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Sevoflurane Depresses Myocardial Contractility Less than Halothane during Induction of Anesthesia in Children

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Background: **Cardiovascular stability is an important prerequisite for any new volatile anesthetic. We compared echocardiographically derived indices of myocardial contractility during inhalation induction with sevoflurane and halothane in children.**

Methods: **Twenty children were randomized to receive either halothane or sevoflurane for inhalation induction of anesthesia. No preoperative medications were given. Myocardial contractility was evaluated at baseline and at sevoflurane and halothane end-tidal concentrations of 1.0 minimum alveolar concentration (MAC) and 1.5 MAC.**

Results: **There were no differences between groups in patient age, sex, physical status, weight, or height. Equilibration times and MAC multiples of sevoflurane and halothane were comparable. Vital signs remained stable throughout the study. Left ventricular end-systolic meridional wall stress increased with halothane but remained unchanged with sevoflurane. Systemic vascular resistance decreased from baseline to 1 MAC and 1.5 MAC with sevoflurane. Halothane depressed contractility as assessed by the stress-velocity index and stress-shortening index, whereas contractility remained within normal limits with sevoflurane. Total minute stress and normalized total mechanical energy expenditure, measures of myocardial oxygen consumption, did not change with either agent.**

Conclusions: **Myocardial contractility was decreased less during inhalation induction of anesthesia with sevoflurane compared with halothane in children. Although the induction of anesthesia with sevoflurane or halothane was equally well tolerated, the preservation of myocardial contractility with sevoflurane makes it an attractive alternative for inducing anesthesia in children. (Key words: Anesthetic, volatile: sevoflurane; halothane. Heart: contractility; myocardial function. Measurement techniques: echocardiography. Anesthesia: pediatric.)**

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SMOOTHNESS and rapidity of anesthetic induction, a pleasant odor with lack of airway irritability, and patient acceptance are highly desirable characteristics for inhalation anesthetics. Although halothane has traditionally been the induction agent of choice because of these properties, sevoflurane also has a pleasant odor, which promotes patient acceptance.[1,2]

Cardiovascular stability is also an important characteristic for any new volatile anesthetic. Preliminary studies in adults indicate that sevoflurane, similar to isoflurane, depresses systolic, diastolic, and mean arterial pressure in a dose-dependent manner, but patient heart rate after incision is greater in those given isoflurane.[3] In children, systolic arterial pressure transiently decreases at 1 minimum alveolar concentration (MAC) of isoflurane[4] but is better preserved compared with baseline values than with halothane.[5] Although the negative chronotropic and inotropic effects of halothane in children have been documented,[6] there are few data using more sensitive indices of cardiac assessment during induction of anesthesia, especially indices that distinguish among preload, afterload, and load-independent contractility. This study compared the myocardial and hemodynamic ef-

fects of sevoflurane and halothane during inhalation induction in children.

Materials and Methods

After receiving approval by the Clinical Investigation Committee of Children's Hospital, informed parental consent, and the assent of children capable of giving it (generally those older than 8 y), 20 children ages 2 to 12 y who were having elective non-body-cavity surgery with an anticipated duration of at least 1 h were randomized to receive either halothane or sevoflurane in an open-label, comparative study. Patients were specifically excluded from the study if they had a history of asthma, pneumonia (within 1 y), a previously difficult tracheal intubation, congenital or acquired heart disease, central nervous system disease, gastrointestinal diseases with gastroesophageal reflux, renal failure, muscle disease with the potential for malignant hyperthermia, metabolic disease, hepatitis, or use of drugs known to affect MAC or to induce hepatic microsomal enzymes within the past 6 months.

No preoperative medications were given. Anesthesia was induced in an induction room adjacent to the operating room area using a circle system and a standard anesthesia machine (Ohmeda Excel 210; Madison, WI) with a sevoflurane (7% maximum output, Penlon PPV_{Σ}; Penlon Ltd., Abingdon, UK) or halothane vaporizer (5% maximum output Dräger Vapor 19.1; North American Dräger, Telford, PA). Physiologic monitoring was accomplished with an automated blood pressure cuff (Dinamap 1846 SX; Critikon, Tampa, FL), an electrocardiogram monitor (Hewlett-Packard model M1175A, series 5000; Hewlett-Packard, Rockville, MD), and a pulse oximeter (Nellcor 200; Nellcor, Hayward, CA). Respiratory gases (inspired and end-tidal [ET] oxygen, nitrous oxide, halothane, and sevoflurane) were monitored by an infrared spectroscope (Datex Capnomac Ultima; Helsinki, Finland) that was calibrated weekly. These data were recorded in real-time *via* the RS 422 port of the Hewlett-Packard monitor and archived in epochs of 15 s with a data-acquisition system (LabView, Version 2.0; National Instruments, Austin, TX) on a Macintosh Centris 650 computer (Apple Computers, Cupertino, CA).

Sevoflurane was provided by Abbott Laboratories (Abbott Park, IL) and halothane was available as a part of normal stock pharmaceuticals. Sevoflurane was stored at room temperature in the operating room pharmacy.

A baseline echocardiographic evaluation of left ventricular function was performed, after which anesthetic induction was begun with 70% nitrous oxide and 30% oxygen at a total fresh gas flow of 5 l/min. Increasing inspired concentrations of the selected volatile agent were introduced, and nitrous oxide was discontinued when the patient was unconscious. Echocardiographic evaluations were repeated at predetermined, age-adjusted ET concentrations of 1 MAC and 1.5 MAC for each agent.[7-10] The ET concentration at that point was recorded and the patient's trachea intubated. In all cases, the ET nitrous oxide concentration was less than 0.5% before echocardiography. The maximum vaporizer inspired concentration did not exceed 7% for sevoflurane or 3.5% for halothane.

An intravenous catheter was inserted after loss of consciousness and clinical assessment of readiness (usually at 1 MAC ET for each anesthetic), and Ringers lactate solution was begun at a maintenance rate of 4 to 8 $ml \cdot kg^{-1} \cdot h^{-1}$. Muscle relaxants were not given and patients breathed spontaneously throughout the study.

Echocardiographic data were collected using an ultrasound system with two-dimensional-directed M-mode and continuous-wave Doppler capability (Hewlett-Packard Sonos 1000 or 1500; Andover, MA). High-speed (100 mm/s) hard-copy and videotaped M-mode echocardiograms were obtained of the left ventricular short axis, with a simultaneous phonocardiogram, electrocardiogram, and indirect carotid pulse tracing. Continuous-wave Doppler recording of aortic blood flow was obtained from the suprasternal notch.

High-quality hard-copy tracings of three cardiac cycles for each patient at baseline and at 1.0 and 1.5 MAC equivalents were chosen for analysis. Using a SummaSketch II digitizing pad (Summagraphics Corp., Seymour, CT), the left ventricular septal and posterior free wall endocardial and epicardial surfaces, along with the simultaneous carotid pulse and Doppler aortic blood flow tracings, were manually digitized as previously described by Colan and associates.[11] Using custom software developed in our echocardiographic laboratory, left ventricular end-systolic wall stress (ESSm), rate-corrected velocity of circumferential fiber shortening (VCFc), total systolic stress, and fractional shortening were calculated and compared with normal values.[12] Fractional shortening was calculated using the formula

$$FS = \frac{LVEDD - LVESD}{LVEDD}$$

where LVEDD = left ventricular short-axis end-diastolic

dimension, and LVESD = left ventricular end-systolic dimension.

Wall stress was calculated using the formula

$$\text{ESSm} = \frac{(P)(D)\ 1.35}{(h)(1 + (h/D))(4)}$$

where P = pressure, D = dimension, h = left ventricular posterior wall thickness, and 1.35 = conversion factor from milligrams of mercury to grams per square centimeter.

Rate-corrected VCFc was calculated using the formula

$$\text{VCFc} = \frac{\text{FS}}{\text{rate-corrected ejection time}}$$

and rate-corrected ejection time = ejection time divided by the square root of the R-R interval (to correct to a heart rate of 60 bpm).

Stroke volume, cardiac output, and systemic vascular resistance were compared with normal values from our laboratory.

In addition, normalized total mechanical energy expenditure, one recently validated measure of myocardial oxygen consumption (MVO_2), was calculated using the formula:

$$\text{Normalized TME} = \frac{(\text{MEP} \times \text{EDV}) + \text{SW}}{\text{LV wall volume}}$$

where MEP = mean ejection pressure, EDV = end-diastolic volume, and SW = stroke work.[13] ($SW = \int P \times dV$)

Data are reported as mean ± SD, unless otherwise noted. Because there is an age and body surface area-dependent variation of fractional shortening, VCFc, and ESSm, Z scores rather than absolute values were used to normalize these calculations, with age- and growth-related means taken from values established for healthy children[12]:

$$\text{Z Score} = \frac{(\text{value} - \text{mean})}{\text{S.D.}}$$

$$\text{Normal} = -2 \text{ to } +2$$

The sample size was based on a previous study of cardiac index during halothane anesthesia in infants,[14] with an 80% power to detect differences at the 0.05 (two-tailed) level of significance. Continuous data, parametrically distributed between groups, were analyzed using one-way analysis of variance. Analysis of variance for repeated measures was used for multiple treatments within the same group; to compare two groups with multiple treatments within groups, a two-way analysis of variance with repeated measures was used. Probability values for multiple comparisons were corrected with the Bonferroni multiple comparison test. A probability value less than 0.05 was considered significant.

Table 1. Patient Demography

	Halothane [mean (±SD)]	Sevoflurane [mean (±SD)]
Age (yr)	8.9 (2.9)	8.1 (3.2)
Sex (M:F)	5:5	4:6
ASA Physical Status 1:2 (n)	9:1	10:0
Weight (kg)	30.5 (11.3)	33.4 (10.8)
Height (cm)	133.5 (20.6)	134.7 (21.4)

Results

Twenty patients were enrolled in the study, ten in the halothane group and ten in the sevoflurane group. There were no differences between the two groups with regard to patient age, sex, physical status, weight, or height (table 1). Equilibration times were 6.4 (±3) min to 1 MAC ET halothane, 7 (±1.9) min to 1 MAC ET sevoflurane, 6 (±1.9) min to 1.5 MAC ET halothane, and 7.5 (±4.6) min to 1.5 MAC ET sevoflurane (all nonsignificant). End-tidal agent and $ETCO_2$ concentrations were not different between groups at the time of echocardiogram evaluation. End-tidal halothane and sevoflurane were 0.96 (±.07) MAC and 0.97 (±0.07) MAC at the 1 MAC study level, and were 1.45 (±0.15) MAC and 1.4 (±0.1) MAC at the 1.5 MAC study level, respectively. End-tidal carbon dioxide pressure was 31.9 (±5.3) mmHg and 31.5 (±2.5) mmHg at the 1 MAC level, and 34.4 (±7.9) mmHg and 32 (±2.8) mmHg at the 1.5 MAC level (halothane and sevoflurane, respectively; all nonsignificant).

Blood pressure and heart rate remained stable throughout the induction period. Two-way analysis of variance with repeated measures revealed no difference in heart rate between halothane and sevoflurane. Systolic blood pressure decreased from baseline to 1 MAC and then increased from 1 MAC to 1.5 MAC with both halothane and sevoflurane ($P = 0.03$ and 0.001, respectively). There was no difference between the two groups with respect to the degree of decrease or increase ($P = 0.21$ and 0.71, respectively). Diastolic blood pressure decreased from baseline to 1 MAC and then increased from 1 MAC to 1.5 MAC with sevoflurane ($P = 0.04$; fig. 1).

Echocardiographic Data

Left ventricular shortening fraction and VCFc decreased with administration of both anesthetic agents,

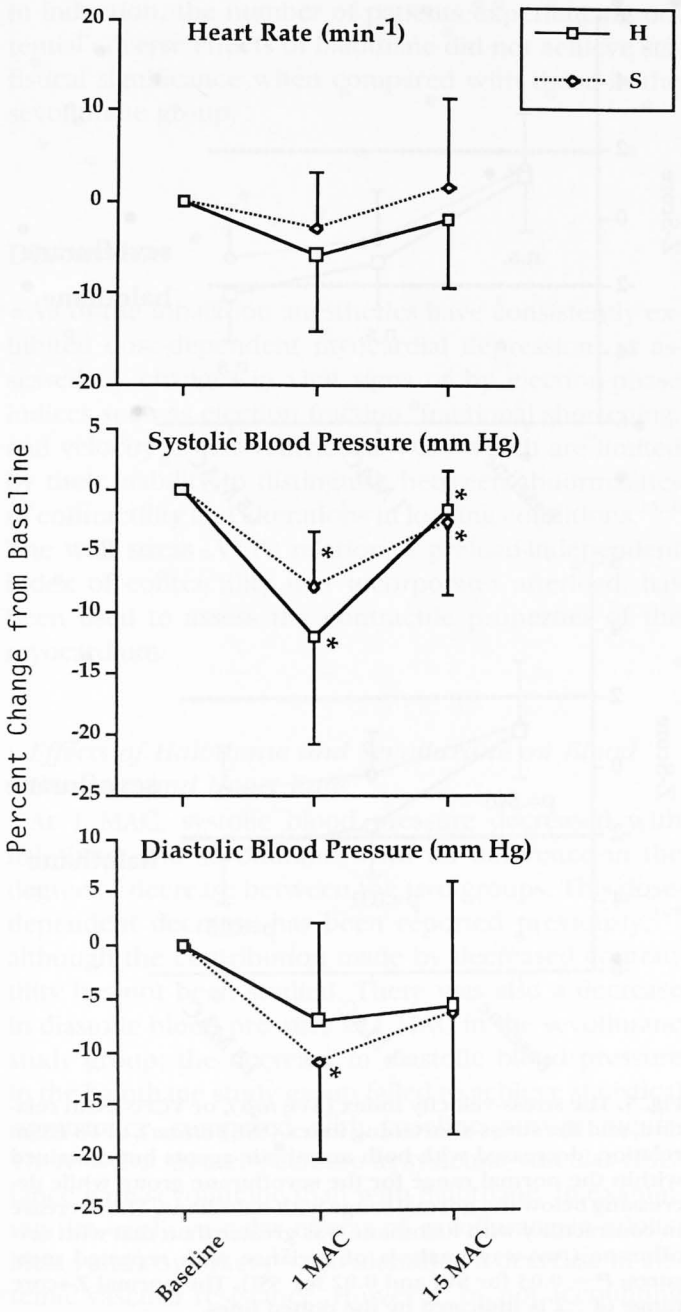


Fig. 1. Blood pressure and heart rate were stable throughout the induction of anesthesia in both groups. Although heart rate did not differ from baseline, systolic blood pressure decreased at 1 minimum alveolar concentration (MAC) with halothane and sevoflurane, returning to baseline at 1.5 MAC. Diastolic blood pressure decreased at 1 MAC with sevoflurane, returning to baseline at 1.5 MAC.

but halothane produced a significantly greater depression of both shortening fraction ($P < 0.01$) and VCFc ($P < 0.05$; fig. 2). Systemic vascular resistance, although starting at a lower point in the sevoflurane group than the halothane group, did not decrease from baseline with halothane but decreased from baseline to 1 MAC and 1.5 MAC with sevoflurane ($P < 0.05$; fig. 3). End-systolic wall stress increased with halothane but remained unchanged with sevoflurane (fig. 4); this difference was significant ($P < .05$). The stress-velocity index, or VCFc - ESSm relation, and the stress-shortening index, or FS-ESSm relation, decreased with both anesthetic agents but remained within the normal range with sevoflurane while decreasing to less than the normal range with halothane (fig. 5). The decrease in stress-

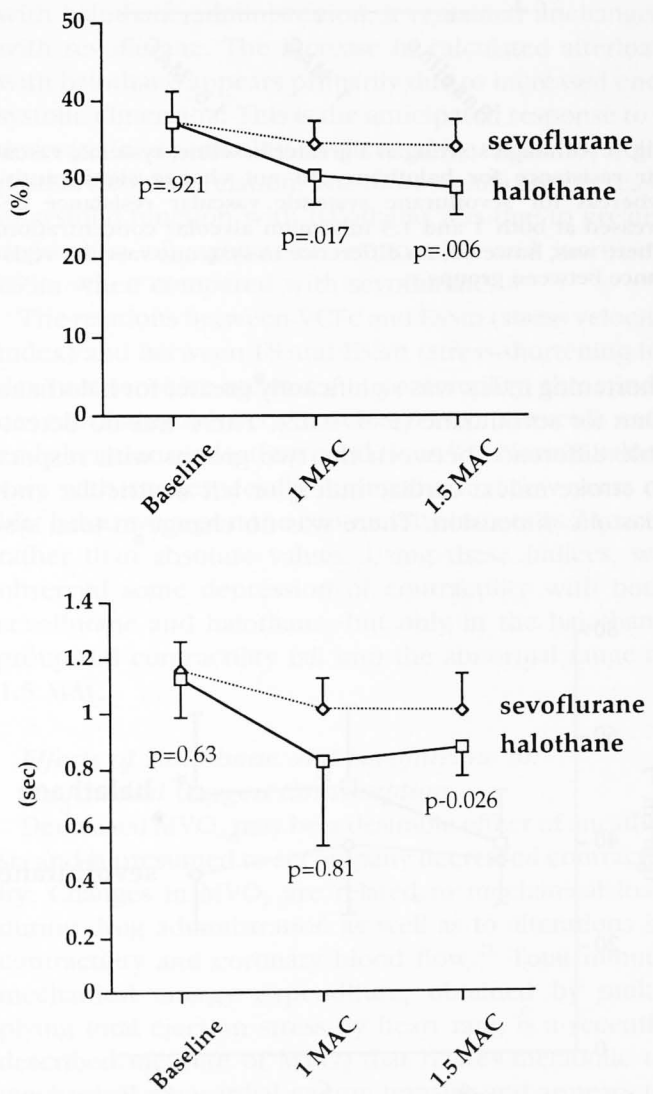


Fig. 2. Left ventricular shortening fraction; (SF; *top*) and velocity of ventricular circumferential fiber shortening corrected for heart rate (VCFc; *bottom*) decreased with both anesthetic agents. Halothane decreased shortening fraction (two-way analysis of variance with repeated measures; $P = 0.003$) and VCFc (two-way analysis of variance with repeated measures; $P = 0.018$) more than sevoflurane.

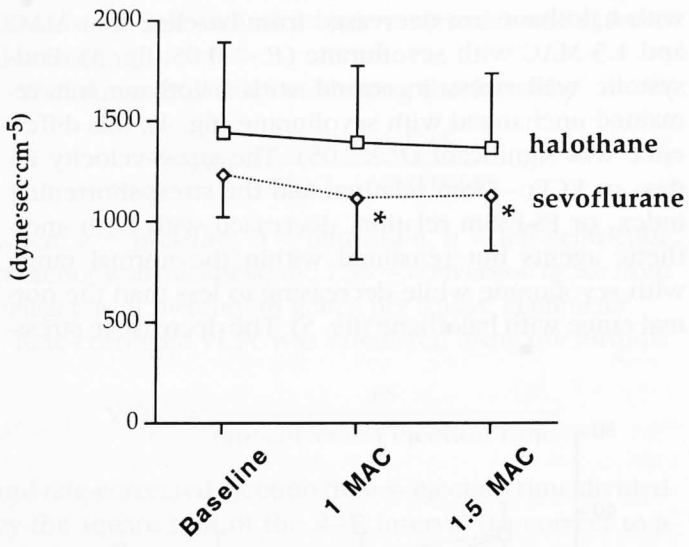


Fig. 3. Although starting at a greater baseline, systemic vascular resistance for halothane did not change significantly, whereas for sevoflurane systemic vascular resistance decreased at both 1 and 1.5 minimum alveolar concentration. There was, however, no difference in systemic vascular resistance between groups.

shortening index was significantly greater for halothane than for sevoflurane ($P \leq 0.02$). There was no detectable difference between the two groups with respect to stroke index, cardiac index, or left ventricular end-diastolic dimension. There was no change in total sys-

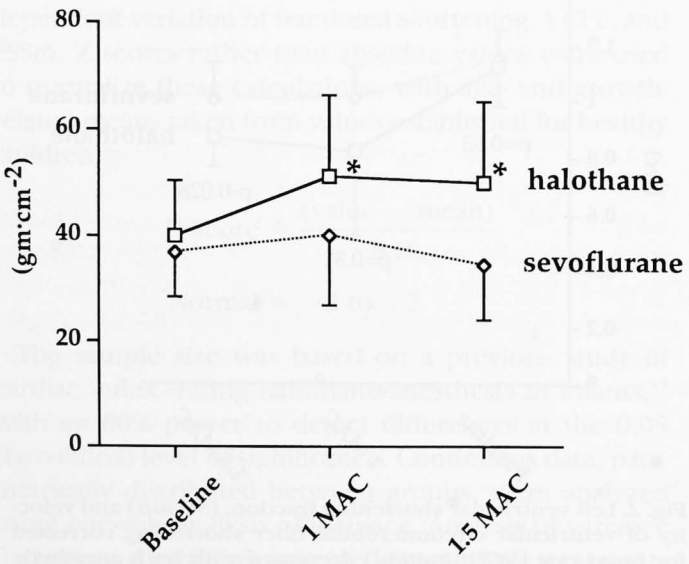
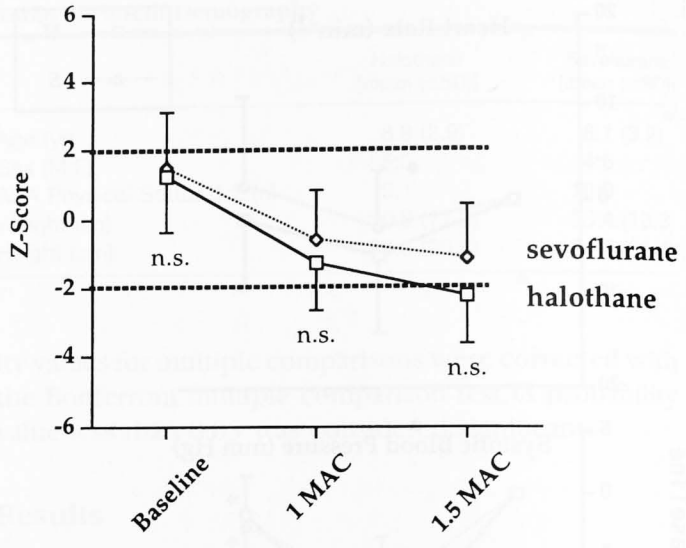


Fig. 4. End-systolic wall stress, a preload-independent measurement of afterload, increased at 1 and 1.5 minimum alveolar concentration with halothane; there was no change from baseline with sevoflurane.



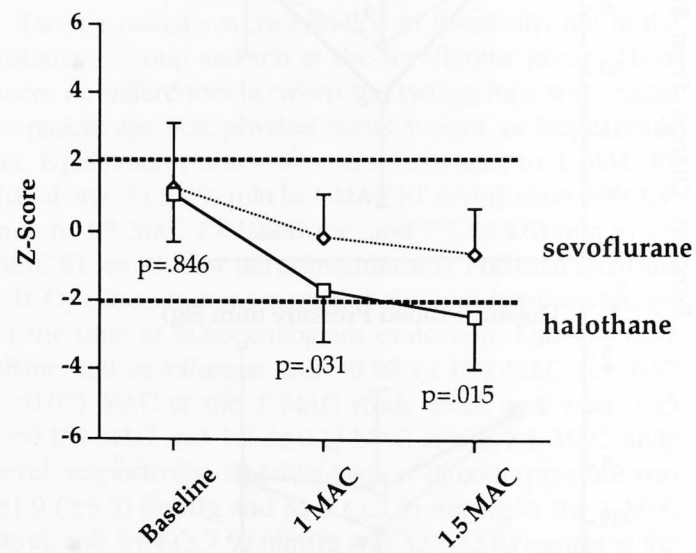


Fig. 5. The stress-velocity index (SVI; *top*), or VCFc-ESSm relation, and the stress-shortening index (SSI; *bottom*), or FS-ESSm relation, decreased with both anesthetic agents but remained within the normal range for the sevoflurane group while decreasing below the normal range with halothane. The decrease in contractility with halothane was greater than that with sevoflurane (two-way analysis of variance with repeated measures; $P = 0.03$ for SVI and 0.02 for SSI). The normal Z-score range of ±2 is indicated by the dotted lines.

tolic wall stress, total minute stress, and total mechanical energy expenditure with either halothane or sevoflurane.

Adverse Events during Induction and Emergence

Although three patients receiving halothane had self-limited episodes of premature ventricular beats, two with bigeminy, and one patient had mild coughing early

in induction, the number of patients experiencing potential adverse effects of halothane did not achieve statistical significance when compared with those in the sevoflurane group.

Discussion

All of the inhalation anesthetics have consistently exhibited dose-dependent myocardial depression, as assessed by changes in vital signs or by ejection-phase indices such as ejection fraction, fractional shortening, and velocity of left ventricular VCF, which are limited by their inability to distinguish between abnormalities of contractility and alterations in loading conditions.[15,16] The wall stress-VCFc relation, a preload-independent index of contractility that incorporates afterload, has been used to assess the contractile properties of the myocardium.

Effects of Halothane and Sevoflurane on Blood Pressure and Heart Rate

At 1 MAC, systolic blood pressure decreased with halothane and sevoflurane, with no difference in the degree of decrease between the two groups. This dose-dependent decrease has been reported previously,[3-5] although the contribution made by decreased contractility has not been studied. There was also a decrease in diastolic blood pressure at 1 MAC in the sevoflurane study group; the decrease in diastolic blood pressure in the halothane study group failed to achieve statistical significance compared with baseline measurements. There was a greater decrease in systemic vascular resistance with sevoflurane than with halothane. In examining the cardiovascular effects of sevoflurane in adults, Malan and coworkers[17] also identified a decrease in systemic vascular resistance. However, by not accounting for concomitant changes in left ventricular dimensions and wall thickness, which alter the forces resisting muscle shortening, systemic vascular resistance is an inadequate measure of the afterload faced by individual myofibrils.

At 1.5 MAC, the decrease in systolic blood pressure with halothane and sevoflurane and the decrease in diastolic blood pressure with sevoflurane reverted to baseline values. This compensation with time may reflect a homeostatic adjustment in preload, afterload, and contractility.

Effects of Halothane and Sevoflurane on Contractility

Not surprisingly, FS and VCFc, ejection-phase indices of myocardial contractility that depend on both afterload and preload, were altered by the administration of anesthetic agents. End-systolic wall stress is a measure of myocardial afterload (the force resisting muscle shortening)[18]; it is derived from end-systolic left ventricular pressure, dimension, and wall thickness. Using a different method of calculating end-systolic stress, Malan and coworkers[17] reported a decrease in ESSm with sevoflurane. In our study, although ESSm increased with halothane administration, it remained unchanged with sevoflurane. The increase in calculated afterload with halothane appears primarily due to increased end-systolic dimension. This is the anticipated response to a decrease in contractility, as dictated by the end-systolic pressure-volume relation. The more significant decrease in systolic function with halothane was due to greater depression of myocardial contractility and increased ESSm when compared with sevoflurane.

The relations between VCFc and ESSm (stress velocity index) and between FS and ESSm (stress-shortening index) are sensitive measures of contractility; these indices can distinguish between changes in contractile state and alterations in loading conditions.[18,19] Normal values vary with age, especially during the first few years of life[20]; thus we report the contractility indices as Z-scores rather than absolute values. Using these indices, we observed some depression of contractility with both sevoflurane and halothane, but only in the halothane group did contractility fall into the abnormal range at 1.5 MAC.

Effects of Halothane and Sevoflurane on Myocardial Oxygen Consumption

Decreased MVO_2 may be a desirable effect of anesthesia and is presumed to accompany decreased contractility. Changes in MVO_2 are related to mechanical load during drug administration as well as to alterations in contractility and coronary blood flow.[21] Total minute mechanical energy expenditure, obtained by multiplying total ejection stress by heart rate, is a recently described measure of MVO_2 that relates metabolic to mechanical myocardial energy transfer and appears to be more closely related to MVO_2 than other currently available noninvasive indices of myocardial energetics. Normalized total mechanical energy expenditure, the sum of external energy (stroke work) and an internal energy index of heat (left ventricular end-diastolic vol-

ume times left ventricular mean ejection pressure), is believed to be a contractility-independent index of MVO_2.[13] In the current study, decreases in contractility were accompanied by stable total minute stress, suggesting that there was no significant decrease in MVO_2 despite decreased contractility during halothane administration and no difference in MVO_2 between patients given halothane and those given sevoflurane. Normalized total mechanical energy expenditure also did not change with administration of either anesthetic and was not different in the two groups. Thus the usual assumptions about the potential benefit of decreased contractility during anesthesia may be inaccurate. These findings in children, however, may not be applicable to adults, who may have both chronic left ventricular dysfunction and impaired coronary blood flow superimposed on any acute effects of inhalation anesthetics.

We chose to avoid some common clinical practices during our echocardiographic measurements of contractility. Other than for the first minute of halothane or sevoflurane introduction, we discontinued the use of nitrous oxide, and all echocardiographic measurements were taken with an ET concentration of less than 0.5% for nitrous oxide, because we wished to measure the effects of halothane and sevoflurane in the absence of any cardiovascular system effects that nitrous oxide might have.[22-25] In addition, the effects of nitrous oxide may be different when halothane or sevoflurane are added, and it would be difficult to then distinguish the contribution made by nitrous oxide to the findings on vital signs or contractility. Finally, many pediatric anesthesiologists induce anesthesia with a spontaneous breathing technique and a potent inhalation agent, and after briefly using nitrous oxide for the benefits of the concentration effect, they switch to 100% oxygen before laryngoscopy and endotracheal intubation.

We did not administer anticholinergic medications such as atropine or glycopyrrolate, frequently given to counteract the potentially adverse hemodynamic effects of a halothane inhalation induction.[6] Although blood pressure and heart rate may appear to be better preserved, halothane-induced myocardial depression can only be partially antagonized by vagolysis.[26,27] In addition, we did not use controlled ventilation or neuromuscular blocking agents, for any influence these techniques might have on contractility, either alone or in combination. Malan and coworkers[17] found less cardiovascular depression with spontaneous ventilation compared with controlled ventilation in adult volunteers receiving sevoflurane.

Study Limitations

This was an open-label, randomized study, and thus observer-dependent data points, particularly those made by the anesthesiologist, are subject to bias because of knowledge of the agent used. Echocardiographic data, on the other hand, were recorded on hard copy and were digitized without previous knowledge of the anesthetic agent used, which reduced observer bias. In addition, vital signs and respiratory gas concentrations were sampled using a real-time data acquisition system that collected data points in epochs of 15 s, eliminating bias during collection.

Although the NPO interval and initial volume of fluid administration may influence preload-dependent contractility measurements, and our patients had a variable period of abstinence from food ranging from 6 to 12 h before induction of anesthesia, the preload-independent indices used in this study are not affected by such variations in food-intake status.

In conclusion, we found less direct myocardial depression during inhalation induction of anesthesia with sevoflurane compared with halothane as measured by echocardiographically derived preload-dependent and preload-independent indices. Although induction of anesthesia with sevoflurane or halothane was equally well tolerated by patients, the preservation of myocardial performance with sevoflurane make it an attractive alternative for inhalation induction of anesthesia in children.

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