

# Potential of Lobar Hypoxic Pulmonary Vasoconstriction by Intermittent Hypoxia in Dogs

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Based on previous whole lung findings, the authors tested the hypothesis that lobar hypoxic pulmonary vasoconstriction (HPV) would be potentiated by repeated intermittent lobar hypoxic challenges. In sixteen open-chested pentobarbital-anesthetized dogs they found that repetitive selective hypoxia of the left lower lobe (LLL) (Group I = LLL nitrogen ventilation,  $n = 8$ ; Group II = LLL absorption atelectasis,  $n = 8$ ) caused the percentage decrease in the electromagnetically measured fraction of the cardiac output perfusing the LLL ( $\dot{Q}_{LLL}/\dot{Q}_t$ ) to become progressively greater (increased LLL HPV) through the first three hypoxic challenges in Group I and through the first four hypoxic challenges in Group II. In four dogs in each group, after eight sequential hypoxic challenges with the initial standard method had been performed, the alternative method was performed three times. There was no significant difference between the eighth LLL HPV response and the subsequent three. These findings indicate that 1) the mechanism of blood flow decrease to atelectatic lung is probably the same as for nitrogen-ventilated lung, namely, by HPV, and 2) in order to maximize HPV in the nonventilated lung during one lung ventilation, several repeated intermittent cycles of deflation-inflation to the lung should be performed during the initiation of one lung ventilation. (Key words: Hypoxia; hypoxic pulmonary vasoconstriction. Lung; atelectasis; blood flow; pulmonary artery; shunting; vascular resistance. Oxygen: blood levels.)

THE PULMONARY VASCULATURE responds to alveolar hypoxia with vasoconstriction and the phenomenon is called hypoxic pulmonary vasoconstriction (HPV). When the whole lung (both lungs) is made hypoxic, pulmonary artery pressure (PAP) and total pulmonary vascular resistance (PVR) increases. However, the whole lung HPV-induced increases in PAP and PVR have been shown to progressively increase in magnitude as a function of the number of intermittent whole lung hypoxic challenges until the fifth or sixth hypoxic challenge. Thereafter the whole (both) lung HPV response (increased PAP and PVR) plateaus at a stable maximum.<sup>1</sup>

Based on these whole lung HPV findings, it is reasonable to hypothesize that the magnitude of

regional HPV may also increase as a function of the number of intermittent regional hypoxic challenges. This has potential clinical implication since the initiation of one-lung anesthesia ordinarily involves only one hypoxic challenge to the nonventilated lung; therefore, HPV in the nonventilated lung may not be maximal. The purpose of this experiment was to test this hypothesis by quantitating the magnitude of regional HPV as a function of the number of repeated intermittent regional hypoxic challenges. Our regional hypoxic challenges consisted of lobar atelectasis and nitrogen ventilation.

## Methods

Our experimental preparation has been previously described<sup>2-7</sup> and is only summarized here. Sixteen mongrel dogs (18-26 kg) were anesthetized with intravenous pentobarbital, 25 mg/kg; the trachea was intubated and the lungs were ventilated with 100 per cent  $O_2$  by one side of a dual-piston Harvard<sup>®</sup> respirator. Through a T5-T6 intercostal thoracotomy, electromagnetic flow probes (Statham SP 7515) were placed around the main and left lower lobe (LLL) pulmonary arteries. LLL blood flow was expressed as a fraction of the cardiac output ( $\dot{Q}_{LLL}/\dot{Q}_t$ ). Femoral artery, pulmonary artery (PAP) and left atrial ( $P_{la}$ ) pressures were measured directly. The LLL bronchus was cannulated distal to a ligature and ventilated with 100 per cent  $O_2$  independently and synchronously with the rest of the lung (RL). Tidal volumes and external dead space in each ventilated compartment were manipulated to produce equal airway pressures and end-tidal  $CO_2$  concentrations of approximately 5 per cent (Beckman LB-2<sup>®</sup>). Respiratory rate was adjusted to achieve  $Pa_{CO_2}$  of approximately 40 torr.

In eight dogs the experimental sequence consisted of changing the ventilating gas mixture of the LLL from 100 per cent  $O_2$  to 95 per cent  $N_2$  and 5 per cent  $CO_2$ <sup>1</sup> (Group I, LLL  $N_2$  ventilation) until a new decreased steady state  $\dot{Q}_{LLL}/\dot{Q}_t$  was obtained (10 min). The LLL was then ventilated with 100 per cent  $O_2$  until a new increased steady state normoxic control  $\dot{Q}_{LLL}/\dot{Q}_t$  was achieved. The LLL  $N_2$  ventilation-to- $O_2$  ventilation sequence was repeated for a total of eight intermittent hypoxic challenges in each dog (fig. 1,

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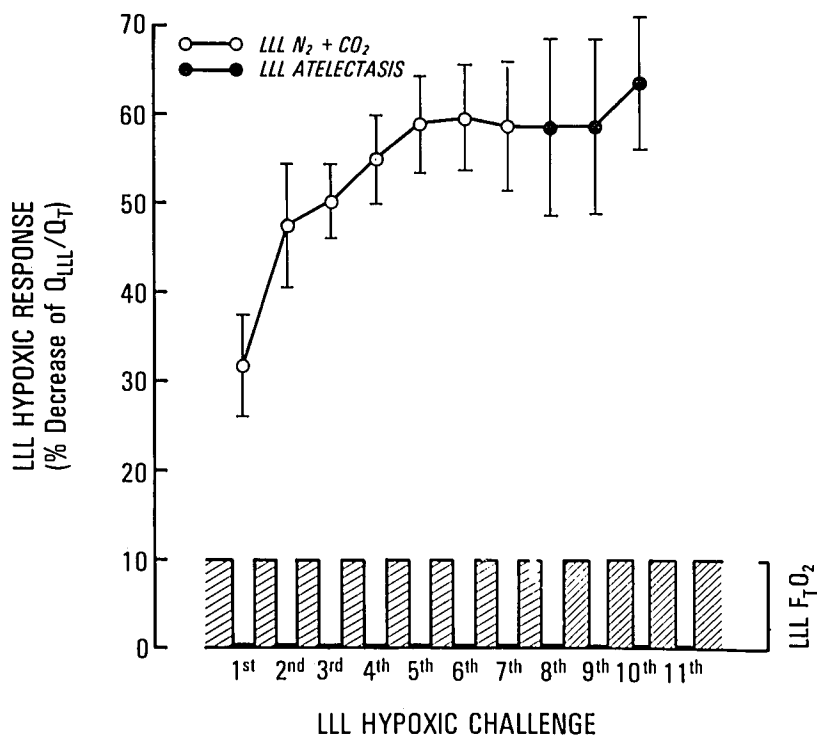
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FIG. 1. Left lower lobe (LLL) hypoxic response (per cent decrease)  $\dot{Q}_{LLL}/\dot{Q}_I$  as a function of repeated ( $n = 11$ ) intermittent hypoxic challenges for Group I.



open circles). In four of the Group I dogs, three additional hypoxic challenges (numbers 9, 10, 11, closed circles in fig. 1) were obtained utilizing absorption atelectasis of the LLL. After ventilation of the LLL with 100 per cent  $O_2$ , the LLL endobronchial tube was occluded and the LLL allowed to undergo absorption atelectasis until a new decreased steady state  $\dot{Q}_{LLL}/\dot{Q}_I$  was obtained (~10 min). The LLL was then reexpanded and ventilated with 100 per cent  $O_2$  until a new increased control  $\dot{Q}_{LLL}/\dot{Q}_I$  was achieved and the sequence repeated for a total of three times.

In eight additional dogs the experimental sequence consisted of ventilating both lung compartments with 100 per cent  $O_2$  and then occluding the LLL endobronchial tube until complete absorption atelectasis had occurred (Group II, LLL absorption atelectasis) and a new decreased steady state  $\dot{Q}_{LLL}/\dot{Q}_I$  was achieved (~10 min). The LLL was then expanded until no gross atelectasis was visible and ventilated with 100 per cent  $O_2$  as previously until a new increased steady state control  $\dot{Q}_{LLL}/\dot{Q}_I$  was achieved. The LLL absorption atelectasis- $10-O_2$  ventilation sequence was repeated for a total of eight intermittent hypoxic challenges in each dog (fig. 2, closed circles). In four of the Group II dogs, three additional hypoxic challenges (numbers 9, 10, 11, open circles in fig. 2) were obtained utilizing 95 per cent  $N_2$  and 5 per cent  $CO_2$  ventilation of the LLL as described above.

In all dogs, all  $\dot{Q}_{LLL}/\dot{Q}_I$  changes (decreases and in-

creases) were allowed sufficient time to reach a steady state and required approximately 10 min (range 7–13 min). The LLL HPV response is expressed as the percentage decrease in  $\dot{Q}_{LLL}/\dot{Q}_I$  (per cent decrease  $\dot{Q}_{LLL}/\dot{Q}_I$ ). All results are expressed as means  $\pm$  SE and were analyzed by the F test and Student's paired t test with  $P < 0.05$  considered significant.

### Results

The eight LLL group I HPV responses (per cent decrease  $\dot{Q}_{LLL}/\dot{Q}_I$ ) with nitrogen and carbon dioxide ventilation are shown in figure 1. The initial LLL HPV response was  $31.8 \pm 5.9$  per cent and was significantly less than LLL responses two through eight (range 47.4–59.47 per cent) with  $P < 0.01$ . However, the second through the eighth LLL HPV responses were not significantly different from one another although comparison of the second to the third LLL HPV response yielded a  $P < 0.075$ . Responses 9, 10, 11, (LLL absorption atelectasis) were not significantly different from the eighth LLL nitrogen ventilation HPV response.

The eight Group II LLL HPV responses during atelectasis are shown in figure 2. The initial LLL HPV response was  $24.0 \pm 7.0$  per cent and was significantly less than responses three through eight (range 43.2–61.5 per cent) with  $P < 0.05$  but not significantly different from the second LLL HPV re-

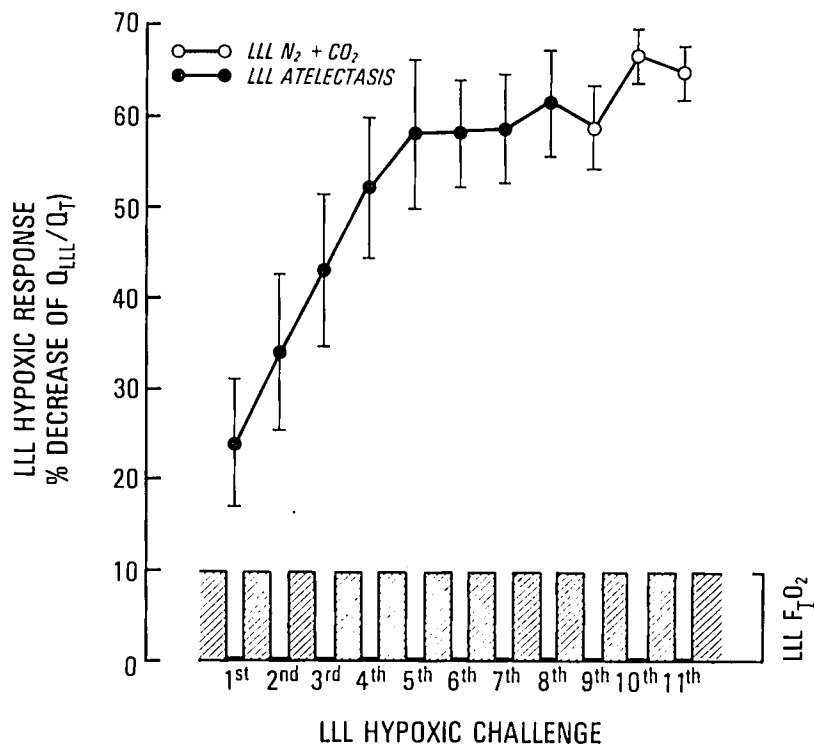


FIG. 2. Left lower lobe (LLL) hypoxic response (per cent decrease  $\dot{Q}_{LLL}/\dot{Q}_T$ ) as a function of repeated ( $n = 11$ ) intermittent hypoxic challenges for Group II.

sponse. The second LLL HPV response was  $34.0 \pm 8.5$  per cent and was significantly different at  $P < 0.05$  from the third LLL HPV response of  $43.2 \pm 8.3$  per cent ( $P < 0.05$ ). The third LLL HPV response was significantly different ( $P < 0.05$ ) from the fourth through the eighth LLL HPV response. However the fourth through the eighth LLL HPV responses were not significantly different from one another. Responses 9, 10, 11 (LLL nitrogen ventilation) were not significantly different from the eighth LLL atelectasis HPV response. Comparison of the effects of hypoxic challenges shown in figure 1 with those of the same hypoxic challenge in figure 2 revealed no significant difference between the two groups.

Table 1 shows the mean PAP,  $P_{Ia}$  and  $\dot{Q}_T$  during LLL oxygen ventilation and LLL hypoxia for both LLL nitrogen ventilation (Group I) and LLL absorption atelectasis (Group II). Although the direction of change in these variables was consistent between LLL oxygen ventilation and LLL hypoxia for the two groups, the changes in the mean values were small and

not significant. The control LLL oxygen ventilation  $\dot{Q}_{LLL}/\dot{Q}_T$  for Group I and Group II were very similar ( $19.9 \pm 3.3$  and  $21.4 \pm 2.2$  per cent, respectively) and  $\dot{Q}_{LLL}/\dot{Q}_T$  did not vary significantly from these values during the ten subsequent LLL oxygen ventilation periods in each group (range for Group I: 19.1–23.0 per cent; range for Group II: 20.7–23.8 per cent).

## Discussion

We have found that repeated (2–4 times) intermittent hypoxic challenges to a lobe of the lung potentiates and finally maximizes lobar HPV. Before discussing these findings, consideration should be given to the experimental model employed: specifically the use of different animals for Groups I and II, the use of the LLL as the hypoxic test segment and the effect of time on the LLL HPV response.

Our results strongly support the use of different animals for our lobar nitrogen ventilation and absorption atelectasis groups. In the four animals in

TABLE 1. Hemodynamic Effects of LLL Hypoxia

	LLL 100 Per Cent Oxygen			LLL Hypoxia		
	PAP (torr)	$P_{Ia}$ (torr)	$\dot{Q}_T$ (ml/min)	PAP (torr)	$P_{Ia}$ (torr)	$\dot{Q}_T$ (ml/min)
LLL $N_2$ Ventilation	$14.5 \pm 0.5$	$7.3 \pm 0.3$	$1885 \pm 86$	$14.6 \pm 0.4$	$7.4 \pm 0.3$	$1864 \pm 76$
LLL Atelectasis	$13.0 \pm 0.4$	$6.1 \pm 0.2$	$2080 \pm 107$	$13.3 \pm 0.2$	$6.2 \pm 0.2$	$2048 \pm 102$

each group in whom the alternative method of induction of lobar hypoxia was used (LLL HPV responses 9, 10, and 11) after the standard group method (LLL HPV responses 1–8), there was no significant difference (either statistically, biologically, or physiologically) between the last standard method LLL HPV response (number 8) and the three alternative method LLL HPV responses (numbers 9, 10, 11). Thus, exposure of our animals to one form of alveolar hypoxia caused the animals to respond maximally to the other form of alveolar hypoxia and precluded the animals from serving as their own controls for both groups. Within each group, however, cannulation of the LLL bronchus resulted in a variable, but brief (2–4 min) period of nonventilation of the O<sub>2</sub> filled LLL. It is possible then that our first LLL hypoxic challenge was really the second. With the exception of this relatively internal constant error, we were required to use animals that had no prior history of exposure to alveolar hypoxia.

We have previously shown that the LLL experiences a significantly greater percentage decrease in blood flow in response to alveolar hypoxia than does a single lung (either right or left).<sup>5</sup> Therefore, the use of the LLL as our hypoxic test segment would permit a clearer resolution of significant differences between the hypoxic challenges than would use of a poorer HPV responding single lung. Thus, it is possible that repeated intermittent human one-lung hypoxic challenges would not result in as large a favorable improvement in blood flow distribution as our present canine lobar results would predict.

In the present experiments lobar HPV increased in magnitude in the first 1–1.5 hours following the completion of instrumentation of the animals (the time period necessary to perform the first three to four LLL HPV responses). How do we know that the LLL HPV response would not have improved during this time period irrespective of the interposed repeated intermittent hypoxic challenges? There are only two other likely modes of oxygen exposure history for the LLL during this time period other than repeated intermittent hypoxia; namely continuous hypoxia or continuous normoxia. We have both direct and indirect evidence that neither of these modes of LLL oxygen exposure history would have resulted in increased LLL HPV.

We have previously directly shown in the same experimental model<sup>4</sup> that the first exposure of the LLL to continuous hypoxia (LLL nitrogen ventilation alone, without 5 per cent CO<sub>2</sub>) for one hour resulted in a  $\dot{Q}_{LLL}/\dot{Q}_l$  that initially decreased and then oscillated in a progressively damped fashion. The final  $\dot{Q}_{LLL}/\dot{Q}_l$  (after the oscillations damped) was greater

than the initial maximum  $\dot{Q}_{LLL}/\dot{Q}_l$  decrease which represents a small *decrease* in LLL HPV with time. The second exposure of the LLL to continuous hypoxia (LLL absorption atelectasis and nitrogen ventilation with 5 per cent CO<sub>2</sub>) for slightly more than one hour resulted in a stable decreased  $\dot{Q}_{LLL}/\dot{Q}_l$ . Following both the first and second periods of continuous hypoxia, the LLL was made normoxic which caused  $\dot{Q}_{LLL}/\dot{Q}_l$  to increase to a value not different from the previous LLL oxygen ventilation values. Thus, neither the first nor the second exposure of the LLL to continuous hypoxia results in a spontaneous (solely time related) potentiation of lobar HPV. This conclusion has been reached by others.<sup>8,9</sup>

There are several indirect reasons why a period of one hour of LLL normoxia following instrumentation should not be expected to potentiate LLL HPV. First, the LLL is normally always normoxic; this is presumably the environment that the LLL has always been in and should not be expected to enhance the mechanism(s) necessary for the production of HPV. Second, we have had a large experience with our instrumentation and catheterization techniques,<sup>2-7</sup> and we do not feel that these interventions have temporally damaged the LLL. In support of this contention are the two facts that our initial and the subsequent ten control normoxic  $\dot{Q}_{LLL}/\dot{Q}_l$  were normal and relatively uniform, and the ventilatory characteristics of the LLL were normal (LLL airway pressure and end-tidal CO<sub>2</sub> were equal to the rest of the lung with a normal LLL tidal volume and external dead space). Third, during the course of this experimental experience (2–7) we have observed both large and small initial LLL HPV responses after both long and short time periods of LLL normoxia following the surgical period. Thus, variation in LLL responsiveness to hypoxia from dog to dog initially seems to be more dependent on inherent individual variation<sup>10</sup> than on differences in surgical preparation.

Our findings have both a basic science implication and a potential clinical application. The basic science implication is that the mechanism of blood flow decrease in atelectatic lung is likely the same as in nitrogen-ventilated lung, namely, by HPV.<sup>7</sup> This contention is supported by several of our findings. First, if a mechanical interference (kinked or twisted vessels) to blood flow was responsible for the initial decreased atelectatic lobe blood flow<sup>11</sup> then such a factor would not be expected to demonstrate potentiation with repeated atelectatic experiences. Yet, we found the clearest potentiation of lobar HPV with our absorption atelectasis Group II. The potentiation of lobar HPV can not represent simple progressive mechanical distortion of the LLL since the LLL was fully ex-

panded following each atelectatic experience and the eleven control oxygen ventilation  $\dot{Q}_{LLL}/\dot{Q}_t$  were essentially constant (nonchanging oxygen  $\dot{Q}_{LLL}/\dot{Q}_t$  baseline) and continuous hypoxia of the LLL (either LLL atelectasis and/or LLL nitrogen ventilation with  $\text{CO}_2$ ) results in a stable decreased  $\dot{Q}_{LLL}/\dot{Q}_t$  (nonchanging hypoxic  $\dot{Q}_{LLL}/\dot{Q}_t$  baseline).<sup>4</sup> Second, the slopes and heights of the curves in figures 1 and 2 were nearly identical and further indicate that there was no constant difference between Group I and II. Third, the lack of difference between the last standard group method LLL HPV response (number 8) and three alternative method LLL HPV response (numbers 9, 10, 11) strongly suggests a common mechanism of decreased blood flow in the two groups and approximates the experimental design of a previous experiment which came to the same conclusion.<sup>7</sup> The precise mechanism responsible for the HPV response is unknown but may involve release of a vasoactive metabolite into the pulmonary interstitial compartment<sup>12</sup> or may result from a direct effect of alveolar hypoxia on the vessel wall.<sup>13</sup>

The potential clinical implication of our findings is concerned with the manner in which one-lung ventilation is instituted. Normally, the lung that is to be deflated is first ventilated with 100 per cent  $\text{O}_2$ . The airway to that lung is then clamped and the lung is allowed to undergo absorption atelectasis. Thus, the induction of one-lung ventilation normally involves only one hypoxic challenge to the nonventilated lung; our findings suggest that under these circumstances HPV in that lung would not be maximal. Our findings suggest that an improvement in the *initiation* of one-lung ventilation would be to employ several cycles of deflation-inflation to the lung which is to be deflated in order to maximize hypoxic vasoconstriction in that lung. In order to avoid creating a large negative pulmonary interstitial pressure and therefore pulmonary edema in the re-expanding lung<sup>14,15</sup> each inflation should be performed slowly (over a few seconds). Under these circumstances (short duration of atelectasis, slow re-expansion)<sup>16</sup> we would anticipate that the benefit-risk ratio would be maximized.

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