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The Minimum Alveolar Concentration (MAC) and Hemodynamic Effects of Halothane, Isoflurane, and Sevoflurane in Newborn Swine

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To determine the minimum alveolar concentration (MAC) and hemodynamic responses to halothane, isoflurane, and sevoflurane in newborn swine, 36 fasting swine 4–10 days of age were anesthetized with one of the three volatile anesthetics in 100% oxygen. MAC was determined for each swine. Carotid artery and internal jugular catheters were inserted and each swine was allowed to recover for 48 h. After recovery, heart rate (HR), systemic systolic arterial pressure (SAP), and cardiac index (CI) were measured awake and then at 0.5, 1.0, and 1.5 MAC of the designated anesthetic in random sequence. The (mean ± SD) MAC for halothane was 0.90 ± 0.12%; the MAC for isoflurane was 1.48 ± 0.21%; and the MAC for sevoflurane was 2.12 ± 0.39%. Awake (mean ± SD) measurements of HR, SAP, and CI did not differ significantly among the three groups. Compared to the awake HR, the mean HR decreased 35% at 1.5 MAC halothane ($P < 0.001$), 19% at 1.5 MAC isoflurane ($P < 0.005$), and 31% at 1.5 MAC sevoflurane ($P < 0.005$). Compared to awake SAP, mean SAP measurements decreased 46% at 1.5 MAC halothane ($P < 0.001$), 43% at 1.5 MAC isoflurane ($P < 0.001$), and 36% at 1.5 MAC sevoflurane ($P < 0.005$). Mean SAP at 1.0 and 1.5 MAC halothane and isoflurane were significantly less than those measured at equipotent concentrations of sevoflurane ($P < 0.005$). Compared to awake CI, mean CI measurements decreased 53% at 1.5 MAC halothane ($P < 0.001$) and 43% at 1.5 MAC isoflurane ($P < 0.005$). Mean CI did not change significantly between the awake measurement and 1.5 MAC sevoflurane. Mean CI at both 1.0 and 1.5 MAC halothane and isoflurane were significantly less than those measured at equipotent concentrations of sevoflurane ($P < 0.01$). We conclude that both halothane and isoflurane depress the hemodynamics in newborn swine to a significantly greater extent than does sevoflurane at equipotent concentrations. (Key words: Anesthesia: neonatal; pediatric. Anesthetics: volatile: halothane; isoflurane; sevoflurane. Animal: swine. Heart: cardiac output; myocardial function; anesthetics. Potency: anesthetic; MAC.)

SEVOFLURANE is a halogenated methyl isopropyl volatile anesthetic currently under investigation.[1,2] This anesthetic is believed to be a particularly suitable induction agent for pediatric anesthesia because of its low blood–gas partition coefficient (0.60–0.66),[3,4] its pleasant, nonirritating odor, and its potency in adults (MAC is 1.7–2.05%).[1,2] The low blood–gas partition coefficient of sevoflurane should speed the induction of anesthesia by increasing the rate of rise of the alveolar to inspired anesthetic partial pressures of sevoflurane compared to that for halothane or isoflurane.[5] In a similar manner, the low blood–gas partition coefficient should speed recovery from anesthesia. Eger and Johnson have demonstrated that the low blood–gas partition coefficient of sevoflurane speeds recovery from anesthesia in rats.[6] They attributed the rapid recovery from sevoflurane anesthesia to its lower solubility in blood. These characteristics together indicate that sevoflurane may have a role in pediatric anesthesia.

The routine use of volatile anesthetics in neonates has been questioned in the past because of reports of hemodynamic instability at moderate anesthetic concentrations.[7] However, recent studies have demonstrated that neonates are no more susceptible to hemodynamic instability during anesthesia with volatile agents than are older infants, providing that equipotent concentrations of the volatile anesthetic are used.[8] In order to compare the MAC and hemodynamic effects of sevoflurane to halothane and isoflurane in a model of newborns, we undertook the current study in newborn swine.

Materials and Methods

With approval from the Animal Care Committee of The Hospital for Sick Children, 36 fasting unpremedicated Yorkshire swine, 4–10 days of age (5.4 ± 1.6 days, mean ± SD) and weighing 1.1–3.0 kg (2.1 ± 0.4 kg) were studied.

Each swine was anesthetized with one of three volatile anesthetics—halothane, isoflurane, or sevoflurane—in

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100% oxygen. The trachea was intubated with a Portex endotracheal tube (3.0 mm internal diameter) and the lungs were mechanically ventilated to maintain normocapnia (Pa_{CO_2} 35–45 mmHg) using a Bain circuit and a model PR2 Puritan-Bennett ventilator. The swine were continuously monitored with an electrocardiogram and a rectal temperature probe (Yellow-Springs model no. 43TK). Normothermia (37.5–38.5° C) was maintained with the aid of an overhead radiant heater. End-tidal gas was sampled manually in small incremental volumes *via* a 19-G catheter that was inserted into the breathing circuit and positioned so that the tip of the catheter was 1–2 cm from the distal end of the endotracheal tube. The end-tidal anesthetic concentration was measured with a Beckman LB2 infrared analyzer calibrated for the particular volatile anesthetic. The Beckman LB2 was calibrated using standard techniques described previously.[9]

After an end-tidal anesthetic concentration approximating 1.0 MAC was administered for 15 min, duplicate end-tidal gas samples were aspirated manually 5–10 min apart and the end-tidal anesthetic concentration analyzed immediately.[10] The coronary ligament of a hoof was clamped with a hemostat clamp for 30–45 s. Each swine was observed for "move" or "no-move" responses to the clamp. A move response was defined as withdrawal of one or more extremities. Tachycardia, changes in respiration, and coughing were not considered move responses. If the swine moved, the anesthetic concentration was increased by 10%; if the swine did not move, the concentration was decreased by 10%. The move/no move responses were repeated at 15-min intervals until at least two cross-over pairs of move/no move responses were obtained. MAC was defined as the average of the end-tidal anesthetic concentrations of the closest move/no-move responses.

After determining the MAC, the right external jugular vein and the right internal carotid artery were cannulated with no. 5 French polyethylene umbilical artery catheters under direct vision. Each swine was then allowed to recover for 48 h. After recovery, each swine was studied awake and at 0.5, 1.0, and 1.5 MAC of the designated anesthetic. The anesthetic concentrations were administered in random sequence after induction of anesthesia with the designated agent and tracheal intubation. Ventilation was adjusted to maintain normocapnia (35–45 mmHg). Arterial blood samples were analyzed for carbon dioxide and oxygen tensions and *p*H. Normothermia was maintained as described above.

After the desired end-tidal concentration had been administered for at least 15 min, the hemodynamic responses were recorded. The arterial pressure was measured with a Statham transducer (model P23) that was calibrated with a mercury manometer and zeroed at the midthoracic level before each study. The electrocardiogram and the arterial waveform were recorded on a Gould model no. 8188-4400 strip chart recorder. Cardiac output was measured in duplicate with a dye dilution technique (indocyanine green). Indocyanine green dye was injected as a rapid intravenous bolus into the internal jugular venous catheter. Blood was then aspirated continuously at a fixed rate (20 ml/min) through the carotid artery catheter. The concentration of dye in the blood was measured using a Waters densitometer.

The concentration of dye was plotted against time, and the resultant relationship corrected for recirculation of dye. This correction was accomplished by electronically extrapolating the exponential washout portion of the curve to the baseline with the use of an analogue computer. The dye curve was then integrated electronically against time to yield the area under the curve, which equals cardiac output. The blood removed was reinfused into the swine when the cardiac output measurement was completed. Cardiac index (CI) was calculated as the cardiac output per kilogram body weight ($l \cdot min^{-1} \cdot kg^{-1}$).

Maintenance fluid (dextrose 5% in 0.2% sodium chloride) was administered at 4 $ml \cdot kg^{-1} \cdot h^{-1}$. After the studies were completed, the swine were killed with an overdose of barbiturate.

Each swine was examined for patency of the ductus arteriosus by auscultation of the thorax preoperatively and direct inspection of the ductus through a thoracotomy incision postmortem.[11]

Statistical significance ($P < 0.05$) was determined using repeated measures analysis of variance (ANOVA) with the Tukey test for multiple comparisons within groups and one-way ANOVA with the Tukey test for multiple comparisons between groups.[12]

Results

The age and weight (mean ± SD) of the three groups of swine did not differ significantly (table 1). The MAC (mean ± SD) values for the three anesthetics are listed in the table 1. The ductus arteriosus was closed in all swine.

Awake measurements of heart rate did not differ significantly among the three volatile anesthetics. Compared to awake heart rate (HR) measurements, mean HR decreased significantly at 0.5, 1.0, and 1.5 MAC halothane, isoflurane, and sevoflurane (fig. 1). Mean HR decreased 35% between awake measurements and 1.5 MAC halothane ($P < 0.001$), 19% between awake measurements and 1.5 MAC isoflurane ($P < 0.005$), and 31% between awake measurements and 1.5 MAC sevoflurane ($P < 0.005$).

TABLE 1. Demographic Variables and MAC Measurements

	Halothane	Isoflurane	Sevoflurane
Number of swine	12	12	12
Age (days)	6.8 ± 1.8	6.0 ± 1.6	5.4 ± 1.6
Weight (kg)	2.5 ± 0.78	2.3 ± 0.64	2.1 ± 0.69
MAC (%)	0.90 ± 0.12	1.48 ± 0.21	2.12 ± 0.39

Data are means ± SD.

Awake measurements of systemic systolic arterial pressure (SAP) did not differ significantly among the three volatile anesthetics. Compared to awake measurements, mean SAP decreased significantly at 0.5, 1.0, and 1.5 MAC halothane, isoflurane and sevoflurane (Figure 2). Mean SAP decreased 46% at 1.5 MAC halothane ($P < 0.001$), 43% at 1.5 MAC isoflurane ($P < 0.001$), and 36% at 1.5 MAC sevoflurane ($P < 0.05$) compared to awake values. Systemic SAPs at both 1.0 and 1.5 MAC halothane and isoflurane were significantly less than those measured at the same MAC values of sevoflurane ($P < 0.005$)(fig. 2).

Awake measurements of CI did not differ significantly among the three volatile anesthetics. Compared to awake measurements, mean CI decreased significantly at 0.5, 1.0, and 1.5 MAC halothane and isoflurane (fig. 3). CI decreased 53% at 1.5 MAC halothane ($P < 0.001$) and 43% at 1.5 MAC isoflurane ($P < 0.005$) compared to awake values (fig. 3). CI did not change significantly with MAC multiples of sevoflurane up to 1.5 MAC. Mean CI measurements at both 1.0 and 1.5 MAC halothane and isoflurane were significantly less than those measured at equipotent concentrations of sevoflurane ($P < 0.01$).

There were no instances of bradycardia or malignant hyperthermic reactions during this study. None of the swine became acidotic or alkalotic during the studies.

Discussion

The MAC of halothane and isoflurane in newborn swine were in close agreement with those determined previously in human newborns.[8,9] The relative potency of these two anesthetics in newborn swine as indicated by the ratio of their MAC values, 0.61, was similar to their relative potency in human neonates, 0.54. This latter observation is consistent with the findings of Scheller *et al.* in adult rabbits and humans.[2] If the relative potency of halothane and sevoflurane in newborn swine were also

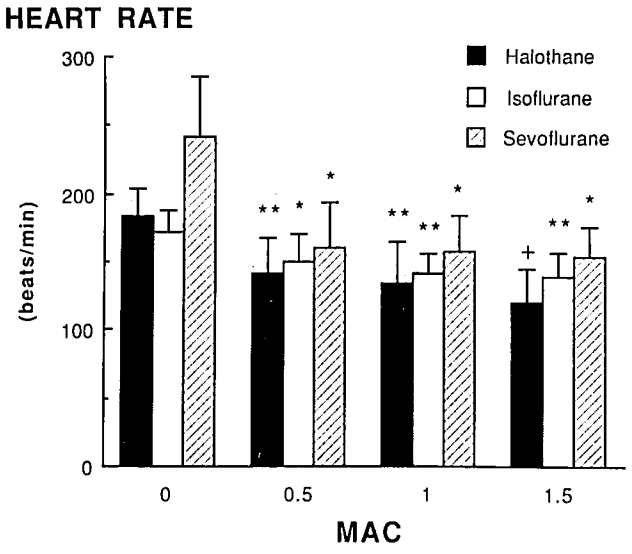

FIG. 1. Heart rate measurements awake and at 0.5, 1.0, and 1.5 MAC halothane, isoflurane, and sevoflurane. *$P < 0.05$; **$P < 0.005$; and +$P < 0.001$ compared to awake values. Mean heart rate at 1.5 MAC halothane was 28% less than that at 1.5 MAC sevoflurane ($P < 0.01$). Data are means ± SD.

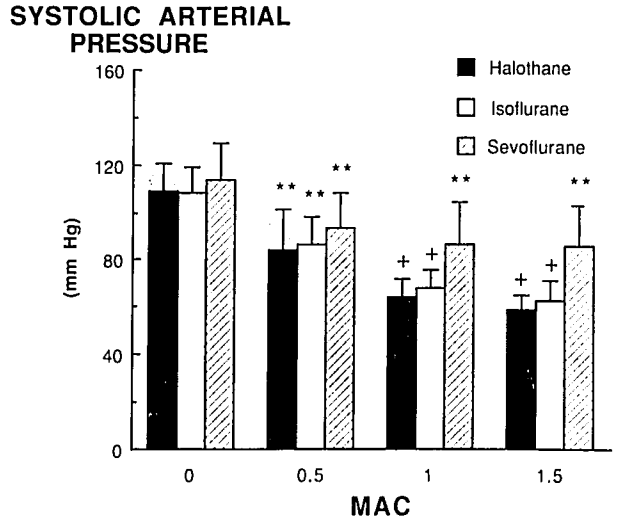

FIG. 2. Systemic systolic arterial pressure measurements awake and at 0.5, 1.0, and 1.5 MAC halothane, isoflurane, and sevoflurane. **$P < 0.005$ and +$P < 0.001$ compared to awake values. Systemic systolic arterial pressures at both 1.0 and 1.5 MAC halothane and isoflurane were significantly less than those measured at the same MAC values of sevoflurane ($P < 0.005$). Data are means ± SD.

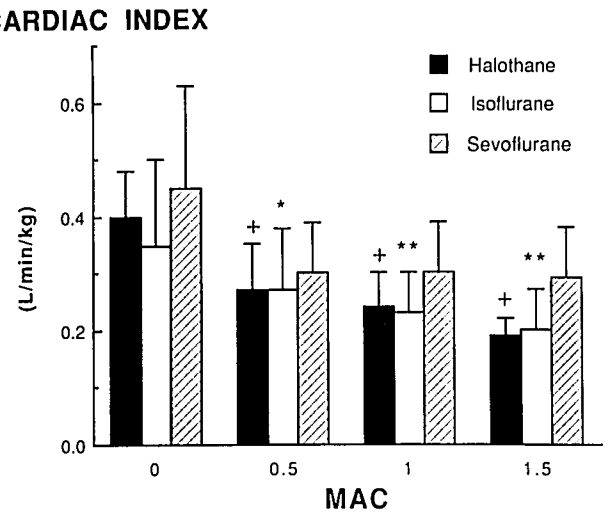

FIG. 3. Cardiac index measurements awake and at 0.5, 1.0, and 1.5 MAC halothane, isoflurane, and sevoflurane. *$P < 0.05$; **$P < 0.005$; and +$P < 0.01$ compared to awake values. Cardiac index did not change significantly with sevoflurane during the study. Mean cardiac index measurements at both 1.0 and 1.5 MAC halothane and isoflurane were significantly less than those measured at equipotent concentrations of sevoflurane ($P < 0.001$). Data are means ± SD.

similar to that in newborn humans, then the results of the current study together with previous data[8] would lead us to predict that the MAC of sevoflurane in human newborns is 2.05%. Validation of the MAC of sevoflurane in human newborns awaits clinical trials.

It is commonly believed that volatile anesthetics depress the circulation in the newborn.[7] These data indicate that halothane significantly depresses HR, systemic SAP, and CI in newborn swine compared to awake measurements. This is in agreement with the findings of Boudreaux et al.[13] We also found that isoflurane depresses the SAP and CI at 1.0 and 1.5 MAC compared to awake measurements. This is supported in part by the results of Schieber *et al.*[14] In contrast, sevoflurane depresses systemic SAP and CI in newborn swine to a significantly lesser extent than do halothane and isoflurane at both 1.0 and 1.5 MAC. These results suggest that sevoflurane depresses the cardiovascular system of the newborn less than do equipotent concentrations of halothane and isoflurane.

There are several reasons to study the swine as a model of newborn human cardiovascular physiology. The anatomy of the cardiovascular system in the swine is similar to that in humans. In the newborn swine, the ductus arteriosus functionally closes within 48 h of birth.[11] Cardiovascular function and reflexes in the newborn swine mature relatively rapidly and reach the level of human infant by approximately 2 weeks of age.[15-17] For these reasons, together with their availability and low cost, newborn swine between 2 and 10 days of age are appropriate for studies of newborn cardiovascular physiology.

Investigators agree that a supramaximal stimulus should be used to elicit the withdrawal response during MAC studies. Such a stimulus depends on several factors, including the intensity and location of the stimulus.[18,19] In the current study, we found that newborn swine consistently withdrew an extremity in response to hoof clamping even though they did not respond to tail clamping at the same anesthetic concentration. This suggested to us that tail clamping was a less intense stimulus than was hoof clamping. The MAC values obtained using hoof clamping for both halothane and isoflurane in newborn swine in this study were significantly less than those with tail clamping in previous studies.[13,14] Eger *et al.* documented similar differences between hoof and tail clamping in the determination of the MAC of halothane in adult swine.[20] These findings and our own support the use of hoof clamping for the determination of MAC in newborn swine.

In summary, we found that sevoflurane depresses systemic SAP and cardiac output in newborn swine to a lesser extent than do halothane and isoflurane at 1.0 and 1.5 MAC. These differences are both statistically and clinically significant, and suggest that further studies to investigate the effects of sevoflurane on the cardiovascular system in human newborns are warranted.

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