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Increased Pulmonary Perfusion Worsens Ventilation-Perfusion Matching

Karen B. Domino, M.D., Barbara L. Eisenstein, M.A.,† Tim Tran, M.D.,† Michael P. Hlastala, Ph.D.‡*

Background: **Severe exercise and administration of vasopressors may adversely affect pulmonary gas exchange in humans. The role of increases in pulmonary perfusion in worsening ventilation-perfusion ($\dot{V}_A/\dot{Q}$) relationships is unclear, however, because concomitant changes in ventilation and alveolar gas composition occur. The purpose of this study was to determine whether increasing of lobar blood flow increased $\dot{V}_A/\dot{Q}$ heterogeneity in the absence of changes in respiratory parameters.**

Methods: **Six pentobarbital-anesthetized dogs underwent bilateral thoracotomies, left upper lobectomy, and placement of an electromagnetic flow probe on the left lower lobe (LLL) pulmonary artery, and catheters were inserted into the LLL pulmonary artery distal to the flow probe and confluent trunk of the LLL pulmonary vein. A bronchial divider was inserted to allow separate ventilation of the right lung and LLL. Blood flow to the LLL ($\dot{Q}_{LLL}$) was increased in random order to two and three times baseline blood flow by opening an arteriovenous fistula and partially occluding the right pulmonary artery. Minute ventilation and alveolar P_{CO_2} of the lobe were unchanged due to use of constant tidal volume and respiratory rate and inspiration of variable amounts of carbon dioxide. $\dot{V}_A/\dot{Q}$ distributions of the LLL were obtained using the multiple inert gas elimination technique. The tracer inert gas arterial-alveolar difference ([a-A]D) area was used to assess $\dot{V}_A/\dot{Q}$ mismatch.**

Results: **Increasing $\dot{Q}_{LLL}$ increased mean pulmonary artery pressure in the LLL (LLL Ppa). The P_{O_2} of the LLL pulmonary venous blood remained unchanged, as the mixed venous oxygen tension ($P\bar{v}_{O_2}$) was markedly increased. $\dot{V}_A/\dot{Q}$ inequality was increased, indicated by a 40% increase in the [a-A]D area when $\dot{Q}_{LLL}$ was increased to two times greater than baseline $\dot{Q}_{LLL}$ and a 58% increase in the [a-A]D area with three times greater than baseline $\dot{Q}_{LLL}$. The [a-A]D area was highly correlated with the lobar blood flow ($r = 0.97$) and LLL Ppa ($r = 0.97$).**

Conclusions: **Marked increases in lobar blood flow and Ppa worsened pulmonary gas exchange. The degree of impairment was correlated with the degree of increase in lobar perfusion. However, increased lobar perfusion did not affect LLL pulmonary venous blood oxygenation because the decrease in P_{O_2}, due to increased $\dot{V}_A/\dot{Q}$ mismatch, was opposed by an increase in P_{O_2}, due to increased $P\bar{v}_{O_2}$. (Key words: Lung: blood flow; gas exchange; ventilation-perfusion ratio. Measurement technique: multiple inert gas elimination technique.**

IN the normal lung, perfusion is well matched to ventilation, resulting in efficient pulmonary gas exchange. Increases in pulmonary perfusion ($\dot{Q}$), as occur with vigorous exercise or with administration of inotropic agents, may adversely affect pulmonary gas exchange because of a mechanical redistribution of $\dot{Q}$. Severe exercise increased ventilation-perfusion ($\dot{V}_A/\dot{Q}$) mismatch or heterogeneity by 100% or more in humans, when performed at both sea level and at simulated altitude.[1–3] The degree of impairment in gas exchange was correlated with increases in both pulmonary blood flow and minute ventilation. Infusion of inotropic drugs also increased $\dot{V}_A/\dot{Q}$ heterogeneity[4] and reduced arterial oxygen tension (Pa_{O_2}).[5–7] In critically ill patients, dopamine had a greater adverse effect on gas exchange than dobutamine.[4] Interestingly, dopamine increased pulmonary artery pressure (Ppa) to a greater degree than did dobutamine in these patients.[4]

The role of increased pulmonary perfusion *per se* in impairing $\dot{V}_A/\dot{Q}$ matching is unclear in the above studies, because many factors that affect the distributions of ventilation and perfusion changed simultaneously. Changes in tidal volume,[8,9] alveolar carbon dioxide tension,[10] and drug effects[4] may affect the matching of ventilation and perfusion. To control for these variables, we developed an anesthetized dog model in which blood flow to the left lower lobe (LLL) was manipulated, while maintaining steady systemic hemodynamics, minute ventilation, and alveolar gas composition.[11,12] We previously found a modest (50%) in-

* Associate Professor of Anesthesiology.

† Research Technician.

‡ Professor of Physiology and Biophysics and of Medicine.

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Address reprint requests to Dr. Domino: Department of Anesthesiology, Harborview Medical Center, Seattle, Washington 98104.

crease in pulmonary blood flow increased $\dot{V}_A/\dot{Q}$ heterogeneity by 25%.[12] As the $\dot{V}_A/\dot{Q}$ mismatch was smaller than that observed during exercise,[2] this study suggested either that the degree of impairment was correlated with the amount of pulmonary blood flow or that changes in ventilation were also important in impairing gas exchange during exercise.

The purpose of the present study was to investigate the effects of larger increases (100% and 200%) of pulmonary blood flow on $\dot{V}_A/\dot{Q}$ matching, using a similar dog model. Constant minute ventilation (tidal volume and respiratory rate) and alveolar carbon dioxide tension were maintained by adjusting the amount of carbon dioxide in the inspired gas mixture. Gas exchange was assessed by use of the multiple inert gas elimination technique.[13,14] This technique provides information about the pattern of $\dot{V}_A/\dot{Q}$ relationships in the lung and specifically determines intrapulmonary shunt and dead space. We predicted that the larger increase in lobar blood flow would further increase $\dot{V}_A/\dot{Q}$ heterogeneity.

Methods and Materials

Instrumentation

This study was approved by the University of Washington Animal Care Committee. Six mongrel dogs of either sex (25–30 kg) were anesthetized with pentobarbital sodium (30 mg/kg intravenously, supplemented with 60–90 mg hourly); after tracheal intubation, their lungs were ventilated with a fraction of inspired oxygen ($F_{I_{O_2}}$) of 0.50 at a tidal volume and respiratory rate adjusted to maintain normocapnia. Diaphragmatic paralysis was secured with succinylcholine (100 mg intramuscularly, supplemented with 20–40 mg intravenously hourly).

The experimental preparation is illustrated in figure 1 and has been described in detail elsewhere.[11] Carotid and pulmonary arterial catheters were placed *via* peripheral cut-down. Bilateral thoracotomies were performed. To facilitate isolation of the LLL pulmonary venous circulation, the left upper lobe was surgically resected. The LLL pulmonary vein was cannulated retrograde *via* the left atrial appendage. Because the LLL pulmonary vein has two to four contributory branches, the catheter was positioned in the main trunk of the lobar vein just proximal to its junction with the left atrium. The sampling catheter was positioned midstream within the lumen of a 1-cm-long, 5-mm-ID, 9-mm-OD rigid tube. Previous work has demonstrated

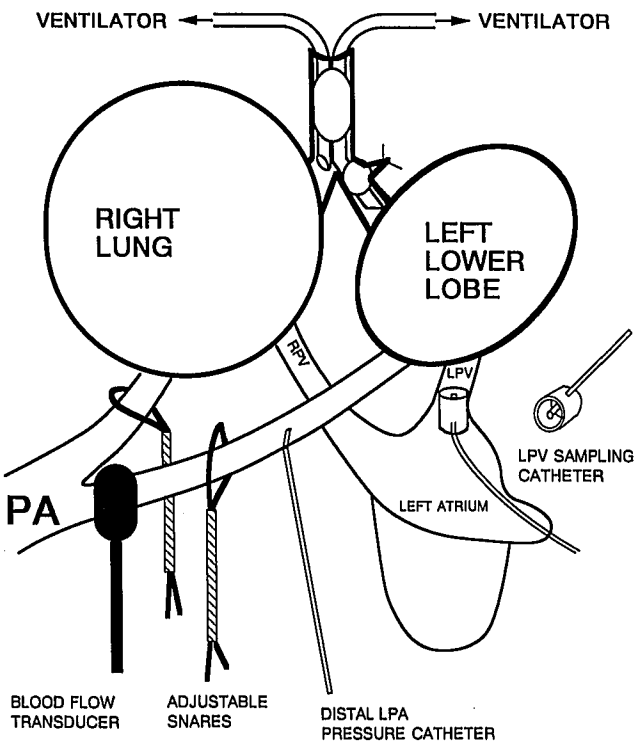

Fig. 1. Experimental preparation; left upper lobe was resected. Bronchial divider was inserted to independently ventilate right lung and left lower lobe (LLL). Adjustable vascular snares were placed on right pulmonary artery and on left pulmonary artery (LPA) distal to an electromagnetic flow probe (blood flow transducer). Pressure monitoring catheter was placed in LPA distal to snare. The LLL pulmonary venous catheter was inserted into the confluent trunk of the LLL pulmonary veins (LPV). LLL pulmonary venous blood was sampled within the lumen of a 1-cm-long rigid tube, shown in cross section at right (LPV sampling catheter). Arteriovenous fistula not shown.

that a mixed sample of pulmonary venous blood is obtained from the LLL pulmonary venous catheter.[11] An adjustable arteriovenous fistula was constructed between the left subclavian artery and the right atrium.

LLL pulmonary blood flow ($\dot{Q}_{LLL}$) was measured by an electromagnetic flow probe (In Vivo Metric Systems, Healdsburg, CA) placed around the left main pulmonary artery. The flow probe was precalibrated *in situ*. Adjustable vascular snares were placed around the right pulmonary artery and left pulmonary artery distal to the flow probe. LLL Ppa was measured by a catheter inserted into the left pulmonary artery distal to the flow probe and vascular snare. Both thoracotomies were covered with plastic to conserve heat and moisture. After completion of the surgical preparation, heparin

(7,500 U intravenously followed by 500 U intravenously hourly) was administered.

With the animal supine, a bronchial divider (left Broncho-Cath, Mallinckrodt, Argyle, NY) was placed through a tracheostomy to allow separate ventilation of the LLL and right lung. The right lung was ventilated with a tidal volume of 9 ml/kg. The LLL was ventilated with a tidal volume of 4.5 ml/kg. The LLL was ventilated with a relatively greater volume per lung mass, and a constant respiratory rate of 18–20 breaths/min was chosen to permit constant alveolar carbon dioxide when LLL perfusion was increased. Carbon dioxide was added to the LLL inspired gas mixture to maintain constant alveolar carbon dioxide. Five centimeters of water of positive end-expiratory pressure was administered to compensate for the absence of distending transpulmonary pressure with the chest open. Tidal volume of LLL and right lung was measured by spirometer (Warren E. Collins, Braintree, MA), and minute ventilations of LLL and right lung were calculated.

Inert Gas Measurements

The multiple inert gas elimination technique was adapted to assess gas exchange of the LLL.[11] A dilute solution of six inert gases (sulfur hexafluoride, ethane, cyclopropane, halothane, diethyl ether, and acetone) dissolved in 5% dextrose was infused into a peripheral vein for at least 60 min before the first samples for inert gas analysis were drawn. Inert gas partial pressures were measured in blood simultaneously collected from the main pulmonary artery and the LLL pulmonary vein and in mixed expired gas from the LLL. Duplicate samples were obtained at each study phase. Exhaled gas specimens were maintained at >40° C before analysis to avoid condensation and loss of highly soluble gases.

The concentrations of inert gases in the gas samples were measured on a gas chromatograph (Varian 3300, Walnut Creek, CA) equipped with a flame ionization detector and an electron capture detector. The gas extraction method of Wagner *et al.* was used to determine the concentration of inert gases in the blood samples.[15]

Experimental Protocol

After a 60-min stabilization period, the effect of 100% and 200% increases in $\dot{Q}_{LLL}$ on gas exchange were studied in each dog. Minute ventilation of the LLL was kept constant, and carbon dioxide was added to the inspired gases to the LLL in varying amounts to maintain constant LLL end-tidal P_{CO_2} of 36–38 mmHg. The respiratory rate was set at 18–20 breaths/min to yield a Pa_{CO_2} of 36 mmHg in the first control phase.

The experimental protocol was as follows: phase 1 = baseline $\dot{Q}_{LLL}$ ($\dot{Q}_{baseline}$); phase 2 = $\dot{Q}_{LLL}$ increased by 100% to two times above $\dot{Q}_{baseline}$ ($\dot{Q}_{2\times}$) by opening the arteriovenous fistula; phase 3 = $\dot{Q}_{LLL}$ increased by 200% to three times above $\dot{Q}_{baseline}$ ($\dot{Q}_{3\times}$) by opening the arteriovenous fistula and by partially occluding the right pulmonary artery; and phase 4 = $\dot{Q}_{baseline}$. The order of $\dot{Q}_{2\times}$ and $\dot{Q}_{3\times}$ was randomized. If necessary, the pulmonary artery snares were adjusted during the final baseline phase, so that $\dot{Q}_{LLL}$ equaled $\dot{Q}_{LLL}$ in the first baseline phase.

Measurements

After 20 min of stable hemodynamics and LLL end-tidal P_{CO_2} in each phase, hemodynamic, blood gas, and inert gas measurements were made. These included heart rate, systemic arterial pressure (Psa), LLL Ppa, LLL pulmonary venous pressure (Plpv), LLL airway pressure (Paw), and $\dot{Q}_{LLL}$ by electromagnetic flow probe. Blood gases (P_{O_2}, P_{CO_2}, and *p*H; Instrumentation Laboratory 813, Lexington, MA) and hemoglobin (Instrumentation Laboratory 282 Co-Oximeter) were determined in arterial (a), mixed venous ($\bar{v}$), and LLL pulmonary venous (lpv) blood.

Inert gases were measured in mixed venous and LLL pulmonary venous blood and in LLL mixed expired gas. After completion of the experiment, the dogs were killed by an overdose of sodium thiopental, and the LLL was obtained for wet-weight to dry-weight analysis using the cyanomethemoglobin method to estimate blood content.[16]

Data Analysis

Gas exchange was assessed by changes in the perfusion and ventilation distributions predicted by the 50-compartment model of Evans and Wagner[13,14] and by the arterial-alveolar difference ([a-A]D) area derived from retention and excretion data of the tracer inert gases.[17,18] We previously described the adaptation of these analyses to our model.[11] Inert gas shunt ($\dot{Q}_S/\dot{Q}_T$), inert gas dead space (V_D/V_T), mean $\dot{V}_A/\dot{Q}$ ratio of the perfusion and ventilation distributions (mean $\dot{V}_A/\dot{Q}$ of $\dot{Q}$ and mean $\dot{V}_A/\dot{Q}$ of $\dot{V}$, respectively), log standard deviations of the perfusion ($\log SD_{\dot{Q}}$) and ventilation ($\log SD_{\dot{V}}$) distributions, percentage of perfusion to low $\dot{V}_A/\dot{Q}$ units ($\dot{V}_A/\dot{Q}$ ratio 0.001–0.1), and percentage of perfusion and ventilation to high $\dot{V}_A/\dot{Q}$ units ($\dot{V}_A/\dot{Q}$ ratio of 10–100) were calculated from the 50-compartment model.

Table 1. Hemodynamic and Blood Gas Data

	$\dot{Q}_{baseline}$	$\dot{Q}_{2x}$	$\dot{Q}_{3x}$
$\dot{Q}_{LLL}$ (ml/min)	830 ± 70	1630 ± 130*	2510 ± 160*†
Psa (mmHg)	123 ± 8	112 ± 12*	107 ± 12*
HR (beats/min)	184 ± 12	216 ± 7*	207 ± 7*
LLL Ppa (mmHg)	20 ± 1	29 ± 3*	36 ± 3*†
Plpv (mmHg)	13 ± 1	18 ± 1*	19 ± 1*
Paw (mmHg)	7.7 ± 0.6	8.3 ± 0.8	8.4 ± 0.9
Pa_{O_2} (mmHg)	262 ± 5	264 ± 3	254 ± 3*
Pa_{CO_2} (mmHg)	36 ± 1	35 ± 1	36 ± 1
*p*H	7.32 ± 0.01	7.30 ± 0.01	7.28 ± 0.02*
$P\bar{v}_{O_2}$ (mmHg)	47 ± 1	72 ± 3*	73 ± 4*
$Plpv_{O_2}$ (mmHg)	266 ± 2	260 ± 10	253 ± 3
PI_{CO_2} (mmHg)	13 ± 2	18 ± 2*	6 ± 3*†
$Plpv_{CO_2}$ (mmHg)	38 ± 1	38 ± 1	39 ± 1
Hb (g/dl)	12.1 ± 0.8	13.6 ± 0.8*	14.3 ± 1.0*
Blood temperature (° C)	37.6 ± 0.8	37.9 ± 0.2	38.0 ± 0.3

Values are mean ± SE.

$\dot{Q}_{baseline}$ = baseline $\dot{Q}_{LLL}$; $\dot{Q}_{2x}$ = $\dot{Q}_{LLL}$ increased by 100% compared to baseline; $\dot{Q}_{3x}$ = $\dot{Q}_{LLL}$ increased by 200% compared to baseline; LLL = left lower lobe; $\dot{Q}_{LLL}$ = LLL blood flow; Psa = systemic arterial pressure; HR = heart rate; LLL Ppa = LLL pulmonary artery pressure; Plpv = LLL pulmonary venous pressure; Paw = peak LLL airway pressure; Pa_{O_2} = arterial O_2 tension; Pa_{CO_2} = arterial CO_2 tension; $P\bar{v}_{O_2}$ = mixed venous O_2 tension; $Plpv_{O_2}$ = LLL pulmonary venous O_2 tension; PI_{CO_2} = inspired CO_2 tension; $Plpv_{CO_2}$ = LLL pulmonary venous CO_2 tension; Hb = blood hemoglobin.

* $P < 0.05$ compared with $\dot{Q}_{baseline}$.

† $P < 0.05$ compared with $\dot{Q}_{2x}$.

The retention and excretion data of the six inert gases also were analyzed directly to derive the tracer inert gas [a-A]D area. The [a-A]D area can be subdivided into a retention (R) component (difference between the measured retention curve plotted against inert gas solubility and the predicted retention curve for an ideal homogeneous lung with the same shunt and dead space) and an excretion (E) component (difference between the measured excretion curve plotted against inert gas solubility and the predicted excretion curve for an ideal homogeneous lung plotted against inert gas solubility). The R[a-A]D area increases more in the presence of low $\dot{V}_A/\dot{Q}$ regions (as in pulmonary edema) and the E[a-A]D area increases more in the presence of high $\dot{V}_A/\dot{Q}$ regions (as with pulmonary embolism).[17] The [a-A]D area is derived by adding the retention and excretion components. This measure of $\dot{V}_A/\dot{Q}$ heterogeneity is useful in that it provides an assessment of inert gas data that is independent of the 50-compartment model, thereby avoiding the mathematical assumptions of this model. Increases in log $SD_{\dot{Q}}$, log $SD_{\dot{V}}$, and [a-A]D area and its components are all indicative of increases in $\dot{V}_A/\dot{Q}$ heterogeneity. The log $SD_{\dot{Q}}$ is most sensitive to changes in the perfusion distribution relative to $\dot{V}_A/\dot{Q}$ ratio. Log $SD_{\dot{V}}$ is most sensitive to changes in the ventilation distribution relative to $\dot{V}_A/\dot{Q}$ ratio. The [a-A]D area reflects changes in both distributions.

Statistics

Because the hemodynamic, blood gas, and inert gas data in the final baseline phase did not differ from those in the first baseline phase (paired comparison *t* test), the results of the two baseline phases were averaged for subsequent statistics and presentation. All pressure, flow, blood gas, and inert gas data were analyzed by an analysis of variance for repeated measures, with significant differences further analyzed by the Duncan *post hoc* test. Multiple regression analyses of the relationship of $\dot{Q}_{LLL}$ and LLL Ppa to the [a-A]D area, log $SD_{\dot{Q}}$, and log $SD_{\dot{V}}$ were performed. Multiple regression analyses of the relationship of $\dot{Q}_{LLL}$, LLL Ppa, Plpv, $P\bar{v}_{O_2}$, interaction of $P\bar{v}_{O_2}$ and Plpv, and pulmonary perfusion pressure (LLL Ppa - Plpv) to the [a-A]D area and between the log $SD_{\dot{Q}}$ and the R[a-A]D area also were performed. Linear and polynomial regression analyses of the relationship of changes in $\dot{Q}_{LLL}$ and LLL Ppa to the [a-A]D area were performed. $P < 0.05$ was deemed significant. Means ± SE are presented in results.

Results

The experimental preparation was stable during the protocol. LLL minute ventilation (2,490 ± 350 ml/min), Pa_{CO_2}, $Plpv_{CO_2}$, Paw, and blood temperature did not vary, and changes in Psa, heart rate, Pa_{O_2}, *p*H, and hemoglobin had little physiologic significance (table 1). The wet-to-dry weight ratio of the LLL was 6.9 ± 0.3, compared to a laboratory control value of 4.8 ± 0.1.

Increasing $\dot{Q}_{LLL}$ significantly increased LLL Ppa ($P < 0.001$) by 45% during $\dot{Q}_{2x}$ and 80% during $\dot{Q}_{3x}$ (table 1). During $\dot{Q}_{2x}$, Plpv ($P < 0.01$) and $P\bar{v}_{O_2}$ ($P < 0.001$) were increased compared to $\dot{Q}_{baseline}$. However, further increases in Plpv and $P\bar{v}_{O_2}$ were not noted when $\dot{Q}_{LLL}$ was raised to $\dot{Q}_{3x}$. Despite the increase in $P\bar{v}_{O_2}$ with increased $\dot{Q}_{LLL}$, $Plpv_{O_2}$ remained unchanged from $\dot{Q}_{baseline}$ (table 1).

The effect of increasing $\dot{Q}_{LLL}$ on gas exchange measured by the multiple inert gas elimination technique is illustrated in a representative dog in figures 2 and 3. Increasing $\dot{Q}_{LLL}$ shifted the perfusion and venti-

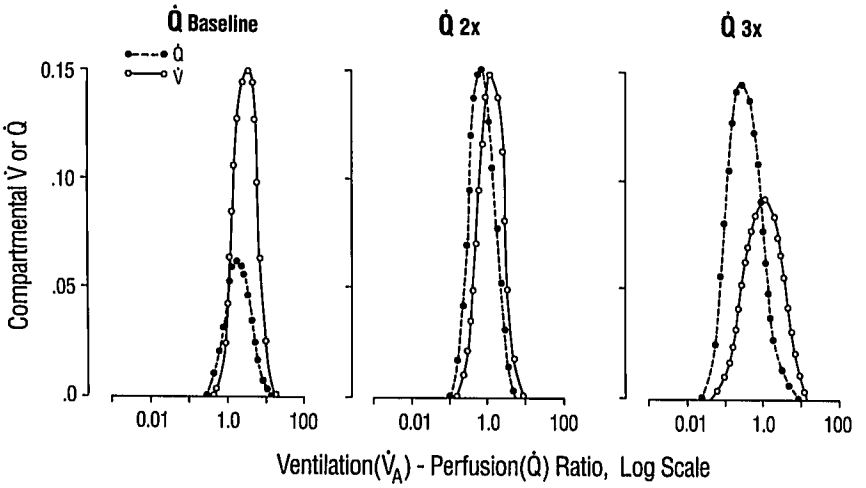

Fig. 2. Effect of increasing LLL blood flow ($\dot{Q}_{LLL}$) on ventilation-to-perfusion ($\dot{V}_A/\dot{Q}$) distributions relative to $\dot{V}_A/\dot{Q}$ ratio in a single representative dog. $\dot{Q}_{baseline}$ = first baseline phase; $\dot{Q}_{2x}$ = $\dot{Q}_{LLL}$ increased by 100% compared to baseline; $\dot{Q}_{3x}$ = $\dot{Q}_{LLL}$ increased by 200% compared to baseline. As $\dot{Q}_{LLL}$ was increased, the perfusion distribution (closed circles) was shifted to a lower mean $\dot{V}_A/\dot{Q}$ ratio. Although in this dog the perfusion distribution became progressively broader, statistical analysis including all dogs revealed that log $SD_{\dot{Q}}$ was not changed. The ventilation distribution (open circles) also shifted to a lower mean $\dot{V}_A/\dot{Q}$ ratio and became progressively broader (increased log $SD_{\dot{V}}$).

lation distributions to a lower mean $\dot{V}_A/\dot{Q}$ ratio (mean $\dot{V}_A/\dot{Q}$ of $\dot{Q}$ and $\dot{V}$, $P < 0.01$; table 2). The ventilation distribution became broader, reflected by a 29% increase in log $SD_{\dot{V}}$ with $\dot{Q}_{2x}$ and a 35% increase with $\dot{Q}_{3x}$ ($P < 0.001$). The perfusion distribution did not become significantly broader (log $SD_{\dot{Q}}$; table 2), although four of six dogs exhibited an increase in log $SD_{\dot{Q}}$ with increased blood flow. The percentage of ventilation of high $\dot{V}_A/\dot{Q}$ units and perfusion of $\dot{Q}s/\dot{Q}T$ and low $\dot{V}_A/\dot{Q}$ units also exhibited a trend to increase with increasing $\dot{Q}_{LLL}$, which was not statistically significant (table 2).

The [a-A]D area was increased by 40 ± 10% during $\dot{Q}_{2x}$ and 58 ± 8% during $\dot{Q}_{3x}$ ($P < 0.001$; fig. 4). The excretion components were increased more than the retention components ($\dot{Q}_{2x}$: 49% and 25% increase, respectively; $\dot{Q}_{3x}$: 60% and 40% increase, respectively; table 2).

The multiple regression analysis revealed a significant correlation of $\dot{Q}_{LLL}$ with the [a-A]D area (r = 0.97, $P < 0.001$; fig. 4) and log $SD_{\dot{V}}$ (r = 0.97, $P < 0.001$; not shown). Significant correlations of LLL Ppa with [a-A]D (r = 0.97, $P < 0.001$; fig. 5) and log $SD_{\dot{V}}$ (r = 0.92, $P < 0.001$; not shown) also were observed. A similar

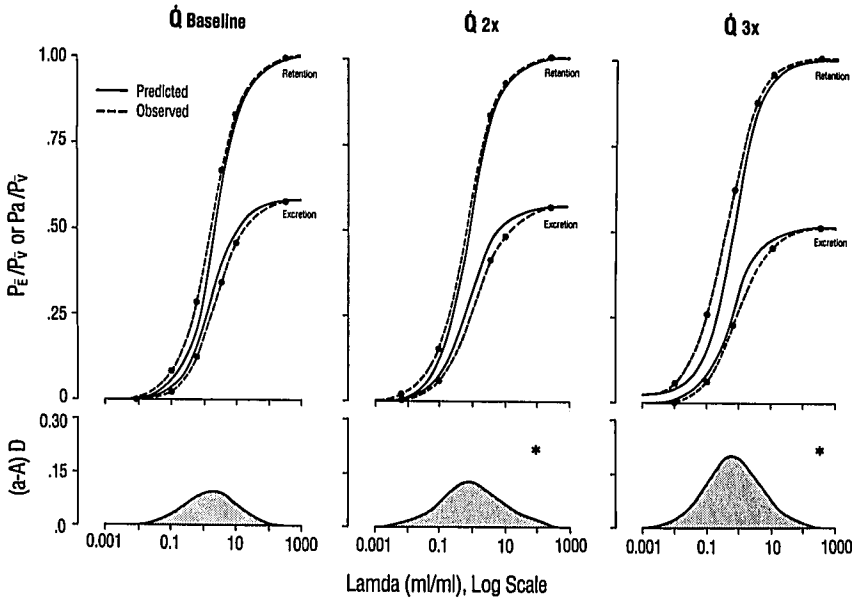

Fig. 3. Effect of increasing $\dot{Q}_{LLL}$ on the retention (R) and excretion (E) curves (top) and the inert gas arterial-alveolar difference ([a-A]D; bottom) plotted against inert gas solubility in the same dog as in figure 1. Solid lines in top part of the figure represent values predicted for a homogenous lung with identical shunt and dead space. The dashed lines represent observed values. The best-fit retention and excretion curves were derived from the six different tracer inert gases over a wide range of solubility. With increasing $\dot{Q}_{LLL}$, the difference in areas between the measured retention curve and the homogeneous retention curve (R[a-A]D area) and between the measured excretion curve and the homogeneous excretion curve (E [a-A]D area) were increased compared to $\dot{Q}_{baseline}$. Added together, these form the [a-A]D area shown in the lower portion of the figure. The [a-A]D area became progressively larger with increasing $\dot{Q}_{LLL}$. *$P < 0.01$ compared to $\dot{Q}_{baseline}$ (comparing all animals).

Table 2. Gas Exchange of the Left Lower Lobe

	$\dot{Q}_{baseline}$	$\dot{Q}_{2x}$	$\dot{Q}_{3x}$
Mean $\dot{V}_A/\dot{Q}$ of $\dot{Q}$	1.4 ± 0.2	0.6 ± 0.1*	0.4 ± 0.1*
Log $SD_{\dot{Q}}$	0.82 ± 0.03	0.82 ± 0.04	0.88 ± 0.06
Mean $\dot{V}_A/\dot{Q}$ of $\dot{V}$	4.4 ± 0.9	3.1 ± 0.8*	2.6 ± 0.9*
Log $SD_{\dot{V}}$	1.30 ± 0.20	1.68 ± 0.18*	1.76 ± 0.14*
$\dot{Q}_S/\dot{Q}_T$ (%)	0.2 ± 0.1	0.3 ± 0.1	0.6 ± 0.3
$\dot{Q}$ low $\dot{V}_A/\dot{Q}$ (%)	0.3 ± 0.2	0.3 ± 0.1	2.9 ± 1.8
V_D/V_T (%)	41 ± 3	38 ± 4	40 ± 5
$\dot{Q}$ high $\dot{V}_A/\dot{Q}$ (%)	1.5 ± 0.6	0.9 ± 0.3	0.7 ± 0.3
$\dot{V}$ high $\dot{V}_A/\dot{Q}$ (%)	14 ± 5	18 ± 6	17 ± 6
R[a-A]D area	0.20 ± 0.03	0.25 ± 0.05	0.28 ± 0.05*
E[a-A] area	0.29 ± 0.08	0.43 ± 0.10*	0.46 ± 0.09*

Values are mean ± SE.

$\dot{Q}_{baseline}$ = baseline $\dot{Q}_{LLL}$; $\dot{Q}_{2x}$ = $\dot{Q}_{LLL}$ increased by 100% compared to baseline; $\dot{Q}_{3x}$ = $\dot{Q}_{LLL}$ increased by 200% compared to baseline. Mean $\dot{V}_A/\dot{Q}$ of $\dot{Q}$ = mean ventilation-perfusion ($\dot{V}_A/\dot{Q}$) ratio of the perfusion distribution; log $SD_{\dot{Q}}$ = log standard deviation of the perfusion distribution; mean $\dot{V}_A/\dot{Q}$ of $\dot{V}$ = mean $\dot{V}_A/\dot{Q}$ ratio of the ventilation disribution; log $SD_{\dot{V}}$ = log standard deviation of the ventilation distibution; $\dot{Q}_S/\dot{Q}_T$ = inert gas shunt; $\dot{Q}$ low $\dot{V}_A/\dot{Q}$ = blood flow to low-$\dot{V}_A/\dot{Q}$ units; V_D/V_T = inert gas dead space; $\dot{Q}$ high $\dot{V}_A/\dot{Q}$ = blood flow to high-$\dot{V}_A/\dot{Q}$ units; $\dot{V}$ high $\dot{V}_A/\dot{Q}$ = ventilation to high-$\dot{V}_A/\dot{Q}$ units; R[a-A]D = retention component of arterial-alveolar difference area; E[a-A]D = excretion component of arterial-alveolar difference area.

* $P < 0.05$ compared with $\dot{Q}_{baseline}$.

relationship was observed with pulmonary perfusion pressure (LLL Ppa-Plpv). $\dot{Q}_{LLL}$ and Ppa did not significantly affect log $SD_{\dot{Q}}$ ($r = 0.617$, $P = 0.06$). The multiple regression analysis revealed that $P\bar{v}_{O_2}$ and Plpv and their interaction did not affect $\dot{V}_A/\dot{Q}$ heterogeneity independent of changes in $\dot{Q}_{LLL}$. R[a-A]D area correlated highly with log $SD_{\dot{Q}}$ ($r = 0.98$, $P < 0.001$).

Discussion

The aim of this study was to determine the effects of large increases in pulmonary blood flow on $\dot{V}_A/\dot{Q}$ matching in dogs with normal lungs in the absence of changes in ventilation and alveolar carbon dioxide. We found that increasing LLL blood flow two to three times above basal flow increased $\dot{V}_A/\dot{Q}$ heterogeneity, measured by the [a-A]D area, by 40% and 58%, respectively. Within the range studied, increases in pulmonary blood flow increased $\dot{V}_A/\dot{Q}$ mismatch in a linear manner. Although the increase in $\dot{V}_A/\dot{Q}$ heterogeneity occurred throughout the range of finite $\dot{V}_A/\dot{Q}$ regions, the relatively greater increase in the excretion than the retention component of the [a-A]D area suggests that increases in high $\dot{V}_A/\dot{Q}$ regions were important. $Plpv_{O_2}$ did not change because the decrease in $Plpv_{O_2}$ (due to

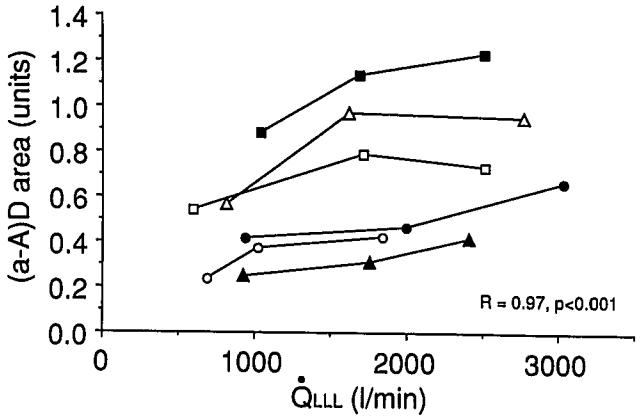

Fig. 4. Effect of increasing $\dot{Q}_{LLL}$ (x axis) on the arterial-alveolar difference ([a-A]D) area index of $\dot{V}_A/\dot{Q}$ heterogeneity (y axis). Data from each dog is shown. Multiple regression analysis revealed a significant correlation of the [a-A]D area with $\dot{Q}_{LLL}$ ($r = 0.97$, $P < 0.001$).

an increase in $\dot{V}_A/\dot{Q}$ mismatch) was balanced by an increase in $Plpv_{O_2}$ (due to increased $P\bar{v}_{O_2}$).

We assessed heterogeneity of pulmonary gas exchange by parameters calculated from both the 50-compartment model and direct analysis of retention and excretion data. We believe that the direct analysis of retention and excretion solubility curves to yield the [a-A]D areas is a superior method to detect $\dot{V}_A/\dot{Q}$ heterogeneity in the normal lung.[11,12] We have proposed that the retention and excretion components of the [a-A]D area are better and more sensitive measures of $\dot{V}_A/\dot{Q}$ heterogeneity in the normal lung. Unlike log

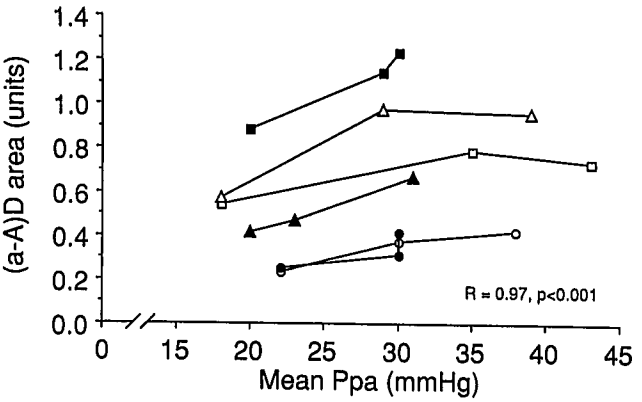

Fig. 5. Effect of increasing LLL pulmonary artery pressure (Ppa, x axis) on the arterial-alveolar difference ([a-A]D) area index of $\dot{V}_A/\dot{Q}$ heterogeneity (y axis). Data from each dog is shown. Multiple regression analysis revealed a significant correlation of the [a-A]D area with Ppa ($r = 0.97$, $P < 0.001$).

$SD_{\dot{Q}}$ and log $SD_{\dot{V}}$, R[a-A]D and E[a-A]D areas are not subject to a mathematical transformation that constrains them to a minimal value. Although R[a-A] area is less intuitive than log $SD_{\dot{Q}}$, because it is not related to a specific $\dot{V}_A/\dot{Q}$ distribution, R[a-A] area is more specific and more quantitative and correlated highly with log $SD_{\dot{Q}}$ ($r = 0.98$).

By using the multiple inert gas elimination technique to specifically assess gas exchange, our study confirms and extends the results of prior work that suggest that marked increases in pulmonary perfusion may increase venous admixture and reduce Pa_{O_2}. In the presence of diffuse lung disease, such as in patients with adult respiratory distress syndrome (ARDS) and animals with noncardiogenic pulmonary edema, intrapulmonary shunt was increased when cardiac output was increased.[5,19,20-23] Lemaire *et al.*[5] found a direct relationship between pulmonary perfusion and intrapulmonary shunt in patients with ARDS who received extracorporeal bypass. They observed increases in intrapulmonary shunt in 69 patients with ARDS whose cardiac output was increased by venoarterial bypass, plasma volume expansion, or infusion of dopamine or dobutamine.[5] Dopamine, which raised mean pulmonary artery pressure by 5 mmHg, also caused more $\dot{V}_A/\dot{Q}$ mismatch than dobutamine, which did not affect pulmonary artery pressure in critically ill patients whose lungs were mechanically ventilated.[4] Administration of dopamine impaired pulmonary gas exchange in lambs with pulmonary hypertension induced by breathing a hypoxic gas mixture.[24] However, the net effect of increased cardiac output on arterial blood oxygenation is complex. The effect of increases in $P\bar{v}_{O_2}$, which tend to increase Pa_{O_2}, is balanced against an increasing shunt, which tends to decrease Pa_{O_2}.[5,20,22] Hence, dopamine reduced Pa_{O_2} in mechanically ventilated patients[5,6,21,22] and animals[7] when $P\bar{v}_{O_2}$ had little change. However, under other circumstances, dopamine did not affect Pa_{O_2}.[22,24,25]

Studies investigating the effect of increasing pulmonary blood flow on gas exchange in the normal lung have been less plentiful. Most of the work examines the effect of severe exercise on gas exchange in humans. $\dot{V}_A/\dot{Q}$ heterogeneity was increased by 100% during vigorous exercise. $\dot{V}_A/\dot{Q}$ mismatch was greater when exercise was performed at simulated altitude (10,000–15,000 feet above sea level), and it was reversed by breathing oxygen.[1,3] The degree in impairment of gas exchange was correlated with changes in both hemodynamic and respiratory variables. Vigorous exercise markedly reduced $P\bar{v}_{O_2}$ and increased cardiac output by three to four times, Ppa by two to three times, and pulmonary capillary wedge pressure by five to six times, with greater increases in Ppa observed at simulated altitude.[2,3]

Because drug effects,[4] presence of lung disease,[10] and changes in respiratory variables[8-10] all may affect $\dot{V}_A/\dot{Q}$ matching in these studies, we developed a dog model with normal lungs[11,12] in which perfusion to the LLL was manipulated, while maintaining constant alveolar carbon dioxide and minute ventilation. We previously studied the effect of modest increases of lobar blood flow on $\dot{V}_A/\dot{Q}$ heterogeneity using this model.[12] We found that a 50% increase in pulmonary blood flow increased $\dot{V}_A/\dot{Q}$ heterogeneity by 25%, measured by the [a-A]D area. Previously, only modest elevations of lobar blood flow were studied to avoid the complicating effects of increases in $P\bar{v}_{O_2}$, changes in systemic hemodynamics, or development of pulmonary edema on gas exchange. Unfortunately, a 50% increase in LLL blood flow was the maximum that could be achieved in this preparation, even when the right pulmonary artery was totally constricted. The present study allowed changes in $P\bar{v}_{O_2}$ and Plpv to occur with increasing $\dot{Q}_{LLL}$, which were necessary to broaden and extend our findings to higher levels of pulmonary blood flow,

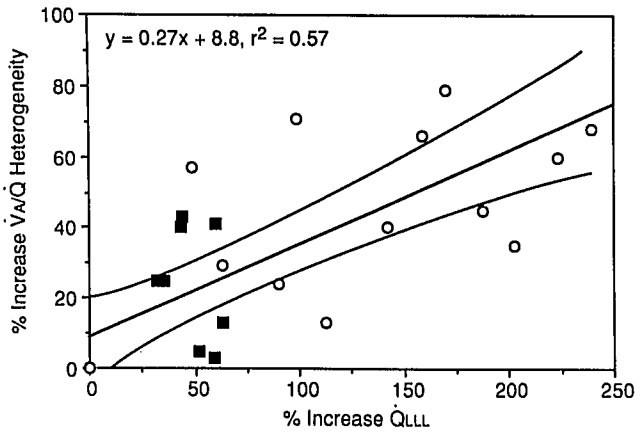

Fig. 6. Relationship of increasing pulmonary blood flow with impairment in $\dot{V}_A/\dot{Q}$ matching, as measured by increases in the arterial-alveolar difference area index. The percentage increase of lobar blood flow is on the x axis and the percentage increase in $\dot{V}_A/\dot{Q}$ heterogeneity compared to baseline is on the y axis. Data from reference 12 are indicated by solid squares and data from the present study are indicated by open circles. The data are linear, and the regression equation and 95% confidence intervals are indicated in the figure.

as might occur during emergence from anesthesia, posttraumatic stress, hypervolemic therapy, or with aggressive administration of inotropic drugs for hemodynamic support.

The results of our two studies are pooled in figure 6, which illustrates the impairment of $\dot{V}_A/\dot{Q}$ matching, as measured by increases in the [a-A]D area index, with increasing lobar blood flow. For each animal, the data for each blood flow were compared to the mean values of the two baseline periods. Within the range studied, increasing lobar blood flow inhibited $\dot{V}_A/\dot{Q}$ matching in a linear manner ($r = 0.76$, $P < 0.001$). Higher order polynomial regressions did not improve the fit of the relationship with lobar blood flow. Inclusion of the previously published data (50% increase in lobar blood flow)[12] did not affect the regression. Figure 6 shows that the previously obtained data from reference 12 (squares) fits well with the present data (circles). The relationship of inhibition of $\dot{V}_A/\dot{Q}$ matching with pulmonary artery pressure was best described by a second order polynomial [% increase in $\dot{V}_A/\dot{Q}$ inequality = 1.13 + 1.31 (% increase in Ppa) − 0.007 (% increase in Ppa)^2]. The relationship between Ppa and $\dot{Q}_{LLL}$ also was curvilinear, as might be expected from normal pulmonary pressure-flow relationships.

Extrapolation of our data would predict that a 430% increase in pulmonary blood flow would cause a 100% increase in $\dot{V}_A/\dot{Q}$ heterogeneity. This increase is consistent with that observed during vigorous exercise. Our results, therefore, suggest that increases in pulmonary perfusion by itself may significantly impair pulmonary gas exchange. As we did not study extremely large increases in pulmonary blood flow, our study cannot determine whether even greater levels of pulmonary blood flow would continue to increase $\dot{V}_A/\dot{Q}$ heterogeneity in a linear or a curvilinear manner.

Gas exchange during control baseline conditions was comparable with that previously obtained with this preparation.[11,12] Baseline $\dot{V}_A/\dot{Q}$ heterogeneity, the mean $\dot{V}_A/\dot{Q}$ ratio of the ventilation distribution, and the percentage of ventilation to high $\dot{V}_A/\dot{Q}$ regions in the lobe were all greater than are typically observed in normal, closed-chest dogs. The etiology of these changes in baseline $\dot{V}_A/\dot{Q}$ heterogeneity is not clear. We previously speculated that they may be due to an artifact of the surgical preparation such as distortion of the lobe with left upper lobectomy, changes in lobar blood flow associated with surgical trauma, the presence of an electromagnetic flow probe, and vascular occluder on the LLL pulmonary artery, or resistance of LLL pulmonary venous outflow by the pulmonary venous catheter.[12] We believe that the increases in $\dot{V}_A/\dot{Q}$ heterogeneity were not an artifact of the open-chest preparation, although transpleural excretion of diethyl ether and acetone has been reported in open-chest preparations.[26,27] The small reduction in the retention of ether and acetone due to their transpleural flux would not exceed 1% and, therefore, should not significantly influence $\dot{V}_A/\dot{Q}$ measurements.[26] Additionally, significant flux of these highly soluble inert gases may be secondary to the continuous insufflation of air into the thoracic cavity, which was not done in our study.

The etiology of greater $\dot{V}_A/\dot{Q}$ inequality with increased pulmonary perfusion is unclear and was not specifically investigated in our study. Possible factors may be the development of interstitial edema,[23] increased $P\bar{v}_{O_2}$,[20,23,28–30] increased Ppa and pulmonary vascular recruitment,[20,23,26,29] or increased lobar venous pressure.[31]

Moderate edema was present in the LLL, indicated by an elevated wet-to-dry weight ratio of 6.9 (compared to laboratory control of 4.8). Moderate edema of both lungs (wet-to-dry weight ratio of 6.0) has occurred in the past with this model.[11,12] The slightly greater wet-to-dry weight ratio in the present study may be secondary to the markedly increased lobar blood flow. However, the development of interstitial edema does not completely account for the increased $\dot{V}_A/\dot{Q}$ heterogeneity with elevated pulmonary perfusion. Gas exchange during the first baseline period obtained before did not differ from gas exchange during the second baseline period obtained after the increase in blood flow. As only 30 min elapsed from the time samples were drawn in the last increased $\dot{Q}_{LLL}$ phase and the final baseline phase, it is unlikely that the edema would be markedly reduced. Clearance of edema fluid takes place over a longer time course.[32] For instance, approximately one-third of autologous serum instilled into airspaces was removed in 4 h.[32] Additionally, gas exchange abnormalities are not closely correlated with the amount of edema. Significant interstitial edema may develop before abnormalities in gas exchange occur.[33,34]

Increased $P\bar{v}_{O_2}$ has been shown to increase pulmonary shunt in several animal models with lung disease[28,29] or isolated lobes.[30] However, increased $P\bar{v}_{O_2}$ in normal dogs ventilated with room air, while holding cardiac output constant, reduced venous admixture, and in lungs ventilated with 100% O_2, it had no effect. These

data, as well as ours (*e.g.*, $\dot{V}_A/\dot{Q}$ heterogeneity was increased linearly with increased pulmonary blood flow, unrelated to $P\bar{v}_{O_2}$), suggest that increased $P\bar{v}_{O_2}$ contributed little to causing the $\dot{V}_A/\dot{Q}$ inequality in our study in normal lung.

Increasing Ppa may be an important factor responsible for increased $\dot{V}_A/\dot{Q}$ inequality with elevation of pulmonary blood flow. Raising cardiac output and Ppa by 60%, while maintaining a constant mixed venous oxygen tension, increased venous admixture by 60% in dogs ventilated with room air.[28] No effect was noted when $F_{I_{O_2}}$ was 1.0.[28] Pulmonary vascular recruitment (*e.g.*, opening of previously closed lung vessels) is probably responsible for the adverse effect of increased Ppa on gas exchange.[20] Increased intraregional heterogeneity due to greater perfusion of zone 1 lung with perfusion of corner vessels or high $\dot{V}_A/\dot{Q}$ areas near the periphery of the lung may have occurred in our preparation. It is less likely that inhibition of hypoxic pulmonary vasoconstriction (HPV) by increased vascular pressures would contribute to the $\dot{V}_A/\dot{Q}$ inequality.[31] Dopamine and dobutamine, which impair gas exchange, do not directly inhibit HPV.[7] Additionally, HPV is relatively unimportant in the preservation of $\dot{V}_A/\dot{Q}$ matching in normal dogs.[35]

We cannot rule out a concurrent influence of increases in pulmonary outflow pressure (*e.g.*, Plpv) on $\dot{V}_A/\dot{Q}$ matching, as Plpv also increased as the lobar blood flow was elevated. An increase in Plpv may have occurred in our study because of limitations in outflow with extremely high blood flows through the pulmonary venous catheter. Gas exchange in calves with normal lungs was optimal at left atrial pressures between 4 and 12 mmHg.[36] However, only left atrial pressures above 18 mmHg resulted in physiologically significant increases in shunt and dead space. Unfortunately, Ppa values also were increased in this study,[36] so the role of independent increases in the left atrial pressure were not studied. As Plpv values were lower in our study, the adverse effect of elevated pulmonary outflow pressures on gas exchange is likely to be small. Additionally, the relationship between pulmonary perfusion pressure and the [a-A]D area index was similar to that between Ppa and [a-A]D area.

In conclusion, our study found that increasing pulmonary perfusion independently increased $\dot{V}_A/\dot{Q}$ mismatch, even in the normal lung. The clinical implications of our study are that increases in pulmonary blood flow and pulmonary artery pressure may increase $\dot{V}_A/\dot{Q}$ inequality and, in some patients, worsen Pa_{O_2}. As the increase in $\dot{V}_A/\dot{Q}$ heterogeneity was directly correlated with the degree of increase in pulmonary perfusion, we predict that inotropic agents that result in higher pulmonary artery pressures would have a greater adverse effect on Pa_{O_2}. Likewise, marked release of catecholamines in the severely traumatized patient, as during the resection of a pheochromocytoma and during anesthetic emergence, also may increase $\dot{V}_A/\dot{Q}$ mismatch. Pa_{O_2} may be reduced in such circumstances if the effect of increase in shunt on Pa_{O_2} is greater that the effect on Pa_{O_2} due to an increase in $P\bar{v}_{O_2}$.

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