Dynamic response of local pulmonary blood flow to alveolar gas tensions: experiment

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PARADOWSKI, LINDA J., AND BRYDON J. B. GRANT. *Dynamic response of local pulmonary blood flow to alveolar gas tensions: experiment.* J. Appl. Physiol. 66(6): 2559–2564, 1989.—The purpose of this study was to investigate the mechanism that causes a damped oscillatory response of local pulmonary blood flow to local hypoxia. The left lower lobe (LLL) of 10 anesthetized dogs was ventilated independently but synchronously with the rest of the lungs. Blood flow to the LLL as a proportion of total flow ($\dot{Q}_{LLL}/\dot{Q}_T$) was measured during the on-transient of the hypoxic response when LLL inspirate was changed from O_2 to N_2. There was a damped oscillatory response of $\dot{Q}_{LLL}/\dot{Q}_T$ to hypoxia (34 of 40 trials). In contrast, the off-transient was always monotonic. There was no enhancement of the steady state or dynamic hypoxic response with repeated challenges. Local alveolar hypercapnia caused a damped oscillatory response in the presence of local hypoxia (15 of 20 trials), but there was no response in the presence of local hyperoxia. We conclude that *1*) the dynamic pulmonary vascular response to O_2 and CO_2 are not additive because the response to CO_2 is attenuated by hyperoxia and *2*) the damped oscillatory response that occurs during hypoxia is the result of changes of local alveolar CO_2 per se.

hypoxic pulmonary vasoconstriction; local pulmonary blood flow control by alveolar gas tensions; oscillations

THE RESPONSE OF PULMONARY blood flow to an abrupt change of alveolar O_2 tension ($P_{A_{O_2}}$) is not instantaneous but changes over time until a new level is attained that is sustained over an indefinite period (2, 7, 12). This response can be separated into two components: the time course of the change in flow is called the dynamic response, and the change in the sustained level of flow is the steady-state response.

Two types of dynamic response of lobar blood flow to hypoxia have been encountered in the dog (2). First, a monotonic change in blood flow may occur with a progressive decrease until a steady-state level is achieved. Second, a damped oscillatory response may occur in which lobar blood flow decreases and then fluctuates in a cyclical manner but the amplitude of the fluctuations progressively diminishes over time until a new steady state level is achieved. The type of response elicited depends on the local alveolar CO_2 tension ($P_{A_{CO_2}}$). The damped oscillatory response to lobar hypoxia occurs when there is a decrease in local $P_{A_{CO_2}}$ as a result of the decrease in lobar blood flow. When CO_2 is added to the lobar inspirate during the hypoxic challenge to maintain the level of the local $P_{A_{CO_2}}$ constant, a monotonic decrease in lobar blood flow occurs (2).

Grant and Schneider (6) developed a mathematical model that successfully simulated Benumof's experimental data. Their model consisted of a monoexponential response of lobar blood flow to a change of $P_{A_{O_2}}$ and a damped oscillatory response as the result of a coupling between the dual vasoconstrictor and vasodilator effects of $P_{A_{CO_2}}$ on local pulmonary blood flow (1, 14). There are several implications from these studies that required further investigation. First, the model proposed by Grant and Schneider (6) has a linear response in the sense that the effects of O_2 and CO_2 are additive. Therefore, the character of the dynamic response to hypoxia (on-transient) should be similar to the dynamic response when the hypoxia is replaced by hyperoxia (off-transient). Previous reports only described the hypoxic on-transient response; data on the off-transient are lacking. Second, previous studies only reported the effects of hypoxia with hypocapnia or hypoxia with eucapnia. If the damped oscillatory response is the result of changes of CO_2 as they suggested, then a damped oscillatory response to hypercapnia would be anticipated.

To address these issues we have performed two series of experiments. In the first series of experiments, we compared the dynamics of the on-transient and the off-transient. In addition, we tested the stability of the hypoxic pulmonary vascular response to repeated challenge. Previous investigators have reported an enhancement of the strength of the hypoxic response to repeated challenge (9, 10, 13). This finding, however, has not been uniform (4, 8). In the second series of experiments, we determined the pulmonary vascular response to hypercapnia under hypoxic and hyperoxic conditions.

METHODS

Experimental preparation. Anesthesia was induced in a mongrel dog weighing ~20 kg with an intravenous injection of 2 ml/kg body wt of a solution containing α-chloralose (60 mg/ml) and sodium tetraborate (46 mg/ml). Anesthesia was maintained with a continuous infusion of a 1:1.85 dilution of that solution at a rate of 1.32 ml·kg body $wt^{-1}\cdot h^{-1}$. An endotracheal tube was placed, and ventilation was maintained with one side of a dual Harvard pump at a rate of 12–14 breaths/min and a tidal volume of 15–20 ml/kg. A femoral artery catheter was placed for monitoring arterial blood pressure and for obtaining blood samples to measure arterial pH, P_{CO_2}, and P_{O_2}. A flow-directed balloon-tipped catheter was

positioned in the pulmonary artery to measure cardiac output by thermodilution. A femoral vein catheter was inserted for drug and fluid administration during the experiment. The dog was paralyzed with pancuronium bromide (0.1 mg/kg iv) with repeated doses as was required. A left thoracotomy was performed through the fifth intercostal space to allow Statham electromagnetic flow probes to be placed around the main and left lower lobe (LLL) pulmonary arteries. The flow probes had been calibrated previously with saline. In all experiments, LLL pulmonary blood flow was measured continuously and expressed as a proportion of total pulmonary blood flow ($\dot{Q}_{LLL}/\dot{Q}_T$). Values for $\dot{Q}_T$ obtained from the main pulmonary flow probe agreed well with values obtained by thermodilution (±10%).

A reinforced cannula (Rusch) was secured in the LLL bronchus that enabled the LLL to be ventilated synchronously but independently of the rest of the lung with the other side of the dual Harvard pump (Natick, MA). The LLL and the rest of the lung were ventilated with 5 cmH_2O positive end-expiratory pressure to avoid atelectasis in this open chested preparation. Airway pressures in the lobe and the rest of the lung were measured with a Validyne (Northridge, CA) differential pressure transducer relative to atmospheric pressure. Tidal volume of the lobe was adjusted so that peak airway pressures were equal to those measured in the rest of the lung. Dead space to the lobe was added to equalize alveolar (end-tidal) CO_2 level to that of the rest of the lung. The frequency of the respirator was adjusted to obtain an end-tidal CO_2 of ~5%. The LLL was ventilated with specific gas mixtures of O_2, CO_2, and N_2. The rest of the lung was ventilated with 100% O_2 throughout the experiment. Airway gas fractions of O_2 and CO_2 were measured continuously either from the lobe or the rest of the lung with a Perkin-Elmer mass spectrometer.

All electrical signals were recorded on an eight-channel Gould recorder and an eight-channel Hewlett-Packard FM tape recorder. The signals were then converted from analog-to-digital form with a NorthStar Horizon computer. The signals were processed on line, and the following variables were averaged over one cardiac cycle at end-expiration every 15 s: $\dot{Q}_{LLL}$, $\dot{Q}_T$, $\dot{Q}_{LLL}/\dot{Q}_T$, heart rate, femoral arterial pressure, pulmonary arterial pressure, respiratory rate, and inspired oxygen fraction.

Protocols. In the first series of experiments, the LLL was ventilated initially with 100% O_2. The lobar inspirate was changed to 100% N_2 for 60 min followed by 100% O_2 for 30 min on four successive occasions. This protocol was repeated in 10 dogs. We measured the on-transient and the off-transient response to hypoxia. Because of the reduction in lobar pulmonary blood flow and the Bohr-Haldane effect, the local alveolar hypoxia is always associated with concomitant local alveolar hypocapnia in this preparation (6).

The second series of experiments was designed to determine the dynamic response to hypercapnia. For the sake of clarity, a summary of the purpose of key changes of lobar inspirate (interventions) is provided in Table 1. The order in which changes of the lobar inspirate were made and the duration of exposure to each gas mixture are shown in Fig. 1. The LLL inspirate was changed from 100% O_2 to 10% CO_2-90% O_2 to determine the response to local hypercapnia in the presence of local alveolar hyperoxia. The LLL was ventilated subsequently with 100% O_2 and the inspirate changed to 100% N_2 to measure the hypoxic response with concomitant local alveolar hypocapnia. The LLL inspirate was then changed from 100% N_2 to 10% CO_2-90% N_2 to measure the hypercapnic response in the presence of local alveolar hypoxia. The LLL was subsequently ventilated with 100% O_2. The lobar inspirate was then changed to 10% CO_2-90% N_2 to measure the hypoxic response with concomitant local alveolar hypercapnia. This intervention was designed to contrast with the concomitant hypocapnia that occurs when the lobar inspirate is changed from 100% O_2 to 100% N_2.

TABLE 1. *Summary of experimental maneuvers in second series of experiments*

Intervention	Change of Lobar Inspirate: From	Change of Lobar Inspirate: To	Response Measured
I	100% O_2	100% N_2	Hypoxic response with concomitant local alveolar hypocapnia
II	100% O_2	10% CO_2-90% N_2	Hypoxic response with concomitant local alveolar hypercapnia
III	100% O_2	10% CO_2-90% O_2	Hypercapnic response in presence of local alveolar hyperoxia
IV	100% N_2	10% CO_2-90% N_2	Hypercapnic response in presence of local alveolar hypoxia

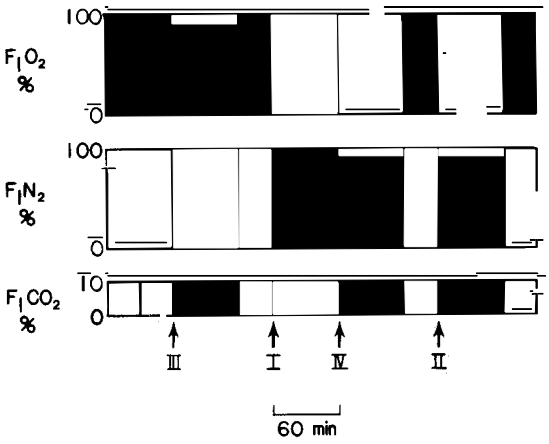

FIG. 1. Protocol for second series of experiments. Diagram shows gas composition of left lower lobe inspirate and its duration of administration. Key changes are labeled by Roman numerals. See Table 1 for explanation of purpose of these interventions. $F_{I_{N_2}}$, $F_{I_{O_2}}$, $F_{I_{CO_2}}$, inspired N_2, O_2, and CO_2 concentrations.

Data analysis. The nature of the pulmonary vascular response to changes of O_2 and CO_2 was characterized from graphical displays of $\dot{Q}_{LLL}/\dot{Q}_T$ against time. We assigned the reaction to one of three categories: nonreactive, monotonic, or damped oscillatory response.

A nonreactive response was defined as <10% change in $\dot{Q}_{LLL}/\dot{Q}_T$ from its initial value over a period of 30 min. To distinguish between a monotonic and damped oscillatory response, we used an objective statistical approach

for the first series of experiments. Nonlinear regression equations to describe the time course of $\dot{Q}_{LLL}/\dot{Q}_T$ were fitted to the experimental data for each period by the least-squares method with a Marquardt procedure (3). Two equations were used. A single-exponential expression of $\dot{Q}_{LLL}/\dot{Q}_T$ as a function of time (t) to identify monotonic responses

$$\dot{Q}_{LLL}/\dot{Q}_T(t) = a_1 + a_2 \exp(-t/a_3) \quad (1)$$

where a_1 is the final steady-state value of $\dot{Q}_{LLL}/\dot{Q}_T(t)$, a_2 is the steady-state change of $\dot{Q}_{LLL}/\dot{Q}_T$ from its initial value of $\dot{Q}_{LLL}/\dot{Q}_T(t)$ so that the initial value is $a_1 + a_2$, and a_3 is the time constant. An exponential expression with a cosine term to identify damped oscillatory responses

$$\dot{Q}_{LLL}/\dot{Q}_T(t) = b_1 + b_2 \exp(-b_3 b_4 t) \cdot \cos\left[(1 - b_3^2)^{1/2} b_4 t\right] \quad (2)$$

where b_1 is the final steady-state value of $\dot{Q}_{LLL}/\dot{Q}_T(t)$, b_2 is the steady-state change of $\dot{Q}_{LLL}/\dot{Q}_T$ from its initial value so that the initial value of $\dot{Q}_{LLL}/\dot{Q}_T(t)$ is $b_1 + b_2$, and b_3 is the damping ratio. A damping ratio of 0 would imply that there were sustained oscillations. A damping ratio of 1 would indicate no oscillatory behavior: a critically damped system. Damping ratios of intermediate values are related inversely to the rapidity that the oscillations resolve over time. b_4 is the natural frequency of the response and is a measure of the periodicity of the oscillations.

The justification for the higher-order equation (*Eq. 2* rather than *Eq. 1*) to describe a damped oscillatory rather than a monotonic response was assessed from the residual sum of squares. If there was a significant reduction in the residual sum of squares with *Eq. 2* compared with *Eq. 1* by analysis of variance (11), then a damped oscillatory response occurred, otherwise the response was considered to be monotonic. In all cases the decision was obvious from inspection of the data. Therefore, we used a simpler approach for the second series of experiments. The damping ratio and the cycle time were measured graphically (5). This graphic approach gave similar results to the curve-fitting approach.

Statistical methods. For all statistical tests the 5% level of significance was accepted. To assess for variation between repeated trials we used analysis of variance with a two-way classification. To determine whether there was a difference in the type of response that occurs with hypoxia, we used Cochran's Q test. Correlation was tested with the standard Pearson method. Bonferroni adjustments were made for multiple comparisons.

RESULTS

First series of experiments. The average $\dot{Q}_{LLL}/\dot{Q}_T$ expressed as a fraction was 20% under steady-state control conditions (LLL inspirate 100% O_2). Because of the variation of $\dot{Q}_{LLL}/\dot{Q}_T$ between preparations, the changes of $\dot{Q}_{LLL}/\dot{Q}_T$ are expressed as a percent of control values obtained when the LLL was ventilated with 100% O_2. There was no significant change in the steady-state response during the on-transient or the off-transient (Table 2).

There is a marked difference between the type of dynamic response recorded during the on-transient (Fig. 2) and the off-transient (Fig. 3). Of the trials 85% were damped oscillatory responses for the on-transient, 10% were monotonic responses and 5% were nonreactive (Fig. 4). In contrast, 95% of the trials were monotonic responses for the off-transient, 5% were nonreactive (Fig. 4). There is no significant change in the character of the response with repeated trials and the quantitative measures of the dynamic responses. Overall, the damped oscillatory response during the on-transient had a natural frequency of 0.23 ± 0.05 (SD) rad/min. The mean damping ratio was 0.47 ± 0.29. The wide variation of damping ratio can be explained in part by the variation in the steady-state response between dogs. There was a positive correlation between the magnitude of the steady-state change of $\dot{Q}_{LLL}/\dot{Q}_T$ and the damping ratio ($r = 0.578$, $P < 0.007$). The damped oscillatory response was the result of fluctuations of $\dot{Q}_{LLL}$ rather than $\dot{Q}_T$. We compared $\dot{Q}_{LLL}$ and $\dot{Q}_T$ under three conditions in the

TABLE 2. *Sequential measurements of hypoxic challenge in first series of experiments*

		Trial No. 1	2	3	4
		On-transient			
Steady-state change of $\dot{Q}_{LLL}/\dot{Q}_T$, %	40	46±26	54±21	55±25	51±25
Damping ratio		0.44±0.34	0.47±0.27	0.53±0.22	0.40±0.26
Natural frequency, rad/min	34	0.22±0.06	0.23±0.07	0.24±0.03	0.24±0.05
		Off-transient			
Steady-state change of $\dot{Q}_{LLL}/\dot{Q}_T$, %	40	49±21	52±24	52±22	52±23
Time constant, min	38	6.5±6.5	8.0±6.5	6.6±3.2	4.3±2.1

Values are means ± SD; n, no. of observations. Change of proportion of pulmonary blood flow to left lower lobe ($\dot{Q}_{LLL}/\dot{Q}_T$) is expressed as percent of control values while left lower lobe was ventilated with pure O_2. Natural frequency can be converted to cycles/min by dividing 6.28 by value expressed in rad/min.

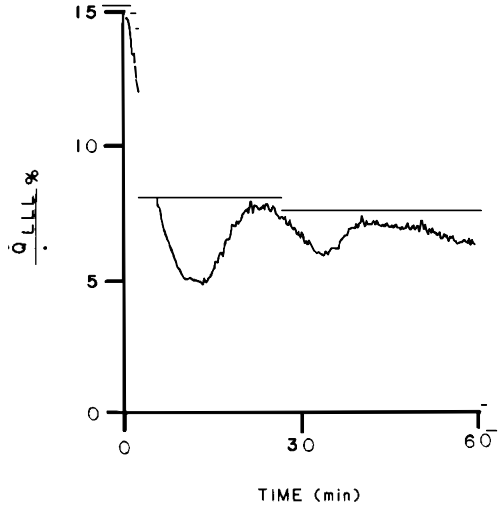

FIG. 2. Pulmonary vascular response to hypoxia (on-transient). Proportion of total pulmonary blood flow to left lower lobe ($\dot{Q}_{LLL}/\dot{Q}_T$) is plotted against time. At *time 0*, left lobar inspirate is changed from pure O_2 to pure N_2.

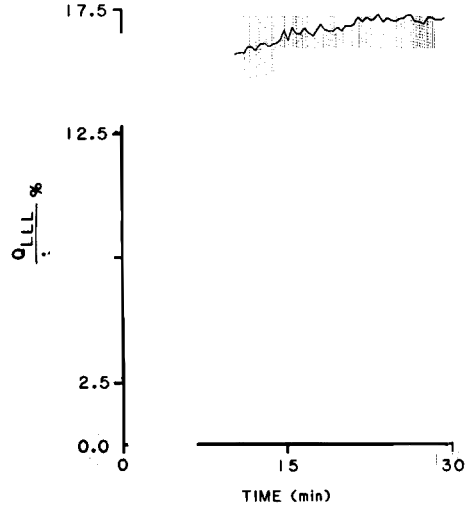

FIG. 3. Pulmonary vascular response to hyperoxia (off-transient). Proportion of total pulmonary blood flow to left lower lobe ($\dot{Q}_{LLL}/\dot{Q}_T$) is plotted against time. At *time 0*, left lobar inspirate is changed from pure N_2 to pure O_2.

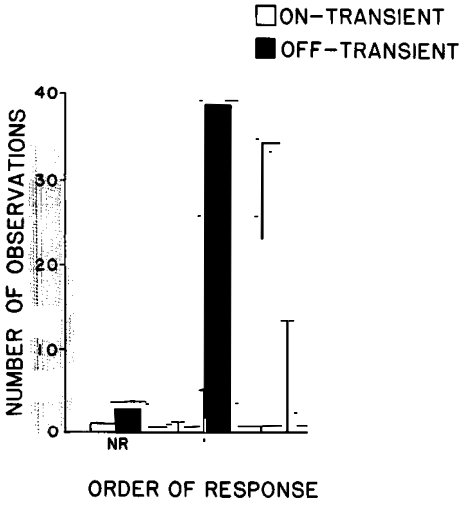

FIG. 4. Difference in dynamics of pulmonary vascular response to hypoxia (first series of experiments). Number of responses characterized as nonreactive (NR), monotonic (1), or damped oscillatory (2) are shown for both on- and off-transients.

hypoxic challenges that showed this response: *1*) during control period of hyperoxia, *2*) during the hypoxic response when $\dot{Q}_{LLL}/\dot{Q}_T$ was minimal, and *3*) when $\dot{Q}_{LLL}/\dot{Q}_T$ was maximal. We found significant differences ($P < 0.0001$) for $\dot{Q}_{LLL}$ [0.33 ± 0.11, 0.14 ± 0.75, and 0.2 ± 0.075 (SD) l/min, respectively], whereas $\dot{Q}_T$ was unchanged [1.7 ± 0.75, 1.8 ± 0.9, and 1.8 ± 0.85 (SD) l/min, respectively].

The monotonic response to hyperoxia had a mean time constant of 5.9 ± 2.0 (SD) min. In the subgroup of five occasions where both the on-transient and the off-transient yielded monotonic responses, the time constants were similar for the hypoxic response (10 ± 6.4 min) and for the hyperoxic response (9.1 ± 7.4 min). None of these estimates of the dynamic pulmonary vascular response showed any significant variation with repeated challenge (Table 2).

Second series of experiments. We studied 10 dogs to compare the dynamic and steady-state characteristics of the lobar pulmonary vascular response to hypercapnia during hyperoxia and hypoxia. Arterial blood gases were measured with every change in alveolar inspirate. As can be seen from Table 3, the addition of CO_2 to the LLL inspirate did not affect any major systemic changes of pH or P_{CO_2}.

The response of lobar blood flow to local alveolar hypoxia was enhanced by the addition of CO_2 to the inspirate. When the lobar inspirate is changed from 100% O_2 to 100% N_2, $\dot{Q}_{LLL}/\dot{Q}_T$ decreased to 69.6 ± 36.6% (SD) of control values. When the lobar inspirate was changed from 100% N_2 to 10% CO_2-90% N_2, $\dot{Q}_{LLL}/\dot{Q}_T$ decreased to 50 ± 23% of its control value on 100% O_2. The magnitude of this change is not significantly different from the decrease of $\dot{Q}_{LLL}/\dot{Q}_T$ when the lobar inspirate is changed directly from 100% O_2 to 10% CO_2-90% N_2 (30.2 ± 6.7%). Under hyperoxic conditions, the addition of 10% CO_2 to lobar inspirate had no effect on $\dot{Q}_{LLL}/\dot{Q}_T$ in all 10 dogs.

The dynamic responses of lobar blood flow to the four interventions are shown in Table 4. Not only was there a predominantly damped oscillatory response to hypoxia with concomitant hypocapnia (*intervention I*) as observed in the first series of experiments, but the same type of dynamic response was observed when there was concomitant hypercapnia (*intervention II*). In fact, a damped oscillatory response to local alveolar hypercapnia was observed under hypoxic conditions (*interventions II* and *IV*), but under hyperoxic conditions, there was no response to local hypercapnia (*intervention III*).

As in the first series of experiments, we found that the damped oscillatory responses were the result of fluctuations of $\dot{Q}_{LLL}$ rather than $\dot{Q}_T$. During the hypoxic challenge with concomitant hypercarbia we compared each

TABLE 3. *Arterial blood gas composition in second series of experiments*

Inspirate to LLL	pH	P_{CO_2}, Torr	P_{O_2}, Torr
100% O_2	7.45±0.03	30±2	319±25
90% O_2-10% CO_2	7.45±0.03	26±2	307±24
100% N_2	7.46±0.03	26±1	155±28
90% N_2-10% CO_2	7.42±0.03	29±2	212±37

Values are means ± SD; n = 10 expts. Arterial blood samples for measurement of pH, P_{CO_2}, and P_{O_2} were obtained after each inspired gas mixture to left lower lobe (LLL) had been administered for 60 min.

TABLE 4. *Dynamic responses recorded in second series of experiments*

Intervention	Response		
	Nonreactive	Monotonic	Damped oscillatory
I. Hypoxia with concomitant hypocapnia	0	1	9
II. Hypoxia with concomitant hypercapnia	10	0	0
III. Hypercapnia under hyperoxic conditions	0	4	6
IV. Hypercapnia under hypoxic conditions			

Total number of observations is 10 for each intervention.

variable under three conditions: *1*) during control period of hyperoxia, *2*) during the hypoxic response when $\dot{Q}_{LLL}/\dot{Q}_T$ was minimal, and *3*) when $\dot{Q}_{LLL}/\dot{Q}_T$ was maximal. We found significant differences ($P < 0.0001$) for $\dot{Q}_{LLL}$ (0.30 ± 0.11, 0.12 ± 0.09, and 0.18 ± 0.12 l/min, respectively), whereas $\dot{Q}_T$ was unchanged (2.0 ± 0.54, 2.1 ± 0.66, and 1.99 ± 0.66 l/min, respectively).

The damped oscillatory response of lobar $\dot{Q}$ to hypoxia with concomitant hypocapnia (*intervention I*) had a damping ratio of 0.36 ± 0.29 and a cycle time of 28.4 ± 13 min. The damped oscillatory response of lobar $\dot{Q}$ to hypercapnia under hypoxic conditions (*intervention III*) had a damping ratio and a cycle time that did not attain statistical significant difference: 0.11 ± 0.09 and 30.5 ± 15.5 min, respectively. The damped oscillatory response to local alveolar hypoxia with concomitant hypercapnia (*intervention II*) had a damping ratio (0.4 ± 0.2) similar to the damped oscillatory response to hypoxia with concomitant hypocapnia, but the cycle time (16.9 ± 5.9 min) was significantly shorter ($P < 0.05$).

DISCUSSION

Comparison of our results to others. For our first series of experiments, we compared our data with those of Benumof et al. (2). We expressed his experimental data in our own system of data analysis. For Benumof's results, we found that lobar blood flow ($\dot{Q}_{LLL}/\dot{Q}_T$) decreases 47% in response to hypoxia with a damping ratio of 0.42 and a natural frequency of 0.24 rad/min. This result is remarkably close to our results of a mean damping ratio of 0.47 and natural frequency of 0.23 rad/min.

Our results are also similar to the results of Chen et al. (4), who found no enhancement of the hypoxic pulmonary vascular response by repeated challenges of hypoxia that have been reported by others (9, 10, 13). The lack of enhancement is probably because sufficient time elapsed after completion of surgery before data collection began for our animals to recover from any depression of the hypoxic response. Although this result sheds no light on the nature of this phenomenon, it does indicate that our preparation has a stable hypoxic response over the period of data collection.

Dynamics of the pulmonary vascular response to O_2 and CO_2. The striking result obtained in the first series of experiments was the difference between the on- and off-transient (Figs. 2 and 3). The on- and off-transients should have the same dynamic response in a linear system. Instead, we found a predominantly damped oscillatory response during the on-transient and a consistently monotonic response during the off-transient. This result indicates that there is a marked nonlinearity in the system. Although the response to hyperoxia was observed only for 30 min, this period is adequate to detect an oscillatory response with a cycle time of 26 min observed in the response to hypoxia. Another feature of the results that indicates that the system is nonlinear is the positive correlation between the damping ratio and the magnitude of the steady-state response. The greater the steady-state response, the less oscillatory behavior was demonstrated. If the dynamic response to hypoxia is linear, then the damping ratio should be independent of the magnitude of the response. We found that local alveolar hypercapnia affects local $\dot{Q}$ under hypoxic conditions but not under hyperoxic conditions. Therefore the most likely source of this nonlinearity is an interaction between the effects of lobar $P_{A_{O_2}}$ and $P_{A_{CO_2}}$ on local $\dot{Q}$.

Interaction between the effects of alveolar O_2 and CO_2. An interaction between the effects of O_2 and CO_2 has been suggested in earlier experimental data by Viles and Shepherd (15) and Barer and Shaw (1), but the form of this interaction was not defined. Two forms of this interaction can be identified. The interaction may result from an effect of lobar $P_{A_{CO_2}}$ altering the dynamic characteristics of the dynamic hypoxic response. For example, the dynamic characteristics of the hypoxic response may depend on the level of lobar $P_{A_{CO_2}}$. The hypocapnia associated with hypoxia may alter the time constants of the hypoxic response to convert a monotonic response under eucapnic conditions into a damped oscillatory response under hypocapnic conditions (*proposition 1*). Alternatively, the interaction may be the result of an effect of lobar $P_{A_{O_2}}$ on the dynamics of the effects of lobar $P_{A_{CO_2}}$ on local $\dot{Q}$ (*proposition 2*). The fact that Benumof et al. (2) found that eucapnia abolished the dynamic oscillatory vascular response to hypoxia is consistent with both propositions.

Our second series of experiments attempted to distinguish between these two possible $P_{A_{O_2}}$-$P_{A_{CO_2}}$ interactions. The crucial result is that the damped oscillatory response of lobar blood flow to hypoxia occurs under hypercapnic conditions. This result is incompatible with the proposition that the dynamic oscillatory hypoxic vascular response is solely the result of the presence of hypocapnia. Therefore our first proposition is rejected. Under hyperoxic conditions, hypercapnia has no effect on lobar blood flow that supports the proposition that it was alveolar O_2 that altered the effect of lobar alveolar CO_2 on local $\dot{Q}$. An effect of local alveolar CO_2 on lobar blood flow only occurs under hypoxic conditions.

Some observations made during the first series of experiments also concur with this view. The positive correlation between damping ratio and the magnitude of the steady-state response may result from a combination of a strong component of hypoxic vasoconstriction and a weak component of vasodilation because of the concomitant hypocapnia. Therefore, oscillatory effects of a weak hypocapnic response become less apparent as the magnitude of the steady-state response increases. Furthermore, on occasions when there was a monotonic response during the on-transient, a monotonic response with similar time constant was recorded during the off-transient. Therefore, without the damped oscillatory response to changes of CO_2 the local pulmonary vascular response does behave like a linear system.

The model proposed by Grant and Schneider (6) predicted that the damped oscillatory response was the result of changes of local alveolar CO_2 per se. These results and the results of previous experiments (2) are consonant with this idea. Benumof et al. (2) showed that if the changes of local alveolar CO_2 are prevented during a hypoxic challenge then a monotonic decrease in lobar

blood flow occurs in response to local hypoxia. We both showed that hypoxia associated with hypocapnia causes a damped oscillatory response. The present experiments show that hypoxia associated with hypercapnia also causes a damped oscillatory response. Therefore, it seems reasonable to conclude that the damped oscillatory response is the result of local changes of CO_2 because both increases and decreases in alveolar CO_2 cause a damped oscillatory response and maintaining a constant level of CO_2 will prevent it from occurring. Therefore, this prediction of the model appears to be correct. On the other hand, the model does not predict the monotonic off-transient that we observed in the first series of experiments, nor does it predict the lack of response to local hypercapnia in the presence of local hyperoxia. Therefore, these experiments indicate that the mathematical model needs to be revised to include at least an interaction between the effects of O_2 on the pulmonary vascular response to CO_2.

We have been unable to abolish the damped oscillatory response with α or β sympathetic blockers or with cyclooxygenase inhibitors in pilot experiments. We also tested the effects of leukotriene inhibitor Piripost (Upjohn, Kalamazoo, MI), but severe hypotension rendered the results uninterpretable. Therefore, the biochemical basis of the damped oscillatory response remains to be elucidated.

We thank P. Krawczyk, S. Neth, and C. Theophilos for technical assistance and M. Barber and B. Sauka for preparation of the manuscript.

This work was supported by a grant-in-aid from the American Heart Association and with funds from the West Palm Beach Chapter of the American Heart Association and by National Heart, Lung, and Blood Institute (NHLBI) Grant HL-41011. B. J. B. Grant is a recipient of NHLBI Research Career Development Award HL-01418. L. J. Paradowski is a recipient of a Parker B. Francis Fellowship for pulmonary research.

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Received 21 March 1988; accepted in final form 19 January 1989.

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