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A Comparison of the Respiratory Effects of Sevoflurane and Halothane in Infants and Young Children

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Background: **This study compared the respiratory effects of sevoflurane with those of halothane in anesthetized infants and young children.**

Methods: **Infants were randomized to receive 1 minimum alveolar concentration (MAC) halothane or sevoflurane in a mixture of nitrous oxide and oxygen. Anesthetic management included the use of a laryngeal mask. Flow, airway pressure, and the end-tidal carbon dioxide pressure ($P_{ET_{CO_2}}$) were measured during spontaneous ventilation and airway occlusions. Respiratory inductive plethysmography was used to assess chest wall motion.**

Results: **Measurements were obtained in 30 infants and young children (mean (SD) age, 14.5 (5.9) months), 15 of whom received sevoflurane and 15 received halothane. Some respiratory depression, as indicated by a $P_{ET_{CO_2}}$ of 45 mmHg (6 kPa), was present in both groups. Minute ventilation and respiratory frequency were significantly lower during sevoflurane than halothane anesthesia (4.5 compared with 5.4 (l/m^2)/min, and 37.5 compared with 46.7 breaths/min, respectively, $P < 0.05$). There was no difference in respiratory drive, but the shape of the flow waveform differed according to anesthetic agent, with peak inspiratory flow reached later, and peak expiratory flow reached earlier, in the sevoflurane group. There was also significantly less thoracoabdominal asynchrony during sevoflurane anesthesia.**

Conclusions: **Minute ventilation and respiratory frequency were lower in infants during 1 MAC sevoflurane in nitrous oxide than during halothane anesthesia. However, these differences may not be clinically relevant at these concentrations, given the modest increase in $P_{ET_{CO_2}}$. Differences in parameters of breath timing and shape between sevoflurane and halothane suggest different effects of these anesthetic agents on ventilatory control. (Key words: Anesthesia; breathing patterns; laryngeal mask; respiratory control; respiratory inductive plethysmography.)**

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SEVOFLURANE may offer several advantages over halothane anesthesia.[1] However, studies in adults have suggested that the respiratory depression seen with sevoflurane is more pronounced than with halothane and that respiratory drive is lower.[2] Similarly, in a study of children aged 2–6 yr, greater respiratory depression, evidenced by a higher expired carbon dioxide level, was reported at 1.5 minimum alveolar concentration (MAC) sevoflurane in oxygen compared with halothane anesthesia.[3] Because only limited data are available for younger patients, we thought that it was important to examine the comparative effects of sevoflurane and halothane on respiration in infants and toddlers, in whom developmental aspects of respiratory mechanics and control may predispose them to increased respiratory depression during anesthesia.[4–6]

The null hypothesis to be tested in this study was that there was no difference in ventilatory depression in infants and young children while breathing sevoflurane in nitrous oxide or halothane in nitrous oxide. The principle aim was to compare the respiratory effects of sevoflurane with those of halothane by measuring end-tidal carbon dioxide ($P_{ET_{CO_2}}$), minute ventilation, tidal

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volume (V_T), and respiratory rate during tidal breathing. Additional measures of ventilatory control were undertaken to assist in interpretation of any differences in the main outcome parameters. These included (1) analysis of the flow waveform for parameters of respiratory drive, timing and shape,[7] (2) examination of the inspiratory effort during brief airway occlusion to assess respiratory drive,[8] and (3) assessment of chest wall motion by measuring thoracoabdominal asynchrony using respiratory inductive plethysmography.

Materials and Methods

Patients

Infants and young children were eligible for our study if they were aged 6–24 months, healthy, had fasted, had no history of cardiovascular disease or chest wall deformity, and were undergoing elective peripheral limb surgery or hypospadias repair. The study received institutional ethics committee approval, and parents gave written informed consent.

Anesthetic Management

Patients were premedicated with oral atropine (20 μg/kg) and randomized to receive either halothane or sevoflurane in 66% nitrous oxide in oxygen (6 l/min) to induce and maintain anesthesia. A modified Jackson Rees (Mapleson F) circuit was used. After induction, the inspired concentrations of halothane and sevoflurane were reduced to 1% and 2.5%, respectively, for maintenance. No attempt was made to titrate the inspired concentration of anesthetic to a target end-tidal concentration.

A laryngeal mask, inserted immediately after induction, was used for airway management. After induction of anesthesia, a regional anesthetic was performed with 0.25% bupivacaine. Infants received either a caudal anesthetic (0.75 ml/kg) for hypospadias and lower limb surgery or a brachial plexus block (0.5 ml/kg) for upper limb surgery. The infant was then placed in the supine position. The respiratory inductive plethysmography bands (SomnoStar PT, NIMS; Sensormedics, the Netherlands) were applied, and the pneumotachograph with a pressure port was inserted between the laryngeal mask and the anesthetic T-piece. The end-tidal concentration of each agent was measured distal to the pneumotachograph (Datex Capnograph Ultima, Helsinki, Finland). Patients breathed the maintenance concentration of the selected agent for 15 min, after which time the end-tidal concentration of each vapor was recorded. The study was completed before the commencement of surgery, and anesthesia was continued in accordance with the clinical practice of the anesthesiologist. The MAC-adjusted concentrations, *i.e.*, the fractional MAC and the total MAC multiple, were calculated. In the calculation of fractional MAC, the age-corrected MAC of halothane was assumed to be 0.9%[9] and that of sevoflurane was thought to be 2.5%.[10] In the calculation of the total MAC multiple, 66% nitrous oxide was assumed to increase the MAC multiple by 0.5 and 0.7 for sevoflurane and halothane, respectively.[10]

Measuring Equipment

Flow was measured with a heated pneumotachograph (Hans Rudolph 3500; linear range, 0–35 l/min; Kansas City, MO), attached to a piezo-resistive pressure transducer (±0.2 kPa [2 cm H_2O], 431 SCXL0040N; Sensym Inc., Milipitas, CA). Volume was integrated digitally from the flow signal. The airway pressure was measured with a differential pressure transducer (±50 cmH_2O; 5 kPa; 511 SCX010N, Sensym Inc.) *via* a side port attached to the 15-mm connector of the laryngeal mask. Carbon dioxide tension was measured with a sidestream analyzer (Datex Capnograph Ultima) that sampled from a port distal to the pneumotachograph at a rate of 200 ml/min. The accuracy of the carbon dioxide analyzer was verified with a known mixture of 7% carbon dioxide.

To perform airway occlusions the pneumotachograph was connected to an appropriately sized, non-rebreathing valve (Hans Rudolph 2200's) which separated the inspiratory and expiratory flow. A pneumatically activated, hand operated balloon-type shutter (Hans Rudolph 9300) was interposed in the inspiratory limb to produce airway occlusions. At a flow of 100 ml/s, the resistance of the apparatus was 3.2 $cmH_2O \cdot l^{-1} \cdot s^{-1}$ (0.31 $kPa \cdot l^{-1} \cdot s^{-1}$) during spontaneous ventilation. This increased to 9.0 $cmH_2O \cdot l^{-1} \cdot s^{-1}$ (0.88 $kPa \cdot l^{-1} \cdot s^{-1}$) when the shutter was *in situ*. Dead space of the measuring apparatus was approximately 9 ml by water displacement. The pressure transducer was calibrated with a water manometer and checked at the start and end of each study. Flow was calibrated with a rotameter and the volume validated, at the start and end of each study, with a volumetric 100-ml syringe (Hans Rudolph) using 66% nitrous oxide in oxygen. Respiratory inductive plethysmography signals for the rib cage and abdomen were measured with 1.5-cm respibands, placed at

the level of the fourth intercostal interspace and umbilicus, respectively.

Data Collection

Two separate computerized data acquisition set-ups were used to digitize, record, and analyze the data. Flow and pressure at the airway opening were collected using ANADAT (RHT InfoDat, Montreal, Canada), and rib cage and abdominal signals were recorded simultaneously using RespiEvents (SomnoStar PT, NIMS). Data were collected after the administration of the regional anesthetic and before surgical incision, during both spontaneous ventilation and respiratory efforts during end-expiratory airway occlusions. Data during spontaneous ventilation were recorded for 3 min, 15–20 min after induction of anesthesia. The carbon dioxide sample port was then exchanged for the balloon occlusion device. Airway occlusion was timed from the real-time display of flow. After a minimum of five regular, spontaneous breaths, an airway occlusion was performed at end expiration and held until the infant had made a complete respiratory effort. This procedure was repeated until four technically acceptable occlusions had been performed.

Data Analysis

The $P_{ET_{CO_2}}$ value was obtained as the highest value of the expiratory carbon dioxide signal from each breath. Analog outputs of flow, airway pressure, and carbon dioxide were digitized and sampled at 50 and 100 Hz for the spontaneous ventilation and occlusion data, respectively. Signals were interpolated and analyzed on a breath-by-breath basis. The V_T, respiratory rate, minute ventilation, and parameters of ventilatory timing, including the total (t_{tot}), inspiratory (t_I), and expiratory (t_E) time, were calculated from the pneumotachograph flow signal.

The time to peak tidal inspiratory and expiratory flow were measured (fig. 1), from which the inspiratory (t_{PTIF}/t_I) and expiratory (t_{PTEF}/t_E) flow ratios were calculated.[11,12] These parameters assess the shape of the flow waveforms and the extent to which inspiratory and expiratory flow are modulated.[11,12] The inspiratory duty cycle (t_I/t_{tot}), mean inspiratory flow (V_T/t_I), and the inspiratory (C_I/t_I) and expiratory (C_E/t_E) centroids[7] were also calculated. The latter reflect the overall shape of the inspiratory and expiratory flow profiles in a manner that is relatively insensitive to noise because all the data, rather than a single sample at peak flow, are used. Centroids with a value of 0.5 indicate a symmetrical

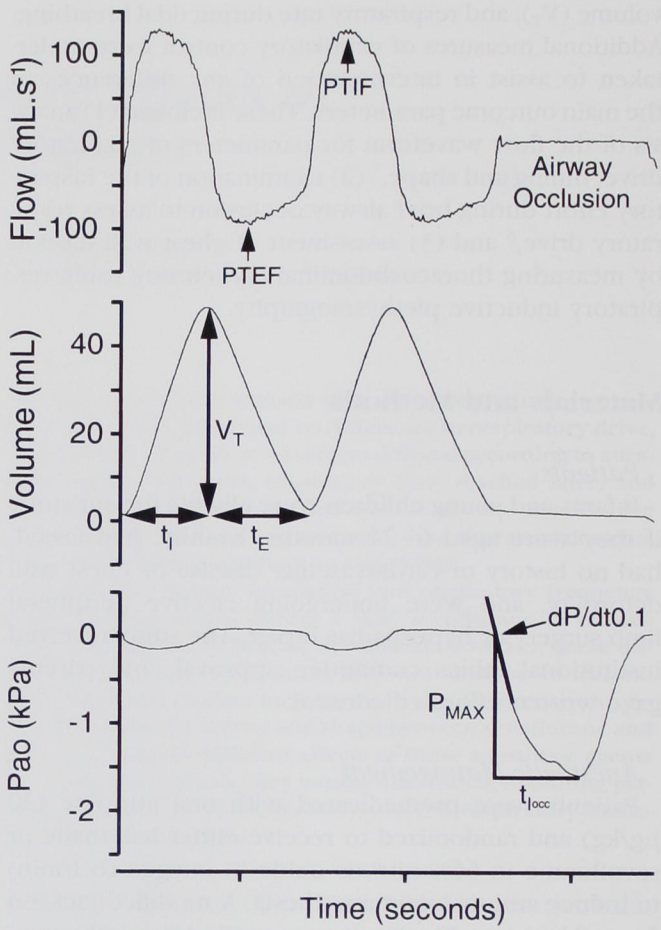

Fig. 1. Data analysis before and during an airway occlusion. The technique for measurement of inspiratory time (t_I), maximal pressure during inspiratory effort against an occlusion (P_{MAX}), and the change in pressure with time during the first 0.1 s of occlusion ($dP/dt_{0.1}$) are shown. The time intervals to peak tidal inspiratory (t_{PTIF}) and expiratory (t_{PTEF}) flow were calculated from the zero flow crossing to their respective peak flows (1 kPa = 10.2 cmH_2O).

waveform, whereas those with a ratio less than or greater than 0.5 indicate flow profiles that are skewed to the left or right, respectively.[7] The reported values for parameters obtained during spontaneous ventilation, including the $P_{ET_{CO_2}}$, were the mean of at least 50 breaths.

Acceptance criteria for data obtained during airway occlusions included absence of any volume leak and a minimum of five breaths between consecutive occlusions. Ventilatory drive was measured from the maximal negative pressure during airway occlusion (P_{MAX}) and the inspiratory pressure achieved 0.1 s after commencement of the occlusion ($P_{0.1}$).[8] The latter was derived as follows (see also fig. 1):

$$P_{0.1} = 0.1 \cdot dP/dt_{0.1}$$

$P_{0.1}$ data were only accepted if the slope of the occluded pressure waveform ($dP/dt_{0.1}$) was linear during the first 100 ms of the occlusion ($r^2 \geq 0.97$ by linear regression). Reported values for $P_{0.1}$ and P_{MAX} were the mean of a minimum of four occluded efforts.

Thoracoabdominal asynchrony was assessed from the "phase relation of the total breath" using the Respi-Events software. This parameter quantifies the percentage agreement between the direction of rib cage and abdomen signals during the total breath and here is called the "thoracoabdominal phase lag." A value of 0% indicates synchronous movement throughout the breath, whereas a value of 100% indicates total paradox, values that are analogous to phase angles of 0 and 180 degrees, respectively, when measured from Lissajous loops.[13]

Statistical Analysis

Differences between the sevoflurane and halothane groups in the outcome variables of $P_{ET_{CO_2}}$, minute ventilation, V_T, and respiratory rate were assessed with unpaired *t* tests and calculation of the 95% CI for the group mean difference (sevoflurane − halothane). A probability value ≤0.05 was considered significant. Differences in the explanatory mechanisms were assessed with the 95% CI of the mean differences between the sevoflurane and halothane groups, whereby a 95% CI that does not encompass zero corresponds to a probability value <0.05.[14]

Results

Measurements of minute ventilation, V_T, $P_{ET_{CO_2}}$, and respiratory rate were performed in 30 infants. Satisfactory occlusion data were obtained in 27 of these patients (sevoflurane n = 14, halothane n = 13), failures being due to equipment problems in one infant and technically unacceptable data (see Methods) in two infants. Patient characteristics for the sevoflurane and halothane groups were similar (table 1). Both groups had a preponderance of male patients. Caudal blockade was the predominant technique of regional nerve block. As expected, the expired to inspired concentration of vapor (Fe:Fi) ratio was significantly higher in the sevoflurane group.

Table 2 summarizes respiratory function results. Mild respiratory depression, evidenced by a $P_{ET_{CO_2}}$ of 45 mmHg (6 kPa), occurred in both groups. Minute ventilation was lower in the sevoflurane compared with the halothane group (4.5 *vs.* 5.4 $l \cdot m^2 \cdot min^{-1}$, respectively; $P < 0.05$). This reflected the slower respiratory frequency during sevoflurane (38 *vs.* 47 breaths/min during halothane, $P < 0.01$), whereas mean V_T was identical (5.5 ml/kg) in both groups.

Table 1. Patient Characteristics

	Sevoflurane	Halothane
n	15	15
Age (mo)	14.5 (5.9)	14.6 (5.9)
Weight (kg)	11.1 (2.6)	10.0 (1.7)
Height (cm)	80.8 (9.5)	77.0 (7.7)
BSA (m^2)	0.51 (0.1)	0.47 (0.1)
Gender (M:F)	13:2	11:4
Regional block (CB:BB)	12:3	11:4
Fe/Fi	0.94 (0.03)	0.84 (0.04)*
End-tidal %	2.35 (0.1)	0.84 (0.1)
MAC fraction	0.94 (0.1)	0.91 (0.1)
Total MAC multiple in N_2O	1.4	1.8

Numerical data are presented as mean (SD).

BSA = body surface area; M = male; F = female; CB = caudal block; BB = brachial plexus block; Fe/Fi = ratio of the expired to inspired anesthetic vapor during respiratory measurements; End-tidal % = end-tidal concentration of anesthetic vapor; MAC = minimum concentration of anesthetic vapor to prevent movement to pain in 50% of the population; MAC fraction = Fe vapor alone MAC.

* $P < 0.05$) by unpaired *t* test.

Expiratory time was significantly longer in the sevoflurane group, as was the time to reach peak tidal inspiratory flow. Whereas there was no statistical difference in the inspiratory duty cycle (t_I/t_{tot}), there were differences in other indices of the breath shape, namely the tidal inspiratory and expiratory flow ratios and inspiratory and expiratory centroids. Inspiratory flows peaked later, and expiratory flows peaked earlier in the sevoflurane group. There were no statistical differences in the respiratory drive parameters of $P_{0.1}$, maximal pressure during occlusion, or mean inspiratory flow according to anesthetic agent (table 2). However, there was less thoracoabdominal asynchrony in the sevoflurane group than in the halothane group, as evidenced by the mean phase lags of 28.1% and 44.5%, respectively. There was no relation between age and the magnitude of the phase lag in this population of infants.

Discussion

The results from this study suggest that, although $P_{ET_{CO_2}}$ is similar in infants and young children anesthe-

Table 2. Ventilatory Effects of Sevoflurane and Halothane

	Sevoflurane	Halothane	95% Confidence Intervals of the Difference
Primary outcome parameters			
$P_{ET_{CO_2}}$ (mmHg)	45.8 (7.5)	45.0 (6.8)	−4.4, 6.2
Minute ventilation (l/m^2)/min	4.5 (1.1)	5.4 (0.8)	−1.60, −0.12*
Tidal volume (ml/kg)	5.5 (0.8)	5.5 (0.7)	−0.6, 0.6
Respiratory rate (breath/min)	37.5 (7.2)	46.7 (8.5)	−15.2, −3.2†
Explanatory mechanisms			
Timing			
Inspiratory time (s)	0.66 (0.14)	0.57 (0.11)	−0.01, 0.19
Time to peak inspired flow (s)	0.36 (0.14)	0.25 (0.06)	0.03, 0.19*
Expiratory time (s)	1.00 (0.25)	0.75 (0.14)	0.09, 0.41*
Time to peak expired flow (s)	0.21 (0.06)	0.23 (0.05)	−0.06, 0.03
Shape			
Duty cycle (t_I/t_{tot})	40 (5.0)	43 (4.0)	−6.0, 0.0
Inspiratory flow ratio (t_{PTIF}/t_I) %	53.3 (9.8)	42.1 (6.1)	4.9, 17.4*
Expiratory flow ratio (t_{PTEF}/t_E) %	22.0 (7.0)	31.0 (10.0)	−16.0, −2.0*
Inspiratory centroid (C_I/t_I) %	53.0 (6.0)	48.0 (2.0)	2.0, 8.0*
Expiratory centroid (C_E/t_E) %	37.0 (9.0)	45.0 (3.0)	−13.0, −3.0*
Drive			
Mean inspiratory flow (V_T/t_I) ml/s	191 (54)	210 (39)	−55, 17
$P_{0.1}$ (cmH_2O)	5.10 (3.6)	6.22 (2.7)	−3.6, 0.14
Maximal pressure during occlusion (cmH_2O)	20.4 (8.2)	18.2 (7.6)	−4.1, 8.3
Thoracoabdominal asynchrony			
Phase lag (PhRTB) %	28.1 (14.5)	44.5 (12.9)	−28.2, −4.6*

Data are mean (SD), and 95% confidence intervals of the difference (sevoflurane-halothane). For conversion to SI units (kPa), divide pressure in mmHg by 7.5, and those in cmH_2O by 10.2

* $P < 0.05$, † $P < 0.01$ by unpaired *t* test.

tized with 1 MAC sevoflurane or halothane in nitrous oxide, there are differences in both the absolute and relative parameters of respiratory timing, such that minute ventilation and respiratory frequency are significantly lower in those receiving sevoflurane. However, interpretation of these data require careful consideration of all potentially confounding factors.

The difficulties in achieving identical anesthetic depth in comparative studies of different anesthetic agents are well recognized.[9,10,15,16] In the current study, 1% halothane or 2.5% sevoflurane, approximately equivalent to 1 MAC for each agent, were administered. Lerman *et al.*[10] suggested that the MAC-sparing effect of nitrous oxide is greater for halothane than for sevoflurane. Therefore, after age adjustment and allowance for the fact that the gases were administered in nitrous oxide, the corrected total MAC multiple would be 1.4 for the sevoflurane group compared with 1.8 in the halothane group, effectively biasing the sevoflurane group to a slightly lighter plane of anesthesia. Thus the differences were observed between the two agents were, if anything, underestimated. Studies in older children have also reported a reduction in respiratory rate during sevoflurane compared with halothane anesthesia, but only at or above 1.5 MAC anesthesia.[3]

The finding of similar values for $P_{ET_{CO_2}}$ in the sevoflurane and halothane groups, despite the reduced minute ventilation in the former, is intriguing. The potential problems in using $P_{ET_{CO_2}}$ as an estimate of alveolar ventilation are well recognized, and inaccuracies could have arisen in the current study as a result of the use of a proximal rather that a distal sample site[15] and the occurrence of a relatively rapid respiratory rate in these infants, which limited the duration of an end-expiratory plateau.[16] However, because the respiratory rate was slower in those receiving sevoflurane, we would not expect such errors to mask a relative reduction in alveolar ventilation in this group. Although they were not assessed formally, in the current study we noted little change in $P_{ET_{CO_2}}$ during manual assisted ventilation when the end expiratory plateau was longer. This suggests that, although the values of $P_{ET_{CO_2}}$ must be interpreted cautiously, they are unlikely to have introduced any systematic bias. The findings of this study

may indicate that, in contrast to minute ventilation, alveolar ventilation is similar during sevoflurane and halothane anesthesia at 1 MAC, a result, perhaps, of a more efficient pattern of breathing in the former. In the current study, we used a laryngeal mask, which has a much lower resistance than an endotracheal tube.[17] This was reflected in the higher weight-corrected tidal volumes (5.5 ml/kg) in both groups than have been reported previously in intubated infants anesthetized with halothane.[6,18-20]

Ventilatory Control

Current concepts of ventilatory control model a neural network whose discharge may be characterized by the magnitude and duration of the electrical discharge and the pattern of recruitment of inspiratory neurons.[8,21] These concepts provide the rationale for the analysis of the mechanical transforms of this neural output, namely airflow and airway pressure.

Respiratory Drive. Although respiratory drive, assessed by $P_{0.1}$, has been reported to be lower during sevoflurane than halothane anesthesia in adults,[2] in this study of infants we found no difference in respiratory drive, as evidenced by similar values for $P_{0.1}$, maximal pressure generated during occlusions, and the mean inspiratory flow (V_T/t_I) (table 2).

Ventilatory Timing. Although there were differences in both absolute and relative ventilatory timing parameters between the sevoflurane and halothane groups, the inspiratory duty cycle (t_I/t_{tot}) was similar, mean values in both groups being consistent with those reported in intubated children anesthetized with 1 MAC halothane,[22] in adults,[2] and in unintubated children recovering from halothane anesthesia.[7] The inspiratory duty cycle has been shown to be relatively unaffected by anesthesia.[2,19,20,23]

Shape of the Flow Waveform. A large diversity of flow waveforms exist at rest. However, studies in resting humans have suggested a signature flow waveform, or "personalité ventilatoire."[24,25] Thus demonstration of a flow waveform characteristic for a specific anesthetic agent is noteworthy. Both the expiratory centroid and expiratory flow ratio were significantly less during sevoflurane than halothane anesthesia, indicating that peak expiratory flows were attained earlier during sevoflurane anesthesia. For comparison, the expiratory flow ratio ($t_{PTEF}:t_E$) in healthy children recovering from halothane anesthesia has been reported to range from 34% to 73%.[7] Several factors have been shown to influence this ratio, including respiratory mechanics, activity of extrapulmonary muscles, vagal input, and changes in respiratory rate.[11,12,26] In this study, the lower ratio during sevoflurane anesthesia was primarily due to the lengthening of expiratory time compared with halothane, because time to reach peak expiratory flow was similar in both groups (table 2).

In contrast, the inspiratory flow ratio and the inspiratory centroid were higher (indicating that peak inspiratory flow was attained relatively later) during sevoflurane compared with halothane anesthesia (table 2). These skewed inspiratory flow waveforms during sevoflurane anesthesia are in contrast to the symmetrical patterns reported in the halothane group and in a previous study of children recovering from halothane anesthesia.[7] Although the clinical relevance of this finding is unknown, the shape of the inspiratory flow waveform may reflect the recruitment pattern of the inspiratory motor neuron pool.[25]

Chest Wall Pattern

A further aspect of the recruitment pattern of the inspiratory motor neurons is the pattern of chest wall motion. There was more thoracoabdominal asynchrony, evidenced by more phase lag, during halothane than during sevoflurane anesthesia (table 2). This is consistent with the loss of intercostal tone, which has been shown to occur with halothane.[27,28]

Conclusions

We found a lower minute ventilation and respiratory frequency, but similar levels of ventilatory depression, as reflected by changes in $P_{ET_{CO_2}}$, in infants anesthetized with 1 MAC sevoflurane in nitrous oxide, compared with those anesthetized with 1 MAC halothane. There was evidence that sevoflurane affected both absolute and relative parameters of respiratory timing in a manner different from that of halothane. Although the clinical importance of these observations is unknown, they may indicate that sevoflurane and halothane have different effects on the recruitment pattern of the inspiratory motor neurons.

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