BASIC RESEARCH

MINIMUM ALVEOLAR CONCENTRATIONS AND HEMODYNAMIC EFFECTS OF TWO DIFFERENT PREPARATIONS OF SEVOFLURANE IN PIGS

Denise A. Otsuki,[I] Denise T. Fantoni,[II] Carla Holms,[I] Jose Otavio C. Auler Jr.[III]

doi: 10.1590/S1807-59322010000500011

Otsuki DA, Fantoni DT, Holms C, Auler-Junior JOC. Minimum alveolar concentrations and hemodynamic effects of two different preparations of sevoflurane in pigs. Clinics. 2010(65)5:531-7.

BACKGROUND: Original sevoflurane (Sevo A) is made with water, while a generic sevoflurane (Sevocris) is produced with propylene glycol as a stabilizing additive. We investigated whether the original and generic sevoflurane preparations differed in terms of their minimum alveolar concentration (MAC) values and hemodynamic effects.
METHODS: Sixteen pigs weighing 31.6±1.8 kg were randomly assigned to the Sevo A or Sevocris groups. After anesthesia induction via mask with the appropriate sevoflurane preparation (6% in 100% oxygen), the MAC was determined for each animal. Hemodynamic and oxygenation parameters were measured at 0.5 MAC, 1 MAC and 1.5 MAC. Histopathological analyses of lung parenchyma were performed.
RESULTS: The MAC in the Sevo A group was 4.4±0.5%, and the MAC in the Sevocris group was 4.1±0.7%. Hemodynamic and metabolic parameters presented significant differences in a dose-dependent pattern as expected, but they did not differ between groups. Cardiac indices and arterial pressures decreased in both groups when the sevoflurane concentration increased from 0.5 to 1 and 1.5 MAC. The oxygen delivery index (DO_2I) decreased significantly at 1.5 MAC.
CONCLUSION: Propylene glycol as an additive for sevoflurane seems to be as safe as a water additive, at least in terms of hemodynamic and pulmonary effects.

KEYWORDS: Inhalant anesthetics; Sevoflurane; Minimum alveolar concentration; Pigs.

INTRODUCTION

Sevoflurane is a fluorinated hydrocarbon that stands out among today's inhaled anesthetics due to its low solubility (blood: gas partition coefficient of 0.68), non-irritating effects on the respiratory tract and pleasant smell. These properties allow for rapid and smooth anesthesia induction even without pre-medication and offer good control over the depth of anesthesia, a factor that is important in patients with compromised hemodynamic status.[1]

Depending on storage and usage conditions, sevoflurane can be degraded into different compounds, including the highly pungent hydrofluoric acid, a substance known to be nephrotoxic and irritating to the respiratory tract mucous membrane. This sevoflurane decomposition reaction involves a metallic impurity, an acid (a Lewis acid) and a substance capable of receiving an electron pair to trigger the decomposition reaction. A number of compounds, both organic and inorganic, including H_2O, butylated hydroxytoluene, methylparaben, propylparaben, propofol and thymol, can inhibit the Lewis acid reaction. A liquid additive (water) was developed as a stabilizer to the original sevoflurane (Sevorane®, Abbott) to prevent the production of the inorganic fluorides. Cristália Laboratories developed a new sevoflurane formula (Sevocris®, Cristalia, São Paulo) containing 0.026% p/p of propylene glycol as a stabilizer.[2] This new product was introduced into the Brazilian market in September 2004, after being granted

[I] Laboratory of Medical Investigation, LIM/08 (Anesthesiology), Faculdade de Medicina da Universidade de São Paulo - São Paulo/SP, Brazil.
[II] Department of Surgery, Faculdade de Medicina Veterinária e Zootecnia da Universidade de São Paulo - São Paulo/SP, Brazil.
[III] Department of Anesthesia and Surgical Intensive Care, Heart Institute of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo - São Paulo/SP, Brazil.
Email: lim08@usp.br
Tel: 55 11 3061-7293
Received for publication on December 09, 2009
First review completed on December 28, 2009
Accepted for publication on February 03, 2010

the approval of ANVISA, Brazil's Regulatory Agency. Propylene glycol is a product utilized in several medications, via different routes, and has been considered a GRAS product (Generally Recognized as Safe) by the US Food and Drug Administration.[3] It can be used as an antimicrobial preservative, disinfectant, humectant, solvent, vitamin stabilizer and water-miscible co-solvent.

Given this information, we conducted a comparative study of sevoflurane with water additive versus with propylene glycol additive under experimental conditions in pigs. We compared the MAC, hemodynamic and metabolic effects and relevant lung histopathological analyses.

MATERIALS AND METHODS

The study protocol and design were approved by the Ethics and Animal Investigation Committee at our institution and were performed according to the recommendations of the National Institutes of Health guidelines for ethical animal research. Sixteen young male Large White x Landrace pigs weighing 30 to 35 Kg (31.6±1.8 Kg) were fasted overnight with free access to water and were randomly assigned to the Sevo A or Sevocris groups. After induction of anesthesia via mask with the assigned sevoflurane (6% in 100% oxygen), animals were orally intubated (7 mm internal diameter cuffed endotracheal tube, Hi-Lo, National Catheter, Argyle, NY). The lungs were mechanically ventilated (Primus, Dräger Medical, Lubeck, Germany) using volume-controlled ventilation, 40% FiO_2, tidal volume of 8 mL/kg, PEEP of 5 cmH_2O, which was the respiratory frequency adjusted to keep end-tidal CO_2 between 35 and 45 mmHg. Anesthesia was maintained with 5% sevoflurane in 40% oxygen.

A continuous infusion of lactated Ringer (Baxter, São Paulo, Brazil) was provided at a rate of 5 $mL.kg^{-1}.h^{-1}$ throughout all experiments. The temperature was maintained within normal limits for pigs (38.7-39.9°C) using warm blankets (Medi-therm II, Gaymar Industries, Orchard Park, NY, USA).

Instrumentation

After local anesthetic infiltration (10 mL 2% lidocaine with vasoconstrictor), the right femoral artery was surgically exposed and catheterized for arterial pressure measurements and blood collection. The right jugular vein was also catheterized with a pulmonary artery catheter (7.5 F Edwards CCO catheter connected to Edwards Vigilance CCO Monitor; Edwards Lifesciences Corp., Irvine, CA, USA). The position of the pulmonary artery catheter was confirmed by typical waveforms. All intravascular catheters were zeroed to atmospheric pressure. The midpoint between the anterior and posterior chest walls was taken as the zero reference point for pressure measurements.

The STAT-Mode of the Edwards Vigilance CCO Monitor was used in each experiment, which displayed the actual cardiac output values registered over the past 60 seconds. The last five measurements of CO were averaged. The electrocardiogram and intravascular pressures, mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), pulmonary artery wedge pressure (PAWP) and central venous pressure (CVP) were monitored continuously (MP40, Philips). Numerical values of intravascular pressures from the monitor screen were recorded at established points of the protocol. After instrumentation, animals were allowed to stabilize for 60 minutes.

Hemodynamic indices

The derivative indexes were recorded directly from monitors during the experiment: the pulmonary vascular resistance index (PVRI), systemic vascular resistance index (SVRI), right and left ventricular stroke work index (RVSWI and LVSWI), right stroke volume index, (RSVI), right ventricle ejection fraction (RVEF) and right ventricular end-diastolic volume (RVEDV). The cardiac index (CI) was calculated according to calculated body surface ($k.BW^{2/3}$, where k = 0.09, BW=body weight).[4, 5]

Venous admixture and oxygenation indices

Arterial and mixed venous blood samples were collected for pH, partial pressure of arterial oxygen (PaO_2), partial pressure of arterial carbon dioxide ($PaCO_2$), arterial oxygen saturation (SaO_2), partial pressure of mixed venous oxygen (PvO_2) and mixed venous saturation (SvO_2) (ABL 555; Radiometer, Copenhagen, Denmark). The oxygen delivery index (DO_2I), oxygen consumption index (VO_2I) and extraction ratio (O_2ER) were calculated utilizing conventional formulas.

Determination of MAC

The method for the determination of MAC in this study has been described elsewhere.[6,7]

The end-tidal concentration of sevoflurane was maintained at the intended level for a 15 min equilibration period. After 15 min of equilibration, the pig was stimulated on a dew claw with a hemostat clamped to a full ratchet lock for 60 s. The leg was moved back and forth. If there were no purposeful movements in response to the stimulus (withdrawal of the clamped foot or gross movements of either legs or head), the end-tidal sevoflurane was

decreased by 10%, and the protocol was repeated following a 15 min anesthetic equilibration period. If there was purposeful movement in response to the stimulation, the end-tidal concentration was increased by 5%, and following equilibration, the stimulation was repeated. The site of the stimulations was changed slightly to prevent sensitization or desensitization to subsequent stimuli. The expiratory concentration of the agent halfway between that allowing and that not allowing movement in response was the MAC of that agent for each specific animal.

After MAC determination, systemic hemodynamics, respiratory data and blood gases were collected at 0.5, 1.0 and 1.5 MAC, observing a 15 min equilibrium period after each concentration change.

Histopathological analysis

At the end of the experiment, while still under anesthesia, animals received a 1-g bolus of thiopental followed by 25 mEq of potassium chloride. Lung samples were collected from the left diaphragmatic lobe (from zones 1, 2 and 3). A sample from the middle portion of the trachea was also collected. The lung and trachea samples were prepared for optical analyses, fixed in 10% formaldehyde and stained with hematoxylin and eosin.

The pathologist, who was blinded to the experimental protocol, described the analysis according to the combined assessment of neutrophils, eosinophils, mastocytes, and mononuclear cell accumulation, pulmonary interstitial edema, alveoli collapse, and congestion in the prepared sample lamina using an optical microscope at a magnification of 10x. In a subjective manner, the observer quantified the positive findings in the samples from different regions of the lung as none (0), discrete (1), moderate (2), or intense (3).

Statistical analysis

MAC values were analyzed using the Student´s *t*-test. Hemodynamic and other parametric data were analyzed within groups and between groups using an analysis of variance (ANOVA) for repeated measurements with two factors (SigmaStat 3.11, Systat Software Inc, San Jose, USA). When appropriate, post hoc analyses were performed with the Tukey test. $P<0.05$ was considered statistically significant. Values are presented as means (SD).

RESULTS

The MAC for the Sevo A group was 4.4% (0.5), whereas it was 4.1% (0.7) for the Sevocris group. Body weights, MAC values and times to achieve sternal recumbence and to orotracheal intubation are presented in Table 1.

Hemodynamic, respiratory and oxygenation parameters are described in Tables 2 and 3.

Table 1 - Body weight, MAC, time to sternal recumbency and orotracheal intubation.

	Sevo A	Sevocris
Body weight (kg)	31.3 (1.9)	31.9 (1.9)
MAC (%)	4.4 (0.5)	4.1 (0.7)
Sternal recumbency (s)	116 (96)	112 (36)
Orotracheal intubation (s)	659 (433)	620 (275)

Mean (SD)

Hemodynamic parameters presented significant differences in a dose-dependent pattern as expected, but did not differ between groups. Cardiac indices decreased significantly in both groups when the sevoflurane concentration increased from 0.5 to 1 and 1.5 MAC. We also observed a significant decrease in blood pressure and mean pulmonary artery pressure at all concentrations compared to 0.5 MAC. Heart rate decreased significantly when MAC was augmented from 0.5 to 1.0 and 1.5, but the values remained in the physiological range for this group of animals, and bradycardia was not verified. SvO_2 and DO_2I decreased significantly at 1.5 MAC when compared to 0.5 and 1.0 MAC.

Regarding histopathological analyses, no evidence of neutrophils, eosinophils, mastocytes, mononuclear cell accumulation, pulmonary interstitial edema, alveoli collapse, or congestion was found in lung optical microscopy of both groups. Also, no histopathological changes were found in the trachea.

DISCUSSION

The main finding in this study was that hemodynamic and metabolic responses at equipotent doses were similar between water-added sevoflurane (Sevo A) and propylene glycol-added sevoflurane (Sevocris).

Under the conditions of this study, the MAC of Sevo A was 4.4% (0.5), and the MAC of Sevocris was 4.1% (0.7). These values are higher than most published reports, in which sevoflurane MAC values range between 2.1% and 4.4% in pigs.[8-13]

Several factors may account for the variations in published sevoflurane MAC values, including different age groups of pigs, body temperature, pre-anesthetic and induction agents, the type and site of noxious stimulus and the defined end-point for determination of purposeful

Table 2 - Hemodynamic data.

	Group	0.5 MAC	1.0 MAC	1.5 MAC
CI (L/min/m^2)	Sevo A	5.5 (1.3) *	4.2 (0.8)	3.2 (1.0) * †
	Sevocris	6.2 (0.7) *	4.7 (1.1)	3.6 (1.2) * †
HR (beat/min)	Sevo A	129 (20)	122 (17)	110 (16) * †
	Sevocris	138 (19) *	115 (15)	104 (13) †
MAP (mmHg)	Sevo A	81 (15) *	66 (7)	45 (10) * †
	Sevocris	90 (17) *	68 (10)	52 (11) * †
CVP (mmHg)	Sevo A	8 (2)	9 (2)	9 (2)
	Sevocris	7 (2) *	9 (1)	10 (1) †
MPAP (mmHg)	Sevo A	23 (3) *	21 (2)	19 (3) * †
	Sevocris	22 (3) *	21 (3)	20 (3) †
PAWP (mmHg)	Sevo A	11 (2)	12 (2)	12 (1)
	Sevocris	11 (1)	11 (1)	12 (2)
SVRI (dynes.sec/cm^5/m^2)	Sevo A	1076 (211)	1106 (185)	896 (201) * †
	Sevocris	1080 (201)	1047 (260)	959 (193)
PVRI (dynes.sec/cm^5/m^2)	Sevo A	171 (34)	183 (30)	187 (61)
	Sevocris	153 (35)	165 (41)	184 (63)
LVSWI (gm-m/m^2/beat)	Sevo A	41 (12) *	26 (6)	13 (6) * †
	Sevocris	47 (13) *	33 (6)	20 (9) * †
RVSWI (gm-m/m^2/beat)	Sevo A	8 (2) *	6 (1)	4 (2) * †
	Sevocris	9 (1) *	7 (2)	5 (2) * †
SVI (mL/m^2/beat)	Sevo A	44 (9) *	34 (5)	28 (6) * †
	Sevocris	45 (6)	41 (8)	34 (9) * †
EDVI (mL/m^2)	Sevo A	159 (33)	157 (52)	156 (58)
	Sevocris	162 (30)	148 (19)	146 (11)

Mean (SD); CI=cardiac index; HR=heart rate; MAP=mean arterial pressure; CVP=central venous pressure; MPAP=mean pulmonary artery pressure; PCWP=pulmonary artery wedge pressure; SVRI=systemic vascular resistance index; PVRI=pulmonary vascular resistance index; LVSWI=left ventricular stroke work index; RVSWI=right ventricular stroke work index; SVI=stroke volume index; EDVI=right ventricular end-diastolic volume index. * P<0.05 compared to 1 MAC; † P<0.05 compared to 0.5 MAC.

movement in response to the applied stimulus (Table 4). [6, 7, 14] The stimulus applied in our study was dewclaw clamping, which has been reported to be a supramaximal stimulus[6] and which remained constant during the entire study. The site of stimulus was changed slightly between stimulations to prevent sensitization or desensitization to subsequent stimuli. In the study of Hecker,[10] where the pigs had almost the same weight and were submitted to the same nociceptive stimulation as in the present study, the MAC was lower, which may have been due to the previous use of azaperone and propofol. Holmström and Åkeson,[13] in animals weighing 20.1± 0.7 kg, obtained a MAC of 4.4 90 minutes after propofol administration, which is the same value reported in the present investigation. On the other hand, Moeser et al.,[12] studying animals weighing 19 ±0.4 kg and with no other agent than sevoflurane, obtained a MAC of 3.5±0.17. In the present investigation, weight, age, sex, and stimuli were similar in both groups, demonstrating that the two anesthetics showed the same behavior with regard to MAC.

The hemodynamic results are close to those described in the literature for sevoflurane. In healthy human volunteers and in dogs, the cardiac index, arterial pressure and pulmonary arterial pressure decrease in a dose-dependent manner.[15,16] In infants, sevoflurane did not alter the cardiac index at any concentration compared to awake values but significantly decreased blood pressure and systemic vascular resistance compared to awake values at all concentrations.[17]

Special focus has been given to the effects of volatile anesthetics on heart rate because desflurane (and to a lesser extent isoflurane) can initiate major increases in heart rate that might predispose select patient populations to myocardial ischemia.[18] The results with sevoflurane are conflicting, varying across different species, age groups and anesthetic techniques. Sevoflurane has not been associated with increases in heart rate in healthy volunteers, in patients,[19] or in children.[17] Bernard et al.,[16] in dogs, noted

Table 3 - Respiratory and oxygenation data.

	Group	0.5 MAC	1.0 MAC	1.5 MAC
RR (mpm)	Sevo A	19 (2)	19 (2)	19 (2)
	Sevocris	20 (2)	20 (2)	20 (2)
P Peak (cmH_2O)	Sevo A	22 (3)	21 (3)	21 (3)
	Sevocris	20 (4)	20 (3)	20 (3)
P Plato (cmH_2O)	Sevo A	20 (3)	20 (3)	20 (3)
	Sevocris	19 (3)	19 (3)	19 (3)
$Compl_{Dyn}$ (mL/cmH_2O)	Sevo A	23 (5) *	26 (6)	27 (6) †
	Sevocris	24 (5)	26 (4)	26 (5)
Vt (mL)	Sevo A	339 (22) *	359 (29)	370 (39) * †
	Sevocris	335 (22) *	350 (28)	362 (22) * †
$EtCO_2$ (mmHg)	Sevo A	44 (2)	43 (2)	41 (2) * †
	Sevocris	44 (2)	43 (4)	41 (4) †
pH art	Sevo A	7.454 (0.024)	7.463 (0.026)	7.477 (0.025)
	Sevocris	7.464 (0.024)	7.472 (0.041)	7.459 (0.060)
$PaCO_2$ (mmHg)	Sevo A	45 (2)	44 (3)	40 (5)
	Sevocris	44 (2)	43 (5)	42 (8)
PaO_2 (mmHg)	Sevo A	174 (36)	166 (40)	160 (43)
	Sevocris	181 (20)	162 (27)	157 (33)
SaO_2 (%)	Sevo A	99.2 (0.5)	99.0 (0.5)	98.9 (0.9)
	Sevocris	99.4 (0.2)	99.1 (0.4)	99.0 (0.7) †
Lactate (mmol/L)	Sevo A	1.1 (0.3)	1.1 (0.3)	1.5 (1.0)
	Sevocris	1.0 (0.2)	1.1 (0.3)	1.3 (0.3)
PvO_2 (mmHg)	Sevo A	47 (5)	45 (6)	36 (5) * †
	Sevocris	50 (3) *	45 (5)	38 (6) * †
SvO_2 (%)	Sevo A	77.3 (7.3)	76.1 (7.3)	62.5 (14.7) * †
	Sevocris	81.6 (3.9)	76.0 (6.2)	64.7 (12.4) * †
DO_2I ($mL/min/m^2$)	Sevo A	825 (172) *	606 (56)	434 (96) * †
	Sevocris	880 (66) *	671 (176)	498 (156) * †
VO_2I ($mL/min/m^2$)	Sevo A	173 (19)	142 (33)	143 (31)
	Sevocris	175 (22)	162 (32)	162 (12)
O_2ER (%)	Sevo A	23 (7)	24 (6)	35 (12) * †
	Sevocris	20 (3)	25 (6)	36 (13)* †
Temp (°C)	Sevo A	38.3 (0.4)	38.4 (0.5)	38.5 (0.5)
	Sevocris	38.6 (0.6)	38.6 (0.4)	38.7 (0.5)

Mean (SD); RR=respiratory rate; P peak=airway peak pressure; P plato=airway plato pressure; $Compl_{Dyn}$=dynamic compliance; Vt=tidal volume; $EtCO_2$=end-tidal CO_2; pH art=arterial pH; $PaCO_2$=partial pressure of arterial CO_2; PaO_2=partial pressure of arterial oxygen; SaO_2=arterial oxygen saturation; Lactate=arterial lactate; PvO_2=partial pressure of mixed venous oxygen; SvO_2=mixed venous saturation; DO_2I=oxygen delivery index; VO_2I=oxygen consumption index; O_2ER=oxygen extraction ratio; Temp=temperature. * $P<0.05$ compared to 1 MAC; † $P<0.05$ compared to 0.5 MAC.

significant increases in heart rate from the awake state during the administration of 1.2-2.0 MAC. In the present study, heart rate decreased when the MAC was augmented from 0.5 to 1.0 and 1.5, but the values obtained remained in the physiological range for this group of animals, and bradycardia was not verified.

The effects of both tested sevofluranes on cardiac performance (LVSWI, RVSWI, SVI and EDVI) were the same and are in accordance with the literature. The influence of sevoflurane on performance of the right ventricle (RV) was studied by Kerbaul and colleagues, who observed a significant decrease in the RV stroke work with 1 and 1.5 MAC of sevoflurane. [20]

Ventilation was kept constant in order to maintain the

Table 4 - MAC (means±SD) results and methods employed in previous studies of pigs on sevoflurane.

Reference	Age (weeks)	Weight (Kg)	Anesthesia protocol	Nociceptive stimulation	Temperature (°C)	MAC (%)
Lerman et al.[8]	newborn	2.1±0.4	mask induction	hoof coronary ligament clamping	37.5-38.5	2.12±0.39
Allaouchiche et al. [9]	12-14	23±2	after ketamine and propofol	dewclaw clamping	38.6±0.6	2.4
Hecker et al. [10]	NS	30.8±2.6	3 h after azaperone, 45 min after propofol	dewclaw clamping	38.1	2.53±0.47
Manohar and Parks[11]	22-25	58.7±1.8	mask induction	tail clamping	39.7±0.1	2.66±0.6
Moeser et al. [12]	9	19±4	mask induction	dewclaw clamping	38.1	3.5±0.17
Holmström and Åkeson [13]	NS	20.1±0.7	90 min after propofol	dewclaw clamping	38.0±0.2	4.4±0.1

NS=not stated.

levels of carbon dioxide, which may influence cardiovascular function. The decreases in the oxygenation parameters, verified with the increases in MAC, may be associated with cardiovascular depression. The changes were more pronounced when MAC was raised to 1.5, contributing to a significant decrease in SvO_2 and PvO_2, while the oxygen extraction rate increased. Lactate remained unchanged with 1.0 MAC and increased slightly with 1.5.

No lung histopathological changes were associated with the two compositions of sevoflurane tested. The literature describes how sevoflurane may be degraded by metallic substances resulting in fluoridric acid, which may cause damage to the respiratory tract mucous membrane when inhaled, and many other fluoride-degrading products. To inhibit acid formation, substances such as water and, more recently, propylene glycol have been added to sevoflurane. A test conducted with a sevoflurane sample with 260 ppm of propylene glycol, heated to a temperature above 60°C in the presence of alumina, did not show significant change in the content of individual and total impurities when compared to those of the dry sevoflurane. The fluoride content of this sample was 0.051 µg/mL, which complied with specifications set by the USP Pharmacopoeia Forum, which determines a maximum fluoride limit of 2 µg/mL. [2]

The exact mechanism through which propylene glycol stabilizes sevoflurane is not entirely clear, but it is possible to infer that propylene glycol and the Lewis acid form a compound that is highly efficient for blocking the action of metallic impurities on sevoflurane.

With regard to the possible toxicological effects of propylene glycol, hyperosmolality lactic acidosis, a central nervous system dysfunction, and cardiovascular disturbances were observed in patients receiving etomidate in a 35% propylene glycol vehicle.[21, 22] In the present investigation, the sevoflurane contained 0.026% of propylene glycol, which is far less than the amount contained in etomidate formulation.

Moreover, after a study conducted by Bau et al. in which propylene glycol was a constituent of an aerosol formulation, the authors concluded that, under normal conditions of exposure, propylene glycol via inhalation is of limited toxicological relevance.[23]

In conclusion, propylene glycol as a sevoflurane additive can be used as safely as water as an additive, at least in terms of hemodynamic and pulmonary effects.

REFERENCES

1. Eger EI, 2nd. New inhaled anesthetics. Anesthesiology. 1994;80:906-22.

2. Cristalia, inventor WO/2005/023175. Stable pharmaceutical composition of fluoroether compound for anesthetic use, method for stabilizing a fluoroether compound, use of stabilizer agent for precludind the degradation of a fluoroether compound. 2005 17.03.2005.

3. FDA U. Database of Select Committee on GRAS Substances (SCOGS) Reviews. 1973.

4. Shoemaker W. Invasive and noninvasive physiologic monitoring. In: Shoemaker WA S, Grenvik A, Holbrook PR, Thompson, WL, ed. Textbook of Critical Care. 3rd ed. Philadelphia: WB Saunders Company. 1995:252-66.

5. Guyton AJ, CE, Coleman, TG. Normal cardiac output and its variation. In: Guyton AJ, CE; Coleman TG, ed. Cardiac output and its regulation. 2nd ed. Philadelphia: WB Saunders Company. 1973:3-29.

6. Eger EI, 2nd, Johnson BH, Weiskopf RB, Holmes MA, Yasuda N, Targ A, et al. Minimum alveolar concentration of I-653 and isoflurane in pigs: definition of a supramaximal stimulus. Anesthesia and analgesia. 1988;67:1174-6.

7. Quasha AL, Eger EI, 2nd, Tinker JH. Determination and applications of MAC. Anesthesiology. 1980;53:315-34.

8. Lerman J, Oyston JP, Gallagher TM, Miyasaka K, Volgyesi GA, Burrows FA. The minimum alveolar concentration (MAC) and hemodynamic effects of halothane, isoflurane, and sevoflurane in newborn swine. Anesthesiology. 1990;73:717-21.

9. Allaouchiche B, Duflo F, Tournadre JP, Debon R, Chassard D. Influence of sepsis on sevoflurane minimum alveolar concentration in a porcine model. British journal of anaesthesia. 2001;86:832-6.

10. Hecker KE, Baumert JH, Horn N, Reyle-Hahn M, Heussen N, Rossaint R. Minimum anesthetic concentration of sevoflurane with different xenon concentrations in swine. Anesthesia and analgesia. 2003;97:1364-9.

11. Manohar M, Parks CM. Porcine systemic and regional organ blood flow during 1.0 and 1.5 minimum alveolar concentrations of sevoflurane anesthesia without and with 50% nitrous oxide. The Journal of pharmacology and experimental therapeutics. 1984;231:640-8.

12. Moeser AJ, Blikslager AT, Swanson C. Determination of minimum alveolar concentration of sevoflurane in juvenile swine. Research in veterinary science. 2008;84:283-5.

13. Holmstrom A, Akeson J. Cerebral blood flow at 0.5 and 1.0 minimal alveolar concentrations of desflurane or sevoflurane compared with isoflurane in normoventilated pigs. Journal of neurosurgical anesthesiology. 2003;15:90-7.

14. Eger EI, 2nd, Saidman LJ, Brandstater B. Minimum alveolar anesthetic concentration: a standard of anesthetic potency. Anesthesiology. 1965;26:756-63.

15. Malan TP Jr., DiNardo JA, Isner RJ, Frink EJ Jr., Goldberg M, Fenster PE, et al. Cardiovascular effects of sevoflurane compared with those of isoflurane in volunteers. Anesthesiology. 1995;83:918-28.

16. Bernard JM, Wouters PF, Doursout MF, Florence B, Chelly JE, Merin RG. Effects of sevoflurane and isoflurane on cardiac and coronary dynamics in chronically instrumented dogs. Anesthesiology. 1990;72:659-62.

17. Wodey E, Pladys P, Copin C, Lucas MM, Chaumont A, Carre P, et al. Comparative hemodynamic depression of sevoflurane versus halothane in infants: an echocardiographic study. Anesthesiology. 1997;87:795-800.

18. Ebert TJ, Harkin CP, Muzi M. Cardiovascular responses to sevoflurane: a review. Anesthesia and analgesia. 1995;81(6 Suppl):S11-22.

19. Rolf N, Van Aken H. Cardiovascular effects of sevoflurane. Der Anaesthesist. 1998;47 Suppl 1:S11-8.

20. Kerbaul F, Bellezza M, Mekkaoui C, Feier H, Guidon C, Gouvernet J, et al. Sevoflurane alters right ventricular performance but not pulmonary vascular resistance in acutely instrumented anesthetized pigs. Journal of cardiothoracic and vascular anesthesia. 2006;20:209-16.

21. Van de Wiele B, Rubinstein E, Peacock W, Martin N. Propylene glycol toxicity caused by prolonged infusion of etomidate. Journal of neurosurgical anesthesiology. 1995;7:259-62.

22. Doenicke A, Roizen MF, Nebauer AE, Kugler A, Hoernecke R, Beger-Hintzen H. A comparison of two formulations for etomidate, 2-hydroxypropyl-beta-cyclodextrin (HPCD) and propylene glycol. Anesthesia and analgesia. 1994;79:933-9.

23. Bau SK, Aspin N, Wood DE, Levison H. The measurement of fluid deposition in humans following mist tent therapy. Pediatrics. 197;48:605-12.