Isoflurane and Sevoflurane Anesthesia in Pigs with a Preexistent Gas Exchange Defect

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Background: Decreased arterial partial pressure of oxygen (Pa_{O_2}) during volatile anesthesia is well-known. Halothane has been examined with the multiple inert gas elimination technique and has been shown to alter the distribution of pulmonary blood flow and thus Pa_{O_2}. The effects of isoflurane and sevoflurane on pulmonary gas exchange remain unknown. The authors hypothesized that sevoflurane with a relatively high minimum alveolar concentration (MAC) would result in significantly more gas exchange disturbances in comparison with isoflurane or control.

Methods: This study was performed in a porcine model with an air pneumoperitoneum that generates a reproducible gas exchange defect. After a baseline measurement of pulmonary gas exchange (multiple inert gas elimination technique) during propofol anesthesia, 21 pigs were randomly assigned to three groups of seven animals each. One group received isoflurane anesthesia, one group received sevoflurane anesthesia, and one group was continued on propofol anesthesia (control). After 30 min of volatile anesthesia at 1 MAC or propofol anesthesia, a second measurement (multiple inert gas elimination technique) was performed.

Results: At the second measurement, inert gas shunt was 15 ± 3% (mean ± SD) during sevoflurane anesthesia *versus* 9 ± 1% during propofol anesthesia ($P = 0.02$). Blood flow to normal ventilation/perfusion ($\dot{V}_A/\dot{Q}$) lung areas was 83 ± 5% during sevoflurane anesthesia *versus* 89 ± 1% during propofol anesthesia ($P = 0.04$). This resulted in a Pa_{O_2} of 88 ± 11 mmHg during sevoflurane anesthesia *versus* 102 ± 15 mmHg during propofol anesthesia ($P = 0.04$). Inert gas and blood gas variables during isoflurane anesthesia did not differ significantly from those obtained during propofol anesthesia.

Conclusions: In pigs with an already existent gas exchange defect, sevoflurane anesthesia but not isoflurane anesthesia causes significantly more gas exchange disturbances than propofol anesthesia does.

VOLATILE anesthetics are known to decrease the arterial partial pressure of oxygen (Pa_{O_2}).[1] One recognized mechanism behind this phenomenon is the inhibition of hypoxic pulmonary vasoconstriction (HPV).[1,2] HPV represents an autonomic regulatory mechanism of the pulmonary circulation whose primary function is to divert blood flow away from poorly aerated lung areas, thereby improving ventilation/perfusion ($\dot{V}_A/\dot{Q}$) matching. HPV is a function of both decreased alveolar partial pressure of oxygen ($P_{A_{O_2}}$) and decreased mixed venous partial pressure of oxygen ($P\bar{v}_{O_2}$).[3] Inhibition of this local vasoconstriction may modify the distribution of blood flow in the lung. Considerable research was performed regarding the effect of halothane on HPV, pulmonary gas exchange, and Pa_{O_2}. Besides the proven influence of halothane on the HPV,[4] halothane alters the distribution of pulmonary ventilation and blood flow,[5] major determinants of pulmonary $\dot{V}_A/\dot{Q}$ matching and thus of Pa_{O_2}. In the latter study, Dueck *et al.*[5] showed that halothane anesthesia redistributes pulmonary blood flow toward lung areas with low and zero $\dot{V}_A/\dot{Q}$ ratios in patients with chronic obstructive lung disease. Meanwhile, halothane has been widely replaced by isoflurane and sevoflurane as standard anesthetics. Contrasting with halothane, the effects of these newer anesthetics on the distribution of pulmonary blood flow and ventilation remain uncertain. In patients with reactive airway disease and chronic obstructive pulmonary disease, however, volatile anesthetics are favored, but further increases of $\dot{V}_A/\dot{Q}$ mismatch during inhalational anesthesia are undesirable in these patients. Isoflurane and sevoflurane might be contraindicated when gas exchange defects are present. In the current study, we sought to examine how isoflurane and sevoflurane affect pulmonary gas exchange in a porcine model with preexisting right-to-left shunt. We hypothesized that sevoflurane resulted in significantly more gas exchange disturbances in comparison with isoflurane or control.

Methods

Animal Preparation

After approval of the Federal Animal Investigational Committee of Vienna, Austria, this study was performed in 21 healthy, 16- to 18-week-old pigs weighing 40–45 kg. Animals were fasted overnight but had free access to water. Already in the stable, pigs were premedicated with azaperone (4 mg/kg intramuscular) and atropine (0.01 mg/kg intramuscular) 1 h before surgery. Anesthesia was induced using propofol (2–4 mg/kg intravenous). After intubating the trachea, the lungs were ventilated in a volume-controlled mode (SA-2, semi-open circle; Dräger, Lübeck, Germany) at an inspiratory fraction of oxygen of 0.3 (oxygen enriched air), a tidal volume of 10 ml/kg, and 17 breaths/min. Positive end-expiratory pressure was set to 5 cm H_2O. Respiratory rate was then adjusted to achieve an arterial partial pressure of carbon dioxide (Pa_{CO_2}) between 35 and 40 mmHg. Respirator settings were not changed there-

after. Until the baseline measurement, anesthesia was maintained using propofol (6 mg · kg^{-1} · h^{-1}) and piritramide (30 mg). Ringer's solution (6 ml · kg^{-1} · h^{-1}) and a 3% gelatin solution (4 ml · kg^{-1} · h^{-1}) were administered throughout the study period. A standard lead II electrocardiograph was used to monitor cardiac rhythm. If cardiovascular variables indicated a reduced depth of anesthesia during the preparatory phase, additional propofol and piritramide were administered. Body temperature was maintained between 38 and 39°C using an electric heating blanket.

Generating a Standardized Pulmonary Gas Exchange Defect

In the current study, the pigs' peritoneal cavities were insufflated with purified air at a pressure of 15 cm H$_2$O because pneumoperitoneum results in a reproducible redistribution of pulmonary blood flow to lung areas with a $\dot{V}_A/\dot{Q}$ ratio of zero (shunt).[6] The intraperitoneal pressure was then continuously monitored and maintained at 15 cm H$_2$O using a manometer (VBM Kontroll Inflator; VBM Medizintechnik, Sulz, Germany).[6]

Hemodynamic Measurements and Calculations

A 7-French catheter was advanced into the aorta for withdrawal of arterial blood and measurement of mean arterial blood pressure. A 7-French pulmonary artery catheter was advanced into a pulmonary artery to measure mean pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac output (thermodilution technique) and to withdraw mixed venous blood. All catheters were saline-filled and connected to standard pressure transducers that had been zeroed to ambient pressure at the level of the right atrium. Pulmonary vascular resistance index (dyn · s · cm^{-5} · kg^{-1}) was then calculated according to the standard formula.

Blood Gas and Inert Gas Measurements

Arterial and mixed venous blood gases were measured with a blood gas analyzer (Chiron, East Walpol, MA). $\dot{V}_A/\dot{Q}$ distributions were determined using the multiple inert gas elimination technique as previously described.[7–9] Briefly, a mixture of six inert gases, including sulfur hexafluoride, ethan, cyclopropane, halothane, ether, and acetone dissolved in saline, was infused *via* an auricular vein at a rate of 3 ml · kg^{-1} · h^{-1}. This infusion was started 1 h before the first set of measurements. Ten-milliliter mixed venous and arterial blood samples were collected in duplicate into heparinized matched-barrel glass syringes. Mixed expired gas samples of 30 ml were collected from a heated mixing chamber. All samples were kept at a temperature of 38.5°C and then analyzed. Gas extraction was performed as described by Wagner *et al.*[7] Concentrations of inert gases were measured using gas chromatography (HP-5890, Series II; Hewlett-Packard, Wilmington, DE). $\dot{V}_A/\dot{Q}$ distributions

were determined from inert gas data by using the 50-compartment model of Wagner *et al.*[7–9] Calculation of $\dot{V}_A/\dot{Q}$ distributions in subjects anesthetized with volatile anesthetics requires a different approach to obtain the retention–solubility relation of the inert gases because the chromatographic peaks of isoflurane and sevoflurane superpose the halothane peak, one of the six inert tracer gases. Because halothane could not be measured chromatographically from samples taken during isoflurane or sevoflurane anesthesia, calculation of the retention–solubility curve was performed using five inert gases in all measurements after baseline. In measurements taken at baseline, six tracer gases were used for calculation. Measures to obtain the isolated chromatographic halothane peak during isoflurane or sevoflurane anesthesia, such as increasing the gas chromatograph's oven temperature during the experimental runs,[10] were dropped for two reasons. First, the chromatogram of sevoflurane has an extremely wide basis at the standard temperature of the method, which could only be narrowed using much higher oven temperatures or increased carrier gas flow rates. This in turn results in decreased or lost discrimination of less-soluble tracer gases. Furthermore, for isolation of sevoflurane's chromatographic peak, temperatures above the allowed maximum temperature (180°C) for packed columns used are needed. Second, halothane represents one point in the unbowed section of the retention–solubility curve. Calculation of the distribution using five gases omitting halothane results only in a negligible deviation from the calculation with six gases.

Distributions of $\dot{V}_A$ and $\dot{Q}$ are presented as:

1. blood flow to unventilated lung units, *shunt flow* ($\dot{V}_A/\dot{Q} < 0.005$)
2. blood flow to poorly ventilated lung units, *low $\dot{V}_A/\dot{Q}$* (low $\dot{V}_A/\dot{Q} > 0.005$–0.1)
3. blood flow to normally ventilated lung units, *normal $\dot{V}_A/\dot{Q}$* ($\dot{V}_A/\dot{Q} > 0.1$–10)
4. blood flow to poorly perfused lung units, *high $\dot{V}_A/\dot{Q}$* ($\dot{V}_A/\dot{Q} > 10$–100)
5. ventilation of nonperfused lung units, *alveolar dead space* ($\dot{V}_A/\dot{Q} > 100$)

The residual sum of squares was used as an indicator of fit of the data to this 50-compartment model.[9]

Experimental Protocol

Between completed animal preparation and baseline measurement, 30 min were allowed for corrections of body temperature and corrections of the fluid status (targeted by central venous pressure and pulmonary capillary wedge pressure) in all animals. Pigs were randomly assigned to three groups. After generating an air pneumoperitoneum 30 min before the baseline measurement, all groups received propofol until the baseline measurement, which included hemodynamic, blood gas, and inert gas measurements. Isoflurane (n = 7), sevoflu-

rane (n = 7), or propofol (n = 7, control) anesthesia was continued for 30 min, and then a second set of measurements was performed. Isoflurane and sevoflurane were administered at 1 human MAC end-tidal concentration (1.15% and 2.0%,[11] respectively). Control group animals received propofol at 6 mg · kg^{-1} · h^{-1}.

Statistical Analysis

Repeated-measures two-way analysis of variance was used to determine statistical intergroup and intragroup significance. Two-sided tests were used. Nonparametric tests were additionally used in the analysis of the amount of blood flow to lung areas with a low $\dot{V}_A/\dot{Q}$ ratio. Significant results were analyzed *post hoc* using the Newman–Keuls test. $P < 0.05$ was considered significant. Data are presented as mean ± SD. Sample size (n = 7) was based on data from a pilot study performed in three animals for a type I error of 0.05 and a power of 0.9.

Results

Comparing baseline values, no significant intergroup difference was found in any parameter.

Respiratory Data

Respiratory minute volume remained stable. Values are shown in table 1.

Hemodynamic Findings and Calculations

Data are presented in table 2. Except for an increase in heart rate during sevoflurane anesthesia, no significant differences were detected. Other measured or calculated variables, including mean pulmonary artery pressure, pulmonary capillary wedge pressure, pulmonary vascular resistance index, and cardiac index, remained unchanged during the study period.

Blood Gas and Inert Gas Measurements and Calculations

Data are presented in tables 1 and 2 and figure 1. Inert gas shunt was significantly increased in animals treated with sevoflurane, whereas isoflurane had no influence on this variable. Blood flow to lung areas with a normal $\dot{V}_A/\dot{Q}$ ratio and a normal Pa$_{O_2}$ were significantly depressed in animals treated with sevoflurane. Residual sums of squares were comparable throughout the measurements. Considering all measurements performed, 88% of the sums of squares were less than 5.3, and 97.6% were less than 10.6. At the second measurement calculated using five inert gases, 90.4% of the residual sums of squares were less than 5.3, and 95.2% were less than 10.6. Other inert gas or blood gas variables remained statistically unchanged throughout the measurements. Venous admixture in percent of cardiac output was calculated using the standard formula corrected for an

Table 1. Respiratory, Inert Gas, and Acid–Base Status Variables

	Baseline	+ 30 min
RMV (l/min)		
Control	8.0 ± 0.6	7.8 ± 0.7
Isoflurane	7.9 ± 0.9	7.8 ± 0.9
Sevoflurane	8.4 ± 0.4	8.4 ± 0.4
Log SDQ		
Control	0.8 ± 0.3	0.8 ± 0.3
Isoflurane	0.9 ± 0.3	0.9 ± 0.2
Sevoflurane	0.7 ± 0.4	1.0 ± 0.3
Log SDV		
Control	0.7 ± 0.3	0.7 ± 0.3
Isoflurane	0.8 ± 0.3	0.8 ± 0.2
Sevoflurane	0.7 ± 0.4	1.1 ± 0.3
Temperature (°C)		
Control	38.8 ± 0.2	38.3 ± 0.3
Isoflurane	38.6 ± 0.4	38.6 ± 0.5
Sevoflurane	38.5 ± 0.4	38.5 ± 0.4
Hemoglobin (mg/dl)		
Control	8.9 ± 0.4	9.1 ± 0.6
Isoflurane	9.3 ± 0.6	9.0 ± 0.5
Sevoflurane	9.8 ± 0.3	9.6 ± 0.4
Pa$_{CO_2}$ (mmHg)		
Control	35.6 ± 3.3	37.2 ± 3.2
Isoflurane	35.3 ± 2.5	33.6 ± 3.9
Sevoflurane	38.3 ± 4.8	39.4 ± 6.6
*p*Ha		
Control	7.51 ± 0.03	7.49 ± 0.05
Isoflurane	7.51 ± 0.05	7.52 ± 0.06
Sevoflurane	7.48 ± 0.04	7.49 ± 0.05
Ppeak (cm H$_2$O)		
Control	20 ± 1	20 ± 1
Isoflurane	20 ± 1	21 ± 2
Sevoflurane	20 ± 1	20 ± 1

Data are displayed as mean ± SD. At baseline (left column), all animals were anesthetized using propofol. The right column reflects values after 30 min of inhalational anesthesia or control.

RMV = respiratory minute volume; log SDQ = log SD of the distribution of perfusion; log SDV = log SD of the distribution of ventilation; temperature = body temperature, Pa$_{CO_2}$ = arterial partial pressure of carbon dioxide; *p*Ha = arterial *p*H; Ppeak = peak airway pressure.

inspiratory fraction of oxygen of 0.3. At baseline, venous admixtures were 18 ± 4% (control group), 18 ± 3% (isoflurane group), and 17 ± 5% (sevoflurane group). At the second measurement, venous admixtures were 18 ± 2% (control group), 20 ± 7% (isoflurane group), and 23 ± 6% (sevoflurane group).

Discussion

In the current study, we examined the influence of isoflurane and sevoflurane on pulmonary gas exchange. In comparison with a control group anesthetized with propofol, sevoflurane but not isoflurane further impaired gas exchange in a pig model with a preexisting gas exchange defect. Propofol was selected for the control group because it is not known to alter Pa$_{O_2}$.[12] Multiple inert gas elimination technique analysis showed that during sevoflurane anesthesia, blood flow to lung areas with a $\dot{V}_A/\dot{Q}$ ratio of zero (shunt) was increased, whereas blood flow to lung areas with a normal $\dot{V}_A/\dot{Q}$ ratio was

Table 2. Hemodynamic and Blood Gas Variables and Calculations

	Baseline	+ 30 min
HR (beats/min)		
Control	116 ± 18	112 ± 14
Isoflurane	114 ± 6	122 ± 10
Sevoflurane	116 ± 22	130 ± 8*
MAP (mmHg)		
Control	96 ± 9	96 ± 8
Isoflurane	102 ± 7	92 ± 9
Sevoflurane	100 ± 15	90 ± 15
MPAP (mmHg)		
Control	25 ± 1	25 ± 3
Isoflurane	24 ± 3	24 ± 3
Sevoflurane	24 ± 4	24 ± 4
PCWP (mmHg)		
Control	16 ± 1	15 ± 1
Isoflurane	15 ± 1	15 ± 1
Sevoflurane	15 ± 1	16 ± 1
PVRI (dyn · s · cm^{-5} · kg^{-1})		
Control	4,755 ± 786	5,349 ± 1,997
Isoflurane	4,831 ± 1,860	4,129 ± 1,712
Sevoflurane	4,535 ± 1,371	4,910 ± 2,266
Pvo$_2$		
Control	44 ± 2	47 ± 2
Isoflurane	47 ± 2	45 ± 1
Sevoflurane	45 ± 4	43 ± 3
CI (ml · kg^{-1} · min^{-1})		
Control	150 ± 7	152 ± 12
Isoflurane	152 ± 9	152 ± 5
Sevoflurane	157 ± 16	154 ± 21

Data are displayed as mean ± SD. At baseline (left column), all animals were anesthetized using propofol. The right column reflects values after 30 min of inhalational anesthesia or control.

* $P < 0.05$ in comparison to control.

HR = heart rate; MAP = mean aortic pressure; MPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVRI = pulmonary vascular resistance index; Pvo$_2$ = mixed venous partial pressure of oxygen; CI = cardiac index.

reduced. Pao$_2$ was correspondingly decreased. Calculating the pulmonary vascular resistance index, no reduction indicating inhibition of HPV was observed during inhalational anesthesia. The influence of inhalational anesthetics on HPV seems to be ambivalent. Based on a number of studies, Nunn[13] concluded that inhalational anesthetics inhibit HPV by direct action, whereas they may intensify HPV by reducing mixed venous Po$_2$ (Pvo$_2$) as a result of decreasing cardiac output. In our experiment, neither isoflurane nor sevoflurane at 1 MAC had any effect on cardiac output or Pvo$_2$. Comparing our results with those Dueck *et al.*[10] found in humans shows that the effects of sevoflurane are comparable to those of halothane. Both drugs apparently redistribute pulmonary blood flow away from lung areas with a normal $\dot{V}_A/\dot{Q}$ ratio toward lung areas with a lower $\dot{V}_A/\dot{Q}$ ratio or shunt. Why sevoflurane but not isoflurane exerts this influence on pulmonary blood flow cannot be determined from our data. Possible reasons include the different inspiratory concentrations applied and the different physical properties of the examined volatile anesthetics. Also, methodologic reasons should be considered. How-
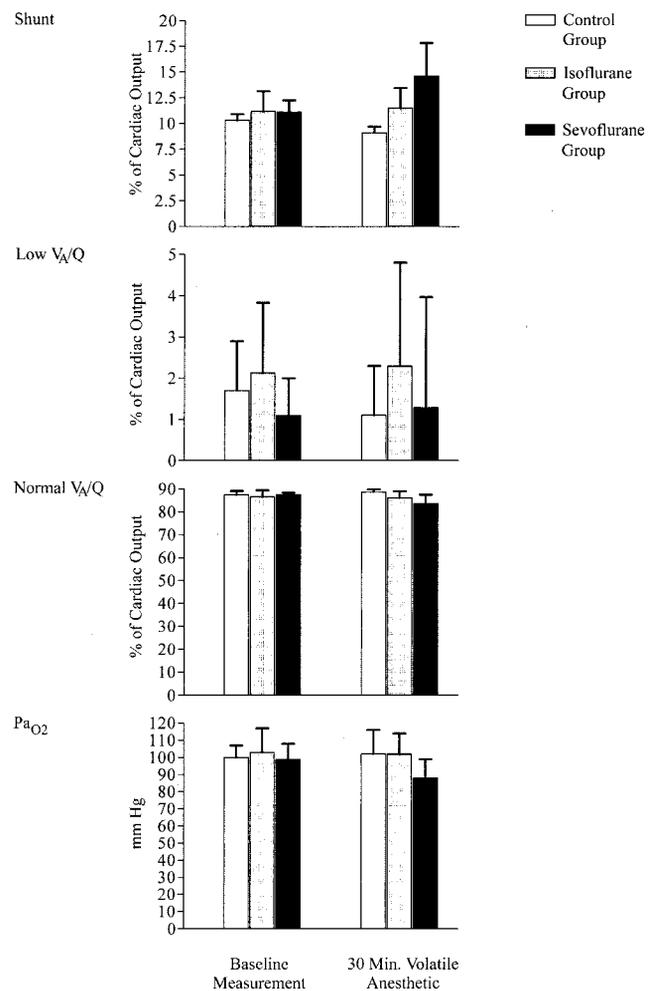

Fig. 1. (*Left*) At baseline, all animals were anesthetized using propofol. (*Right*) Values after 30 min of inhalational anesthesia or control. Shunt = blood flow to lung areas with zero ventilation; low $\dot{V}_A/\dot{Q}$ = blood flow to lung areas with a low ventilation/perfusion ratio; normal $\dot{V}_A/\dot{Q}$ = blood flow to lung areas with a normal ventilation/perfusion ratio; Pao$_2$ = arterial partial pressure of oxygen. Data are mean ± SD; error bars indicate SD; *P* values refer to intergroup comparison. Numeric data at the second measurement were as follows: shunt: control (9 ± 1%) *versus* isoflurane (11 ± 2%), *P* = 0.2; control *versus* sevoflurane (15 ± 3%), *P* = 0.02. Low $\dot{V}_A/\dot{Q}$: control (1.1 ± 1.2%) *versus* isoflurane (2.5 ± 2.3%), *P* = 0.8; control *versus* sevoflurane (1.3 ± 2.8%), *P* = 0.5. Normal $\dot{V}_A/\dot{Q}$: control (89 ± 1%) *versus* isoflurane (86 ± 3%), *P* = 0.2; control *versus* sevoflurane (83 ± 5%) , *P* = 0.04. Pao$_2$: control (102 ± 15 mmHg) *versus* isoflurane (102 ± 12 mmHg), *P* = 0.9; control *versus* sevoflurane (88 ± 11 mmHg) , *P* = 0.04.

ever, gas exchange was not affected by acid–base status disturbances because the corresponding variables remained stable.

Three limitations of this study should be mentioned. First, pulmonary data obtained in a porcine model cannot be fully transposed to humans because pigs lack collateral ventilation. Second, the animals we used were examined while in the supine position, which is not a physiologic position for a pig but allowed unrestricted thoracic movements, resulting in normal respiratory me-

chanics. Third, inhibition of HPV is possibly very subtle at a hyperoxic inspiratory fraction of oxygen of 0.3.

We conclude that sevoflurane but not isoflurane further impairs pulmonary gas exchange in a porcine model with a previously existing gas exchange defect. Further studies in humans are warranted to determine the effect of inhalational anesthetics on pulmonary gas exchange in patients presenting with pulmonary disease.

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