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Arterial and Mixed Venous Kinetics of Desflurane and Sevoflurane, Administered Simultaneously, at Three Different Global Ventilation to Perfusion Ratios in Piglets with Normal Lungs

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- The role of lung gas exchange in whole-body kinetics can be studied by direct measurements of anesthetic partial pressures in mixed venous (P_{mv}) and arterial (P_{art}) blood samples
- Washin and washout of desflurane should be more rapid than sevoflurane because sevoflurane has higher gas solubilities in blood and tissues

What This Article Tells Us That Is New

- The washin and washout kinetics of simultaneously administered desflurane and sevoflurane were assessed in seven piglets by measuring P_{mv} and P_{art} during uptake and elimination under normal, low, and high ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) conditions
- Faster arterial kinetics for desflurane were generally maintained for both washin and washout under all $\dot{V}_A/\dot{Q}$ conditions
- The low $\dot{V}_A/\dot{Q}$ condition decreased the differences in scaled P_{art} between 0 and 5 min; the high $\dot{V}_A/\dot{Q}$ condition increased these differences from the low $\dot{V}_A/\dot{Q}$ value to a value approaching or exceeding the value for normal $\dot{V}_A/\dot{Q}$
- Mixed venous kinetics were slower than arterial kinetics for washin and washout and were less influenced by $\dot{V}_A/\dot{Q}$

ABSTRACT

Background: Previous studies have established the role of various tissue compartments in the kinetics of inhaled anesthetic uptake and elimination. The role of normal lungs in inhaled anesthetic kinetics is less understood. In juvenile pigs with normal lungs, the authors measured desflurane and sevoflurane washin and washout kinetics at three different ratios of alveolar minute ventilation to cardiac output value. The main hypothesis was that the ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) of normal lungs influences the kinetics of inhaled anesthetics.

Methods: Seven healthy pigs were anesthetized with intravenous anesthetics and mechanically ventilated. Each animal was studied under three different $\dot{V}_A/\dot{Q}$ conditions: normal, low, and high. For each $\dot{V}_A/\dot{Q}$ condition, desflurane and sevoflurane were administered at a constant, subanesthetic inspired partial pressure (0.15 volume% for sevoflurane and 0.5 volume% for desflurane) for 45 min. Pulmonary arterial and systemic arterial blood samples were collected at eight time points during uptake, and then at these same times during elimination, for measurement of desflurane and sevoflurane partial pressures. The authors also assessed the effect of $\dot{V}_A/\dot{Q}$ on paired differences in arterial and mixed venous partial pressures.

Results: For desflurane washin, the scaled arterial partial pressure differences between 5 and 0 min were 0.70 ± 0.10, 0.93 ± 0.08, and 0.82 ± 0.07 for the low, normal, and high $\dot{V}_A/\dot{Q}$ conditions (means, 95% CI). Equivalent measurements for sevoflurane were 0.55 ± 0.06, 0.77 ± 0.04, and 0.75 ± 0.08. For desflurane washout, the scaled arterial partial pressure differences between 0 and 5 min were 0.76 ± 0.04, 0.88 ± 0.02, and 0.92 ± 0.01 for the low, normal, and high $\dot{V}_A/\dot{Q}$ conditions. Equivalent measurements for sevoflurane were 0.79 ± 0.05, 0.85 ± 0.03, and 0.90 ± 0.03.

Conclusions: Kinetics of inhaled anesthetic washin and washout are substantially altered by changes in the global $\dot{V}_A/\dot{Q}$ ratio for normal lungs.

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An understanding the kinetics of inhaled anesthetic uptake and elimination is fundamental to the clinical practice of anesthesia. Although the impact of different body compartments (*e.g.*, vessel rich group or viscera; muscle group; fat; specific organs) in uptake and elimination kinetics is well-established by many previous studies,[1–19] the role of lung gas exchange efficiency is less appreciated.[2,20–26] Our study examines the role of the global lung ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$; where ($\dot{V}_A$ represents alveolar minute ventilation and $\dot{Q}$ represents cardiac output value) on the washin and washout kinetics of desflurane and sevoflurane in pigs with normal lungs expected to have a unimodal and narrow $\dot{V}_A/\dot{Q}$ distribution. The global lung $\dot{V}_A/\dot{Q}$ ratio was manipulated by changes in both minute ventilation and cardiac output.

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Submitted for publication January 29, 2021. Accepted for publication August 12, 2021. From the Hedenstierna Laboratory, Department of Surgical Sciences (M.K., A.K., T.S., A.L.), Clinical Physiology, Department of Medical Sciences (G.H.), and Department of Anesthesia and Intensive Care (A.L.), Uppsala University, Uppsala, Sweden; Oscillogy LLC, Pittsburgh, Pennsylvania (J.E.B.); Department of Anesthesiology and Perioperative Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania (J.E.B.); and Department of Anesthesiology and Intensive Care Medicine, Otto von Guericke University, Magdeburg, Germany (M.K., A.K., T.H., T.S.).

To assess washin and washout kinetics, we measured anesthetic partial pressures in mixed venous (P_{mv}) and arterial (P_{art}) blood samples at multiple times during uptake and elimination of desflurane and sevoflurane for three different lung $\dot{V}_A/\dot{Q}$ ratios. The benefits of direct measurements of arterial and mixed venous partial pressures in blood, for studies of inhaled anesthetic kinetics, are well recognized.[15,17,24,27,28] Because of the technical difficulties in making these measurements, however, and the invasiveness, the majority of kinetic studies have measured either gas phase samples alone (*e.g.*, end-tidal partial pressure)[4,9–13,19,29–31] or end-tidal partial pressure and P_{art}.[21–23,25,32,33] Direct measurements of P_{art} and P_{mv} provide kinetic information that specifically focuses on pulmonary blood, and are well-suited for examining the role of lung gas exchange in whole-body kinetics. We compared P_{art} and P_{mv} kinetics for different $\dot{V}_A/\dot{Q}$ conditions graphically, and also analyzed the differences in partial pressures between fixed time points. Our primary hypothesis was that the kinetics of P_{art} and P_{mv} washin and washout would be altered by differences in the global $\dot{V}_A/\dot{Q}$ ratio.

The experimental maneuvers we used to alter $\dot{V}_A/\dot{Q}$ could potentially have confounding effects on tissue kinetics that would also impact P_{mv} and P_{art}, independent of the pulmonary effects. To more specifically examine the effect of global $\dot{V}_A/\dot{Q}$ on the pulmonary contribution to washin and washout kinetics, we also assessed the differences between P_{art} and P_{mv} and compared these differences between the three experimental $\dot{V}_A/\dot{Q}$ conditions. Our secondary hypothesis was that an increased global $\dot{V}_A/\dot{Q}$ ratio is associated with increased separation between P_{art} and P_{mv}.

Compared to desflurane, sevoflurane has higher gas solubilities in blood, tissues of the vessel rich group, muscle, and fat, suggesting that desflurane washin and washout should be more rapid than sevoflurane washin and washout.[13,34] Kinetics of desflurane have been confirmed to be faster than sevoflurane in several experimental studies.[13,35,36] The effect of overall lung $\dot{V}_A/\dot{Q}$ ratio, however, on differences in kinetics between sevoflurane and desflurane has not been reported. Our third hypothesis was that kinetics of washin and washout, as assessed by both arterial and mixed venous measurements, are faster for desflurane than for sevoflurane, and that this kinetic difference is maintained at both high and low $\dot{V}_A/\dot{Q}$ ratios.

Materials and Methods

Ethics Approval

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 guidelines laid out in the *Guide for the Care and Use of Laboratory Animals, 8th edition*.[37] The estimation of sample size was based on a previous experimental porcine study,[24] which used an analogous experimental setup. Power calculation using a two-sided paired *t* test at a significance level of 5% ($\alpha = 0.05$), a SD of 1.6 min for the time to 90% washin for desflurane,[24] and a power of 80% ($\beta = 0.20$) revealed that at least seven animals were needed to detect a difference of more than 50% (time to 90% washin of 4.4 min for baseline condition; absolute difference from baseline condition of 2.2 min) between the $\dot{V}_A/\dot{Q}$ conditions in the volatile washin period.

Animals

Seven juvenile, 2.5-month-old piglets (weight, mean ± SD 25 ± 2 kg) of Yorkshire/Norwegian country breeds of either sex (five males and two females), were used in the study. The animals fasted overnight with free access to water. The experiments were conducted between 8:00 AM and 3:00 PM. All piglets underwent the same preparatory algorithm (induction and maintenance of anesthesia, monitoring).

Anesthetic Management

As described previously in detail,[24,25] 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 a 7.0-mm ID 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, The Netherlands), followed by a continuous infusion of 2.5 mg · kg^{-1} · h^{-1} rocuronium. Anesthesia was maintained by continuous intravenous infusions of fentanyl (0.04 mg · kg^{-1} · h^{-1}; Leptanal; Janssen-Cilag AB, Sweden), midazolam (0.12 mg · kg^{-1} · h^{-1}; midazolam Actavis; Actavis Group, Iceland), and propofol (Diprivan; Astra, Sweden) *via* 18-gauge 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 a 9-mm ID cuffed endotracheal tube (Mallinckrodt, Ireland). Thereafter, the lungs were mechanically ventilated in volume-controlled mode, with fractional inspired oxygen tension of 0.4 and positive end-expiratory pressure set at 5 cm H_2O by a Servo 900 C ventilator (Maquet Critical Care, Sweden). The tidal volume was set to 10 ml/kg, inspiratory:expiratory ratio was set at 1:2, and respiratory frequencies were adjusted to achieve a normal end-tidal carbon dioxide 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 $NICO_2$ system that included volumetric capnometry (Respironics Novametrix, Inc., USA). 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 pulmonary artery catheter was used 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 measured by thermal dilution in duplicate and averaged for every time point for which blood samples were taken for desflurane and sevoflurane measurements.

All pigs received a right carotid arterial catheter for continuous arterial pressure measurements and for blood sampling (20-gauge; 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 pig blood (ABL 500 and OSM 3; Radiometer, Denmark). Finally, a suprapubic urinary catheter (Sympakath; Ruesch AG, Switzerland) was placed to monitor urine output.

Administration of Simultaneous Inhaled Anesthetics

Sevoflurane and desflurane were administered simultaneously *via* two KION ventilators (Siemens-Elema AB, Sweden) in an open system. The separate KION ventilators and their individual vaporizers were used to prepare controlled fresh gas flows and concentrations of each agent separately, and then the gas streams were combined for delivery to the animal by a third ventilator. Sevoflurane (Sevorane; Abbvie, Sweden) and desflurane (Suprane; Baxter International, USA) were administered with the vaporizers set at 0.3 volume% for sevoflurane and at 1 volume% for desflurane. The two KION ventilators were set to spontaneous breathing with equal fresh gas flow. The inspiratory limbs were connected to a 2.5-l mixing chamber, which connected to the low pressure port of the Servo 900 C ventilator. The total fresh gas flow was set to exceed double minute ventilation to make delivered gas fractions close to inspired gas fractions (0.15 volume% for sevoflurane and 0.5 volume% for desflurane after dilution in the mixing chamber). We used the lowest possible inspired fractions of sevoflurane and desflurane that delivered an acceptable signal-to-noise ratio in the arterial blood. This was done to minimize cardiovascular and pulmonary effects of the volatile agents.

Measurement of Sevoflurane and Desflurane by Micropore Membrane Inlet Mass Spectrometry

Arterial and mixed venous blood samples were collected in glass syringes (5 ml; FORTUNA OPTIMA; Luer-lock, Poulten & Graf GmbH, Germany) coated with EDTA for analysis by micropore membrane inlet mass spectrometry (MMIMS System; Oscillogy LLC, USA). The system uses a polymer membrane confined to multiple small micropores that separate the blood sample from the mass spectrometer and high-vacuum system. As blood samples flow over this membrane, gases diffuse through the membrane into the mass spectrometer for direct analysis of the gas partial pressures in the blood sample.[38,39] Sevoflurane ion currents were measured at the mass/charge ratio of 131. Desflurane ion currents were monitored at a mass/charge ratio of 101 and corrected for spectral overlap from sevoflurane. Before the animal experiments, we assessed spectral overlap in the mass spectrometer using pure, air-diluted desflurane and sevoflurane vapors and found no overlap of desflurane on the sevoflurane 131 peak, but an overlap of 0.337 of the 131 peak for sevoflurane on the 101 peak for desflurane.

Baseline Measurement of Global Alveolar $\dot{V}_A/\dot{Q}$

For each $\dot{V}_A/\dot{Q}$ condition (normal, low, high) during the base line period before inhaled anesthetic administration, data were collected for *post hoc* determination of the global $\dot{V}_A/\dot{Q}$ ratio. Cardiac output was measured in duplicate and averaged. Fifteen volumetric capnometry waveforms, with exclusion of waveforms with obvious artifacts, were selected from 2 min of $NICO_2$ data stored for *post hoc* analysis. The alveolar minute ventilation reported by the $NICO_2$ for each breath was averaged over these 15 breaths. The $NICO_2$ system calculates alveolar minute ventilation as exhaled minute ventilation minus airways and apparatus dead space, as determined by the Fowler method.[40] Averaged alveolar minute ventilation was then divided by averaged cardiac output to calculate $\dot{V}_A/\dot{Q}$ for each baseline period for each pig, and $\dot{V}_A/\dot{Q}$ was averaged across the seven pigs.

Experimental Protocol

Baseline

After an alveolar recruitment maneuver (40 cm H_2O for 10 s) and 30 min of stabilization after instrumentation, baseline hemodynamic, ventilation, and gas exchange data were obtained. After this baseline period, each animal underwent all three $\dot{V}_A/\dot{Q}$ conditions in nonrandomized order (normal, low, high), without blinding.

Normal $\dot{V}_A/\dot{Q}$

At the normal minute ventilation setting and for unmanipulated cardiac output, the inhaled anesthetics were begun at time zero. Arterial and mixed venous blood samples were obtained simultaneously after 0, 1, 2, 5, 10, 20, 30, and 45 min (washin). Thereafter, the inhalation of the volatile agents was discontinued, and the sampling sequence was repeated (washout).

Low Ventilation, High Cardiac Output

After completion of the washout and 15 min of stabilization, a continuous infusion of dobutamine was titrated with the target of doubling the cardiac output. When this goal was reached (mean, 5.4 mcg · kg^{-1} · min^{-1}), the minute ventilation was decreased to 40% of the control state by adjustment of the respiratory rate, keeping the tidal volume constant. The washin and washout sequence was repeated. The dobutamine infusion was discontinued and the minute ventilation normalized.

High Ventilation, Low Cardiac Output

In a final step after a stabilization period of about 30 min, a transfemorally placed Fogarty catheter (8-French; Edwards Lifesciences Nordic AB, Sweden) was inflated in the right atrium to decrease cardiac output, with a target of 30% reduction in cardiac output. The minute ventilation was increased by 40% by adjustment of the respiratory rate, keeping tidal volume constant, and the washin and washout sequence was again repeated.

The experimental protocol is depicted graphically in figure 1.

At the end of each study, the animals were euthanized with an intravenous injection of potassium chloride while under general anesthesia.

Graphic and Statistical Analysis

Hemodynamic and respiratory variables (tables 1 and 2) were tested for normality by the Shapiro–Wilk test (Sigmaplot version 13; Systat Software Inc., USA).

For each individual animal, and each of the three $\dot{V}_A/\dot{Q}$ conditions, arterial (P_{art}) and mixed venous (P_{mv}) mass spectrometer signals from the micropore membrane inlet mass spectrometry by the Micropore Membrane Inlet Mass Spectrometry System were scaled to that individual's arterial signal at the end of the 45-min desflurane and sevoflurane administration. For each $\dot{V}_A/\dot{Q}$ condition, the scaled signals at each time point were averaged across the seven animals and 99% CI determined using the Student's *t* distribution, and plotted as the means and CI for each time and each $\dot{V}_A/\dot{Q}$ condition (figs. 2 and 3). The mean values for washin and washout were also replotted for side-by-side comparisons of the effects of $\dot{V}_A/\dot{Q}$ condition on kinetics (fig. 4), and side-by-side comparisons of desflurane *versus* sevoflurane kinetics (fig. 5).

For each gas, each individual, and each $\dot{V}_A/\dot{Q}$ condition, we calculated the differences in scaled partial pressures between two time points to characterize the shapes of the washin and washout curves. For uptake, the fast phase of washin was characterized by the scaled partial pressure difference between 5 min and 0 min (SPP5-SPP0). The slow phase of washin was characterized by the scaled partial pressure difference between 30 min and 5 min (SPP30-SPP5). For elimination, the fast phase of washout was characterized by the scaled partial pressure difference between 0 min and 5 min (SPP0-SPP5). The slow phase of washout was characterized by the scaled partial pressure difference between 5 min and 30 min (SPP5-SPP30). Means and 95% CIs for these shape parameters are plotted in figure 6.

Secondary analysis of the scaled partial pressure differences was carried out by two-way ANOVA for repeated measures (Sigmaplot version 13; table 3). Individual analyses were carried out for each phase of washin or washout (fast phase and slow phase), for uptake and elimination, and for arterial and mixed venous measurements, yielding eight total analyses. Data sets were first tested for normality (Shapiro–Wilk) and equal variance (Brown–Forsythe), and all data sets passed both tests. Two-way ANOVA (first factor gas with two levels; second factor $\dot{V}_A/\dot{Q}$ condition, with three levels) for repeated measures (seven pigs) was carried out, and if significant differences ($P < 0.05$) were found, all-pairwise multiple comparison procedures were carried out *post hoc* (Holm–Sidak method). Significant differences are labeled in figure 6.

For each gas and each $\dot{V}_A/\dot{Q}$ condition, differences between P_{art} and P_{mv} were calculated at each time point (fig. 7). Areas under the ($P_{art} - P_{mv}$) *versus* time curves were

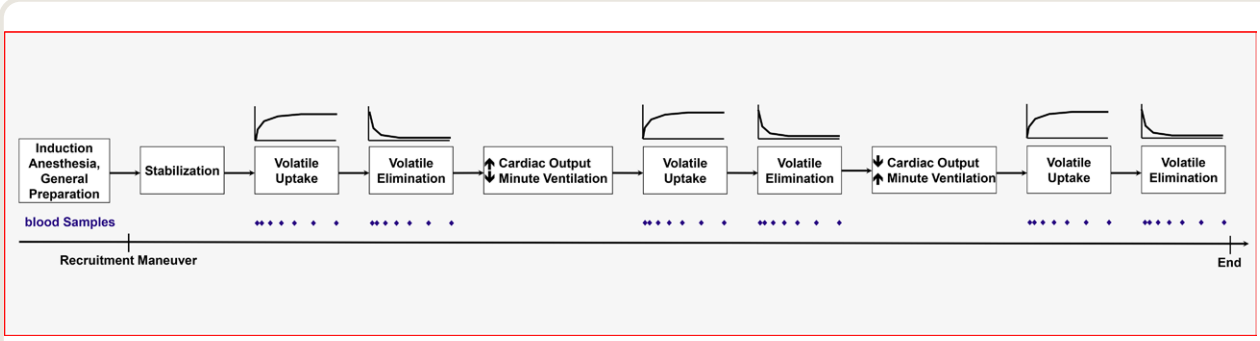

Fig. 1. Schematic of experimental protocol.

Table 1. Hemodynamic, Ventilation, and Gas Exchange Data—Uptake

	Normal $\dot{V}_A/\dot{Q}$			Low $\dot{V}_A/\dot{Q}$			High $\dot{V}_A/\dot{Q}$		
	0 Min	5 Min	30 Min	0 Min	5 Min	30 Min	0 Min	5 Min	30 Min
Hemodynamics									
CO, l/min	3.6 ± 0.8	3.5 ± 0.6	3.3 ± 0.7	6.6 ± 0.5	6.8 ± 0.4	6.5 ± 0.6	2.6 ± 0.3	2.4 ± 0.3	2.2 ± 0.2
MAP, mmHg	82 ± 10	76 ± 11	67 ± 11	84 ± 9	88 ± 6	83 ± 4	45 ± 2	45 ± 4	43 ± 2
MPAP, mmHg	22 ± 2	22 ± 2	22 ± 4	27 ± 3	29 ± 3	29 ± 3	21 ± 5	19 ± 2	18 ± 2
CVP, mmHg	11 ± 3	11 ± 1	11 ± 2	11 ± 2	11 ± 2	12 ± 2	10 ± 2	9 ± 1	9 ± 2
HR, 1/min	98 ± 12	89 ± 11	80 ± 16	123 ± 29	138 ± 19	130 ± 21	110 ± 17	113 ± 21	145 ± 37
Ventilation									
RR, 1/min	21 ± 1	21 ± 1	21 ± 1	15 ± 1	15 ± 0	15 ± 1	30 ± 1	30 ± 1	30 ± 1
$\dot{V}_E$, l/min	5.7 ± 0.6	5.9 ± 0.7	5.9 ± 0.7	3.8 ± 0.2	3.9 ± 0.3	3.9 ± 0.2	8.2 ± 0.4	8.3 ± 0.4	8.3 ± 0.4
Alveolar minute ventilation, l/min	3.0 ± 0.3	—	—	1.9 ± 0.4	—	—	3.8 ± 0.4	—	—
V_T, ml	278 ± 24	282 ± 23	283 ± 26	236 ± 31	250 ± 13	253 ± 17	275 ± 11	278 ± 9	279 ± 11
P_{MAX}, cm H_2O	19.1 ± 1.6	19.3 ± 1.4	19.9 ± 0.9	18.9 ± 1.9	19 ± 1.8	19.3 ± 1.5	21.7 ± 1.6	22.1 ± 1.8	22.7 ± 1.6
P_{MEAN}, cm H_2O	9.4 ± 0.8	9.7 ± 0.5	9.7 ± 0.5	9.1 ± 0.7	9.1 ± 0.7	9.1 ± 0.7	10.4 ± 0.5	10.3 ± 0.5	10.6 ± 0.5
PEEP, cm H_2O	5.9 ± 0.4	6 ± 0	5.9 ± 0.4	6.1 ± 0.7	5.9 ± 0.4	5.9 ± 0.4	6.1 ± 0.7	6 ± 0	5.9 ± 0.4
C_{dyn}, ml/cm H_2O	26 ± 4	25 ± 4	24 ± 2	23 ± 3	24 ± 2	22 ± 2	23 ± 3	22 ± 3	20 ± 3
Gas exchange									
Pao_2, mmHg	195 ± 8	187 ± 14	182 ± 10	134 ± 12	135 ± 11	133 ± 14	180 ± 9	164 ± 21	158 ± 12
$Paco_2$, mmHg	51 ± 5	50 ± 5	54 ± 5	68 ± 7	71 ± 8	78 ± 12	42 ± 3	43 ± 6	44 ± 5
$Petco_2$, mmHg	49 ± 5	47 ± 5	46 ± 6	68 ± 14	68 ± 14	70 ± 14	39 ± 2	37 ± 3	37 ± 4
Sao_2, %	97 ± 1	98 ± 1	97 ± 1	96 ± 1	96 ± 1	95 ± 1	98 ± 1	97 ± 1	97 ± 1
Pvo_2, mmHg	42 ± 1	40 ± 5	38 ± 7	53 ± 3	56 ± 4	45 ± 22	26 ± 3	23 ± 2	22 ± 2
$Pvco_2$, mmHg	67 ± 11	69 ± 7	72 ± 8	73 ± 6	80 ± 7	83 ± 5	69 ± 12	66 ± 12	73 ± 13
Svo_2, %	57 ± 4	51 ± 8	46 ± 12	72 ± 11	68 ± 2	66 ± 3	21 ± 8	18 ± 5	15 ± 5

All data passed the Shapiro–Wilk W test for normality and are presented as mean ± SD.

C_{dyn}, dynamic compliance; CO, cardiac output; CVP, central venous pressure; HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; $Paco_2$, arterial carbon dioxide tension; Pao_2, arterial oxygen tension; PEEP, positive end-expiratory pressure; $Petco_2$, end-tidal pressure of carbon dioxide; P_{MAX}, peak airway pressure; P_{MEAN}, mean airway pressure; $Pvco_2$, mixed venous carbon dioxide tension; Pvo_2, mixed venous oxygen tension; RR, respiratory rate; Sao_2, arterial oxygen saturation; Svo_2, mixed venous oxygen saturation; $\dot{V}_E$, minute ventilation; V_T, tidal volume; $\dot{V}_A/\dot{Q}$, ventilation/perfusion ratio.

calculated by the trapezoidal rule, and the areas were analyzed by two-way ANOVA for repeated measures (table 4). If significant differences ($P < 0.05$) were found, all pairwise multiple comparison procedures were carried out *post hoc* (Holm–Sidak method).

Arterial scaled partial pressure data were also analyzed by t90 and t10 analyses (table 5). For each animal, each gas, and each $\dot{V}_A/\dot{Q}$ condition, data points for scaled arterial signals during uptake were connected with straight line segments, and then the time point corresponding to the scaled signal reaching 0.90 (t90) was determined from this curve. Similarly, data points for scaled arterial signals during elimination were connected with straight line segments, and then the time point corresponding to the scaled signal reaching 0.10 (t10) was determined from this curve. Differences in means between desflurane *versus* sevoflurane, and between $\dot{V}_A/\dot{Q}$ conditions, were assessed by two-way repeated measures ANOVA.

Results

All seven piglets that entered the study completed the entire study. All measurements of arterial and mixed venous desflurane and sevoflurane partial pressures were completed at all time points, and there were no rejections for artifact.

Table 1 presents the hemodynamic, ventilation and respiratory mechanics, and gas exchange data for the three $\dot{V}_A/\dot{Q}$ conditions for three time points: the beginning of uptake, 5 min into uptake, and 30 min into uptake (45 min into uptake = time 0 for elimination and is presented in table 2). Table 2 presents data for time points in the elimination period. The hemodynamics, respiratory mechanics, and gas exchange were stable over the uptake and elimination of desflurane and sevoflurane (administered simultaneously) and were not systematically affected by the changing inhaled anesthetic concentrations at these low doses. Compared to the normal $\dot{V}_A/\dot{Q}$ condition, dobutamine administration increased cardiac output from 3.3 l/min to 6.5 l/min in the low $\dot{V}_A/\dot{Q}$ condition, and reduction of respiratory rate decreased alveolar minute ventilation from 2.9 l/min to 2.0 l/min. In the high $\dot{V}_A/\dot{Q}$ condition, inflation of the atrial balloon reduced cardiac output to 2.2 l/min, and the increase in respiratory rate increased alveolar minute ventilation to 3.7 l/min.

The kinetics of desflurane partial pressures in arterial and mixed venous blood during washin are shown in figure 2, top (fig. 2A to 2C), for the three conditions of $\dot{V}_A/\dot{Q}$: (1) normal $\dot{V}_A/\dot{Q}$ of 0.91; (2) low $\dot{V}_A/\dot{Q}$ of 0.32; and (3) high

Table 2. Hemodynamic, Ventilation and Gas Exchange Data—Elimination

	Normal $\dot{V}_A/\dot{Q}$			Low $\dot{V}_A/\dot{Q}$			High $\dot{V}_A/\dot{Q}$		
	0 Min	5 Min	45 Min	0 Min	5 Min	45Min	0 Min	5 Min	45 Min
Hemodynamics									
CO, l/min	3.3 ± 0.6	3.7 ± 0.7	3.6 ± 0.2	6.5 ± 0.5	5.9 ± 1.6	6.6 ± 0.3	2.2 ± 0.2	2.1 ± 0.2	2.1 ± 0.2
MAP, mmHg	73 ± 11	74 ± 10	73 ± 10	85 ± 3	84 ± 4	90 ± 3	45 ± 3	46 ± 4	44 ± 4
MPAP, mmHg	22 ± 3	22 ± 3	23 ± 1	28 ± 2	26 ± 11	30 ± 3	18 ± 2	19 ± 3	21 ± 2
CVP, mmHg	11 ± 1	12 ± 1	12 ± 2	12 ± 3	12 ± 3	11 ± 2	9 ± 2	9 ± 1	9 ± 1
HR, 1/min	83 ± 16	83 ± 13	81 ± 10	131 ± 23	126 ± 17	136 ± 21	161 ± 34	169 ± 35	190 ± 34
Ventilation									
RR, 1/min	21 ± 1	21 ± 1	21 ± 1	15 ± 1	15 ± 0	15 ± 1	30 ± 1	30 ± 1	30 ± 1
$\dot{V}_E$, l/min	5.9 ± 0.7	5.8 ± 0.6	5.8 ± 0.6	3.9 ± 0.2	3.8 ± 0.2	3.8 ± 0.3	8.2 ± 0.4	8.2 ± 0.4	8.2 ± 0.3
Alveolar minute ventilation, l/min	2.9 ± 0.3	—	—	2.0 ± 0.2	—	—	3.7 ± 0.4	—	—
V_T, ml	281 ± 25	277 ± 28	276 ± 26	252 ± 15	246 ± 15	246 ± 16	276 ± 12	273 ± 12	272 ± 11
P_{MAX}, cm H_2O	21 ± 1	21 ± 1	21 ± 2	19 ± 2	19 ± 2	20 ± 2	22 ± 2	23 ± 2	24 ± 1
P_{MEAN}, cm H_2O	9.9 ± 0.4	9.9 ± 0.4	9.9 ± 0.4	9.3 ± 0.8	9.6 ± 0.8	9.9 ± 0.7	10.6 ± 0.5	10.7 ± 0.5	10.7 ± 0.5
PEEP, cm H_2O	5.9 ± 0.4	5.9 ± 0.4	6.0 ± 0.6	5.7 ± 0.5	5.9 ± 0.4	5.9 ± 0.4	5.9 ± 0.4	5.9 ± 0.4	5.9 ± 0.4
C_{dyn}, ml/cm H_2O	23 ± 3	22 ± 2	22 ± 2	22 ± 2	22 ± 2	21 ± 2	20 ± 2	16 ± 8	18 ± 2
Gas exchange									
Pao_2, mmHg	179 ± 12	182 ± 18	184 ± 17	132 ± 12	130 ± 13	128 ± 14	154 ± 20	160 ± 22	163 ± 22
$Paco_2$, mmHg	53 ± 7	53 ± 7	51 ± 3	74 ± 6	79 ± 6	73 ± 9	42 ± 5	43 ± 6	42 ± 4
$Petco_2$, mmHg	48 ± 6	48 ± 5.	48 ± 5	70 ± 14	71 ± 15	71 ± 15	37 ± 3	37 ± 3	37 ± 3
Sao_2, %	97 ± 1	97 ± 1	97 ± 1	95 ± 1	95 ± 1	95 ± 1	97 ± 1	97 ± 1	97 ± 1
Pvo_2, mmHg	38 ± 7	39 ± 8	37 ± 4	55 ± 4	47 ± 23	53 ± 3	22 ± 2	24 ± 3	23 ± 3
$Pvco_2$, mmHg	68 ± 7	70 ± 5	69 ± 5	87 ± 7	92 ± 16	82 ± 8	70 ± 12	71 ± 10	70 ± 10
Svo_2, %	48 ± 14	48 ± 14	46 ± 8	65 ± 3	65 ± 3	65 ± 4	14 ± 5	16 ± 5	13 ± 3

All data passed the Shapiro–Wilk W test for normality and are presented as mean ± SD.

C_{dyn}, dynamic compliance; CO, cardiac output; CVP, central venous pressure; HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; $Paco_2$, arterial carbon dioxide tension; Pao_2, arterial oxygen tension; PEEP, positive end-expiratory pressure; $Petco_2$, end-tidal pressure of carbon dioxide; P_{MAX}, peak airway pressure; P_{MEAN}, mean airway pressure; $Pvco_2$, mixed venous carbon dioxide tension; Pvo_2, mixed venous oxygen tension; RR, respiratory rate; Sao_2, arterial oxygen saturation; Svo_2, mixed venous oxygen saturation; $\dot{V}_E$, minute ventilation; V_T, tidal volume; $\dot{V}_A/\dot{Q}$, ventilation/perfusion ratio.

$\dot{V}_A/\dot{Q}$ of 1.73. The arterial and mixed venous data for desflurane partial pressures during washout are shown in figure 2, bottom (fig. 2D to 2F). Sevoflurane washin and washout data are shown in figure 3.

Side-by-side comparisons of the results for all three $\dot{V}_A/\dot{Q}$ conditions are presented in figure 4, where lines connecting the mean values are shown without CI or symbols to enhance readability. For desflurane (fig. 4A), for washin, the experimental interventions that altered $\dot{V}_A/\dot{Q}$ slowed arterial increases toward equilibrium for both interventions, with more slowing for the low $\dot{V}_A/\dot{Q}$ condition. Washin kinetics as measured in mixed venous blood were also slowed by both interventions, with more slowing for the high $\dot{V}_A/\dot{Q}$ condition. For desflurane washout, compared to normal $\dot{V}_A/\dot{Q}$, low $\dot{V}_A/\dot{Q}$ slowed arterial kinetics, and high $\dot{V}_A/\dot{Q}$ accelerated arterial kinetics. The mixed venous kinetics, however, were slowed by both $\dot{V}_A/\dot{Q}$ perturbations, in the low $\dot{V}_A/\dot{Q}$ condition paralleling the slower arterial washout, and in the high $\dot{V}_A/\dot{Q}$ condition contrasting the faster arterial washout.

For sevoflurane (fig. 4B), the low $\dot{V}_A/\dot{Q}$ condition slowed arterial washin compared to normal $\dot{V}_A/\dot{Q}$, whereas high $\dot{V}_A/\dot{Q}$ had little effect on arterial washin. Compared to normal $\dot{V}_A/\dot{Q}$, neither intervention had much effect on mixed venous washin kinetics. For sevoflurane washout, very similar to the desflurane results, high $\dot{V}_A/\dot{Q}$ accelerated arterial kinetics, and low $\dot{V}_A/\dot{Q}$ slowed arterial kinetics, whereas both interventions slowed mixed venous kinetics.

Side-by-side visual comparisons of desflurane and sevoflurane are presented in figure 5, where lines connecting the mean values are shown without CI or symbols to enhance readability. In nearly all side-by-side comparisons, desflurane kinetics were slightly faster than sevoflurane kinetics, with two exceptions: the kinetics were nearly equivalent for mixed venous washin in the low $\dot{V}_A/\dot{Q}$ condition, and mixed venous washin was slightly faster for sevoflurane than for desflurane in the high $\dot{V}_A/\dot{Q}$ condition.

Figure 6A shows the mean and CI, for the uptake period, for the scaled partial pressure difference between 5 min and 0 min (SPP5-SPP0, the fast phase shape parameter for uptake) as influenced by gas (sevoflurane *vs.* desflurane), sample site (arterial *vs.* mixed venous), and $\dot{V}_A/\dot{Q}$ condition (normal, low, or high). For arterial samples, the order of magnitude for SPP5-SPP0 compared between $\dot{V}_A/\dot{Q}$ conditions was normal ≈ high > low for both gases, where a larger SPP5-SPP0 indicates faster kinetics. For desflurane washin, the SPP5-SPP0 values were 0.70 ± 0.10, 0.93 ± 0.08, and 0.82 ± 0.07 for the low, normal, and high $\dot{V}_A/\dot{Q}$ conditions (mean ± 95% CI). For sevoflurane washin, the SPP5-SPP0 values were 0.55 ± 0.06, 0.77 ± 0.04, and 0.75

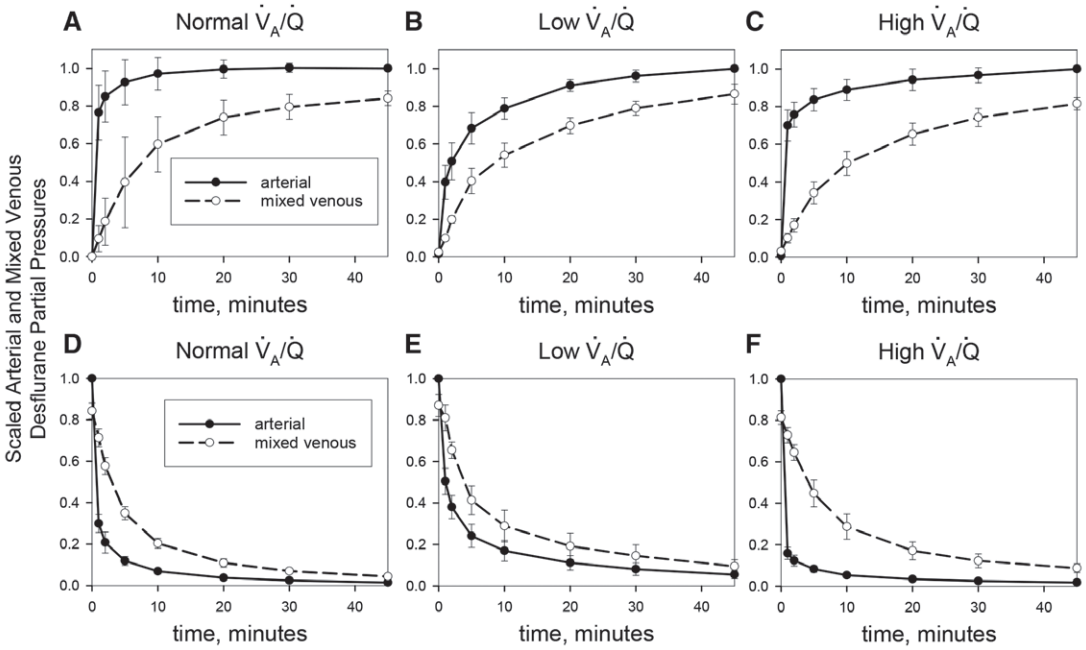

Fig. 2. Scaled desflurane partial pressures in arterial blood (*solid line* and *filled circles*) and mixed venous blood (*dashed line* and *open circles*) during the uptake period (*upper, A to C*), for the three ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) conditions (normal, low, and high). Mean values for seven pigs, with 99% CI; no excluded data points. Partial pressures for each pig are scaled to the arterial partial pressure at the end of uptake (45 min) for that pig. Scaled desflurane partial pressures during the elimination period are shown in the *lower* panels (*D to F*). No excluded data points. Partial pressures for each pig are scaled to the arterial partial pressure at the end of uptake (45 min) for that pig.

± 0.08 for the low, normal, and high $\dot{V}_A/\dot{Q}$ conditions. The ANOVA analysis found that for both gases, the high $\dot{V}_A/\dot{Q}$ group SPP5-SPP0 was significantly different from low, and the normal $\dot{V}_A/\dot{Q}$ was significantly different from low. The normal $\dot{V}_A/\dot{Q}$ was significantly different from high $\dot{V}_A/\dot{Q}$ for desflurane but not for sevoflurane. As assessed by the arterial samples, desflurane washin was faster than sevoflurane washin, an effect found to be significant in the ANOVA analysis. For the mixed venous samples, for desflurane, the order of SPP5-SPP0 was normal > low > high, and all three differences were significant in the ANOVA analysis. The $\dot{V}_A/\dot{Q}$ condition made little difference to the magnitude of SPP5-SPP0 for sevoflurane, for mixed venous measurements. As assessed by the mixed venous samples, desflurane washin kinetics were faster than sevoflurane washin kinetics, a difference identified as statistically significant in the ANOVA analysis.

Figure 6B shows the mean and CI, for the uptake period, for the scaled partial pressure difference between 30 min and 5 min (SPP30-SPP5, the slow phase shape parameter for uptake). For arterial samples, the order of magnitude for SPP30-SPP5 compared between $\dot{V}_A/\dot{Q}$ conditions was low > high ≈ normal for both gases. The ANOVA analysis found that for both gases, the normal $\dot{V}_A/\dot{Q}$ group SPP30-SPP5 was significantly different from low, and for sevoflurane, the high $\dot{V}_A/\dot{Q}$ was significantly different from low. As assessed by the arterial samples, sevoflurane washin was slightly faster than desflurane washin, an effect that was statistically significant in the ANOVA analysis. For the mixed venous samples, for desflurane, the order of SPP30-SPP5 was high > low > normal, but the differences were small. $\dot{V}_A/\dot{Q}$ condition made little difference to the magnitude of SPP30-SPP5 for sevoflurane, for mixed venous measurements. As assessed by the mixed venous samples, sevoflurane washin kinetics were faster than desflurane washin kinetics, and this difference was statistically significant in the ANOVA analysis.

Figure 6C shows the mean and CI, for the elimination period, for the scaled partial pressure difference between 0 minutes and 5 minutes (SPP0-SPP5, the fast phase shape parameter for elimination). For arterial samples, the order of magnitude for SPP0-SPP5 compared between $\dot{V}_A/\dot{Q}$ conditions was high > normal > low for both gases. For desflurane washout, the SPP0-SPP5 values were 0.76 ± 0.04, 0.88 ± 0.02, and 0.92 ± 0.01 for the low, normal, and high $\dot{V}_A/\dot{Q}$ conditions (mean ± 95% CI). For sevoflurane washout, the SPP0-SPP5 values were 0.79 ± 0.05, 0.85 ± 0.03, and 0.90 ± 0.03 for the low, normal, and high $\dot{V}_A/\dot{Q}$ conditions. All three differences (normal *vs.* low, normal *vs.* high, and high *vs.* low), for sevoflurane, were statistically significant in the ANOVA analysis. For desflurane, normal *versus* low and

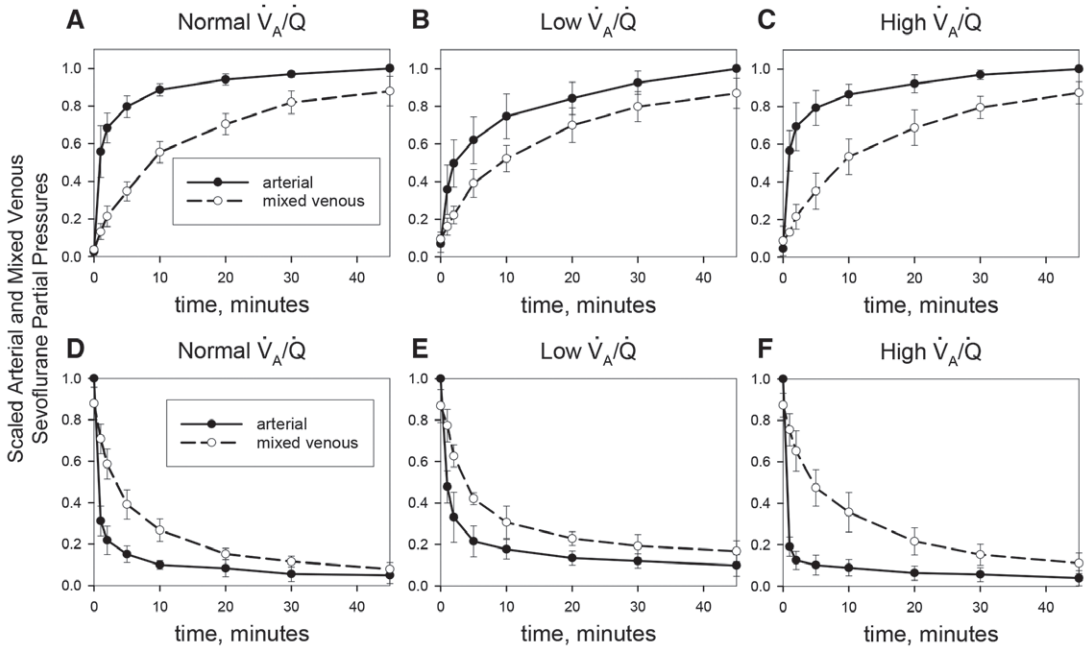

Fig. 3. Scaled sevoflurane partial pressures in arterial blood (*solid line* and *filled circles*) and mixed venous blood (*dashed line* and *open circles*) during the uptake period (*upper, A to C*), for the three ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) conditions (normal, low, and high). Mean values for seven pigs, with 99% CI; no excluded data points. Partial pressures for each pig are scaled to the arterial partial pressure at the end of uptake (45 min) for that pig. Scaled sevoflurane partial pressures during the elimination period are shown in the *lower* panels (*D to F*). No excluded data points. Partial pressures for each pig are scaled to the arterial partial pressure at the end of uptake (45 min) for that pig.

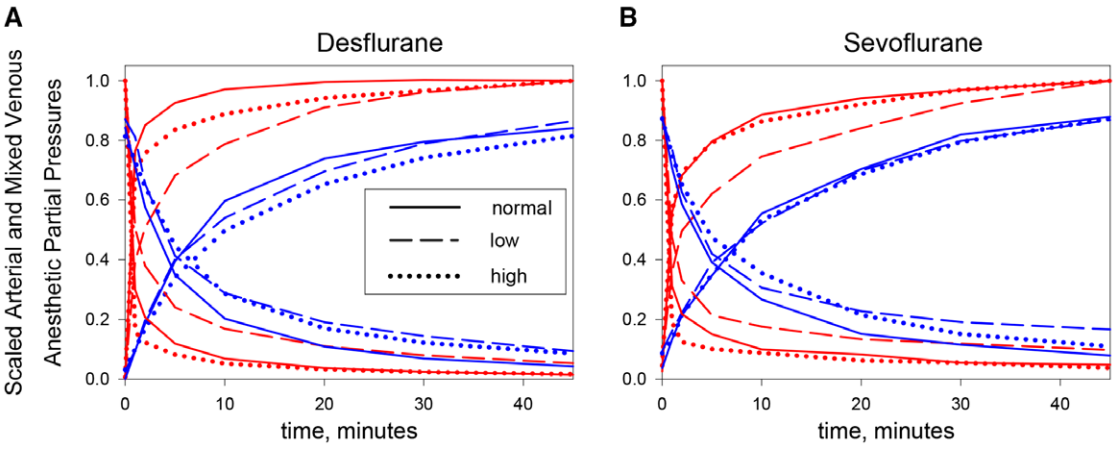

Fig. 4. Side-by-side comparisons of the effects of ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) conditions on washin and washout curves for desflurane (*A*) and sevoflurane (*B*). For clarity, the CI and symbols from figures 2 and 3 are omitted, and only the lines connecting time points are presented. Normal $\dot{V}_A/\dot{Q}$ is represented with *solid lines*, low $\dot{V}_A/\dot{Q}$ with *dashed lines*, and high $\dot{V}_A/\dot{Q}$ with *dotted lines*. Arterial measurements are represented in *red*, and mixed venous measurements are represented in *blue*.

high *versus* low were significantly different. As assessed by the arterial samples, desflurane washout speed was approximately equal to the speed of sevoflurane washout, with no significant difference in the ANOVA analysis. For the mixed venous samples, for both gases, the order of SPP0-SPP5 was normal > low > high, but the differences were small, and none of the differences between the $\dot{V}_A/\dot{Q}$ groups were significant for either gas. As assessed by the mixed venous

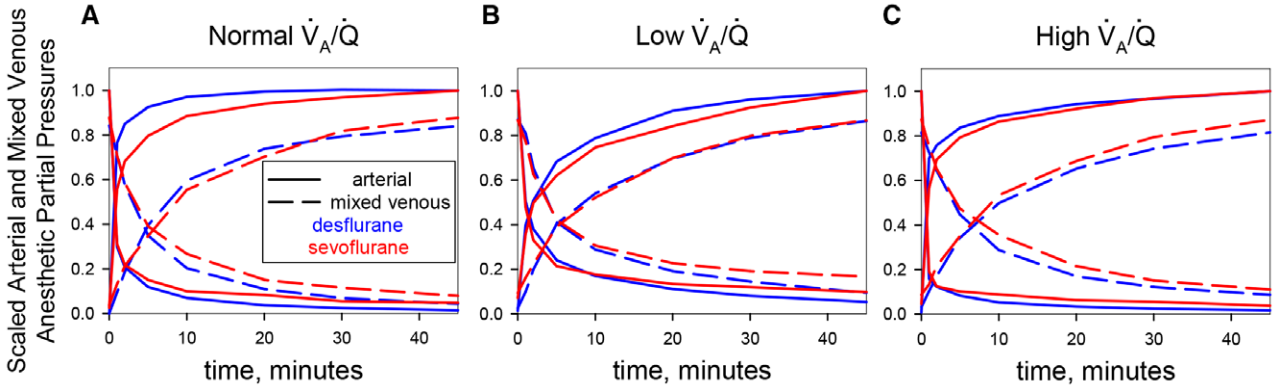

Fig. 5. Side-by-side comparisons of uptake and elimination kinetics for desflurane *versus* sevoflurane, for the three ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) conditions. For clarity, the CI and symbols from figures 2 and 3 are omitted, and only the lines connecting time points are presented. Desflurane in *blue*, sevoflurane in *red*; arterial measurements represented by *solid lines*, mixed venous by *dashed lines*.

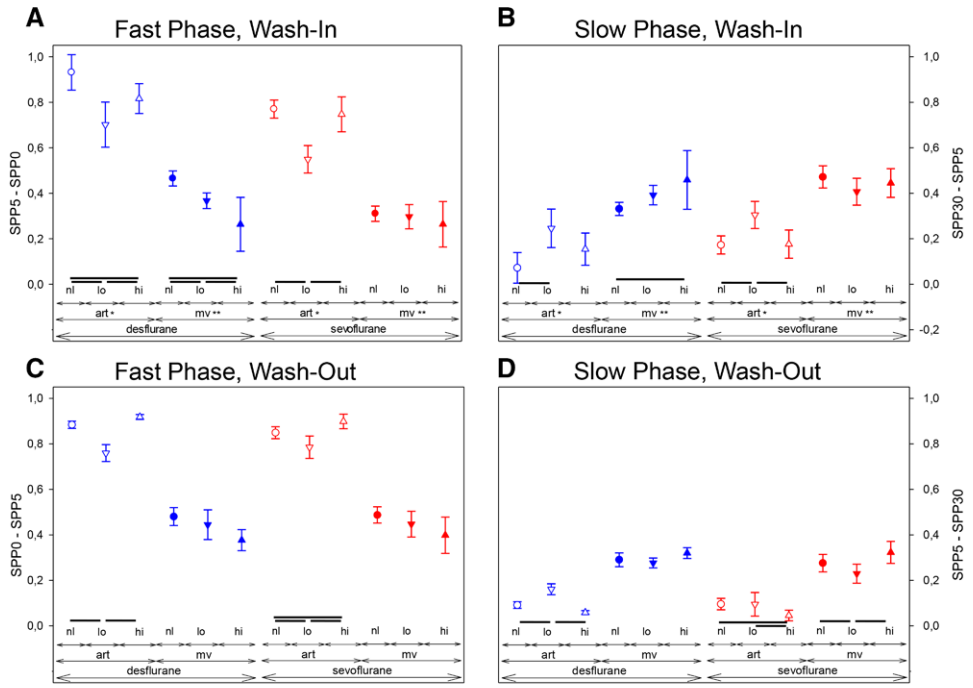

Fig. 6. Means and 95% CIs for the curve shape parameters describing the fast and slow phases of washin and washout. The fast phases of washin curves are characterized by the difference in scaled partial pressure between 5 min and 0 min (SPP5-SPP0; *A, upper left*). The slow phases of washin curves are characterized by the difference in scaled partial pressure between 30 min and 5 min (SPP30-SPP5; *B, upper right*). For washout (*lower, C and D*), fast and slow phases are characterized by SPP0-SPP5 (*C, lower left*), and SPP5-SPP30 (*D, lower right*). "nl, lo, hi" represent the ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) condition (normal, low, and high $\dot{V}_A/\dot{Q}$) . The $\dot{V}_A/\dot{Q}$ condition is also encoded by symbol shape: *circle* = normal, *inverted triangle* = low, *triangle* = high. "art" = arterial measurements, "mv" = mixed venous measurements, also encoded in the symbols (*open* = arterial, *filled* = mixed venous). Desflurane in *blue*, sevoflurane in *red. Overhead lines* connecting $\dot{V}_A/\dot{Q}$ conditions signify significant differences ($P < 0.05$) between the conditions from the ANOVA analysis. *Significant differences ($P < 0.05$) between desflurane and sevoflurane from the ANOVA analyses of arterial samples. **Significant differences ($P < 0.05$) between desflurane and sevoflurane from the ANOVA analyses of mixed venous samples.

Table 3. Results of the Two-way Repeated Measures ANOVA for Arterial and Mixed Venous Shape Parameters for Washin and Washout of the Anesthesia Gases

		Washin						Washout					
		Arterial			Mixed Venous			Arterial			Mixed Venous		
Source of Variation	Degrees of Freedom	Mean Square	F Ratio	*P* Value	Mean Square	F Ratio	*P* Value	Mean Square	F Ratio	*P* Value	Mean Square	F Ratio	*P* Value
SPP5 – SPP0 (fast phase shape parameter)													
Subject	6	0.009			0.007			0.0006			0.008		
Gas	1	0.17	60.5	< 0.001	0.06	10.7	0.017	0.0009	0.57	0.479	0.001	0.62	0.462
$\dot{V}_A/\dot{Q}$	2	0.19	21.7	< 0.001	0.05	9.36	0.004	0.07	69.6	< 0.001	0.03	7.58	0.007
Gas × $\dot{V}_A/\dot{Q}$	2	0.009	2.27	0.145	0.02	3.68	0.057	0.004	2.61	0.114	0.0003	0.18	0.838
SPP30 – SPP5 (slow phase shape parameter)													
Subject	6	0.006			0.006			0.0006			0.002		
Gas	1	0.04	23.9	0.003	0.02	6.06	0.049	0.007	4.61	0.076	0.004	3.29	0.12
$\dot{V}_A/\dot{Q}$	2	0.09	11.3	0.002	0.01	1.70	0.224	0.02	32.7	< 0.001	0.02	10.6	0.002
Gas × $\dot{V}_A/\dot{Q}$	2	0.005	1.55	0.252	0.02	4.98	0.027	0.005	4.09	0.044	0.002	1.88	0.195

Gas, levels of gas, either desflurane or sevoflurane; $\dot{V}_A/\dot{Q}$, levels of ventilation/perfusion ratio, either normal, low, or high; gas × $\dot{V}_A/\dot{Q}$, interaction of gas and $\dot{V}_A/\dot{Q}$.

samples, speeds of sevoflurane and desflurane washout were approximately equal.

Figure 6D shows the mean and CI, for the elimination period, for the scaled partial pressure difference between 5 min and 30 min (SPP5-SPP30, the slow phase shape parameter for elimination). For arterial desflurane samples, the order of magnitude for SPP5-SPP30 was low > normal > high, and the normal *versus* low and high *versus* low comparisons were identified as significant in the ANOVA analysis. For arterial sevoflurane samples, the order of magnitude for SPP5-SPP30 was normal ≈ low > high, and the normal *versus* high and low *versus* high comparisons were identified as significant in the ANOVA analysis. For the mixed venous samples, the order of magnitude for SPP5-SPP30 compared between $\dot{V}_A/\dot{Q}$ conditions was high > normal > low, for both gases, but the differences were small, and only for sevoflurane were the normal *versus* low and high *versus* low differences significant. As assessed by both arterial and mixed venous samples, desflurane and sevoflurane washout had similar slow phase kinetics.

Table 3 presents the two-way repeated measures ANOVA analyses of the data in figure 6.

Figure 7, upper (fig. 7A to 7C), presents the results for the arterial-mixed venous differences in anesthetic partial pressure *versus* time ($P_{art} - P_{mv}$) for the uptake period. Figure 7, lower (fig. 7D to 7F), presents the results for the partial pressure differences *versus* time ($P_{mv} - P_{art}$) for the elimination period. Table 4 presents the areas under the curves for these plots and the results for two-way repeated measures ANOVA analysis of these area-under-the-curve results. There was an association between higher $\dot{V}_A/\dot{Q}$ and more separation between the arterial and mixed venous partial pressures for both washin and washout.

All data points were included for every plot for figures 2 to 7 and for their ANOVA analyses (tables 3 and 4)

Table 5 shows the results of the t90 (time for the scaled signal to reach 90% of its final value, on uptake) and t10 (time for the scaled signal to reach 10% of its initial value, on elimination) analyses for the arterial washin and washout data. For table 5, all animal subjects, $\dot{V}_A/\dot{Q}$ groups, and data points were included for the washin t90 ANOVA analysis. For the t10 washout analysis, three animals in the low $\dot{V}_A/\dot{Q}$ group did not reach 10% at 45 minutes, and these data points were excluded from the analysis. The remaining t10 data points passed tests for normality and equal variance after log transformation, and two-way repeated measures ANOVA was carried out on the log-transformed data.

Discussion

Our study experimentally examined the effects of global lung $\dot{V}_A/\dot{Q}$, for normal lungs, expected to have a unimodal and narrow $\dot{V}_A/\dot{Q}$ distribution, on the arterial and mixed venous kinetics of desflurane and sevoflurane during uptake and elimination. Previous studies that have explored the

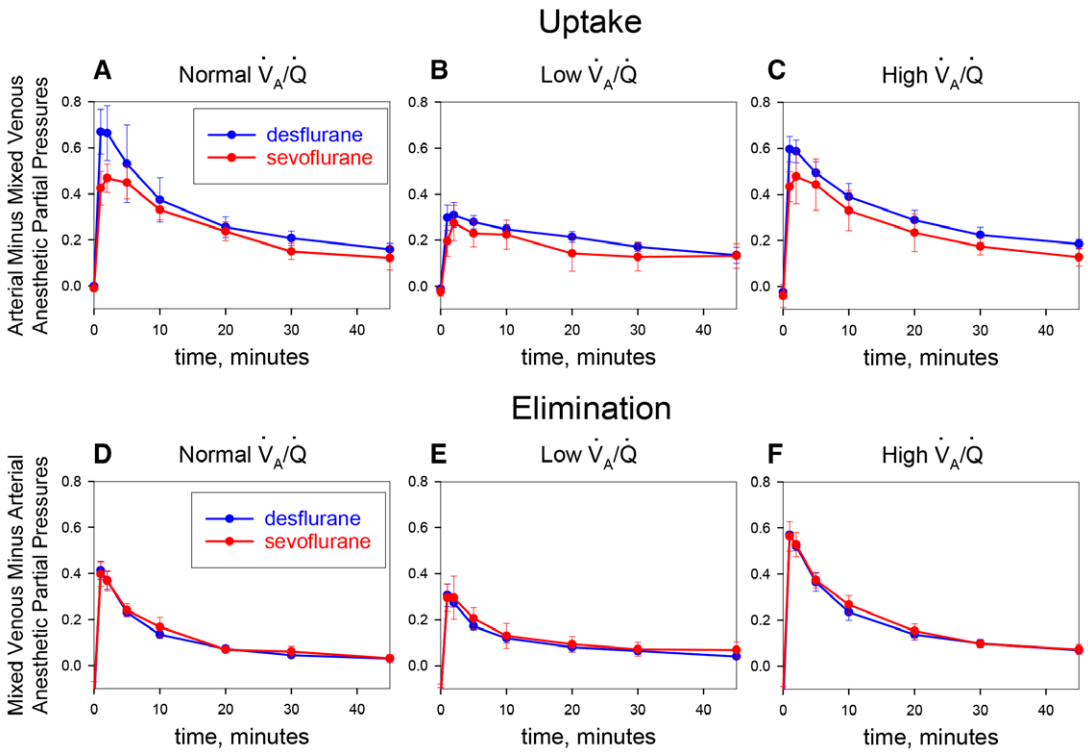

Fig. 7. Arterial minus mixed venous scaled partial pressure differences during the uptake period (*upper, A to C*), for the three ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) conditions (normal, low, and high). Mixed venous minus arterial scaled partial pressure differences during the elimination period are shown in the *lower* panels (*D to F*). Desflurane represented in *blue*, sevoflurane in *red*. Mean values and 95% CIs, no outliers excluded.

effects of lung gas exchange inefficiency on uptake and elimination kinetics have focused on $\dot{V}_A/\dot{Q}$ distribution abnormalities, including shunt,[20,21,23] dead space,[22] and other types of abnormal $\dot{V}_A/\dot{Q}$ distributions.[20,24–26] Also, some previous experimental and mathematical modeling studies have investigated the effects of individual changes in minute ventilation or cardiac output on anesthetic kinetics,[2,6–8,14,15,30,41,42] or parallel changes in both cardiac output and minute ventilation.[5]

The interventions that produced the three different $\dot{V}_A/\dot{Q}$ conditions (normal, low, and high $\dot{V}_A/\dot{Q}$) caused marked changes in the time course of P_{art} and P_{mv} for both washin and washout (figs. 2 to 4), suggesting that the global $\dot{V}_A/\dot{Q}$ ratio has an important impact on uptake and elimination kinetics. The majority of the scaled partial pressure differences between 0 and 5 minutes, and between 5 and 30 minutes, were substantially different between the $\dot{V}_A/\dot{Q}$ conditions (fig. 6), supporting the visual impression from figures 2 to 4 that $\dot{V}_A/\dot{Q}$ markedly affects washin and washout kinetics.

Although individual comparisons between different experimental conditions (desflurane *vs.* sevoflurane; normal *vs.* low *vs.* high $\dot{V}_A/\dot{Q}$; arterial *vs.* mixed venous measurements; uptake period *vs.* elimination period; and fast *vs.* slow phases) are complex and vary with the individual comparisons, several general features emerge from the data presented in figures 4 to 6. First, desflurane was generally faster than sevoflurane, most prominently for arterial measurements during washin (figs. 5 and 6A). The desflurane–sevoflurane kinetic differences were also observed for the slow phase of washout (fig. 5) for both arterial and mixed venous measurements.

Second, the experimental interventions to create the different $\dot{V}_A/\dot{Q}$ conditions generally had a substantial impact on the anesthetic kinetics, most prominently for arterial measurements for both washin and washout. Compared to the normal $\dot{V}_A/\dot{Q}$ condition, the low $\dot{V}_A/\dot{Q}$ condition decreased the differences in scaled arterial partial pressures between 0 and 5 minutes, whereas the high $\dot{V}_A/\dot{Q}$ condition increased these differences from the low $\dot{V}_A/\dot{Q}$ value to a value approaching or exceeding the value for normal $\dot{V}_A/\dot{Q}$.

Third, the assessment of anesthetic kinetics from mixed venous measurements produces different results than assessment from arterial measurements. Mixed venous kinetics were not only slower than arterial kinetics for both washin and washout but also less influenced by $\dot{V}_A/\dot{Q}$ (fig. 4).

Our experimental design prioritized the creation of a wide range of global $\dot{V}_A/\dot{Q}$ for assessing the effects of $\dot{V}_A/\dot{Q}$

Table 4. Two-way Repeated Measures ANOVA Analysis of the Area under the Curve for Washin ($P_{art} - P_{mv}$) and Washout ($P_{mv} - P_{art}$) and Pairwise Multiple Comparison (Holm–Sidak)

	Desflurane Normal $\dot{V}_A/\dot{Q}$	Desflurane Low $\dot{V}_A/\dot{Q}$	Desflurane High $\dot{V}_A/\dot{Q}$	Sevoflurane Normal $\dot{V}_A/\dot{Q}$	Sevoflurane Low $\dot{V}_A/\dot{Q}$	Sevoflurane High $\dot{V}_A/\dot{Q}$
Uptake						
AUC mean, min	13.27	9.17	13.73	10.79	7.33	11.07
Two-way repeated measures ANOVA for AUC $P_{art} - P_{mv}$						
Source of Variation	Degrees of freedom	Type III sum of squares	Mean square	F ratio	*P* value	
Subject	6	42.2	7.04			
Gas	1	57.0	57.0	61.2	< 0.001	
Gas × subject	6	5.59	0.93			
$\dot{V}_A/\dot{Q}$	2	148	73.9	11.1	0.002	
$\dot{V}_A/\dot{Q}$ × subject	12	80.1	6.68			
Gas × $\dot{V}_A/\dot{Q}$	2	1.29	0.64	0.32	0.733	
Pairwise Multiple Comparison for AUC $P_{art} - P_{mv}$						
Comparison	Diff of Means	t	*P* value			
Desflurane *vs.* sevoflurane	2.33	7.82	< 0.001			
High $\dot{V}_A/\dot{Q}$ *vs.* low $\dot{V}_A/\dot{Q}$	4.15	4.25	0.003			
Normal $\dot{V}_A/\dot{Q}$ *vs.* low $\dot{V}_A/\dot{Q}$	3.78	3.87	0.004			
High $\dot{V}_A/\dot{Q}$ *vs.* normal $\dot{V}_A/\dot{Q}$	0.38	0.39	0.707			
Elimination						
AUC mean, min	4.49	4.29	7.84	4.96	4.97	8.33
Two-way repeated measures ANOVA for AUC $P_{mv} - P_{art}$						
Source of variation	Degrees of freedom	Type III sum of squares	Mean square	F ratio	*P* value	
Subject	6	14.4	2.41			
Gas	1	3.09	3.09	26.7	0.002	
Gas × subject	6	0.69	0.12			
$\dot{V}_A/\dot{Q}$	2	108	54.2	74.7	< 0.001	
$\dot{V}_A/\dot{Q}$ × subject	12	8.71	0.73			
Gas × $\dot{V}_A/\dot{Q}$	2	0.10	0.05	0.09	0.919	
Pairwise multiple comparison for AUC $P_{mv} - P_{art}$						
Comparison	Diff of means	t	*P* value			
Sevoflurane *vs.* desflurane	0.54	5.17	0.002			
High $\dot{V}_A/\dot{Q}$ *vs.* low $\dot{V}_A/\dot{Q}$	3.46	10.7	< 0.001			
High $\dot{V}_A/\dot{Q}$ *vs.* normal $\dot{V}_A/\dot{Q}$	3.36	10.4	< 0.001			
Normal $\dot{V}_A/\dot{Q}$ *vs.* low $\dot{V}_A/\dot{Q}$	0.10	0.30	0.767			

AUC, area under the curve; $\dot{V}_A/\dot{Q}$, ventilation/perfusion ratio.

on kinetics. For the low $\dot{V}_A/\dot{Q}$ condition, we decreased ventilation while simultaneously increasing cardiac output; for the high $\dot{V}_A/\dot{Q}$ condition, the opposite changes were induced. These perturbations, however, could have also influenced tissue blood flow and distribution of tissue flow between the several tissue groups, thereby altering the kinetics of P_{art} and P_{mv} independent of the effects of the $\dot{V}_A/\dot{Q}$ condition on lung factors. The increase in tissue blood flow from increased cardiac output, for example, is expected to alter the tissue time constants and speed tissue uptake and elimination. The dobutamine infusion that increased total blood flow might also have altered the distribution of blood flow between the vessel rich group, the muscle group, and fat, and could have altered tissue kinetics in unpredictable ways. The atrial occlusion used to reduce cardiac output could also lead to alterations in flow distribution by altering the contributions of superior and inferior caval flow to total cardiac output. Similar effects could result from the mechanical changes in thoracic pressure with manipulation of minute ventilation. Hypocarbia and hypercarbia from altered minute ventilation could also alter the distribution of flows between tissues. The overall effects of these potential confounding factors are complicated and difficult to predict, and would be very difficult to control experimentally.

We therefore attempted to look more specifically at the effects of global $\dot{V}_A/\dot{Q}$ and lung gas exchange on kinetics, and minimize potential confounding from tissue effects, by also examining the differences between P_{art} and P_{mv}. At high $\dot{V}_A/\dot{Q}$, as $\dot{V}_A/\dot{Q}$ approaches infinity, we would expect alveolar partial pressure and arterial partial pressure to approach the partial pressure of inspired gas (open circuit inspired partial pressure for uptake, 0 for elimination) and to be more separated from P_{mv}. At low $\dot{V}_A/\dot{Q}$, as $\dot{V}_A/\dot{Q}$ approaches 0, we would expect P_{alv} and P_{art} to approach P_{mv}. At any given time, the P_{art}-P_{mv} difference reflects the extent of equilibration of mixed venous blood as it traverses the lung, and the time-averaged difference should be less dependent on

Table 5. Arterial t90 (Washin) and t10 (Washout)

	Desflurane	Sevoflurane
t90, min		
Normal $\dot{V}_A/\dot{Q}$	4.6 ± 4.3*	12.5 ± 3.7*
Low $\dot{V}_A/\dot{Q}$	19.0 ± 2.5*†	25.7 ± 6.2*†
High $\dot{V}_A/\dot{Q}$	12.7 ± 7.2*†	15.5 ± 5.4*‡
t10, min		
Normal $\dot{V}_A/\dot{Q}$	6.2 ± 1.1*	12.5 ± 6.4*
Low $\dot{V}_A/\dot{Q}$	23.2 ± 6.6†	31.8 ± 3.9†
High $\dot{V}_A/\dot{Q}$	3.6 ± 1.1*†‡	9.2 ± 8.1*†‡

Presented as mean ± SD.

*$P < 0.05$ between gases. †$P < 0.05$ *vs.* control within same gas. ‡$P < 0.05$ *vs.* low $\dot{V}_A/\dot{Q}$ within same gas.

t90, time for scaled arterial partial pressure to reach 90% of its value at 45 min, for wash-in; t10, time for scaled arterial partial pressure to reach 10% of its value at 45 min, for washout;

$\dot{V}_A/\dot{Q}$, ventilation/perfusion ratio.

confounding tissue kinetic effects than direct comparisons of P_{art} *versus* P_{art}, and P_{mv} *versus* P_{mv}. Our results support the concept that higher $\dot{V}_A/\dot{Q}$ widens the gap between P_{art} and P_{mv} (fig. 7; table 4), and if all other factors were equal, a higher $\dot{V}_A/\dot{Q}$ would therefore accelerate the kinetics of both uptake and elimination.

Our study also provides a side-by-side comparison of desflurane *versus* sevoflurane kinetics under different $\dot{V}_A/\dot{Q}$ conditions (figs. 2, 3, 5, and 6). Previous experimental studies in small pigs[13] and in human volunteers[35,36] have established that washin and washout are faster for desflurane than for sevoflurane, as assessed by end-tidal anesthetic measurements. The effect of global $\dot{V}_A/\dot{Q}$ on this relationship, however, has not been previously reported. Our results (figs. 5 and 6) demonstrate that faster arterial kinetics for desflurane are generally maintained at all three $\dot{V}_A/\dot{Q}$ conditions for both washin and washout. Of interest, however, is the finding that for mixed venous kinetics, these kinetic differences are sometimes reversed—for example, in the high $\dot{V}_A/\dot{Q}$ condition during uptake (fig. 5C).

Our study has several limitations. We did not directly measure the $\dot{V}_A/\dot{Q}$ distributions in our piglets. Previous measurements in this normal pig model in our laboratory, however, have shown normal distributions, *i.e.*, a single, narrow primary $\dot{V}_A/\dot{Q}$ mode with little shunt or alveolar dead space.[24,25] Our experiments were not blinded, and the order of $\dot{V}_A/\dot{Q}$ conditions was not randomized. To create a wide range of $\dot{V}_A/\dot{Q}$, $\dot{V}$ and $\dot{Q}$ were both altered simultaneously, rather than fixing the $\dot{Q}$ constant and varying $\dot{V}$, and *vice versa*. Finally, the fractional weights of the tissue groups and fractional flows to these groups in our juvenile piglets are unlikely to exactly match the corresponding values in adult human patients.

Our study also has several strengths. The mass spectrometer–based measurement system we used features high sensitivity, allowing the use of subanesthetic partial pressures that would be expected to have little effect on cardiac output, distributions of cardiac output, or ventilation mechanics and lung $\dot{V}_A/\dot{Q}$ distributions. Anesthetic gas partial pressures were measured directly in small blood samples, with no extraction into a gas phase, no errors from extraction techniques, and no dependence on individual variations in solubility.[38,39] We measured mixed venous as well as arterial anesthetic partial pressures to fully characterize anesthetic entry into, and exit from, pulmonary blood. Finally, the combination of small blood sample volumes and rapid analysis time facilitated relatively dense sampling times during washin and washout.

In summary, the global $\dot{V}_A/\dot{Q}$ ratio for normal lungs had substantial and complex effects on the washin and washout kinetics for desflurane and sevoflurane, most prominently for the arterial measurements. Increased $\dot{V}_A/\dot{Q}$ ratio was associated with increased arterial–mixed venous differences for the anesthetic gases. For all three $\dot{V}_A/\dot{Q}$ ratios, desflurane kinetics were faster than sevoflurane kinetics.

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Competing Interests

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

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