Effect of Local Antigen Inhalation and Hypoxia on Lobar Blood Flow in Allergic Dogs[1-3]

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SUMMARY

To determine the local pulmonary vascular response to inhaled antigen and alveolar hypoxia in canine asthma, 8 of 42 skin-test-positive dogs were selected from a preliminary study of airway reactivity to antigen challenge with an extract of *Ascaris suum*. In an anesthetized, open-chest preparation subjected to left cervical vagotomy, the proportion of pulmonary blood flow to the left lower lobe ($\dot{Q}$ lobe/$\dot{Q}$ lung) was estimated by an insoluble gas-elimination method.

Continuous inhalation of antigen to the left lower lobe caused a transient decrease in $\dot{Q}$ lobe/$\dot{Q}$ lung during inspiration of a hyperoxic gas mixture; it did not affect the local hypoxic vascular response. The local decrease in blood flow during antigen challenge was positively correlated with the airway responsiveness determined in the preliminary study. There was no evidence that the decrease in blood flow was caused by a change in airway pressure in the left lower lobe. We conclude that the chemical mediators of asthma caused the vascular response to antigen challenge, but did not abolish the local hypoxic vascular response.

Introduction

This study was stimulated by some results obtained in this laboratory by Wagner and colleagues (1) during measurements of ventilation-perfusion ratio distributions by the inert gas technique in asthmatic patients. They found, as have others (2–5), that a transient hypoxemia occurs with isoproterenol inhalation, and they showed that this was caused by an increase in blood flow to lung units with low ventilation-perfusion ratios. These results suggest that the drug preferentially decreased pulmonary vascular resistance in those areas (6). Initially, it was believed that this was due to the release of hypoxic pulmonary vasoconstriction in units with low ventilation-perfusion ratios. However, breathing pure O_2 did not affect the distribution of ventilation-perfusion ratios. Furthermore, Wanner and colleagues (7–9) have suggested that the chemical mediators of asthma may suppress the pulmonary vascular response to hypoxia in both dog and sheep. If hypoxic pulmonary vasoconstriction cannot explain the effect of isoproterenol on the distribution of blood flow in asthma, perhaps other factors are operating.

To investigate blood flow distribution in asthma, we have developed a new approach with a canine model of experimental asthma. The antigen (an extract of *Ascaris suum*) was administered as an aerosol by continuous inhalation to the left lower lobe (LLL), so that the partitioning of pulmonary blood flow in response to antigen challenge and local alveolar hypoxia could be measured. Before antigen administration to LLL, left cervical vagotomy was performed to decrease local bronchoconstriction and to prevent reflex

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bronchoconstriction from occurring in the rest of the lung (10). This approach avoided systemic hypoxia and minimized the mechanical effects of antigen inhalation on pulmonary mechanics.

Methods

Selection of dogs from a preliminary study. Forty-two healthy mongrel dogs (weight, 18 to 30 kg) were subjected to preliminary study to determine their skin and airway response to dilutions of *A. suum* extract (Greer Labs, N.C., supplied as 1 in 10 wt/vol solution with protein concentration of 11 mg/ml). The dogs were anesthetized with sodium thiamylal (20 mg/kg of body weight, given intravenously) and were intubated with a low-pressure cuff Portex endotracheal tube. Ventilation was maintained with a Harvard pump (Millis, Mass.) and set to give a baseline end-tidal P_{CO_2} of approximately 40 mm Hg measured with a Perkin-Elmer MGA-1100 mass spectrometer. Transpulmonary pressure was measured with a Validyne MP45 (Northridge, Ca.) differential pressure transducer; one side was attached to a balloon catheter system placed at mid-esophageal level; the other side was attached to a multi-side-holed catheter introduced via the endotracheal tube, just proximal to the carina. Air flow was measured with a no. 2 Fleisch pneumotachygraph and a Statham PM15 differential pressure transducer (Gould Inc., Oxnard, Ca). Tidal volume was recorded as the electronically integrated flow signal. All signals were recorded on a Brush multichannel recorder (Gould Inc.). Airflow resistance was calculated by measuring transpulmonary pressure, subtracting the elastic component of this pressure, and dividing by the instantaneous flow (11). The average value of resistance was used from estimates made on 5 consecutive breaths at an inspiratory flow of 0.25 L/s.

The bronchial challenge procedure entailed administration of *A. suum* extract as an aerosol for 3 min. The aerosol was generated by a Bird Mark VII respirator and micronebulizer (Palm Spring, Ca.; range of particle size, 0.5 to 4 μm) from 4 ml of *A. suum* extract in solutions of either 1 in 1,000 or 1 in 100 (wt/vol). Approximately 2.5 ml of solution were delivered during the 3-min period. Pulmonary resistance was measured under baseline conditions 10 min after administration of the 1:1,000 dilution of *A. suum* and, if there was no response, 10 min after administration of the 1:100 dilution.

In addition to the bronchial challenge procedures, skin tests were performed on the anterior chest wall with an intradermal injection of 0.1 ml of control fluid, and 1:1,000 and 1:100 dilutions of *A. suum* extract. Positive responses were recorded if the *A. suum* injections produced more than 10 mm of induration after 15 min and the control injection was negative. Of the 42 dogs, 8 were selected for the main experiments on the basis of airway responsiveness to inhaled *A. suum* extract.

Experimental preparation. Each animal selected from the preliminary studies was subjected to the main experiment 2 to 9 days later. The dogs were anesthetized with 30 mg of sodium pentobarbital/kg of body weight, given intravenously, and were paralyzed with 1.5 mg of gallamine/kg of body weight, given intravenously. After intubation with a cuffed endotracheal tube, the dogs were ventilated with one side of a dual Harvard pump. Catheters were placed in the femoral artery and a peripheral hind limb vein, and a Swan-Ganz catheter was positioned in the main pulmonary artery. Pulmonary arterial pressure was monitored by Bio-Tec BT 70 pressure transducer (Pasadena, Ca.); the level of the right atrium was used for zero reference. Femoral arterial blood pressure was monitored by a Statham P23BB pressure transducer (Gould Inc.). Mean blood pressure could be determined electrically. Esophageal temperature was monitored and maintained at 37 ± 2° C with a heat lamp and a warming blanket. The left vagus in the neck was dissected free from surrounding tissue and cut to prevent reflex effects of the local antigen challenge on the rest of the lung. After thoracotomy through the left fifth and sixth intercostal space, a cannula was inserted through an incision in the left lower lobe (LLL) bronchus and sutured securely to avoid leaks into the air or adjacent lobes. The LLL inspirate was passed through an ultrasonic nebulizer (U.S. 670, Hosp. Med. Corp., Denver, Co.; mass median particle size, 6.5 μm; geometric SD, 1.54 μm) attached to the LLL bronchial cannula. When required, a solution of *A. suum* extract (1 in 100, wt/vol) was introduced through a gas-tight side hole into the nebulizer. This system allowed an aerosol of *A. suum* extract to be added to the LLL inspirate when required, and delivered approximately 15 ml of solution/h.

The LLL was ventilated independently but synchronously with the rest of the lung (ROL). Inspired gas to LLL was either 95 % O_2 plus 5 % CO_2, or 95 % N_2 plus 5 % CO_2; the inspirate to ROL was 100 % O_2. The ventilator was set to maintain an arterial P_{CO_2} (Pa_{CO_2}) of 40 mm Hg. Arterial pH, Pa_{CO_2} and arterial P_{O_2} (Pa_{O_2}) were measured with Radiometer BMS3, Mk 2 (Copenhagen) electrodes. The proportion of ventilation to LLL was set to equalize peak inspiratory and expiratory pressures of LLL with those of the ROL (measured by a Bio-Tec BT70 pressure transducer). Once the ventilator settings were made, they were not altered during an experiment, unless stated otherwise. Airway O_2 and CO_2 dry gas fractions were measured with the mass spectrometer, from either LLL or ROL, but never simultaneously with airway pressure measurements. The expired gas from LLL and ROL was led through separate mixing boxes (approximately 2 and 10 L for the LLL and ROL boxes, respectively). From the mixing boxes, the inspired gas tubing was attached to 2 separate gas-tight bottles to maintain LLL and ROL on positive end-expiratory pressure (5 to 7 cm H_2O) of identical magnitude. Maintenance of positive end-expiratory pressure during expiration provided a means of checking the system for leaks during the experiment.

Measurement of lobar pulmonary flow. The proportion of pulmonary blood flow to LLL ($\dot{Q}$ lobe/$\dot{Q}$ lung) was estimated by an insoluble inert gas-elimination method. Sulfur hexafluoride (SF_6) is a highly insoluble gas that is eliminated almost entirely (> 90 %) from all

lung units with a ventilation-perfusion ratio greater than 0.08. Under these conditions, SF_6 output is proportional to pulmonary blood flow. We continuously infused SF_6 dissolved in isotonic saline into a peripheral vein with a Harvard infusion pump at a rate of 1.2 ml/min. The SF_6 output from LLL relative to total SF_6 output (from LLL and ROL) was calculated from the relative expired ventilations and mixed expired concentrations of SF_6 from LLL and ROL. The mixed expired SF_6 concentrations were measured in duplicate samples of gas obtained from the mixing boxes by gas chromatography, as previously described by our laboratory (12). The relative expired ventilation rate from LLL and ROL was measured with a dry spirometer (Ohio Medical Products, Madison, Wis.).

Protocol. Collection of data was started after completion of experimental procedures (approximately 3 h). Additional sodium pentobarbital to prevent inadequate anesthesia, and gallamine to prevent spontaneous respiration, were given at intervals to avoid administering drug during hypoxic challenge or during the first 40 min of *A. suum* challenge to LLL.

At least 2 periods of LLL hypoxia were induced before and during inhalation of *A. suum* extract. The LLL hypoxia was induced by changing the inspired gas to LLL from 95 % O_2 plus 5 % CO_2 to 95 % N_2 plus 5 % CO_2. Measurements of $\dot{Q}$ lobe/$\dot{Q}$ lung were made before hypoxia, 20 min after lobar hypoxia, and 20 min after returning the lobe to the hyperoxic gas mixture. The 20-min period of LLL hypoxia was sufficient to achieve a steady-state vascular response under these conditions, in which the 5 % CO_2 in the LLL inspirate minimizes changes in LLL alveolar CO_2 fractions (13).

Administration of *A. suum* extract to LLL was started when the lobe was ventilated with the hyperoxic gas mixture. Measurements of $\dot{Q}$ lobe/$\dot{Q}$ lung were made at 10-min intervals for 40 min before hypoxic challenge. Once started, administration of *A. suum* extract to LLL was continued throughout the rest of the experiment.

To determine whether or not the changes in local blood flow were caused by alterations in airway pressure, LLL airway pressure was decreased transiently toward the end of some experiments. The changes in LLL airway pressure were equalized with those of the ROL by decreasing LLL tidal volume for 20 min during administration of *A. suum*. Measurements of $\dot{Q}$ lobe/$\dot{Q}$ lung were made before the ventilator settings were changed, during the change, and after the ventilator was returned to its former setting. This procedure was carried out while LLL was ventilated with 95 % O_2 plus 5 % CO_2 to minimize possible changes of LLL alveolar gas tensions during the decreased LLL ventilation.

At the end of each experiment the lungs were examined microscopically, and specimens were taken from the left and right lower lobes for histologic examination.

Analytic methods. The hypoxic vascular response was calculated as the decrease in $\dot{Q}$ lobe/$\dot{Q}$ lung (expressed as a percentage) with LLL hypoxic challenge from the average of pre- and post-control levels during hyperoxic inspired gas mixtures to LLL. If $\dot{Q}$ lobe/$\dot{Q}$ lung obtained during LLL hypoxia was intermediate between control values, the response was considered indeterminate. The hypoxic vascular response was also calculated as the percentage decrease of $\dot{Q}$ lobe/$\dot{Q}$ lung from control values. The average response was compared before and during *A. suum* administration by the Wilcoxon matched paired test. All statistical methods were nonparametric (14); Kendall's tau was used for correlation tests. Significance was accepted at the 5 % level.

Results

Selection of dogs. All 42 dogs had positive reactions to skin tests with *A. suum* extract. Only 7 dogs had a definite airway response, as judged by the change in pulmonary resistance (R_L). All 7 dogs were selected for the main experiment, together with one other dog that had no significant airway response to *A. suum* extract. The degree of airway responsiveness varied considerably between dogs and was measured as the percentage increase in R_L from baseline values (table 1). Each animal was ranked in ascending order of airway responsiveness. A low rank was assigned to dogs that failed to respond to the lower concentration of *A. suum* extract, but did respond to higher concentration. A higher rank was assigned to dogs that responded to the lower concentration of antigen; in these cases, it was unnecessary to proceed to the higher concentration of antigen. The mean ± SD changes in R_L with inhalation of antigen ranged from 1.2 ± 0.7 to 3.3 ± 2.2 cm H_2O/L/s after inhalation of antigen (n = 8).

Main experiment. The protocol of the main

TABLE 1

AIRWAY RESPONSIVENESS DETERMINED IN PRELIMINARY STUDIES

	Rank Order of Airway Responsiveness							
	1	2	3	4	5	6	7	8
Δ R_L% from baseline*	10	110	160	210	350	110	370	540
Concentration of *A. suum*, wt/vol	1:100					1:1,000		

* Δ R_L% is the percentage change in pulmonary resistance from baseline values at a given concentration of *Ascaris suum* extract in solution.

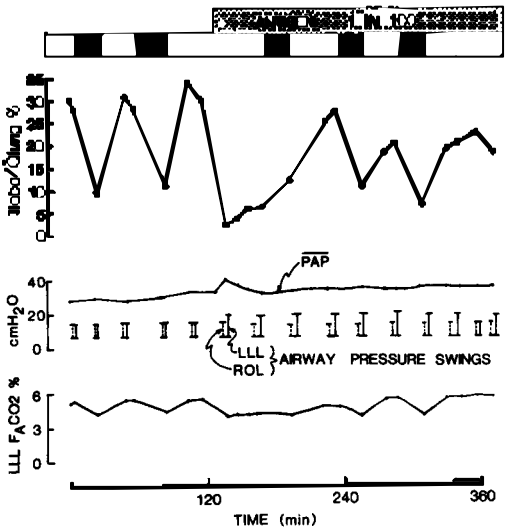

Fig. 1. Example of data obtained during the course of one experiment. The abscissa is duration of data collection, in min. From the top is shown, period of antigen challenge to left lower lobe (stippled area); left lower lobe inspirate—either 95 % O_2, 5% CO_2 (white sections) or 95% N_2, 5% CO_2 (black sections); left lower lobe pulmonary blood flow as proportion of over-all flow ($\dot{Q}$ lobe/$\dot{Q}$ lung); mean pulmonary arterial blood pressure, airway pressure swings of left lower lobe (LLL), and rest of the lungs (ROL); and LLL end-tidal CO_2 fraction (LLL F_ACO_2%).

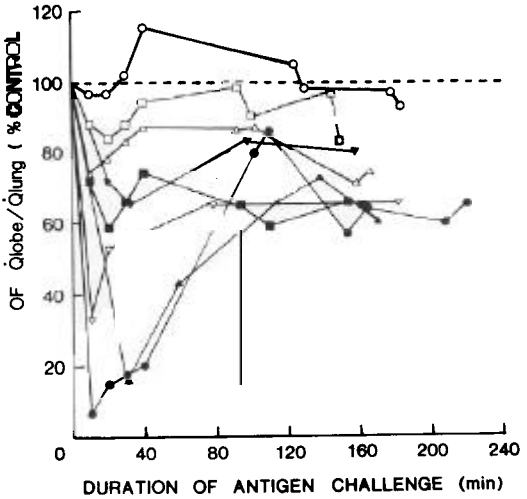

Fig. 2. Response of lobar blood flow ($\dot{Q}$ lobe/$\dot{Q}$ lung) to antigen challenge with hyperoxic inspired gas mixtures for all experiments. The response (ordinate) as a percentage of control value immediately before the start of antigen challenge is plotted against the duration of antigen challenge in min (abscissa).

experiment is shown in figure 1 for the dog with the greatest airway reactivity, as judged from the preliminary study. Before local inhalation of antigen, lobar blood flow decreased during both periods of local alveolar hypoxia. Shortly after local challenge with antigen was begun, and while LLL was ventilated with the hyperoxic gas mixture, there was a dramatic decrease in lobar blood flow that remained low for more than 30 min, then partially recovered despite an intervening period of hypoxia. With continuing of antigen challenge, lobar blood flow failed to regain its former values, although a hypoxic vascular response could still be elicited. The striking changes in lobar blood flow after antigen challenge occurred despite the sustained increase in lobar airway pressure swings. There was no change in ROL airway pressure swings. This experiment showed the greatest variation in pulmonary arterial pressure and of LLL alveolar CO_2 fraction (figure 1) observed in this study.

Effects of local antigen challenge on lobar blood flow. In all experiments, a similar time course of $\dot{Q}$ lobe/$\dot{Q}$ lung response to antigen challenge was seen: a maximal decrease of variable extent within the first 30 min, followed by a partial recovery (figure 2). The one exception occurred in the dog that showed no airway responsiveness to antigen (figure 2, open circles). In this animal, lobar blood flow remained fairly constant during antigen challenge. The data points were taken when the LLL inspirate was the hyperoxic gas mixture. Therefore, any changes in alveolar gas tensions could not account for the considerable variation of vascular response to antigen between experiments.

Lobar blood flow response to antigen and airway pressures. In contrast to the transient vascular response, the LLL airway swings showed a sustained, and remarkably similar, increase with antigen challenge in most cases (figure 3). In all experiments, including one experiment (figures 2 and 3, inverted open triangles) in which left cervical vagotomy was not performed, ROL airway pressure swings were unaffected by LLL antigen challenge.

The effect of the increased LLL airway pressure swings on $\dot{Q}$ lobe/$\dot{Q}$ lung was assessed in 4 experiments. The stroke volume of the pump that ventilated LLL was transiently decreased while LLL was ventilated with the hyperoxic gas mixture during antigen administration. Results are shown in figure 4: the mean ± SD change in $\dot{Q}$ lobe/$\dot{Q}$ lung was -0.2 ± 3.7 %. We conclude from this result that the increased LLL airway pressure swings did not affect $\dot{Q}$ lobe/$\dot{Q}$ lung.

Source of variability of lobar blood flow response to antigen. To determine the source of variation of the local vascular response to antigen, the maximal decrease of $\dot{Q}$ lobe/$\dot{Q}$ lung was correlated with a number of variables. There was no significant correlation with changes in LLL airway pressure swings, arterial blood gas composition, acid-base status, the delay between preliminary study and the main experiment, the extent of hypoxic vascular response, or changes in mean pulmonary arterial pressure. The only variable that was significantly correlated (τ = 0.71; p = 0.015; n = 7) with maximal decrease in $\dot{Q}$ lobe/$\dot{Q}$ lung during antigen challenge was the airway responsiveness of the dog determined in the preliminary study (figure 5). Only the 7 experiments in which the antigen was given in a 1:100 dilution were used in this analysis. One experiment was excluded because the aerosolized *A. suum* extract was given in a 1:1,000 dilution (figures 2 and 3, inverted closed triangles). There was also a significant positive correlation (τ = 0.62; p = 0.035; n = 7) between the percentage decreases from control values of $\dot{Q}$ lobe/$\dot{Q}$ lung after 2 h of antigen challenge and the ranked order or airway responsiveness.

Hypoxic lobar blood flow response. Because $\dot{Q}$ lobe/$\dot{Q}$ lung on hyperoxic gas mixtures was lowered by antigen challenge, the hypoxic $\dot{Q}$ response differed depending on whether it was calculated as the decrease in $\dot{Q}$ lobe/$\dot{Q}$ lung, expressed as a percentage, or as the percentage decrease of $\dot{Q}$ lobe/$\dot{Q}$ lung. However, either method of calculation led to the same conclusion: there was no significant difference between the hypoxic lobar $\dot{Q}$ response before or during antigen challenge in the 7 airway-responsive dogs (figure 6). The mean ± SD decrease in $\dot{Q}$ lobe/$\dot{Q}$ lung, % was 9.1 ± 7.6 % before and 8.0 ± 4.6 % during antigen challenge (n = 7); corresponding $\dot{Q}$ lobe/$\dot{Q}$ lung values during LLL hypoxia, expressed as percentages of the control values, were 62 ± 28 and 56 ± 16 %, respectively. In the one animal with no airway response to antigen inhalation, there was no progressive increase in hypoxic vascular response. There was no significant change in hypoxic vascular response between the first and second periods of hypoxia, before (n = 8) or during antigen challenge (n = 7).

Systemic changes. The main experiment required dogs to be anesthetized for as long as 12 h. To assess stability of the preparation during the period of data collection (as long as 6 h), arterial blood gas tensions, acid-base status, and mean pulmonary and femoral arterial blood pressures were compared during the course of the experi-

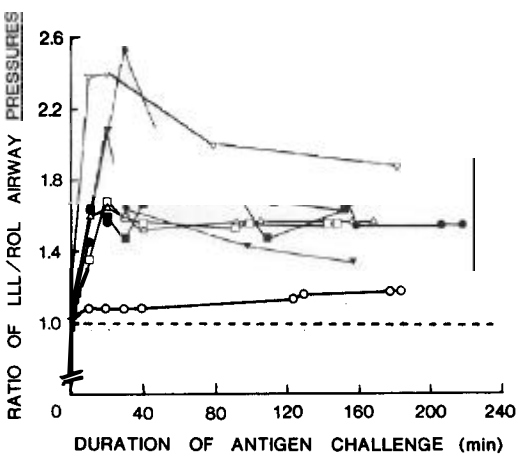

Fig. 3. Changes in lobar airway pressure swings in response to antigen challenge. The lobar airway pressure swings are expressed as a ratio of left lower lobe (LLL) airway pressure swings to those recorded in the rest of the lungs (ROL). Each experiment is plotted individually; symbols for each experiment correspond to those shown in figure 2.

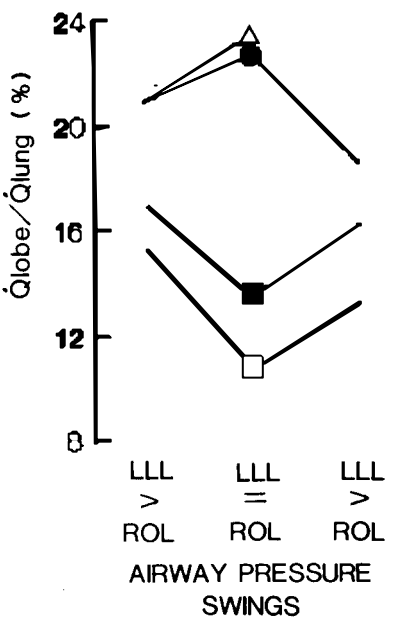

Fig. 4. Changes in the proportion of pulmonary blood flow to the left lower lobe ($\dot{Q}$ lobe/$\dot{Q}$ lung), % when airway pressures swings of the left lower lobe (LLL) were equalized with those of the rest of the lung (ROL) by decreased LLL stroke volume of the pump, while hyperoxic gas mixtures were delivered (LLL = ROL). Pre- and post-control values of $\dot{Q}$ lobe/$\dot{Q}$ lung are also shown (LLL > ROL).

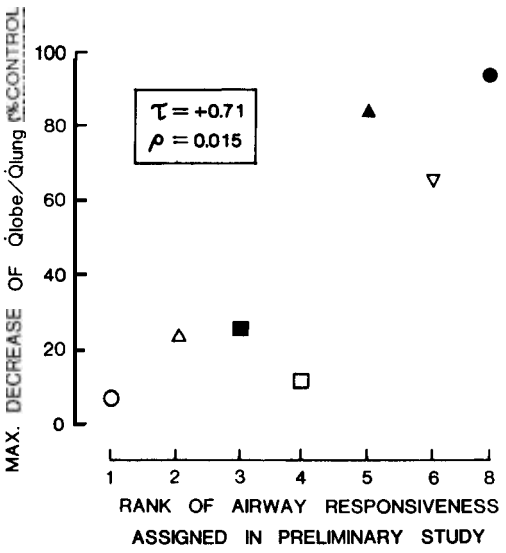

Fig. 5. Correlation between maximal decrease in the proportion of pulmonary blood flow to the left lower lobe (Q̇ lobe/Q̇ lung), expressed as percentage change from control level (ordinate) and airway responsiveness, expressed in ranked order from table 1 (abscissa). The correlation coefficient is expressed in terms of Kendall's tau. Each symbol represents one experiment corresponding to figures 3 and 4.

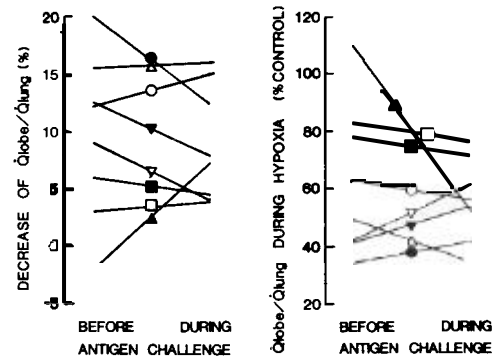

Fig. 6. Local hypoxic pulmonary vascular response before and during antigen challenge. *Left.* The hypoxic response, expressed as the percentage decrease from the control value of the proportion of pulmonary blood flow to the left lower lobe (Q̇ lobe/Q̇ lung). *Right.* The decrease in Q̇ lobe/Q̇ lung, expressed as a percentage of the control value. Data from all experiments are plotted. Symbols for each experiment correspond to those in figures 3 to 5.

ment. There were no significant changes in arterial pH, Pa_{O_2}, or mean femoral arterial blood pressure during the experiment, although the base deficit increased and Pa_{CO_2} decreased by small but significant amounts (table 2). During LLL alveolar hypoxia, Pa_{O_2} remained greater than 100 mm Hg, unless the hypoxic vascular response was blunted. Antigen administration to LLL had no significant effects on arterial blood gas tensions, pH, or mean femoral arterial blood pressure, but mean pulmonary arterial blood pressure showed a small, but significant, increase. Autopsy showed nontenacious secretions in the LLL bronchi of the airway responsive dogs but none in the airways of other lobes. Some interstitial and perivascular edema was seen histologically, as is typical in dogs anesthetized for this duration, but there was no alveolar flooding. Apart from the secretions in the LLL airways, the autopsy findings were indistinguishable from those obtained in a similar preparation where no antigen had been given.

Discussion

Criticism of methods. An animal model of asthma is particularly useful for the study of local pulmonary vascular responses in this condition. It allows an invasive approach so that the investigator can conduct the study under closely controlled conditions.

We believe that the increase in LLL airway pressure swings during antigen challenge did not affect Q̇ lobe/Q̇ lung. This conclusion is based on the following observations. First, reduction of the increased LLL airway pressure swings had no significant effect on Q̇ lobe/Q̇ lung (figure 4). Second, the transient nature of the vascular response contrasted with the sustained change of LLL airway pressure swings. Third, there was no significant correlation between the change in the distribution of pulmonary blood flow and that in airway pressure.

To minimize the mechanical changes in LLL with antigen challenge and to avoid reflex effect on the rest of the lung (10), left cervical vagotomy was performed. This procedure was probably unnecessary, because ligation of the LLL bronchial cannula probably denervated the lobe. Indeed, vagotomy was omitted in one experiment and no increase of ROL airway pressure swings was noted. Although antigen was given only to LLL and generalized reflex effects were avoided, humoral agents may also cause generalized effects. Inhaled antigen can cross the alveolar-capillary barrier in the rabbit, although immunization reduces the transfer into the blood of antigenically intact protein (15). Furthermore, at least one of the chemical mediators of asthma has been detected in systemic arterial blood (16). Apart from a variable increase in mean pulmonary arterial pressure at the start of antigen challenge, no sys-

TABLE 2

ARTERIAL BLOOD GAS COMPOSITION, ACID-BASE STATUS, AND MEAN PULMONARY AND FEMORAL ARTERIAL PRESSURES DURING THE MAIN EXPERIMENT

	Arterial pH	Pa_{CO_2} (mm Hg)	Pa_{O_2} (mm Hg)	BE (mEq/L)	$\overline{PAP}$ (cm H_2O)	$\overline{BP}$ (mm Hg)
Initial	7.36 ± 0.05	39 ± 3	411 ± 115	−3.5 ± 3.5*	27 ± 3*	117 ± 18
Antigen challenge	7.34 ± 0.05	41 ± 6	430 ± 61	−4.0 ± 2.5	33 ± 5†	121 ± 23
Final	7.33 ± 0.04	38 ± 9‡	398 ± 71	−6.0 ± 2.5‡	33 ± 4	121 ± 21

Mean ± SD data for all experiments (n = 8) at the start of data collection (initial), after 30 min of antigen inhalation in the left lower lobe (antigen challenge), and at the end of each experiment (final).

Definitions of abbreviations: Pa_{CO_2} = arterial Pco_2; Pa_{O_2} = arterial Po_2; BE = base excess; $\overline{PAP}$ = mean pulmonary arterial pressure; $\overline{BP}$ = mean femoral arterial blood pressure.

* Significant ($p \leq 0.05$) difference between initial and final values.

† Significant difference between initial and antigen challenge values.

‡ Significant difference between antigen challenge and final value.

temic effects were observed. Therefore, any generalized effects of humoral agents must have been diluted in contrast to the local effects of antigen challenge.

The measurement of local blood flow was indirect. This approach is advantageous because it avoided surgical disturbance of the pulmonary vasculature, but had the disadvantage of neglecting any right-to-left shunt. It is unlikely that shunt flow would substantially modify interpretation of the data for the following reasons. First, Pa_{O_2} and, therefore, the alveolar-arterial Po_2 gradient, were hardly affected by LLL antigen challenge (table 2). Therefore, the dramatic changes in $\dot{Q}$ lobe/$\dot{Q}$ lung cannot be explained solely by development of shunt flow within LLL. Second, pulmonary shunt rarely occurs with antigen challenge in the dog (17).

Local vascular response to antigen challenge. On hyperoxic gas mixtures, the local vascular response to antigen challenge cannot be explained by changes in local alveolar gas tensions. Can this response be related to an alteration of lobar mechanics? Although the changes in $\dot{Q}$ lobe/$\dot{Q}$ lung with LLL antigen challenge cannot be related to the changes in airway pressure swings, a transient mechanical distortion of lobar architecture at a microscopic level might have been responsible for the vascular response. This possibility cannot be excluded, but it seems unlikely that such dramatic changes in local blood flow could occur without visible macroscopic changes in the lobe during antigen challenge. Some other cause for the local vascular response to antigen seems more probable.

The correlation between the vascular and airway responsiveness to antigen suggests that the chemical mediators of asthma might have been responsible for the decrease in local blood flow. The chemical mediators of asthma may not only affect bronchoconstriction, but may also cause vasoconstriction. Indeed, the pulmonary arteries and veins lie in close proximity to the airways. If the chemical mediators of asthma cause vasoconstriction, perhaps the early and late phases of the response are due to differences in the rate of production, release, metabolism, or duration of action among the various mediators. Alternatively, local mediator release might have been responsible for the initial decrease in $\dot{Q}$ lobe/$\dot{Q}$ lung, and the partial recovery of $\dot{Q}$ lobe/$\dot{Q}$ lung occurred because the mediators entered the systemic circulation and affected the rest of the pulmonary vasculature.

Local vascular response to alveolar hypoxia. The hypoxic challenge was maximal; LLL alveolar Po_2 was decreased from approximately 600 to 25 mm Hg. Therefore, changes in the shape of the local $\dot{Q}$-alveolar Po_2 response curve with antigen challenge cannot be excluded. Nevertheless, the data indicate that the hypoxic vascular response is not abolished by antigen challenge. Others have reported that an increase in the magnitude of the hypoxic vascular response can occur during the course of an experiment (18, 19). We have found no evidence from the data that this phenomenon occurred.

Comparison of results with others. In contrast to the results of this study, Wanner and associates (7) found that antigenic challenge to allergic dogs failed to increase total pulmonary vascular resistance, despite moderate degrees of arterial hypoxemia. However, their approach to studying the pulmonary circulation in canine asthma was quite different. In their preparation, the antigen inhalation was global, and moderate systemic hypoxemia was produced. In our preparation, antigen inhalation and a severe alveolar hypoxic

challenge were localized, but systemic hypoxemia was avoided. Another major difference between the 2 preparations was that the LLL was denervated. Denervation of LLL might have altered the proportions of mediators released, or avoided a compensatory pulmonary vasodilation by neuronal pathways. Indeed, a decrease in pulmonary vasomotor tone has been observed in a portion of the lung unaffected by microembolism mediated by the β-sympathetic pathways (20). Although the precise reason for the different results has not been established, the data from both studies raise the possibility that changes in the pulmonary circulation in asthma may not be due to mechanical events within the lung alone. The chemical mediators of asthma may also have a direct effect on the pulmonary vasculature as well as the bronchial tree.

Relevance to gas exchange in asthma. Regardless of the precise mechanism, the demonstration of a local decrease in pulmonary blood flow in response to antigen challenge has important implications for gas exchange in human asthma. Indeed, topographic decreases in local blood flow in asthmatic patients have been reported (21, 22) and have been associated with a decrease in local alveolar ventilation (23). If chemical mediators of asthma decrease local ventilation by their effect on the airways, a concomitant decrease in local pulmonary blood flow would reduce the changes of local ventilation-perfusion ratios. Therefore, a decrease in local perfusion would tend to decrease the deleterious effects of asthma on pulmonary gas exchange.

References

1. Wagner PD, Dantzker DR, Iacovoni VE, Tomlin WC, West JB. Ventilation-perfusion inequality in asymptomatic asthma. Am Rev Respir Dis 1978; 118:511-24.
2. Chick TW, Nicholson DP, Johnson RL Jr. Effects of isoproterenol on distribution of ventilation and perfusion in asthma. Am Rev Respir Dis 1973; 107: 869-73.
3. Ingram RH Jr, Krumpe PE, Duffell GM, Maniscalco B. Ventilation-perfusion changes after aerosolized isoproterenol in asthma. Am Rev Respir Dis 1970; 101:364-70.
4. Knudson RJ, Constantine HP. An effect of isoproterenol on ventilation-perfusion in asthmatic versus normal subjects. J Appl Physiol 1967; 22:402-6.
5. Tai E, Read J. Response of blood gas tensions to aminophylline and isoproterenol in patients with asthma. Thorax 1967; 22:543-9.
6. Field GB. The effects of posture, oxygen, isoproterenol and atropine on ventilation-perfusion relationships in the lung in asthma. Clin Sci 1967; 32: 279-88.
7. Wanner A, Friedman M, Baier H. Study of the pulmonary circulation in a canine asthma model. Am Rev Respir Dis 1977; 115:241-50.
8. Cohn MA, Baier H, Wanner A. Failure of hypoxic pulmonary vasoconstriction in the canine asthma model. J Clin Invest 1978; 61:1463-70.
9. Kung M, Abraham WM, Oliver WR Jr, Hughes JR, Wanner A. Modification of hypoxic pulmonary vasoconstriction by antigen challenge in sensitive sheep (abstract). Am Rev Respir Dis 1979; 119: 377.
10. Gold WM, Kessler GF, Yu DFC. Role of vagus nerves in experimental asthma in allergic dogs. J Appl Physiol 1972; 33:719-25.
11. Marshall R. Objective tests of respiratory mechanics. In: Fenn WO, Rahn H, eds, Handbook of physiology, sec 3, Respiration, vol. II. Washington DC: American Physiological Society, 1965:1404-11.
12. Wagner PD, Naumann PF, Laravuso RB. Simultaneous measurement of eight foreign gases in blood by gas chromatography. J Appl Physiol 1974; 36:600-5.
13. Benumof JL, Mathews JM, Wahrenbrock EA. Cyclic hypoxic pulmonary vasoconstriction induced by concomitant carbon dioxide changes. J Appl Physiol 1976; 41:466-9.
14. Siegal S. Nonparametric statistics for the behavioral sciences. Tokyo: McGraw-Hill Kogakusha, 1956.
15. Braley JF, Dawson CA, Moore VL, Cozzini BO. Absorption of inhaled antigen into the circulation of isolated lungs from normal and immunized rabbits. J Clin Invest 1978; 61:1240-6.
16. Gold WM, Meyers GL, Dain DS, Miller RL, Bowne HR. Changes in airway mast cells and histamine caused by antigen aerosol in allergic dogs. J Appl Physiol 1977; 43:271-5.
17. Rubinfeld AR, Wagner PD, West JB. Gas exchange during acute experimental canine asthma. Am Rev Respir Dis 1978; 118:525-36.
18. Unger M, Atkins M, Briscoe WA, King TKC. Potentiation of pulmonary vasoconstriction response with repeated intermittent hypoxia. J Appl Physiol 1978; 42:662-7.
19. Miller MA, Hales CA. Stability of hypoxic pulmonary vasoconstriction in dogs (abstract). Am Rev Respir Dis 1979; 119:382.
20. Kenley GP, Brody MJ. Studies on the mechanisms of pulmonary vascular responses to miliary pulmonary embolism. Circ Res 1977; 41:807-14.
21. Woolcock AJ, McRae J, Morris JG, Read J. Abnormal pulmonary blood flow distribution in bronchial asthma. Australas Ann Med 1966; 15:196-203.
22. Henderson LL, Tauxe WN, Hyatt RE. Lung scanning of asthmatic patients with ^{131} I-MAA. South Med J 1967; 60:795-804.
23. Heckscher T, Bass H, Oriol A, Rose B, Anthonisen NR, Bates DV. Regional lung function in patients with bronchial asthma. J Clin Invest 1968; 47:1063-70.