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Intermittent Hypoxia Increases Lobar Hypoxic Pulmonary Vasoconstriction

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The author tested the hypothesis that in a canine lobar hypoxic pulmonary vasoconstriction (HPV) model, the passage of time alone would eliminate a previously observed association between increasing lobar HPV and repeated intermittent hypoxia of the lung lobe. The HPV model included electromagnetic measurement of the fraction of the cardiac output perfusing the left lower lobe (Q_{LLL}/Q_t) and ventilation of the left lower lobe (LLL) independent of, but still synchronous with, the rest of the lung. Following surgical preparation of the model, the LLL and the rest of the lung were ventilated with 100% O_2 and no further manipulations or procedures were performed for 120–150 min. The LLL then was made intermittently hypoxic four times by ventilation with 95% N_2 and 5% CO_2 and the LLL HPV response was quantified as the per cent decrease in Q_{LLL}/Q_t. The LLL was kept either normoxic or hypoxic until the Q_{LLL}/Q_t ratio was stable for several minutes. The first three LLL hypoxic exposures caused a significant progressive increase in LLL HPV response (from 37.8 to 54.7 to 61.3%) while the second LLL HPV response required significantly less time (16.6 min) to reach a stable decreased Q_{LLL}/Q_t value compared with the first LLL HPV response (26.4 min). Animals with the smallest initial LLL HPV response increased their HPV response the most, and animals with the largest initial LLL HPV response increased their HPV response the least with repeated LLL hypoxic exposures. The conclusion that intermittent hypoxia increases HPV has important implications for the conduct of HPV experiments and the interpretation of blood-gas changes during one-lung ventilation for thoracic surgery. (Key words: Hypoxia: alveolar; hypoxic pulmonary vasoconstriction. Lung: blood flow; pulmonary artery; vascular resistance. Oxygen: alveolar.)

BASED UPON ANIMAL STUDIES done in this laboratory it recently was claimed that repeated intermittent hypoxic challenges to a lobe of the dog lung increases lobar hypoxic pulmonary vasoconstriction (HPV) over a time period of 60–120 min.[1] However, the experimental design consisted of instituting the repeated intermittent hypoxic challenges immediately after instrumentation of the lung lobe (cannulation of lobar bronchus, placement of circumferential flowprobe around lobar artery). It is possible, therefore, that a very recent past history of vessel manipulation prevented the vessels from responding to hypoxia normally (*i.e.*, maximally) for a period of time. If a waiting period had been interposed between vessel manipulation and the initiation of the repeated intermittent hypoxic challenges, perhaps no increases in lobar HPV would have been observed.[2] There is evidence to support this contention; in a small group of dogs (n = 4) with an intact chest wall and a tracheal divider in place, an initially weak single-lung (one lung, unilateral) response to 100% N_2 ventilation (11% decrease in the blood flow to the lung) improved significantly (30% decrease in the blood flow to the lung) by simply ventilating the lung in question with room air for several hours.[3] The purpose of this investigation was to test the effect of passage of time alone on the magnitude of the HPV response of a lung lobe by allowing a normoxic rest period of 120–150 min to pass after instrumentation of the test lobe, and then exposing the test lobe to repeated intermittent exposures of nitrogen and carbon dioxide ventilation.

Methods

The experimental preparation has been described previously[1] and will only be summarized here. Eight mongrel dogs weighing 17–29 kg were anesthetized

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with 25 mg/kg pentobarbital, iv, and paralyzed with 0.2 mg/kg pancuronium bromide, iv. The trachea then was intubated and the lungs ventilated with 100% O_2 with one pump of a dual-piston Harvard® ventilator. Following a left T5–T6 intercostal space thoracotomy, electromagnetic flow probes (Statham® SP 7515) were placed around the main and left lower lobe (LLL) pulmonary arteries. LLL blood flow is expressed as a fraction of the cardiac output (Q_{LLL}/Q_t). Femoral artery, pulmonary artery (via the femoral vein), and left atrial (via the left atrial appendage) pressures were transduced at the vertical level of the left atrium (FAP, PAP, and LAP, respectively). The LLL bronchus was cannulated distal to a ligature and ventilated independently but synchronously with the rest of the lung (RL) with 100% O_2 with the second pump of the dual piston ventilator with 100% O_2. Tidal volumes and external dead space in each ventilated compartment (LLL and the rest of the lung) were manipulated to produce equal airway pressures and end-tidal CO_2 concentrations of approximately 5% (Bechman LB-2®). Respiratory rate was adjusted to achieve Pa_{CO_2} close to 40 mmHg (±3 mmHg SD).

After completion of the above operative period, both the LLL and the rest of the lung were ventilated with 100% O_2 for 120–150 min and no other manipulations were performed. Following this waiting period, the experimental sequence was begun. This consisted of changing the ventilating gas mixture of the LLL from 100% O_2 to 95% N_2 and 5% CO_2 until a new (decreased) steady-state Q_{LLL}/Q_t was obtained (and an unchanging PAP, LAP, and Q_t); the LLL HPV response is quantified as the percentage reduction in Q_{LLL}/Q_t (% decrease Q_{LLL}/Q_t). The time required to first achieve the new decreased Q_{LLL}/Q_t plateau also was noted. The LLL then was ventilated with 100% O_2 until a new (increased) steady-state normoxic control Q_{LLL}/Q_t was achieved (and an unchanging PAP, LAP, and Q_t). The above ventilation and measurement sequence was repeated for a total of four intermittent hypoxic challenges in each dog; all Q_{LLL}/Q_t changes (decreases and increases) were allowed sufficient time to reach a steady state of at least several minutes duration. All results are expressed as means ± SE and were analyzed by Student's t test for paired data with $P < 0.05$ considered significant.

During the experimental sequence, anesthesia and paralysis were maintained with 3 mg/kg pentobarbital, iv, and 0.05 mg/kg pancuronium, iv, respectively, whenever signs of inadequate anesthesia (increased heart rate, FAP, Q_t) or paralysis (movement, breathing) were present. Ringer's lactate with 5% dextrose was infused at a rate of 100 ml/h. Arterial blood gases were measured periodically (Corning® 165/2 blood-gas analyzer) and sodium bicarbonate was infused iv to correct any metabolic acidosis. Blood temperature was monitored (Yellow Springs Instrument Telethermometer®) and maintained at 37 ± 2° C with the use of a heating lamp.

Results

Table 1 shows the changes in pulmonary vascular pressures, compartmental blood flows and resistances during the four intermittent LLL hypoxic exposures. During each LLL hypoxic exposure, Q_{LLL}/Q_t decreased and PAP, pulmonary vascular resistance of the LLL and total lung (PVR_{LLL} and PVR_t, respectively) increased significantly. Total cardiac output (Q_t), FAP, LAP, and PVR of the rest of the lung (PVR_{RL}) did not change significantly during any of the LLL hypoxic ventilations. There were no significant differences between any of the above hemodynamic parameters during any one LLL normoxic period compared with any other LLL normoxic period.

The four LLL HPV responses (% decrease Q_{LLL}/Q_t) and time to first achievement of a stable maximum LLL HPV response are shown in figure 1. The first three LLL HPV responses significantly and progressively increased; the fourth LLL HPV response was not significantly different from the third LLL HPV. The first LLL HPV took significantly longer to reach a stable maximum plateau value than did LLL HPV responses 2–4; LLL HPV responses 2–4 displayed a progressive downward (shortening) response-time trend.

There was a significant and linear relationship between the initial (first) LLL HPV response (% decrease Q_{LLL}/Q_t) and the ratio of the initial (first) to final (fourth) LLL HPV response (fig. 2). A low initial/final LLL HPV response ratio indicates a large increase, whereas a high initial/final LLL HPV response ratio indicates only a small increase in the LLL HPV response with intermittent hypoxic exposures. Thus, animals with an initially relatively small LLL HPV response increased their HPV response the most, and animals with an initially relatively large LLL HPV response increased their HPV response the least with intermittent LLL hypoxic exposures.

Discussion

Exposure of a lobe of the lung to repeated intermittent hypoxic episodes increased the lobar hypoxic pulmonary vasoconstriction response even when a 120–150 min normoxic waiting period was interposed between surgical preparation and the start of the hypoxic exposures. The design of this experiment was identical to a previous experiment from this laboratory[1] except

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TABLE 1. Pulmonary Vascular Pressures, Compartmental Blood Flow, and Resistances during Four Intermittent Left Lower Lobe Hypoxic Exposures (Means ± SE)

	Exposure							
	1		2		3		4	
Hemodynamic variable	LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2
Q_{LLL}/Q_t (%)	19.6 ± 2.0	12.4* ± 2.1	21.0 ± 2.1	9.7* ± 1.7	20.0 ± 1.7	8.1* ± 1.3	21.2 ± 1.8	8.2* ± 1.2
Q_t (l/min)	2.52 ± 0.55	2.31 ± 0.47	2.06 ± 0.45	2.03 ± 0.42	1.98 ± 0.40	1.97 ± 0.41	1.92 ± 0.39	1.90 ± 0.39
PAP (mmHg)	14.5 ± 0.7	15.8* ± 0.7	15.0 ± 0.8	16.1* ± 0.8	15.5 ± 0.9	16.4* ± 0.9	16.0 ± 0.6	17.0* ± 0.7
LAP (mmHg)	5.8 ± 0.5	5.6 ± 0.6	5.9 ± 0.6	5.9 ± 0.6	6.6 ± 0.6	6.5 ± 0.6	7.3 ± 0.7	7.1 ± 0.7
PVR_{LLL} (dyn·s·cm^{-5})	1,804 ± 290	3,979* ± 925	2,231 ± 488	5,770* ± 1,318	2,267 ± 495	6,873* ± 1,432	2,205 ± 507	6,752* ± 1,641
PVR_{RL} (dyn·s·cm^{-5})	447 ± 80	495 ± 89	559 ± 98	543 ± 92	526 ± 91	533 ± 86	549 ± 86	508 ± 73
PVR_t (dyn·s·cm^{-5})	351 ± 58	427* ± 73	435 ± 72	484* ± 78	418 ± 70	486* ± 76	430 ± 66	483* ± 64

LLL = left lower lobe; LLL-O_2 = LLL normoxic; LLL-N_2 = LLL hypoxic (95% N_2, 5% CO_2); Q_{LLL}/Q_t = fraction of the cardiac output perfusing the LLL; Q_t = total cardiac output; PAP = mean pulmonary artery pressure; LAP = mean left atrial pressure; PVR = pulmonary vascular resistance; PVR_{LLL} = PVR of the LLL; PVR_{RL} = PVR of the rest of the lung; PVR_t = PVR of the total lung.
* $P < 0.025$ compared with the corresponding LLL-O_2 period.

FIG. 1. The first three intermittent exposures of the left lower lobe (LLL) to hypoxia (95% N_2 and 5% CO_2) caused a significant and progressive increase in the LLL hypoxic pulmonary vasoconstriction (HPV) response [measured as the per cent decrease in the fraction of the cardiac output perfusing the LLL (% decrease Q_{LLL}/Q_t), see left-hand ordinate, open circles]. The second LLL hypoxic exposure required significantly less time for Q_{LLL}/Q_t to reach a stable decreased value (see right-hand ordinate, closed circles). The statistical significance notations in the figure result from the application of *t* tests.

for the 120–150 min waiting period. In terms of temporally corresponding events, the first hypoxic challenge in the present experiment corresponded with the fourth hypoxic challenge of the previous experiment (fig. 3). Since only a very small and statistically nonsignificant increase in the test lobe HPV response occurred following the fourth hypoxic challenge in the previous experiment, it is possible, but unlikely, that less of an increase in test lobe HPV would have occurred in the present experiment if the waiting period had been longer. It seems reasonable, however, to exclude time alone as the cause of most of the observed increase in test lobe HPV.

These findings are consistent with observations made by other workers using a wide variety of experimental conditions and techniques. Thus, putting aside the question of the time-alone factor, intermittent hypoxia has been reported to increase HPV in a quantitative manner in one study of whole-lung (both lungs, bilateral) hypoxia[4] and in a qualitative manner in several studies of single-lung (one lung, unilateral) hypoxia.[5–8] However, it should be noted that the whole-lung studies[4] are not directly comparable with the present studies because they involve a very different pathophysiology,[2] and the

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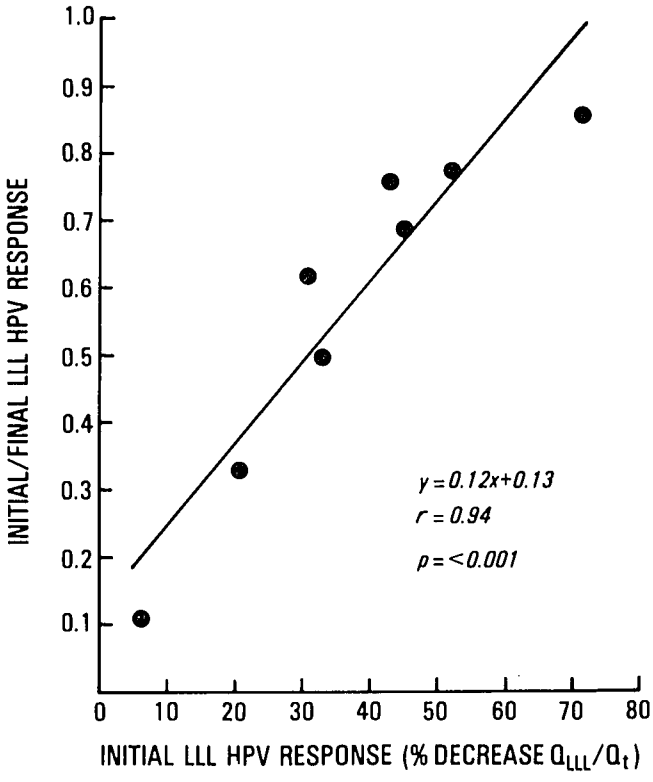

FIG. 2. The magnitude of the initial left lower lobe (LLL) hypoxic pulmonary vasoconstriction (HPV) response [measured as the per cent decrease in the fraction of the cardiac output perfusing the LLL (% decrease Q_{LLL}/Q_t, see abscissa)] correlated very well with the amount of increase in the LLL HPV response that occurred after four intermittent exposures of the LLL to 95% N_2 and 5% CO_2 [expressed as the ratio of the initial (first) to final (fourth) LLL HPV response].

single-lung studies[5-8] do not offer any quantitative result or experimental sequence (time factor) details.

In the present study there was considerable variation among individual dogs in the magnitude of the initial HPV response. These findings are in good agreement with previous experiments from this laboratory using similar experimental methods,[9] and with numerous studies by other workers[10-15] that show that even when experimental conditions are apparently similar, there is great variation in the magnitude of the HPV response between various species[10-12] and between individuals in a given species.[3,9,10,13-16]

The determinants of variation in the magnitude of the initial HPV response are an important consideration because, as figure 2 suggests, if there were no variation in the magnitude of the initial HPV response then there might not be any increase in the HPV response with repeated intermittent hypoxia. The size of the lung compartment is probably the most important single determinant of the exact expression of an HPV response; that is, whether blood flow redistribution (small hypoxic compartment) or increases in pulmonary artery pressure (large lung compartment) will occur.[17,18] When the size of the hypoxic lung compartment is taken into account, the group results of many apparently widely divergent studies actually form a smooth changing continuum between the two possible extreme HPV expressions.[17] However, even when the size of the hypoxic compartment is held constant, there is still considerable variation in the magnitude of the HPV response between individuals in a given group.[9] Other important factors that may contribute to the variation in the magnitude of the HPV between individuals are the absolute level of pulmonary vascular pressure,[19] temperature,[20] alveolar[21] and arterial and mixed venous[22] CO_2 tensions, arterial[23] and mixed venous[24] O_2 tensions, anesthetics,[25] release of modifying bioactive substances[13] (amines, adenosine,[26] prostaglandins[14,16], infection,[27] age,[15,28] chronicity of preexisting lung disease,[13,29] and even gender differences.[30] An example of possible initial HPV response magnitude-increase in HPV response interaction may be found with prostaglandin release. Recent HPV studies in sheep[14] with intermittent hypoxia, and dogs[16] divided animals into "non-reactor" and "reactor" groups (as could have been done in the pres-

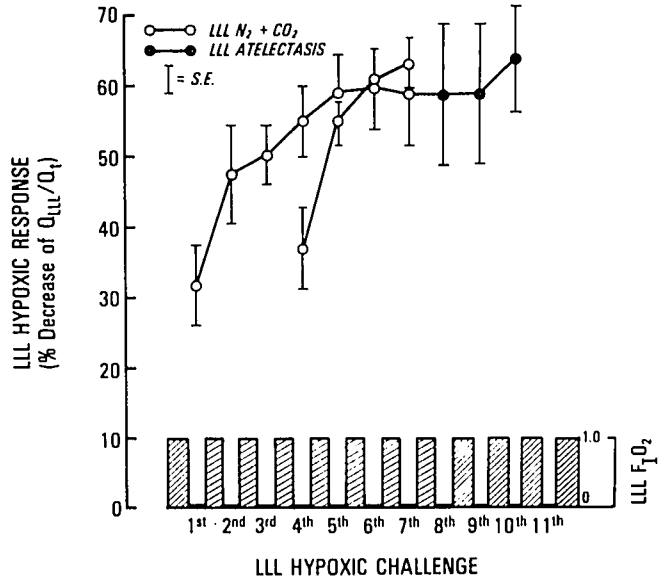

FIG. 3. Superimposition of the results from the present experiments (with post-surgical preparation waiting period, open circles beginning with the fourth LLL hypoxic challenge) onto the results from our previous experiment (without post-surgical preparation waiting period, open circles beginning with the first LLL hypoxic challenge). A few of the SE bars have been deleted from the data points from figures 1 of both the present paper and reference 1 for clarity of presentation. Symbols and abbreviations are the same as in figure 1 of the present paper.

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ent study using a 30% decrease in Q_{LLL}/Q_t dividing line) and showed that these differences in the magnitude of the initial HPV response, and by inference differences in the degree of increase in HPV response, are related to enhanced production of inhibitory vasodilator prostaglandins in the "non-reactors."

It is unlikely that the 20% decrease in cardiac output that we observed during the experiment (and, therefore, perhaps some decrease in mixed venous and alveolar oxygen tensions) can provide an explanation for the increase in the left lower lobe HPV response for several reasons. First, although cardiac output decreased by 20% between the first and fourth left lower lobe hypoxic exposures, decreases in cardiac output of this magnitude from an initial stroke volume level of 100 ml/kg can cause only small decreases in mixed venous oxygen tension. Second, changes in mixed venous oxygen tension near the normal value do not affect HPV.[31,32] Third, and perhaps as an explanation for the second reason, mixed venous oxygen tension-induced decreases in alveolar oxygen tension near the lower limit of alveolar oxygen tension do not change HPV; this is because the dose (alveolar oxygen tension) -response (change in Q_{LLL}/Q_t) curve is sigmoid (upright "S), and the lower alveolar oxygen tension range (below 40 mmHg) is on the flat bottom portion of the curve.[19]

The notion that the smallest initial HPV responses will increase the most and that the largest initial HPV responses will increase the least implies that the distribution (SD) of the final HPV responses for a group should be somewhat smaller than the distribution of the initial HPV responses (taking into consideration the absolute size of the HPV response), and that was indeed the case in the present study. Data from the whole lung HPV potentiation study[4] also support the same conclusion where the linear inverse relationship between initial HPV response and the initial/final HPV response ratio (as in fig. 2) had an $r = 0.54$ and $P < 0.075$ for $n = 12$ dogs. The data in the other reports dealing with HPV potentiation[1,3] also mildly support this implication.

I conclude that intermittent hypoxia maximizes the magnitude of HPV responses from initially submaximal levels. The increase in HPV occurs the most in animals with the smallest initial HPV response and visa versa. The progressively increasing HPV responses require progressively decreasing time to achieve stability. These present findings reemphasize the conclusion that experiments concerned with the determinants of HPV should not use the first measured HPV response as a control response but rather a later and larger plateau HPV response. These findings also indicate that an increasing HPV responsiveness should be another determinant, along with size of unventilated lung, cardiac output, and metabolic status, of Pa_{O_2} during the intermittent one-lung hypoxic conditions of thoracic surgery.

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