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The Minimum Alveolar Concentration (MAC) of Isoflurane in Preterm Neonates

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Studies in fetal lambs suggested that the minimum alveolar concentration (MAC) in preterm neonates may be less than that in full-term neonates and older infants. To determine the MAC of isoflurane in preterm neonates, 20 patients < 32 weeks gestation at birth and 16 patients 32–37 weeks gestation at birth, all less than 1 month post-natal age, were studied. Following tracheal intubation, the neonates were anesthetized with a predetermined end-tidal concentration of isoflurane in oxygen and air. The move-no move responses to skin incision were recorded, and MAC was determined using the "up-and-down" technique. Heart rate and systolic arterial pressure were recorded awake, before skin incision, and after skin incision. MAC (mean ± SD) of isoflurane in preterm neonates < 32 weeks gestation was 1.28 ± 0.17%, and MAC in neonates 32–37 weeks gestation was 1.41 ± 0.18% ($P < 0.05$). Although heart rate did not decrease significantly in either group during the study, systolic arterial pressure decreased between 20 and 30% below awake values both before and after skin incision in both age groups ($P < 0.01$). We conclude that the MAC of isoflurane in preterm neonates < 32 weeks gestation is significantly less than that in preterm neonates 32–37 weeks gestation, and that systolic arterial pressure decreases to a similar extent at ~1 MAC isoflurane in both age groups. (Key words: Age: infants, preterm. Anesthetic requirements: MAC. Anesthetics, volatile: isoflurane. Circulation: heart rate; hypotension; systolic arterial pressure. Monitoring: end-tidal concentration.)

THE EFFECT OF AGE on the minimum alveolar concentration (MAC) of volatile anesthetics in humans has been investigated in several studies.[1-5] MAC of both halothane and isoflurane increases with decreasing age and reaches a maximum value in infants 1–6 months of age.[1,4,5] However, MAC is significantly less in full-term neonates than in older infants 1–6 months of age.[4,5] Gregory *et al.* reported that the MAC of halothane in fetal lambs was only 29% of that in newborn lambs,[6] and speculated that MAC in preterm neonates may be significantly less than that in full-term neonates.[7]

Previously, the hemodynamic effects of volatile anesthetics in infancy raised concerns about profound cardiovascular depression during anesthesia in this age group. Diaz and Lockhart suggested that neonates were more susceptible to hypotension during halothane anesthesia than were older infants 1–6 months of age.‡ However, subsequent studies proved that at equipotent concentrations (~1 MAC) of both halothane and isoflurane, neonates were no more susceptible to hypotension than were older infants 1–6 months of age.[4,5] Friesen and Henry recently reported that systolic arterial pressure decreased significantly during halothane and isoflurane anesthesia in preterm neonates.[8] However, the MAC for these agents in preterm neonates was not determined. To compare the physiological effects of volatile anesthetics in the preterm neonate, we determined the MAC of isoflurane in two groups of preterm neonates less than 1 month post-natal age who were either <32 weeks or 32–37 weeks gestational age.

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Methods

This study was approved by our Human Subject Review Committee. Thirty-six unpremedicated preterm neonates presenting for surgery within 30 days of birth were studied. The patients were divided into two groups according to gestational age at birth: 20 preterm neonates <32 weeks gestation, and 16 preterm neonates 32–37 weeks gestation. Gestational age was assessed by an attending neonatologist using fetal data (in utero ultrasound) and physical examination (Dubowitz and Dubowitz[9]).

Preterm neonates were included in this study only if they fulfilled the criteria listed in table 1. If hemodynamic instability prior to surgery (including inotropic support or antiarrhythmic medication), abnormal serum electrolyte concentrations, endocrinopathy, or a chromosomal defect was present, the patient was excluded.

The operating room was warmed to 27–30° C before each patient arrived. Patient temperature was maintained with an overhead radiant heater and a warming blanket. On arrival in the operating room, each patient

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‡ Diaz JH, Lockhart CH: Is halothane really safe in infancy? (Abstract) ANESTHESIOLOGY 51:S313, 1979

TABLE 1. Inclusion Criteria for Preterm Neonates

Clinical Factors	Inclusion Criteria
Respiratory	$F_{I_{O_2}} \leq 33\%$ $P_{a_{CO_2}} \leq 50$ mmHg Airway pressure ≦ 25/5 mmHg No bronchopulmonary dysplasia (according to x-ray diagnosis)
Cardiovascular	No right-to-left intracardiac shunt No untreated congestive heart failure
Neurological	Intracranial hemorrhage—Grade 2 or less (determined by ultrasound) Absence of focal neurological deficit (motor or sensory)
Temperature	36–38° C (rectal, esophageal, or nasopharyngeal)
Drugs	No narcotics, muscle relaxants, or other drugs known to affect MAC within the preceding 48 h

was monitored with an EKG, esophageal and rectal temperature probes, and pulse oximeter. Arterial blood pressure was measured with either the appropriate sized blood pressure cuff and radial doppler ultrasound probe or an intra-arterial cannula. The end-tidal carbon dioxide partial pressure was measured with a Puritan-Bennett infrared capnometer. The capnometer was calibrated before each study using a commercially prepared gas mixture containing 5% carbon dioxide, and the measurements were corrected for ambient pressure. An intravenous cannula was inserted prior to induction of anesthesia. Non-intubated patients were pre-oxygenated, and their tracheas were intubated with either a 2.5 (infants < 1500 gm) or 3.0 (infants ≧ 1500 gm) mm internal diameter oral endotracheal tube prior to induction of anesthesia. Atropine and muscle relaxants were not administered before or during the study. All patients were ventilated with a mixture of air and oxygen using a Sechrist ventilator and the Jackson Rees modification of the Ayre's t-piece. The lowest inspired concentration of oxygen which maintained the arterial oxygen saturation between 85% and 90% was used. A condenser humidifier (Portex humidivent®) was interposed between the elbow connector and the Ayre's t-piece. Positive end-expiratory pressure was limited to 2 cm H_2O or less. Ventilation and fresh gas flow were adjusted to maintain an end-tidal carbon dioxide partial pressure between 30 and 45 mmHg.

End-tidal gas was sampled through a 19-gauge Deseret Intracath® catheter inserted to within 1 cm of the distal end of the endotracheal tube. The catheter hub was fitted tightly into a modified elbow connector. A 1-meter length of narrow-bore nylon tubing with Luer locks connected the catheter hub with a nylon three-way stopcock. This stopcock allowed either continuous measurement of carbon dioxide partial pressure or collection of end-tidal gas for determination of the partial pressure of isoflurane. End-tidal gas was obtained by manually aspirating 0.5–1.0-ml aliquots of gas per breath into a 20-ml glass syringe fitted with a nylon stopcock. End-tidal gas was aspirated during the latter half of the expiratory phase of respiration, corresponding to the period when the airway pressure was midway between the peak inspired pressure and zero. The deadspace of the collection system was flushed repeatedly before collecting between 15 and 20 ml of end-tidal gas for each analysis. Isoflurane was administered from TEC III isoflurane vaporizers. The concentration of isoflurane in the end-tidal gas samples was measured immediately after collection in a Beckman LB2 infrared anesthetic gas analyzer and corrected for carbon dioxide (see below). The inspired concentrations of isoflurane at the distal and proximal ends of the endotracheal tube were also measured. The inspired concentration of isoflurane was increased in small increments until the desired end-tidal concentration was attained. All end-tidal concentrations were measured in duplicate (5 min apart) to verify steady-state conditions. The mean end-tidal concentration (mean of the duplicate measurements) of isoflurane was maintained for at least 10 min before skin incision.

The Beckman LB2 infrared gas analyzer was calibrated using air containing known concentrations of isoflurane. The isoflurane mixtures were prepared by injecting calibrated microliter volumes of liquid isoflurane into a large bottle of known volume. Before the liquid isoflurane was injected into the bottle, an aliquot of air was aspirated and analyzed in the LB2 to ensure that the bottle was free of isoflurane. Liquid isoflurane was then injected into the bottle. Atmospheric pressure was maintained within the bottle by allowing the air mixture to expand into a glass syringe. The contents of the bottle were then thoroughly mixed. The LB2 was calibrated using concentrations of isoflurane between 0.2 and 4.0% (corrected for ambient temperature and pressure). A calibration curve relating the calculated and analyzed isoflurane concentrations was constructed to correct for the alinearity of the LB2 detector. For *in vivo* measurements, the LB2 values were also corrected for the presence of carbon dioxide (concentrations between 4% and 7%) by subtracting 0.01%.§ Humidification (at 40° C) was shown to have no effect on the LB2 detector.§

The technique used to determine MAC was adapted from the "Up and Down Technique" by Dixon.[10] The objective of this technique is to bracket an end-tidal

§ Unpublished data.

concentration that is MAC for the anesthetic being studied.

The first patient in each group was equilibrated at an end-tidal concentration approximating the MAC of isoflurane in full-term neonates.[5] The end-tidal concentration of isoflurane in each subsequent patient was either increased or decreased by 0.2% isoflurane from that given to the previous infant in the same gestational group, depending on the response of the previous patient (move or no-move respectively) to skin incision. A move response after skin incision was defined as flexion or withdrawal of one or more extremities. Those patients within the same gestational age group who were studied prior to the first pair of opposite responses to skin incision (move/no-move) were excluded.

We calculated MAC to be the mean isoflurane concentration of the respective patients in each group. To determine the standard error of MAC, we divided each group into subgroups of four patients each,¶ and calculated the mean anesthetic concentration for each subgroup. The standard error was the variance of the mean isoflurane concentrations of the subgroups within each respective age group.[10]

All patients were horizontal and supine during the equilibration period. Neonates undergoing surgery for ligation of a patent ductus arteriosus were placed in the right lateral decubitus position after equilibration of the end-tidal isoflurane concentration, but before skin incision.

Heart rate, systolic arterial pressure, temperature, end-tidal carbon dioxide partial pressure, end-tidal isoflurane concentration, and oxygen saturation were recorded awake and frequently thereafter, including immediately before and after skin incision. Lactated Ringer's solution (between 5 and 15 ml/kg) was given intravenously to maintain the systolic arterial pressure ≧ 40 mmHg.

Statistical significance ($P < 0.05$) was determined using ANOVA, the Student-Newman-Keuls test, and paired and unpaired t tests.

RESULTS

The mean gestational age, weight (at the time of surgery), and post-natal age of the two groups of preterm neonates were significantly different ($P < 0.001$) (table 2). The oxygen requirements of the two groups were not significantly different. The indications for surgery in preterm neonates <32 weeks gestational age included: patent ductus arteriosus ligation (n = 16), and laparotomy for bowel obstruction or atresia (n = 4), and in those 32–37 weeks gestational age: laparotomy for bowel obstruction or atresia (n = 9), tracheo-esophageal fistula repair (n = 3), closure of gastroschisis (n = 2), resection of sacral teratoma (n = 1), and closure of myelomeningocele (without neurological deficit) (n = 1). Three preterm neonates <32 weeks gestation at birth and two 32–37 weeks gestation at birth were fed with breast milk up to the day of surgery.

¶ The patients in each subgroup consisted of four consecutively studied patients.

TABLE 2. Demographic Data for Preterm Neonates

	Gestational Age Group	
	<32 Weeks	32–37 Weeks
Gestational age (weeks)	27.3 ±2.0	34.7* ±1.2
Weight† (gm)	974.0 ±240.1	2289.3* ±404.8
Post-natal age (days)	18.1 ±10.4	3.6* ±4.03
Preoperative FI_{O_2}	0.24 ±0.04	0.22 ±0.03

Data are mean ± SD
* $P < 0.001$ from < 32 weeks.
† At surgery.

The move/no-move responses of the preterm neonates in both gestational age groups are shown in figure 1. The MAC (± SD) of isoflurane was significantly less in neonates <32 weeks gestation, 1.28 ± 0.17% than in neonates 32–37 weeks gestation, 1.41 ± 0.18% ($P < 0.05$). Four of five breast-fed patients moved in response to skin incision.

Heart rate and systolic arterial pressure responses were similar for the two groups of preterm neonates. Heart rate did not change significantly in either age

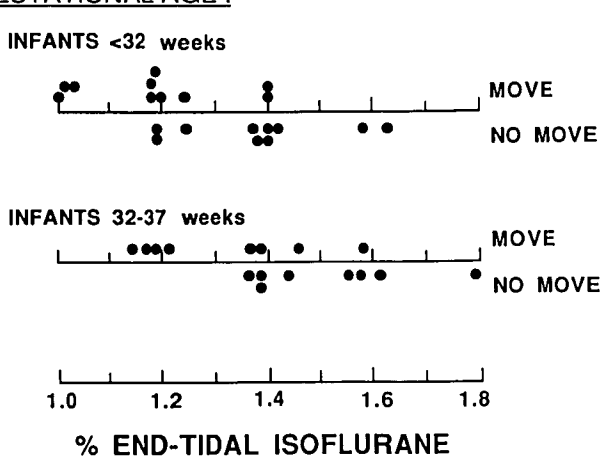

FIG. 1. Each circle represents the move or no-move response of one patient. The MAC of isoflurane (mean ± SD) in preterm neonates < 32 weeks gestation (n = 20) (upper line) was 1.28 ± 0.17%, whereas that in neonates 32–37 weeks gestation (n = 16) (lower line) was 1.41 ± 0.18% ($P < 0.05$).

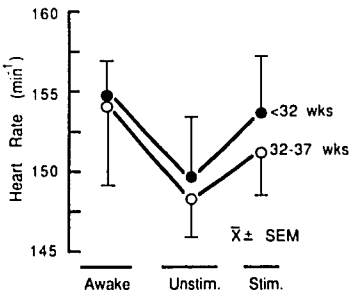

FIG. 2. Heart rate did not change significantly in either group at ~1 MAC isoflurane before or after skin incision compared to awake values. Data are mean ± SEM. Awake = immediately before induction of anesthesia, Unstim. = at ~1 MAC isoflurane before skin incision, Stim. = maximum response at ~1 MAC isoflurane after skin incision.

group during the study (fig. 2). In contrast, systolic arterial pressure decreased to the same extent in both groups after induction of anesthesia ($P < 0.001$), and remained significantly below awake values after skin incision (<32 weeks gestation age, $P < 0.001$, and 32–37 weeks gestational age, $P < 0.01$) (fig. 3). The incidence of hypotension (defined as a transient systolic arterial pressure ≦ 40 mmHg) in preterm neonates <32 weeks gestational age, 25%, was not significantly different from the 20% incidence in neonates 32–37 weeks gestational age. Seven preterm neonates <32 weeks gestational age who underwent patent ductus arteriosus ligation had received indomethacin. No patient received indomethacin within 5 days of surgery.

The ventilatory variables (ventilatory rates and $P_{ET_{CO_2}}$) did not differ significantly between the two groups. The mean (±SD) ventilatory rate in preterm neonates <32 weeks gestational age was 34.5 ± 7.5 breaths per minute, whereas that in preterm neonates 32–37 weeks gestational age was 36.4 ± 12.4 breaths

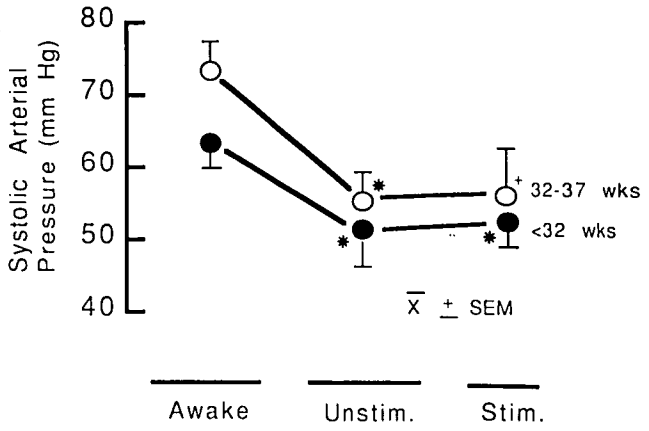

FIG. 3. Systolic arterial pressure decreased significantly in both groups at ~1 MAC isoflurane before skin incision and after skin incision compared to awake values. Data are mean ± SEM. *$P < 0.001$, †$P < 0.01$ from awake values. Awake = immediately before induction of anesthesia, Unstim. = at ~1 MAC isoflurane before skin incision, Stim. = maximum response at ~1 MAC isoflurane after skin incision.

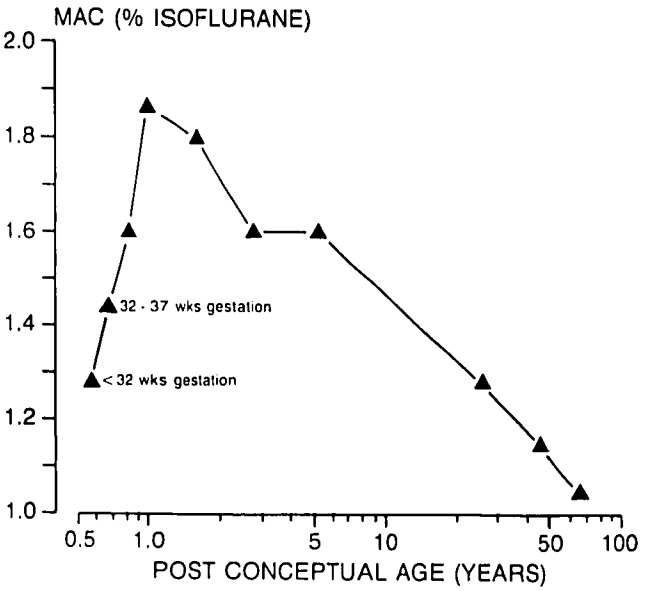

FIG 4. The MAC of isoflurane and post-conceptual age. Data for full-term neonates, infants, and children were adapted from Cameron CB, Robinson S, Gregory GA: The minimum alveolar concentration of isoflurane in children. Anesth Analg 63:418–420, 1984, with permission; and, for adults, from Stevens WC, Dolan WM, Gibbons RT, White A, Eger EI II, Miller RD, DeJong RH, Elashoff RM: Minimum alveolar concentrations (MAC) of isoflurane with and without nitrous oxide in patients of various ages. ANESTHESIOLOGY 42:197–200, 1975, with permission. Values for post-conceptual age were obtained by adding 40 weeks to the mean post-natal age for each age group. The MAC of isoflurane in preterm neonates is significantly less than in full-term neonates and older infants 1–6 months of age ($P < 0.005$).

per minute. The $P_{ET_{CO_2}}$ in preterm neonates <32 weeks gestational age was 36.4 ± 6.7 mmHg, whereas that in preterm neonates 32–37 weeks gestational age was 36.9 ± 6.7 mmHg. Arterial carbon dioxide partial pressures were within 3 mmHg of the end-tidal values in the six patients in whom arterial blood gases were determined. The capnograms which were recorded in 12 preterm neonates revealed normal respiratory patterns. Arterial oxygen saturation did not change significantly during the study period in either group.

The relationship between the MAC of isoflurane and post-conceptual age (fig. 4) is based on data from the present study and from two previous studies.[3,5] The MAC of isoflurane decreases significantly with both increasing and decreasing post-conceptual age from a maximum value of 1.86% in infants 10–16 months post-conceptual age (corresponding to 1–6 months post-natal age).

Discussion

We found that MAC of isoflurane was significantly less in preterm neonates <32 weeks gestational age than

in preterm neonates 32–37 weeks gestational age ($P < 0.05$), and both were significantly less than MAC in full-term neonates[5] ($P < 0.001$ and $P < 0.005$, respectively) (fig. 4).

Systolic arterial pressure decreased between 20 and 30% after induction of anesthesia compared to awake values. This decrease in systolic arterial pressure is similar to that reported previously at lower isoflurane concentrations.[8] The decrease in arterial pressure in the present study is not surprising when one considers that the awake systolic arterial pressures exceeded the published values for preterm infants,[7] and that many of the infants were relatively hypovolemic. We attributed the increased awake arterial pressures in these neonates to reflex hypertension in response to manipulation, transfer, and positioning on the operating room table. The significant decrease in systolic arterial pressure may also be attributed in part to hypovolemia secondary to third space loss of fluid in neonates with bowel obstruction or to diuretic therapy in those neonates with a patent ductus arteriosus. Intravenous administration of balanced salt solution or plasma (5–15 ml/kg) restored the systolic arterial pressure (*i.e.*, ≧ 40 mmHg) to acceptable values.[7]

Potent inhalational agents attenuate the baroreflex response in the neonatal animal[11–13] and human,[4,5,14] and in the preterm infant.[15] In the present study, heart rate did not change significantly following induction of anesthesia or skin incision, even in the presence of significant decreases in systolic arterial pressure. This supports the notion that ~1 MAC of isoflurane attenuates the depressor axis of the baroreflex response in preterm neonates. Because cardiac output in small infants depends on a rapid heart rate and an adequate circulating blood volume,[16] attenuation of the baroreflex response prevents the reflex increase in heart rate during hypotension, and may thereby compromise organ perfusion.

To determine MAC in preterm neonates, an accurate and reproducible technique for collecting end-tidal gas samples is required.[4,17] It is possible that the end-tidal gas samples were contaminated with either inspired gas or gas containing no isoflurane. End-tidal gas may have been contaminated with inspired gas from airway dead-space, or non-perfused or underperfused alveoli. This would have increased the partial pressure of isoflurane in the end-tidal gas sample. In the present study, we minimized the extent of this contamination by modifying our collection technique. We aspirated only 0.5–1.0 ml of end-tidal gas per breath manually from the distal end of the endotracheal tube, instead of using a continuous sampling technique from the elbow connector. The validity of distal sampling of end-tidal gas was verified with normal capnograms and an arterial-alveolar P_{CO_2} difference of less than 3 mmHg in those neonates with arterial cannulae.[18] These factors together contributed to accurate and reproducible end-tidal gas samples in this study.

End-tidal gas may also have been contaminated with gas containing no isoflurane from the Sechrist ventilator or ambient room air. We determined that there was no contamination of end-tidal gas with oxygen from the Sechrist ventilator, providing the gas flow from the anesthetic machine was greater than that from the Sechrist ventilator.** However, contamination of end-tidal gas samples with ambient room air could not be ruled out in every patient. The close agreement between end-tidal and arterial P_{CO_2}, and between inspired isoflurane concentrations measured proximally and distally in the endotracheal tube, indicated that substantial dilution of end-tidal gas samples was unlikely. We conclude that dilutional errors of a magnitude sufficient to significantly affect MAC were unlikely.

MAC determinations are valid only if the end-tidal partial pressure closely approximates arterial anesthetic partial pressure. To obtain an end-tidal sample in which the anesthetic partial pressure agrees closely with the arterial anesthetic partial pressure, preterm neonates with ventilation/perfusion mismatch and/or increased dead space (*i.e.*, bronchopulmonary dysplasia, severe respiratory distress syndrome, and intracardiac right-to-left shunts) were excluded from this study. The presence of a decreased ventilation/perfusion ratio (*i.e.*, R → L intrapulmonary shunt) in preterm neonates <32 weeks gestational age could have led us to overestimate MAC.[19,20]

Although arterial partial pressures of isoflurane were not determined, the ratio of alveolar to inspired partial pressures of isoflurane was approximately 1.0 after 20 min of steady-state anesthesia (*i.e.*, at the time of skin incision) in most preterm neonates. Because the alveolar-arterial partial pressure gradient is small when the inspired-alveolar gradient is small,[21,22] the partial pressure of isoflurane in the vessel-rich tissue group, alveoli, and inspired gas were all similar at the time of skin incision. The lower blood/gas solubility,[23] lower vessel-rich tissue solubility,[24] reduced proportion of muscle tissue, and greater proportion of vessel-rich[7] tissue in the neonate when compared to children and adults would support such an assumption.

If the concept of MAC is to be considered valid, the preterm neonate must be capable of responding with a move/no-move response to a standard nociceptive stimulus.[17] Maturational development of reflex and behavioral responses to pain parallels the increase in anesthetic requirements in full-term infants from the neona-

** Unpublished data.

tal period up to 6 months of age.[25,26] The response of preterm neonates to painful stimuli, such as the insertion of intravenous cannulae or endotracheal tubes, confirms their ability to respond to pain in a manner similar to that in full-term neonates. Therefore, we submit that the move/no-move response to skin incision is sufficiently mature in the preterm neonate to use it to determine anesthetic requirements.

The factors responsible for the increase in MAC from preterm neonates <32 weeks gestational age to full-term infants 1–6 months of age (fig. 4) remain speculative. Progesterone,[27] endorphins,[28] and structural changes in the central nervous system[29,30] have all been implicated to explain these changes in MAC, but all remain unproven.

Is general anesthesia necessary for preterm neonates? Although some clinicians have practiced relaxant-only or minimum-anesthetic techniques out of concern for cardiovascular depression,[31] we do not support this practice. Recent evidence indicates that preterm neonates perceive and respond to pain. Preterm infants who are lightly anesthetized with nitrous oxide and d-tubocurare are capable of mounting significant hormonal responses to surgery and these responses can be significantly attenuated by the addition of fentanyl.[32] This is not surprising in light of the increased metabolic activity reported in those areas of the brain responsible for processing pain signals in neonates and infants less than 3 months of age.[33] Without adequate anesthesia, preterm neonates may move in response to surgical stimuli (fig. 1). Furthermore, increases in systolic arterial pressure and central venous pressure may be important factors in the pathogenesis of intraventricular hemorrhage.[34] Fentanyl-pancuronium anesthesia has been recommended for preterm neonates and infants to attenuate the hormonal and circulatory responses to surgery, although, in both studies, systolic arterial pressure remained at the upper limit of normal.[35,36] We found that isoflurane is a safe and reliable anesthetic which maintains systolic arterial pressure within the normal range in preterm neonates.

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