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Effect of Increased Intracranial Pressure on Regional Hypoxic Pulmonary Vasoconstriction

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The effects of increased intracranial pressure (ICP) and increased cardiac output ($\dot{Q}_T$) on the pulmonary vascular response to regional alveolar hypoxia were compared in pentobarbital-anesthetized, closed-chested dogs. A bronchial divider was inserted, the right lung (RL) was continuously ventilated with 100% O_2, and the left lung (LL) was ventilated with either 100% O_2 (hyperoxia) or a hypoxic gas mixture (hypoxia). Sulfur hexafluoride (SF_6) was used to measure differential lung blood flow and the multiple inert gas technique assessed gas exchange. The response to LL alveolar hypoxia (hypoxic pulmonary vasoconstriction, HPV) was studied in each animal prior to, during, and after the ICP was increased by infusing mock cerebrospinal fluid (CSF) into a lateral ventricle so that cerebral perfusion pressure was 25 mmHg. During both control periods, $\dot{Q}_T$ was randomly altered by opening (high $\dot{Q}_T$) or closing (normal $\dot{Q}_T$) two arteriovenous fistulas. Increasing ICP significantly increased $\dot{Q}_T$ ($P < 0.01$), pulmonary artery pressure (PAP) ($P < 0.05$), and mixed venous oxygen tension ($P\bar{v}_{O_2}$) ($P < 0.05$), compared with normal $\dot{Q}_T$ controls. Opening the arteriovenous fistulas achieved similar increases in $\dot{Q}_T$ ($P < 0.01$), PAP ($P < 0.05$), and $P\bar{v}_{O_2}$ ($P < 0.05$). The percentage of blood flow to the LL ($\dot{Q}_L/\dot{Q}_T$%) during hyperoxia was 43.9 ± 0.8% (mean ± SE) and did not vary with manipulation of $\dot{Q}_T$ or ICP. $\dot{Q}_L/\dot{Q}_T$% during LL hypoxia was significantly increased by both increased ICP (24.6 ± 3.5%) and high $\dot{Q}_T$ (23.1 ± 1.0%) compared with normal $\dot{Q}_T$ (16.8 ± 2.1) controls ($P < 0.05$). Therefore, flow diversion with HPV was reduced equally by both increasing ICP and increasing $\dot{Q}_T$ ($P < 0.05$). Ventilation–perfusion matching was unchanged by increased ICP. These results suggest that impaired oxygenation with increased ICP may be partly secondary to an attenuation of regional HPV, caused by increased cardiac output. (Key words: Brain: increased intracranial pressure. Heart: cardiac output. Lung, circulation: hypoxic pulmonary vasoconstriction. Measurement technique: multiple inert gas elimination technique.)

HYPOXEMIA, ventilation–perfusion ($\dot{V}_A/\dot{Q}$) mismatch, and increased pulmonary shunting ($\dot{Q}_s/\dot{Q}_t$) commonly occur in patients with severe head injuries, in the absence of overt neurogenic pulmonary edema, hypoventilation, aspiration, atelectasis, or reduced cardiac output.[1–4] A twofold increase in $\dot{Q}_s/\dot{Q}_t$ occurs when intracranial pressure (ICP) is increased to over 100 mmHg in animals.[5] When ICP is increased, the sympathetic nervous system is activated and catecholamines are released from the adrenal medulla.[6] Cardiac output ($\dot{Q}_T$), mixed venous oxygen tension ($P\bar{v}_{O_2}$), pulmonary artery pressure (PAP), and pulmonary venous pressure are all increased.[7–9] These hemodynamic changes may inhibit regional hypoxic pulmonary vasoconstriction (HPV), resulting in reduced diversion of flow away from hypoxic to normoxic lung regions.[10,11] The present study compared the effects of increased ICP to the effects of increased $\dot{Q}_T$ on the pulmonary vascular response to regional alveolar hypoxia in closed-chested dogs.

Materials and Methods

ANESTHETIC AND SURGICAL PREPARATION

Six male dogs (23–27 kg) were anesthetized with pentobarbital sodium (30 mg/kg iv, supplemented with 25–50 mg hourly). The trachea was intubated and the lungs were ventilated with 100% O_2. Muscle paralysis was secured with pancuronium (0.1 mg/kg, supplemented as necessary). With the animal in the prone position, a cannula was inserted into a lateral ventricle of the brain using a stereotaxic frame. The animal was then turned supine for completion of the remainder of the surgical preparation. A pulmonary artery catheter and a femoral arterial catheter were inserted by peripheral cutdowns. For manipulation of cardiac output, two Teflon-coated 6 mm ID arteriovenous fistulas were constructed, one between a femoral artery and vein and the other between an internal carotid artery and external jugular vein.

A Kottmeir® (Rusch, New York) double-lumen endobronchial tube was inserted through a subcricoid tracheostomy to allow separate ventilation of the right (RL) and left (LL) lungs. Complete lung isolation was verified by demonstration that oxygen cross-contamination of the left lung did not occur when it was ventilated with a hypoxic gas mixture and by the absence of air bubbles escaping from one limb of the endobronchial tube, when the other was hyperinflated. Both lungs were then ventilated synchronously by a Harvard dual-piston ventilator and 3 cmH_2O PEEP was administered by water seal. Tidal volumes were selected to produce equal peak airway pressures (15 cmH_2O) and Pa_{CO_2} of 40 ± 4 mmHg.

ICP, right atrial (CVP), systemic arterial (MAP), PAP, pulmonary capillary wedge (PCWP), and right and left airway (P_{aw}) pressures, and end-tidal P_{CO_2} and LL mixed expired P_{O_2} were measured by standard techniques. Cardiac output, obtained by thermodilution in triplicate, using iced D5/W, and mixed venous hemoglobin oxygen

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saturation were measured (American Edwards Laboratory oximetric cardiac output computer, Santa Ana, California). Intravenous fluid was given to maintain PCWP at 10 mmHg. Urine output was collected from a Foley catheter. Body temperature, measured by blood temperature, was maintained at 37 ± 1° C with heating lamps, pads, and heated humidified gases. $NaHCO_3$ was given when necessary to correct metabolic acidosis.

Differential Lung Flow and Inert Gas Measurements

Multiple inert gas elimination technique measurements were performed using standard methods.[12,13] A dilute solution of six inert gases [sulfur hexafluoride (SF_6), ethane, cyclopropane, halothane, diethyl ether, and acetone] was infused intravenously with an infusion pump for at least 20 min prior to the experimental measurements. Inert gas partial pressures were measured in blood simultaneously collected from the carotid artery (Pa) and the main pulmonary artery ($P\bar{v}$) and in mixed expired gas samples from the RL ($P_{\bar{E}_{RL}}$) and LL ($P_{\bar{E}_{LL}}$). Exhaled gas samples were maintained at greater than 40° C before analysis to avoid condensation and loss of highly soluble gases. RL and LL minute ventilation ($\dot{V}_{\bar{E}_{RL}}$ and $\dot{V}_{\bar{E}_{LL}}$, respectively) were measured by in-line spirometers (Boehringer, Wynnewood, Pennsylvania).

The concentrations of inert gases in the gas samples were measured on a gas chromatograph (Varian 3300, Walnut Creek, California) equipped with a flame ionization detector and electron capture detector (for SF_6). The gas extraction method of Wagner *et al.*[12] was used to determine the concentration of the inert gases in the blood samples.

LL ($\dot{Q}_L$) and RL ($\dot{Q}_R$) blood flows were calculated using the Fick principle for SF_6:

$$\dot{Q}_R = (\dot{V}_{\bar{E}_{RL}} \times P_{\bar{E}_{RL}})/\lambda(P\bar{v} - Pa),$$

$$\dot{Q}_L = (\dot{V}_{\bar{E}_{LL}} \times P_{\bar{E}_{LL}})/\lambda(P\bar{v} - Pa).$$

The percentage flow to LL ($\dot{Q}_L/\dot{Q}_T\%$) was calculated by:

$$[\dot{Q}_L/(\dot{Q}_L + \dot{Q}_R)] \times 100.$$

Gas exchange of the lung as a whole was assessed by calculating total lung (TL) relative retentions (R) and excretion (E) of inert gases by:

$$R = Pa/P\bar{v},$$

$$E = P_{\bar{E}_{TL}}/P\bar{v},$$

where

$$P_{\bar{E}_{TL}} = [(\dot{V}_{\bar{E}_{RL}} \times P_{\bar{E}_{RL}}) + (\dot{V}_{\bar{E}_{LL}} \times P_{\bar{E}_{LL}})]/(\dot{V}_{\bar{E}_{RL}} + \dot{V}_{\bar{E}_{LL}}).$$

$\dot{V}_A/\dot{Q}$ distributions were obtained using the ridge-regression algorithm of Evans and Wagner.[13] Inert gas shunts ($\dot{Q}_s/\dot{Q}_t$), dead spaces (V_D/V_T), mean $\dot{V}_A/\dot{Q}$ ratio of the perfusion distribution (mean $\dot{V}_A/\dot{Q}$ of $\dot{Q}$) and of the ventilation distribution (mean $\dot{V}_A/\dot{Q}$ of $\dot{V}$), and log standard deviations of the perfusion (log $SD_{\dot{Q}}$) and ventilation (log $SD_{\dot{V}}$) distributions were obtained from the model. Increases in log $SD_{\dot{Q}}$ and log $SD_{\dot{V}}$ are quantitative indices of increases in $\dot{V}_A/\dot{Q}$ mismatch or heterogeneity.[13]

Experimental Design

The RL was ventilated continuously with 100% O_2 throughout the experiment. The LL was ventilated with either 100% O_2 (hyperoxia) or a hypoxic gas mixture (4% O_2, 3% CO_2, balance N_2) (hypoxia). During LL hypoxia $\dot{V}_{\bar{E}}$ was increased by increasing respiratory rate to maintain a constant Pa_{CO_2}. Prior to the experimental sequence, three 10-min trials of hypoxic ventilation of the LL were alternated with 100% O_2 ventilation to demonstrate stable, reproducible pulmonary vascular responses to hypoxia.[14]

The HPV response to LL hypoxia was studied in each animal before and after (controls) and during increased ICP. During both control periods $\dot{Q}_T$ was altered by opening (high $\dot{Q}_T$) or closing (normal $\dot{Q}_T$) the two arteriovenous fistulas in counterbalanced order. During increased ICP the fistulas remained closed. ICP was slowly (over 45 min) increased using an infusion of mock cerebrospinal fluid (CSF).[15] The mock CSF was infused into the lateral ventricular catheter by a roller pump connected through a Windkessel reservoir to maintain a cerebral perfusion pressure (MAP − ICP) of 25 mmHg. ICP was measured by the same catheter by shutting off the pump for 30 s and allowing ICP to plateau. Approximately 100 ml of mock CSF was infused per hour; 50–80 mEq of $NaHCO_3$ was given intravenously during the increased ICP phase to prevent metabolic acidosis. ICP and hemodynamics were allowed to return to normal for 2 h following mock CSF infusion. In pilot studies we also attempted to have an increased ICP and normal $\dot{Q}_T$ phase, induced by concurrent hypovolemia. However, the animals died with this manipulation, and it was omitted from this study.

Measurements and Calculations

After 20 min of stable conditions in each phase, arterial and mixed venous blood gases [Instrumentation Laboratory (IL) 813, Lexington, Massachusetts], inert gases, hemoglobin (IL 282 co-oximeter), temperature, ICP, MAP, PCWP, right and left P_{aw}, and $\dot{Q}_T$ by thermodilution were measured. $\dot{Q}_L/\dot{Q}_T\%$ was calculated by flows determined by SF_6.[16] LL flow diversion was calculated as:

(Hyperoxia $\dot{Q}_L/\dot{Q}_T\%$ − Hypoxia $\dot{Q}_L/\dot{Q}_T\%$)/Hyperoxia $\dot{Q}_L/\dot{Q}_T\%$.

Gas exchange was analyzed in the first normal $\dot{Q}_T$ and high $\dot{Q}_T$ control phases and the increased ICP phase during 100% oxygen ventilation. The animals were killed with an overdose of pentobarbital sodium and the right lower and left lower lobes were quickly removed, weighed, and prepared for gravimetric analysis. Blood-free wet weight-to-dry weight ratios[17] were made using the cyanmethemoglobin method to estimate blood content.

Statistics

The hemodynamic, blood gas, and flow data were analyzed by a within-subjects two-factor analysis of variance (ANOVA). The flow diversion and gas exchange data were compared by a within-subjects ANOVA for repeated measurements. The Newman-Keuls test was used for comparison of specific differences between means. Wet-to-dry weight ratios of the lungs were compared with concurrent hyperoxic laboratory controls by a group comparison *t* test. Data are expressed as mean ± SE; $P < 0.05$ was deemed significant.

Results

General Experimental Conditions

Right P_{aw} (6.7 ± 0.1 mmHg), left P_{aw} (6.6 ± 0.1 mmHg), and temperature (37.3 ± 0.1° C) did not change during the experiment. Pa_{CO_2} and *p*H in the high $\dot{Q}_T$ and increased ICP phases were not different than in the normal $\dot{Q}_T$ phases. However, Pa_{CO_2} was lower and *p*H correspondingly higher in all hyperoxia phases compared with values during hypoxia phases (table 1). Before raising ICP in the control groups it was 10 ± 2 mmHg. ICP was increased by the mock CSF infusion to 125 ± 5 mmHg to yield a cerebral perfusion pressure of 25 ± 1 mmHg. ICP remained increased (72 ± 3 mmHg) after the CSF infusion was stopped, despite opening the ventricular cannula to air and waiting 2 h to allow systemic hemodynamics to return to control conditions. Because all other hemodynamic and blood gas data were not statistically different between the two control groups, the repeat phases were averaged.

Effects of Increased $\dot{Q}_T$ and ICP on HPV

Increasing ICP significantly increased $\dot{Q}_T$, PAP, and MAP without change in PCWP or Pa_{O_2} (table 1). Similar increases in $\dot{Q}_T$, $P\bar{v}_{O_2}$, and PAP were obtained by opening the arteriovenous fistulas (table 1). Hypoxic ventilation of the LL resulted in an increase in PAP and decreases in Pa_{O_2} and $P\bar{v}_{O_2}$ in all conditions (table 1).

Hyperoxic $\dot{Q}_L/\dot{Q}_T$% was 43.9 ± 0.8% and did not vary with manipulation of ICP or $\dot{Q}_T$. During LL hypoxia $\dot{Q}_L/\dot{Q}_T$% was lower with normal $\dot{Q}_T$ (16.8 ± 2.1%) compared with high $\dot{Q}_T$ (23.1 ± 1.0%) and increased ICP (24.6 ± 3.5%) (table 1). Therefore, flow diversion with LL hypoxia was reduced to the same degree by both increasing ICP and $\dot{Q}_T$ (fig. 1).

Effects of Increased $\dot{Q}_T$ and ICP on Gas Exchange

The mean $\dot{V}_A/\dot{Q}$ ratio of the perfusion and ventilation distributions decreased with increased $\dot{Q}_T$ and ICP (table 2). Otherwise, gas exchange and $\dot{V}_A/\dot{Q}$ heterogeneity were not significantly affected by raising $\dot{Q}_T$ and ICP (table 2). Lung wet weight-to-dry weight ratios were significantly ($P < .001$) increased in the study animals (5.69 ± 0.17) compared with hyperoxic laboratory controls (4.76 ± 0.06).

TABLE 1. Hemodynamic and Blood Gas Effects

	Normal $\dot{Q}_T$		High $\dot{Q}_T$		Increased ICP	
	Bilateral Hyperoxia	LL Hypoxia	Bilateral Hyperoxia	LL Hypoxia	Bilateral Hyperoxia	LL Hypoxia
$\dot{Q}_T$ (ml/min)	2.8 ± 0.1	2.7 ± 0.1	4.1 ± 0.2†	4.4 ± 0.2†	4.3 ± 0.4†	5.0 ± 0.4*†
MAP (mmHg)	128 ± 7	130 ± 6	120 ± 6	128 ± 5	147 ± 6†	153 ± 11†
PAP (mmHg)	18.5 ± 0.4	22.2 ± 0.5*	21.8 ± 0.9†	26.4 ± 1.1*†	24.0 ± 1.0†	26.9 ± 1.7†
PCWP (mmHg)	9.2 ± 0.3	9.3 ± 0.6	9.9 ± 0.6	11.0 ± 0.5	10.9 ± 1.0	10.9 ± 1.5
CVP (mmHg)	7.3 ± 0.3	7.4 ± 0.6	7.7 ± 0.4	8.3 ± 0.4	7.5 ± 0.5	7.8 ± 0.9
Pa_{O_2} (mmHg)	474 ± 14	207 ± 28*	472 ± 11	205 ± 13*	467 ± 16	173 ± 21*
Pa_{CO_2} (mmHg)	37 ± 1	43 ± 1*	34 ± 1	41 ± 1*	39 ± 2	44 ± 2*
*p*H (U)	7.35 ± 0.01	7.29 ± 0.01*	7.37 ± 0.01	7.30 ± 0.01*	7.32 ± 0.02	7.28 ± 0.02*
Hb (g/dl)	12.8 ± 0.5	13.1 ± 0.6	12.5 ± 0.5	12.8 ± 0.5	14.3 ± 0.8†	14.1 ± 0.9†
$P\bar{v}_{O_2}$ (mmHg)	60 ± 4	54 ± 4*	77 ± 6†	65 ± 4*†	75 ± 5†	63 ± 4*†
$\dot{Q}_L/\dot{Q}_T$ (%)	44.2 ± 1.5	16.8 ± 2.1*	43.8 ± 1.3	23.1 ± 1.0*†	43.6 ± 2.4	24.6 ± 3.5*†

All measurements under steady state conditions at end-expiration. Values are mean ± SE (n = 6).

* Significantly different from hyperoxia value under same study phase.

† Significantly different from normal $\dot{Q}_T$ value under same ventilation condition.

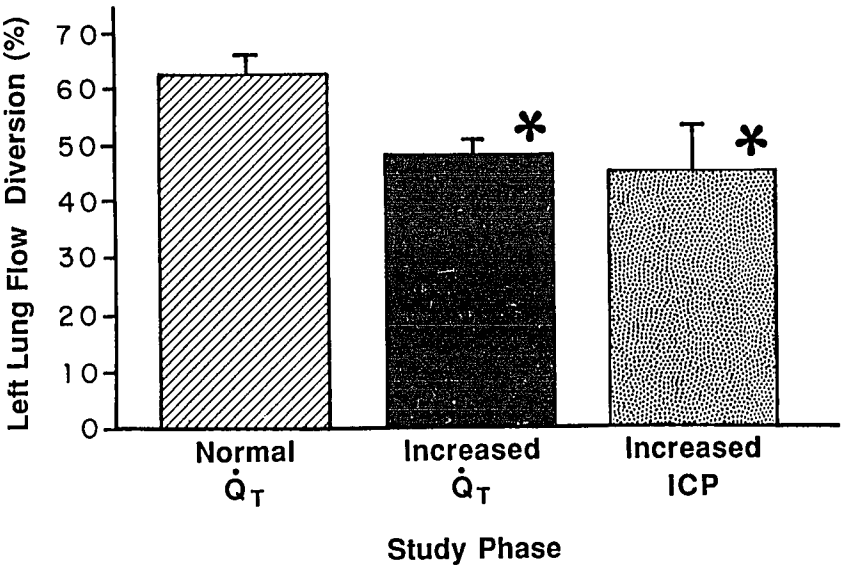

FIG. 1. Effects of increased $\dot{Q}_T$ and increased ICP on flow diversion during left lung hypoxia. *X* axis is study phase; *Y* axis is left lung flow diversion (percent). Data are mean ± SE. *$P < 0.05$, *versus* normal $\dot{Q}_T$.

Discussion

This study demonstrates that elevation of ICP by a mock CSF infusion to yield a cerebral perfusion pressure of 25 mmHg attenuated regional HPV in closed-chested dogs. The reduction in flow diversion away from the hypoxic lung is secondary to high ICP-induced changes in cardiac output, PAP, and mixed venous oxygen tension. $\dot{V}_A/\dot{Q}$ mismatch did not occur in our model of increased ICP.

Arterial hypoxemia is a common concomitant of CNS injury.[1-4] In some patients hypoxemia may be secondary to alveolar hypoventilation due to impaired ventilatory patterns, progressive atelectasis, aspiration, low cardiac output, fat embolism, pulmonary contusion, or diffuse pulmonary edema.[4,18] Florid neurogenic pulmonary edema is rare in the head trauma patient.[1-4,19] The massive sympathoadrenal release of catecholamines may cause alveolar flooding by increasing capillary hydrostatic pressure,[9,20] increasing endothelial cell permeability,[21] obstructing lymphatic drainage,[20] and pulmonary microembolism.[20] Intravascular thrombosis and platelet aggregation may occur because of release of brain thromboplastin into the systemic circulation.[20] However, many patients with isolated CNS injury are hypoxemic without clinical or physiologic evidence of lung abnormalities.[1,22-24] In these patients hypoxemia is associated with increased pulmonary shunting and $\dot{V}_A/\dot{Q}$ abnormalities.[22,23] Although this may represent a subclinical form of neurogenic pulmonary edema, it more likely represents a disruption of lung regulatory mechanisms that match perfusion to ventilation.[22-24] Disruption of $\dot{V}_A/\dot{Q}$ matching may also interfere with the ability to preserve oxygenation in cases where distinct lung pathology occurs.

TABLE 2. Gas Exchange during Hyperoxia

	Normal $\dot{Q}_T$	High $\dot{Q}_T$	Increased ICP
Mean $\dot{V}_A/\dot{Q}$ of $\dot{Q}$	1.2 ± 0.2	0.7 ± 0.1*	0.6 ± 0.1*
Log $SD_{\dot{Q}}$	0.489 ± 0.048	0.473 ± 0.055	0.503 ± 0.042
Mean $\dot{V}_A/\dot{Q}$ of $\dot{V}$	1.6 ± 0.2	1.0 ± 0.2*	1.0 ± 0.2*
Log $SD_{\dot{V}}$	0.753 ± 0.146	0.636 ± 0.183	0.952 ± 0.184
$\dot{Q}_s/\dot{Q}_t$	0.009 ± 0.003	0.012 ± 0.004	0.009 ± 0.003
V_D/V_T	0.436 ± 0.026	0.398 ± 0.029	0.399 ± 0.036
Low $\dot{V}_A/\dot{Q}$	0	0.003 ± 0.002	0

* Significantly different from normal $\dot{Q}_T$.

HPV is an important regulatory mechanism that preserves oxygenation by maintaining matching of perfusion to ventilation in the lung. The pulmonary vasculature constricts in areas that are hypoxic or atelectatic, resulting in diversion of blood flow to well-ventilated, normoxic lung regions.[25]

The HPV response of a particular lung segment is influenced by multiple variables, including alveolar P_{O_2},[26] cardiac output,[11] pulmonary arterial and pulmonary venous pressures,[10] surgical trauma,[14] *p*H,[10] and Pa_{CO_2}.[27] Increases in cardiac output are associated with increases in $\dot{Q}_s/\dot{Q}_t$ in normal lungs,[11] oleic acid injured lungs,[11,28] and lungs with atelectasis.[29] The increase in $\dot{Q}_s/\dot{Q}_t$ is thought to be secondary to the inhibition of HPV, due to an increase in $P\bar{v}_{O_2}$.[30] The intensity of the hypoxic stimulus for HPV is a function of both alveolar gas and mixed venous blood oxygen tension.[26] The alveolar influence usually predominates; however, the $P\bar{v}_{O_2}$ effect becomes important as alveolar P_{O_2} decreases.[26]

We studied regional HPV in dogs in which ICP was increased by infusion of mock CSF into a lateral ventricle. Pentobarbital-anesthetized dogs were used because they are large enough for instrumentation and they exhibit a

stable HPV response.[25] They are also relatively resistant to the development of florid pulmonary edema.[7,31] We used the differential lung excretion of SF_6 to measure separate lung blood flow because infusion of SF_6 is noninvasive. Carlsson *et al.*[16] have demonstrated an excellent correlation between measuring differential lung flow by SF_6 and electromagnetometry. We found an excellent correlation in $\dot{Q}_L/\dot{Q}_T$% measured by electromagnetometry and SF_6 in seven pilot dogs ($r = 0.85$).

ICP was increased slowly over 30 min and the CSF infusion rate was adjusted to maintain a cerebral perfusion pressure of 25 mmHg for more than 80 min. We used a cerebral perfusion pressure of 25 mmHg because previous studies had demonstrated that changes in Pa_{O_2}[32] and $\dot{Q}_s/\dot{Q}_t$[5] do not occur at lower levels of ICP (<100 mmHg).

Marked intracranial hypertension creates medullary ischemia due to decreased cerebral perfusion pressure and brain stem distortion,[33] resulting in activation of medullary sympathetic and vagal centers.[34] In general, marked sympathetic activation with release of catecholamines from the adrenal medulla occurs[6,8] so that cardiac output and systemic and pulmonary arterial pressure are increased.[8,20] Left ventricular end-diastolic and left atrial pressure may also be elevated.[7,8,20] In addition, there is pulmonary venous vasoconstriction,[9] a decrease in pulmonary vascular compliance,[35] and a change in the permeability of the pulmonary capillary membrane.[21] In our canine model raising ICP to reduce cerebral perfusion pressure to 25 mmHg significantly increased MAP, PAP, cardiac output, and $P\bar{v}_{O_2}$ and did not affect CVP or PCWP. The increases in cardiac output, PAP, and $P\bar{v}_{O_2}$ that we observed when ICP was elevated were similar in magnitude to those occurring with opening of the arteriovenous fistulas. We did not observe the hemodynamic changes that typically accompany fulminant neurogenic pulmonary edema.[20]

When ICP was increased to yield a cerebral perfusion pressure of 25 mmHg, the percentage of blood flow to the hypoxic left lung ($\dot{Q}_L/\dot{Q}_T$%) was increased (table 1). Because $\dot{Q}_L/\dot{Q}_T$% was not altered by increased ICP during hyperoxic conditions, diversion of blood flow away from the hypoxic LL was reduced (fig. 1). However, flow diversion was also reduced to a similar extent by opening the arteriovenous fistulas. This result suggests that the reduction in HPV with increased ICP is mediated by concurrent increases in cardiac output, $P\bar{v}_{O_2}$, and PAP, rather than a direct CNS or sympathetic nervous system effect. Additional support for this conclusion is derived from our observation that the HPV response (and associated cardiovascular hemodynamics) in our controls before ICP was increased was unchanged from those afterwards, despite persistent elevation of ICP (70 mmHg). Although the *p*H was slightly lower and Pa_{CO_2} slightly higher in all hypoxic compared with all normoxic phases, attenuation of the HPV response by increased ICP cannot be explained by changes in these variables. Pa_{CO_2} and *p*H during increased ICP phases were not different from those during normal $\dot{Q}_T$ phases (table 1).

Increased ICP for 60–90 min increased lung H_2O slightly compared with hyperoxic laboratory controls. However, hypoxemia and marked gas exchange abnormalities did not occur. This finding is consistent with the observation that gas exchange abnormalities depend on the amount of edema, with little impairment occurring with mild increases in lung water as noted in our study.[36] Increased ICP decreased the mean $\dot{V}_A/\dot{Q}$ of the perfusion and ventilation distributions due to increased pulmonary blood flow and cardiac output. The remainder of multiple inert gas elimination technique data show $\dot{V}_A/\dot{Q}$ heterogeneity tended to increase, but not significantly, by increases in ICP. Perhaps more edema would have accumulated with resultant impairment of gas exchange if the ICP had been increased for a longer period of time.

Although the reduction in HPV after increased ICP was statistically significant, the changes in arterial blood gases and ventilation–perfusion matching were of little biologic significance under the conditions of our study. We used dogs with normal lungs with the LL as the hypoxic test segment. ICP was elevated slowly and sustained for only 60–90 min. It is difficult to extrapolate the importance of our findings to the clinical setting because of differences in species; size of hypoxic test segment; FI_{O_2}, ICP level, duration of increase, and type of brain injury; and the presence or absence of lung disease. HPV is probably not as significant as collateral ventilation in maintaining matching of ventilation and perfusion in dogs.[37] HPV may be more important in humans. Therefore, attenuation of HPV may contribute more to hypoxemia in patients, especially those with areas of low $\dot{V}_A/\dot{Q}$ and those with distinctly abnormal lungs.

In conclusion, regional HPV in closed-chested dogs was attenuated by increasing ICP with mock CSF infusion to yield a cerebral perfusion pressure of 25 mmHg. However, the changes in flow diversion observed with increases in ICP were those expected for the altered pressure, flow, and HPV stimulus conditions encountered. We conclude that increasing ICP for brief durations does not by itself specifically influence the normal pulmonary vascular response to hypoxia.

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