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Pulmonary Vasoregulation by Arginine Vasopressin in Conscious, Halothane-anesthetized, and Pentobarbital-anesthetized Dogs with Increased Vasomotor Tone

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Background: **Arginine vasopressin (AVP) is an important "stress" hormone that is known to play a key role in cardiovascular homeostasis of the systemic circulation. In contrast, the effects of AVP on the pulmonary circulation have not been extensively investigated, and the extent to which general anesthesia alters the pulmonary vascular response to AVP is entirely unknown. Our first objective was to assess the effects of AVP on the pulmonary vascular pressure–flow relation in chronically instrumented conscious dogs in the setting of an acute elevation in pulmonary vasomotor tone. Our second objective was to investigate the effects of halothane and pentobarbital anesthesia on the pulmonary vascular response to AVP after inducing the same degree of pulmonary preconstriction achieved in the conscious state.**

Methods: **Conditioned, mongrel dogs were chronically instrumented to measure the left pulmonary vascular pressure–flow ($LP\dot{Q}$) relation. $LP\dot{Q}$ plots were generated by continuously measuring the pulmonary vascular pressure gradient (pulmonary arterial pressure minus left atrial pressure) and left pulmonary blood flow during gradual (~1 min) inflation of a hydraulic occluder around the right pulmonary artery, which directed total pulmonary blood flow through the left pulmonary circulation. $LP\dot{Q}$ plots were generated in conscious (n = 10), halothane-anesthetized (n = 9) and pentobarbital-anesthetized (n = 7) dogs. In each condition, $LP\dot{Q}$ plots were measured at baseline, during the intravenous administration of the thromboxane analog U46619 and during the cumulative administration of AVP (2–19 $ng \cdot kg^{-1} \cdot min^{-1}$, intravenous) in the presence of U46619 preconstriction.**

Results: **U46619 caused acute pulmonary vasoconstriction ($P < 0.01$) in conscious dogs. In this setting of U46619 preconstriction, AVP caused pulmonary vasodilation ($P < 0.05$) in the conscious state. In contrast, despite identical levels of U46619 preconstriction, the pulmonary vasodilator response to AVP was either reversed to vasoconstriction ($P < 0.05$) or abolished during halothane and pentobarbital anesthesia.**

Conclusions: **These results indicate that AVP exerts a significant pulmonary vasodilator response in the setting of acute pulmonary vasoconstriction in conscious dogs. However, the pulmonary vascular response to this stress hormone is markedly altered during halothane and pentobarbital anesthesia. (Key words: Anesthetics, intravenous: pentobarbital. Anesthetics, volatile: halothane. Hormones: arginine vasopressin. Lung(s): circulation; pressure–flow relation. Pharmacology: U46619.)**

ARGININE vasopressin (AVP) causes profound vasoconstriction in various systemic vascular beds, and its release is widely recognized as an important mechanism of cardiovascular homeostasis in response to several pathophysiologic stimuli (*e.g.*, systemic hypotension).[1,2] The extent to which AVP exerts a vasoactive influence on the pulmonary circulation has been studied less extensively. Work from our own laboratory indicates that in conscious dogs with normal vasomotor tone, AVP can cause either pulmonary vasoconstriction or vasodilation depending on the integrity of AVP V_1 receptors.[3,4] In contrast, after acute preconstriction of the isolated, perfused rat lung, AVP causes pulmonary vasodilation that is mediated through V_1 receptor activation and is attenuated by nitric oxide synthase inhibition.[5–7] Despite the importance of this "stress" hormone in cardiovascular regulation, the effects of general anesthesia on the pulmonary vascular response to AVP are entirely unknown.

Our previous studies concerning the pulmonary vascular effects of AVP in conscious dogs were performed without preconstriction of the pulmonary circulation.[3,4] The preexisting level of vasomotor tone is

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known to alter the pulmonary vascular response to a number of vasoactive agents.[8–10] Thus, our first objective was to investigate the pulmonary vascular response to AVP in conscious dogs in the setting of acute preconstriction of the pulmonary circulation. This was achieved by the intravenous administration of the potent vasoconstrictor U46619, a thromboxane analog. Our second objective was to identify the extent to which halothane and pentobarbital anesthesia modify the pulmonary vascular response to AVP compared with that measured in the same animals in the conscious state.

Materials and Methods

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

Surgery for Chronic Instrumentation

Ten conditioned male mongrel dogs (27 ± 1 kg), free of microfilaria, were premedicated with morphine sulfate (10 mg, intramuscular) and anesthetized with pentobarbital sodium (20 mg/kg, intravenous) and fentanyl citrate (15 μg/kg, intravenous). After tracheal intubation, the lungs were mechanically ventilated, and halothane (~1.2% end-tidal) was administered.

With sterile surgical techniques, a left thoracotomy was performed through the fifth intercostal space. The pericardium was incised ventral to the phrenic nerve. Heparin-filled Tygon catheters (1.02 mm ID, Norton, Akron, OH) were inserted into the descending thoracic aorta, left and right atrium, and main pulmonary artery. The catheters were secured *via* purse-string sutures. After careful dissection and isolation, a hydraulic occluder (18 mm ID, Jones, Silver Springs, MD) was positioned around the right main pulmonary artery. An electromagnetic flow probe (10 mm ID, Zepeda, Seattle, WA) was placed around the left main pulmonary artery. The pericardial edges were loosely apposed. The free ends of the catheters, occluder, and flow probe were threaded through the chest wall, and were tunneled subcutaneously to a final position between the scapulae. A chest tube placed in the left thorax before closure was removed on the 1st day after surgery.

Morphine sulfate (10 mg, intramuscular) was administered postoperatively for pain, as required. Cephazolin (2 g, intravenous) was administered intraoperatively and for 10 days postoperatively (cephalexin 2 g/day, oral). The dogs were allowed to recover for at least 2 weeks before experimentation.

Experimental Measurements

Vascular pressures were measured by connecting the fluid-filled catheters to strain-gauge manometers (P23 ID, Gould Statham, Cleveland, OH). Pressures were referenced to atmospheric pressure with the transducers positioned at midchest at the level of the spine. Heart rate was calculated from the phasic aortic pressure trace. Left pulmonary blood flow ($L\dot{Q}$) was measured by connecting the flow probe to an electromagnetic flowmeter (SWF-4rd, Zepeda). The flow probe was calibrated *in vivo* on a weekly basis by the thermal dilution technique. Calibration was achieved by acutely inserting a balloon-tipped thermal dilution catheter (7-French) into the pulmonary artery through a percutaneous jugular puncture after topical anesthesia (lidocaine hydrochloride spray). The catheter was positioned 2–3 cm distal to the pulmonic valve. The right pulmonary artery occluder was then inflated to completely occlude the right pulmonary artery, which directed total pulmonary blood flow through the left pulmonary artery and flow probe. $L\dot{Q}$ was then measured by thermal dilution (9520A, American Edwards, Irvine, CA) with multiple 5-ml sterile iced injectates of 5% dextrose in water. Values for $L\dot{Q}$ have been referenced to body weight ($ml \cdot min^{-1} \cdot kg^{-1}$). The aortic and pulmonary arterial catheters were used to draw blood samples to measure systemic arterial and mixed venous blood gases, respectively. Systemic arterial and mixed venous *p*H, carbon dioxide tension (P_{CO_2}), and oxygen tension (P_{O_2}) were measured with a blood-gas analyzer (ABL-3, Radiometer, Copenhagen, Denmark), and oxyhemoglobin saturation (S_{O_2}) was measured with a hemoximeter (OSM-3, Radiometer).

Drug Preparation

All solutions were prepared on the day of the experiment. The thromboxane analog U46619 (9,11-dideoxy-11_α,9_α-epoxymethano-prostaglandin $F_{2\alpha}$, Upjohn, Kalamazoo, MI) was suspended in 95% ethanol and stored as a stock solution at −20°C. On the day of the experiment, 360 μg were dissolved in 60 ml of 0.9% saline. AVP (Bachem, Torrance, CA) was diluted in 0.9% saline from a stock solution stored at −20°C.

Experimental Protocols

All experiments were performed with each healthy, chronically instrumented dog lying on its right side in

a quiet laboratory environment. Continuous left pulmonary vascular pressure–flow ($LP\dot{Q}$) plots were used to assess the vasoactive effects of the various pharmacologic interventions on the pulmonary circulation. $LP\dot{Q}$ plots were constructed by continuously measuring the pulmonary vascular pressure gradient (pulmonary arterial pressure minus left atrial pressure [PAP−LAP]) and $L\dot{Q}$ during gradual (~1 min) inflation of the hydraulic occluder implanted around the right pulmonary artery. This technique to measure the $LP\dot{Q}$ relation is highly reproducible and has little or no effect on systemic hemodynamics, blood gases or the zonal condition of the left lung.[11]

In protocol 1, we investigated the effects of cumulative doses of AVP on the $LP\dot{Q}$ relation in conscious dogs after preconstriction with U46619. For each conscious dog (n = 10), $LP\dot{Q}$ plots were generated on the same day without previous drug administration (baseline), after preconstriction of the pulmonary circulation with U46619 (0.12 ± 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$, intravenous), and after the cumulative intravenous administration of AVP (2, 4, 8, and 19 $ng \cdot kg^{-1} \cdot min^{-1}$). The dose of U46619 was titrated to achieve an approximate doubling of PAP−LAP (at the same value of $L\dot{Q}$) from baseline values in each conscious dog. $LP\dot{Q}$ plots were obtained 10–15 min after each incremental dose of AVP, when vascular pressures and $L\dot{Q}$ had achieved new steady state values. We have verified that U46619 preconstriction is stable over the time course of this experiment and in the experiments of protocols 2 and 3.

In protocol 2, we investigated the effects of halothane anesthesia on the pulmonary vascular response to AVP in the presence of U46619 preconstriction. A $LP\dot{Q}$ plot was first obtained in each dog (n = 9) in the conscious state. Halothane anesthesia was then induced by mask and was supplemented with a subanesthetic dose of thiopental sodium (3 mg/kg, intravenous) to minimize excitatory behavior. After induction, the trachea of each dog was intubated and ventilation was controlled (Harvard respirator, South Natick, MA) without positive end-expiratory pressure. Tidal volume was fixed at 15 ml/kg. Supplemental O_2 (fractional inspiratory O_2 concentration ~0.26) was administered to maintain systemic arterial $P_{O_2} > 100$ mmHg. Respiratory rate was adjusted to 10–13 breaths/min to match systemic arterial and mixed venous *p*H and P_{CO_2} to values measured in the conscious state. End-tidal CO_2 was monitored continuously during the experiment (78356A, Hewlett-Packard, Andover, MA). End-tidal halothane concentration was measured in seven experiments with an anesthesia gas analyzer (120, Siemens), which was calibrated with a gas of known (1.0%) halothane concentration. After induction, halothane was allowed to equilibrate for 1 h to achieve steady state conditions. At this time, end-tidal halothane concentration was 1.1%–1.3%, and plasma thiopental concentration had decreased to negligible amounts.[12] $LP\dot{Q}$ plots were then obtained in the baseline condition, after preconstriction of the pulmonary circulation with U46619 (0.15 ± 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$, intravenous), and after the cumulative intravenous administration of AVP as described in protocol 1. The dose of U46619 was titrated to achieve the same degree of pulmonary vasomotor tone in the conscious and anesthetized states.

In protocol 3, we investigated the effects of pentobarbital anesthesia on the pulmonary vascular response to AVP in the presence of U46619 preconstriction. A $LP\dot{Q}$ plot was first obtained in each dog (n = 7) in the conscious state. After administration of pentobarbital sodium (30 mg/kg, intravenous), each dog's trachea was intubated and the lungs were ventilated with respiratory parameters identical to those set in protocol 2. After a 1-h equilibration, $LP\dot{Q}$ plots were obtained in the baseline condition, after preconstriction of the pulmonary circulation with U46619 (0.12 ± 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$, intravenous), and after the cumulative intravenous administration of AVP. Supplemental doses (130 mg, intravenous) of pentobarbital were administered as required to maintain an adequate depth of anesthesia.

The order of experiments in protocols 2 and 3 was randomized, and the experiments were performed at least 1 week apart. Of the ten dogs studied in protocol 1, nine were studied in protocol 2 and seven were studied in protocol 3.

Data Analysis

Phasic and mean vascular pressures and $L\dot{Q}$ were displayed continuously on an 8-channel strip-chart recorder (2800, Gould Brush, Eastlake, OH). Mean pressures and $L\dot{Q}$ were obtained with passive electronic filters with a 2-s time constant. All vascular pressures and $L\dot{Q}$ were measured at end-expiration. Vascular pressures were referenced to atmospheric pressure before and after each $LP\dot{Q}$ plot. The analog pressure and $L\dot{Q}$ signals were also digitally converted and multiplexed (Medical Systems, PCM-8, Greenvale, NY) and stored on videotape (videocasette recorder VC-H857U, Sharp, Japan) for later analysis. The $LP\dot{Q}$ relation is lin-

ear by inspection over the empirically measured range of $L\dot{Q}$. As a result, linear regression analysis was used to calculate the slope and intercept for PAP−LAP (or PAP-0 if LAP < 0 mmHg) as a function of $L\dot{Q}$ in each individual experiment. The correlation coefficient for each protocol averaged 0.98 or higher. Multivariate analysis of variance in the form of Hotelling's T^2 was used to assess 1) the effects of halothane and pentobarbital anesthesia on the slopes and intercepts in each individual experiment compared with values measured in the conscious state, and 2) the effects of AVP on the regression parameters obtained from each individual experiment compared with values measured during U46619 administration.[13] PAP−LAP intercept values were calculated at the midrange of empirically measured $L\dot{Q}$ in each experiment to minimize the variance in the PAP−LAP intercept and avoid the use of intercept values outside the range of our empirical measurements. Thus, PAP−LAP was not measured at $L\dot{Q}$ = 0 $ml \cdot min^{-1} \cdot kg^{-1}$. One-way analysis of variance was used to assess the effects of cumulative doses of AVP on PAP−LAP at a common value of $L\dot{Q}$ (60 $ml \cdot min^{-1} \cdot kg^{-1}$) in the presence of U46619 preconstriction in each protocol. Two-way analysis of variance was used to assess the effects of anesthesia and the pharmacologic agonists on steady state hemodynamics and blood gases. Values are reported as means ± SEM.

Results

Conscious State

Compared with the baseline (no drug) condition, the thromboxane analog U46619 increased ($P < 0.01$) PAP−LAP at each common value of $L\dot{Q}$, a result showing that U46619 caused active pulmonary vasoconstriction in conscious dogs (fig. 1). In the presence of U46619 preconstriction, the intravenous administration of AVP (19 $ng \cdot kg^{-1} \cdot min^{-1}$) caused a partial reversal of U46619 preconstriction; that is, AVP resulted in active pulmonary vasodilation ($P < 0.05$) in conscious dogs with increased pulmonary vasomotor tone (fig. 1). The dose–response relation for AVP on the $LP\dot{Q}$ relation in conscious dogs is summarized in figure 2, which presents values for PAP−LAP at $L\dot{Q}$ = 60 $ml \cdot min^{-1} \cdot kg^{-1}$. After preconstriction with U46619, low doses (2 and 4 $ng \cdot kg^{-1} \cdot min^{-1}$, intravenous) of AVP had no significant effect on PAP−LAP, whereas higher doses (8 and 19 $ng \cdot kg^{-1} \cdot min^{-1}$, intravenous) of AVP caused active pulmonary vasodilation ($P < 0.05$) in conscious dogs.

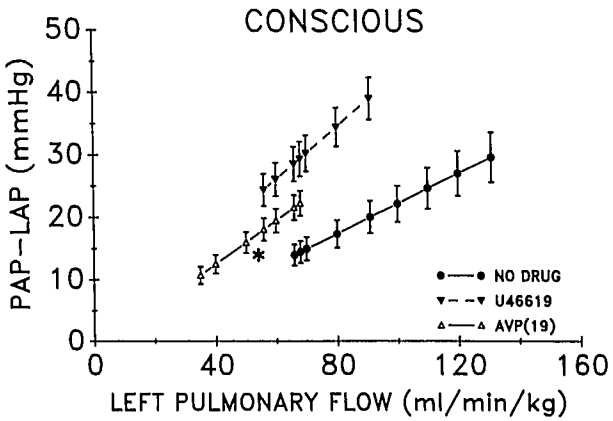

Fig. 1. Composite left pulmonary vascular pressure–flow ($LP\dot{Q}$) plots in 10 conscious dogs at baseline (no drug), after preconstriction with U46619, and after intravenous administration of arginine vasopressin (AVP) (19 $ng \cdot kg^{-1} \cdot min^{-1}$). Compared with the no drug condition, U46619 increased ($P < 0.01$) the pulmonary vascular pressure gradient (pulmonary arterial pressure minus left atrial pressure [PAP−LAP]) over the entire range of left pulmonary blood flow, a result showing that U46619 caused active pulmonary vasoconstriction. After preconstriction with U46619, this dose of AVP caused pulmonary vasodilation (*$P < 0.05$) in the conscious state.

U46619 increased steady state systemic arterial pressure (SAP) and PAP and decreased $L\dot{Q}$ (table 1), had no effect on systemic arterial blood gases, and decreased mixed venous *p*H and S_{O_2} (table 2). In the presence of U46619 preconstriction, AVP increased steady state SAP and LAP and decreased PAP, heart rate and $L\dot{Q}$ (table 1). During U46619 preconstriction, AVP decreased systemic arterial and mixed venous *p*H, increased mixed venous P_{CO_2}, and decreased mixed venous P_{O_2} and S_{O_2} (table 2).

Halothane Anesthesia

Halothane caused a small but significant ($P < 0.03$) downward shift in the baseline (no drug) $LP\dot{Q}$ relation compared with values measured in the conscious state (fig. 1 *vs.* fig. 3). U46619 caused active pulmonary vasoconstriction ($P < 0.01$) during halothane anesthesia (fig. 3). However, in contrast to the conscious state, in the presence of U46619 preconstriction this dose of AVP elicited an active pulmonary vasoconstrictor response ($P < 0.05$) during halothane anesthesia (fig. 3). The dose–response relation for AVP on the $LP\dot{Q}$ relation during halothane anesthesia is summarized in figure 4, which presents values for PAP−LAP at $L\dot{Q}$ = 60 $ml \cdot min^{-1} \cdot kg^{-1}$. After preconstriction with U46619, all doses of AVP resulted in active pulmonary

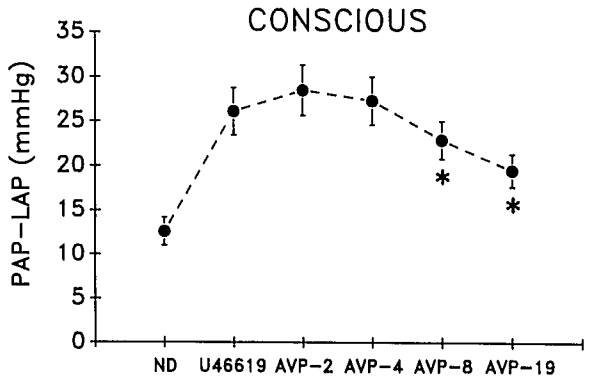

Fig. 2. Values of the pulmonary vascular pressure gradient (pulmonary arterial pressure minus left atrial pressure [PAP–LAP]) at left pulmonary blood flow ($L\dot{Q}$) = 60 $ml \cdot min^{-1} \cdot kg^{-1}$ in the no drug (ND) condition, after U46619 preconstriction, and during the cumulative administration ($ng \cdot kg^{-1} \cdot min^{-1}$, intravenous) of arginine vasopressin (AVP) in 10 conscious dogs. After U46619 preconstriction, AVP resulted in pulmonary vasodilation (*$P < 0.05$) at the two highest doses.

vasoconstriction ($P < 0.05$) during halothane anesthesia.

U46619 increased steady state SAP, PAP and LAP and decreased $L\dot{Q}$ (table 1), and decreased mixed venous P_{O_2} and S_{O_2} (table 2). In the presence of U46619 preconstriction, AVP increased steady state LAP and decreased $L\dot{Q}$ (table 1). During U46619 preconstriction, AVP decreased systemic arterial and mixed venous *p*H, and decreased mixed venous P_{O_2} and S_{O_2} (table 2).

Pentobarbital Anesthesia

Pentobarbital caused a modest ($P < 0.02$) downward shift in the baseline (no drug) $LP\dot{Q}$ relation compared with values measured in the conscious state (fig. 1 *vs.* fig. 5). U46619 caused active pulmonary vasoconstriction ($P < 0.01$) during pentobarbital anesthesia (fig. 5). However, in contrast to both the conscious and halothane-anesthetized states, in the presence of U46619 preconstriction this dose of AVP had no significant effect on the $LP\dot{Q}$ relation during pentobarbital anesthesia (fig. 5). The dose–response relation for AVP on the $LP\dot{Q}$ relation during pentobarbital anesthesia is summarized in figure 6, which presents values for PAP–LAP at $L\dot{Q}$ = 60 $ml \cdot min^{-1} \cdot kg^{-1}$. After preconstriction with U46619, the two lowest doses of AVP resulted in active pulmonary vasoconstriction ($P < 0.05$) during pentobarbital anesthesia, whereas the two highest doses failed to significantly alter the $LP\dot{Q}$ relation.

U46619 increased steady state SAP and PAP (table 1), and decreased mixed venous *p*H, P_{O_2} and S_{O_2} (table 2). In the presence of U46619 preconstriction, AVP increased SAP and LAP (table 1), decreased systemic arterial P_{CO_2}, and decreased mixed venous *p*H, P_{O_2} and S_{O_2} (table 2).

Discussion

There were two major results in this study. First, in the setting of acute U46619-induced preconstriction, AVP caused active pulmonary vasodilation in conscious dogs. Second, despite matched degrees of U46619 preconstriction, the AVP-induced pulmonary vasodilator response observed in the conscious state was either reversed to pulmonary vasoconstriction or abolished during halothane and pentobarbital anesthesia.

By studying chronically instrumented dogs, we were able to assess the pulmonary vascular response to AVP in the same animal in the conscious and anesthetized states. We used multipoint $LP\dot{Q}$ plots to assess the effects of AVP on the pulmonary circulation. This experimental approach avoids the problems inherent in the interpretation of single-point calculations of pulmonary vascular resistance[1-4] and distinguishes between

Table 1. Baseline Hemodynamics

	No Drug	U46619	AVP (19)
SAP (mmHg)			
Conscious	102 ± 4	117 ± 3*	133 ± 2*†
Halothane	75 ± 3‡	89 ± 3*‡	93 ± 6*‡
Pentobarbital	87 ± 3‡	112 ± 3*	134 ± 6*†
PAP (mmHg)			
Conscious	18 ± 2	29 ± 2*	23 ± 1*†
Halothane	18 ± 1	25 ± 2*	24 ± 1*
Pentobarbital	15 ± 1	26 ± 2*	25 ± 2*
LAP (mmHg)			
Conscious	5 ± 1	5 ± 1	12 ± 1*†
Halothane	4 ± 1	6 ± 1*	10 ± 1*†
Pentobarbital	3 ± 1	5 ± 1	10 ± 1*†
HR (bpm)			
Conscious	86 ± 4	81 ± 5	55 ± 2*†
Halothane	97 ± 4‡	94 ± 4‡	97 ± 4‡
Pentobarbital	112 ± 6‡	111 ± 8‡	99 ± 7‡
$L\dot{Q}$ ($ml \cdot min^{-1} \cdot kg^{-1}$)			
Conscious	66 ± 4	56 ± 3*	35 ± 3*†
Halothane	67 ± 5	52 ± 4*	35 ± 4*†
Pentobarbital	62 ± 5	53 ± 7	39 ± 4*

* $P < 0.05$ *versus* no drug; † $P < 0.05$ *versus* U46619; ‡ $P < 0.05$ *versus* conscious. Arginine Vasopressin (AVP) administered intravenously at a dose of 19 $ng \cdot kg^{-1} \cdot min^{-1}$.

Table 2. Baseline Blood Gases

Systemic Arterial	No Drug	U46619	AVP (19)
pH			
Conscious	7.39 ± 0.01	7.39 ± 0.01	7.36 ± 0.01*†
Halothane	7.41 ± 0.01	7.40 ± 0.01	7.37 ± 0.01*†
Pentobarbital	7.43 ± 0.01	7.41 ± 0.01	7.39 ± 0.01*
pCO_2 (mmHg)			
Conscious	38 ± 1	35 ± 2	36 ± 1
Halothane	35 ± 1	35 ± 1	33 ± 1
Pentobarbital	34 ± 1	35 ± 1	32 ± 1*†
pO_2 (mmHg)			
Conscious	96 ± 2	98 ± 3	98 ± 2
Halothane	136 ± 11‡	124 ± 7‡	130 ± 8‡
Pentobarbital	140 ± 10‡	119 ± 13	117 ± 12
SO_2 (%)			
Conscious	95.3 ± 0.3	95.4 ± 0.3	94.6 ± 0.4
Halothane	97.2 ± 0.3‡	96.7 ± 0.4‡	96.8 ± 0.3‡
Pentobarbital	97.5 ± 0.3‡	96.6 ± 0.7‡	96.0 ± 0.9‡
Mixed Venous			
pH			
Conscious	7.37 ± 0.01	7.36 ± 0.01*	7.32 ± 0.01*†
Halothane	7.37 ± 0.01	7.35 ± 0.01	7.32 ± 0.01*†
Pentobarbital	7.40 ± 0.01	7.37 ± 0.01*	7.34 ± 0.01*†
pCO_2 (mmHg)			
Conscious	42 ± 1	41 ± 2	45 ± 1*†
Halothane	41 ± 1	42 ± 1	44 ± 2
Pentobarbital	38 ± 2	41 ± 1	41 ± 2
pO_2 (mmHg)			
Conscious	47 ± 2	43 ± 1	37 ± 2*†
Halothane	49 ± 1	43 ± 2*	38 ± 1*†
Pentobarbital	49 ± 1	41 ± 2*	35 ± 1*†
SO_2 (%)			
Conscious	70.7 ± 1.3	64.6 ± 1.5*	50.2 ± 3.0*†
Halothane	73.2 ± 1.0	63.3 ± 2.3*	53.3 ± 2.5*†
Pentobarbital	74.9 ± 1.5	62.7 ± 1.7*	49.8 ± 1.9*†

* $P < 0.05$ *vs.* no drug; † $P < 0.05$ *vs.* U46619; ‡ $P < 0.05$ *vs.* conscious.

vasoactive and passive (flow-dependent) effects of the various interventions on the pulmonary circulation. These techniques have allowed us to systematically investigate the effects of general anesthesia on neural,[15,16] humoral,[17,18] and local[19,20] mechanisms of pulmonary vascular regulation.

We have previously observed that AVP causes active pulmonary vasoconstriction in conscious dogs in the absence of U46619 preconstriction.[3] In addition, we have observed an AVP-induced pulmonary vasodilator response in conscious dogs after inhibition of AVP V_1 receptors, implying that AVP may cause pulmonary vasodilation *via* activation of V_2 receptors.[4] Consistent with this possibility, Johns has reported that desmopressin, a V_2 receptor agonist, relaxes precontracted rat pulmonary arterial rings.[21] In contrast, Walker and

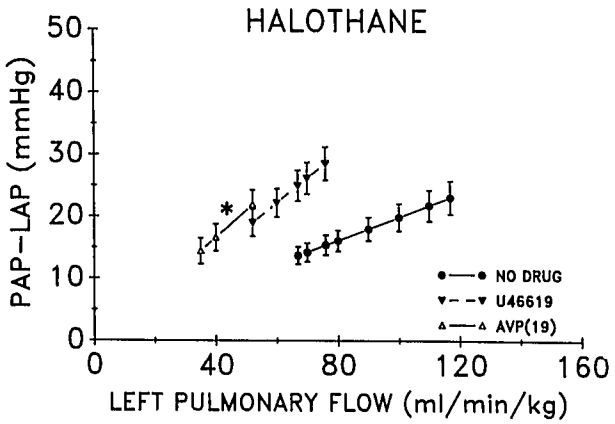

Fig. 3. Composite left pulmonary vascular pressure–flow (LPQ) plots in nine halothane-anesthetized dogs at baseline (no drug), after U46619 preconstriction, and after the intravenous administration of arginine vasopressin (AVP) (19 $ng \cdot kg^{-1} \cdot min^{-1}$). After preconstriction with U46619, this dose of AVP caused pulmonary vasoconstriction (*$P < 0.05$) during halothane anesthesia.

coworkers have reported that AVP has little or no effect on the rat pulmonary circulation at low vasomotor tone[5] but causes pulmonary vasodilation when vasomotor tone is increased with either hypoxia[5] or U46619.[6,7] This pulmonary vasodilator response to AVP is attenuated by V_1 receptor block[6] and by nitric oxide synthase inhibition.[7] Based on these results, these investigators have concluded that AVP-induced pulmonary vasodi-

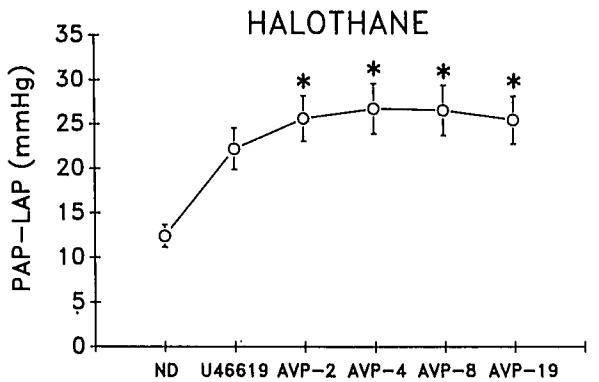

Fig. 4. Values of the pulmonary vascular pressure gradient (pulmonary arterial pressure minus left atrial pressure [PAP–LAP]) at left pulmonary blood flow (LQ) = 60 $ml \cdot min^{-1} \cdot kg^{-1}$ in the no drug (ND) condition, after U46619 preconstriction, and during the cumulative administration ($ng \cdot kg^{-1} \cdot min^{-1}$, intravenous) of arginine vasopressin (AVP) in nine halothane-anesthetized dogs. After U46619 preconstriction, all doses of AVP resulted in pulmonary vasoconstriction (*$P < 0.05$).

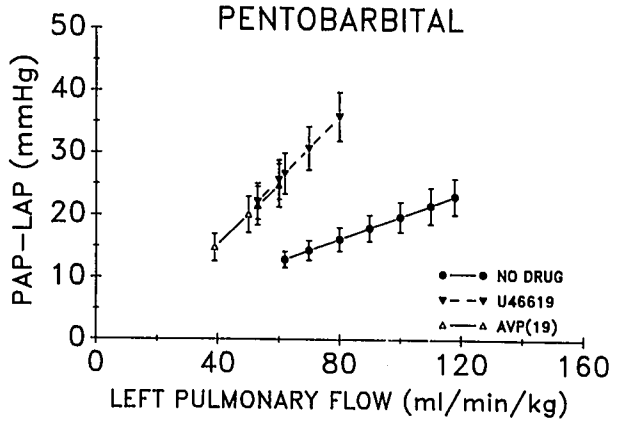

Fig. 5. Composite left pulmonary vascular pressure–flow ($LP\dot{Q}$) plots in seven pentobarbital-anesthetized dogs at baseline (no drug), after U46619 preconstriction, and after the intravenous administration of arginine vasopressin (AVP) (19 $ng \cdot kg^{-1} \cdot min^{-1}$). After preconstriction with U46619, this dose of AVP had no effect on the pulmonary circulation during pentobarbital anesthesia.

lation in the rat results from V_1 receptor activation and the subsequent release of the endothelium-derived relaxing factor, nitric oxide (NO).[7] Jin and colleagues also have observed that AVP causes pulmonary vasodilation in the rat pulmonary circulation preconstricted with hypoxia, and that this response is inhibited by V_1 receptor block.[22–24] These investigators have suggested that the pulmonary vasodilator response to AVP is mediated by the V_1 receptor–activated release of atrial natriuretic peptide, which is known to exert a pulmonary vasodilator influence in the rat.[25,26] We did not investigate the mechanism of AVP-induced pulmonary vasodilation in conscious dogs after U46619 preconstriction in this study. We have previously observed that the pulmonary vasodilator response to AVP in conscious dogs (without preconstriction and in the presence of V_1 receptor block) is not altered by sympathetic β-adrenoreceptor block, cholinergic receptor block or cyclooxygenase pathway inhibition.[4] This indicates that the pulmonary vasodilator response to AVP in that setting is not mediated by β-adrenoreceptor or cholinergic receptor activation or by vasodilator metabolites of the cyclooxygenase pathway. Based on the results of these previous studies, it is possible that the mechanism of AVP-induced pulmonary vasodilation is multifactorial, involving both V_1 receptor–activated release of NO and a direct V_2 receptor–mediated vasodilation.

We have recently reported that halothane anesthesia markedly attenuates the pulmonary vasodilator response to bradykinin.[19] In conscious dogs, the pulmonary vasodilator response to bradykinin is not altered by cyclooxygenase pathway inhibition,[27] but it is abolished by NO synthase inhibition.[11] If AVP-induced pulmonary vasodilation during U46619 preconstriction is mediated by endothelium-derived relaxing factor–NO, as suggested in a study by Russ and Walker,[7] halothane may alter the pulmonary vasodilator response to AVP *via* its inhibitory effects on endothelium-derived relaxing factor–NO. However, it is unlikely that this mechanism is responsible for the effects of pentobarbital anesthesia on AVP-induced pulmonary vasodilation, because pulmonary vasodilation mediated by endothelium-derived relaxing factor–NO is not altered during pentobarbital anesthesia.[19]

Baseline SAP was reduced in both anesthesia protocols. Administration of U46619 increased SAP to conscious values during pentobarbital anesthesia. However, SAP remained significantly lower than conscious values during halothane anesthesia. This effect could have indirectly modified the pulmonary vascular response to AVP during halothane anesthesia (*e.g.*, *via* reflex modulation). Differential changes in blood gases in response to AVP are clearly not responsible for the effects of halothane and pentobarbital anesthesia on the pulmonary vascular response to AVP. The AVP-induced decreases in systemic arterial and mixed venous *p*H, and mixed venous P_{O_2} and S_{O_2} were virtually iden-

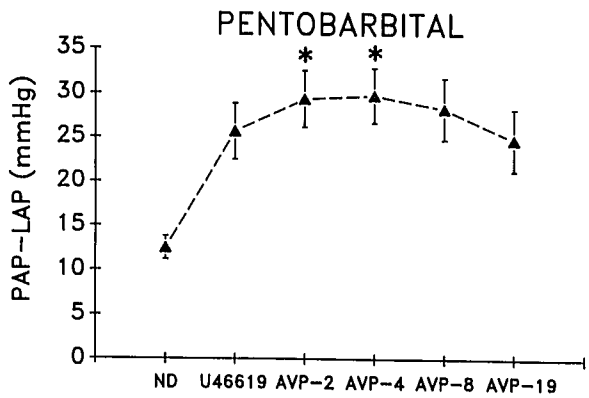

Fig. 6. Values of the pulmonary vascular pressure gradient (pulmonary arterial pressure minus left atrial pressure [PAP–LAP]) at left pulmonary blood flow ($L\dot{Q}$) = 60 $ml \cdot min^{-1} \cdot kg^{-1}$ in the no drug (ND) condition, after U46619 preconstriction, and during the cumulative administration ($ng \cdot kg^{-1} \cdot min^{-1}$, intravenous) of arginine vasopressin (AVP) in seven pentobarbital-anesthetized dogs. After U46619 preconstriction, low doses of AVP resulted in pulmonary vasoconstriction (*$P < 0.05$), and high doses of AVP had no significant effect on the pulmonary circulation.

tical in the conscious and anesthetized states (table 2). The effect of mechanical ventilation during anesthesia on the pulmonary vascular response to AVP is unknown. We attempted to minimize this potential influence by measuring the LP$\dot{Q}$ relation at end-expiration.

Both pentobarbital and halothane had small but statistically significant effects on the baseline (no drug) LP$\dot{Q}$ relation compared with values measured in the conscious state. We have previously reported that pentobarbital had no net effect on the baseline pressure–flow relation,[16] whereas halothane caused active pulmonary vasoconstriction.[12] A major difference between those studies and the current study is our techniques for generating pressure–flow plots. In our earlier work,[12,16] baseline pressure–flow plots were constructed over a 30-min period by step-wise inflation of a hydraulic occluder implanted around the thoracic inferior vena cava, which decreased venous return and cardiac output. This method resulted in a concomitant decrease in SAP to ~50 mmHg during generation of the pressure–flow plot, which led to the activation of a variety of mechanisms (*e.g.*, increased sympathetic adrenoreceptor activity caused by arterial baroreceptor activation) that can modulate the pulmonary circulation. Thus, the "baseline" pressure–flow relation in our earlier studies represented the integrated pulmonary vascular response to several endogenous vasoactive stimuli. The pulmonary vascular responses to pentobarbital and halothane in our previous studies may have involved an effect of the anesthetics on one or more of these endogenous vasoactive mechanisms. In contrast, our current technique for generating pressure–flow plots has little or no effect on systemic hemodynamics, and should not result in sympathetic activation. Consistent with this concept, we have observed minimal or no effect of sympathetic α- and β-adrenoreceptor block on the baseline pressure–flow relation with our current technique,[28] but marked effects of sympathetic adrenoreceptor block on the baseline pressure–flow relation with the inferior vena cava constriction technique.[29]

In conscious dogs, a significant pulmonary vasodilator response to AVP was observed at an infusion rate of 8 $ng \cdot kg^{-1} \cdot min^{-1}$. Based on our previous work,[3] this dose of exogenous AVP should have resulted in a plasma AVP concentration of ~280 pg/ml. We also observed significant pulmonary vasoconstriction in response to AVP at an even lower dose (2 $ng \cdot kg^{-1} \cdot min^{-1}$) during general anesthesia. The changes in plasma AVP achieved in the current study exceed circulating concentrations of AVP associated with dehydration. However, they fall well within the range of plasma AVP resulting from pathophysiologic stimuli (*e.g.*, hemorrhage), in which AVP concentration can exceed 500 pg/ml.

In summary, AVP resulted in active pulmonary vasodilation in conscious dogs after U46619 preconstriction. The AVP-induced pulmonary vasodilator response was either reversed or abolished during halothane and pentobarbital anesthesia. Thus, vasoactive regulation of the pulmonary circulation by this important stress hormone is altered during general anesthesia. This effect has potentially important clinical implications. For example, pulmonary vasomotor tone is increased during cardiopulmonary bypass.[30] Moreover, systemic hypotension associated with cardiopulmonary bypass stimulates the endogenous release of AVP.[31,32] In this setting, the effect of general anesthesia to reverse AVP-induced pulmonary vasodilation to vasoconstriction could have an adverse effect on right ventricular function in an already compromised right ventricle. Finally, this effect of general anesthesia on AVP regulation of the pulmonary circulation must be taken into account in the interpretation of results of experimental studies that use these agents as background anesthetics.

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