

## Minimum Alveolar Concentration of Desflurane and Hemodynamic Responses in Neonates, Infants, and Children

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We sought to determine the minimum alveolar concentration (MAC) and hemodynamic responses to desflurane in 72 fasting and unpremedicated full-term neonates, infants, and children up to 12 yr of age. The patients were divided into six groups ( $n = 12$ ) according to age. After awake tracheal intubation, neonates were anesthetized with desflurane in oxygen and air. Infants > 1 month of age and all older children were anesthetized with desflurane in 100% oxygen, and their tracheas were intubated without muscle relaxation. MAC was determined using the "up-and-down technique" and logistic regression. Heart rate and systolic arterial pressure were recorded awake, at  $\approx 1$  MAC desflurane before skin incision and at  $\approx 1$  MAC during the peak hemodynamic responses to skin incision. We found that the relationship between MAC (mean  $\pm$  standard deviation) as determined by the up-and-down technique and age was quadratic, reaching a maximum value in infants 6-12 months of age: in neonates 0-1 month MAC was  $9.16 \pm 0.02\%$ , in infants 1-6 months  $9.42 \pm 0.06\%$ , in infants 6-12 months  $9.92 \pm 0.44\%$ , in children 1-3 yr  $8.72 \pm 0.59\%$ , in children 3-5 yr  $8.62 \pm 0.45\%$ , and in children 5-12 yr  $7.98 \pm 0.43\%$ . MAC values obtained using logistic regression were similar. Heart rate decreased an average of 16% before skin incision in infants 6-12 months of age and children 1-3 and 3-5 yr of age when compared to awake values ( $P < 0.025$ ) but did not change significantly in the remaining three groups. Heart rate returned to or was greater than awake values after incision in all groups. Systolic arterial pressure decreased significantly before skin incision in all groups ( $P < 0.05$ ) but returned toward awake values after incision. We conclude that 1) the MAC of desflurane in infants and children depends on age, although the difference between the MAC in neonates and that in older infants is much smaller than that reported previously with both halothane and isoflurane and 2) hemodynamic responses to  $\approx 1$  MAC desflurane are similar in neonates, infants, and children up to 12 yr of age. (Key words: Anesthesia; neonatal, pediatrics. Anesthetic; potency; MAC. Anesthetics, volatile; desflurane. Circulation: heart rate; systolic arterial pressure. Monitoring: end-tidal anesthetic concentration.)

AGE has an important effect on the minimum alveolar concentration (MAC) of inhalational anesthetics, particularly in the pediatric range.<sup>1-4</sup> As age decreases, MAC increases, reaching a maximum value in infants 1-6 months of age, and decreases thereafter with decreasing age.<sup>3-5</sup> Using this relationship, Lerman *et al.* found that

at equipotent concentrations of inhalational anesthetics, the incidence of hypotension in neonates was similar to that in older infants,<sup>4</sup> thus dispelling the notion that neonates are at greater risk of circulatory depression during inhalational anesthesia than are older infants.

Desflurane is a new polyfluorinated methyl ethyl ether with physical properties that differ from those of isoflurane, including lower blood-gas (0.42) and lower tissue-blood partition coefficients.<sup>6,7</sup> The low partition coefficients should facilitate both a rapid increase and decrease in alveolar and tissue anesthetic partial pressures during induction of and emergence from anesthesia with desflurane. Therefore, this study was designed to determine the MAC of desflurane and the hemodynamic responses to  $\approx 1$  MAC desflurane in six groups of infants and children.

### Materials and Methods

After approval from our Human Subjects Review Committee, informed written consent was obtained from the parents of 81 full-term neonates, infants, and children up to 12 yr of age. All patients were fasted, unpremedicated, and ASA physical status 1 or 2, and were scheduled for surgery that required both skin incision and tracheal intubation: surgery included repair of defects of the gastrointestinal system in neonates and superficial lower abdominal, penile, or plastic surgery in older infants and children. Patients were precluded from the study if respiratory, cardiovascular, or neurologic diseases or a genetic defect were present; if a history of malignant hyperthermia were obtained; if medication known to affect MAC had been administered within 48 h of surgery; if the patient had been a preterm and was < 1 yr postnatal age; or if a tourniquet was required during surgery. Patients were assigned to one of six groups according to age: group 1, full-term neonates 0-1 month of age (< 28 days postnatal age); group 2, 1-6 months; group 3, 6-12 months; group 4, 1-3 yr; group 5, 3-5 yr; and group 6, 5-12 yr. All patients were monitored with a continuous electrocardiogram, pulse oximeter, and end-tidal and inspired desflurane and carbon dioxide concentrations using a Datex 254 Airway Gas Monitor, as well as an arterial blood pressure (Doppler) device, precordial stethoscope, and temperature probe. Heart rate and systolic arterial blood pressure were recorded awake, after at least 10 min at the designated end-tidal concentration of desflurane before skin incision and during the peak hemody-

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namic responses within the first 2 min after skin incision at the same concentration of desflurane.

For neonates and infants 1–6 months of age, the operating room was prewarmed to 25–30° C, whereas for older infants and children, the operating room was maintained at 21–25° C. After awake tracheal intubation, neonates were anesthetized with desflurane in a mixture of oxygen and air. Infants > 1 month of age and children up to 12 yr of age were anesthetized with stepwise increases in the inspired concentration of desflurane, up to 25% in oxygen. In the infants and older children, the tracheas were intubated under deep desflurane anesthesia in oxygen. Desflurane was delivered by a modified DM5000 anesthetic machine and a pressurized vaporizer. After tracheal intubation, ventilation was controlled using an Ohmeda 7000 or Air Shields Ventimeter ventilator and Jackson-Rees's modification of the Ayre's T piece. Ventilation and the fresh gas flow were adjusted to maintain the end-tidal carbon dioxide tension between 35 and 45 mmHg. Positive end-expiratory pressure was avoided. Temperature was maintained within acceptable limits by prewarming the operating room, interposing a heat-and-moisture exchanger between the elbow connector of the T-piece and the fresh gas line, and positioning all patients on a warming blanket. All patients were supine and horizontal during the period of equilibration of alveolar and inspired concentrations of desflurane. Lactated Ringer's solution or 5% albumin was administered intravenously as required to maintain systolic arterial pressure > 40 mmHg in neonates and > 60 mmHg in older infants and children during equilibration of desflurane before skin incision. Atropine and muscle relaxants were omitted.

End-tidal gas was sampled through a 19-G (standard wire gauge) Deseret Intracath® catheter inserted through the elbow connector to within 1 cm of the distal end of the tracheal tube. The catheter hub was fitted tightly into the elbow connector. The end-tidal concentrations of desflurane and carbon dioxide were analyzed continuously with a calibrated Datex 254 Airway Gas Monitor and displayed and stored on a PSION LZ64 computer.<sup>8</sup> This computer displayed the concentrations of desflurane in tenths of a percent for concentrations greater than 10% and in hundredths of a percent for concentrations less than 10%.

MAC was determined with the "up-and-down technique" of Dixon.<sup>9</sup> The objective of this technique is to bracket an end-tidal concentration that is MAC with all-or-none responses to the initial skin incision. The response to skin incision was recorded as "movement" or "no movement." A movement response was defined as either flexion or withdrawal of one or more extremities in response to skin incision. Breathholding, grimacing, and movement of the head were not accepted as a movement response.

The end-tidal concentration of desflurane administered to the first patient in each age group approximated the MAC in adults 18–31 yr of age (7.25%).<sup>10</sup> The end-tidal concentration of desflurane administered to successive patients was determined by the response of the preceding patient in the same age group. The difference in end-tidal concentration of desflurane between successive patients was 0.5%. If the preceding patient moved in response to skin incision, then the concentration of desflurane administered to the next patient in that age group was increased by 0.5%. This continued until a no-movement response was observed. If the preceding patient did not move, then the concentration of desflurane administered to the next patient in that age group was decreased by 0.5%. The first two patients entered into each age group were the first two consecutive patients with opposite responses to skin incision. These and the subsequent 10 patients constituted the 12 patients required in each age group.

#### STATISTICAL ANALYSIS

Based on the up-and-down technique, MAC was the mean of the end-tidal concentrations of desflurane at skin incision in the 12 patients in each age group. To determine the standard deviation of MAC,<sup>9</sup> each age group was divided into three subgroups, where a subgroup was defined as four consecutive patients within that age group. The standard deviation of MAC was the standard deviation of the mean concentrations of the three subgroups within each age group.

The MAC for each age group was also estimated by logistic regression using the computer program BMDPLR.<sup>11</sup> The response for the logistic model was taken as the logarithmic odds of movement *versus* no movement. The fitted equation was used to solve for the concentration of desflurane at which 50% of the patients moved (ED<sub>50</sub>). Thus, the MAC was determined to be the ED<sub>50</sub> of the logistic equation. The variance of the ED<sub>50</sub> was estimated from a first-order Taylor approximation to the ED<sub>50</sub>.<sup>12</sup> The ED<sub>50</sub>s and the estimated variances were calculated at the average age for each of the six age groups.

Heart rate and systolic arterial pressure were analyzed awake, at  $\approx$  1 MAC desflurane before skin incision, and at  $\approx$  1 MAC desflurane after skin incision (peak response) using repeated measures analysis of variance and the Student-Newman-Keuls test. Statistical significance was accepted at  $P < 0.05$ .

#### Results

Of the 81 patients enrolled in the study, 72 were accepted for the determination of MAC. These patients were assigned to one of six groups according to age (table).



TABLE 1. Demographic, MAC, and Blood Pressure Data

Group	Age*	Weight* (kg)	MAC (%)*		Decrease in SAP† (%)	Incidence of Hypotension‡
			Up-and-down Technique	Logistic Regression		
Neonates <28 days	13 ± 9.5 days	3.3 ± 0.89	9.16 ± 0.02	9.29 ± 4.1	34	5 (42)
Infants 1–6 months	2.8 ± 1.3 months	5.7 ± 0.87	9.42 ± 0.06	9.39 ± 1.1	34	7 (58)
6–12 months	8.3 ± 1.7 months	8.9 ± 1.32	9.92 ± 0.44	9.96 ± 1.98	26	5 (42)
Children 1–3 yr	1.8 ± 0.6 yr	12.5 ± 1.54	8.72 ± 0.59	8.73 ± 0.33	28	3 (25)
3–5 yr	3.7 ± 0.6 yr	15.1 ± 1.56	8.62 ± 0.45	8.54 ± 0.10	27	5 (42)
5–12 yr	7.5 ± 1.7 yr	25.7 ± 7.24	7.98 ± 0.43	8.16 ± 0.36	22	2 (17)

\* Data are means ± SD.

† Mean percent decrease in systolic arterial pressure (SAP) at ≈1 MAC desflurane compared to awake pressures.

‡ Number of patients whose SAP decreased &gt;30% at ≈1 MAC compared to awake pressure (percentage of patients within that age group in parentheses).

The movement and no-movement responses for individual patients according to age are shown in figure 1. The relationship between age and the MAC of desflurane was quadratic (fig. 2); that is, MAC (using the up-and-down technique) increased from  $9.16 \pm 0.02\%$  in neonates to a maximum value of  $9.92 \pm 0.44\%$  in infants 6–12 months of age and then decreased thereafter. The MAC in neonates was only 7.7% less than that in infants 6–12 months of age.

Two separate logistic regression models were fitted to the movement and no-movement data: one was fitted for

neonates and infants < 12 months of age, and a second was fitted for children 1–12 yr of age (table 1). In neonates and infants, logistic regression yielded 4- to 20-fold greater variances in the MAC values than did the up-and-down technique.

Fluids were required to maintain a minimum systolic arterial pressure in anesthetized neonates. Neonates received  $5.58 \pm 4.14$  ml/kg lactated Ringers' solution after induction of anesthesia with desflurane but before skin incision to maintain a systolic pressure  $\geq 40$  mmHg. None of the older infants and children required any fluids during the equilibration period to maintain a minimum systolic pressure.

The hemodynamic responses to desflurane differed among the six age groups. Before skin incision, heart rate decreased significantly in infants 6–12 months and children 1–3 and 3–5 yr ( $P < 0.025$ ) but was maintained in neonates, infants 1–6 months, and children 5–12 yr of

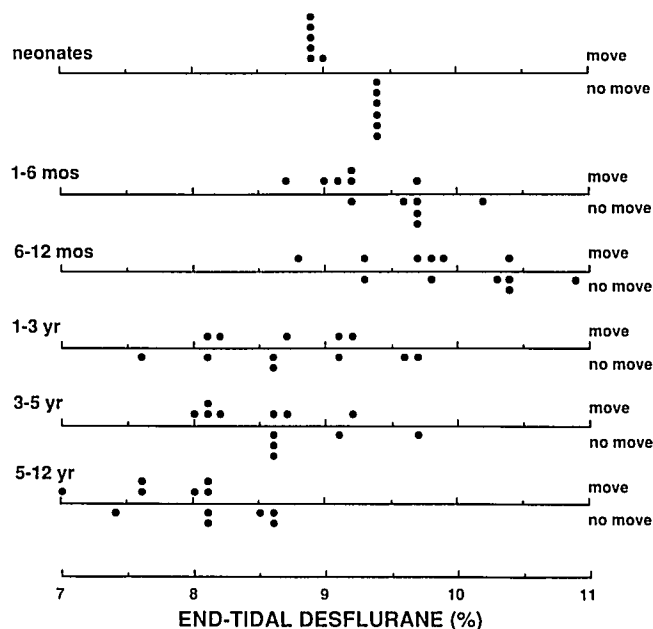


FIG. 1. Each circle represents the response of one patient to skin incision. The position of the circle along the horizontal axis represents the mean end-tidal concentration of desflurane during the 10 min immediately before skin incision. The MAC for each age group (mean concentration for the 12 patients in each group) is shown in figure 2.

## MAC DESFLURANE

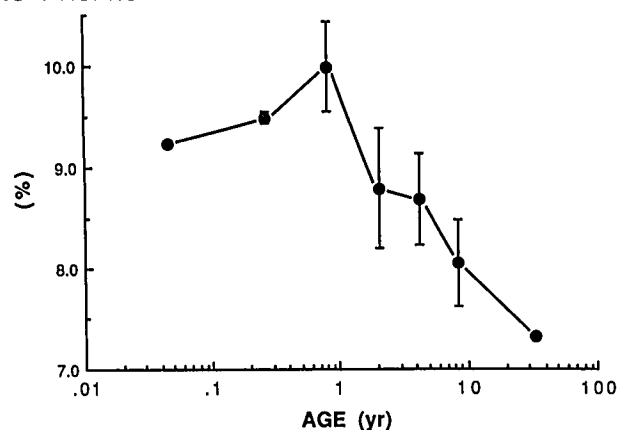


FIG. 2. The MAC of desflurane in neonates, infants, and children as determined by the "up-and-down" technique. Data for adults was obtained from reference 10. Data are means ± SD.



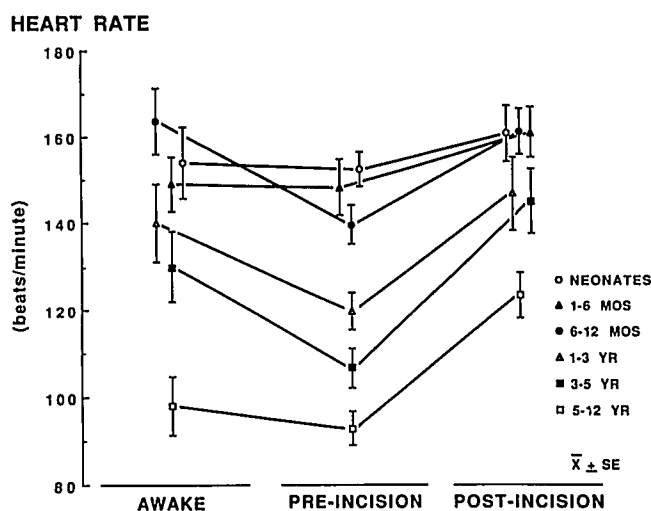


FIG. 3. Heart rate decreased significantly in infants 6–12 months and children 1–3 and 3–5 yr of age at  $\approx 1$  MAC desflurane before skin incision compared to awake values ( $P < 0.025$ ) but returned toward awake values after skin incision. Heart rate did not change significantly at  $\approx 1$  MAC desflurane in neonates, infants 1–6 months, and children 5–12 yr of age compared to awake values.

age compared to awake values (fig. 3). After skin incision, heart rate returned to awake values in infants 6–12 months and children 1–3 and 3–5 yr and increased significantly above awake values in infants 1–6 months and children 5–12 yr of age ( $P < 0.005$ ).

Before skin incision, systolic arterial pressure decreased significantly in all age groups when compared to awake values ( $P < 0.05$ ) (fig. 4). After skin incision, systolic arterial pressure returned toward awake values in infants 1–6 months and children 1–3 and 3–5 yr of age but remained significantly less than awake values in neonates, infants 6–12 months, and children 5–12 yr of age ( $P < 0.005$ ). The mean percentage decrease in systolic arterial pressure at  $\approx 1$  MAC desflurane decreased as age increased (table 1). The incidence of hypotension, defined as a 30% decrease in systolic arterial pressure compared with awake values, was similar in all age groups (table 1).

### Discussion

The relationship between age and the MAC of desflurane in infants and children is similar to that reported previously for halothane<sup>4</sup> and isoflurane.<sup>3</sup> For all three inhalational anesthetics, MAC increases with age reaching a maximum value during infancy and decreases thereafter with increasing age. However, the relationship between age and the MAC of desflurane differs from those for halothane and isoflurane in two respects. First, the MAC of desflurane peaks in infants 6–12 months of age, whereas those of halothane and isoflurane peak in younger infants, 1–6 months of age.<sup>3,4</sup> The explanation for this observation is unclear.

Second, the MAC of desflurane in neonates is only 7.7% less than the peak value in infancy (fig. 2). This is approximately one third and one half the values obtained previously with halothane, 25%,<sup>4</sup> and isoflurane, 17%,<sup>3</sup> respectively. The explanation for this difference is unclear.

It has been suggested that nominal or quantal responses (such as movement or no-movement responses) may be analyzed in a quantitative manner and with less risk of bias or error in the  $ED_{50}$  with probit or logit analysis than with the traditional up-and-down technique.<sup>13</sup> To address this issue, we analyzed the quantal responses by both techniques (table 1). We found that the fit of a single logistic model revealed no evidence of a quadratic effect. This contradicted the observed relationship between the MAC of desflurane using the up-and-down technique and age (fig. 2). It was also unexpected given our knowledge of the relationship between the MAC values of halothane and isoflurane, and age.<sup>1,3,4</sup> Therefore, we chose to fit two logistic models: one model for patients  $\leq 1$  yr and a second model for patients 1–12 yr of age. The 1-yr age limit for these models was based on our observation that the maximum concentration of desflurane in the quadratic relationship between MAC (based on the up-and-down technique) and age occurred in infants approximately 1 yr of age. Logistic regression analysis using the two models yielded estimates of MAC that were similar to those obtained with the up-and-down technique for the respective age groups (table 1). However, the variances of the MAC values for neonates and infants  $< 1$  yr of age with logistic regression analysis were greater than with the up-and-

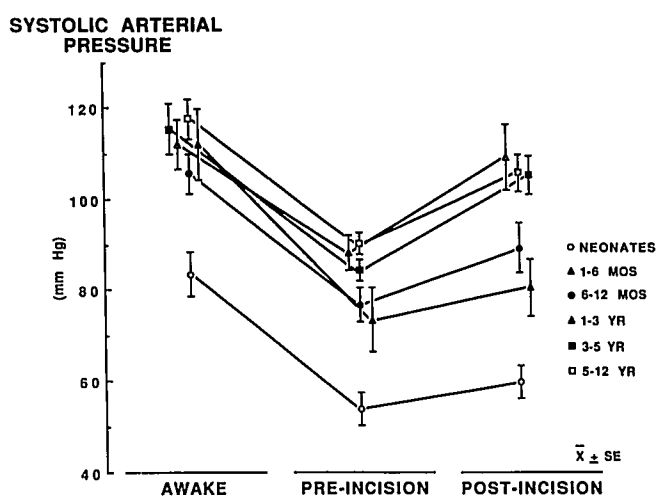


FIG. 4. Systolic arterial pressure decreased significantly at  $\approx 1$  MAC desflurane before skin incision compared to awake values. After skin incision, systolic pressure returned toward awake values in infants 1–6 months and children 1–3 and 3–5 yr of age but remained significantly less than awake values in neonates, infants 6–12 months, and children 5–12 yr of age ( $P < 0.005$ ).



down technique. The discrepancy in the variances between the two techniques is unclear. To be conservative, the wider confidence intervals from the logistic model are recommended.

The hemodynamic responses to  $\approx 1$  MAC desflurane are similar to those for isoflurane.<sup>14</sup> In adults, desflurane decreases mean arterial pressure and systemic vascular resistance in a dose-related manner and decreases cardiac output at 1.0 MAC while increasing it at 1.5 and 2.0 MAC.<sup>15</sup> Heart rate remains stable at 1.0 MAC but increases at 1.5 and 2.0 MAC.<sup>15</sup> In the present study, systolic arterial pressure decreased 30% at  $\approx 1$  MAC desflurane before incision compared to awake values, while heart rate either decreased significantly or remained unchanged. Similar hemodynamic responses have been reported in adults anesthetized with desflurane<sup>15</sup> and in neonates and infants anesthetized with halothane.<sup>4</sup> These data indicate that the hemodynamic effects of  $\approx 1$  MAC desflurane in infants and children are within acceptable clinical limits.

Previous studies have shown that inhalational anesthetics attenuate the baroreflex in infants and children.<sup>16</sup> In those studies, heart rate decreased or remained unchanged despite a significant decrease in systolic arterial pressure at  $\approx 1$  MAC before surgical stimulation. In the present study, heart rate decreased or remained unchanged at  $\approx 1$  MAC desflurane despite a 30% decrease in systolic arterial pressure. These data suggest that like halothane, desflurane attenuates the baroreflex response in infants and children at  $\approx 1$  MAC levels.

Although desflurane has several characteristics that may be attractive for pediatric anesthesia, its irritant effects on the airway are of concern. Breathholding, coughing, laryngospasm, and systemic arterial desaturation occur frequently in infants and children who are anesthetized with desflurane.<sup>17,18</sup> Thus, the widespread use of desflurane as an induction agent in infants and children may be severely limited by its irritant effects on the upper airway.

In summary, we found that age influences the MAC of desflurane in neonates, infants, and children in a manner similar to that of other inhalational anesthetics. The hemodynamic responses to  $\approx 1$  MAC desflurane before and after surgical incision in neonates and infants are similar to previous data for halothane.

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