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Enhancement of Hypoxic Pulmonary Vasoconstriction by Metabolic Acidosis in Dogs

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The effects of HCl infusion on multipoint mean pulmonary arterial pressure (PAP)/cardiac index (CI) plots in pentobarbital-anesthetized dogs whose lungs were ventilated alternately in hyperoxia (fraction of inspired O_2 [FI_{O_2}], 0.4) and hypoxia (FI_{O_2}, 0.1) were investigated. Over the range of CI studied (1 to 5 $l \cdot min^{-1} \cdot m^{-2}$), hypoxia increased PAP in 22 dogs (responders) and did not affect PAP in 16 other dogs (nonresponders). In eight nonresponders, two repetitions of alternated 0.4 and 0.1 FI_{O_2} exposures did not restore hypoxic pulmonary vasoconstriction (HPV), defined as a hypoxia-induced increase in PAP at a given flow. Intravenous infusion of 2 M HCl (2 mmol $\cdot kg^{-1} \cdot h^{-1}$) decreased arterial *p*H from normal to around 7.20 in eight responders and eight nonresponders. This metabolic acidosis increased PAP at all levels of CI in hyperoxia and in hypoxia in all the dogs, enhanced HPV in the responders, and restored HPV in the nonresponders. In eight responders, 2 M HCl infusion (2 mmol $\cdot kg^{-1} \cdot h^{-1}$) together with a 7% sodium bicarbonate infusion (adjusted to maintain arterial *p*H unchanged) did not affect hyperoxic or hypoxic PAP/CI plots. Pretreatment with 1 g acetylsalicylic acid iv (6 dogs) did not affect the pulmonary vasoreactivity to HCl-induced (2 M HCl, 2 mmol $\cdot kg^{-1} \cdot h^{-1}$) metabolic acidosis. It was concluded that in intact dogs: 1) metabolic acidosis enhances HPV; 2) at the given dose, HCl does not produce pulmonary vascular effects unrelated to the circulating blood pH; and 3) it is unlikely that the pulmonary vasoreactivity to metabolic acidosis is mediated by products of the cyclooxygenase pathway. (Key words: Acid base equilibrium. Acidosis: metabolic. Lung: hypoxic pulmonary vasoconstriction.)

HYPOXIC PULMONARY vasoconstriction (HPV) is an intrapulmonary adaptation mechanism that diverts blood away from hypoxic regions of the lung. Depending on the size of the hypoxic compartment, the outcome of the constriction ranges from a reduction of hypoxemia to an increase in right ventricular afterload.[1] Factors influencing the hypoxic pressor response are therefore of physiological and clinical importance.

There are controversial reports regarding the effects of metabolic acidosis on HPV. Metabolic acidosis induced by acid infusion has been observed either not to affect,[2–5] to increase,[6–8] or to decrease[9,10] hypoxia-induced increases in pulmonary arterial pressure (PAP) or pulmonary vascular resistance (PVR). At least a part of these discrepancies can be explained by differences in experimental preparations and protocols. But another confounding factor may have been circulating blood *p*H-independent effects of acid infusion: Orr *et al.*[11] recently showed in cats that hydrochloric acid (HCl) infusion can induce pulmonary vasoconstriction even if arterial blood *p*H is maintained unchanged by NaOH infusion.

Yamaguchi *et al.*[12] reported that metabolic alkalosis blunted HPV and increased prostacyclin synthesis in isolated rat lungs and in anesthetized dogs. Shams *et al.* suggested that HCl infusion-induced pulmonary vasoconstriction could be mediated by thromboxane A_2.[13] Farrukh *et al.*[14] observed that acidosis inhibited prostacyclin synthesis in rabbits. It is therefore possible that previously reported pulmonary vascular responses to changes in acid-base status would be mediated by products of the cyclooxygenase pathway of arachidonic acid metabolism.

We conducted experiments in intact dogs 1) to re-evaluate the effects of metabolic acidosis on HPV, 2) to detect potential circulating blood *p*H-independent effects of HCl infusion on pulmonary hemodynamics, and 3) to test the effects of metabolic acidosis in dogs pretreated with a cyclooxygenase blocker. Pulmonary vascular pressures were measured at several levels of flow in order to discriminate between active and passive (flow-dependent) changes in PAP.[15] We previously reported this methodological approach to evaluate the effects of hypoxia and pharmacological interventions on pulmonary vascular tone in intact dogs.[16,17]

Materials and Methods

Thirty-eight mongrel dogs (weight, 21–32 kg; mean, 26 kg) were anesthetized with sodium pentobarbital (30 mg/kg iv), paralyzed with pancuronium bromide (0.2 mg/kg iv), and had their lungs ventilated (Elema 900 B Servo-ventilator, Siemens, Solna, Sweden) *via* a cuffed endotracheal tube (FI_{O_2}, 0.4; respiratory rate, 12 breaths per min; and tidal volume, 15–20 ml/kg adjusted to maintain arterial P_{CO_2} around 35 mmHg). No PEEP was used. Pentobarbital (2 mg/kg) and pancuronium (0.2 mg/kg) were repeated hourly to maintain anesthesia and prevent spontaneous respiratory efforts. Throughout the experiment, glucose 5% in saline 0.45% was infused (4 ml $\cdot kg^{-1} \cdot h^{-1}$) in a left external jugular vein catheter inserted by cutdown and advanced into the central circu-

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lation. Temperature was maintained at 37–38° C with an electric heating pad. Initial metabolic acidosis, when present, was corrected by sodium bicarbonate. The experiments were conducted in accordance with the Guiding Principles in the Care and Use of Animals of the Council of the American Physiological Society and approved by the Animal Care Committee of our institution. Absence of heartworms was ascertained at autopsy after each experiment.

A thermistor-tipped Swan Ganz catheter (model 93A-131-7F, Edwards Laboratories, Santa Ana, CA) was inserted *via* the right external jugular vein and positioned by means of pressure monitoring in a branch of the pulmonary artery for measurements of PAP, pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP), and mixed venous blood sampling. A polyethylene catheter was placed in the abdominal aorta *via* the right femoral artery for systemic arterial pressure (SAP) measurements and arterial blood sampling. A balloon catheter (Percor Stat-DL 10.5 Fr, Datascope Corp., Paramus, NJ) was advanced into the inferior vena cava through a right femoral venotomy. Inflation of this balloon produced a titratable decrease in cardiac output by reducing venous return. A large-bore polyethylene cannula (ID 3 mm) was inserted into the left femoral artery and vein to act as an arteriovenous fistula. Increasing venous return by opening this fistula resulted in an increase in cardiac index (CI) by an average of 0.4 $l \cdot min^{-1} \cdot m^{-2}$. Thrombus formation along the catheters was prevented by injecting sodium heparin, 150 U/kg iv, just before insertion and administering 50 U/kg iv every 2 h thereafter.

Pulmonary and systemic vascular pressures were measured using transducers (Spectramed Inc., Bilthoven, Netherlands) and the HERES computer system (ACEC, Charleroi, Belgium) and recorded on a 4-channel Gould recorder (model 2400 S, Gould Inc., Instruments Division, Cleveland, OH). The zero reference was leveled at midchest, and vascular pressures were measured at end-expiration. Heart rate (HR) was determined from a continuously monitored electrocardiographic lead. Cardiac output was measured by thermodilution using injections of 10 ml of 0.9% sodium chloride at 0° C, a computer (9520-A, Edwards Laboratories), and an automated pneumatic pump electronically synchronized on the ventilatory cycle and was calculated as the mean of three determinations. Arterial and mixed venous *p*H, P_{CO_2}, and P_{O_2} were measured immediately after drawing the samples with an automated analyzer (ABL 2, Radiometer, Copenhagen, Denmark) and corrected for temperature. Body surface area (m^2) was calculated as 0.112 × weight $(kg)^{2/3}$.[18]

In all of the dogs, after ensuring steady-state conditions for 20 min at $F_{I_{O_2}}$ of 0.4 (stable SAP, PAP, CI, and HR), a first multipoint (4 to 6 points) PAP/CI plot was generated from hemodynamic determinations at baseline (1 point), after opening the arteriovenous fistula (1 point), and after stepwise incremental inflations of the inferior vena cava balloon with occluded fistula (2 to 4 points). The same procedure was repeated after 10 min at $F_{I_{O_2}}$ of 0.1. One multipoint PAP/CI plot was generated in 20 min. When hypoxia did not change PAP by more than 2 mmHg at CI of 3 $l \cdot min^{-1} \cdot m^{-2}$ (these values of PAP at normalized CI were obtained after linear regression analysis), the dog was considered a nonresponder.

In eight dogs (nonresponders), the sequence of PAP/CI plots at 0.4 and at 0.1 $F_{I_{O_2}}$, consecutively, was repeated twice in order to test the stability of the nonresponder property in our model.

In 16 dogs (eight responders and eight nonresponders), 2 M HCl was infused 2 mmol/kg in 60 min *via* the left external jugular vein catheter to decrease the arterial *p*H from normal values to values around 7.20. This acidemia was then maintained constant by adjusting the HCl infusion rate (generally one-fourth of the initial perfusion rate). Concentrated solutions were used to avoid excessive amounts of fluids. After 10 min of stabilization (*i.e.*, 70 min after beginning of acid infusion), a second set of PAP/CI plots at 0.4 and 0.1 $F_{I_{O_2}}$, successively, was obtained.

In eight dogs (responders), 3.2 ± 0.1 mmol/kg sodium $NaHCO_3$ 7% was administered in the right atrium *via* the proximal port of the Swan Ganz catheter during 2 M HCl infusion (2 $mmol \cdot kg^{-1} \cdot h^{-1}$) in order to prevent any change in *p*H. As in the previous experiments, 70 min after the beginning of acid infusion, a second set of PAP/CI plots at $F_{I_{O_2}}$ of 0.4 and 0.1, successively, was obtained.

In six dogs, 1 g acetylsalicylic acid was given iv just after the induction of anesthesia. The first sequence of two PAP/CI plots (at $F_{I_{O_2}}$ of 0.4 and then at 0.1) was performed around 60 min after acetylsalicylic acid administration. Then, 2 M HCl was infused 2 $mmol \cdot kg^{-1} \cdot min^{-1}$ to decrease the arterial *p*H from normal values to values around 7.20. After 10 min of stabilization (*i.e.*, 70 min after beginning of acid infusion), the HCl infusion rate was adjusted and a second set of PAP/CI plots at $F_{I_{O_2}}$ of 0.4 and 0.1, successively, was obtained.

The PAP/CI coordinates were analyzed by linear regression analysis (least-squares method) and were considered to fit a linear relationship if the experimental relationship appeared linear and the value of the correlation coefficient was >0.95. The CI was considered to be an independent variable and PAP the dependent variable. To obtain composite PAP/CI plots, PAPs interpolated from the regression analysis from individual dogs were averaged at 1 $l \cdot min^{-1} \cdot m^{-2}$ intervals of CI from 1 to 5 $l \cdot min^{-1} \cdot m^{-2}$ and presented as mean $P \pm$ SEM. The blood gases and hemodynamic data were analyzed by repeated-measures analysis of variance for three factors: CI, $F_{I_{O_2}}$, and *p*H. When the effect of a factor reached the $P < 0.05$

significance level, Student's paired *t* tests were performed to compare specific situations.

Results

Manipulation of Cardiac Output

Stepwise inflations of the inferior vena cava balloon or opening the arteriovenous fistula allowed manipulations of CI between values of approximately 1 to 5 $l \cdot min^{-1} \cdot m^{-2}$. The PAP/CI relationships were linear in all experimental conditions, with correlation coefficients ranging from 0.95 to 1. Blood gases mainly changed by a decrease in mixed venous P_{O_2} at the lowest CI (tables 1–5).

Effects of Hypoxia

Hypoxia markedly decreased arterial and mixed venous P_{O_2} with no or slight changes in arterial pH, P_{CO_2}, and Pv_{CO_2}. Variable increases in CI and PAP occurred at maximal flow, whereas PCWP and RAP remained unchanged (tables 1–5). At a given CI, hypoxia increased PAP in the 22 responder dogs (figs. 1, 2, and 3) but did not significantly affect PAP in the 16 nonresponder dogs (figs. 4 and 5).

Reproducibility of the Absence of HPV in Nonresponder Dogs

Repeating hypoxia twice slightly reduced arterial P_{O_2} at $F_{I_{O_2}}$ of 0.4 (table 1) but did not affect PAP at all levels of CI studied in hyperoxia as well as in hypoxia (fig. 5).

Effects of HCl-induced Metabolic Acidosis

Infusion of 2 M HCl (2 mmol/kg in 60 min) reduced arterial *p*H, increased PAP with variable increases in CI at both $F_{I_{O_2}}$ values, and increased mixed venous P_{O_2} in hyperoxia (tables 2 and 3). Hemoglobin levels remained unchanged during the experiments. During the first 60 min of acid infusion, arterial *p*H decreased slowly whereas PAP increased progressively. Hydrochloric acid administration increased PAP over the entire range of CI studied (except at the lowest CI) at both values of $F_{I_{O_2}}$ in responder (fig. 1) as well as in nonresponder (fig. 4) dogs. The changes in PAP were more marked in hypoxia than in hyperoxia so that the hypoxic pressor response was enhanced in responder dogs and restored in nonresponder dogs when expressed as PAP ($F_{I_{O_2}}$ 0.1) minus PAP ($F_{I_{O_2}}$ 0.4) or (PAP − PCWP) ($F_{I_{O_2}}$ 0.1) minus (PAP − PCWP) ($F_{I_{O_2}}$ 0.4) at constant CI.

Effects of HCl Without Metabolic Acidosis

$NaHCO_3$ was administered together with 2 M HCl (2 $mmol \cdot kg^{-1} \cdot h^{-1}$) so that arterial *p*H remained un-

TABLE 1. Effects of Two Repetitions of Alternated 0.4 and 0.1 $F_{I_{O_2}}$ Exposures on Blood Gases and Hemodynamics in Eight Nonresponder Dogs

		$F_{I_{O_2}}$ 0.4			$F_{I_{O_2}}$ 0.1		
	CI	1	2	3	1	2	3
pH_a	H	7.39 ± 0.01	7.35 ± 0.01	7.35 ± 0.01	7.40 ± 0.02	7.39 ± 0.01	7.41 ± 0.01
	L	7.39 ± 0.01	7.38 ± 0.01	7.38 ± 0.01	7.41 ± 0.01	7.39 ± 0.01	7.41 ± 0.02
Pa_{O_2} (mmHg)	H	208 ± 12	196 ± 14*	190 ± 14*	39 ± 1*	35 ± 2	38 ± 2
	L	202 ± 13	184 ± 16	174 ± 18*	42 ± 2*	39 ± 2	39 ± 2
Pa_{CO_2} (mmHg)	H	33 ± 1	33 ± 1	34 ± 2	31 ± 1*	33 ± 1	32 ± 1
	L	31 ± 1	32 ± 1	31 ± 1	27 ± 1*	30 ± 1	29 ± 1
Pv_{O_2} (mmHg)	H	56 ± 2	55 ± 2	47 ± 7	31 ± 1*	29 ± 1	31 ± 2
	L	36 ± 2	36 ± 2	37 ± 2	25 ± 1*	24 ± 1	25 ± 1
Pv_{CO_2} (mmHg)	H	34 ± 1	36 ± 1	37 ± 1	33 ± 1	35 ± 2	34 ± 1
	L	38 ± 2	39 ± 2	38 ± 2	35 ± 1	36 ± 2	37 ± 1
CI ($l \cdot min^{-1} \cdot m^{-2}$)	H	4.82 ± 0.32	5.28 ± 0.57	5.24 ± 0.47	5.71 ± 0.55	6.96 ± 0.46*	6.63 ± 0.52
	L	1.54 ± 0.16	2.01 ± 0.23*	2.09 ± 0.22*	2.08 ± 0.26*	2.14 ± 0.14	2.10 ± 0.27
HR (beats per min)	H	146 ± 14	143 ± 14	142 ± 15	169 ± 10	161 ± 11	149 ± 12
	L	168 ± 14	166 ± 13	165 ± 15	150 ± 13	160 ± 14	160 ± 13
Mean systemic arterial pressure (mmHg)	H	112 ± 6	119 ± 7	113 ± 9	127 ± 10	114 ± 9	124 ± 10
	L	73 ± 8	80 ± 10	82 ± 9	74 ± 8	75 ± 9	77 ± 12
Mean pulmonary arterial pressure (mmHg)	H	15 ± 1	16 ± 1	16 ± 1	17 ± 1*	20 ± 2	20 ± 2
	L	8 ± 1	8 ± 1	9 ± 1*	9 ± 1*	9 ± 1	9 ± 1
Pulmonary capillary wedge pressure (mmHg)	H	6 ± 1	8 ± 1	8 ± 1	6 ± 0	7 ± 1	7 ± 1
	L	3 ± 1	3 ± 1	3 ± 1	4 ± 1	3 ± 1	3 ± 1
Right arterial pressure (mmHg)	H	5 ± 1	4 ± 1	4 ± 1	4 ± 1	4 ± 1	4 ± 1
	L	2 ± 1	2 ± 1	2 ± 1	2 ± 1	2 ± 1	2 ± 1

Values are expressed as mean ± SEM. CI = cardiac index. H and L = the highest and the lowest CI.

* $P < 0.05$ second, third, and fourth columns *versus* first, fifth, and sixth columns *versus* fourth.

TABLE 2. Effects of 2 M HCl (2 mmol · kg^{-1} · h^{-1}) on Blood Gases and Hemodynamics in Eight Responder Dogs

		FI_{O_2} 0.4		FI_{O_2} 0.1	
	CI	Base	HCl	Base	HCl
pH_a	H	7.35 ± 0.01	7.20 ± 0.01*	7.41 ± 0.01*	7.22 ± 0.01*
	L	7.38 ± 0.01	7.19 ± 0.01*	7.41 ± 0.01*	7.18 ± 0.01*
Pa_{O_2} (mmHg)	H	194 ± 13	215 ± 6	40 ± 1*	40 ± 1
	L	201 ± 14	210 ± 7	41 ± 2*	48 ± 2
Pa_{CO_2} (mmHg)	H	37 ± 1	33 ± 1	31 ± 1*	32 ± 2
	L	33 ± 1	30 ± 2	29 ± 1*	27 ± 1
Pv_{O_2} (mmHg)	H	55 ± 2	67 ± 1*	31 ± 1*	32 ± 1
	L	35 ± 2	43 ± 2*	26 ± 1*	23 ± 1
Pv_{CO_2} (mmHg)	H	43 ± 3	38 ± 2	35 ± 1*	36 ± 2
	L	42 ± 2	43 ± 2	35 ± 1*	40 ± 2
CI (l · min^{-1} · m^{-2})	H	4.16 ± 0.32	4.45 ± 0.27	4.70 ± 0.32	4.48 ± 0.33
	L	1.45 ± 0.14	1.53 ± 0.15	1.88 ± 0.17	1.32 ± 0.11
HR (beats per min)	H	157 ± 9	161 ± 6	155 ± 8	156 ± 6
	L	159 ± 8	170 ± 8	155 ± 7	146 ± 8
Mean systemic arterial pressure (mmHg)	H	114 ± 6	129 ± 5*	138 ± 10*	150 ± 8
	L	72 ± 6	95 ± 7*	76 ± 5	75 ± 7
Mean pulmonary arterial pressure (mmHg)	H	14 ± 1	18 ± 2*	23 ± 2*	32 ± 2*
	L	8 ± 1	10 ± 1	14 ± 1*	14 ± 2
Pulmonary capillary wedge pressure (mmHg)	H	5 ± 1	5 ± 1	6 ± 1	6 ± 1
	L	3 ± 1	3 ± 1	4 ± 1	3 ± 1
Right arterial pressure (mmHg)	H	4 ± 1	3 ± 1	4 ± 1	4 ± 1
	L	3 ± 1	2 ± 1	3 ± 1	2 ± 0

Values are expressed as mean ± SEM. CI = cardiac index. H and L = the highest and the lowest CI.

* $P < 0.05$ second and third columns *versus* first, fourth column *versus* third.

changed. Variable increases in CI and PAP occurred at maximal flow (table 4), but at a constant flow, PAP was not affected at both values of FI_{O_2} (fig. 2). Hypoxia-induced rises in PAP or in PAP − PCWP at constant CI were unaffected. There was no real change in Pv_{CO_2} after $NaHCO_3$ infusion (table 4).

TABLE 3. Effects of 2 M HCl (2 mmol · kg^{-1} · h^{-1}) on Blood Gases and Hemodynamics in Eight Nonresponder Dogs

		FI_{O_2} 0.4		FI_{O_2} 0.1	
	CI	Base	HCl	Base	HCl
pH_a	H	7.37 ± 0.01	7.18 ± 0.01*	7.39 ± 0.01	7.18 ± 0.01*
	L	7.36 ± 0.01	7.17 ± 0.01*	7.35 ± 0.01	7.16 ± 0.01*
Pa_{O_2} (mmHg)	H	215 ± 5	215 ± 9	41 ± 1*	42 ± 2
	L	207 ± 13	202 ± 15	42 ± 1*	47 ± 1
Pa_{CO_2} (mmHg)	H	33 ± 1	33 ± 1	31 ± 1*	31 ± 1
	L	30 ± 1	28 ± 1	29 ± 1	27 ± 1
Pv_{O_2} (mmHg)	H	57 ± 2	71 ± 3*	33 ± 1*	33 ± 2
	L	37 ± 1	43 ± 2*	25 ± 1*	24 ± 2
Pv_{CO_2} (mmHg)	H	37 ± 1	39 ± 2	35 ± 1	37 ± 1
	L	40 ± 1	44 ± 2	37 ± 1	42 ± 2*
CI (l · min^{-1} · m^{-2})	H	3.82 ± 0.17	4.05 ± 0.36	4.76 ± 0.24*	4.54 ± 0.46
	L	1.43 ± 0.08	1.29 ± 0.04	1.83 ± 0.12*	1.36 ± 0.06
HR (beats per min)	H	144 ± 10	161 ± 8	157 ± 7	153 ± 6
	L	161 ± 12	155 ± 11	152 ± 10	151 ± 9
Mean systemic arterial pressure (mmHg)	H	109 ± 6	114 ± 9	124 ± 7	134 ± 11
	L	71 ± 8	71 ± 9	59 ± 3	64 ± 7
Mean pulmonary arterial pressure (mmHg)	H	13 ± 1	17 ± 1*	17 ± 1*	26 ± 2*
	L	7 ± 0	8 ± 1	8 ± 1*	10 ± 1
Pulmonary capillary wedge pressure (mmHg)	H	5 ± 0	4 ± 1	5 ± 1	5 ± 1
	L	2 ± 1	2 ± 0	3 ± 0	2 ± 1
Right arterial pressure (mmHg)	H	4 ± 1	3 ± 1	3 ± 1	3 ± 1
	L	1 ± 1	1 ± 0	1 ± 0	1 ± 1

Values are expressed as mean ± SEM. CI = cardiac index. H and L = the highest and the lowest CI.

* $P < 0.05$ second and third columns *versus* first, fourth column *versus* third.

TABLE 4. Effects of 2 M HCl (2 mmol·kg^{-1}·h^{-1}) Together with $NaHCO_3$ on Blood Gases and Hemodynamics in Eight Responder Dogs

		FI_{O_2} 0.4		FI_{O_2} 0.1	
	CI	Base	HCl + $NaHCO_3$	Base	HCl + $NaHCO_3$
pH_a	H	7.39 ± 0.01	7.39 ± 0.01	7.41 ± 0.01	7.39 ± 0.01
	L	7.38 ± 0.01	7.39 ± 0.02	7.39 ± 0.01	7.35 ± 0.02
Pa_{O_2} (mmHg)	H	204 ± 7	205 ± 6	35 ± 2*	34 ± 2
	L	207 ± 5	203 ± 6	37 ± 2*	38 ± 2
Pa_{CO_2} (mmHg)	H	36 ± 1	39 ± 1*	35 ± 1	37 ± 1
	L	34 ± 1	35 ± 1	31 ± 1	35 ± 2
Pv_{O_2} (mmHg)	H	56 ± 1	61 ± 1*	28 ± 2*	26 ± 2
	L	37 ± 2	39 ± 2	22 ± 1*	24 ± 4
Pv_{CO_2} (mmHg)	H	39 ± 1	42 ± 1	38 ± 1	42 ± 1*
	L	44 ± 1	46 ± 1	39 ± 1*	44 ± 3
CI (l·min^{-1}·m^{-2})	H	3.90 ± 0.16	4.90 ± 0.37*	5.59 ± 0.31*	6.06 ± 0.15
	L	1.50 ± 0.12	1.63 ± 0.11	1.91 ± 0.12	2.08 ± 0.15
HR (beats per min)	H	134 ± 8	153 ± 5	169 ± 5	165 ± 5
	L	177 ± 9	181 ± 5	157 ± 10	163 ± 7
Mean systemic arterial pressure (mmHg)	H	116 ± 8	128 ± 7	143 ± 8	158 ± 5
	L	93 ± 11	93 ± 12	75 ± 8	79 ± 7
Mean pulmonary arterial pressure (mmHg)	H	14 ± 1	17 ± 1*	27 ± 4*	33 ± 4*
	L	8 ± 1	8 ± 1	15 ± 1*	16 ± 1
Pulmonary capillary wedge pressure (mmHg)	H	5 ± 1	6 ± 1	6 ± 1	6 ± 1
	L	2 ± 1	2 ± 1	4 ± 1	3 ± 1
Right arterial pressure (mmHg)	H	3 ± 1	3 ± 1	4 ± 1	4 ± 1
	L	2 ± 1	1 ± 1	2 ± 1	2 ± 1

Values are expressed as mean ± SEM. CI = cardiac index. H and L = the highest and the lowest CI.

* $P < 0.05$ second, third and fourth columns *versus* first, fourth column *versus* first.

EFFECTS OF HCl-INDUCED METABOLIC ACIDOSIS AFTER ACETYLSALICYLIC ACID ADMINISTRATION

After cyclooxygenase blockade, all the dogs were responders. The HCl administration increased PAP over the entire range of CI studied at both FI_{O_2} values (table 5 and fig. 3). The changes in PAP were more marked in hypoxia so that the hypoxic pressor response was enhanced when expressed as PAP (FI_{O_2} 0.1) minus PAP (FI_{O_2} 0.4) or (PAP − PCWP) (FI_{O_2} 0.1) minus (PAP − PCWP) (FI_{O_2} 0.4) at constant CI.

TABLE 5. Effects of 2 M HCl (2 mmol·kg^{-1}·h^{-1}) on Blood Gases and Hemodynamics in Six Dogs Pretreated with 1 g Acetylsalicylic Acid (ASA)

		FI_{O_2} 0.4		FI_{O_2} 0.1	
	CI	ASA	HCl	ASA	HCl
pH_a	H	7.38 ± 0.02	7.20 ± 0.00*	7.40 ± 0.02	7.18 ± 0.01*
	L	7.39 ± 0.01	7.18 ± 0.02*	7.40 ± 0.03	7.16 ± 0.02*
Pa_{O_2} (mmHg)	H	165 ± 8	178 ± 5	33 ± 2*	35 ± 2
	L	171 ± 9	174 ± 4	40 ± 1*	41 ± 2
Pa_{CO_2} (mmHg)	H	39 ± 2	37 ± 2	37 ± 2	37 ± 2
	L	36 ± 1	32 ± 1	32 ± 2	33 ± 2
Pv_{O_2} (mmHg)	H	56 ± 3	58 ± 3	26 ± 2*	27 ± 2
	L	38 ± 2	50 ± 2	21 ± 1*	24 ± 2
Pv_{CO_2} (mmHg)	H	43 ± 3	45 ± 2	41 ± 3	43 ± 3
	L	47 ± 3	48 ± 3	43 ± 3	45 ± 3
CI (l·min^{-1}·m^{-2})	H	4.62 ± 0.50	5.42 ± 0.71	5.43 ± 0.22	5.80 ± 0.51
	L	1.62 ± 0.10	1.40 ± 0.12	1.73 ± 0.20	1.90 ± 0.21
HR (beats per min)	H	143 ± 10	154 ± 6	160 ± 6	142 ± 4
	L	167 ± 10	152 ± 9	155 ± 11	147 ± 3
Mean systemic arterial pressure (mmHg)	H	128 ± 5	138 ± 7	151 ± 8	152 ± 8
	L	93 ± 9	85 ± 7	69 ± 11	77 ± 15
Mean pulmonary arterial pressure (mmHg)	H	16 ± 1	20 ± 2*	29 ± 1*	37 ± 3*
	L	9 ± 1	11 ± 1*	12 ± 1*	18 ± 2*
Pulmonary capillary wedge pressure (mmHg)	H	6 ± 1	7 ± 1	7 ± 1	9 ± 1
	L	3 ± 1	4 ± 1	3 ± 1	3 ± 1
Right arterial pressure (mmHg)	H	4 ± 1	4 ± 1	4 ± 1	6 ± 1
	L	2 ± 1	2 ± 1	2 ± 1	2 ± 1

Values are expressed as mean ± SEM. CI = cardiac index. H and L = the highest and the lowest CI.

* $P < 0.05$ second and third columns *versus* first, fourth column *versus* third.

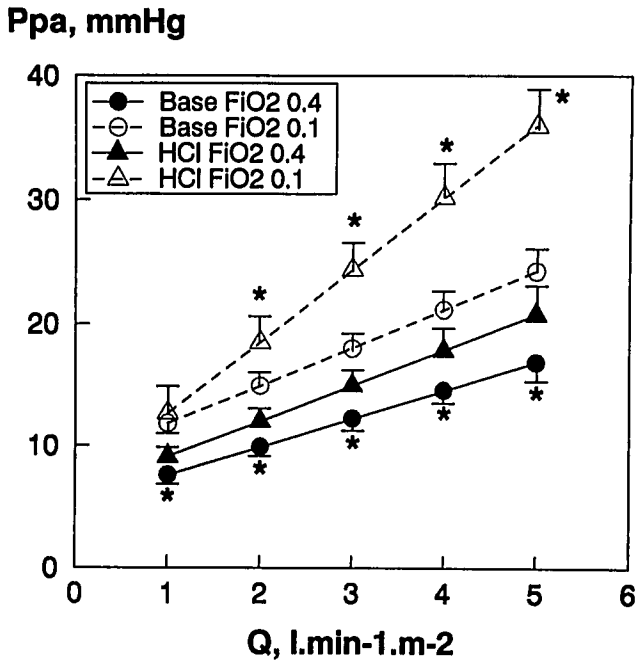

FIG. 1. Composite plots of mean pulmonary arterial pressure (Ppa) *versus* cardiac index (Q) in hyperoxia (FI_{O_2} 0.4) and in hypoxia (FI_{O_2} 0.1) before and after 2 M HCl infusion in eight responder dogs. Pulmonary vascular tone was increased at both FI_{O_2} and hypoxic pulmonary vascoconstriction was enhanced. *$P < 0.05$ HCl compared with baseline at the same FI_{O_2}.

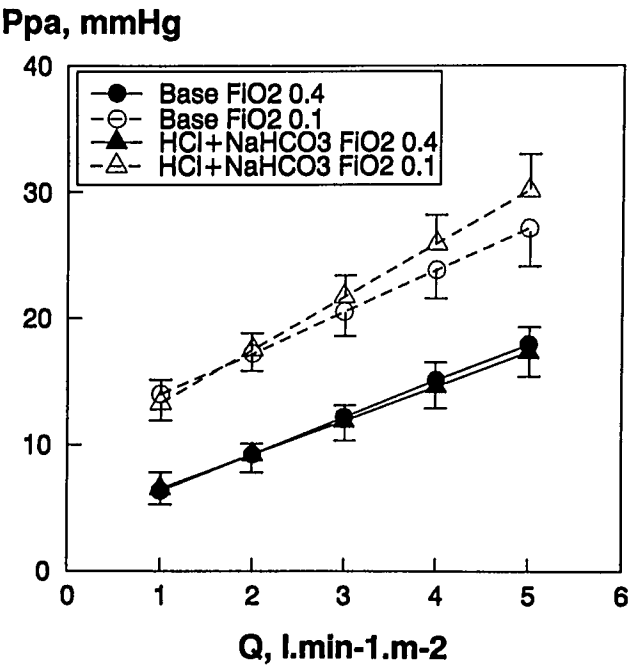

FIG. 2. Composite plots of mean pulmonary arterial pressure (Ppa) *versus* cardiac index (Q) in hyperoxia (FI_{O_2} 0.4) and in hypoxia (FI_{O_2} 0.1) before and after concomitant infusions of $NaHCO_3$ and of 2 M HCl in eight responder dogs. At each level of Q, Ppa was unaffected in hyperoxia as in hypoxia.

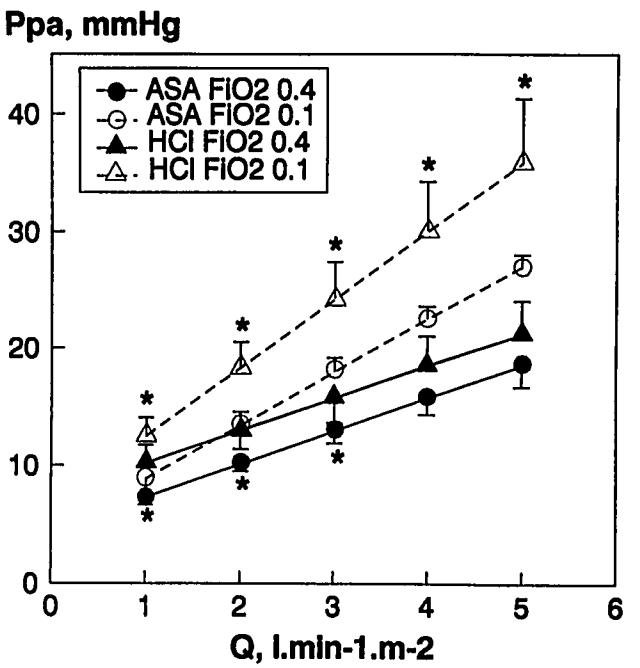

FIG. 3. Composite plots of mean pulmonary arterial pressure (Ppa) *versus* cardiac index (Q) in hyperoxia (FI_{O_2} 0.4) and hypoxia (FI_{O_2} 0.1) before and after 2 M HCl infusion in six dogs pretreated with 1 g acetylsalicylic acid. Pulmonary vascular tone was increased at both FI_{O_2} and HPV was enhanced. *$P < 0.05$ HCl compared with baseline at the same FI_{O_2}.

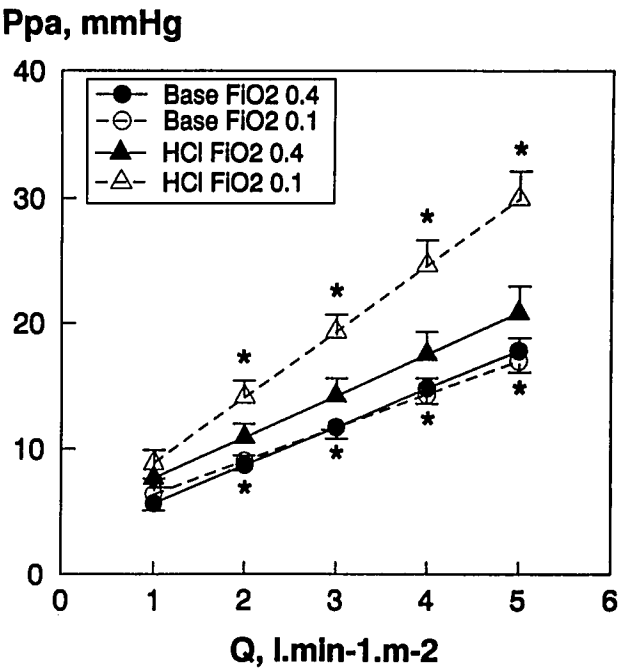

FIG. 4. Composite plots of mean pulmonary arterial pressure (Ppa) *versus* cardiac index (Q) in hyperoxia (FI_{O_2} 0.4) and in hypoxia (FI_{O_2} 0.1) before and after 2 M HCl infusion in eight nonresponder dogs. Pulmonary vascular tone was increased at both FI_{O_2} and hypoxic pulmonary vasoconstriction was restored. *$P < 0.05$ HCl compared with baseline at the same FI_{O_2}.

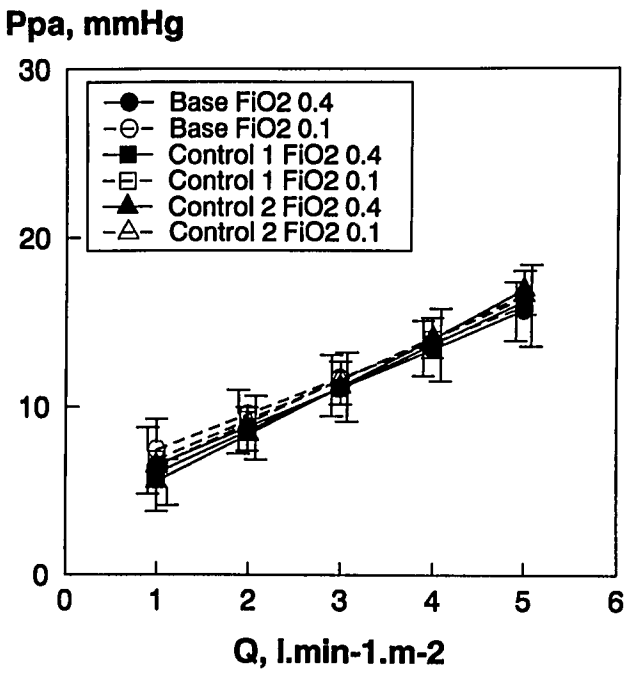

FIG. 5. Composite plots of mean pulmonary arterial pressure (Ppa) *versus* cardiac index (Q) in alternated hyperoxia (FI_{O_2} 0.4) and hypoxia (FI_{O_2} 0.1) exposures repeated two times (control 1 and control 2) in eight nonresponder dogs. Hyperoxic and hypoxic Ppa/Q plots were unchanged.

Discussion

The present results show that increasing blood concentration of H^+ without change in Pa_{CO_2} enhances HPV and indicate that at the given dose, HCl does not produce pulmonary vascular effects unrelated to the circulating blood *p*H. The results also show that the pulmonary vasoreactivity to metabolic acidosis is not affected by cyclooxygenase inhibition.

One of the best ways to assess the pulmonary vascular tone is to measure PAP at several levels of flow.[15,17,19] In the present study, PAP/CI relations were linear in all experimental conditions, in keeping with previous studies in intact dogs.[16,17,19] Left atrial pressure (LAP) was not kept constant while CI was manipulated. Therefore, the use of (PAP − PCWP)/CI instead of PAP/CI plots would be preferable if LAP was always the effective outflow pressure of the pulmonary vasculature and if PCWP was always a correct estimation of LAP. These two assumptions are probably incorrect in hypoxia and at low CI.[19-21] It has to be noted that at a given level of CI, PCWP was not affected by either hypoxia, HCl infusion, or HCl and $NaHCO_3$ administrations, which excludes passive influences on PAP by these interventions. In the present study, replacing PAP/CI with (PAP − PCWP)/CI plots did not affect the significance of any of the observed pulmonary vascular tone changes.

During the generation of PAP/CI plots, changes in Pv_{O_2}, SAP, and pulmonary vascular pressures occurred and could have affected pulmonary vascular tone, particularly in hypoxia.[22-24] However, Pv_{O_2}, SAP, and PCWP values at a given flow were similar in all hypoxic experimental conditions. Nevertheless, PAP/CI plots represent an integrated response of the intact pulmonary circulation to several vasoactive stimuli rather than being truly passive in hyperoxia and only affected by a decrease in alveolar P_{O_2} in hypoxia. Also taking into account that PAP cannot be measured at very low or zero CI in intact animals and that the validity of extrapolating PAP/CI plots may be questioned, we compared PAP at several levels of CI rather than comparing slopes (taken as incremental resistance) and extrapolated pressure intercepts (taken as an averaged closing pressure of the pulmonary vessels) of the PAP/CI plots.

We previously reported that a sequence of alternated hyperoxic (FI_{O_2} 0.4) and hypoxic (FI_{O_2} 0.1) PAP/CI plots is reproducible up to two times in responder dogs[16] and that the magnitude of hypoxia-induced increase in PAP at a given CI remains constant during the time needed to construct a PAP/CI plot.[17] In the present study, we show that two repeated hypoxic challenges do not restore HPV in nonresponder dogs.

Hydrochloric acid infusion has been reported to induce respiratory[25] and pulmonary vascular[11,13,26,27] effects independently of a decrease in arterial blood *p*H. These effects were transient and not repeatable by a second infusion of acid in the same animal. The results of Shams *et al.*[13] suggest that acid exposure of blood stimulates thromboxane synthesis and release from platelets, which in turn leads to pulmonary hypertension and hyperventilation, but the observed PAP changes were associated with a decrease in Pa_{O_2}, and thus different from those observed in the present study. Moreover, our results were not affected by cyclooxygenase blockade. Lloyd[3] reported that increasing the HCl infusion rate could result in much larger PAP changes for similar blood *p*H variations. It is possible that the animal species, the infusion site, the acid concentration, or the infusion rate play a role in the genesis of circulating blood *p*H-independent effect of HCl. In our experimental design, we did not observe circulating blood *p*H-unrelated effects at the given HCl dosage.

Many studies have reported that metabolic acidosis alters HPV, but not all agree on the degree or direction. In isolated perfused rat lungs, HPV was reduced by the addition of 1 N lactic acid to the perfusate at constant P_{CO_2}.[10] In intact dogs exposed to generalized hypoxia, lactic acid infusion at controlled Pa_{CO_2} resulted in reduction of the hypoxia-induced increases in PVR and PAP but did not alter CI.[9] In both studies, the FI_{O_2} in hypoxia was much lower than in the present one. It is possible that an increase in H^+ enhances HPV during moderate

hypoxia but that this potentiation does not persist during severe hypoxia.[9] In awake dogs, mild acidosis (pH 7.30) produced by an infusion of 0.4 M HCl did not affect HPV.[4] In newborn calves, Rudolph and Yuan[7] observed that the lower the pH, the greater the pulmonary vascular resistance response to P_{O_2} reduction. In both studies, however, changes in pulmonary hemodynamics were obscured by changes in CI and Pa_{CO_2}. Viles and Shepherd[5] indeed reported a pH-independent vasodilating effect of CO_2 on the pulmonary vasculature. In cat left lower lobe preparations, acetic or lactic acid increased the slope and pressure intercept of pressure/flow lines during both normoxic and hypoxic conditions, and hypoxia-induced rises in PAP were increased in eight of 11 cats.[6] Exceptions were usually associated with a large rise in normoxic PAP caused by the acid. In cats having open chest surgery, lactic acid caused an increase in PAP at constant CI in normoxia, but the additional increase produced by hypoxia during acidemia (pH 7.07) was not greater than the response to hypoxia with normal pH[28]; in this study, however, severe hypocapnia was maintained throughout the experiments. Using short-term acid infusions in anesthetized dogs, Bergofsky *et al.*[2] showed that the increment in PVR per unit decrement in arterial pH was similar during ambient air breathing and acute hypoxia. The changes in intracellular pH, however, were possibly too short to affect HPV. In perfused cat lungs, Viles and Shepherd[5] observed a depression of the hypoxic response with alkalosis and restoration of the response with acidosis. Measurements at normal pH and P_{CO_2} were not recorded, however; therefore, it is not possible to conclude whether the response to acidemia was greater or less than would have been seen with normal pH and P_{CO_2}. In neonatal calves having left lower lobe preparations, HPV was accentuated during acidemia, but acidosis was produced by both acid infusion and increased FI_{CO_2}.[8] In excised dog lobe preparations, it appeared that HPV was probably maximal and rather invariant over the pH range of 7–7.3; however, the author noted that the responsiveness of the preparation changed markedly with time.[3] Our data show that metabolic acidosis enhances HPV. Differences with previous reports seem to be mainly related to the stability of our experimental preparation, the level of hypoxia, the strict control of CI and P_{CO_2}, the absence of pH-independent effects, and the integrity of pulmonary vascular tone regulation.

A marked interspecies and interindividual variability is characteristic of HPV.[29] The hypoxic pressor response is naturally absent in around 20% of dogs in our laboratory. The present experiments show that metabolic acidosis restores HPV in these nonresponders. In view of the finding that cyclooxygenase inhibitors also restore HPV in nonresponders[30,31] and the report that prostacyclin synthesis may be involved in the blunting of HPV by alkalosis,[12] it could be speculated that the mechanism of restoration and enhancement of HPV by acidosis is related to inhibition of production of prostacyclin or other vasodilator prostaglandins. Recent experiments of Farrukh and co-workers[14] in rabbits suggest that acidosis does inhibit prostacyclin synthesis; however, the pH values studied were not in the physiological range. Our results do not confirm this hypothesis but instead suggest that the acidosis-mediated increase in HPV is not mediated by the metabolites of the action of the cyclooxygenase on arachidonic acid.

In hyperoxia, HCl infusion increased Pv_{O_2} without significantly changing Pa_{O_2} and CI. This could be due either to a decrease in O_2 consumption (not measured in the present study) or to the pH-induced right shift of the oxyhemoglobin dissociation curve.

In summary, our results show that metabolic acidosis enhances HPV and suggest that this effect is not mediated by cyclooxygenase metabolites.

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