

# Effect of Bronchoconstriction-induced Ventilation–Perfusion Mismatch on Uptake and Elimination of Isoflurane and Desflurane

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## ABSTRACT

**Background:** Increasing numbers of patients with obstructive lung diseases need anesthesia for surgery. These conditions are associated with pulmonary ventilation/perfusion ( $\dot{V}_A/Q$ ) mismatch affecting kinetics of volatile anesthetics. Pure shunt might delay uptake of less soluble anesthetic agents but other forms of  $\dot{V}_A/Q$  scatter have not yet been examined. Volatile anesthetics with higher blood solubility would be less affected by  $\dot{V}_A/Q$  mismatch. We therefore compared uptake and elimination of higher soluble isoflurane and less soluble desflurane in a piglet model.

**Methods:** Juvenile piglets ( $26.7 \pm 1.5$  kg) received either isoflurane ( $n = 7$ ) or desflurane ( $n = 7$ ). Arterial and mixed venous blood samples were obtained during wash-in and wash-out of volatile anesthetics before and during bronchoconstriction by methacholine inhalation (100  $\mu\text{g}/\text{ml}$ ). Total uptake and elimination were calculated based on partial pressure measurements by micropore membrane inlet mass spectrometry and literature-derived partition coefficients and assumed end-expired to arterial gradients to be negligible.  $\dot{V}_A/Q$  distribution was assessed by the multiple inert gas elimination technique.

**Results:** Before methacholine inhalation, isoflurane arterial partial pressures reached 90% of final plateau within 16 min and decreased to 10% after 28 min. By methacholine nebulization, arterial uptake and elimination delayed to 35 and 44 min. Desflurane needed 4 min during wash-in and 6 min during wash-out, but with bronchoconstriction 90% of both uptake and elimination was reached within 15 min.

**Conclusions:** Inhaled methacholine induced bronchoconstriction and inhomogeneous  $\dot{V}_A/Q$  distribution. Solubility of inhaled anesthetics significantly influenced pharmacokinetics: higher soluble isoflurane is less affected than fairly insoluble desflurane, indicating different uptake and elimination during bronchoconstriction. (**ANESTHESIOLOGY 2017; 127:800-12**)

THE rising prevalence of the chronic obstructive pulmonary disease and asthma may increase the number of patients suffering from these conditions who are in need of anesthesia for surgery. This is important for clinical anesthesia, because these diseases are associated with pulmonary ventilation/perfusion ( $\dot{V}_A/Q$ ) mismatch that may affect uptake and elimination of volatile anesthetics.<sup>1</sup>

Theoretical considerations on the basis of an electrical analog model by Eger and Severinghaus<sup>2</sup> in the 1960s suggested that pure shunt, that is, the most extreme form of  $\dot{V}_A/Q$  mismatch, would delay uptake of volatile anesthetic agents with lower blood solubility. This was later confirmed by an experimental model published by Stoelting and Longnecker.<sup>3</sup> However, the effects on volatile anesthetic elimination were not considered. Moreover, the effects of  $\dot{V}_A/Q$  scatter, which is in general the dominating cause of gas

### What We Already Know about This Topic

- Inhalational anesthetic arterial kinetics depends on not only alveolar ventilation and pulmonary perfusion but also their distribution, agent solubility, and mixed venous kinetics
- Methacholine inhalation causes bronchoconstriction, shifts mean ventilation to regions with higher ventilation/perfusion ratios, and broadens perfusion dispersion with increased perfusion in low ventilation/perfusion regions and interpulmonary shunt
- Inhaled methacholine delayed desflurane uptake and elimination in a piglet model

### What This Article Tells Us That Is New

- Compared with the fairly insoluble desflurane, the uptake and elimination of the more soluble isoflurane in piglets was less affected by methacholine-induced bronchoconstriction and ventilation/perfusion scatter

This article is featured in “This Month in Anesthesiology,” page 1A. Corresponding article on page 741. This article has a video abstract. Part of the work presented in this article has been presented by M.K., A.K., and T.S. at the American Society of Anesthesiologists’ 2016 Annual Meeting in Chicago, Illinois, October 22 to 26, 2016. M.K. and A.K. contributed equally to this article.

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exchange disturbance in obstructive lung diseases, have not been studied in depth.

Previously presented data from a porcine lung obstructive model regarding uptake and elimination of desflurane, a volatile anesthetic with very low blood solubility (blood/gas partition coefficient,  $0.498 \pm 0.522$  in humans and  $0.502 \pm 0.054$  in pigs),<sup>4</sup> demonstrated that both uptake and elimination are delayed by bronchoconstriction.<sup>5</sup> On the basis of these considerations we hypothesized that a volatile anesthetic with a higher blood solubility (isoflurane; blood/gas partition coefficient of  $1.32 \pm 0.04$  in humans and  $1.07 \pm 0.05$  in pigs)<sup>4</sup> would be less affected by a methacholine-induced increase in  $\dot{V}_A/Q$  scatter.

Therefore, the objective of the present experimental study in piglets was to compare the uptake and elimination of inhalational anesthetics with high and low blood solubility. The null hypothesis was that methacholine inhalation-induced bronchoconstriction affects the pharmacokinetics of isoflurane and desflurane to a similar extent.

## Materials and Methods

The animal ethics committee of Uppsala University (Uppsala, Sweden) approved this prospective nonrandomized animal study. The care and handling of animals were in accordance with the National Institutes of Health (Bethesda, Maryland) guidelines for ethical animal treatment.<sup>6</sup>

### Animals

Juvenile, 2-month-old piglets (weight,  $26.7 \pm 1.5$  kg) of Yorkshire–Norwegian country breeds were used in the study. The animals fasted overnight with free access to water. All of the piglets underwent the same preparatory algorithm (induction and maintenance of anesthesia and monitoring). The experiments were conducted consecutively, no randomization procedures were used to assign animals to conditions, and no attempts were made to blind experimenters to condition.

Seven of the animals were used for assessment of uptake–elimination of isoflurane (isoflurane group) and seven for measurement of uptake–elimination of desflurane (desflurane group). Parts of the data from six of the animals in the desflurane group have previously been reported.<sup>5</sup>

### Anesthetic Management

As described previously in detail,<sup>5,7</sup> anesthesia was induced by an intramuscular injection of xylazine (2.2 mg/kg; Rompun, Bayer, Germany) and tiletamine–zolazepam (6 mg/kg; Zoletil, Virbac, France). The pigs were placed in the supine position, and the trachea was intubated orally with an ID 7-mm cuffed endotracheal tube (Mallinckrodt, Ireland). After testing for hind limb reflex absence, muscle relaxation was induced with an intravenous bolus of 2 mg/kg rocuronium (Esmeron, N.V. Organon, Netherlands), followed by a continuous infusion of  $2.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  rocuronium. Anesthesia was maintained by continuous intravenous infusions of

fentanyl ( $0.04 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ; Leptanal, Janssen-Cilag AB, Sweden), midazolam ( $0.12 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ , midazolam Actavis, Actavis Group, Iceland), and propofol (Diprivan, Astra, Sweden) via 18-G catheters (Becton Dickinson, Germany) placed in ear veins.

After intubation and during mechanical ventilation, a median tracheotomy was performed, and the orotracheal tube was replaced by an ID 9-mm cuffed endotracheal tube (Mallinckrodt). Thereafter, the lungs were mechanically ventilated with intermittent positive pressure ventilation with fractional inspired oxygen tension of 0.4 and positive end-expiratory pressures of 5 cm H<sub>2</sub>O provided by a KION anesthesia ventilator (Maquet Critical Care). Fresh gas flow was set to exceed double minute ventilation to make delivered gas fractions close to inspired gas fractions. The tidal volume was set to 10 mg/kg, and respiratory frequencies were adjusted to achieve a normal  $\text{PaCO}_2$  of 40 to 45 mmHg.

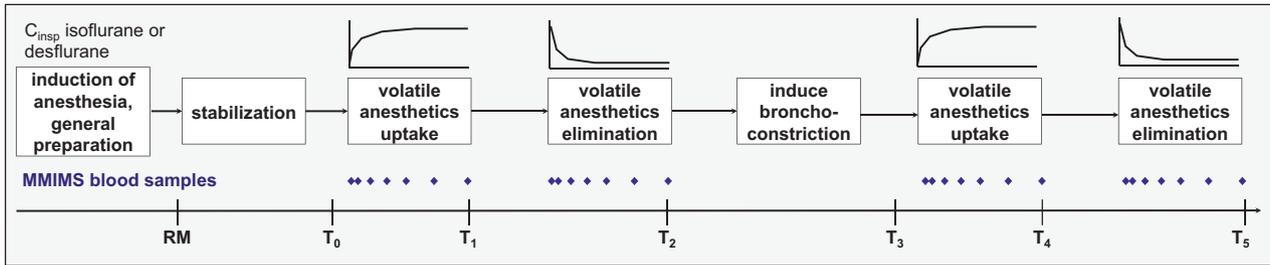
Ventilation variables were measured at the proximal end of the endotracheal tube with a standard anesthesia monitor (SC 9000 XL, Siemens, Germany) and additionally assessed by a NICO<sub>2</sub> system (Respironics Novamatrix, Inc., USA). These measurements were averaged more than 15 cycles for analysis. Volatile anesthetic concentrations were monitored continuously with an infrared analyzer (Capnomac Ultima, Datex Ohmeda, Finland), calibrated to the manufacturer's standards.

A flow-directed pulmonary artery catheter (7.0 French, Swan-Ganz thermodilution catheter, Baxter, USA) and a central venous catheter (4.0 French, Becton-Dickinson Critical Care Systems, Singapore) were inserted *via* the right external jugular vein. The balloon tip of the pulmonary artery catheter was located in the wedge position for cardiac output measurements and mixed venous blood sampling. The pulmonary artery catheter was repositioned before each experimental step to ensure that the tip was always located in regions with high pulmonary blood flow. Cardiac output was repeatedly measured at every experimental time point. All of the pigs received a right carotid arterial catheter for continuous arterial pressure measurements and for blood sampling (20 G, Becton-Dickinson Critical Care Systems).

Blood gas analysis was performed immediately after bubble-free blood sampling with standard blood gas electrodes specifically set up to analyze porcine blood (ABL 500 and OSM 3, Radiometer, Denmark). Finally, a suprapubic urinary catheter (Sympakath, Ruesch AG, Switzerland) was placed to monitor urine output.

### Multiple Inert Gas Elimination Technique

In the desflurane group, determination of  $\dot{V}_A/Q$  distribution was performed in all of the animals using the multiple inert gas elimination technique (MIGET) at baseline and during nebulization of methacholine before second desflurane administration. In isoflurane pigs, MIGET was performed in three animals using the same time points to verify the methacholine effect during nebulization (fig. 1).



**Fig. 1.** Study workflow indicating the following experimental steps: T<sub>0</sub> = baseline; T<sub>1</sub> = uptake of the volatile anesthetic agent in the healthy pig; T<sub>2</sub> = after volatile anesthetic wash-out in the healthy pig; T<sub>3</sub> = methacholine nebulization; T<sub>4</sub> = second uptake of the volatile anesthetic with methacholine; T<sub>5</sub> = after second volatile anesthetic wash-out with methacholine. Please note that determination of ventilation/perfusion ratio ( $\dot{V}_A/Q$ ) by multiple inert gas elimination technique (MIGET) was performed at T<sub>0</sub> and at T<sub>3</sub>. MMIMS = micropore membrane inlet mass spectrometry; RM = alveolar recruitment maneuver; T = time point; volatile = volatile anesthetic, that is, isoflurane or desflurane. The diamonds indicate the measurement points.

MIGET has been described in detail in an earlier publication.<sup>5</sup> In brief, six inert gases with different solubilities in blood were infused into a peripheral vein at a constant rate. Simultaneously, arterial and mixed venous blood, as well as mixed expired gas samples, were obtained. Thereafter, blood samples were equilibrated with nitrogen in a shaking water bath. The gas samples were analyzed for their inert gas partial pressures by gas chromatography (Gas Chromatograph Model 5890, Series II, Hewlett-Packard, USA). The retention of these six gases was calculated as the ratio of arterial to mixed venous partial pressure and excretion as the ratio of mixed expired to mixed venous partial pressure. These values were processed by the algorithm of Evans and Wagner<sup>8</sup> to obtain compatible  $\dot{V}_A/Q$  distributions.

The calculated parameters were log SD of perfusion and log SD of ventilation describing the dispersion or broadness of the respective distribution and mean Q and mean V representing the mean values of perfusion or ventilation. The obtained data related to  $\dot{V}_A/Q$  distribution were perfusion of lung regions with  $\dot{V}_A/Q$  less than 0.005, perfusion of lung regions with 0.005 less than  $\dot{V}_A/Q$  less than 0.1 (*i.e.*, low  $\dot{V}_A/Q$  regions), ventilation of lung regions with 10 less than  $\dot{V}_A/Q$  less than 100 (*i.e.*, high  $\dot{V}_A/Q$  regions), and ventilation of lung regions with  $\dot{V}_A/Q$  greater than 100 (dead space [ $V_D/V_T$ ]). As a quality indicator for the fit of the model, the remaining sum of squares is reported.

### Measurement of Isoflurane and Desflurane by Micropore Membrane Inlet Mass Spectrometry

Arterial and mixed venous blood samples were collected in glass syringes coated with EDTA (FORTUNA OPTIMA 5 ml, Luer-lock, Poulten & Graf GmbH, Germany) for analysis by micropore membrane inlet mass spectrometry (MIGET by MMIMS System, Oscillopy LLC, USA). The system consists of a polymer membrane confined to multiple small micropores that separate the blood sample from the mass spectrometer and high-vacuum system, and gases diffuse through this membrane into the mass spectrometer for analysis. Because tonometry is not necessary, the native blood samples flowed over the micropore membrane inlet mass spectrometry (MMIMS) probes, and the volatile gas

partial pressures were analyzed directly by measuring the ion current of the mass/charge ratio ( $m/e$ ) at  $m/e = 51$  for isoflurane and  $m/e = 101$  for desflurane.<sup>9–12</sup>

### Experimental Protocol

**Baseline (T<sub>0</sub>).** Following an alveolar recruitment maneuver<sup>13</sup> (40 cm H<sub>2</sub>O for 10 s) and 30 min of stabilization after instrumentation, baseline hemodynamic, ventilation, and gas exchange data were obtained.

**Healthy State (T<sub>1</sub> and T<sub>2</sub>).** Either isoflurane (Forene, Abbott Laboratories, USA) or desflurane (Suprane, Baxter Int., USA) was administered *via* the KION ventilator (Maquet Critical Care, Sweden) with the vaporizer set at 1 vol% for isoflurane or at 5 vol% for desflurane in an open system. Fresh gas flow was set to exceed double minute ventilation. Arterial and mixed venous blood samples were obtained simultaneously after 0, 1, 2, 5, 10, 20, and 30 min and after 45 and 60 min only for isoflurane (volatile anesthetic uptake, wash-in). Thereafter, the inhalation of the volatile agent was stopped and the sampling sequence was repeated (volatile anesthetic elimination, wash-out).

### Bronchoconstriction and Repetition of Wash-in and Wash-out (T<sub>3</sub> to T<sub>5</sub>)

Methacholine (100 µg/ml in saline, acetyl-β-methacholine chloride, Sigma-Aldrich Inc., USA) was intermittently aerosolized using an ultrasonic nebulizer (Siemens Model 63 02 595 E400E) to maintain a constant increase of respiratory resistance with doubling of peak inspiratory pressure in each pig throughout this experimental step. The uptake and elimination sampling for each volatile agent were repeated at the given time schedule.

At the end of each experiment, the animals were euthanized with an intravenous injection of potassium chloride while under general anesthesia. The workflow of the experimental protocol is presented in figure 1.

### Analysis of Data

Nonlinear regression analysis of the MMIMS data was performed with Sigmaplot version 11 (Systat Software Inc., USA). The curves are displayed as means of each data point

with SD. As a first step, the individual data for a single pig were calculated. For this, the end-plateau signal of the respective arterial wash-in curve of each piglet before methacholine nebulization ( $T_1$  in fig. 1) was set as reference value (= 1.0). The arterial and mixed-venous data obtained during bronchoconstriction were scaled to this signal and fitted to a double exponential function ( $a + c = 1$ ):

$$(I) \text{ wash-in: } y = f(t) = a(1 - e^{-bt}) + c(1 - e^{-dt})$$

$$(II) \text{ wash-out: } y = f(t) = a(e^{-bt}) + c(e^{-dt})$$

### Calculation of Uptake and Elimination of the Volatile Anesthetics

The measured (dry) end-tidal partial concentration in vol% for the volatile anesthetics was converted to partial pressure (millimeters of mercury) and corrected for water vapor at the respective body temperature. Correction for water vapor was as follows:

$$(III) P_t \text{ H}_2\text{O} = 3.10594 + 0.59886 \cdot t - 0.00561 \cdot t^2 + 0.00058 \cdot t^3 \text{ (millimeters of mercury)}^{14}$$

The end-tidal partial pressure was assumed to be approximately equal to arterial partial pressure at the end of the wash-in of the volatile anesthetics, before methacholine inhalation. Therefore, the maximum healthy arterial wash-in mass spectrometry signal was calibrated to the corrected end-tidal partial pressure of the volatile anesthetic. The resulting calibration factor (millimeters of mercury per microamp) was then applied to the raw mass spectrometer ion current values of the arterial and mixed venous samples to derive the partial pressures of the volatile anesthetics in the respective blood samples. The Ostwald coefficient for the respective anesthetic in pigs<sup>15</sup> was applied and the uptake calculated analogous to Peyton<sup>16</sup> as follows:

$$(IV) \text{ Uptake} = (p_a \text{An} - p_{mv} \text{An}) \times \lambda \times Q \text{ (milliliters of the volatile per minute)}$$

where  $p_a \text{An}$  is the arterial partial pressure of the anesthetic,  $p_{mv} \text{An}$  is the mixed venous partial pressure of the anesthetic,  $\lambda$  is the Ostwald coefficient of the anesthetic, and  $Q$  is the cardiac output. The data were calculated separately for each piglet and were averaged for the respective groups afterward.

### Statistical Analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS version 23, IBM Corporation, USA). The estimation of sample size was based on a previous experimental porcine study,<sup>5</sup> which used an analogous experimental setup. Power calculation using two-sided  $t$  test at a significance level of 5% ( $\alpha = 0.05$ ) and a power of 80% ( $\beta = 0.20$ ) revealed that at least four animals per group were needed to detect a difference of more than 20% in the volatile wash-in period. The change of the time period to

90% (p90) of the maximum arterial anesthetic partial pressures was defined as the primary variable.

The data were tested for normal distribution with the Shapiro–Wilk  $W$  test and are presented as means and SDs in the case of normal distribution (cardiopulmonary and ventilation variables). The analysis of normally distributed data was performed by a repeated-measures one-way ANOVA with *post hoc* Bonferroni correction. The sequential changes of the relative mass spectrometry signal (representing blood partial pressures of volatiles) in each group were assessed by a repeated-measures general linear model (type III sums of squares). Subsequent between-group comparisons were performed by two-way ANOVA using the independent variables group and time. *Post hoc* multiple comparisons were performed by the Bonferroni procedure applied to all of the pairwise comparisons.

The area under the wash-in and wash-out curves was calculated before and during methacholine-induced bronchoconstriction for anesthetic uptake and elimination, and grouped values were compared by a two-sided  $t$  test.  $\dot{V}_A/Q$  distributions were directly compared for each individual measurement in each animal by the Kolmogorov–Smirnov two-sample test, treating each paired measurement as an independent observation (*i.e.*, without accounting for intraindividual versus interindividual differences). The differences were considered to be statistically significant for all of the procedures if the  $P$  value was less than 0.05.

## Results

There were no differences regarding biometric variables between both groups, and there were also no intraoperative difficulties that might have affected the data.

### Hemodynamics, Ventilation, and Gas Exchange before Methacholine Nebulization

The wash-in of isoflurane up to 1 vol% or desflurane (5 vol%) in the inspired gas in normal piglets before methacholine-induced bronchoconstriction had no significant effect on hemodynamics, respiratory mechanics, ventilation, or global gas exchange variables as compared with the initial baseline data with intravenous anesthesia (tables 1 and 2).

### Hemodynamics, Ventilation, and Gas Exchange during Methacholine Nebulization

Hemodynamics, alveolar ventilation, and gas exchange variables were significantly changed after the administration of methacholine by inhalation. Mean pulmonary artery pressure increased, whereas mean arterial pressure, cardiac output, and systemic vascular resistance remained constant. Pulmonary vascular resistance nearly doubled by methacholine nebulization in all of the piglets.

The respiratory system resistance increased more than fourfold with methacholine; the peak airway pressure was at least doubled, and alveolar ventilation significantly decreased.

**Table 1.** Hemodynamics and Gas Exchange Data in the Isoflurane Group before and during Methacholine Nebulization at Different Experimental Time Points

Variable	Isoflurane Group (n = 7)					
	Without Methacholine			During Methacholine Nebulization		
	T <sub>0</sub>	T <sub>1</sub>	T <sub>2</sub>	T <sub>3</sub>	T <sub>4</sub>	T <sub>5</sub>
Pao <sub>2</sub> , mmHg	198±21	192±8	192±14	102±17*	97±28*	104±27*
Paco <sub>2</sub> , mmHg	45±3	44±4	45±4	49±7	56±8*	55±9*
Sao <sub>2</sub> , %	99±1	99±1	99±1	95±1*	93±5*	95±3*
PmvO <sub>2</sub> , mmHg	40±3	38±2	39±2	36±3	36±5	33±4*
PmvCO <sub>2</sub> , mmHg	59±8	53±3	55±6	64±10	66±12	70±11
HR, 1/s	117±16	100±13	98±15	96±14*	108±11	102±4
MAP, mmHg	76±8	67±8	85±9	76±12	73±9	69±7
MPAP, mmHg	20±2	20±2	20±2	31±5*	31±6*	33±7*
CVP, mmHg	8±2	8±1	8±1	9±2	9±1	9±1
CO, l/min	3.2±0.6	2.8±0.7	3.0±0.6	2.9±0.5	3±0.3	2.8±0.5
PVR, dyn*s/cm <sup>5</sup>	263±52	326±61	339±92	588±218*	585±180*	659±204*
SVR, dyn*s/cm <sup>5</sup>	1816±607	1763±536	2139±510	1843±403	1688±343	1765±486
Venous admixture, %	6.7±3.6	7.1±3.7	6.2±2.7	12.2±1.2*	17±6.4*	11.4±4.4

The values are presented as mean ± SD.

\*P < 0.05 as compared with baseline before methacholine administration.

CO = cardiac output; CVP = central venous pressure; HR = heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; PaCO<sub>2</sub> = arterial partial pressure of carbon dioxide; PaO<sub>2</sub> = arterial partial pressure of oxygen; PmvCO<sub>2</sub> = mixed venous partial pressure of carbon dioxide; PmvO<sub>2</sub> = mixed venous partial pressure of oxygen; PVR = pulmonary vascular resistance; SaO<sub>2</sub> = arterial oxygen saturation; SVR = systemic vascular resistance; T = experimental time point.

**Table 2.** Hemodynamics and Gas Exchange Data in the Desflurane Group before and during Methacholine Administration at Different Experimental Time Points

Variable	Desflurane Group (n = 7)					
	Without Methacholine			During Methacholine Nebulization		
	T <sub>0</sub>	T <sub>1</sub>	T <sub>2</sub>	T <sub>3</sub>	T <sub>4</sub>	T <sub>5</sub>
Pao <sub>2</sub> , mmHg	207±14	189±18	209±15	73±18*	64±17*	68±15*
Paco <sub>2</sub> , mmHg	40±3	39±2	37±3	46±8*	48±10*	57±3*
Sao <sub>2</sub> , %	99±0	99±0	99±0	90±4*	85±7*	86±6*
PmvO <sub>2</sub> , mmHg	42±2	39±2	40±3	37±6	36±8	37±5
PmvCO <sub>2</sub> , mmHg	47±4	47±2	45±3	60±4*	64±4*	67±3*
HR, 1/s	112±13	106±9	103±12	106±20	109±18	115±21
MAP, mmHg	89±19	87±14	91±13	91±16	78±14	91±16
MPAP, mmHg	19±2	18±2	18±2	31±2*	31±2*	32±3*
CVP, mmHg	6±1	7±1	7±2	9±2	9±2	9±2
CO, l/min	3.8±0.5	3.2±0.3	3.6±0.6	3.6±0.6	3.5±0.7	4.1±0.7
PVR, dyn*s/cm <sup>5</sup>	261±57	276±37	248±46	506±92*	503±105*	465±110*
SVR, dyn*s/cm <sup>5</sup>	1791±531	1742±510	1923±546	1826±192	1566±157	1603±223
Venous admixture, %	7.1±0.4	6.8±1.2	6.7±1.0	21.5±5.8*	26.8±9.4*	28.6±8.0*

Data are presented as mean ± SD.

\*P < 0.05 as compared with baseline before methacholine administration.

CO = cardiac output; CVP = central venous pressure; HR = heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; PaCO<sub>2</sub> = arterial partial pressure of carbon dioxide; PaO<sub>2</sub> = arterial partial pressure of oxygen; PmvCO<sub>2</sub> = mixed venous partial pressure of carbon dioxide; PmvO<sub>2</sub> = mixed venous partial pressure of oxygen; PVR = pulmonary vascular resistance; SaO<sub>2</sub> = arterial oxygen saturation; SVR = systemic vascular resistance; T = experimental time point.

Gas exchange was severely impaired, as indicated by lower Pao<sub>2</sub> and mixed venous oxygen tension; increased end-tidal pressure of carbon dioxide, Paco<sub>2</sub>, and mixed venous carbon dioxide tension; and increased venous admixture. However, these critical alterations caused by methacholine inhalation

were not altered by either isoflurane or desflurane uptake and elimination (tables 3 and 4). Venous admixture was lower and Pao<sub>2</sub> higher with isoflurane than desflurane during methacholine nebulization, and these differences remained throughout the bronchoconstriction phase.

**Table 3.** Ventilation Parameters in the Isoflurane Group before and during Methacholine Administration at Different Experimental Time Points

Variable	Isoflurane Group (n = 7)					
	Without Methacholine			During Methacholine Nebulization		
	T <sub>0</sub>	T <sub>1</sub>	T <sub>2</sub>	T <sub>3</sub>	T <sub>4</sub>	T <sub>5</sub>
PIF, l/min	30±3	31±3	31±3	30±4	31±4	30±3
PEF, l/min	35±5	36±5	37±5	35±3	37±2	39±3
V <sub>T</sub> , ml	245±21	245±23	243±24	243±17	244±17	240±15
MV, l/min	5.3±0.8	5.5±0.8	5.4±0.8	5.8±0.8	5.8±0.7	5.8±0.6
RR, /min	22±2	22±3	22±3	24±2	24±3	24±2
PEEP, cm H <sub>2</sub> O	6±1	6±2	6±1	6±1	6±0	6±0
PAW <sub>mean</sub> , cm H <sub>2</sub> O	9±1	9±2	9±1	12±2*	14±2*	13±1*
PAW <sub>peak</sub> , cm H <sub>2</sub> O	17±1	17±2	19±2	35±6*	39±6*	38±6*
R <sub>RS</sub> insp, cm H <sub>2</sub> O · l <sup>-1</sup> · s <sup>-1</sup>	5.6±0.7	5.6±0.6	6.3±0.8	25.0±5.3*	28.2±6.7*	25.8±5.5*
R <sub>RS</sub> exp, cm H <sub>2</sub> O · l <sup>-1</sup> · s <sup>-1</sup>	5.7±0.8	5.7±0.6	6.5±1.0	25.4±5.5*	28.7±7.0*	26.4±5.8*
MValv, l	2.8±0.6	2.9±0.6	2.8±0.5	2.6±0.4*	2.5±0.4*	2.4±0.3*
etCO <sub>2</sub> , mmHg	45±3	42±2	44±4	51±3*	49±7*	51±5*
V <sub>D</sub> /V <sub>T</sub>	0.5±0.0	0.5±0.1	0.5±0.0	0.6±0.0*	0.6±0.0*	0.6±0.0*

Data are presented as mean ± SD.

\*P < 0.05 as compared with baseline before methacholine administration.

E<sub>t</sub>CO<sub>2</sub> = end tidal carbon dioxide; MV = minute ventilation; MValv = alveolar minute ventilation; PAW<sub>mean</sub> = mean airway pressure; PAW<sub>peak</sub> = peak airway pressure; PEEP = positive end expiratory pressure; PEF = peak expiratory flow; PIF = peak inspiratory flow; RR = respiratory rate; R<sub>RS</sub> insp = inspiratory respiratory system resistance; R<sub>RS</sub> exp = expiratory system resistance; T = experimental time point; V<sub>D</sub>/V<sub>T</sub> = fractional dead space; V<sub>T</sub> = tidal volume.

**Table 4.** Ventilation Parameters in the Desflurane Group before and during Methacholine Administration at Different Experimental Time Points

Variable	Desflurane Group (n = 7)					
	Without Methacholine			During Methacholine Nebulization		
	T <sub>0</sub>	T <sub>1</sub>	T <sub>2</sub>	T <sub>3</sub>	T <sub>4</sub>	T <sub>5</sub>
PIF, l/min	34±4	36±3	33±4	33±2	35±2	32±3
PEF, l/min	32±5	33±2	31±3	37±3	36±4	37±5
V <sub>T</sub> , ml	260±22	275±18	255±18	256±18	277±23	256±21
MV, l/min	6.1±0.6	6.4±0.6	6.0±0.6	6.3±0.4	6.8±0.3	6.3±0.4
RR, /min	23±2	23±2	23±2	24±2	24±3	25±2
PEEP, cm H <sub>2</sub> O	5±0	5±0	5±0	5±0	5±0	5±0
PAW <sub>mean</sub> , cm H <sub>2</sub> O	8±0	8±0	9±0	12±1*	13±1*	13±1*
PAW <sub>peak</sub> , cm H <sub>2</sub> O	16±2	15±1	17±1	35±4*	37±5*	39±4*
R <sub>RS</sub> insp, cm H <sub>2</sub> O · l <sup>-1</sup> · s <sup>-1</sup>	5.4±0.8	4.8±0.5	6.1±1.5	22.7±3.3*	26.1±6.4*	27.6±5.9*
R <sub>RS</sub> exp, cm H <sub>2</sub> O · l <sup>-1</sup> · s <sup>-1</sup>	5.4±0.8	4.8±0.5	6.2±1.5	23.1±3.4*	26.4±6.5*	28.1±6*
MValv, l	3.7±0.5	3.8±0.4	3.4±0.6	2.6±0.5*	2.8±0.5*	2.6±0.5*
etCO <sub>2</sub> , mmHg	38±3	35±3	37±3	45±9*	49±8*	50±6*
V <sub>D</sub> /V <sub>T</sub>	0.4±0.1	0.4±0.0	0.4±0.1	0.6±0.1*	0.6±0.1*	0.6±0.1

Values are presented as mean ± SD.

\*P < 0.05 as compared with baseline before methacholine administration.

E<sub>t</sub>CO<sub>2</sub> = end tidal carbon dioxide; MV = minute ventilation; MValv = alveolar minute ventilation; PAW<sub>mean</sub> = mean airway pressure; PAW<sub>peak</sub> = peak airway pressure; PEEP = positive end expiratory pressure; PEF = peak expiratory flow; PIF = peak inspiratory flow; RR = respiratory rate; R<sub>RS</sub> insp = inspiratory respiratory system resistance; R<sub>RS</sub> exp = expiratory system resistance; T = experimental time point; V<sub>D</sub>/V<sub>T</sub> = fractional dead space; V<sub>T</sub> = tidal volume.

**Ventilation–Perfusion Matching during Methacholine Nebulization**

The  $\dot{V}_A/Q$  scatter was broadened during isoflurane and desflurane anesthesia (table 5). The ventilation distribution was widened during methacholine inhalation and shifted toward regions with a higher  $\dot{V}_A/Q$  ratio. The main mode of perfusion distribution was also broader, and shunt and perfusion

in areas of low  $\dot{V}_A/Q$  ratios increased up to 17%; the sum of them was similar with either anesthetic (fig. 2; table 5).

**Pharmacokinetics of Isoflurane and Desflurane before and during Methacholine Nebulization**

The inspired volatile anesthetics partial pressures reached a stable plateau after 5 min of uptake. At the end of volatile

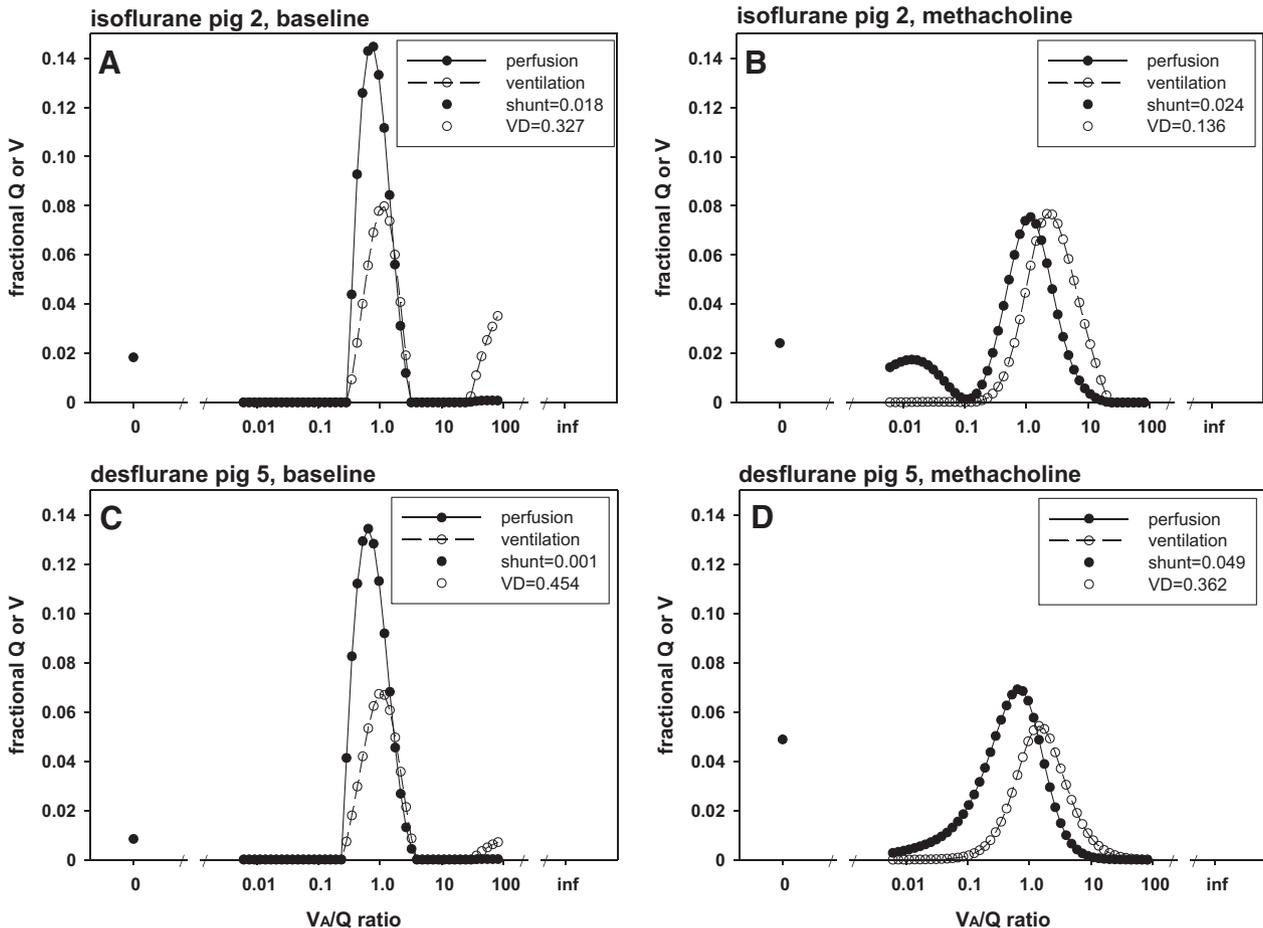
**Table 5.** Multiple Inert Gas Elimination Technique Data in Both Experimental Groups before and during Methacholine Nebulization

Variable	Isoflurane Pigs (n = 3)		Desflurane Pigs (n = 7)	
	Baseline	During MCh Nebulization	Baseline	During MCh Nebulization
% shunt	0.2 (0.1–0.3)	1.3 (0.8–1.9)*	0.8 (0.6–1.1)	6.3 (5.4–12.4)*
% Q in low $\dot{V}_A/Q$	5.4 (2.9–7.9)	15.4 (14.4–16.5)*	0.1 (0.0–1.9)	11.3 (5.6–18.8)*
% Q in normal $\dot{V}_A/Q$	94.1 (91.6–96.6)	81.8 (80.6–82.9)*	99.1 (95.5–99.1)	76.0 (68.6–81.9)*
% Q in high $\dot{V}_A/Q$	0.4 (0.3–0.5)	1.6 (1.2–2.1)*	0.1 (0.0–0.2)	0.9 (0.5–1.3)*
Mean Q	0.6 (0.5–0.7)	0.8 (0.7–0.9)	0.8 (0.7–0.8)	0.7 (0.5–0.8)
% V in low $\dot{V}_A/Q$	0.2 (0.1–0.4)	0.1 (0.0–0.1)	0.1 (0.0–0.1)	0.2 (0.1–0.4)
% V in normal $\dot{V}_A/Q$	60.5 (60.4–61.6)	60.9 (59.8–62.1)	59.2 (55.1–61.4)	61.1 (60.1–61.9)
% V in high $\dot{V}_A/Q$	11.0 (10.2–11.8)	20.5 (18.2–22.8)*	2.3 (0.6–4.8)	6.2 (4.1–8.6)*
% $V_D$	28.2 (27.1–29.4)	19.9 (17.7–22.2)*	38.9 (36.2–42.5)	31.7 (28.7–34.2)*
Mean V	2.1 (2.0–2.3)	3.2 (2.8–3.6)*	1.6 (1.3–1.8)	3.0 (2.7–3.1)*
Log SD <sub>Q</sub>	0.9 (0.8–1.0)	1.8 (1.8–1.8)*	0.6 (0.6–0.8)	1.9 (1.5–2.0)*
Log SD <sub>V</sub>	1.5 (1.4–1.5)	0.90 (0.8–0.9)*	0.8 (0.7–1.0)	0.9 (0.9–1.0)
RSS	1.4 (1.0–1.7)	0.2 (0.1–0.2)*	0.6 (0.4–0.8)	0.1 (0.1–0.2)*

Data are given as median (25th percentile to 75th percentile).

\**P* < 0.05 as compared with the healthy piglets' baseline within the isoflurane or desflurane groups.

log SD<sub>Q</sub> = log SD of perfusion; log SD<sub>V</sub> = log SD of ventilation; MCh = methacholine; Q = pulmonary perfusion; RSS = remaining sum of squared differences, median (25th percentile to 75th percentile);  $\dot{V}_A$  = alveolar ventilation;  $\dot{V}_A/Q$  = ventilation perfusion ratio;  $V_D$  = dead space ventilation;  $V_T$  = tidal volume.



**Fig. 2.** Ventilation and perfusion distribution assessed by multiple inert gas elimination technique. Fractional ventilation (V) and pulmonary perfusion (Q) by different ventilation/perfusion ratios in healthy animals (A and C) and during methacholine inhalation (B and D). The data represent the moments of ventilation and perfusion distribution of a representative pig in each group. Note the difference induced by nebulization of methacholine in comparison with the healthy condition. inf = infinity; MCh = methacholine; VD = dead space.

anesthetic wash-in, the end-expired partial pressures were  $5.6 \pm 0.4$  mmHg for isoflurane and  $35.4 \pm 0.3$  mmHg for desflurane in healthy pigs, which resulted in ratios of expiratory to inspiratory partial pressures of  $0.93 \pm 0.03$  for isoflurane and  $0.95 \pm 0.02$  for desflurane. The ratios of mixed venous to arterial partial pressures were  $0.86 \pm 0.05$  (isoflurane) and  $0.85 \pm 0.03$  (desflurane), respectively.

The arterial and mixed venous partial pressure course for both volatile anesthetics could be expressed by double exponential functions depicting the elimination phase before and during methacholine inhalation. Without methacholine, arterial isoflurane partial pressure reached 90% of the plateau (p90) within 16.4 min during wash-in of the anesthetic, whereas desflurane needed only 4.4 min ( $P < 0.001$ ). The elimination measurements of the volatiles revealed that 90% had been eliminated from the circulation after 27.8 min for isoflurane (fig. 3) and 5.7 min for desflurane ( $P < 0.01$ ; fig. 4).

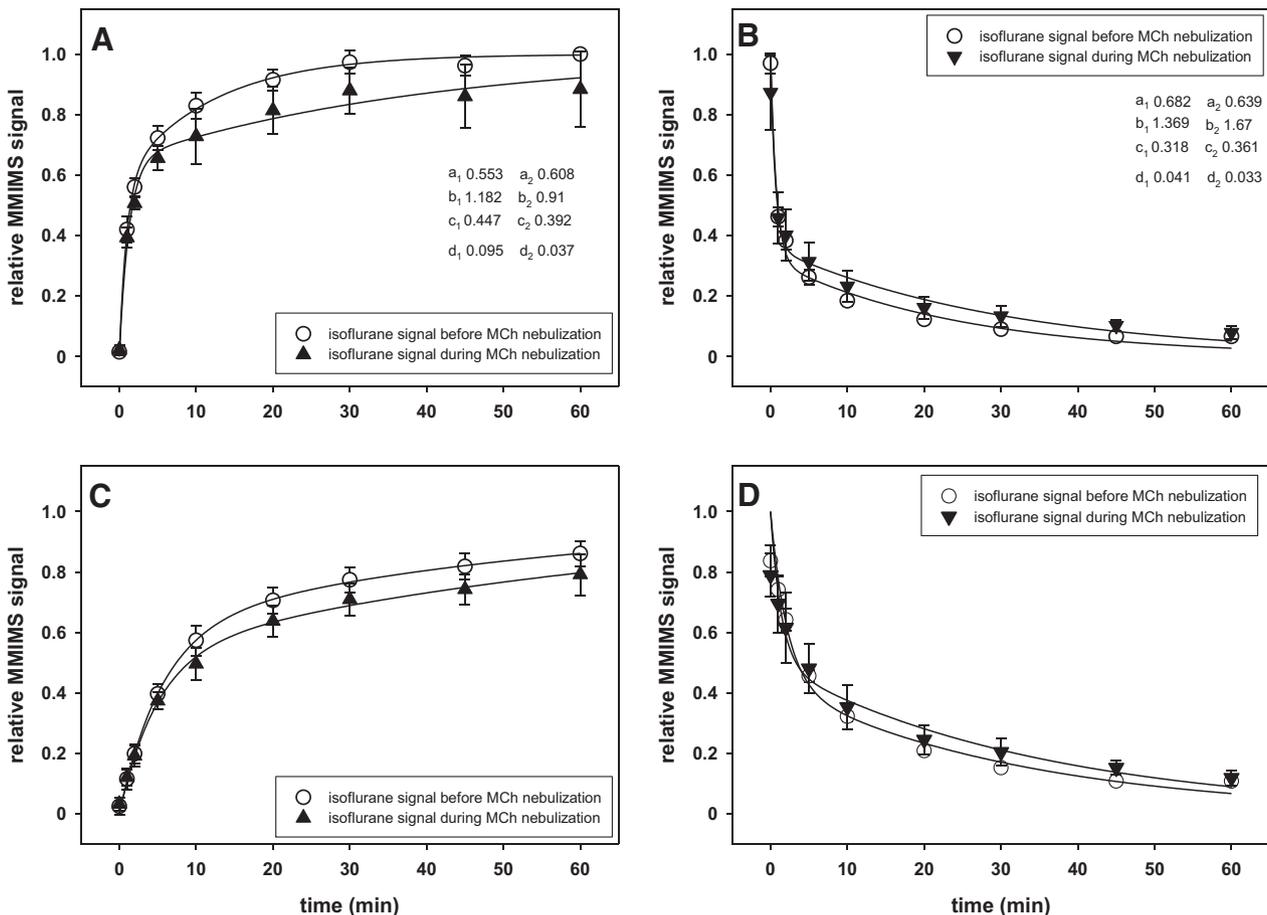
During methacholine-induced bronchoconstriction, the uptake and elimination of both volatile anesthetics were delayed but more significantly for desflurane. Thus, for 1 vol% isoflurane, 90% uptake and elimination (p90)

were reached after 35 min and 44 min, respectively. The p90 for uptake of 5 vol% desflurane was reached within 14.8 min, and 90% of elimination was detected after 14.9 min. The time to 50% of the maximum arterial partial pressure increased only in desflurane piglets by methacholine but not in animals that received isoflurane (figs. 3 and 4; table 6).

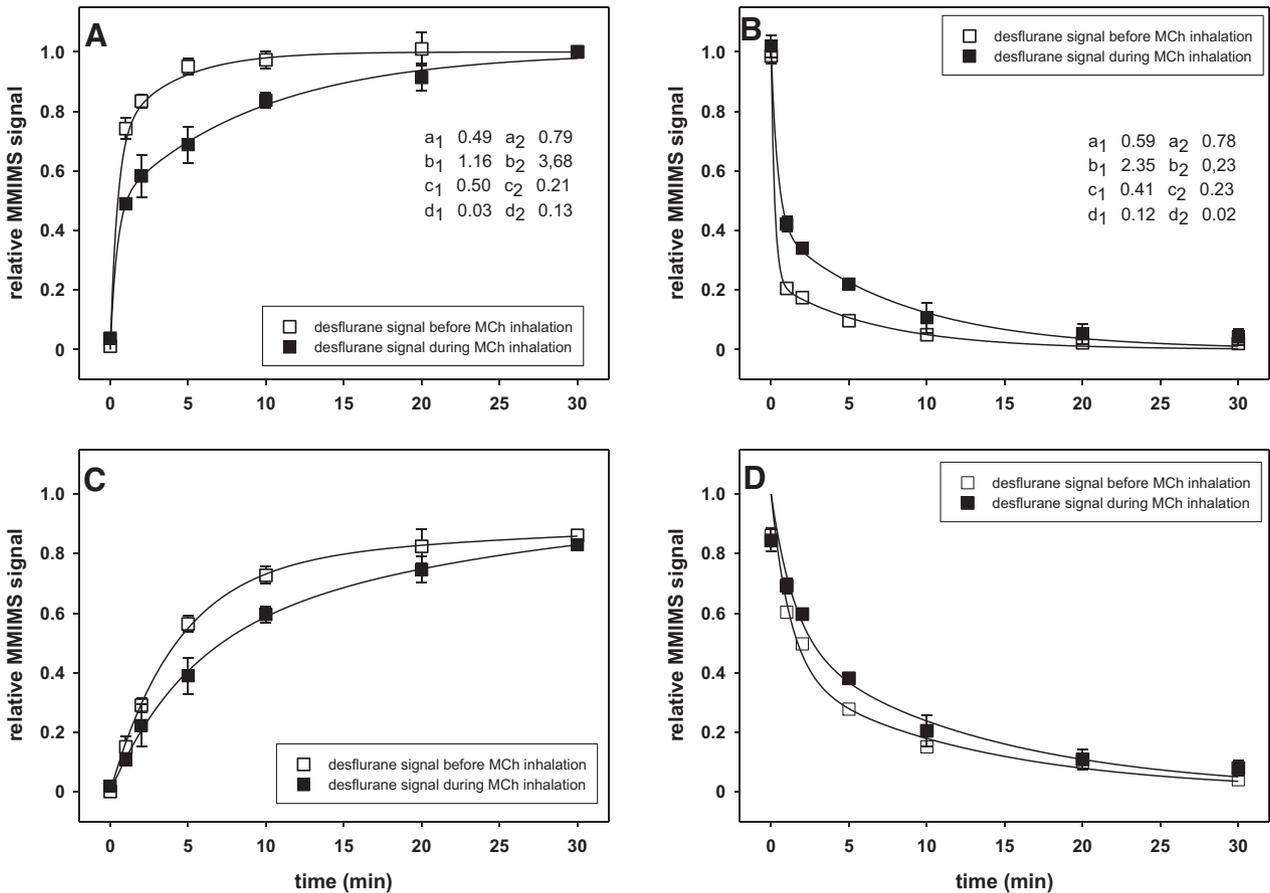
**Calculated Uptake and Elimination**

The uptake of isoflurane (fig. 5A) peaked with  $0.36 \pm 0.09$  ml (vapor) · kg<sup>-1</sup> · min<sup>-1</sup> in healthy piglets at the 2-min time point versus  $0.28 \pm 0.06$  ml (vapor) · kg<sup>-1</sup> · min<sup>-1</sup> during methacholine inhalation ( $P = 0.11$ ). In contrast, desflurane (fig. 5B) peaked at the 1-min time point and was  $1.87 \pm 0.24$  ml (vapor) · kg<sup>-1</sup> · min<sup>-1</sup> before and  $0.90 \pm 0.25$  ml (vapor) · kg<sup>-1</sup> · min<sup>-1</sup> during methacholine-induced bronchoconstriction, thus only 48% of the uptake during the nonobstructed state ( $P < 0.01$ ).

The elimination was greatest at the 1-min time point for both volatile anesthetics,  $0.24 \pm 0.04$  (healthy) versus  $0.22 \pm 0.07$  ml (vapor) · kg<sup>-1</sup> · min<sup>-1</sup> (methacholine,  $P = 0.45$ )



**Fig. 3.** Isoflurane blood partial pressures assessed by micropore membrane inlet mass spectrometry (MMIMS; n = 7). Time course of isoflurane levels during uptake into (A) and elimination (B) from arterial blood and uptake into (C) and elimination (D) from mixed venous blood before and during methacholine nebulization. The data were calculated as mean ± SD of all piglets after scaling the micropore membrane inlet mass spectrometry signals in the individual piglet to the arterial plateau after 60 min. Enclosed are the mean coefficients (a, b, c, and d) of the arterial exponential regression functions, displayed for uptake (1) and elimination (2) of isoflurane. MCh = methacholine.



**Fig. 4.** Desflurane blood partial pressures assessed by micropore membrane inlet mass spectrometry (MMIMS; n = 7). Time course of desflurane levels during uptake (A) into and elimination (B) from arterial blood and uptake (C) into and elimination (D) from mixed venous blood before and during methacholine nebulization. The data were calculated as mean ± SD of all piglets after scaling the micropore membrane inlet mass spectrometry signals in the individual piglet to the arterial plateau after 30 min. Enclosed are the mean coefficients (a, b, c, and d) of the arterial exponential regression functions, displayed for uptake (1) and elimination (2) of desflurane. MCh = methacholine.

**Table 6.** Time Period to Reach 50% and 90% of the Maximum Volatile Arterial Partial Pressures during Uptake (p50, p90) and Elimination (p50, p10) in Minutes

	Before Methacholine Nebulization		During Methacholine Nebulization	
	Isoflurane (n = 7)	Desflurane (n = 7)	Isoflurane (n = 7)	Desflurane (n = 7)
<b>Wash-in</b>				
p50, min	1.4 ± 0.3	0.5 ± 0.3*	1.7 ± 0.2	1.3 ± 0.3†
p90, min	16.4 ± 7.0	4.4 ± 1.6*	35.0 ± 10.8†	14.8 ± 3.0*†
<b>Wash-out</b>				
p50, min	0.9 ± 0.2	0.3 ± 0.1*	1.4 ± 0.4	0.7 ± 0.1†
p10, min	27.8 ± 2.0	5.7 ± 1.8*	43.6 ± 8.5†	14.9 ± 6.4*†

Data are presented as mean ± SD.

\*Indicates differences between the isoflurane and desflurane groups (P < 0.05); †Indicates differences with the corresponding healthy state (P < 0.05).

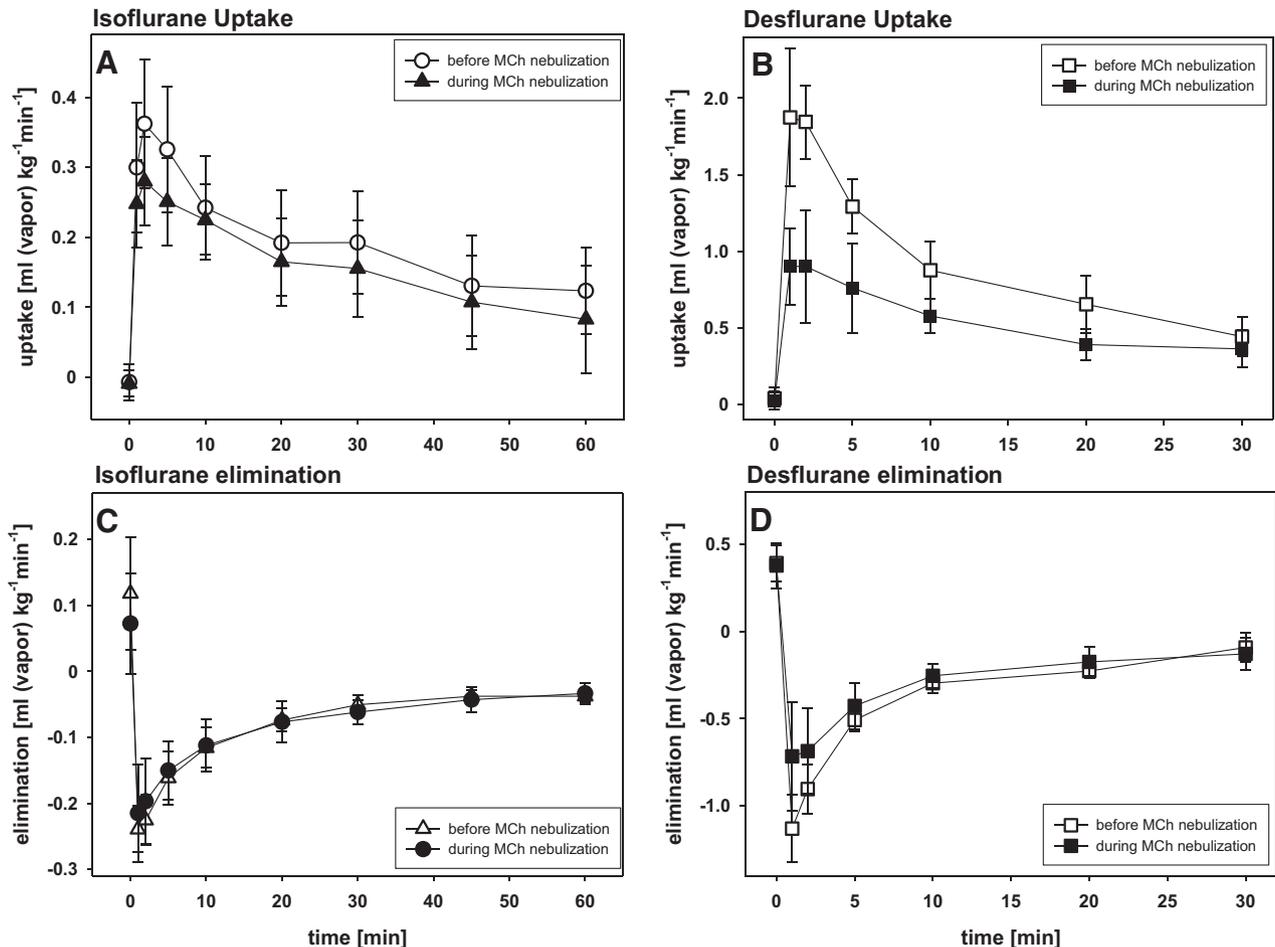
p = Percentage of the maximum arterial volatile partial pressure.

before and during methacholine nebulization for isoflurane (fig. 5C) and  $1.13 \pm 0.19$  (healthy) versus  $0.72 \pm 0.31$  ml (vapor) · kg<sup>-1</sup> · min<sup>-1</sup> (methacholine, P < 0.01) for desflurane (fig. 5D), respectively. Thus, elimination was reduced to 92% by methacholine in the isoflurane group and much

more in the desflurane group, to 64% of the nonobstructed state.

The difference in total uptake and elimination for isoflurane (calculated as area under the curve) was not significantly altered before and during methacholine-induced

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**Fig. 5.** Calculated absolute uptake and elimination of the volatile anesthetics. The uptake of isoflurane and desflurane (A and B;  $n = 7$ ) and elimination (C and D;  $n = 7$ ) from arterial blood before and during methacholine nebulization at sample time points (mean  $\pm$  SD). The data are displayed at the respective time in milliliters of anesthetic (vapor) per kilogram of body weight per minute. MCh = methacholine.

bronchoconstriction. For desflurane, it was decreased during uptake ( $25 \pm 4$  vs.  $15 \pm 3$  ml [vapor]/kg;  $P < 0.001$ ) and during elimination ( $9 \pm 1$  vs.  $8 \pm 3$  ml [vapor]/kg).

## Discussion

The administration of methacholine by nebulization causes, as expected, stable and reproducible bronchoconstriction, characterized by increased peak inspiratory pressure and respiratory system resistance. More importantly, methacholine inhalation results in a shift of mean ventilation distribution toward regions with higher  $\dot{V}_A/Q$  ratios and in a broadening of the perfusion dispersion with increased perfusion in low  $\dot{V}_A/Q$  regions and intrapulmonary shunt. Based mainly on theoretical considerations and limited previous experimental data, this  $\dot{V}_A/Q$  scatter could impair the uptake and elimination of volatile anesthetics.

Methacholine inhalation increased the time to 90% of the maximum arterial partial pressures for both volatile anesthetics and reduced the peak uptake and elimination of desflurane, whereas isoflurane pharmacokinetics

were less affected. The data are broadly consistent with the principle that uptake of less soluble agents relies more on gas exchange in lower  $\dot{V}_A/Q$  lung ratios than more soluble agents. Although our data confirmed that desflurane kinetics were always faster than isoflurane kinetics, desflurane uptake and elimination were more affected by  $\dot{V}_A/Q$  heterogeneity and therefore are likely to exert a larger variability in patients with bronchoconstriction.

Previous studies modeling the kinetics of volatile anesthetics assume that the uptake is perfusion limited<sup>17</sup> and did not consider the distribution of ventilation heterogeneity.<sup>2,18</sup> In the present study, we managed to avoid significant changes in total cardiac output and alveolar minute ventilation throughout the experiments, which allowed us to investigate correctly the effect of  $\dot{V}_A/Q$  scatter.

The arterial kinetics of inhalational anesthetics depend on total alveolar ventilation, pulmonary perfusion, solubility of the agent, distribution of ventilation and perfusion, and mixed venous kinetics.<sup>18</sup> Although cardiac output was constant throughout the study in all animals, the difference

in uptake of the two volatile agents can be explained by their different blood solubilities, by different  $\dot{V}_A/Q$  scatter, and by the extent of intrapulmonary shunt. Previous models<sup>19</sup> and experimental data<sup>3</sup> indicate that shunt may impair uptake and that the effect is even higher for gases with low solubility. We demonstrate here that other modifications of  $\dot{V}_A/Q$  in addition to shunt (*e.g.*, broadening and shift of the distribution modes) can have similar effects. This is of particular interest when considering a patient with bronchoconstriction, who has little or no shunt but substantial ventilation of low  $\dot{V}_A/Q$  regions when awake, and shunt may be small, also during anesthesia.<sup>20</sup>

The bronchodilating effects of desflurane and isoflurane appear different in different species. In humans, desflurane and isoflurane exert similar effects on proximal airway tissues, whereas the effect on distal airways is lower for desflurane than isoflurane.<sup>21</sup> In contrast, experiments on rats revealed similar effects of the two volatile agents in protection from methacholine-induced bronchoconstriction.<sup>22</sup> Although we cannot exclude a differential alleviating effect of the volatile anesthetics on the methacholine-induced bronchoconstriction, it should be noted that respiratory mechanics were not influenced by the added volatile agents before and after methacholine inhalation.

Arterial oxygenation was markedly decreased during methacholine nebulization in both groups of piglets, but the effect was more pronounced in the desflurane group. This can be related to the increased shunt in desflurane piglets. Nunes *et al.*<sup>23</sup> described a shunt of approximately 23% for desflurane and 15% for isoflurane in spontaneously breathing healthy dogs, close to what we have found during methacholine nebulization. Although an influence of the volatile anesthetics themselves on shunt development cannot be excluded and is debated,<sup>24</sup> application of very high oxygen fractions is problematic, because they themselves can lead to significant amounts of shunt.<sup>25,26</sup> Although Nunes *et al.*<sup>23</sup> applied the volatile anesthetics in pure oxygen, in our study a fractional inspired oxygen tension of 0.4 was used, resulting in a  $P_{aO_2}$  of less than 225 mmHg and causing our Riley-shunt calculation to be susceptible to the influence of low  $\dot{V}_A/Q$  scatter.<sup>27</sup>

Methacholine stimulates muscarinic receptors and causes smooth muscle contraction. The  $M_1$  receptor, located in the alveolar wall, is likely to be involved in a parenchymal response, whereas the  $M_3$  receptor, located in the airway smooth muscles, is responsible for airway effects.<sup>28</sup> Aerosolized methacholine leads to constriction of both the airways and the parenchyma by affecting the different receptors and possibly by excessive parenchymal distortion caused by a heterogeneous response of the peripheral airways,<sup>29</sup> prompting heterogeneity of ventilation distribution and altering  $\dot{V}_A/Q$  distribution.

Modern inhalational anesthetics like desflurane have a very low blood solubility resulting in fast induction and fast emergence from anesthesia. The present data suggest that

kinetics of low soluble gases are more impaired by  $\dot{V}_A/Q$  mismatch and therefore could result in greater variability of kinetics between patients than higher soluble anesthetics like isoflurane, enflurane, or halothane. Even for the more soluble agents, the end-tidal volatile agent partial pressure in the presence of  $\dot{V}_A/Q$  mismatch is not necessarily a reliable measure for the arterial blood level, as shown by Frei *et al.*<sup>30</sup> for isoflurane. The molecular weight of the volatile anesthetic could also influence the end-tidal-to-arterial gradient, as suggested by Landon *et al.*<sup>31</sup>

A limitation of our study is that the anatomy of piglet and human lungs differs in ways that could affect translation of results. In contrast to piglets, humans have collateral ventilation,<sup>32</sup> therefore clinical methacholine effects may appear less severe than observed in pigs. However, patients suffering from obstructive lung diseases have been demonstrated to have  $\dot{V}_A/Q$  mismatch in distributions similar to the  $\dot{V}_A/Q$  abnormalities that we have measured in our model.<sup>33</sup>

Other errors could impact our calculations of uptake, including differences in solubility, variations in cardiac output, and errors in the calibration of the infrared analyzer. Although the pigs were placed on heating mats, variations of plus or minus 2°C around the normal body temperature did occur.

Two assumptions were made that allow us to derive uptake from the partial pressures and cardiac output measurements. First, the calculation of the uptake of inhaled agent across the alveolocapillary membrane was based on a calibration factor that assumed that the end-tidal anesthetic partial pressure approximated the arterial anesthetic partial pressure. We believe this to be the case because the pigs' lungs were healthy with minimal  $\dot{V}_A/Q$  abnormality, as evidenced by the absence of a significant alveolar-arterial partial pressure difference for carbon dioxide before methacholine administration. Second, we did not measure blood-gas partition coefficients but retrieved them from the literature<sup>4</sup> and assumed they would match this in the animals used in this study. Because the arterial partial pressure might have been lower than indicated by the end-expired partial pressure, the data presented in figure 5 may slightly overestimate uptake and elimination. The error arising from unmeasured alveolar-arterial differences for the two volatile agents is likely to be small and will effectively only scale the uptake calculations but will not substantially alter the results.

### Conclusions

The difference in solubility of volatile anesthetics has a significant influence on their uptake and elimination in a piglet model of bronchoconstriction and  $\dot{V}_A/Q$  mismatch. The higher soluble isoflurane is affected to a lower degree than the fairly insoluble desflurane. Respiratory diseases account for a large part of morbidity and mortality and are projected to increase in the coming years.<sup>34,35</sup> Significantly more patients suffering from lung conditions associated with  $\dot{V}_A/Q$

mismatch will thus be presented for elective surgery in the future. Therefore, an improved understanding of anesthesia induction and emergence and of anesthesia depth in patients with  $\dot{V}_A/Q$  mismatch undergoing volatile anesthesia seems to be warranted.

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## Competing Interests

Dr. Baumgardner is president of Oscillogy LLC (Pittsburgh, Pennsylvania), the manufacturer of the multiple inert gas elimination technique by micropore membrane inlet mass spectrometry system. The other authors declare no competing interests.

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