial blood gas tensions at severe degrees of inhomogeneity is of considerable interest for two reasons. First, it illustrates that a network of negative-feedback loops can behave in an entirely different fashion from an individual unit. Second, it shows that, under certain conditions, hypoxic vasoconstriction can actually exaggerate changes of $\dot{V}_A/\dot{Q}$ inequality. The positive-feedback behavior depends on the shape of the local vascular response curve to PAO_2, which is not known in humans, so its practical importance is not clear. Furthermore, the positive-feedback behavior may be diminished if the local vascular response is suppressed by pulmonary hypertension (1) due to the hypoxemia caused by the severe inhomogeneity.

The magnitude of the regulatory effects of local $\dot{Q}$ control on gas exchange in a dispersion of $\dot{V}_A/\dot{Q}$ is attenuated by constraining overall blood flow. Although local alveolar hypoxia causes a reduction of local $\dot{Q}$, arterial hypoxemia is associated with an increased cardiac output. Therefore, the question arises as to whether an increased cardiac output nullifies the regulatory effect of local $\dot{Q}$ control. Figure 8 shows that this is not the case. It should be emphasized that these results cannot be used to predict how local $\dot{Q}$ control affects the blood gas tensions in disease because lognormal distributions of $\dot{V}_A/\dot{Q}$ are used in this analysis. In disease, the distribution of $\dot{V}_A/\dot{Q}$ tends to be bimodal (9). The extent to which local $\dot{Q}$ control affects the distribution of $\dot{V}_A/\dot{Q}$ in disease would depend on the proportion of $\dot{Q}$ received by $\dot{V}_A/\dot{Q}$ where $\dot{V}_A/\dot{Q}$ regulation is maximal, and on the $\dot{V}_A/\dot{Q}$ that receive the preponderance of blood flow. Nevertheless, the ability of local $\dot{Q}$ control is only moderate when compared with other feedback systems such as the remarkable ventilatory control of Pa_{CO_2}. However, the capacity of local $\dot{Q}$ control to modify the distribution of $\dot{V}_A/\dot{Q}$ is capable of making a significant contribution to combating the deleterious effects of lung disease.

APPENDIX

Equivalence of OLG and Gain Due to Feedback for a Single Feedback Loop

The fact that Gfb for a single feedback loop is identical to OLG can be proven algebraically. The relationship around the feedback loop in Fig. 1 are as follows.

$$\Delta\dot{Q} = \frac{d\dot{Q}}{dP_{A_{O_2}}} \cdot \Delta P_{A_{O_2}} \tag{6}$$

$$\Delta(\dot{V}_A/\dot{Q}) = \frac{\partial(\dot{V}_A/\dot{Q})}{\partial\dot{V}_A} \cdot \Delta\dot{V}_A + \frac{\partial(\dot{V}_A/\dot{Q})}{\partial\dot{Q}} \cdot \Delta\dot{Q} \tag{7}$$

$$\Delta P_{A_{O_2}} = \frac{\partial P_{A_{O_2}}}{\partial(\dot{V}_A/\dot{Q})} \cdot \Delta(\dot{V}_A/\dot{Q}) \tag{8}$$

Equation 6 describes the controller, and *Eqs. 7* and *8* describe the controlled process (Fig. 1). Under open-loop conditions, there is no change of $\dot{Q}$ due to a change of $P_{A_{O_2}}$ when the system is disturbed by a change of $\dot{V}_A$. Therefore, the change of $\dot{V}_A/\dot{Q}$ for a change of $\dot{V}_A$ can be obtained from *Eq. 7*.

$$\left[\frac{\Delta(\dot{V}_A/\dot{Q})}{\Delta\dot{V}_A}\right]_{open} = \frac{\partial(\dot{V}_A/\dot{Q})}{\partial\dot{V}_A} \tag{9}$$

Under closed-loop conditions, changes of $P_{A_{O_2}}$ do affect $\dot{Q}$. Therefore, all three equations are required to calculate the change of $\dot{V}_A/\dot{Q}$ produced by a change of $\dot{V}_A$. First, $\Delta P_{A_{O_2}}$ from *Eq. 8* is substituted into *Eq. 6*.

$$\Delta\dot{Q} = \frac{d\dot{Q}}{dP_{A_{O_2}}} \cdot \frac{\partial P_{A_{O_2}}}{\partial(\dot{V}_A/\dot{Q})} \cdot \Delta(\dot{V}_A/\dot{Q}) \tag{10}$$

Then $\Delta\dot{Q}$ from *Eq. 10* is substituted into *Eq. 7*.

$$\Delta(\dot{V}_A/\dot{Q}) = \frac{\partial(\dot{V}_A/\dot{Q})}{\partial\dot{V}_A} \cdot \Delta\dot{V}_A + \frac{\partial(\dot{V}_A/\dot{Q})}{\partial\dot{Q}} \cdot \frac{d\dot{Q}}{dP_{A_{O_2}}} \cdot \frac{\partial P_{A_{O_2}}}{\partial(\dot{V}_A/\dot{Q})} \cdot \Delta(\dot{V}_A/\dot{Q}) \tag{11}$$

By rearrangement of *Eq. 11*, we have

$$\left[\frac{\Delta(\dot{V}_A/\dot{Q})}{\Delta\dot{V}_A}\right]_{closed} = \frac{\partial(\dot{V}_A/\dot{Q})}{\partial\dot{V}_A} \Bigg/ \left[1 - \frac{d\dot{Q}}{dP_{A_{O_2}}} \cdot \frac{\partial(\dot{V}_A/\dot{Q})}{\partial\dot{Q}} \cdot \frac{\partial P_{A_{O_2}}}{\partial(\dot{V}_A/\dot{Q})}\right] \tag{12}$$

With small changes of $\dot{V}_A$ and $\dot{V}_A/\dot{Q}$, we can write $d(\dot{V}_A/\dot{Q})/d\dot{V}_A$ in place of $\Delta(\dot{V}_A/\dot{Q})/\Delta\dot{V}_A$. Since $\dot{V}_A/\dot{Q}$ is the controlled variable and $\dot{V}_A$ is the disturbing input, we can evaluate Gfb (*Eq. 3*) from *Eqs. 9* and *12*.

$$Gfb = -\frac{d\dot{Q}}{dP_{A_{O_2}}} \cdot \frac{\partial(\dot{V}_A/\dot{Q})}{\partial\dot{Q}} \cdot \frac{\partial P_{A_{O_2}}}{\partial(\dot{V}_A/\dot{Q})} \tag{13}$$

This expression shows that Gfb for a single feedback loop is identical to OLG.

Evaluation of $(\partial P_A/\partial\dot{Q})$ for a Gas with a Linear Dissociation Curve

The reason for $-(\partial P_{A_{O_2}}/\partial\dot{Q})$ being maximal at a moderately low $\dot{V}_A/\dot{Q}$ can be analyzed algebraically if the O_2 dissociation curve is assumed to be linear. The general expression for a gas with a linear dissociation curve is as follows (see Ref. 11 for derivation).

$$P_A = \frac{(\dot{V}_A/\dot{Q})\cdot P_I + \lambda^*\cdot P\bar{v}}{\dot{V}_A/\dot{Q} + \lambda^*} \quad (14)$$

where P_A is the alveolar gas tension, P_I is the inspired gas tension, $P\bar{v}$ is the mixed venous blood gas tension, and λ^* is Ostwald's solubility coefficient multiplied by the inspired gas fraction of the carrier gas (i.e., N_2). The partial derivative $(\partial P_A/\partial\dot{Q})$ can be obtained by differentiating *Eq. 14* with changes of $\dot{Q}$ expressed as fractional changes.

$$-(\partial P_A/\partial\dot{Q}) = \lambda^*\cdot(\dot{V}_A/\dot{Q})\cdot(P_I - P\bar{v})\cdot(\dot{V}_A/\dot{Q} + \lambda^*)^{-2} \quad (15)$$

When the second derivative of P_A with respect to $\dot{Q}$ is zero, $-(\partial P_A/\partial\dot{Q})$ must be maximal.

$$-(\partial^2 P_A/\partial\dot{Q}^2) = \lambda^*\cdot(\dot{V}_A/\dot{Q})\cdot(P_I - P\bar{v})\cdot (\dot{V}_A/\dot{Q} - \lambda^*)\cdot(\dot{V}_A/\dot{Q} + \lambda^*)^{-3} \quad (16)$$

The second derivative of P_A can be zero only under one condition: when $\dot{V}_A/\dot{Q}$ is equal to λ^*. The value of $-(\partial P_A/\partial\dot{Q})$ can be evaluated at this $\dot{V}_A/\dot{Q}$ by substituting λ^* for $\dot{V}_A/\dot{Q}$ in *Eq. 15*.

$$-(\partial P_A/\partial\dot{Q}) = \frac{(P_I - P\bar{v})}{4} \quad (17)$$

Linear approximations of the O_2 and CO_2 dissociation curves are made over the working range between mixed venous blood and inspired gas compositions. Therefore, the value of λ^* for O_2 is 0.36 between $P\bar{v}_{O_2}$ of 41 Torr and $P_{I_{O_2}}$ of 149 Torr assuming a $P\bar{v}_{CO_2}$ of 46 Torr and a $P_{I_{CO_2}}$ of 0.3 Torr. The value of λ^* for CO_2 over this range is 7.7.

Dependence of the Proportional Change of Local $\dot{Q}$ due to $P_{A_{O_2}}$ on Gfb

In this section, it will be shown algebraically that the proportional change of local $\dot{Q}$ due to a change of $P_{A_{O_2}}$ is dependent on Gfb. By using $\dot{V}_A/\dot{Q}$ as the controlled variable and $\dot{V}_A$ as the disturbing input for negative-feedback control of $\dot{V}_A/\dot{Q}$ in a single lung unit, *Eq. 3* becomes

$$Gfb = \frac{[d(\dot{V}_A/\dot{Q})/d\dot{V}_A]_{open}}{[d(\dot{V}_A/\dot{Q})/d\dot{V}_A]_{closed}} - 1 \quad (18)$$

Equation 18 can be expanded.

$$Gfb = \frac{[(\dot{V}_A + \delta\dot{V}_A)/\dot{Q} - \dot{V}_A/\dot{Q}]/\delta\dot{V}_A}{[(\dot{V}_A + \delta\dot{V}_A)/(\dot{Q} + \delta\dot{Q}) - \dot{V}_A/\dot{Q}]/\delta\dot{V}_A} - 1 \quad (19)$$

By rearrangement and assuming the term $\delta\dot{V}_A\cdot\delta\dot{Q}$ is negligible the following expression is obtained.

$$\frac{\delta\dot{Q}/\dot{Q}}{\delta\dot{V}_A/\dot{V}_A} = \frac{Gfb}{1 + Gfb} \quad (20)$$

Therefore, the fractional change of $\dot{Q}$ for a given fractional change of $\dot{V}_A$ increases as Gfb increases.

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