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Pulmonary Vasoregulation by Cyclooxygenase Metabolites and Angiotensin II after Hypoperfusion in Conscious, Pentobarbital-anesthetized, and Halothane-anesthetized Dogs

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The authors investigated the extent to which endogenously produced metabolites of the cyclooxygenase pathway and angiotensin II modulate the pulmonary vascular response to increasing pulmonary blood flow after a period of systemic and pulmonary hypotension and hypoperfusion (defined as posthypoperfusion) in conscious, pentobarbital-anesthetized, and halothane-anesthetized dogs. The authors tested the hypothesis that vasodilator metabolites of the cyclooxygenase pathway offset the vasoconstrictor influence of angiotensin II to prevent pulmonary vasoconstriction posthypoperfusion. Baseline and posthypoperfusion pulmonary vascular pressure–cardiac index ($P/\dot{Q}$) plots were constructed by stepwise inflation and deflation, respectively, of a hydraulic occluder implanted around the inferior vena cava to vary $\dot{Q}$. In intact (no drug), conscious dogs, the pulmonary vascular $P/\dot{Q}$ relationship posthypoperfusion was not altered significantly compared with baseline. In contrast, after cyclooxygenase inhibition, active flow-independent pulmonary vasoconstriction (12–17%; $P < 0.01$) was observed posthypoperfusion, and this response was abolished entirely by angiotensin converting-enzyme inhibition. During pentobarbital anesthesia, significant pulmonary vasoconstriction (27%; $P < 0.01$) occurred posthypoperfusion in the no-drug condition. However, the magnitude of the posthypoperfusion vasoconstriction was not increased by cyclooxygenase inhibition, nor was it reduced by converting-enzyme inhibition. During halothane anesthesia, pulmonary vasoconstriction was not observed posthypoperfusion in the no-drug condition, but it was unmasked (8–13%; $P < 0.05$) by cyclooxygenase inhibition and attenuated partially by converting-enzyme inhibition. These results indicate that cyclooxygenase metabolites and angiotensin II exert opposing vasodilator and vasoconstrictor effects, respectively, on the pulmonary circulation of conscious dogs posthypoperfusion. These competing mechanisms are active during halothane anesthesia but are abolished during pentobarbital anesthesia. (Key words: Cyclooxygenase inhibition. Enzyme inhibitors, angiotensin converting enzyme inhibitors: captopril. Enzymes, inhibition: converting-enzyme inhibition. Lungs: pulmonary circulation. Monitoring: pressure–flow plots. Pharmacology: indomethacin.)

A GROWING BODY OF EVIDENCE indicates that pulmonary vascular regulation is mediated by a complex interaction between neural, humoral, and local mechanisms. It is important to identify fundamental mechanisms of pulmonary vascular regulation because the pulmonary circulation is the afterload against which the right ventricle must eject blood. Moreover, it is particularly important to identify the extent to which various anesthetic agents modify pulmonary vascular regulatory mechanisms.

We recently demonstrated that an intact autonomic nervous system prevents pulmonary vasoconstriction in conscious dogs when pulmonary blood flow is allowed to increase after a period of hypotension and hypoperfusion (defined as posthypoperfusion).[1] Specifically, we observed that sympathetic beta-adrenergic vasodilation effectively competes with sympathetic alpha-adrenergic vasoconstriction to prevent pulmonary vasoconstriction during the posthypoperfusion period.[1] If anesthesiologists are to provide therapy to modulate pulmonary vasomotor tone after a period of hypoperfusion, then all mechanisms that regulate the pulmonary circulation under these circumstances must be identified.

In the current study, we have used this same physiologic stimulus to investigate the potentially competing roles of endogenously released cyclooxygenase metabolites and angiotensin II in the pulmonary vascular response posthypoperfusion in conscious dogs. There is a strong rationale for investigating the role of these two potential modulators of the pulmonary circulation in the posthypoperfusion period. Cyclooxygenase metabolites and angiotensin II are released in response to this stimulus,[2,3] and these endogenous substances are known to exert vasoactive influences on the pulmonary circulation.[4,5] In addition, an interactive relationship between these two vasoactive mechanisms has been established.[6,7] However, the extent to which these vasoactive mechanisms modulate the pulmonary vascular pressure–cardiac index ($P/\dot{Q}$) relationship posthypoperfusion in a conscious animal is entirely unknown. We first tested the hypothesis that if metabolites of the cyclooxygenase pathway exert a vasodilator influence on the pulmonary circulation posthypoperfusion, then active flow-independent pulmonary vasoconstriction should be observed posthypoperfusion after cyclooxygenase inhibition. Our second hypothesis was that if the pulmonary vasoconstriction un-

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masked by cyclooxygenase inhibition posthypoperfusion was mediated by angiotensin II, then this response should be abolished by angiotensin converting-enzyme inhibition.

Our second objective was to investigate the extent to which pulmonary vascular regulation by cyclooxygenase metabolites and angiotensin II posthypoperfusion is altered during either pentobarbital or halothane anesthesia compared with that measured in the conscious state. The rationale for these studies is that both pentobarbital and halothane anesthesia modify the pulmonary vascular response during the posthypoperfusion period[8,9] and after regulation of the baseline pulmonary vascular $P/\dot{Q}$ relationship by cyclooxygenase metabolites[10,11] and angiotensin II.[12,13]

Materials and Methods

Surgical Preparation

All surgical procedures and experimental protocols were approved by the Institutional Animal Care and Use Committee.

Twenty-five conditioned male mongrel dogs (26–42 kg; mean, 30 kg), free of microfilaria, were premedicated with morphine sulfate (10 mg intramuscularly [im]) and anesthetized with pentobarbital sodium (20 mg/kg intravenously [iv]) and fentanyl citrate (15 μg/kg iv). After tracheal intubation, the lungs were ventilated mechanically. After sterile preparation, a left fifth-interspace thoracotomy was performed, and the pericardium was incised. Heparin-filled Tygon® catheters (1.02 mm ID, Norton) were inserted into the descending thoracic aorta, right atrium, and main pulmonary artery. A hydraulic occluder (20 mm ID, Jones) was positioned loosely around the thoracic inferior vena cava (IVC). After loose apposition of the pericardial edges, the free ends of the catheters and occluder were threaded through the chest wall and tunneled subcutaneously to a final position between the scapulae. A chest tube placed in the left thorax before closure was removed on the first postoperative day. The dogs were given morphine sulfate (10 mg im) postoperatively for pain, as required. Cephazolin (2 g iv) was administered intraoperatively and for 10 days postoperatively (cephalexin: 2 g/day orally). All animals were allowed to recover for at least 2 weeks before experimentation.

On the day of each experiment, a 7-French pulmonary artery catheter was inserted into the pulmonary artery, 2–3 cm beyond the pulmonic valve, through a percutaneous jugular puncture after topical anesthesia (Xylocaine® spray; Astra Pharmaceutical Products, Inc., Westborough, MA). Proper positioning of the pulmonary artery catheter was verified by comparison of pressures measured at its distal port with the chronic pulmonary artery catheter. Pressures from the proximal and distal ports of the pulmonary artery catheter were measured continuously to avoid inadvertent displacement of either port into the right ventricle.

Pulmonary artery wedge pressure (PAWP) was measured by inflation of the balloon at the tip of the pulmonary artery catheter until a stable pressure was achieved over at least three respiratory cycles. With a pulmonary artery catheter of this size, balloon inflation for measurement of PAWP causes the catheter to wedge at a very proximal position in the pulmonary vascular tree, and the subtended region includes the entire right or left lung or an entire lobe. During generation of the pulmonary vascular $P/\dot{Q}$ plots (described below), PAWP equals or exceeds left atrial pressure and is used as the effective outflow pressure to calculate the pulmonary vascular pressure gradient.[14,15] Vascular pressures were measured by attaching the fluid-filled catheters to strain-gauge manometers (Gould Statham P23 ID). All pressures were measured with the transducers positioned at midchest at the level of the spine. Heart rate (HR) was calculated from the phasic aortic pressure trace. Cardiac output was measured by thermal dilution (American Edwards model 9520A), using a 5-ml, sterile, iced injectate of 5% dextrose in water. Reported values of $\dot{Q}$ represent the mean of at least three consecutive cardiac output determinations referenced to body weight (cardiac index) after the initial measurement was discarded. Aortic and pulmonary artery catheters were used to obtain blood samples for arterial and mixed venous *p*H, carbon dioxide tension (P_{CO_2}), oxygen tension (P_{O_2}), and oxyhemoglobin saturation (S_{O_2}), respectively, which were analyzed with standard methods (Radiometer ABL 3® and Instrumentation Laboratories CO-oximeter® model 282).

Experimental Protocols

All experiments were performed with the healthy dogs lying on their right sides in a quiet laboratory environment. For each protocol, the baseline pulmonary vascular $P/\dot{Q}$ plot was generated over ~30 min by stepwise inflation of the hydraulic occluder surrounding the thoracic IVC to decrease venous return and $\dot{Q}$. The pulmonary vascular pressure gradient (pulmonary artery pressure [PAP]–PAWP) was measured at each new steady-state value of $\dot{Q}$. An average of 5 points was obtained during generation of each $P/\dot{Q}$ plot. At the maximum level of IVC constriction, systemic arterial pressure and $\dot{Q}$ were decreased to ~50 mmHg and ~40 $ml \cdot min^{-1} \cdot kg^{-1}$, respectively. After 10–15 min of hypotension and hypoperfusion, the posthypoperfusion $P/\dot{Q}$ plot was generated by stepwise deflation of the IVC occluder over ~30 min to increase venous return and $\dot{Q}$. Only one pair of baseline and posthypoperfusion $P/\dot{Q}$ plots was obtained from a given dog on any single day, and a minimum of 5 days

elapsed between experiments on the same dog. On the day of each experiment, pulmonary vascular pressures and $\dot{Q}$ were measured before any intervention, to document that the pulmonary circulation had returned to its original baseline $P/\dot{Q}$ relationship between experiments. The order of experiments was randomized.

In protocol 1, three sets of experiments were performed in nine unsedated conscious dogs. Baseline and posthypoperfusion pulmonary vascular $P/\dot{Q}$ plots were obtained as follows: 1) without drug administration (no drug); 2) 60 min after the administration of the cyclooxygenase inhibitor, indomethacin (5 mg/kg iv); and 3) 60 min after the combined administration of indomethacin plus the angiotensin converting-enzyme inhibitor, captopril (1 mg/kg plus 1 $mg \cdot kg^{-1} \cdot h^{-1}$ iv). Indomethacin was dissolved in sterile water with 114 g sodium carbonate and infused intravenously at a rate of 3.8 ml/min. The adequacy of cyclooxygenase inhibition was demonstrated by the complete absence of a pulmonary pressor and a systemic hypotensive response to arachidonic acid (1 mg/kg iv). The adequacy of angiotensin converting-enzyme inhibition was demonstrated by the complete absence of a systemic hypotensive response to angiotensin I (60 ng/kg iv).

In protocol 2, baseline and posthypoperfusion $P/\dot{Q}$ plots were obtained in eight dogs in the no-drug condition, during cyclooxygenase inhibition, and during combined cyclooxygenase inhibition and angiotensin converting-enzyme inhibition ~1 h after pentobarbital sodium administration (30 mg/kg iv). Controlled ventilation without positive end-expiratory pressure during pentobarbital anesthesia allowed us to match systemic arterial and mixed venous blood gases to values measured while the animals were in the conscious state. Tidal volume was fixed at 15 ml/kg. Supplemental O_2 (fractional inspired O_2 concentration ~0.26) was administered, and respiratory rate was adjusted between 10 and 13 breaths per min. End-tidal CO_2 was monitored continuously during the experiment (Beckman LB-2®).

In protocol 3, baseline and posthypoperfusion $P/\dot{Q}$ plots were obtained in eight halothane-anesthetized dogs in the no-drug condition, during cyclooxygenase inhibition, and during combined cyclooxygenase inhibition and angiotensin converting-enzyme inhibition. Halothane anesthesia was induced by mask and supplemented with a subanesthetic dose of thiopental sodium (3 mg/kg iv) to minimize excitatory behavior. After induction, lung ventilation was controlled with the use of respiratory parameters identical to values used in protocol 2. The end-tidal halothane concentration was measured with an anesthesia gas analyzer (Siemens model 120), which was calibrated with a gas of known (1.0%) halothane concentration. After induction, halothane was allowed to equilibrate for ~1 h, so that steady-state conditions could be achieved. At this time, the end-tidal halothane concentration ranged from 1.1 to 1.3%, and the plasma thiopental sodium concentration was assumed to have decreased to negligible amounts, based on the results from a previous study.[15]

Data Analysis

Vascular pressures were recorded on magnetic tape (Hewlett-Packard model 3958A) and displayed on an eight-channel stripchart recorder (Gould Brush® model 2800). Mean vascular pressures, measured at end-expiration, were obtained with the use of passive electronic filters with a 2-s time constant. All vascular pressures were referenced to atmospheric pressure at each level of $\dot{Q}$. As described previously,[14,16] least-squares linear regression analysis was used to generate regression parameters for each individual baseline and posthypoperfusion $P/\dot{Q}$ plot. Regression parameters from each individual experiment were used to interpolate pulmonary vascular pressures at 20 $ml \cdot min^{-1} \cdot kg^{-1}$ intervals of $\dot{Q}$ over the empirically measured range of the $\dot{Q}$. Composite $P/\dot{Q}$ plots were obtained by averaging individual experiments within each protocol. For each protocol, two-way analysis of variance with repeated measures and Duncan's multiple range test were used to compare the $P/\dot{Q}$ plots posthypoperfusion with the baseline $P/\dot{Q}$ plots.[17] Student's t test for paired comparisons was used to compare the magnitude of the changes in PAP–PAWP posthypoperfusion compared with baseline in the no-drug condition, after cyclooxygenase inhibition, and after combined cyclooxygenase inhibition and angiotensin converting-enzyme inhibition. Student's t test for paired comparisons also was used to assess the effects of maximal IVC constriction and full release of the IVC constriction on baseline hemodynamics and blood gases for each protocol.

Results

Conscious State

The composite baseline and posthypoperfusion pulmonary vascular $P/\dot{Q}$ plots measured in nine intact (no drug) conscious dogs are shown in figure 1. As we have observed previously,[1] the pulmonary vascular pressure gradient (PAP–PAWP) was virtually identical during posthypoperfusion compared with baseline over the entire range of $\dot{Q}$s studied (*i.e.*, pulmonary vasoconstriction was not observed in intact [no drug] conscious dogs during the posthypoperfusion period).

To test the hypothesis that vasodilator metabolites of the cyclooxygenase pathway prevented pulmonary vasoconstriction posthypoperfusion in the no-drug condition, baseline and posthypoperfusion $P/\dot{Q}$ plots were generated after cyclooxygenase inhibition. As summarized in figure

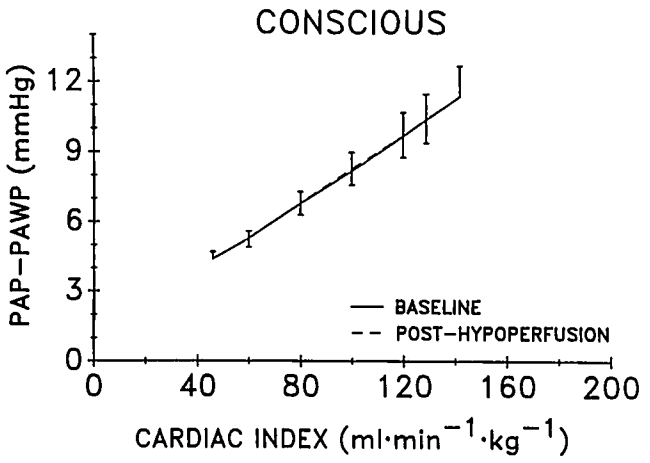

FIG. 1. Baseline (solid line) and posthypoperfusion (dashed line) pulmonary vascular P/Q̇ plots in nine intact (no drug) conscious dogs. The pulmonary vascular pressure gradient (PAP − PAWP) posthypoperfusion was virtually identical to baseline values at each value of cardiac index.

2, in contrast to that in the no-drug condition, PAP–PAWP was increased at every value of Q̇ posthypoperfusion after cyclooxygenase inhibition (*i.e.*, active flow-independent pulmonary vasoconstriction was observed in conscious dogs after cyclooxygenase inhibition during the posthypoperfusion period).

To test the additional hypothesis that the pulmonary vasoconstriction unmasked by cyclooxygenase inhibition was mediated by angiotensin II, baseline and posthypoperfusion P/Q̇ plots were measured after combined cyclooxygenase inhibition and angiotensin converting-enzyme inhibition. As shown in figure 2, PAP–PAWP was unchanged compared with baseline posthypoperfusion after combined cyclooxygenase inhibition and angiotensin converting-enzyme inhibition (*i.e.*, the pulmonary vasoconstriction posthypoperfusion that was unmasked by cyclooxygenase inhibition was abolished entirely by angiotensin converting-enzyme inhibition).

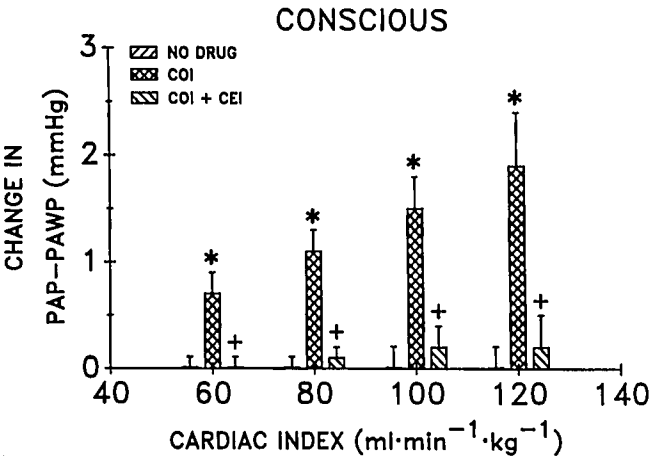

FIG. 2. Changes in PAP − PAWP from baseline values posthypoperfusion in conscious dogs in the no drug condition, after cyclooxygenase inhibition (COI) and after combined COI and angiotensin converting-enzyme inhibition (CEI). PAP − PAWP was unchanged from baseline values posthypoperfusion without drugs and increased (*P < 0.01 compared to baseline) at each value of cardiac index following COI. Combined COI + CEI completely abolished the increases in PAP − PAWP posthypoperfusion († P < 0.05 compared to COI alone).

Pentobarbital Anesthesia

The composite baseline and posthypoperfusion P/Q̇ plots measured in eight otherwise intact (no drug) pentobarbital-anesthetized dogs are shown in figure 3. As we have reported previously,[8] PAP–PAWP was increased at every value of Q̇ posthypoperfusion compared with baseline (*i.e.*, in contrast to the conscious state, active flow-independent pulmonary vasoconstriction was observed posthypoperfusion in pentobarbital-anesthetized dogs during the no-drug condition).

If metabolites of the cyclooxygenase pathway exerted a vasodilator influence on the pulmonary circulation posthypoperfusion in pentobarbital-anesthetized dogs, then the magnitude of pulmonary vasoconstriction posthypoperfusion should be increased after cyclooxygenase inhibition. However, as shown in figure 4, in contrast to the conscious state, the magnitude of pulmonary vasoconstriction posthypoperfusion was either unchanged or decreased after cyclooxygenase inhibition compared with that in the no-drug condition (*i.e.*, cyclooxygenase inhibition did not unmask an additional pulmonary vasoconstrictor response in the posthypoperfusion period). Moreover, the magnitude of pulmonary vasoconstriction post-

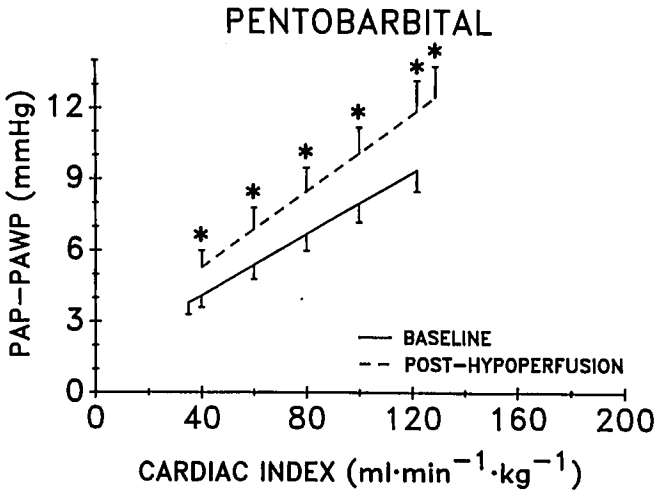

FIG. 3. Baseline and posthypoperfusion pulmonary vascular P/Q̇ plots in eight otherwise intact (no drug) pentobarbital-anesthetized dogs. PAP − PAWP was increased (*P < 0.01 compared to baseline) posthypoperfusion compared to baseline values at each value of Q̇ during pentobarbital anesthesia.

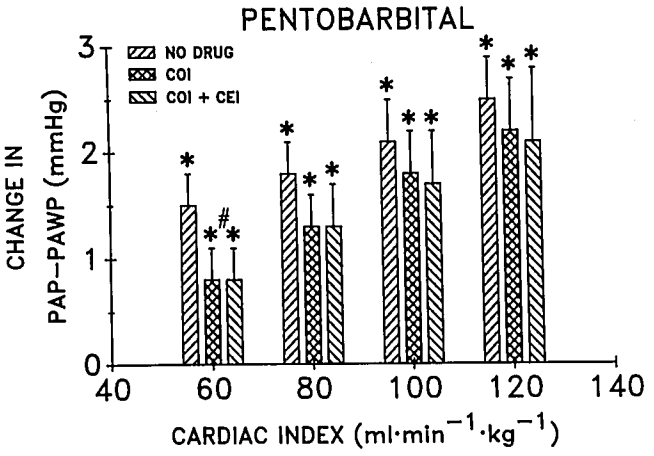

FIG. 4. Changes in PAP − PAWP from baseline values posthypoperfusion in pentobarbital-anesthetized dogs without drugs, after COI, and after combined COI + CEI. PAP − PAWP was increased compared to baseline (*$P < 0.01$) posthypoperfusion in all conditions. The magnitude of the increase in PAP − PAWP posthypoperfusion from baseline values was either unchanged or decreased (#$P < 0.05$ compared to no drugs) after COI either alone or in combination with CEI.

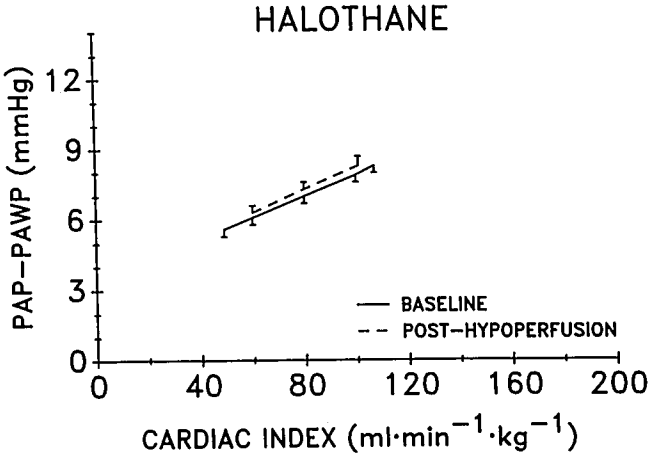

FIG. 5. Baseline and posthypoperfusion pulmonary vascular P/$\dot{Q}$ plots in eight otherwise intact (no drug) halothane-anesthetized dogs. PAP − PAWP posthypoperfusion was unchanged compared to baseline values at each value of cardiac index during halothane anesthesia.

hypoperfusion after combined cyclooxygenase inhibition and angiotensin converting-enzyme inhibition was unchanged compared with that after cyclooxygenase inhibition alone (fig. 4) (*i.e.*, in contrast to the conscious state, angiotensin converting-enzyme inhibition did not abolish the pulmonary vasoconstriction posthypoperfusion in pentobarbital-anesthetized dogs).

HALOTHANE ANESTHESIA

The composite baseline and posthypoperfusion P/$\dot{Q}$ plots measured in eight otherwise intact (no drug) halothane-anesthetized dogs are shown in figure 5. In contrast to that in pentobarbital-anesthetized dogs, PAP–PAWP was unchanged at each value of $\dot{Q}$ posthypoperfusion compared with baseline (*i.e.*, pulmonary vasoconstriction was not observed during halothane anesthesia in the no-drug condition during the posthypoperfusion period).

To test the hypothesis that vasodilator metabolites of the cyclooxygenase pathway prevented pulmonary vasoconstriction posthypoperfusion in halothane-anesthetized dogs in the no-drug condition, baseline and posthypoperfusion P/$\dot{Q}$ plots were generated after cyclooxygenase inhibition. As summarized in figure 6, PAP–PAWP was increased at each value of $\dot{Q}$ posthypoperfusion after cyclooxygenase inhibition (*i.e.*, cyclooxygenase inhibition unmasked pulmonary vasoconstriction during the posthypoperfusion period). Moreover, combined cyclooxygenase inhibition and angiotensin converting-enzyme inhibition attenuated, but did not abolish, the pulmonary vasoconstrictor response posthypoperfusion in halothane-anesthetized dogs (fig. 6).

HEMODYNAMICS

Hemodynamics measured at baseline, during maximum IVC constriction, and after full release of the IVC constriction are summarized in tables 1–3 for conscious, pentobarbital-anesthetized, and halothane-anesthetized dogs, respectively. During maximum IVC constriction, $\dot{Q}$ was decreased to 41–72 ml·min^{-1}·kg^{-1}, which resulted in concomitant decreases in all vascular pressures. HR was increased during maximum IVC constriction in conscious and pentobarbital-anesthetized dogs after cyclooxygenase inhibition and decreased in conscious dogs after combined cyclooxygenase inhibition and angiotensin converting-

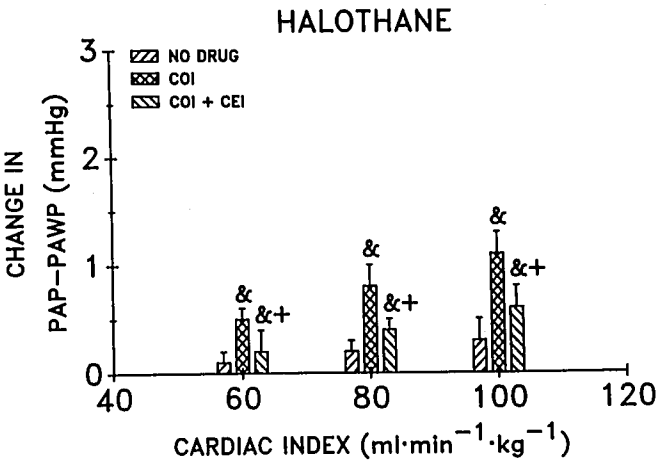

FIG. 6. Changes in PAP − PAWP from baseline values posthypoperfusion in halothane-anesthetized dogs without drugs, after COI, and after combined COI + CEI. PAP − PAWP was unchanged from baseline values posthypoperfusion without drugs and increased (&$P < 0.05$ compared to baseline) at each value of cardiac index after COI. Combined COI + CEI attenuated (†$P < 0.05$ compared to COI alone) but did not abolish the increases in PAP − PAWP posthypoperfusion.

TABLE 1. Hemodynamics: Conscious State

		No Drug	COI	COI + CEI
SAP (mmHg)	Baseline	106 ± 3	102 ± 3	104 ± 7
	Maximum IVCC	57 ± 2*	52 ± 3*	53 ± 5*
	Full release	109 ± 5	98 ± 3	113 ± 8
PAP (mmHg)	Baseline	15.4 ± 1.1	15.2 ± 1.2	15.7 ± 1.0
	Maximum IVCC	5.9 ± 0.6*	6.1 ± 0.8*	5.7 ± 0.8*
	Full release	15.3 ± 0.7	14.7 ± 0.8	15.3 ± 1.1
PAWP (mmHg)	Baseline	5.3 ± 0.7	4.7 ± 0.6	5.3 ± 0.8
	Maximum IVCC	2.0 ± 0.4*	1.8 ± 0.4*	1.7 ± 0.5*
	Full release	6.4 ± 0.5	5.1 ± 0.5	5.9 ± 0.6
RAP (mmHg)	Baseline	4.0 ± 0.9	3.1 ± 0.7	1.3 ± 0.2
	Maximum IVCC	−2.0 ± 0.7*	−2.6 ± 0.5*	−2.6 ± 0.3*
	Full release	4.3 ± 0.6	4.1 ± 0.9	2.7 ± 0.6
$\dot{Q}$ (ml · min^{-1} · kg^{-1})	Baseline	142 ± 20	119 ± 12	180 ± 9
	Maximum IVCC	46 ± 3*	41 ± 3*	50 ± 3*
	Full release	129 ± 21	94 ± 6§	151 ± 13
HR (beats per min)	Baseline	98 ± 8	81 ± 5	99 ± 5
	Maximum IVCC	96 ± 9	102 ± 4†	77 ± 8†
	Full release	90 ± 8	71 ± 4§	74 ± 11

Values are mean ± SE.

COI = cyclooxygenase inhibition; CEI = angiotensin converting-enzyme inhibition.

Symbols indicate significant changes compared with baseline either during maximum inferior vena caval constriction (IVCC) (*$P < 0.01$; †$P < 0.05$) or after full release of IVCC (‡$P < 0.01$, in other tables; §$P < 0.05$).

enzyme inhibition. After full release of the IVC constriction, $\dot{Q}$ returned to baseline values in all protocols except in conscious dogs after cyclooxygenase inhibition. Vascular pressures generally returned to baseline values after full release of the IVC constriction, although increases in systemic arterial pressure and PAP were observed in pentobarbital-anesthetized dogs in the no-drug condition and increases in PAP, PAWP, and right atrial pressure occurred in halothane-anesthetized dogs in the no-drug condition. HR was decreased compared with baseline after full release of the IVC constriction in conscious and pentobarbital-anesthetized dogs after cyclooxygenase inhibition.

SYSTEMIC ARTERIAL AND MIXED VENOUS BLOOD GASES

Systemic arterial and mixed venous blood gases measured at baseline, during maximum IVC constriction, and after full release of the IVC constriction are summarized in tables 4–6 for conscious, pentobarbital-anesthetized, and halothane-anesthetized dogs, respectively. Baseline blood gases were similar across all protocols. IVC constriction generally was characterized by modest mixed venous acidemia and decreases in mixed venous P_{O_2} and S_{O_2}. After full release of the IVC constriction, there were small decreases in systemic arterial and mixed venous *p*H

TABLE 2. Hemodynamics: Pentobarbital-anesthetized State

		No Drug	COI	COI + CEI
SAP (mmHg)	Baseline	102 ± 9	104 ± 5	75 ± 6
	Maximum IVCC	58 ± 6*	59 ± 2*	50 ± 3*
	Full release	114 ± 10§	111 ± 5	78 ± 4
PAP (mmHg)	Baseline	13.8 ± 0.7	15.3 ± 0.9	14.4 ± 1.0
	Maximum IVCC	6.0 ± 0.5*	8.1 ± 0.9*	9.6 ± 1.0*
	Full release	16.5 ± 0.9‡	16.5 ± 1.3	17.4 ± 2.2
PAWP (mmHg)	Baseline	4.8 ± 0.7	5.4 ± 0.6	3.9 ± 0.6
	Maximum IVCC	2.5 ± 0.5*	2.2 ± 0.4*	3.1 ± 0.5
	Full release	5.4 ± 0.8	5.3 ± 0.7	4.3 ± 0.6
RAP (mmHg)	Baseline	2.9 ± 1.0	3.4 ± 0.9	1.9 ± 0.8
	Maximum IVCC	−2.4 ± 0.5*	−2.4 ± 0.6*	−1.6 ± 0.6†
	Full release	3.7 ± 0.8	4.2 ± 0.9	2.7 ± 0.5
$\dot{Q}$ (ml · min^{-1} · kg^{-1})	Baseline	122 ± 12	112 ± 13	156 ± 22
	Maximum IVCC	35 ± 4*	38 ± 4*	72 ± 18*
	Full release	129 ± 11	110 ± 12	160 ± 21
HR (beats per min)	Baseline	122 ± 7	118 ± 7	121 ± 8
	Maximum IVCC	138 ± 5	147 ± 6†	147 ± 11
	Full release	117 ± 7	110 ± 8‡	118 ± 10

Symbols and abbreviations are as in table 1.

TABLE 3. Hemodynamics: Halothane-anesthetized State

		No Drug	COI	COI + CEI
SAP (mmHg)	Baseline	79 ± 3	76 ± 4	55 ± 4
	Maximum IVCC	47 ± 1*	47 ± 4*	41 ± 1*
	Full release	85 ± 3	81 ± 2	53 ± 5
PAP (mmHg)	Baseline	13.6 ± 0.6	14.3 ± 0.5	16.7 ± 0.6
	Maximum IVCC	7.8 ± 0.5*	8.2 ± 0.4*	9.9 ± 0.8*
	Full release	15.0 ± 0.8§	14.9 ± 0.9	16.9 ± 0.6
PAWP (mmHg)	Baseline	5.4 ± 0.4	5.8 ± 0.6	6.9 ± 0.9
	Maximum IVCC	2.3 ± 0.4*	2.7 ± 0.3*	3.8 ± 0.3*
	Full release	6.7 ± 0.6‡	6.0 ± 0.7	7.2 ± 0.7
RAP (mmHg)	Baseline	3.8 ± 0.5	3.3 ± 0.6	4.5 ± 1.2
	Maximum IVCC	−0.4 ± 0.3*	−1.2 ± 0.4*	0.3 ± 0.9*
	Full release	5.1 ± 0.8§	3.6 ± 0.7	5.7 ± 1.0§
$\dot{Q}$ (ml · min^{-1} · kg^{-1})	Baseline	107 ± 4	96 ± 4	145 ± 15
	Maximum IVCC	49 ± 3*	46 ± 2*	70 ± 5*
	Full release	101 ± 6	94 ± 6	131 ± 13
HR (beats per min)	Baseline	109 ± 4	100 ± 3	110 ± 4
	Maximum IVCC	113 ± 2	112 ± 4	100 ± 7
	Full release	110 ± 4	102 ± 3	105 ± 8

Symbols and abbreviations are as in table 1.

and mixed venous S_{O_2}. There were no consistent differences in the changes in systemic arterial or mixed venous blood gases during maximum IVC constriction or after full release of the IVC constriction in conscious, pentobarbital-anesthetized, and halothane-anesthetized dogs.

Discussion

These studies indicate that endogenously released cyclooxygenase metabolites and angiotensin II exert counteracting vasodilator and vasoconstrictor effects, respectively, on the pulmonary circulation of conscious dogs after a period of systemic and pulmonary hypotension and hypoperfusion. Moreover, these competing mechanisms of pulmonary vasoregulation posthypoperfusion are still active in halothane-anesthetized dogs but are abolished completely in pentobarbital-anesthetized dogs. We used chronically instrumented dogs in this study to avoid the potentially confounding effects of acute surgical

TABLE 4. Systemic Arterial and Mixed Venous Blood Gases: Conscious State

		No Drug	COI	COI + CEI
Systemic arterial				
*p*H	Baseline	7.40 ± 0.01	7.38 ± 0.01	7.37 ± 0.01
	Maximum IVCC	7.41 ± 0.01	7.40 ± 0.01	7.37 ± 0.01
	Full release	7.37 ± 0.01§	7.35 ± 0.01‡	7.35 ± 0.01
P_{CO_2} (mmHg)	Baseline	34 ± 1	33 ± 1	33 ± 2
	Maximum IVCC	27 ± 1*	26 ± 1*	29 ± 1
	Full release	33 ± 1	32 ± 2	34 ± 1
P_{O_2} (mmHg)	Baseline	103 ± 3	106 ± 6	105 ± 2
	Maximum IVCC	100 ± 6	105 ± 7	107 ± 7
	Full release	101 ± 4	100 ± 5	111 ± 4
S_{O_2} (%)	Baseline	95.1 ± 0.3	94.9 ± 0.5	95.1 ± 0.5
	Maximum IVCC	93.7 ± 1.1	94.8 ± 0.7	95.0 ± 0.9
	Full release	94.4 ± 0.4	94.3 ± 0.5	95.1 ± 0.4
Mixed venous				
*p*H	Baseline	7.36 ± 0.01	7.36 ± 0.01	7.35 ± 0.01
	Maximum IVCC	7.33 ± 0.02†	7.33 ± 0.02	7.30 ± 0.01*
	Full release	7.33 ± 0.01‡	7.31 ± 0.01‡	7.31 ± 0.01‡
P_{CO_2} (mmHg)	Baseline	40 ± 1	38 ± 1	37 ± 1
	Maximum IVCC	40 ± 1	38 ± 2	40 ± 1*
	Full release	41 ± 1	42 ± 1§	39 ± 1
P_{O_2} (mmHg)	Baseline	49 ± 2	46 ± 2	54 ± 2
	Maximum IVCC	32 ± 1*	28 ± 3*	36 ± 3*
	Full release	46 ± 3	42 ± 3	51 ± 3
S_{O_2} (%)	Baseline	72.5 ± 1.7	71.9 ± 1.7	79.7 ± 2.0
	Maximum IVCC	40.2 ± 3.6*	38.3 ± 5.3*	48.2 ± 5.9*
	Full release	66.4 ± 3.7§	61.3 ± 4.5§	69.9 ± 5.0§

Symbols and abbreviations are as in table 1.

TABLE 5. Systemic Arterial and Mixed Venous Blood Gases: Pentobarbital-anesthetized State

		No Drug	COI	COI + CEI
Systemic arterial				
*p*H	Baseline	7.39 ± 0.01	7.39 ± 0.01	7.38 ± 0.01
	Maximum IVCC	7.34 ± 0.01†	7.37 ± 0.02†	7.36 ± 0.01†
	Full release	7.32 ± 0.01‡	7.34 ± 0.02‡	7.34 ± 0.01§
P_{CO_2} (mmHg)	Baseline	34 ± 1	32 ± 1	32 ± 1
	Maximum IVCC	33 ± 1	29 ± 1†	32 ± 1
	Full release	38 ± 1§	35 ± 1‡	35 ± 1
P_{O_2} (mmHg)	Baseline	108 ± 6	107 ± 4	114 ± 4
	Maximum IVCC	108 ± 5	105 ± 6	110 ± 4
	Full release	105 ± 5	103 ± 4	114 ± 5
S_{O_2} (%)	Baseline	95.0 ± 0.4	95.0 ± 0.3	95.3 ± 0.4
	Maximum IVCC	94.7 ± 0.5	95.0 ± 0.4	95.0 ± 0.6
	Full release	94.2 ± 0.8	94.7 ± 0.4	95.2 ± 0.5
Mixed venous				
*p*H	Baseline	7.37 ± 0.01	7.35 ± 0.01	7.35 ± 0.01
	Maximum IVCC	7.27 ± 0.01*	7.30 ± 0.02*	7.32 ± 0.01
	Full release	7.29 ± 0.01‡	7.30 ± 0.01‡	7.31 ± 0.01§
P_{CO_2} (mmHg)	Baseline	38 ± 1	37 ± 2	38 ± 1
	Maximum IVCC	46 ± 2*	43 ± 2*	39 ± 2
	Full release	43 ± 2§	41 ± 1§	39 ± 1
P_{O_2} (mmHg)	Baseline	46 ± 2	44 ± 2	47 ± 3
	Maximum IVCC	28 ± 1*	26 ± 1*	37 ± 3†
	Full release	51 ± 2§	45 ± 2	52 ± 2
S_{O_2} (%)	Baseline	71.4 ± 1.5	68.3 ± 1.3	66.6 ± 6.6
	Maximum IVCC	31.7 ± 2.1*	33.6 ± 2.6*	49.8 ± 5.2
	Full release	70.3 ± 2.0	65.6 ± 2.5	74.4 ± 2.3

Symbols and abbreviations are as in table 1.

trauma on pulmonary vascular regulation. Most importantly, because of the inherent limitations associated with the interpretation of single-point calculations of pulmonary vascular resistance,[18] particularly when the various interventions result in changes in pulmonary blood flow, we used multipoint P/$\dot{Q}$ plots to investigate pulmonary vascular changes during the posthypoperfusion period in the various conditions of this study. This technique al-

TABLE 6. Systemic Arterial and Mixed Venous Blood Gases: Halothane-anesthetized State

		No Drug	COI	COI + CEI
Systemic arterial				
*p*H	Baseline	7.38 ± 0.01	7.37 ± 0.02	7.37 ± 0.01
	Maximum IVCC	7.37 ± 0.01	7.36 ± 0.02	7.36 ± 0.02
	Full release	7.34 ± 0.01‡	7.34 ± 0.02‡	7.33 ± 0.01§
P_{CO_2} (mmHg)	Baseline	34 ± 1	34 ± 1	35 ± 1
	Maximum IVCC	31 ± 1	32 ± 1	34 ± 1
	Full release	36 ± 1	36 ± 1	35 ± 2
P_{O_2} (mmHg)	Baseline	106 ± 4	115 ± 6	126 ± 4
	Maximum IVCC	103 ± 4	122 ± 5	123 ± 6
	Full release	103 ± 4	118 ± 8	124 ± 7
S_{O_2} (%)	Baseline	94.4 ± 0.5	95.1 ± 0.5	96.1 ± 0.2
	Maximum IVCC	94.5 ± 0.3	95.9 ± 0.2	96.0 ± 0.4
	Full release	94.4 ± 0.4	95.0 ± 0.6	95.7 ± 0.5
Mixed venous				
*p*H	Baseline	7.36 ± 0.01	7.34 ± 0.02	7.34 ± 0.01
	Maximum IVCC	7.32 ± 0.01*	7.31 ± 0.02†	7.31 ± 0.02†
	Full release	7.31 ± 0.01‡	7.30 ± 0.02‡	7.31 ± 0.01§
P_{CO_2} (mmHg)	Baseline	39 ± 2	40 ± 1	39 ± 1
	Maximum IVCC	42 ± 1*	43 ± 1†	40 ± 1
	Full release	42 ± 1§	42 ± 1	41 ± 1
P_{O_2} (mmHg)	Baseline	49 ± 1	47 ± 1	54 ± 3
	Maximum IVCC	34 ± 1*	33 ± 1*	39 ± 2*
	Full release	48 ± 2	46 ± 1	50 ± 3
S_{O_2} (%)	Baseline	69.9 ± 1.2	67.0 ± 1.2	76.8 ± 2.4
	Maximum IVCC	44.3 ± 1.4*	43.5 ± 2.2*	56.6 ± 2.4*
	Full release	67.0 ± 1.6§	64.3 ± 1.5§	71.1 ± 3.3§

Symbols and abbreviations are as in table 1.

lowed us to distinguish between vasoactive and passive flow-dependent changes in the pulmonary circulation during the posthypoperfusion period.

Systemic hypotension results in reflex activation of both the autonomic nervous system and the renin-angiotensin system.[3] We have demonstrated previously that the autonomic nervous system modulates the pulmonary circulation posthypoperfusion in conscious dogs, in that sympathetic beta-adrenergic vasodilation offsets sympathetic alpha-adrenergic vasoconstriction to prevent pulmonary vasoconstriction during the posthypoperfusion period.[1] Because exogenous angiotensin II causes active flow-independent pulmonary vasoconstriction,[4] whereas angiotensin converting-enzyme inhibition results in pulmonary vasodilation in conscious dogs,[4] in this study we hypothesized that angiotensin II, released in response to hypotension and hypoperfusion, would exert a vasoconstrictor effect on the pulmonary circulation during the posthypoperfusion period. We also hypothesized that increased blood flow after hypotension and hypoperfusion would result in the increased production of vasodilator cyclooxygenase metabolites, which could act to offset a direct pulmonary vasoconstrictor effect of angiotensin II. Prostaglandins, primarily prostacyclin, are released tonically by the lung,[7,19,20] and prostaglandin release is stimulated by an increase in pulmonary blood flow.[2] Exogenously administered prostacyclin results in pulmonary vasodilation,[5] whereas cyclooxygenase inhibition causes pulmonary vasoconstriction in conscious dogs.[21,22] There is also an interactive effect between angiotensin II and prostacyclin in the lung. Exogenous angiotensin II stimulates the release of prostacyclin from the lung,[7,23,24] and the pulmonary vasoconstrictor response to angiotensin II is enhanced by cyclooxygenase inhibition.[7,25,26] Moreover, exogenously administered angiotensin II prevents the effects of chronic hypoxia on the pulmonary circulation by stimulating the release of vasodilator prostaglandins.[6] Our results support both of our hypotheses—that active flow-independent pulmonary vasoconstriction is observed posthypoperfusion after cyclooxygenase inhibition in conscious dogs, and that this response is abolished completely by angiotensin converting-enzyme inhibition.

There are several other possible mechanisms—which we believe to be less likely—that could be responsible for these results. One could postulate that the vasoconstriction posthypoperfusion after cyclooxygenase inhibition did not result from inhibition of vasodilator prostaglandins, but rather from shunting of arachidonic acid into the lipoxygenase pathway to produce vasoconstrictor leukotrienes. Biochemical measurements of arachidonic acid metabolites would be helpful in this regard.

A limitation of this study is that we did not attempt to correlate these biochemical measurements with the pulmonary vascular changes that occurred posthypoperfusion. However, it also should be remembered that the production, release, and vasoactive effects of these metabolites are highly focal. Thus, it is unclear how closely plasma measurements will reflect concentrations at the cellular level.[27] Moreover, it also is not apparent why this putative leukotriene-induced vasoconstriction would be abolished by angiotensin converting-enzyme inhibition. Because converting enzyme not only converts angiotensin I to angiotensin II, but also enzymatically degrades bradykinin,[28] it could be postulated that inhibition of the pulmonary vasoconstriction posthypoperfusion after combined cyclooxygenase inhibition and converting-enzyme inhibition resulted from an increased circulating concentration of bradykinin. Bradykinin is a pulmonary vasodilator in this conscious animal model.[29] Bradykinin causes the release of a prostacyclin-like substance from the lung,[24,30] as well as from cultured pulmonary endothelial cells.[31] This latter putative vasodilator mechanism can be discounted in the current study because converting enzyme was administered in the presence of cyclooxygenase inhibition. However, we cannot exclude a possible direct pulmonary vasodilator effect of bradykinin. The development of selective bradykinin receptor antagonists will allow a direct test of this hypothesis.

Differential changes in blood gases are not responsible for the pulmonary vascular effects of cyclooxygenase inhibition or angiotensin converting-enzyme inhibition in the conscious state. Blood gases at baseline and during maximum IVC constriction were similar across all protocols (table 4). After full release of the IVC constriction, there was mild metabolic acidosis, but this was observed in all protocols.

Pulmonary artery wedge pressure was used as the effective outflow pressure to calculate the pulmonary vascular pressure gradient. The position and size of the pulmonary artery catheter cause the catheter to "wedge" in a very proximal position of the pulmonary vascular tree during balloon inflation. Under these conditions, PAWP does not measure a local outflow pressure, but rather the effective downstream pressure in the subtended region.[32] At baseline, before IVC constriction, PAWP and left atrial pressure have similar values because the lung primarily is in a zone 3 condition.[14,15] However, during progressive IVC constriction, the lung condition is transformed to a mixed zone 2–3. In a zone 2 condition, left atrial pressure is negative relative to alveolar pressure and does not function as the effective outflow pressure for the pulmonary circulation.[33] In contrast, PAWP is greater than alveolar pressure during maximum IVC constriction (table 1). We also assume that changes in PAWP are reflected passively by concomitant PAP changes of equal magnitude, which appears to be a reasonable assumption in the dog.[34]

The magnitude of the increase in PAP–PAWP during reperfusion is small in absolute terms. The pulmonary circulation is normally a very low-resistance vascular bed. As a result, a small absolute change in the pulmonary

vascular pressure gradient can be associated with large changes in $\dot{Q}$. For example, it can be seen in table 1 (no-drug condition) that the decrease in PAP–PAWP from baseline to maximum IVC constriction was only 6.2 mmHg. The associated change in $\dot{Q}$ was 96 $ml \cdot min^{-1} \cdot kg^{-1}$. Thus, a 1-mmHg change in PAP–PAWP was associated with a $\dot{Q}$ change of ~ 15 $ml \cdot min^{-1} \cdot kg^{-1}$. Clearly, this example illustrates that small absolute changes in PAP–PAWP can result in physiologically significant changes in $\dot{Q}$. Currently, it is difficult to evaluate the physiologic significance of the 1–2-mmHg increases in PAP–PAWP during the posthypoperfusion period that were unmasked by cyclooxygenase inhibition. However, the previous example suggests that the potential significance of these small absolute changes should not be underestimated.

Pentobarbital sodium is used widely as a background anesthetic in experimental studies of the cardiovascular system. Pentobarbital anesthesia has no net effect on the baseline pulmonary vascular $P/\dot{Q}$ relationship compared with that measured in the conscious state.[8,10,35] However, consistent with our earlier work,[8] active pulmonary vasoconstriction was apparent posthypoperfusion in pentobarbital-anesthetized dogs in the no-drug condition. This is because sympathetic beta-adrenoreceptor vasodilation does not offset sympathetic alpha-adrenoreceptor vasoconstriction during the posthypoperfusion period.[8] In the current study, cyclooxygenase inhibition did not unmask an additional vasoconstrictor response posthypoperfusion, and angiotensin converting-enzyme inhibition did not attenuate the posthypoperfusion pulmonary vasoconstriction. These results strongly imply that neither vasodilator metabolites of the cyclooxygenase pathway nor angiotensin II modulate the pulmonary circulation in pentobarbital-anesthetized dogs during the posthypoperfusion period. Pentobarbital anesthesia also modifies the extent to which endogenously released cyclooxygenase metabolites[10] and angiotensin II[13] modulate the baseline pulmonary vascular $P/\dot{Q}$ relationship. Although the mechanisms responsible for these effects remain to be elucidated, neither controlled ventilation nor blood gases appear to be involved. Despite virtually identical respiratory parameters and blood gases during pentobarbital and halothane anesthesia, differential pulmonary vascular responses posthypoperfusion were observed in these anesthetized states.

In contrast to those during pentobarbital anesthesia, the pulmonary vascular responses posthypoperfusion during halothane anesthesia were qualitatively similar to those observed in the conscious state. A posthypoperfusion pulmonary vasoconstriction was not observed in halothane-anesthetized dogs in the no-drug condition. However, a vasoconstrictor response posthypoperfusion was unmasked by cyclooxygenase inhibition during halothane anesthesia, and this response was attenuated at least partially by angiotensin converting-enzyme inhibition. These results suggest that cyclooxygenase metabolites and angiotensin II modulate the pulmonary circulation in halothane-anesthetized dogs during the posthypoperfusion period, but perhaps to a lesser extent than that observed in the conscious state. In contrast, cyclooxygenase inhibition[11] and angiotensin converting-enzyme inhibition[12] have no effect on the baseline $P/\dot{Q}$ relationship during halothane anesthesia.

Although this was not the focus of our study, it is interesting that reflex tachycardia was not observed in response to systemic hypotension during maximum IVC constriction in conscious dogs in the no-drug condition. We have reported this previously,[1,8,15,35] and the mechanism could involve activation of low-pressure receptors in the IVC during inflation of the IVC occluder.[36] An increase in HR was observed during maximum IVC constriction after cyclooxygenase inhibition in both conscious and pentobarbital-anesthetized dogs, and a decrease in HR was observed in conscious dogs after combined cyclooxygenase inhibition and angiotensin converting-enzyme inhibition. The mechanisms responsible for these effects are unknown.

In summary, the pulmonary vascular response after systemic and pulmonary hypotension and hypoperfusion in conscious dogs involves a complex interaction of multiple vasoregulatory mechanisms. In addition to the regulatory role of the autonomic nervous system,[1] the results of the current study indicate that endogenously released vasodilator metabolites of the cyclooxygenase pathway offset the vasoconstrictor effect of angiotensin II and prevent pulmonary vasoconstriction during the posthypoperfusion period in the conscious state. These competing vasoregulatory mechanisms also modulate the pulmonary vascular response posthypoperfusion during halothane anesthesia, but the efficacy of these vasoactive mechanisms is abolished during pentobarbital anesthesia.

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