The Hemodynamic and Cardiovascular Effects of Isoflurane and Halothane Anesthesia in Children

Wendy J. Wolf, M.D.,* Mary B. Neal, M.D.,† Mary Dahlen Peterson, M.D.‡

The hemodynamic and cardiovascular effects of isoflurane and halothane anesthesia were studied in 15 unpremedicated ASA I children using measurements of heart rate, blood pressure and M-mode echocardiography (echo). The children (ages 2 to 7.3 yr) were randomly assigned to receive either isoflurane (N = 8) or halothane (N = 7) with oxygen. End-tidal carbon dioxide concentrations (range 30–44 mmHg) were monitored throughout the study in each child. The experimental protocol was completed prior to intubation and the initiation of surgery.

Within each anesthetic group, preinduction (control) hemodynamic and echo measurements were compared with measurements obtained at two sequential equipotent end-tidal anesthetic concentrations (0.74% and 2.22% isoflurane; or 0.5% and 1.5% halothane). We also compared the data of the isoflurane group with that of the halothane group at each equipotent end-tidal anesthetic concentration. Preinduction hemodynamic (heart rate, blood pressure) and echo measures (left ventricular dimensions and function) were similar between the two anesthetic groups. With isoflurane or halothane administration, blood pressure decreased significantly, while heart rate remained essentially unchanged. The observed alterations in heart rate and blood pressure were similar in both study groups at each equipotent end-tidal anesthetic concentration. In contrast, there were marked differences in the echo measurements of the two anesthetic groups. Halothane was associated with a significant dose-dependent decrease in echo-measured left-ventricular shortening fraction and mean velocity of circumferential fiber shortening. These echo measurements were not significantly altered by isoflurane at either end-tidal anesthetic concentration. These alterations suggest halothane is associated with significant myocardial depression in normal children, while myocardial function is well preserved during isoflurane anesthesia. (Key words: Anesthesia: pediatric. Anesthetics, volatiles halothane; isoflurane. Heart: myocardial function. Measurement techniques: echocardiography.)

ADVANCES IN PEDIATRIC surgical techniques have resulted in an increasing number of healthy and critically ill children undergoing general anesthesia. For nearly two decades, halothane has been the most commonly used volatile anesthetic agent in children,1,2 even though the myocardial depressant effects of this agent have been well documented.3–7 Recently, isoflurane has provided an alternative to halothane anesthesia in the pediatric patient. Isoflurane has been noted to have some in vitro myocardial depressant effects,8 yet clinical studies in adults consistently suggest myocardial function is well preserved during isoflurane anesthesia.9–11 The hemodynamic effects of isoflurane anesthesia have been examined in infants, but detailed studies have not been performed in older children. When infants (less than 7 months old) received isoflurane with nitrous oxide, they became bradycardic and hypotensive.12 Underlying myocardial function was not assessed in these infants, nor have the myocardial effects of isoflurane been examined in older children.

This study was performed to examine both the hemodynamic and cardiovascular effects of isoflurane administration in children, and to determine whether isoflurane is associated with less myocardial depression than halothane. We hypothesized that children, like adults, would demonstrate preservation of myocardial function during isoflurane anesthesia and show less myocardial depression than children receiving halothane under comparable study conditions. We assessed the myocardial effects of these two anesthetic agents noninvasively, using echocardiographic measurements of left ventricular size and function in the absence of preanesthetic sedation, parasympathetic drugs, or concomitant nitrous oxide administration.

Methods

The hemodynamic and cardiovascular effects of isoflurane and halothane were studied noninvasively in 15 unpremedicated children (mean age 5.7 yr; range 2–7.3 yr) admitted for elective surgical procedures (e.g., herniorrhaphy, strabismus repair, etc.). All patients were ASA Class I. Informed parental consent was obtained prior to enrollment in the protocol approved by our Institutional Review Board. The echocardiographer was blinded to group placement throughout the data collection and interpretation.

The study protocol is outlined in figure 1. The entire study was completed prior to intubation and the initiation of the surgical procedure. Patients were randomly assigned to receive either isoflurane (N = 8) or halothane (N = 7) anesthesia. Subjects had no food or liquids during the 8 h prior to surgery. No child received preanesthetic medications. Preinduction (control) heart rate, systolic, diastolic, and mean blood pressures, and echocardi-
Cardiovascular Effects of Anesthetic Agents in Children

Cardiovascular effects of anesthetic agents were assessed noninvasively by M-mode echocardiograms obtained with a Hoffrein 800 M-mode Ultrasonograph. Patients were examined in the supine or left lateral decubitus position using either a 5.0 mHz or 3.5 mHz single crystal transducer. From the left parasternal position, the left ventricular chamber and mitral valve leaflets were visualized, and recordings were obtained at the level of the mitral valve chordae. The transducer was angled superiorly and medially from this position to record the aortic valve tracing and left atrium. Measurements of the left ventricular cavity were recorded at 50 mm/s, while the aortic valve tracings were recorded at 100 mm/s. Measurements were averaged from a minimum of three cardiac cycles at end-expiration and were made in accordance with the recommendations of the American Society of Echocardiography.21

Left ventricular end diastolic (LVED), left ventricular end systolic (LVES) dimensions, and posterior wall thickness were measured preinduction and at each equipotent end-tidal anesthetic concentration. Changes in preload during the study were inferred from alterations in the left ventricular diastolic dimensions.22

Echocardiographic measurements of left ventricular function were obtained to assess the cardiovascular effects of each anesthetic agent. The left ventricular shortening fraction (LVSF), which measures the extent of ventricular chamber contraction, was derived from the left ventricular dimensional measurements.23

\[
LVSF(\%) = \frac{LVED - LVES}{LVED}
\]

The mean velocity of circumferential fiber shortening (mVcf) was also used to assess left ventricular function and adds the element of left ventricular ejection time (LVET) to the measurement of chamber contraction.24
TABLE 1. Descriptive Statistics for the Study Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Anesthetic Agent*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Halothane</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>7</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>4.7 ± 0.8†</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>17.7 ± 1.9</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>0.71 ± 0.05</td>
</tr>
<tr>
<td>Preinduction heart rate (beats/min)</td>
<td>102 ± 8</td>
</tr>
<tr>
<td>Mean blood pressure preinduction (mmHg)</td>
<td>91 ± 6</td>
</tr>
</tbody>
</table>

* No statistically significant differences were noted between the groups for any of the variables.
† Values are Mean ± SEM.

\[
mVcf = \frac{LVED - LVES}{LVED \times LVET}
\]

The systolic time-interval ratio (PEP/LVET) was obtained as an additional index of left ventricular function.26 The pre-ejection period (PEP), which represents electromechanical coupling and the isovolumic phase of ventricular contraction, was measured from the onset of the Q wave of the ECG to aortic valve opening. LVET was measured from aortic valve opening to valve closure.

These echocardiographic measurements are considered complimentary indices of left ventricular function; however, they are sensitive to alterations in preload, afterload, and heart rate. The effect of these different variables on the echocardiographic measurements are addressed in the "Discussion."

![Graph showing changes in heart rate and mean blood pressure](image)

**Fig. 2.** Changes in heart rate (solid line) and mean blood pressure (dashed line) with increasing concentrations of isoflurane (○) or halothane (●). Values are mean ± SEM. Significant changes within each group from preinduction are noted (*P < 0.05).

The experimental data were analyzed as a two-factor, repeated-measure experiment26 with the following defined factors: 1) dosage level (preinduction, level 1, level 2); and 2) anesthetic agent (halothane or isoflurane). A two-way analysis of variance with a repeated measure was performed in order to test the significance of the two defined factors and their possible interaction. Because an interaction was present between the anesthetic agent and dosage level on the measurements of LVSF, mVcf, PEP, and PEP/LVET, the difference between the two anesthetic agents was tested at each equipotent end-tidal anesthetic concentration using the Fisher's modified least-significant difference method.20 A comparison of the effects of anesthetic concentration on these measured variables against preinduction measurements was performed using the Dunnett's test. Significance was selected at the \( P < 0.05 \) level. All values are expressed as the mean and standard error of the mean (±SEM).

**Results**

The patients in each study group were comparable with respect to age, sex, weight, and body surface area. There were no significant differences between the study groups with regard to preinduction heart rate or blood pressure measurements (table 1). During the study period, \( ETCO_2 \) ranged between 30 and 44 mmHg with identical mean values in both groups. One child in each anesthetic group required transient positive-pressure mask ventilation for hypercarbia \( (ETCO_2 = 44 \text{ mmHg}) \). Because the hemodynamic and echo data from these two patients did not differ from the remainder of their group, their data were included in the analysis.

Neither halothane nor isoflurane altered heart rate significantly from preinduction (fig. 2). Mean blood pressure (MBP) decreased significantly in both groups during induction. The absolute decrease in MBP was most pronounced at dosage level 1 with a 21 ± 4 mmHg decrease in the halothane group \( (P < 0.05) \), and a 12 ± 3 mmHg decrease in the isoflurane group \( (P < 0.05) \). The MBP at each equipotent end-tidal anesthetic concentration was similar for both anesthetic agents.

Preinduction echocardiographic measurements of left ventricular dimension and function were not significantly different between the two study groups (table 2). LVED and LVES dimensions were not significantly altered by either halothane or isoflurane administration (fig. 3).

Following induction, significant differences in measured left ventricular function were noted between the two agents (table 2). With increasing concentrations of halothane, LVSF decreased significantly in a dose-dependent manner. In contrast, isoflurane did not significantly alter LVSF at either dosage level (fig. 4). The effect of both anesthetic agents on mVcf were similar to the changes noted in LVSF for each anesthetic group (table 2). The two anesthetic agents also caused differential al-
TABLE 2. Echocardiographic Measurements of the Study Groups Preinduction and during Anesthetic Administration (Mean ± SEM)

<table>
<thead>
<tr>
<th>Echocardiographic Measurement</th>
<th>Preinduction</th>
<th>Dosage Level 1</th>
<th>Dosage Level 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVED Dimension (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td>3.6 ± 0.1</td>
<td>3.5 ± 0.1</td>
<td>3.4 ± 0.1</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>3.5 ± 0.1</td>
<td>3.5 ± 0.2</td>
<td>3.5 ± 0.2</td>
</tr>
<tr>
<td>LVES Dimension (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td>2.3 ± 0.1</td>
<td>2.5 ± 0.2</td>
<td>2.4 ± 0.1</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>2.2 ± 0.1</td>
<td>2.1 ± 0.1</td>
<td>2.2 ± 0.1</td>
</tr>
<tr>
<td>LVSF (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td>36.5 ± 2.5</td>
<td>29.9 ± 2.0*</td>
<td>27.4 ± 1.3*</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>36.5 ± 0.8</td>
<td>37.9 ± 1.7</td>
<td>36.2 ± 1.7</td>
</tr>
<tr>
<td>mVcf (circ/s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td>1.32 ± 0.10</td>
<td>1.00 ± 0.08*</td>
<td>1.00 ± 0.04*</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1.31 ± 0.05</td>
<td>1.40 ± 0.06</td>
<td>1.30 ± 0.08</td>
</tr>
<tr>
<td>PEP (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td>64 ± 3</td>
<td>67 ± 2</td>
<td>82 ± 3*</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>66 ± 5</td>
<td>54 ± 4*</td>
<td>53 ± 3*</td>
</tr>
<tr>
<td>LVET (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td>282 ± 5</td>
<td>287 ± 10</td>
<td>284 ± 5</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>282 ± 12</td>
<td>273 ± 7</td>
<td>270 ± 7</td>
</tr>
<tr>
<td>PEP/LVET</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td>0.23 ± 0.01</td>
<td>0.24 ± 0.01</td>
<td>0.29 ± 0.01*</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>0.23 ± 0.02</td>
<td>0.20 ± 0.02*</td>
<td>0.20 ± 0.01*</td>
</tr>
</tbody>
</table>

LVED = Left ventricular end diastolic; LVES = Left ventricular end systolic; LVET = Left ventricular ejection time; LVSF = Left ventricular shortening fraction; mVcf = Mean velocity of circumferential fiber shortening; PEP = Preejection period.

* Significant changes from preinduction measurements (P < 0.05).

...terations in the PEP/LVET ratio. The PEP showed a dose-dependent prolongation during halothane administration, while isoflurane significantly shortened this interval (table 2); however, the LVET was not significantly affected by either anesthetic agent. The cumulative effect of these alterations in the PEP caused the PEP/LVET ratio to decrease during isoflurane administration and increase in a dose-dependent manner during halothane anesthesia.

**Discussion**

Information regarding the cardiovascular effects of anesthetic agents in adults has been predominately obtained by invasive techniques. Because invasive monitoring is rarely used in children undergoing routine anesthesia, noninvasive hemodynamic measurements such as heart rate and blood pressure have often been used to evaluate the cardiovascular effects of anesthetic agents in children. These hemodynamic measurements are not reliable indicators of the myocardial effects of these agents because they are also significantly affected by changes in preload and afterload.

Echocardiography is an accurate, reproducible method to assess left ventricular function and correlates well to angiographic measurements of myocardial function. Echocardiography provides a reasonable alternative to invasive measurements of myocardial function in children and permits a more accurate assessment of the myocardial effects of anesthetic agents than monitoring peripheral hemodynamic variables such as heart rate and blood pressure.

Adults and children receiving halothane anesthesia characteristically have a significant decrease in blood
pressure with minimal alterations in heart rate.\textsuperscript{5,6} The children receiving halothane in this study showed similar changes, with an insignificant decrease in heart rate and a marked decrease in blood pressure. Adults receiving isoflurane typically have a mild to moderate increase in heart rate, with a significant decrease in blood pressure.\textsuperscript{9-11} In the present study, isoflurane caused an insignificant increase in heart rate, while blood pressure decreased markedly. Halothane and isoflurane administration caused similar hemodynamic alterations in the children of both study groups. If the alterations of heart rate and blood pressure were used as the sole indicator of underlying myocardial function, halothane and isoflurane would appear to be equivalent myocardial depressants, since both caused comparable hypotension and minimal variations in heart rate. Echocardiography, however, demonstrated significant differences in underlying left ventricular function in the two study groups that were not reflected by the observed alterations in heart rate and blood pressure.

Serial echocardiographic measurements of myocardial function must be carefully interpreted because heart rate, preload, afterload, and contractility may independently or collectively alter the echo measurements of myocardial function. Heart rate was insignificantly changed from preinduction by both anesthetic agents; therefore, heart rate alterations were not a factor contributing to the observed change in left ventricular function. The effect of halothane and isoflurane on preload is still relatively unknown. In clinical adult studies using echocardiography to assess preload status, Rathod et al.\textsuperscript{9} found a significant decrease in LVED dimension at 0.95\% end-tidal halothane,\textsuperscript{9} while Gerson et al. noted a significant increase in LVED dimension with increasing concentrations of halothane.\textsuperscript{6} In the present study and a previous report by Barash et al.,\textsuperscript{7} there were no significant changes in LVED measurements at any concentration of halothane, suggesting preload remains relatively constant in children during halothane administration. The effects of isoflurane on preload are not well described, but Bastard et al.\textsuperscript{7} found no change in pulmonary capillary wedge pressure in adults with ischemic heart disease during isoflurane anesthesia.\textsuperscript{50} This is consistent with our observations that the LVED dimension (preload) remained unchanged during isoflurane administration.

In both study groups, heart rate and preload were relatively constant; therefore, the changes observed in the echocardiographic measurements reflect alterations in either myocardial contractility and/or afterload. In animal and human studies, halothane does not characteristically change total systemic vascular resistance,\textsuperscript{3,5} while isoflurane causes vasodilation with a fall in systemic vascular resistance.\textsuperscript{9,11} The measurement of LVSF is sensitive to changes in contractility and afterload. Since total systemic vascular resistance (afterload) is usually constant during halothane administration, the significant decrease in LVSF in the halothane group suggests diminished left ventricular contractility. In contrast, the LVSF was relatively constant during isoflurane anesthesia, despite the fact that with vasodilation and decreased vascular resistance, the LVSF should increase. This observation suggests isoflurane may, indeed, cause some degree of mild myocardial depression;\textsuperscript{5} however, a decrease in afterload could mask this depressant effect, leaving measured ventricular function unchanged.

The differential myocardial effects of these two anesthetic agents was also evident by comparing the changes in the PEP/LVET. Halothane prolonged the PEP/LVET ratio due to significant shortening of the PEP (isovolumic contraction time), while isoflurane caused a decrease in this ratio due to shortening of the PEP. The PEP prolongation is consistent with myocardial depression during halothane administration. The shortening of the PEP with isoflurane is probably due to the effect of systemic vasodilation rather than reflecting an improvement in the contractile state of the ventricle.

Clinical comparisons of inhalational anesthetic agents must consider the effects of agent differences in blood/gas and tissue/blood partition coefficients. End-tidal anesthetic concentration measurements offer a noninvasive estimate of tissue anesthetic concentrations. In this study, end-tidal anesthetic concentrations were monitored and data were obtained after a 5-min period at a stable end-tidal concentration. In accordance with the theories of uptake and distribution,\textsuperscript{31} it would appear as if the experimental measurements were recorded at a near steady-state condition. The 5-min period of a stable end-tidal concentration may have been too brief for full tissue equilibration; however, this time period is 1.5 times greater than the presumed time constants for isoflurane and halothane in the vessel-rich group (i.e., myocardial tissue).\textsuperscript{31} If a longer steady-state, end-tidal period had been selected (i.e., equivalent to four or five time-constants), it is likely that the same or even greater degree of differential myocardial effects of these two agents would be demonstrated because both would be present in myocardial tissues in greater concentrations.

In conclusion, our results concur with those of previous investigators\textsuperscript{7} that halothane acts as a myocardial depressant in children. In contrast, myocardial function is well preserved in healthy children receiving isoflurane anesthesia. The divergent cardiovascular effects to these two anesthetic agents were easily detected by echocardiography. Echocardiography provides a far more sensitive and discriminating way to monitor cardiovascular changes than the routine noninvasive hemodynamic measurements of heart rate and blood pressure. It is also apparent that peripheral hemodynamic measurements alone are not sufficiently sensitive to describe the cardiovascular effects of anesthetic agents.

The differential myocardial effects of these two anesthetic agents may be an important consideration in certain
children receiving general anesthesia. Although isoflurane is associated with a minimal reduction in cardiac output in healthy adults, its effect in adults or children with compromised myocardial function is not well known. Adults with ischemic heart disease who received either isoflurane or halothane had diminished cardiac output during anesthesia and surgery; however, the observed decrease in cardiac output was far more significant in the halothane group compared with the isoflurane group. The majority of children undergoing halothane anesthesia tolerate the myocardial depressant effects of halothane without difficulty, but the preservation of myocardial function with isoflurane may be an advantage in children with marginal cardiovascular reserve who require general anesthesia.

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