Anesthesiology
68:92–99, 1988

Multipoint Pulmonary Vascular Pressure/flow Relationships in Hypoxic and in Normoxic Dogs: Effects of Nitrous Oxide With and Without Cyclooxygenase Inhibition

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The authors investigated the effects of 70% nitrous oxide on overall mean pulmonary artery pressure (MPAP)/cardiac index (CI) relationships in 13 intact pentobarbital anesthetized dogs ventilated alternatively in normoxic (fraction of inspired O_2, FI_{O_2} 0.3) and in hypoxic (FI_{O_2} 0.1) conditions. Five-point MPAP/CI plots were constructed by opening an arterio-venous femoral fistula or by stepwise inflations of a balloon in the inferior vena cava. These MPAP/CI plots were rectilinear in all experimental conditions. Over the entire range of CI studied, 1–5 $l \cdot min^{-1} \cdot m^{-2}$, hypoxia increased MPAP in seven dogs ("responders"), and did not affect MPAP in six other dogs ("nonresponders"). Hypoxic pulmonary vasoconstriction (HPV) was restored in "nonresponders" by administration of 1 g acetylsalicylic acid (ASA) intravenously. In "responders," nitrous oxide partially inhibited HPV. In "nonresponders" with a hypoxic pressor response restored by ASA, nitrous oxide enhanced both normoxic and hypoxic pulmonary vascular tone, and did not affect HPV. These results suggest that pulmonary vascular effects of nitrous oxide depend on preexisting pulmonary vascular tone, and may be modulated by cyclooxygenase products of arachidonic acid metabolism. (Key words: Anesthetics, gases: nitrous oxide. Eicosanoids. Lungs: hypoxic pulmonary vasoconstriction. Sympathetic nervous system.)

HYPOXIC PULMONARY VASOCONSTRICTION (HPV) is an intrapulmonary adaptative mechanism which diverts blood away from hypoxic regions of the lung.[1] Inhalational anesthetics are believed to impair this hypoxic regulation of the distribution of pulmonary perfusion and so contribute to the deterioration of pulmonary gas exchange generally seen during anesthesia.[2]

Nitrous oxide has been shown to inhibit HPV in a variety of *in vitro* and *in vivo* non-intact animal preparations.[3–8] It remains, however, unsettled to what extent these observations can be extrapolated to intact animals, including humans. Nitrous oxide has been reported to inhibit unilateral hypoxia-induced pulmonary blood flow diversion in dogs,[9] and to either augment (in dogs)[10] or to slightly reduce (in newborn lambs)[11] hypoxia-induced increases in pulmonary vascular resistance (PVR).

Calculated PVR as mean pulmonary artery pressure (MPAP) minus pulmonary capillary wedge pressure (PCWP) divided by cardiac output does not, in fact, allow discrimination between active and passive (or flow-dependent) changes in pulmonary arterial pressures.[12–14] The appropriate methodology to evaluate the effects of physiologic and/or pharmacologic interventions on pulmonary vascular tone is to obtain pulmonary arterial pressure measurements at several levels of flow.[12–14]

We, therefore, in the present study, characterized pulmonary arterial pressure/flow relationships in intact pentobarbital-anesthetized dogs to investigate the effects of hypoxia with and without nitrous oxide. We chose this model because pentobarbital does not affect pulmonary hemodynamics.[2,5]

A marked interindividual and interspecies variability is characteristic of HPV.[1] The hypoxic pulmonary pressor response appears to be naturally absent in about 20% of humans,[1] sheep,[15] and also, in our experience, in dogs. Cyclooxygenase inhibition restores HPV in these "nonresponders."[15–17] This is most likely explained by a diversion of arachidonic acid metabolism to its 5-lipoxygenase pathway leading to the generation of vasoconstricting leukotrienes that are no longer opposed by vasodilating prostaglandins.[15–17] Since inhalational anesthetics may stimulate the release of arachidonic acid from cell membranes,[18] we also evaluated the effects of nitrous oxide in dogs with HPV restored after cyclooxygenase inhibition.

Methods and Materials

Thirteen mongrel dogs (22–35 kg, mean 25) were anesthetized with sodium pentobarbital (30 $mg \cdot kg^{-1}$ iv), paralyzed with pancuronium bromide (0.2 $mg \cdot kg^{-1}$ iv), and ventilated (Elema® 900 B Servo-ventilator, Siemens Elema, Solna, Sweden) *via* a cuffed endotracheal tube with inspiratory fraction of O_2 (FI_{O_2}) of 0.3 balance nitrogen, respiratory rate 12 $\cdot min^{-1}$, and tidal volume

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Received from the Respiratory Research Unit and the Departments of Intensive Care and Anesthesiology, Erasme University Hospital, Brussels, Belgium. Accepted for publication August 24, 1987.
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15–20 ml·kg^{-1} adjusted to maintain end-expiratory P_{CO_2} between 30 to 35 mmHg. Pentobarbital 2 mg·kg^{-1} iv and pancuronium 0.2 mg·kg^{-1} iv were repeated hourly to maintain anesthesia and prevent spontaneous respiratory efforts. Throughout the experiment, glucose 5% in saline 0.45% was infused 4 ml·kg^{-1}·h^{-1} *via* the left external jugular vein. Temperature was maintained at 37–38° C by use of an electric heating pad.

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 into a branch of the pulmonary artery, for measurements of pulmonary artery pressure, PCWP, right atrial pressure (RAP), and mixed venous blood sampling. A polyethylene catheter was placed into the abdominal aorta *via* the right femoral artery for systemic blood pressure measurement and arterial blood sampling. A balloon catheter (Percor® 45 Datascope, 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 was inserted into the left femoral artery and vein to act as an arterio-venous fistula. Opening this fistula resulted in an increase in cardiac output. Thrombus formation along the catheters was prevented by sodium heparin 150 u·kg^{-1} iv just before insertion and 50 μ·kg^{-1} repeated every 2 h thereafter.

Pulmonary and systemic artery pressures were measured using Bentley transducers 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 levelled 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 in triplicate by thermodilution using injections of 10 ml of normal saline at 0° C, the 9520-A computer (Edwards Laboratories), and an automated pneumatic pump electronically synchronized on ventilatory cycle. Arterial and mixed venous *p*H, P_{CO_2}, and P_{O_2} were measured immediately after drawing the samples by an automated analyzer (ABL-2, Radiometer, Copenhagen, Denmark) and corrected for temperature. End-expiratory P_{CO_2} was measured with an infrared capnometer (model 47217, Hewlett Packard®, Palo Alto, CA). Body surface area was calculated as 0.112 × weight (kg)$^{2/3}$, m^2.

After ensuring steady-state conditions for 20 min at FI_{O_2} 0.3 (stable mean systemic arterial pressure (BP), MPAP, HR, and end-tidal P_{CO_2}), a five-point MPAP/cardiac index (CI) plot was generated from hemodynamic determinations at baseline (1 point), after opening the femoral arterio-venous fistula (1 point), and after stepwise incremental inflations of the inferior vena cava balloon catheter with occluded fistula (3 points). The same procedure was repeated after 6 min of an acute hypoxic challenge at FI_{O_2} 0.1. The average time to generate a five-point MPAP/CI plot was 25 min.

When hypoxia induced a more than 3-mmHg increase in MPAP at identical CI of 3 l·min^{-1}·m^{-2} ("responders," n = 7 dogs), nitrous oxide (FI_{N_2O} 0.7) was administered and, after 20 min, a sequence of two five-point MPAP/CI plots, at FI_{O_2} 0.3-FI_{N_2O} 0.7 and at FI_{O_2} 0.1-FI_{N_2O} 0.7 balance N_2 successively was then repeated.

When hypoxia did not change MPAP by more than 3 mmHg at identical CI of 3 l·min^{-1}·m^{-2} ("nonresponders," n = 6 dogs), a 1-g iv bolus of acetylsalicylic acid (ASA) was given to restore a hypoxic pressor response.[16] After 45 min, two MPAP/CI plots were constructed as described above successively at FI_{O_2} 0.3 and at FI_{O_2} 0.1 without nitrous oxide. This sequence of two MPAP/CI plots was then repeated with nitrous oxide (FI_{N_2O} 0.7).

Blood gas measurements were performed during each FI_{O_2} at the highest and at the lowest cardiac output, respectively.

Inspection of the individual MPAP/CI plots showed them to be essentially rectilinear and, thus, a least squares regression analysis was used to compute slopes and extrapolated pressure intercepts for each MPAP/CI relationship. To obtain composite MPAP/CI plots for each experimental situation, MPAP interpolated from the regression analysis from individual dogs were averaged at 1 l·min^{-1}·m^{-2} intervals of CI from 1 to 5 l·min^{-1}·m^2, and presented as mean ± SEM. A two-factor analysis of variance for repeated measures was used to assess 1° the effects of hypoxia and of drugs on hemodynamics and on blood gases at the highest and at the lowest CI; 2° the effects of hypoxia and of drugs on MPAP at CI levels from 1 to 5 l·min^{-1}·m^{-2}. If the F-ratio of the analysis of variance reached a $P < 0.05$ level, paired Student's *t* tests were performed to compare two specific situations.[19]

Results

Manipulation of Cardiac Output

Cardiac index was manipulated between values around 1 to 5 l·min^{-1}·m^{-2} (tables 1, 2). The BP/CI relationships were non-linear. The MPAP/CI relationships were linear in all experimental conditions with correlation coefficients ranging from 0.95 to 0.99. Blood gases mainly changed by a decrease in mixed venous P_{O_2} at the lowest CI (tables 3, 4).

TABLE 1. Hemodynamics in Seven Dogs ("Responders") Given Nitrous Oxide in Normoxic and in Hypoxic Conditions

	$F_{I_{O_2}}$ 0.3		$F_{I_{O_2}}$ 0.1	
	Without Nitrous Oxide	With Nitrous Oxide	Without Nitrous Oxide	With Nitrous Oxide
CI ($l \cdot min^{-1} \cdot m^{-2}$)				
Highest CI	4.40 ± 0.40	4.16 ± 0.50	4.28 ± 0.46	5.86 ± 0.45*
Lowest CI	1.08 ± 0.13	1.27 ± 0.16	1.45 ± 0.22	1.39 ± 0.10
HR (beats · min^{-1})				
Highest CI	168 ± 6	149 ± 4	157 ± 7*	173 ± 4*
Lowest CI	174 ± 12	182 ± 11	152 ± 6*	178 ± 9*
BP (mmHg)				
Highest CI	128 ± 6	124 ± 5	145 ± 8	150 ± 12
Lowest CI	87 ± 6	95 ± 8	74 ± 4	89 ± 9
MPAP (mmHg)				
Highest CI	17 ± 2	17 ± 1	24 ± 2*	28 ± 2*
Lowest CI	8 ± 1	9 ± 1	11 ± 1*	12 ± 1*
PCWP (mmHg)				
Highest CI	5 ± 1	8 ± 1*	7 ± 1	8 ± 1
Lowest CI	2 ± 1	2 ± 1	2 ± 1	2 ± 1
RAP (mmHg)				
Highest CI	3 ± 1	5 ± 1*	4 ± 1	5 ± 1
Lowest CI	1 ± 1	2 ± 1	2 ± 1	2 ± 1

Values are expressed as mean ± SEM. Second and third columns are compared to the first. Fourth column is compared to the third.

* Significance of changes ($P < 0.05$).

HYPOXIA

Hypoxia markedly decreased arterial and mixed venous P_{O_2} with no changes in arterial *p*H and P_{CO_2} (tables 3, 4). The only hemodynamic changes were an increase in MPAP and a slight decrease in HR in the "responder" dogs (table 1). Over the entire range of CI studied, MPAP was increased in the seven "responder" dogs and unaffected in the six "nonresponder" dogs (figs. 1, 2).

TABLE 2. Hemodynamics in Six Dogs ("Nonresponders") Given Successively Acetylsalicylic Acid and Nitrous Oxide in Normoxic and in Hypoxic Conditions

	$F_{I_{O_2}}$ 0.3			$F_{I_{O_2}}$ 0.1		
	Without Nitrous Oxide	With Acetylsalicylic Acid	With Nitrous Oxide	Without Nitrous Oxide	With Acetylsalicylic Acid	With Nitrous Oxide
CI ($l \cdot min^{-1} \cdot m^{-2}$)						
Highest CI	3.79 ± 0.37	4.26 ± 0.37	3.27 ± 0.22*	4.24 ± 0.25	4.57 ± 0.25	4.19 ± 0.20
Lowest CI	0.97 ± 0.10	1.18 ± 0.14	0.98 ± 0.07	1.24 ± 0.13	1.28 ± 0.11	0.95 ± 0.08
HR (beats · min^{-1})						
Highest CI	161 ± 14	152 ± 9	138 ± 8	156 ± 13	155 ± 8	161 ± 9
Lowest CI	141 ± 7	158 ± 1	165 ± 12	141 ± 6	148 ± 11	155 ± 9
BP (mmHg)						
Highest CI	123 ± 5	125 ± 4	132 ± 4*	126 ± 5	142 ± 6*	147 ± 7
Lowest CI	62 ± 4	83 ± 11	95 ± 8	62 ± 4	75 ± 10	75 ± 6
MPAP (mmHg)						
Highest CI	15 ± 1	18 ± 1	18 ± 1	17 ± 2	28 ± 2*	30 ± 3
Lowest CI	7 ± 1	8 ± 1	8 ± 1	9 ± 1	12 ± 1*	12 ± 2
PCWP (mmHg)						
Highest CI	6 ± 1	7 ± 1	9 ± 1	7 ± 1	7 ± 1	8 ± 1
Lowest CI	4 ± 1	3 ± 1	3 ± 1	3 ± 1	3 ± 1	4 ± 1
RAP (mmHg)						
Highest CI	4 ± 1	4 ± 1	5 ± 1	4 ± 1	4 ± 1	5 ± 1
Lowest CI	2 ± 1	2 ± 1	1 ± 1	2 ± 1	2 ± 1	2 ± 1

Values are expressed as mean ± SEM. Second and fourth columns are compared to the first. Third column is compared to the second. Fifth column is compared to the fourth. Sixth column is compared to the fifth.

* Significance of changes ($P < 0.05$).

TABLE 3. Blood Gases in Seven Dogs ("Responders") Given Nitrous Oxide in Normoxic and in Hypoxic Conditions

	$F_{I_{O_2}}$ 0.3		$F_{I_{O_2}}$ 0.1	
	Without Nitrous Oxide	With Nitrous Oxide	Without Nitrous Oxide	With Nitrous Oxide
*p*Ha				
Highest CI	7.35 ± 0.02	7.30 ± 0.02*	7.36 ± 0.02	7.31 ± 0.02*
Lowest CI	7.38 ± 0.02	7.31 ± 0.01*	7.35 ± 0.02	7.30 ± 0.02*
Pa_{O_2} (mmHg)				
Highest CI	130 ± 8	142 ± 8	35 ± 1*	33 ± 1
Lowest CI	138 ± 9	135 ± 10	41 ± 1*	39 ± 1
Pa_{CO_2} (mmHg)				
Highest CI	36 ± 1	35 ± 1	33 ± 1*	36 ± 1*
Lowest CI	29 ± 1	32 ± 1	29 ± 1	32 ± 2*
$P\bar{v}_{O_2}$ (mmHg)				
Highest CI	56 ± 2	60 ± 2*	27 ± 2*	26 ± 2
Lowest CI	34 ± 2	39 ± 2*	23 ± 1*	22 ± 2

Values are expressed as mean ± SEM. Second and third columns are compared to the first. Fourth column is compared to the third.

* Significance of changes ($P < 0.05$).

CYCLOOXYGENASE INHIBITION BY ASA

Administration of ASA 1 g iv to the "nonresponders" had no effect at $F_{I_{O_2}}$ 0.3, but increased MPAP and BP (the latter at the highest CI only) at $F_{I_{O_2}}$ 0.1 (tables 2, 4). A pulmonary pressor response was restored by ASA over the entire range of CI studied (fig. 2).

NITROUS OXIDE

In the "responders," the main changes after nitrous oxide were a reduction of arterial *p*H at both $F_{I_{O_2}}$ 0.1 and 0.3, an increase of PCWP and in RAP (at the highest CI), and an increase of the highest CI, HR, and MPAP at $F_{I_{O_2}}$ 0.1 (tables 1, 3). Nitrous oxide did not affect pulmonary vascular tone in normoxia, as well as in hypoxia (fig. 1). The hypoxic pressor response, however, was partially inhibited when expressed as MPAP at $F_{I_{O_2}}$ 0.1 minus MPAP at $F_{I_{O_2}}$ 0.3 at a given CI (fig. 3).

In the "nonresponders" after ASA administration, nitrous oxide reduced the highest CI and increased BP (at the highest CI) in normoxia, but had no effect during hypoxia (tables 2, 4). After nitrous oxide, MPAP increased at the highest CI (from 2 to 5 $l \cdot min^{-1} \cdot m^{-2}$) during normoxia, as well as during hypoxia (fig. 4). The hypoxic pressor response on the other hand was unaffected (fig. 3).

TABLE 4. Blood Gases in Six Dogs ("Nonresponders") Given Successively Acetylsalicylic Acid and Nitrous Oxide in Normoxic and in Hypoxic Conditions

	$F_{I_{O_2}}$ 0.3			$F_{I_{O_2}}$ 0.1		
	Without Nitrous Oxide	With Acetylsalicylic Acid	With Nitrous Oxide	Without Nitrous Oxide	With Acetylsalicylic Acid	With Nitrous Oxide
*p*Ha						
Highest CI	7.37 ± 0.01	7.34 ± 0.01	7.32 ± 0.01	7.36 ± 0.01	7.36 ± 0.01	7.34 ± 0.01
Lowest CI	7.36 ± 0.01	7.40 ± 0.02	7.36 ± 0.02	7.36 ± 0.01	7.35 ± 0.01	7.34 ± 0.02
Pa_{O_2} (mmHg)						
Highest CI	142 ± 10	146 ± 5	151 ± 9	38 ± 1*	35 ± 2	36 ± 1
Lowest CI	140 ± 12	141 ± 10	143 ± 14	41 ± 2*	39 ± 1	43 ± 2
Pa_{CO_2} (mmHg)						
Highest CI	34 ± 1	34 ± 1	36 ± 1	33 ± 1	33 ± 1	35 ± 1
Lowest CI	29 ± 1	30 ± 2	30 ± 2	28 ± 1	30 ± 1	29 ± 2
$P\bar{v}_{O_2}$ (mmHg)						
Highest CI	55 ± 2	57 ± 1	55 ± 1	31 ± 2*	28 ± 1	28 ± 1
Lowest CI	33 ± 2	36 ± 3	35 ± 1	24 ± 1*	24 ± 2	21 ± 1

Values are expressed as mean ± SEM. Second and fourth columns are compared to the first. Third column is compared to the second. Fifth column is compared to the fourth. Sixth column is compared to the fifth.

* Significance of changes ($P < 0.05$).

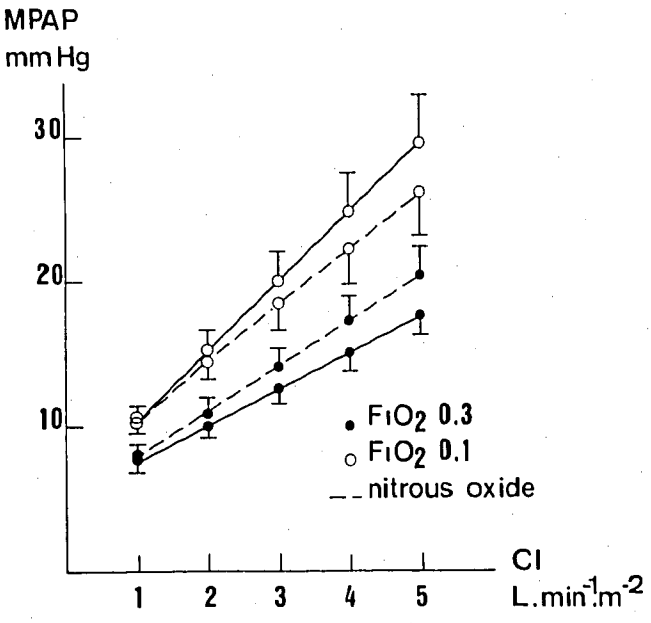

FIG. 1. Composite MPAP (mean ± SEM)/CI plots for seven dogs ("responders") during normoxic and hypoxic conditions before and after 70% nitrous oxide.

Discussion

In the present study, MPAP/CI plots were characterized in intact dogs anesthetized with pentobarbital, paralyzed, and ventilated. Nitrous oxide in this experimental preparation partially inhibited HPV in the animals with a naturally occurring hypoxic pulmonary pressor response. In the animals with a restored hypoxic pulmonary pressor response after cyclooxygenase inhibition by ASA, nitrous oxide did not affect HPV, and increased pulmonary vascular tone in a non FI_{O_2}-dependent manner.

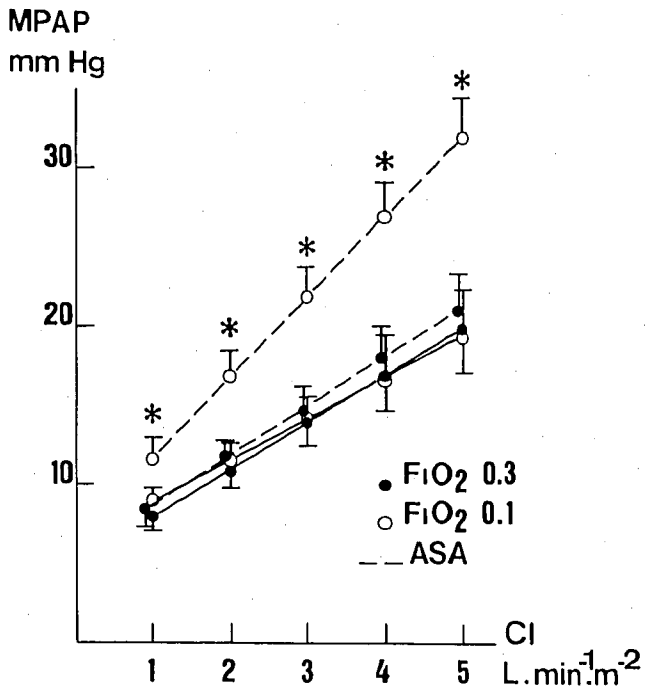

FIG. 2. Composite MPAP (mean ± SEM)/CI plots for six dogs with a weak pressor response to hypoxia ("nonresponders") during normoxic and hypoxic conditions before and after acetylsalicylic acid (ASA) 1 g iv. *$P < 0.05$ FI_{O_2} 0.1 (with drug) *versus* FI_{O_2} 0.1 (without drug).

Pulmonary vascular tone in intact animals and in humans commonly is evaluated by PVR calculated as MPAP minus PCWP (assumed equal to left atrial pressure) divided by cardiac output. This approach is misleading in many clinical and experimental circumstances.[12-14] In isolated lungs, the MPAP/flow relationship is rectilinear over a physiologic range of flows, but becomes curvilinear when flow is very low with a convexity to the pressure axis.[13,20] The extrapolation of the linear part of such curves has a positive pressure intercept corresponding to the closing pressure of the pulmonary vessels.[13,20] In normoxic recumbant intact conscious dogs[14] and in humans,[21] the MPAP/cardiac output plots are linear and the extrapolation of MPAP-PCWP/cardiac output plots passes through the origin, suggesting that closing pressure is exceeded by left atrial pressure as assessed by PCWP.[20] Hypoxia, a variety of diseases, and pharmacologic interventions are capable of affecting the slopes and the pressure intercepts of PAP/flow relationships.[12-14,21] When closing pressure is greater than PCWP and flow varies, the discrimination between active and passive (or flow-dependent) changes in PAP cannot be obtained by single PVR calculations. A correct appreciation of pulmonary hemodynamics then obviously requires measurements of pulmonary vascular pressures at several levels of flow.[12-14]

The MPAP/CI plots in our dogs were rectilinear in all experimental conditions, in keeping with studies on isolated lungs[13,20] and on intact conscious[14] or pentobarbital-anesthetized[17,22] dogs. Individual pressor responses to hypoxia consisted of variable increases in MPAP that were greatest at the highest CI studied, in agreement with reports of increased slopes and/or pressure intercepts of MPAP/flow plots in isolated lungs[23] and in intact conscious[14] or anesthetized[17,22] dogs. The magnitude of the hypoxia-induced increases in MPAP was comparable to reported observations in intact conscious dogs.[14]

Repetition of hypoxic exposures has been shown either to enhance[24,25] or not to affect[26,27] HPV. We have previously shown that, in our experimental preparation, a sequence of alternated normoxic (FI_{O_2} 0.4) and hypoxic (FI_{O_2} 0.1) MPAP/CI plots is reproducible up to two times without change in MPAP at each level of flow.[22] Explanations for reported initial blunting of HPV with subsequent recovery may be a transient re-

lease of vasodilating prostaglandins by surgical trauma to the lungs[26,28] or by small amounts of circulating endotoxin from nonsterile catheterization.[28] We also previously showed that, in our experimental preparation, no decay of the hypoxic pressor response occurred during 25–30-min periods needed for the construction of five-point MPAP/CI plots.[17]

The use of an *in vivo*-intact animal model allows the expression of many potential control mechanisms that contribute to the regulation of the pulmonary circulation. Changes in *p*H,[29] mixed venous P_{O_2},[30] neurohumoral activity,[31] and activation of the baroreflex[32] could have influenced pulmonary vascular tone along with the manipulations of blood flow. Therefore, MPAP/CI plots probably represent an integrated response of the intact pulmonary vasculature to a variety of vasoactive stimuli, rather than truly passive pressure/flow relationships.[31] The lungs of our dogs probably were predominantly in zone III before the stepwise inflations of the inferior vena cava balloon which progressively induced an increased proportion of zone II. Left atrial pressure was not kept constant, and, also, would not correctly be assessed by PCWP determinations at all levels of flow.[14,33] These methodological limitations inherent to the experimental model led us to analyze the changes in MPAP (rather than MPAP-PCWP) at the different levels of flow instead of comparing slopes (taken as incremental resistances) and extrapolated pressure intercepts (taken as averaged critical closing pressures) of the MPAP/CI lines.

In the present experiment, pulmonary vascular pressures were referenced to atmospheric pressure, without taking into account possible drug- or model-induced intrathoracic pressure changes. However, both hypoxia and generation of pressure/flow plots by inferior vena cava constriction have been shown not to affect pleural pressure as measured by the esophageal-balloon technique in conscious dogs.[14] Moreover, it seems reasonable to consider that only very small changes in intrathoracic pressure would be expected after acetylsalicylic acid or nitrous oxide administration in our anesthetized paralyzed and ventilated intact dogs.

The hypoxic pressor response is naturally absent in a certain proportion of humans,[1] sheep,[15] and dogs.[16,17] Administration of drugs that inhibit cyclooxygenase restores HPV in these "nonresponders."[15–17] In the present study, the remarkable difference between responders and non-responders supports the hypothesis that pulmonary vascular reactivity to hypoxia may be regulated by balanced actions of vasoconstricting leukotrienes and vasodilating prostaglandins.[15–17]

Nitrous oxide has little effect on normoxic pulmonary vascular tone in anesthetized dogs or in isolated cat lungs,[4,34–36] but has recently been shown to increase

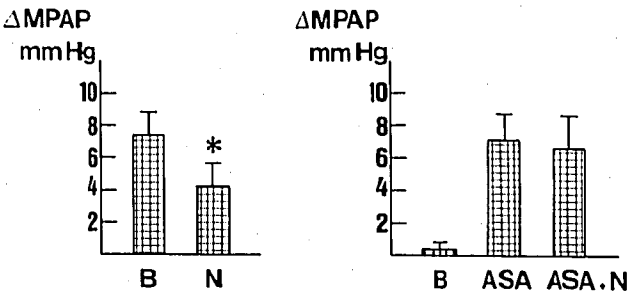

FIG. 3. Mean ± SEM ΔMPAP (MPAP at FI_{O_2} 0.1–MPAP at FI_{O_2} 0.3) for a normalized CI of 3 $l \cdot min^{-1} \cdot m^{-2}$ in seven dogs ("responders") before nitrous oxide (B) and after nitrous oxide (N), and in six dogs ("nonresponders") before nitrous oxide (B), after acetylsalicylic acid (ASA), and after nitrous oxide (N). $P < 0.05$ N *versus* B (left panel).

PVR in awake newborn lambs.[11] Conflicting data have been reported regarding the pulmonary hemodynamic effects of nitrous oxide in humans.[37–41] Some of this variability may be due to the different combinations with other anesthetics and to the presence or absence of preexisting pulmonary hypertension.[38] On the other hand, with the exception of one study,[10] nitrous oxide has consistantly been reported to inhibit HPV,[3–9] and this was also observed in the present experiments on dogs with a hypoxic pressor response ("responders").

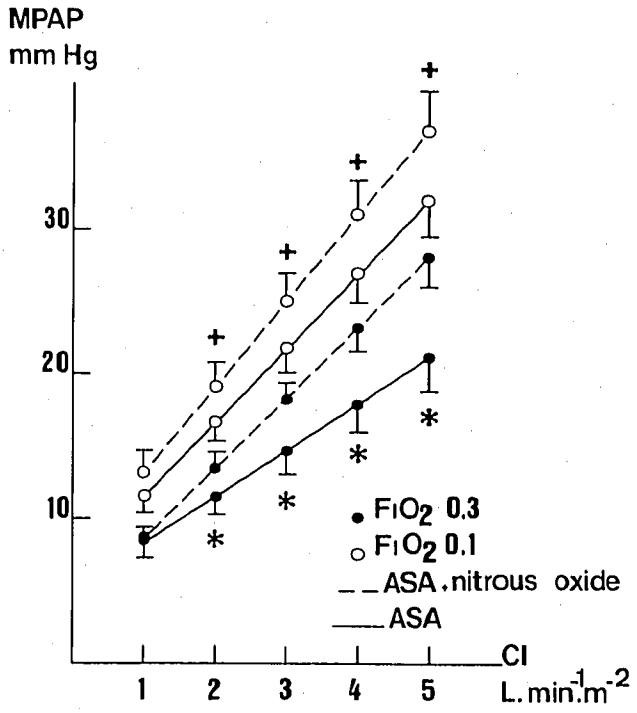

FIG. 4. Composite MPAP (mean ± SEM)/CI plots for six dogs with a restored pressor response to hypoxia ("nonresponders") given acetylsalicylic acid (ASA) 1 g iv) during normoxic and hypoxic conditions before and after 70% nitrous oxide. $^*P < 0.05$ FI_{O_2} 0.3 (without nitrous oxide) *versus* FI_{O_2} 0.3 (with nitrous oxide) $^+P < 0.05$ FI_{O_2} 0.1 (with nitrous oxide) *versus* FI_{O_2} 0.1 (without nitrous oxide).

Vasoconstricting effects of nitrous oxide can be reversed by the administration of the α-blocker phentolamine,[41] suggesting that the sympathetic nervous system may be involved in the hemodynamic effects of this agent. Nitrous oxide has been shown to increase sympathetic outflow from the brain,[42] to inhibit removal of norepinephrine by the lung,[43] and to increase norepinephrine release by nerve endings in a dog pulmonary artery preparation.[44] Murray *et al.*[31] reported that neural antagonists regulate pulmonary vascular pressure/flow relationships in conscious dogs, and that the net effect of the autonomic nervous system during normoxia appears to be pulmonary vasodilation (βeffect). The slight but non-significant changes in pulmonary vascular tone induced by nitrous oxide in the "responders" (vasoconstriction during normoxia and vasodilation during hypoxia) could be due to the increase in circulating and locally released catecholamines. Pulmonary vasoactive properties of catecholamines, indeed, are known to be dependent on the preexisting level of vascular tone.[22,45,46]

Inhaled anesthetics have been reported to stimulate the release of arachidonic acid from cell membranes.[18] In our "nonresponders" treated with ASA, enhanced hypoxic pulmonary vascular tone by nitrous oxide could be explained by an increased generation of vasoconstrictor leukotrienes from increased amounts of precursor available.

In conclusion, the pulmonary vascular effects of nitrous oxide are probably too slight to be of clinical relevance. Inhibition of HPV by nitrous oxide is probably not a mechanism of hypoxemia during anesthesia.

The authors gratefully acknowledge the technical assistance of Marie-Thérèse Gautier.

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