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Mechanical Factors Do Not Influence Blood Flow Distribution in Atelectasis

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The contribution of mechanical factors to the vascular resistance of the atelectatic lung has been studied *in vivo* in the anesthetized open-chest dog. When the left lung was ventilated with an hypoxic gas mixture (while the right lung was ventilated with 100% O_2), left lung blood flow decreased from 0.99 ± 0.11 $l \cdot min^{-1}$ to 0.40 ± 0.08 $l \cdot min^{-1}$ due to hypoxic pulmonary vasoconstriction (hypoxic stimulus P_{SO_2} = 36.1 ± 0.8 mmHg). When the left lung was made atelectatic, blood flow decreased to 0.65 ± 0.11 $l \cdot min^{-1}$, consistent with a weaker hypoxic stimulus (P_{SO_2} = 54.0 ± 3.2 mmHg). With the addition of sodium nitroprusside infused intravenously, left lung blood flow increased to 1.05 ± 0.14 $l \cdot min^{-1}$ during atelectasis, and to 0.61 ± 0.09 $l \cdot min^{-1}$ during hypoxic ventilation, while flow remained at 0.94 ± 0.18 $l \cdot min^{-1}$ during hyperoxic ventilation. When the results were plotted on pressure-flow diagrams, the hyperoxic, hypoxic, and atelectatic lung points fell on the same pressure-flow line in the presence of nitroprusside. It is concluded that hypoxic pulmonary vasoconstriction is the major (but not necessarily only) determinant of increased vascular resistance in the atelectatic lung, and that passive mechanical factors do not measurably affect blood flow distribution during open-chest atelectasis. (Key words: Arteries: pulmonary. Lung: atelectasis. Lung, blood flow: hypoxic pulmonary vasoconstriction; nitroprusside.)

ATELECTASIS IS A common occurrence in anesthetized patients. Atelectasis is intentional when lung collapse or retraction is required for thoracic surgery, or accidental when induced by a combination of lung disease, decreased functional residual capacity, or postural factors. The immediate consequences of atelectasis are intrapulmonary shunt and arterial oxygen desaturation. These do not always occur because the atelectatic lung has increased pulmonary vascular resistance (PVR), which diverts pulmonary blood flow to ventilated lung. This increased PVR is thought to be caused primarily by hypoxic pulmonary vasoconstriction (HPV),[1,2] but mechanical factors are also thought to increase the PVR of collapsed regions of the lung in addition to the HPV effect.[3,4] The present study examines this hypothesis by measuring the change in blood flow when an inflated lung was made hypoxic or atelectatic before and after HPV was abolished with sodium nitroprusside (SNP).[5]

Materials and Methods

ANESTHESIA AND SURGERY

This study received prior approval by the University of Pennsylvania Institutional Animal Care and Use Committee. Seven female dogs of mixed breed (mean weight 18.6 kg, range 12.4–23.4 kg) and free of microfilariae were anesthetized with intravenous pentobarbital (30 $mg \cdot kg^{-1}$ initially, followed by 2 $mg \cdot kg^{-1}$ every ½–1 h) and paralyzed with pancuronium (0.05 $mg \cdot kg^{-1}$ followed by 0.01 $mg \cdot kg^{-1}$ every hour). The trachea was intubated and the lungs ventilated with warm humidified 100% oxygen at 5 cm H_2O PEEP utilizing one side of a dual-piston ventilator (Harvard® Apparatus Pump Respirator model #618). A double-lumen Kottmeier endobronchial tube (Rusch® Inc.) was inserted *via* a tracheostomy. A median sternotomy and left thoracotomy were performed, and complete left lung isolation confirmed visually. Tidal volumes were adjusted to provide equal peak airway pressures of 15–20 cm H_2O to each lung, and were not changed once the experimental protocol was begun. Inspired CO_2 was added to each side to achieve an end-tidal P_{CO_2} of 40 mmHg.

A thermodilution Swan-Ganz catheter (American Edwards® #93A-131H-7F) was inserted percutaneously through a femoral vein; a catheter was inserted in the left internal jugular vein by cutdown for measurement of central venous pressure (CVP). An arterial catheter was inserted in the femoral artery percutaneously. All pressures were measured with transducers (Statham P23BB and Gould-Statham P23DB) zeroed at a point midway along the anterior-posterior dimension of the chest.

Two peripheral arteriovenous (A-V) shunts were prepared, one connecting a femoral artery and vein with a short length of silastic® tubing, and another connecting a carotid artery and an external jugular vein. Heparin was administered intravenously (300 $U \cdot kg^{-1}$, followed by 50 $U \cdot kg^{-1}$ every 30 min) to prevent their occlusion. Cardiac output (CO) was increased by unclamping these

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shunts (high CO); otherwise they were left clamped (normal CO).

When required, sodium nitroprusside (SNP, 200 $\mu g \cdot ml^{-1}$) was infused at a rate (6.2–52 $\mu g \cdot kg^{-1} \cdot min^{-1}$) that reduced mean arterial pressure to 50 mmHg. When an adequate infusion rate of SNP was achieved for an animal, the same rate was used in subsequent phases in that animal. At the end of an infusion period, at least 20 min were allowed for the return of vascular reactivity.

Prior to the experimental sequence, at least three 15-min trials of hypoxic ventilation of the left lung, to an end-tidal P_{O_2} of 30 mmHg, were alternated with 100% oxygen ventilation until consistent hypoxic responses were observed.

The experimental sequence consisted of nine phases. The right lung was ventilated continuously with 100% oxygen with inspired CO_2 added to achieve an end-tidal P_{CO_2} of 40 mmHg. The left lung was ventilated with 100% oxygen with CO_2 added to achieve an end-tidal P_{CO_2} of 40 mmHg (three hyperoxic phases), or with an hypoxic gas mixture of nitrogen, with O_2 and CO_2 added to achieve end-tidal values of 30 and 40 mmHg, respectively (three hypoxic phases), or allowed to undergo reabsorption atelectasis by clamping the left side of the endobronchial tube after a period of oxygen ventilation (three atelectasis phases). During the experimental sequence, three types of hemodynamic manipulations were performed for each of the hyperoxic, hypoxic, and atelectatic conditions: normal cardiac output, high cardiac output, or normal cardiac output with SNP infusion. The order in which the first six ventilation phases were performed was determined separately for each study by prior randomization, with precautions taken to prevent recurrence of the sequence. The three atelectasis phases were also performed in random order, but always after the six ventilation phases. At the end of the study, the animal was killed by clamping the lung hila; the heart and lungs were examined for parasites. Only data from disease-free animals were included in the study.

Measurements

During each experimental phase, airway, systemic (SAP) and pulmonary arterial (PAP), central venous (CVP), and pulmonary artery occlusion (PAOP) pressures, and esophageal temperature were recorded. Systolic, diastolic, and mean vascular pressures and PAOP were measured at end-expiration (5 cm H_2O PEEP), with the zero reference at mid-chest. Thermodilution cardiac output (CO) was measured in triplicate (Edwards® cardiac output computer model #9510A). Arterial and mixed venous blood was sampled for determination of *p*H, P_{O_2}, P_{CO_2}, and hemoglobin. Inspired, end-tidal, and mixed expired O_2 and CO_2 were measured with a Perkin-Elmer® MA1100 mass spectrometer. Blood gases were measured, using a Corning® *p*H/blood gas analyzer (model #168), and corrected to the temperature of the animal.

Calculations

Saturation and content of arterial, mixed venous, and end-capillary blood (using end-tidal P_{O_2} and P_{CO_2}) were estimated by an algorithm for dog hemoglobin.[6] Left lung blood flow during hyperoxic conditions was calculated by multiplying cardiac output by the fractional CO_2 excretion of the left lung.[7] Left lung blood flow during hypoxic ventilation or atelectasis was calculated from blood oxygen contents using a blood mixing equation.[8] The total lung blood flow (cardiac output, $\dot{Q}_T$) is modelled as three components: left lung blood flow ($\dot{Q}_L$), shunt ($\dot{Q}_S$), and blood flow through the hyperoxic right lung ($\dot{Q}_T - \dot{Q}_S - \dot{Q}_L$). By mass balance, total (*i.e.*, bound and dissolved) oxygen transport out of the lung is:

$$\dot{Q}_T \cdot C_{aO_2} = \dot{Q}_L \cdot C_{LO_2} + \dot{Q}_S \cdot C_{\bar{v}O_2} + (\dot{Q}_T - \dot{Q}_S - \dot{Q}_L) \cdot C_{RO_2}, \quad (1)$$

where C_{RO_2} and C_{LO_2} are estimated end-capillary O_2 contents calculated for the alveolar P_{O_2} of the right and left lung, respectively; C_{aO_2} is arterial oxygen content; and $C_{\bar{v}O_2}$ is mixed venous oxygen content. By rearranging,

$$\dot{Q}_L/\dot{Q}_T = [(C_{RO_2} - C_{aO_2}) - \dot{Q}_S/\dot{Q}_T(C_{RO_2} - C_{\bar{v}O_2})]/(C_{RO_2} - C_{LO_2}) \quad (2)$$

The equation may be solved during hypoxic left lung ventilation by assuming that $\dot{Q}_S/\dot{Q}_T$ is unchanged from the value measured during bilateral hyperoxic ventilation with similar cardiac output or SNP administration conditions. During left lung atelectasis, C_{LO_2} equals $C_{\bar{v}O_2}$. Under all conditions (hyperoxia, hypoxia, and left lung atelectasis), shunt ($\dot{Q}_S/\dot{Q}_T$) is assumed to be apportioned to right and left lung in proportion to right and left lung blood flow during bilateral hyperoxic ventilation.

Pulmonary perfusion pressure was the difference between mean pulmonary arterial pressure and PAOP, both measured at end-expiration. The hypoxic stimulus (P_{SO_2}), which is the oxygen tension at the sensor site for HPV, was calculated on the basis of a formula derived from empirical data[9] in rat lungs *in vitro*, where $P_{SO_2} = P_{\bar{v}O_2}^{0.38} \times P_{AO_2}^{0.62}$. During atelectasis, P_{AO_2} was assumed to equal $P_{\bar{v}O_2}$ for the purpose of calculating P_{SO_2}.

Experimental data are reported as means ± standard error of the mean. One-way within-subjects analysis of variance was performed, using the Newman-Kuels test for specific differences. The null hypothesis was rejected for $P < 0.05$.

Results

There were no significant changes in heart rate (181 ± 3 bpm), CVP (1.6 ± 0.1 mmHg), PAOP (7.3 ± 0.2 mmHg), arterial *p*H (7.337 ± 0.037), hemoglobin (10.8 ± 0.2 $g \cdot dl^{-1}$), or esophageal temperature (38.2 ± 0.1° C) between any of the nine experimental phases. Tidal volumes used were 226 ± 7 cc for the right lung and 174 ± 4 cc for the left lung. There was no significant change in tidal volume between phases, except that the left lung was made atelectatic in the last three phases.

Effect of Changing Cardiac Output

Opening the A-V shunts during hyperoxic ventilation of both lungs significantly increased cardiac output from 2.34 to 3.20 $l \cdot min^{-1}$, and mixed venous oxygen tension from 60.9 to 74.8 mmHg, but decreased mean systemic arterial pressure from 135 to 120 mmHg. Left lung blood flow significantly increased from 0.99 to 1.33 $l \cdot min^{-1}$; pulmonary perfusion pressure increased from 12.6 to 15.8 mmHg, but this was not significant. There was no change in arterial P_{O_2}. Similar changes in hemodynamics occurred when the A-V shunts were opened during hypoxic ventilation and atelectasis (table 1).

Effect of Hypoxic Ventilation

Substituting an hypoxic gas mixture for 100% oxygen during ventilation of the left lung did not alter cardiac output or arterial blood pressure, but significantly decreased left lung blood flow from 0.99 to 0.40 $l \cdot min^{-1}$. Pulmonary perfusion pressure increased from 12.6 to 15.9 mmHg, but this was not statistically significant. Arterial oxygen tension decreased significantly from 572.7 to 220.8 mmHg, but no animal became hypoxemic. The decrease in mixed venous oxygen tension was not significant.

Effect of Atelectasis

Absorption of the residual gas in the left lung required less than 20 min, as determined visually. No significant change occurred in cardiac output or systemic arterial pressure. Left lung blood flow decreased significantly to 0.65 $l \cdot min^{-1}$, while the increase in pulmonary perfusion pressure (12.6–15.6 mmHg) was not significant. Arterial and mixed venous blood gases were similar to those found during hypoxic ventilation, except that arterial P_{CO_2} increased significantly compared to hyperoxic ventilation (from 38.5 to 44.5 mmHg).

Effect of Nitroprusside Infusion

During hyperoxic ventilation with the A-V fistulae closed, SNP administration decreased mean arterial pres-

TABLE 1. Hemodynamic and Blood Gas Values (Mean ± SE, n = 7)

Experimental Phase	Mean Arterial Blood Pressure (mmHg)	Mean Pulmonary Artery Pressure (mmHg)	Pulmonary Artery Occlusion Pressure (mmHg)	Mean Pulmonary Perfusion Pressure (mmHg)	Cardiac Output (l/min)	Left Lung Blood Flow (l/min)	Ratio L/R Pulmonary Vascular Resistance	P_{aO_2} (mmHg)	P_{aCO_2} (mmHg)	P_{vO_2} (mmHg)	P_{SO_2} (mmHg)
Hyperoxic											
Normal CO	135.7 ± 6.5	19.4 ± 1.0	6.86 ± 0.71	12.6 ± 1.2	2.34 ± 0.27	0.99 ± 0.11	1.38 ± 0.08	572.7 ± 7.9	38.5 ± 0.8	60.9 ± 5.0	276.8 ± 9.6
High CO	120.0 ± 4.8	22.9 ± 1.5	7.07 ± 0.48	15.8 ± 1.8	3.20 ± 0.27*	1.33 ± 0.13*	1.45 ± 0.12	578.1 ± 8.0	39.4 ± 0.9	74.9 ± 4.0*	284.0 ± 6.4
SNP	57.9 ± 3.9*	16.0 ± 1.1	7.37 ± 0.85	8.7 ± 0.8	2.26 ± 0.43	0.94 ± 0.18	1.44 ± 0.06	533.1 ± 26.6	40.0 ± 0.9	62.3 ± 6.2	278.7 ± 10.7
Hypoxic											
Normal CO	125.7 ± 3.2	23.0 ± 1.9	7.06 ± 0.55	15.9 ± 1.6	2.53 ± 0.22	0.40 ± 0.08*	6.09 ± 0.77*	220.8 ± 36.6*	42.0 ± 0.9	55.3 ± 2.8	36.1 ± 0.8*
High CO	122.1 ± 2.9	25.8 ± 2.0*	7.81 ± 0.61	18.0 ± 1.9*	3.10 ± 0.24*	0.49 ± 0.04*	5.52 ± 0.64*	198.8 ± 31.3*	40.7 ± 0.8	60.3 ± 1.7	38.0 ± 0.8*
SNP	55.7 ± 4.1*†	15.8 ± 1.1†	8.00 ± 1.17	7.8 ± 0.5*†	2.11 ± 0.30	0.61 ± 0.09*	2.42 ± 0.12	74.0 ± 3.2*†	40.0 ± 1.1	45.1 ± 2.9*	32.7 ± 0.8*
Atelectatic											
Normal CO	117.9 ± 6.6	23.0 ± 2.2	7.39 ± 0.77	15.6 ± 1.6	2.35 ± 0.29	0.65 ± 0.11*	2.91 ± 0.46	253.5 ± 38.3*	44.5 ± 1.7*	54.0 ± 3.2*	54.0 ± 3.2*
High CO	110.7 ± 6.1	26.3 ± 2.1*	7.49 ± 0.63	18.9 ± 2.3*	3.17 ± 0.33*†	0.91 ± 0.11	2.62 ± 0.40	299.2 ± 31.3*	43.9 ± 1.7*	64.4 ± 3.2	64.4 ± 3.2*†
SNP	52.9 ± 1.8*	16.8 ± 1.1†	7.06 ± 0.9	9.7 ± 0.9†	2.31 ± 0.29†	1.05 ± 0.14†	1.28 ± 0.11*†	102.4 ± 9.4*†	46.1 ± 2.0*	48.6 ± 3.9*	48.6 ± 3.9*†

* Indicates significant difference from hyperoxic, normal CO ($P < 0.05$).

† Indicates significant difference from corresponding hypoxic or atelectatic, normal CO ($P < 0.05$).

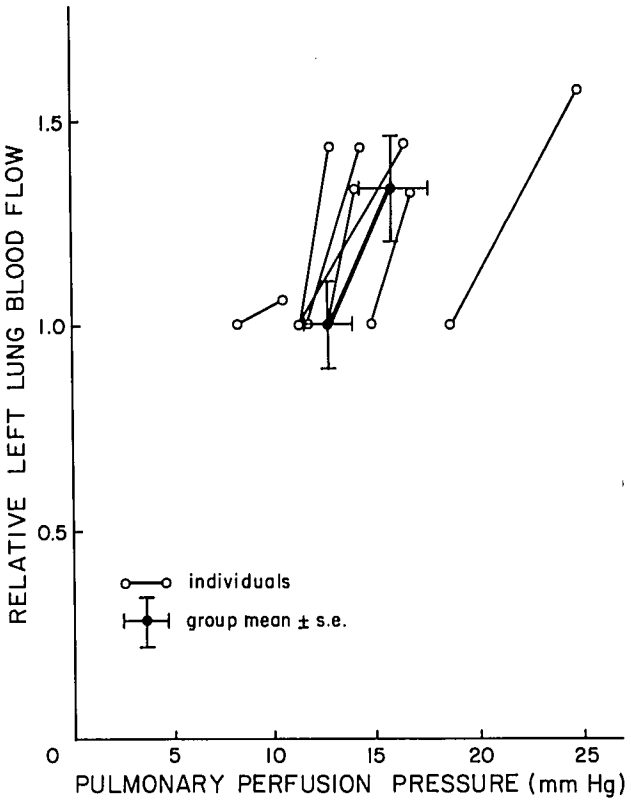

FIG. 1. Pressure-flow relationship for the left lung, calculated relative to the hyperoxic, normal cardiac output condition. Pairs of open circles represent data from individual animals; filled circles represent group means ± SE for normal and high cardiac output. Increasing cardiac output by opening AV shunts increases relative left lung blood flow and pulmonary perfusion pressure.

sure from 135.7 to 57.9 mmHg while cardiac output remained unchanged. Pulmonary perfusion pressure decreased from 12.6 to 8.7 mmHg during hyperoxic ventilation, but this was not significant. SNP increased left lung blood flow during hypoxic conditions (from 0.40 $l \cdot min^{-1}$ to 0.61 $l \cdot min^{-1}$, $P < 0.05$) and during atelectatic conditions (from 0.65 $l \cdot min^{-1}$ to 1.05 $l \cdot min^{-1}$, $P < 0.05$), but not during hyperoxic conditions. Although there was no difference in left lung blood flow between hyperoxia with SNP and atelectatasis with SNP, left lung blood flow during hypoxia with SNP was decreased (0.61 $l \cdot min^{-1}$, $P < 0.05$) in comparison to hyperoxia with SNP (0.94 $l \cdot min^{-1}$).

Pressure-flow Relationships: Hyperoxic Lungs

The pressure and flow data for the hyperoxic lung at normal and high cardiac output, in the absence of SNP, are plotted as a pressure-flow relationship in figure 1, for individual animals, and for the mean group data from table 1. Left lung blood flow is plotted relative to the hyperoxic normal cardiac output control period. In all animals, increased cardiac output increased left lung blood flow and pulmonary perfusion pressure. The error bar for relative blood flow in the hyperoxic normal cardiac output group is the standard deviation divided by the mean left lung blood flow from table 1.

Pressure-flow Relationships: Hypoxic and Atelectatic Lungs

The effect of hypoxia or atelectasis on the left lung is shown in figure 2. The group mean hyperoxic pressure-flow line is taken from figure 1. Hypoxic ventilation caused a shift downward (decreased blood flow) and to the right (increased perfusion pressure). Atelectasis caused a similar but smaller shift.

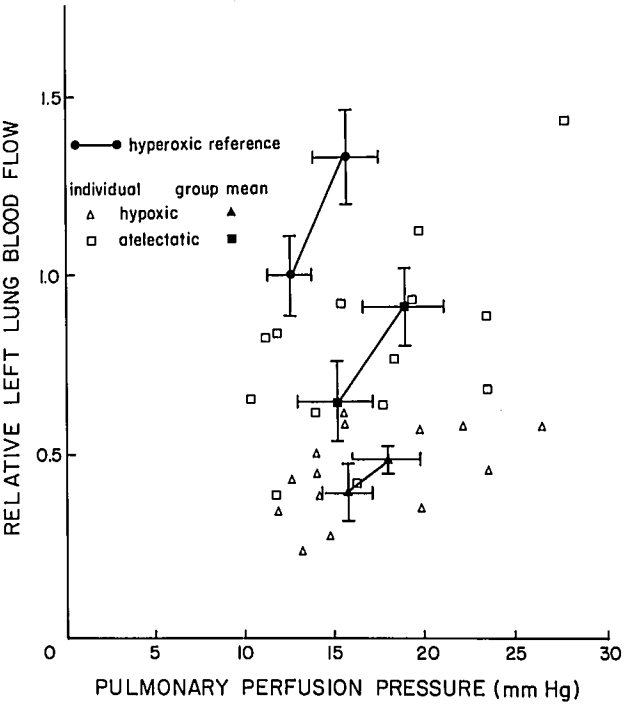

FIG. 2. Pressure-flow relationship for the left lung during hypoxic ventilation and atelectasis, relative to the hyperoxic, normal cardiac output condition. Open squares and open triangles are individual data pairs for atelectatic and hypoxic conditions, respectively. Filled squares and triangles are group means ± SE for atelectasis and hypoxia, respectively; points are paired for normal and high cardiac output conditions. Also shown are the hyperoxic, normal and high cardiac output, group means from figure 1, to serve as reference points. Both atelectasis and hypoxia cause a shift of the pressure-flow line downward and to the right; in this study, hypoxia was associated with a greater shift than was atelectasis, because the hypoxic stimulus was greater during hypoxia.

Pressure-Flow Relationships: Hyperoxic, Hypoxic, and Atelectatic Lungs with SNP

In figure 3, the blood flow and pressure data for the hyperoxic, hypoxic, and atelectatic left lungs during SNP infusion are shown along with the hyperoxic reference line. There was a small leftward displacement of both hyperoxic and atelectatic points during SNP from the hyperoxic reference line, and the two groups were not different with respect to pressure or flow. The hypoxic lung blood flow did not increase with SNP to the same degree as did atelectatic lung blood flow.

Discussion

When a region of lung becomes atelectatic, vascular resistance is increased locally and blood flow is diverted to remaining normal lung. The basis for this increased resistance is thought to be active hypoxic pulmonary vasoconstriction (HPV) stimulated by the mixed venous oxygen tension, as well as a passive mechanical effect of atelectasis causing shrinkage and tortuosity of blood vessels. The current controversy concerns the extent to which these two mechanisms are responsible for the observed blood flow changes.

Several reports have suggested a mechanical component to explain some of the increase in vascular resistance in the atelectatic lung both *in vitro* and *in vivo*. Barer *et al.*[2] studied the effects of bronchial occlusion in cats and dogs on PVR; the increased resistance caused by collapse was reversed by vasodilators or by perfusion of the lung with arterial blood, indicating that increased vasomotor tone was primarily responsible, but that some mechanical effect could not be ruled out.

In a more recent paper, Benumof[1] measured lobar blood flow in dogs; the PVR during ventilation with an hypoxic gas mixture was similar to the resistance measured when the same lobe was made atelectatic, suggesting that all of the increased PVR of atelectatic lungs was due to HPV. However, the hypoxic stimulus was not carefully controlled: mixed venous P_{O_2} was similar for the atelectatic and ventilated lungs, but alveolar P_{O_2} was lower than mixed venous P_{O_2}. The overall hypoxic stimulus was greater for the lung ventilated with the hypoxic gas mixture than for the atelectatic lung. Thus, a greater hypoxic vasoconstrictor response in the presence of a stronger hypoxic stimulus in the ventilated lung may have obscured an increase in the vascular resistance of the atelectatic lung that would have been caused by mechanical deformation of the vessels.

Bjertnaes *et al.*[3] measured vascular resistance in ventilated and atelectatic, isolated and perfused rat lungs. The increase in resistance caused by either hypoxia or atelectasis was partially reversed by inhalational anesthetics, by increasing perfusate P_{O_2}, and by papaverine; about 6% of vascular tone was not removed by vasodilators, suggesting a component of mechanical tone in the atelectatic lung.

The pulmonary vascular resistance of atelectatic and hypoxic lung, as well as the strength of the hypoxic response, are affected by P_{CO_2}. In the ventilated lung, alveolar P_{CO_2} predominates, whereas, in atelectatic lung, tissue P_{CO_2} is determined by mixed venous P_{CO_2}. McFarlane *et al.*[4] found that, in dogs, the vascular resistance of ventilated hypoxic lobes increased when alveolar P_{CO_2} was made to equal mixed venous P_{CO_2}. However, the vascular resistance of the same lobes was increased additionally when they were made atelectatic, although mixed venous P_{CO_2} remained constant, suggesting that some of the increased resistance resulted from mechanical factors associated with atelectasis.

When mixed venous blood is sufficiently oxygenated, the PVR of the atelectatic lung should be equal to that of the ventilated hypoxic lung if HPV is solely responsible for the increased PVR during atelectatic conditions at low $P_{\bar{v}O_2}$. In an experiment by Domino *et al.*,[10] veno-venous bypass was used to increase $P_{\bar{v}O_2}$. The atelectatic left lung resistance decreased when$P_{\bar{v}O_2}$ was greater than 100 mmHg. However, during bypass, the pulmonary artery tone remained high at normal or high mixed venous oxygen tension. A small additional mechanical effect contributing to overall PVR in the atelectatic lung would have been obscured.

The concept that mechanical resistance increases at low lung volumes originated in a paper by Burton and Patel.[11] Excised rabbit lungs were perfused while inflation volume was increased or decreased. PVR increased at low volumes and this was ascribed to "gnarliness" and "kinking" that was apparent angiographically. However, the angiographic appearance of pulmonary blood vessels during atelectasis[12] is identical to the appearance during hypoxic ventilation.[13]

We hypothesize that a major difference between the present results and those of other studies could be attributed to the variability of HPV. The present experiment was designed to avoid this problem. The primary stimuli for HPV are the alveolar and mixed venous P_{CO_2}, but the degree of response is also influenced by secondary variables, such as the size of the hypoxic segment, cardiac output, pulmonary venous pressure, temperature, *p*H, P_{CO_2}, and systemic responses to hypoxemia. In this study, the size of segment was fixed (left lung) and pulmonary venous pressure, *p*H, and temperature were maintained at constant values. It should be noted, however, that P_{CO_2} was increased during certain conditions, and that mild systemic hypoxemia occurred when sodium nitroprusside was administered during the hypoxic or atelec-

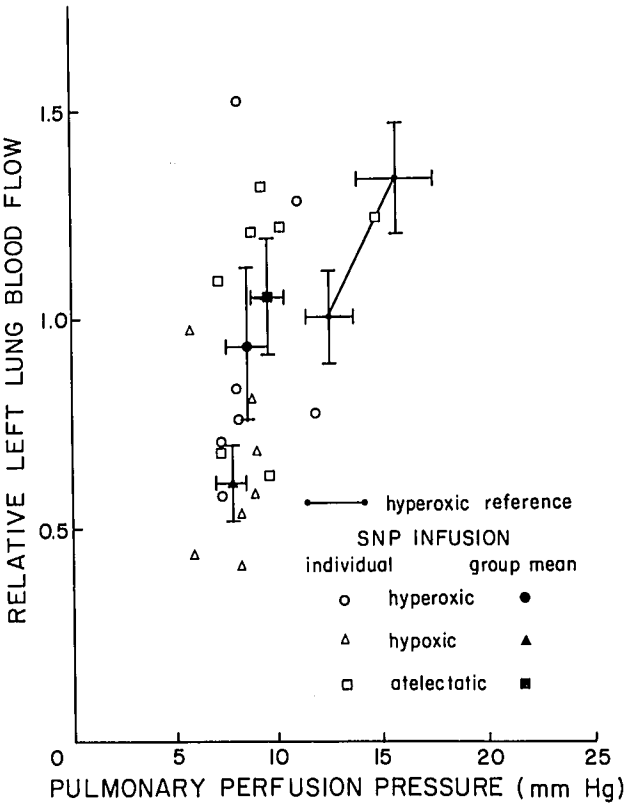

FIG. 3. Pressure-flow relationship for the left lung during SNP infusion, relative to hyperoxic, normal cardiac output conditions. Open circles, triangles, and squares represent data during SNP infusion for the hyperoxic, hypoxic, and atelectatic conditions, respectively. Filled symbols represent the group means ± SE. Also shown are the hyperoxic, normal and high cardiac output group means, to serve as a reference. During SNP infusion, the pressure-flow points are displaced leftward from the hyperoxic pressure-flow line, and are not significantly different between atelectatic and hyperoxic groups with respect to pressure or flow.

tatic phases. The effect of variation of cardiac output on the HPV response to hypoxia and atelectasis was defined in the absence of nitroprusside.

Although PAOP did not change significantly between any of the experimental conditions (table 1), as an estimate of pulmonary venous pressure, PAOP is subject to potential error. When alveolar pressure exceeds left atrial pressure, or when the catheter tip is placed above the level of the left atrium to lodge in Zone 1 or Zone 2 conditions, extravascular pressure exceeds pulmonary venous pressure, the capillary bed is collapsed, and the catheter tip measures the extravascular pressure. When alveolar pressure does not exceed pulmonary venous pressure, an occlusion pressure obtained in Zone 3 is valid if the catheter tip is near the level of the left atrium. When the pulmonary artery is vasoconstricted or occluded, downstream pressure equilibrates slowly or incompletely after balloon inflation, and will tend to overestimate pulmonary venous pressure.

In this study, several factors suggest that the PAOP is a valid estimate of pulmonary venous pressure. First, the dogs are supine, so that the vertical pressure gradient is small. Second, the pressure is measured at end-expiration, when the PEEP (5 cm H_2O or 3.7 mmHg) is less than the measured PAOP (7–8 mmHg), suggesting that the major part of the lung is in Zone 3. Third, during open-chest atelectasis, the entire left lung is in Zone 3 conditions. The balloon occludes most of the left pulmonary artery and is directed to the region with the most flow, so that the downstream path will always include Zone 3 conditions. Fourth, the most important data are obtained during the SNP infusion, when the pulmonary vessels are dilated, so that vasoconstriction will not influence downstream vessel patency.

The pressure-flow relationship may be altered by left atrial or pulmonary venous pressure. As downstream pressure increases, transmural distending pressure of the capillary bed increases, as does the distending pressure of the small pulmonary arterioles. This causes recruitment or distension of the resistance vessels and decreases the degree of constriction developed during hypoxia, thus flattening the curves and shifting the apparent position of the pressure intercept. The hypoxic curve will thus appear to be closer to the hyperoxic curve, suggesting less hypoxic vasoconstriction. In this study, there were no significant differences in PAOP between any of the experimental conditions, and thus pulmonary venous pressure changes do not account for the apparent shift caused by hypoxia, atelectasis, or SNP.

The dual nature of HPV as both diversion of blood flow and increased pulmonary artery pressure is emphasized in the pressure-flow plots of figures 1–3. Pulmonary perfusion pressure was chosen for the abscissa, rather than pulmonary artery pressure, so that variations in left atrial pressure would not shift the apparent pressure-intercept of lines. Relative blood flow was plotted as the ordinate to reduce variance due to different lung or animal sizes. In the hyperoxic lung (fig. 1), increased flow is accommodated with a small increase in pressure; a line connecting the two cardiac output states does not go through the origin, because the lung vasculature is distensible and because recruitment of vessels occurs as pressure increases. The magnitude of the hypoxic shift of the pressure-flow relationship (fig. 2) is determined by the variables of HPV, principally alveolar and mixed venous oxygen tension (30 mmHg and 55 mmHg, respectively, at normal cardiac output). Atelectasis causes a similar but smaller shift (fig. 2), which is consistent with the weaker stimulus of mixed venous oxygen tension alone (54 mmHg

at normal cardiac output). This difference in the hypoxic stimulus reemphasizes the difficulty encountered with direct comparison of hypoxic and atelectatic lung blood flows. Even if the primary variables were more closely matched, other secondary variables (such as P_{CO_2}, *p*H, left atrial pressure, or systemic hypoxemia) contribute to the variability of the response and confound direct comparisons. Such considerations appear to account for the contradictions in the comparisons made previously.[1-4]

The data do not provide evidence for or against a contribution of vasoactive substances released by the lung due to the mechanical stimulus of ventilation, or to the absence of these factors in the atelectatic lung. Several investigators have reported that vasodilator prostaglandins may be released during lung hyperinflation due to PEEP[14] or during high-frequency ventilation,[15] and may have deleterious effects on HPV. At normal inflating pressures and respiratory frequency, the role of endogenous dilator prostaglandin production is controversial. Cyclooxygenase inhibitors may increase[16] or not affect[17] resting pulmonary artery tone, and the controversy may be due to differences in the pharmacologic effects of the particular inhibitors used, or to the specific experimental preparation.[18] Extrapulmonary sources of prostaglandins may contribute to the pulmonary vascular effects of ventilation.

Vasoconstriction and increased blood flow rate stimulate prostacyclin production by vascular endothelium,[19] possibly by inducing shear at the blood-endothelium interface.[20] In the case of unilateral atelectasis, the increase in blood flow and shear stress in the ventilated lung may result in increased local prostacyclin production, and thus decreased flow resistance. What is observed, however, is that pulmonary prostaglandin production is unchanged by acute atelectasis, and that cyclooxygenase inhibition modestly improves the effectiveness of hypoxic vasoconstriction.[21]

There may be many other contributing hormonal or neural factors influencing pulmonary vascular tone and these are predominantly vasodilating.[22] A difference in the expression of these factors between atelectatic and ventilated lungs as determined by selective sampling of pulmonary venous blood has not been reported. In the presence of profound vasodilation such as that caused by SNP in this study, a significant effect caused by differential release of these factors is unlikely.

Sodium nitroprusside increases blood flow to hypoxic[23] and atelectatic[5] lung. This increases shunt and causes systemic hypoxemia, as well as changing other systemic variables. However, the effect of sodium nitroprusside is to abolish smooth muscle tone, and therefore also the variability of HPV that would otherwise occur in the presence of other determinants of active vascular constriction, such as P_{CO_2}, *p*H, and circulating or locally released hormones. The remaining vascular resistance is determined by mechanical factors. The overall decrease in tone will also emphasize the contribution of a small mechanical effect in the atelectatic lung. As shown in figure 3, in the presence of nitroprusside, blood flow through the atelectatic lung is indistinguishable from flow through hyperoxic ventilated lung, and the presence of significant mechanical resistance cannot be demonstrated in the atelectatic lung. The hypoxic lung blood flow does not increase as much as in the atelectatic lung, either because SNP does not abolish HPV as well in the more strongly stimulated hypoxic lung, or because the ventilated lung has more, not less, mechanical resistance than the atelectatic lung. The small but not statistically significant decrease in perfusion pressure of the hyperoxic lung suggests that some tone exists in the hyperoxic state.

The data may be interpreted as in figure 4A. The hypoxic and atelectatic lung PVR is plotted and paired with the PVR that results when SNP is administered. Reversal of vascular resistance at lung volumes less than FRC by vasodilator administration suggests that the PVR must be due to contractile, not mechanical, factors. Consequently, the pulmonary vascular resistance curve may be interpreted as in figure 4B; total PVR at low volumes increases primarily because of pulmonary vasoconstriction stimulated by hypoxia in low $\dot{V}/\dot{Q}$ regions, or stimulated by progressive atelectasis in the poorly ventilated lung.

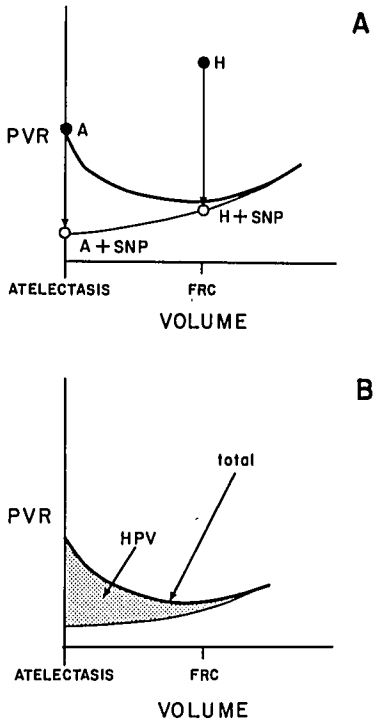

FIG. 4. *A.* Relationship for PVR *versus* lung volume. Data points are plotted for hypoxia with and without SNP, and for atelectasis with and without SNP. The hypoxic lung is assumed to be at FRC at end-expiration. With administration of SNP, PVR decreased more during atelectasis than during hypoxia, demonstrating a reversible component of PVR during atelectasis or hypoxia. *B.* Relationship for PVR *versus* lung volume, including the contribution of HPV. Total PVR increases primarily because of pulmonary vasoconstriction stimulated either by progressive atelectasis or by hypoxia in very low $\dot{V}/\dot{Q}$ regions.

In summary, reversible vasoconstriction accounted for all of the difference in vascular resistance between the atelectatic and the hyperoxic ventilated lung in these dogs. No evidence was found for a mechanical component of vessel collapse or deformation thought to contribute to PVR in the atelectatic lung. While many factors may contribute to vascular tone in the lung, the predominant factor in atelectasis appears to be HPV.

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