Sub-MAC concentrations of desflurane do not inhibit hypoxic pulmonary vasoconstriction in anesthetized piglets

[La vasoconstriction pulmonaire hypoxique n'est pas inhibée par des concentrations de desflurane inférieures à la CAM chez des porcelets anesthésiés]

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Purpose: *In vitro*, halogenated agents reduce the pulmonary vasoconstrictor response to alveolar hypoxia in isolated perfused lungs. However, studies in intact animals have been less convincing. The aim of the present study was to assess the effect of sub-MAC concentrations of desflurane on hypoxic pulmonary vasoconstriction (HPV) in anesthetized piglets using the pressure/cardiac output relationship (P/Q).

Methods: Eleven large white piglets were anesthetized and ventilated mechanically, alternatively in hyperoxia (FiO_2=0.4) and in hypoxia (FiO_2=0.12). Multipoint plots of pulmonary arterial pressure (PAP), or differences between PAP and left atrial pressure (LAP) against Q were generated by gradual inflation of a balloon advanced into the inferior vena cava. P/Q relationships were established in hyperoxia and in hypoxia at baseline, and then with gradual concentrations of desflurane.

Results: In hypoxia, pressure gradients (PAP-LAP) increased significantly at every level of Q, demonstrating active pulmonary vasoconstriction. Desflurane did not affect these P/Q relationships either in hyperoxia, or in hypoxia, when compared with baseline.

Conclusion: Desflurane at a clinically relevant dose has no significant effect on HPV in anesthetized piglets.

Objectif: *La plupart des agents halogénés dont le desflurane inhibent la vasoconstriction pulmonaire hypoxique (VPH) sur le poumon isolé de mammifère. Le but de cette étude est d'évaluer les effets de cet halogéné sur la VPH du porc entier anesthésié, au moyen de la relation pression vasculaire trans-pulmonaire (PAP-POG)/débit cardiaque (Q).*

Matériel et méthodes: *Onze porcs (poids moyen 26 ± 4 kg) ont été inclus, après accord de la Commission d'éthique animale. Après prémédication, et anesthésie iv standardisées, ils ont été équipés d'une pression invasive artérielle fémorale, d'une sonde dans l'artère pulmonaire et d'une pression intra auriculaire G (POG) afin de déterminer les relations (PAP-POG)/débit Q. Le gradient PAP-POG) et le débit Q ont été mesurés durant le gonflement graduel d'un ballon intra-cave destiné à modifier le débit Q. Ces relations (PAP-POG)/Q ont été étudiées en hyperoxie (FiO_2: 0,4) et en hypoxie (FiO_2: 0,12), sans desflurane puis avec desflurane à des concentrations expirées de 2,5 et 5%. Pour chaque relation pression/débit, une équation de régression a été calculée. Une ANOVA pour mesures répétées et un test de Bonferroni ont été utilisés afin de déterminer l'effet du desflurane sur la relation (PAP-POG)/Q.*

Résultats: *En hypoxie, la pente des relations pression/débit a augmenté de façon significative, et ce pour chaque variation de Q mettant ainsi en évidence un phénomène de VPH active. Le desflurane n'a pas eu d'effet significatif sur les relations (PAP-POG)/Q en hyperoxie, ni en hypoxie.*

Conclusion: *Contrairement aux études in vitro, le desflurane n'inhibe pas, de façon significative la VPH du porc entier anesthésié.*

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PULMONARY vasoconstriction in response to acute hypoxia helps maintain arterial oxygen tension.[1] Impairment of this mechanism by inhalational anesthetic agents has been implicated in hypoxemia during anesthesia.[2] *In vitro* studies have demonstrated that halothane, enflurane, isoflurane and sevoflurane inhibit hypoxic pulmonary vasoconstriction (HPV).[3,4] However halogenated agents seem to be less effective pulmonary vasodilators in *in vivo* lung lobes.[5–7]

Desflurane is a recently introduced inhalational anesthetic. Its effects on HPV have been the focus of a few studies. *In vitro* experiments using constant-flow perfused rabbit lung confirmed concentration-dependent inhibition of vasoconstriction by desflurane.[8] Another study, in intact chronically instrumented animals, showed that desflurane did not inhibit HPV.[9]

The present study was designed to assess the effect of two sub-MAC concentrations of desflurane on HPV in intact anesthetized piglets. Piglets where chosen as the study model because of their strong pulmonary vasoconstriction in response to hypoxia,[10] and because their postnatal morphometric pulmonary development closely parallels that of humans.[11] Pulmonary hemodynamics were evaluated by multipoint pulmonary vascular pressures –flow plots (P/Q plots) which provide a quantitative characterization of the pulmonary vascular pressure (P)-cardiac output (Q) relationship.[6,7] Previous experiments have demonstrated that these plots are linear in intact anesthetized piglets.[12]

Material and methods

All experimental procedures were reviewed and approved by the Animal Ethics Committee of La Timone Medical School in Marseille. All procedures were compliant with the *Guiding Principles in the Care and Use of Animals of the American Physiological Society.*

Animal preparation

After a 12-hr fasting period with free access to water, 11 large white piglets (22–30 kg, mean 24 kg) were premedicated with ketamine (20 $mg \cdot kg^{-1}$ *im*), midazolam (0.1 $mg \cdot kg^{-1}$ *im)*, and atropine (0.25 mg *im*), and placed in the supine position. Anesthesia was induced with midazolam (0.1 $mg \cdot kg^{-1}$ *iv*) fentanyl (2 $\mu g \cdot kg^{-1}$ *iv*) and maintained with *iv* infusions of fentanyl (20 $\mu g \cdot kg^{-1} \cdot hr^{-1}$) and midazolam (0.1 $mg \cdot kg^{-1} \cdot hr^{-1}$). Muscle paralysis was achieved with vecuronium bromide 1 $mg \cdot kg^{-1}$ *iv* and maintained with an infusion of vecuronium bromide (2 $mg \cdot kg^{-1} \cdot hr^{-1}$) after tracheostomy had been performed. Lungs were ventilated mechanically via a n6 cuffed tracheostomy tube (Tracheosoft Lanz™ 101-70 ID 6.0 Malindkrodt Medical, Athlone Ireland) with a Servo ventilator B 900 (Siemens, Elema, Sweden) initially set to deliver a FIO_2 of 0.4, a tidal volume of 12–15 $mL \cdot kg^{-1}$ and a respiratory rate adjusted to maintain an arterial $PaCO_2$ between 35 and 40 mmHg. No positive end-expiratory pressure was used. Desflurane was administered using a vaporizer adapted to the ventilator. Inspired and expired fractions of O_2, CO_2 and desflurane were measured using an infrared spectrophotometer Ultima II™ (Datex, Helsinki, Finland).

Throughout the experiment, 0.9% sodium chloride was infused in the left internal jugular vein at a rate of 4 $mL \cdot kg^{-1} \cdot hr^{-1}$. Temperature was maintained at 38–39°C using an electrical heating pad. Metabolic acidosis, when present, was corrected by slow infusion of triaminolacetate (THAM™, Roger Bellon Laboratories, France). All catheters were inserted through peripheral cut-downs.

A thermistor-tipped pulmonary artery catheter (93A-131-7F, Edwards Laboratories, Santa Anna CA, USA) was inserted in the right internal jugular vein, positioned with reference to the right atrium and used to measure right atrial pressure (RAP), mean pulmonary arterial pressure (PAP) and mean capillary wedge pressure (PCWP). It was also used to measure central core temperature and perform mixed venous blood sampling. A polyethylene catheter was placed in the abdominal aorta via the right femoral artery for systemic arterial pressure (SAP) measurements and arterial blood sampling. A balloon catheter (Redigard™, 9F 40 mL, St Jude Medical Inc., Chelmsford MA, USA) was placed in the inferior vena cava (IVC) through a right femoral venotomy. Inflation of this balloon produced a graduable decrease in cardiac output by reducing venous return.

A left thoracotomy was performed to place, into the left atrium, a polyethylene catheter (Liddle LAP 17 G 50.6 cm, Research Medical Inc. Salt Lake City UT, USA) to monitor left atrial pressure (LAP). The thoracotomy was closed hermetically and a chest tube (Argyle 24) inserted in the pleural space, connected to a vacuum-pump and then to a water seal as soon as vacuum was achieved. Thrombus formation along the catheters was prevented by heparin sodium (100 $iu \cdot kg^{-1}$ *iv*) just before insertion and a continuous infusion of 100 $iu \cdot kg^{-1} \cdot hr^{-1}$.

Measures

Pulmonary, cardiac and systemic pressures were measured using disposable transducers (Pressure monitoring kit Baxter S.A., Maurepas, France) connected to a multichannel monitor (Merlin™, Hewlett-Packard Inc.,

TABLE I Effects of gradual concentrations of desflurane on hemodynamic data

	Q	FIO_2 0.4			FIO_2 0.1		
		baseline	*des 2.5%*	*des 5%*	*baseline*	*des 2.5%*	*des 5%*
Q,L·min^{-1}	H	3.0 ± 0.2	3.3 ± 0.2	3.1 ± 0.1	3.2 ± 0.2	3.5 ± 0.2	3.3 ± 0.2
	L	1.6 ± 0.1*	1.8 ± 0.1$^{*\$}$	1.8 ± 0.1*	1.7 ± 0.1*	1.9 ± 0.2*	1.8 ± 0.1*
HR, beats·min^{-1}	H	106 ± 6	131 ± 11$^{\$}$	129 ± 7$^{\$}$	118 ± 15	138 ± 8$^{\#\$}$	153 ± 5$^{\#\$}$
	L	151 ± 10*	146 ± 11*	153 ± 10*	154 ± 9*	162 ± 11*	161 ± 9
SAP, mmHg	H	135 ± 7	108 ± 8$^{\$}$	96 ± 5$^{\$}$	128 ± 10	103 ± 7$^{\$}$	84 ± 4$^{\$}$
	L	78 ± 6*	66 ± 6.$^{*\$}$	56 ± 2$^{*\$}$	72 ± 10*	60 ± 4$^{*\$}$	52 ± 3$^{*\$}$
PAP, mmHg	H	20 ± 1	20 ± 1	20 ± 1	36 ± 1$^{\#}$	36 ± 2$^{\#}$	34 ± 2.$^{\#}$
	L	13 ± 1*	13 ± 1*	14 ± 1*	20 ± 2$^{*\#}$	21 ± 1.$^{*\#}$	20 ± 1$^{*\#}$
LAP, mmHg	H	8 ± 1	8 ± 1	9 ± 1	9 ± 1	9 ± 1	9 ± 1
	L	6 ± 1*	6 ± 1*	7 ± 1*	7 ± 1*	7 ± 1*	7. ± 1*
RAP, mmHg	H	7 ± 1	7 ± 1	7 ± 1	7 ± 1	7 ± 1	8 ± 1
	L	6 ± 1	6 ± 1	6 ± 1	6 ± 1	6 ± 1	7 ± 1
PCWP, mmHg	H	10 ± 1	10 ± 1	10 ± 1	12 ± 1$^{\#}$	11 ± 1$^{\#}$	11 ± 1$^{\#}$
	L	7 ± 1*	8 ± 1*	8 ± 1*	8. ± 1$^{*\#}$	9 ± 1$^{*\#}$	8. ± 1$^{*\#}$

Values are means ± SD; *n*=11 piglets. HQ and LQ=highest and lowest cardiac output respectively. HR=heart rate; SAP= systolic systemic arterial pressure; PCWP=mean capillary wedge pressure; LAP and RAP=mean left and right atrial pressure respectively. Significant difference (P <0.05) between $ column 2, 3 *vs* 1 and 5, 6 *vs* 4; # column 1 *vs* 4, 2 *vs* 5, 3 *vs* 6 at the same level of Q; * between HQ and LQ.

TABLE II Slopes and correlation coefficients of the composites P/Q plots

	FIO_2	*PAP*	*PAP-LAP*	*PAP-PCWP*
Baseline				
Slope (mmHg·L^{-1}·m)	0.4	5.1 ± 0.8	3.4 ± 0.7	2.8 ± 0.7
	0.1	11.5 ± 0.2*	10.1 ± 1.1*	9.4 ± 1.3*
r^2	0.4	0.89	0.94	0.82
	0.1	0.96	0.98	0.93
Desflurane 2.5%				
Slope (mmHg·L^{-1}·min^{-1})	0.4	5.3 ± 0.9	3.1 ± 0.4	3.6 ± 0.7
	0.1	11 ± 0.9*	9.8 ± 2.1*	9.4 ± 2.0*
r^2	0.4	0.91	0.94	0.87
	0.1	0.93	0.93	0.93
Desflurane 5%				
Slope (mmHg·L^{-1}·min^{-1})	0.4	4.2 ± 0.4	2.5 ± 0.4	2.5 ± 0.5
	0.1	9.7 ± 1.1*	7.3 ± 1.2*	7.8 ± 0.8*
r^2	0.4	0.95	0.93	0.81
	0.1	0.94	0.94	0.92

Slopes and correlation coefficients r^2 of the composites P/Q plots in hyperoxia (FIO_2 0.4), in hypoxia (FIO_2 0.12) at baseline, and with desflurane. Values are means ± SD, *n*=11 piglets.

*P <0.01 for comparison of slope at FIO_2 0.4 *vs* slope at FIO_2 0.12 in the same step.

#P <0.05 for comparison of slopes at different steps at the same FIO_2.

Palo Alto CA, USA). Zero reference was located at midchest, and readings were taken at the end of expiration. Heart rate (HR) was determined continuously by the same monitor with three electrocardiographic leads. Cardiac output was measured rapidly at the end of expiration by thermodilution using injections of 5 mL of 0.9 % sodium chloride at 0°C. Cardiac output values correspond to the mean of at least three measurements after elimination of readings 10% higher or lower than the previous value. Hemodynamic data were sampled every 20 sec, digitized and stored on the hard disk of a personal IBM PC/AT (Hewlett Packard Vectra 386 DX 33 and Hewlett Packard software). Arterial and mixed venous pH, PCO_2, PO_2 were measured immedi-

TABLE III Effects of desflurane

	Q	baseline	FIO_2 0.4 des 2.5%	des 5%	baseline	FIO_2 0.1 des 2.5%	des 5%
pHa	H	7.47 ± 0.02	7.44 ± 0.02	7.44 ± 0.01	7.43 ± 0.02	7.45 ± 0.02	7.46 ± 0.01
	L	7.48 ± 0.02	7.46 ± 0.02	7.48 ± 0.01	7.44 ± 0.02	7.46 ± 0.01	7.47 ± 0.01
PAO_2, mmHg	H	193.5 ± 11.7	170.9 ± 6.4	169.1 ± 6.5	42.0 ± 1.0#	45.7 ± 1.2#	44.9 ± 0.9#
	L	187.3 ± 6.5	183.0 ± 12.0	167.9 ± 17.1	47.2 ± 2.0#	47.5 ± 1.5#	48.5 ± 1.7#
$PACO_2$, mmHg	H	37.5 ± 1.4	39.6 ± 0.9	39.0 ± 0.6	40.2 ± 1.2	39.2 ± 1.0	39.4 ± 1.0
	L	34.2 ± 1.5	36.4 ± 1.0*	36.0 ± 1.1	37.5 ± 2.0	36.0 ± 0.6*	36.7 ± 2.0
PVO_2, mmHg	H	41.4 ± 1.2	41.4 ± 1.6	38.7 ± 0.9	25.5 ± 1.0#	25.7 ± 1.1#	27.3 ± 1.0#
	L	30.0 ± 1.3*	29.5 ± 1.9*	26.4 ± 1.4*	22.6 ± 1.3*#	22.2 ± 0.6*#	23.7 ± 0.8*

Values are means ± SD; *n*=11 piglets. HQ and LQ=highest and lowest cardiac output respectively. Significant difference (P <0.05) between $ column 2, 3 *vs* 1 and 5, 6 *vs* 4; # column 1 *vs* 4, 2 *vs* 5, 3 *vs* 6 same level of Q; * between HQ and LQ.

ately after drawing the samples using an automated analyzer (ABL 500, Radiometer, Copenhagen, Denmark); all blood gases values were corrected according to central temperature.

Protocol

After ensuring steady-state conditions for ten minutes at an FIO_2 of 0.4 (stable SAP, PAP, LAP, Q, end-tidal CO_2, and HR), a first four-point P/Q plot was generated in 20 min: the first point corresponding to basal cardiac output followed by one point for each incremental inflation of the vena cava balloon (three points). Construction of each point of the plot lasted five minutes. Then, a similar plot was constructed at an FIO_2 of 0.12 when PaO_2 reached 40–50 mmHg. Previously reported stimulus-response curves for HPV in intact anesthetized ventilated piglets show that the whole-lung hypoxic pressor response is undetectable if FIO_2 is >0.3 and maximal when FIO_2 is 0.12.[13] Similar plots were generated at FIO_2 0.4 and at FIO_2 0.12 with respectively 2.5% and 5% end-tidal desflurane concentrations. At each step of the study and for each level of Q, measures of hemodynamic parameters (SAP, LAP, RAP, PCWP, PAP, HR), arterial and mixed venous blood gases were performed. Repeated exposure to hypoxia was performed to make sure that the magnitude of HPV was constant throughout the experiment. Animals were humanely sacrified at the end of the protocol by *iv* infusions of midazolam (20 mg), fentanyl (500 µg) and KCl 10% (3 g).

Statistical analysis

Visual inspection of the individual PAP/Q, PAP-LAP/Q and PAP-PCWP/Q plots showed them to be linear, and thus a linear regression analysis (least square method) was used to compute slopes. Q was considered to be the independent variable and pressure the dependent variable. To obtain composite P/Q plots, pressures interpolated from the regression analysis from individual piglets were averaged at 0.5 $L \cdot min^{-1}$ intervals of Q from 1.5 to 3.5 $L \cdot min^{-1}$. The blood gases and hemodynamic data were analyzed by analysis of variance for serial measurements. When the significance of a factor was P <0.05, a Bonferroni post-hoc test was performed to compare specific situations. Comparison of slopes of composites P/Q plots were assessed by Student's t test. Data are presented as means ± SD. All analyses were performed with Statview 4™ software Abacus concept) on a Macintosh™ Power PC 6200/75 personal computer.

Results

Manipulation of cardiac output

Stepwise inflations of the IVC balloon induced variations of Q. Mean values ranged from 1.6 to 3.5 $L \cdot min^{-1}$ (Table I). The PAP/Q, PAP-LAP/Q and PAP-PCWP/Q relationships were linear in all experimental conditions (Table II). Blood gases mainly changed by a decrease in mixed venous PO_2 at the lowest Q (Table III).

Baseline values in hyperoxia and hypoxia

Hypoxia markedly decreased arterial and mixed venous PO_2 with no change in pH and $PaCO_2$ (Table II). SAP, LAP, RAP and PCWP were the same in hypoxic and hyperoxic conditions. Over the full range of Q studied, hypoxia increased PAP (P <0.01), while it induced a significant increase in HR for the lowest Q. The main sign of hypoxic pressor response was a significant increase in the slopes of PAP/Q, PAP-LAP/Q and PAP-PCWP/Q relationships (Table II).

Desflurane in hyperoxia

End tidal 2.5% and 5% desflurane significantly increased HR and significantly reduced SAP compared with baseline (P <0.05), whereas PAP, LAP, RAP, PCWP were unchanged. At the lowest Q, desflurane decreased SAP significantly when compared to baseline (P <0.05).

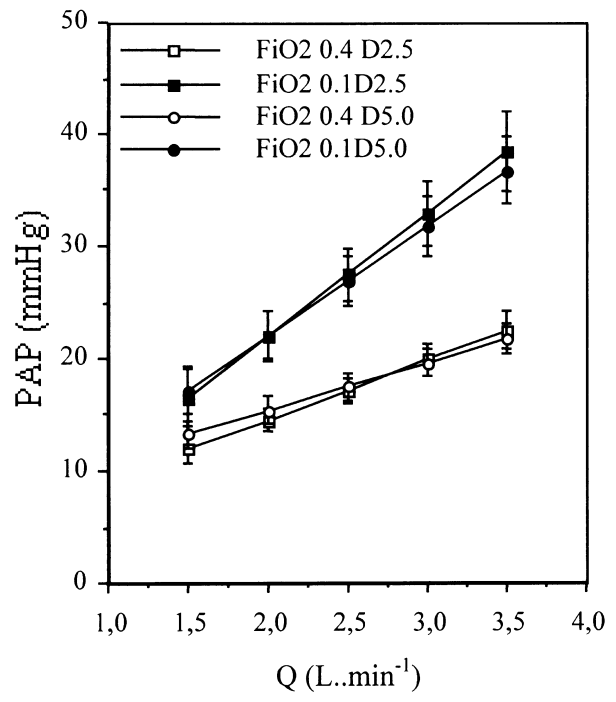

FIGURE 1 Extrapolated plots of PAP *vs* cardiac output (Q) with 2.5% end tidal desflurane in hyperoxia (open squares) and in hypoxia (closed squares), with 5% end tidal desflurane in hyperoxia (open circles) and in hypoxia (closed circles). Values are means ± SEM, *n*=11 piglets.

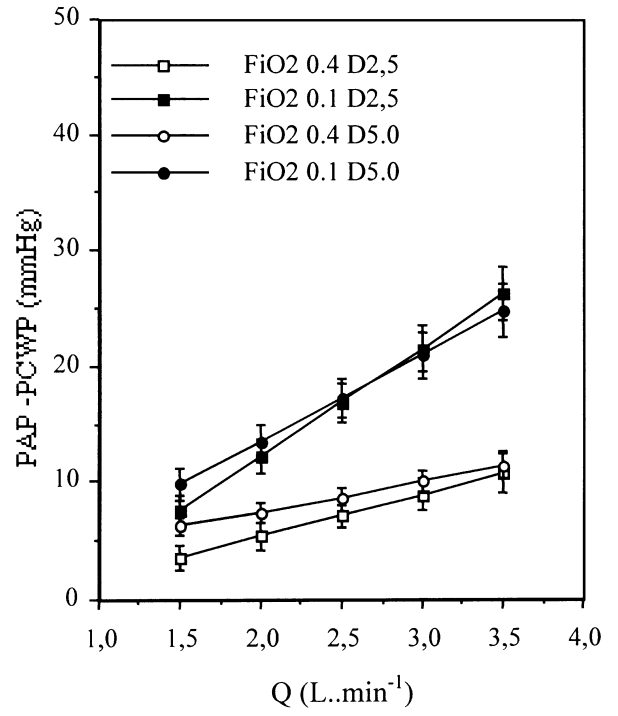

FIGURE 2 Extrapolated plots of PAP - PCWP *vs* cardiac output (Q) with 2.5% end tidal desflurane in hyperoxia (open squares) and in hypoxia (closed squares), with 5% end tidal desflurane in hyperoxia (open circles) and in hypoxia (closed circles). Values are means ± SEM, *n*=11 piglets.

Desflurane in hypoxia

At the highest Q, end tidal 2.5% and 5% desflurane increased HR and significantly reduced SAP compared with baseline. PAP, LAP and PCWP were unchanged (Table I). At lowest Q, desflurane significantly reduced SAP. HPV was not inhibited by 2.5% and 5% end tidal desflurane (Figure 2).

Desflurane had no effect on PaO_2, pHa, PvO_2, $PaCO_2$ at highest Q. At the lowest Q, there was a mild decrease of PvO_2 compared with the highest Q.

Discussion

The present study was designed to assess the effect of two sub-MAC concentrations of desflurane on HPV in intact piglets. P/Q plots were generated in 11 piglets anesthetized with midazolam, fentanyl and ventilated mechanically. Desflurane at a clinically relevant dose induced a marked systemic vasodilation (decrease in SAP with an unchanged Q), but HPV was unaffected by this anesthetic agent. The end tidal concentrations of desflurane studied are equivalent to 0.3 and 0.6 MAC in pigs.[13] Higher concentrations are required to induce a relevant effect on HPV in isolated lung.[8] This concentration was chosen because a higher concentration (1 MAC) induced a vigorous systemic hypotension in piglets. Also, it is equivalent to that used in the clinical settings when in combination with opiates.[14] Opioids are known to reduce the anesthetic requirement (determined by reduction of MAC) in both animals[15] and humans. One study showed a reduction in the MAC of desflurane of approximately 49% after a single dose of fentanyl (3 $\mu g \cdot kg^{-1}$ *iv*).[14]

A previous *in vitro* study had demonstrated that desflurane inhibits HPV in a dose related manner, in constant flow perfused rabbit lung.[8] To our knowledge, only one study has assessed the effects of desflurane on HPV in chronically instrumented and unsedated dogs,[9] and no previous experiment had been performed in anesthetized piglets.

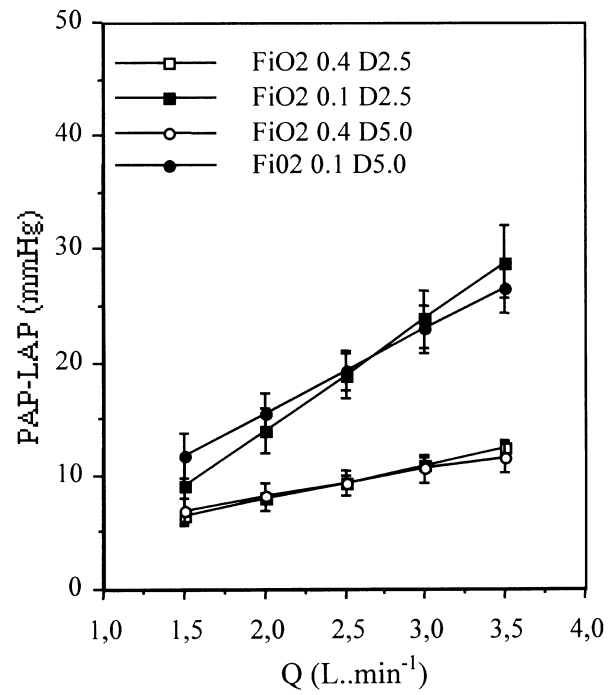

FIGURE 3 Extrapolated plots of PAP - LAP *vs* cardiac output (Q) with 2.5% end tidal desflurane in hyperoxia (open squares) and in hypoxia (closed squares), with 5% end tidal desflurane in hyperoxia (open circles) and in hypoxia (closed circles). Values are means ± SEM, *n*=11 piglets.

The technique used to assess pharmacological and physiological variations in pulmonary vasomotor tone involved generation of multipoint P/Q plots. This technique was developped by Lodato *et al.* in conscious dogs, at two different inspired oxygen concentrations.[12] The IVC occlusion technique by incremental inflation of a balloon catheter produced a titratable decrease in Q. P/Q plots were then generated. The P/Q relationship allows discrimination of vasoactive from passive mechanical effects on the pulmonary circulation. This technique is more relevant than the use of calculated pulmonary vascular resistance (PVR), which does not take in consideration how this resistance varies with Q. However it has a number of limitations including systemic hypotension, changes in blood gases and changes in zonal conditions of the lung. This technique has already been used in mammals to test the effects of anesthetics[5] and of physiologic or metabolic manipulations on HPV.[16,17] The P/Q plots in our piglets were linear in all experimental conditions, in keeping with previous studies in intact anaesthetized[5,6] or unsedated animals.[12]

HPV shows a large inter-individual and inter-species variability.[18] In our experiment, we chose 12-week-old piglets because of their strong pressor response to hypoxia[10] which is greater than that of other mammals and because their postnatal morphometric pulmonary development closely parallels that of humans.[11]

A number of factors may alter pulmonary vascular pressor response to hypoxia in animals. Increasing LAP can reduce HPV in anesthetized animals. This suggests that the whole pulmonary vasculature does not behave as a Starling resistor either in hyperoxia or in hypoxia.[17] In our piglets, LAP remained unchanged throughout study, and so could not have modified pulmonary vascular response to hypoxia.

Although pressor response is usually dependent on PaO_2, changes in mixed venous PvO_2 can be important during hypoxia, and subsequently modify the magnitude of HPV.[19] In our study, hypoxia and low Q led to a marked decrease in PvO_2 in both cases. This decrease could have enhanced HPV.

Pressor responses can be altered by changes in arterial pH and $PaCO_2$.[20] In anesthetized dogs, marked alkalosis induced by artificial hyperventilation during hypoxia has been shown to reduce PAP.[20] In our study, arterial pH and $PaCO_2$ were kept constant at all levels of Q. Therefore, variations of pH and $PaCO_2$ were unlikely to have affected HPV.

Finally, reduction of Q, as was performed in our experiment, activates the arterial baroreceptor reflex. Carotid sinus baroreceptor reflex has been shown to have a direct control on the entire systemic and PAP-flow relationships in anesthetized dogs.[21] In intact conscious dogs, circulatory hypotension resulted in active pulmonary vasoconstriction, primarily mediated by sympathetic $_1$adrenoreceptor activation.[22] In our study, at baseline, baroreceptor reflex was not activated by lowering Q, as suggested by lower PAP at lowest Q in both hyperoxia and hypoxia.

As in previous experiments with other inhaled anesthetics in intact mammals, desflurane induced only systemic vasodilation and had no significant effect on HPV, when used at sub-MAC concentrations. Investigations assessing the effects of halogenated agents on HPV have provided different results, depending on the experimental model. Studies on isolated perfused lungs showed an inhibition of HPV by inhaled agents.[3,4,8] Conversely, experiments with intact mammals showed either an inhibition[23] or no significant effect.[6,9,24]

Associated iv anesthetics

This experiment required general anesthesia and mechanical ventilation. These anesthetic conditions resemble the clinical situation, where desflurane is

administered with fentanyl.[14] This opiate has no recognized effect on pulmonary vascular tone.[25] In our study, we chose an infusion of midazolam rather than pentobarbitone since the former has no demonstrated effect on pulmonary vascular tone.[25,26]

Mechanical ventilation

Intermittent positive pressure ventilation can modify pulmonary circulation by different mechanisms such as a direct compression of alveolar vessels or increased lung volumes.[27] This could explain different results between mechanically ventilated and unsedated intact animals.

In our experiment, we measured pulmonary vascular pressures at the end of expiration when pleural pressure is supposed to be the lowest. However, effects of mechanical ventilation on pulmonary vascular tone cannot be excluded.

Site of action of hypoxia

This site could be different depending on species. In dogs, HPV is thought to occur mainly in pulmonary arteries,[28] whereas in pigs, capillaries may be the major site of vasoconstriction.[29]

Action of the sympathetic nervous system

In anesthetized dogs, chemical sympathectomy or chemodenervation increased PAP at all levels of Q studied both in hypoxia and in hyperoxia.[30] The effect of the sympathetic nervous system in hyperoxic as well as in hypoxic healthy mammals' lungs seems to be a reduction in pulmonary vascular tone.

In our study, administration of desflurane in both hyperoxia and in hypoxia induced a significant increase of HR at highest Q wich was associated with lower systemic arterial pressure. Thus, desflurane could have partially altered the baroreflex. The effect of desflurane on HPV in the intact animal is therefore more apparent than in isolated lung, where the autonomic nervous system is not effective. This could explain discrepancies between *in vitro* and *in vivo* studies on desflurane.

In summary, this experiment assessed the effect of two sub-MAC concentrations of desflurane on HPV in intact, anesthetized, mechanically ventilated piglets. Hypoxia resulted in a significant increase in pressure gradients (PAP-LAP) and (PAP-PCWP), due to active pulmonary vasoconstriction. Desflurane did not influence HPV as evaluated by the pulmonary vascular pressure/Q relationship. These conclusions are different from those described in *in vitro* experiments, but they are in agreement with previous *in vivo* studies on desflurane[9] and sevoflurane.[6]

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