Cardiovascular Effects of Sevoflurane, Isoflurane, Halothane, and Fentanyl–Midazolam in Children with Congenital Heart Disease

An Echocardiographic Study of Myocardial Contractility and Hemodynamics

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Background: The cardiovascular effects of halogenated anesthetic agents in children with normal hearts have been studied, but data in children with cardiac disease are limited. This study compared the effects of halothane, isoflurane, sevoflurane, and fentanyl–midazolam on systemic and pulmonary hemodynamics and myocardial contractility in patients with congenital heart disease.

Methods: Fifty-four patients younger than age 14 scheduled to undergo congenital heart surgery were randomized to receive halothane, sevoflurane, isoflurane, or fentanyl–midazolam. Cardiovascular and echocardiographic data were recorded at baseline and at randomly ordered 1 and 1.5 minimum alveolar concentration, or predicted equivalent fentanyl–midazolam plasma concentrations. The shortening fraction and ejection fraction (using the modified Simpson rule) were calculated. Cardiac index was assessed by the velocity–time integral method.

Results: Halothane caused a significant decrease in mean arterial pressure, ejection fraction, and cardiac index, preserving only heart rate at baseline levels. Fentanyl–midazolam in combination caused a significant decrease in cardiac index secondary to a decrease in heart rate; contractility was maintained. Sevoflurane maintained cardiac index and heart rate and had less profound hypotensive and negative inotropic effects than halothane. Isoflurane preserved both cardiac index and ejection fraction, had less suppression of mean arterial pressure than halothane, and increased heart rate.

Conclusions: Isoflurane and sevoflurane preserved cardiac index, and isoflurane and fentanyl–midazolam preserved myocardial contractility at baseline levels in this group of patients with congenital heart disease. Halothane depressed cardiac index and myocardial contractility.

A NUMBER of anesthetic regimens have been used for pediatric patients with congenital heart disease (CHD). The anesthetic considerations for these patients differ considerably, depending on such factors as shunting, myocardial contractility, ventricular dilation or hypertrophy, outflow tract obstruction, dysrhythmias, and pulmonary hypertension. Respective anesthetic goals would include managing shunt flow to balance systemic and pulmonary circulations, minimizing depression of ventricular function, avoiding increases in heart rate or ventricular contractility, maintaining normal sinus rhythm, and lowering pulmonary vascular resistance. The cardiovascular effects of the halogenated anesthetic agents in children with normal hearts have been well studied,1–4 but data in children with cardiac disease are limited.5–7

Echocardiographic determination of left ventricular (LV) volumes and ejection fraction (EF) in patients with CHD correlates well with angiographic data obtained at cardiac catheterization.8,9 Doppler quantification of cardiac output (CO) has been shown to be reliable in pediatric patients with CHD.10,11 Alverson et al.10 demonstrated excellent agreement between pulsed Doppler quantification of CO and Fick CO values during cardiac catheterization (r = 0.98).10

Although no anesthetic agent is proscribed for patients with CHD, the known effects of each agent should be considered when selecting an anesthetic regimen. When halothane is used in patients with CHD, they are predisposed to dysrhythmias, hypotension, and depression of myocardial contractility.5 Isoflurane has been shown to better preserve contractility, heart rate (HR), and CO in patients with CHD, and has become a common agent for maintenance of anesthesia in patients undergoing congenital heart surgery.5 Sevoflurane, with its ability to be used as an inhaled induction agent and its superiority
over halothane in preserving CO and contractility, is an attractive choice.\textsuperscript{6,7} Fentanyl and midazolam in combination are used because of the perceived ability to promote hemodynamic stability and produce analgesia and amnesia, even in patients with significantly limited cardiac reserve.\textsuperscript{12,13} The purpose of this study was to use transthoracic echocardiography to compare systemic hemodynamics as well as the effects on myocardial contractility of these four anesthetic regimens in patients undergoing surgery for congenital heart defects.

Materials and Methods

After approval by the Institutional Review Board for human subjects of Baylor College of Medicine, Houston, Texas, and informed consent from a parent, patients aged 13 yr or less undergoing congenital heart surgery were enrolled. Patients were excluded from the study if they had a systemic right ventricle resulting in limitations in quantifying myocardial contractility by two-dimensional echocardiography. Similarly, patients with a functional single ventricle were excluded secondary to differences in loading conditions and difficulty comparing CO with patients with biventricular physiology.\textsuperscript{14,15} Patients receiving preoperative mechanical ventilation, opioids, or benzodiazepines were also excluded, as were patients receiving \(\beta\)-adrenergic or \(\beta\)-blocking agents. Patients with previously placed systemic-to-pulmonary artery shunts were not excluded from the study.

Patients were randomized to one of four groups by selecting the first of a stack of prelabeled cards containing equal numbers of cards representing each group. They were thoroughly mixed to ensure randomization and maintained so that the group assignment of the next patient was not known until the card was actually drawn. The four groups were: halothane (Halocarbon Laboratories, River Edge, NJ), isoflurane (Baxter Co., Deerfield, IL), sevoflurane (Abbott Laboratories, North Chicago, IL), or fentanyl (Elkins-Sinn, Cherry Hill, NJ)–midazolam (Roche Pharma, Inc., Humacao, Puerto Rico). All patients received premedication with oral midazolam (see appendix at ANESTHESIOLOGY Web site for doses). These concentrations are associated with sedation, hypnosis, and analgesia for surgery and approximate 1 and 1.5 MAC of the volatile agents.\textsuperscript{20–25} The order of predicted plasma concentrations was always 1 MAC first, because of the lack of time available to allow for the plasma concentrations of the drugs to decrease if the 1.5 MACs were achieved first. The inhaled anesthetics or the fentanyl–midazolam infusion were maintained at a constant end-tidal concentration or infusion rate for 10 min, and a second echocardiogram was performed and vital signs were again recorded. The inhaled agents were then adjusted to the second MAC amount and allowed to equilibrate for 10 min; the fentanyl–midazolam patients were given a second infusion equal to 50% of the first and the maintenance rate was increased by 50% for 10 min. A final echocardiogram was performed and vital signs were repeated.

All patients either received maintenance intravenous fluids until the time of induction, or if no intravenous catheter was present, were allowed to ingest clear liquids until 2 hr before induction. Only maintenance intravenous fluids were administered during the study period. No vasoactive drugs were given aside from the anesthetic agents. Each patient had a right internal jugular vein catheter inserted immediately after tracheal intubation to measure central venous pressure for calculation of systemic vascular resistance. Any hemodynamic
response perceived to be the result of this procedure was allowed to subside before echocardiographic assessment; all measurements were made during periods of steady-state hemodynamics.

Two-dimensional, M-mode, and pulsed Doppler trans-thoracic echocardiography was performed by a pediatric cardiologist using an Acuson 128XP/10 ultrasonic imaging system (Acuson, Inc., Mountain View, CA). The pediatric cardiologist was blinded to the type of anesthetic administered and to the MAC randomization. Studies at baseline, 1 MAC, and 1.5 MAC were each obtained over 3–5 min during steady-state hemodynamics. Each study was performed in the same manner, according to the recommendations of the American Society of Echocardiography Committee on Standards. Analyses were performed off-line after the entire study had been completed using the Echo Reading Station Package version 1.3 (Digisonics Co., Houston, TX). Three values were averaged for all measurements and calculations. Left ventricular end-diastolic dimension and left ventricular end-systolic dimension were measured from the M-mode images, and the shortening fraction (SF) was calculated. Left ventricular end-systolic dimension and SF were not evaluated in the presence of flattened or paradoxical interventricular septal motion. Orthogonal left ventricular end-diastolic volume and left ventricular end-systolic volume were traced, and EF was calculated according to the modified Simpson biplane method. Aortic velocity time integrals were traced, and the aortic annulus was measured. If the echocardiographic image quality over three cardiac cycles for each parameter was not excellent, that parameter was not calculated, resulting in some missing data points. The following parameters were measured or calculated at the three times: HR, MAP, SF, EF, stroke volume index, left ventricular end-diastolic volume index, systemic cardiac index (CI), and systemic vascular resistance index. The anesthetic agent and MAC order was unknown to the echocardiographers during the analyses. (See appendix at ANESTHESIOLOGY Web site for hemodynamic and echocardiographic calculations.)

Statistical Analysis
Data are reported as mean ± standard deviation. Statistical calculations and analyses were performed using Sigma Stat version 2.03 (SPSS, Chicago, IL). Fisher exact test was used to compare incidence of dysrhythmias between groups. Analysis of variance for repeated measures was used to compare parameters at the three MAC measurements within the same group. To compare parameters between the four groups at each MAC amount, a two-way analysis of variance with repeated measures was used. The Tukey test was used for post hoc pairwise comparisons of the mean responses to the different treatment groups, with $P < 0.05$ considered significant.

Results
Fifty-four patients were studied. Patient characteristics and cardiac diagnoses are presented in tables 1, 2, and 3. Of the 54 patients, 17 had a ventricular septal defect as the primary cardiac diagnosis, 10 had an atrial septal defect, six had tetralogy of Fallot, four had aortic stenosis, four had pulmonary atresia with ventricular septal defect, four had a complete atrioventricular canal defect, three had coarctation of the aorta, and six had miscellaneous lesions. There were no statistically significant differences in patient age or weight among the four groups. All patients in the sevoflurane and isoflurane groups remained in sinus rhythm throughout the study period. Dysrhythmias were noted in a total of three patients in the fentanyl–midazolam and the halothane groups. An intermittent junctional rhythm noted at baseline persisted in one patient during the fentanyl–midazolam induction. An accelerated junctional rhythm was noted at 1 MAC in another patient during halothane induction. An accelerated junctional rhythm with premature atrial con-
Effects of the Anesthetics on Heart Rate and Mean Arterial Pressure

Heart rate was preserved at both anesthetic concentrations in the sevoflurane and halothane groups, demonstrating no significant change in either SF or EF. Systolic function was compromised at both MACs in the halothane group, with a decrease in SF and EF. Sevoflurane also demonstrated a decrease in SF at both MACs and a decrease in EF at 1.5 MAC; EF was preserved at 1 MAC.

Effects of the Anesthetics on Calculated Hemodynamic Parameters

Stroke volume index was preserved at 1 and 1.5 MAC in the sevoflurane, the isoflurane, and the fentanyl-midazolam groups. Stroke volume index decreased with halothane at both anesthetic concentrations. Left ventricular end diastolic volume, a measure of left ventricular preload, was not changed from baseline by any anesthetic regimen. Systemic CI was preserved at 1 and 1.5 MAC in the sevoflurane and isoflurane groups. CI decreased at both concentrations in the fentanyl-midazolam group and at 1.5 MAC in the halothane group. Figure 1 shows the changes in cardiac index in each individual patient in the four groups. Systemic vascular resistance index was preserved at 1 and 1.5 MAC in the sevoflurane and the fentanyl-midazolam groups. Systemic vascular resistance index decreased in the halothane group at 1.5 MAC but was preserved at 1 MAC, and decreased at both MACs in the isoflurane group.

Discussion

The effects of these four anesthetic regimens on myocardial contractility and hemodynamics have been evaluated in children with normal hearts.1–4 Holzman et al.1 compared the effects of halothane and sevoflurane on contractility using stress-velocity and stress-shortening indices to eliminate the effects of loading conditions. Wodey et al.5 performed a similar study on infants and also compared Doppler-derived CI. In both studies, halothane caused a significantly greater decrease in contractility than sevoflurane at 1 and 1.5 MAC. In the latter study, CI was preserved with sevoflurane but was significantly decreased with halothane, findings similar to those for our patient population. Murray et al.3,4 how-

Table 3. Physiologic and Anatomic Characteristics

<table>
<thead>
<tr>
<th>Anesthetic Group</th>
<th>F–M</th>
<th>H</th>
<th>S</th>
<th>I</th>
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</thead>
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<tr>
<td>L–R shunt</td>
<td>9</td>
<td>9</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>R–L shunt</td>
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<td>1</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>No shunt</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>RH</td>
<td>8</td>
<td>3</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>RVH</td>
<td>8</td>
<td>4</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>LVH</td>
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<td>5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>LVD</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>↓ LV function</td>
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<td>1</td>
<td>0</td>
<td>0</td>
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</table>

F–M = fentanyl–midazolam; H = halothane; S = sevoflurane; I = isoflurane; L–R = left to right; R–L = right to left; RH = right ventricular hypertrophy; RVH = right ventricular dilation; LVH = left ventricular hypertrophy; LVD = left ventricular dilation; LV = left ventricle.
ever, found differing results from ours with respect to isoflurane; CI was significantly depressed, contrasting with preservation of CI in our population. Friesen et al.\textsuperscript{27} found a greater depression of systolic and mean arterial pressure with 2 MAC halothane in infants from birth to 6 months of age compared with infants and children 6 months or older; this was ascribed to greater depression of contractility in young infants, although no echocar-

Table 4. Measured and Calculated Hemodynamic and Echocardiographic Variables

<table>
<thead>
<tr>
<th>Agent</th>
<th>MAC</th>
<th>HR (beats/min)</th>
<th>MAP (mmHg)</th>
<th>EF (%)</th>
<th>SF (%)</th>
<th>SVI (ml/m²)</th>
<th>LVEDVI (ml/m²)</th>
<th>CI (l · min⁻¹ · m⁻²)</th>
<th>SVRI (dyne · s · cm⁻² · m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane</td>
<td>0</td>
<td>129 ± 22</td>
<td>77 ± 15</td>
<td>63 ± 9</td>
<td>40 ± 5</td>
<td>36 ± 16</td>
<td>44 ± 19</td>
<td>4.49 ± 1.87</td>
<td>1,425 ± 622</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>130 ± 19</td>
<td>60 ± 11*</td>
<td>54 ± 12*</td>
<td>32 ± 7†</td>
<td>28 ± 11*</td>
<td>38 ± 14</td>
<td>3.47 ± 1.17</td>
<td>1,331 ± 529</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>129 ± 17</td>
<td>49 ± 12*</td>
<td>50 ± 13*</td>
<td>30 ± 8†</td>
<td>26 ± 11*</td>
<td>39 ± 12</td>
<td>3.34 ± 1.36*</td>
<td>1,132 ± 503*</td>
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<tr>
<td>Sevoflurane</td>
<td>0</td>
<td>123 ± 32</td>
<td>67 ± 8</td>
<td>68 ± 11</td>
<td>44 ± 7</td>
<td>56 ± 41</td>
<td>37 ± 15</td>
<td>6.91 ± 4.32</td>
<td>1,014 ± 655</td>
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<tr>
<td></td>
<td>1</td>
<td>126 ± 26</td>
<td>58 ± 13*</td>
<td>62 ± 9</td>
<td>39 ± 7</td>
<td>52 ± 31</td>
<td>36 ± 18</td>
<td>6.59 ± 4.04</td>
<td>883 ± 592</td>
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<td></td>
<td>1.5</td>
<td>128 ± 25</td>
<td>58 ± 13*</td>
<td>58 ± 10*</td>
<td>39 ± 9</td>
<td>46 ± 26</td>
<td>35 ± 14</td>
<td>5.78 ± 3.06</td>
<td>782 ± 390</td>
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<tr>
<td>Isoflurane</td>
<td>0</td>
<td>112 ± 27</td>
<td>69 ± 12</td>
<td>63 ± 7</td>
<td>39 ± 5</td>
<td>46 ± 22</td>
<td>46 ± 24</td>
<td>4.96 ± 2.74</td>
<td>1,377 ± 809</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>125 ± 16*</td>
<td>54 ± 9*</td>
<td>62 ± 8</td>
<td>37 ± 4</td>
<td>39 ± 17</td>
<td>40 ± 17</td>
<td>4.82 ± 2.20</td>
<td>1,022 ± 601*</td>
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<tr>
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<td>1.5</td>
<td>128 ± 13*</td>
<td>50 ± 9*</td>
<td>59 ± 9</td>
<td>36 ± 5</td>
<td>39 ± 17</td>
<td>42 ± 19</td>
<td>4.59 ± 2.12</td>
<td>950 ± 513*</td>
</tr>
<tr>
<td>Fentanyl–midazolam</td>
<td>0</td>
<td>106 ± 22‡</td>
<td>66 ± 8</td>
<td>63 ± 6</td>
<td>40 ± 6</td>
<td>46 ± 34</td>
<td>54 ± 25</td>
<td>5.16 ± 4.39</td>
<td>1,261 ± 644</td>
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<tr>
<td></td>
<td>1</td>
<td>87 ± 19‡§</td>
<td>59 ± 11*</td>
<td>60 ± 7</td>
<td>39 ± 5</td>
<td>42 ± 30</td>
<td>47 ± 25</td>
<td>3.79 ± 3.05*</td>
<td>1,540 ± 806</td>
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<td></td>
<td>1.5</td>
<td>82 ± 18‡§</td>
<td>56 ± 11*</td>
<td>59 ± 7</td>
<td>38 ± 7</td>
<td>43 ± 30</td>
<td>52 ± 24</td>
<td>3.67 ± 2.99*</td>
<td>1,559 ± 875</td>
</tr>
</tbody>
</table>

All values are mean ± SD.  
* P < 0.05, one-way analysis of variance, different from 0 minimum alveolar concentration (MAC) within the same anesthetic group. † P < 0.05, two-way analysis of variance, halothane versus sevoflurane and fentanyl–midazolam at 1 and 1.5 MAC. ‡ P < 0.05, two-way analysis of variance, fentanyl–midazolam versus halothane at 0 MAC. § P < 0.05, two-way analysis of variance, fentanyl–midazolam versus halothane, sevoflurane, and isoflurane at 1 and 1.5 MAC.

HR = heart rate; MAP = mean arterial pressure; EF = ejection fraction; SF = shortening fraction; SVI = stroke volume index; LVEDVI = left ventricular end-diastolic volume index; CI = systemic cardiac index; SVRI = systemic vascular resistance index.

Fig. 1. Individual patient cardiac index data for each agent: halothane, n = 14; sevoflurane, n = 12; isoflurane, n = 12; fentanyl–midazolam, n = 9. Patients without adequate echocardiographic views to determine a velocity–time index measurement in the ascending aorta have been deleted. The heavy black line indicates mean value at each anesthetic concentration. MAC = minimum alveolar concentration.
diographic measurements were performed. The infants younger than 6 months of age in our study were equally distributed among the four groups.

Similar anesthetic regimens have also been assessed in patients with CHD; however, these studies differed from ours in experimental design.3–7,10,28,29 Glenski et al.5 compared the effects of isoflurane, halothane, fentanyl, and sufentanil on hemodynamics and M-mode-derived measures of contractility. Similar to our findings, contractility was preserved with isoflurane and depressed with halothane. The narcotic agents differed, however, demonstrating an initial decrease in contractility before subsequent improvement; larger doses may account for the discrepancy. Their study differs from ours in that sevoflurane was not used, only one measurement of inhaled anesthetic was studied, and contractility was assessed by M-mode; EF was not directly measured. In addition, CI, systemic vascular resistance index, left ventricular end-diastolic volume, stroke volume index, MAP, and HR were not evaluated. Knobelsdorff et al.6 compared incremental halothane induction with immediate 8% sevoflurane induction in infants with CHD and reported a significantly greater decrease in EF with halothane; these findings are consistent with our own. This report, however, concerned only the first 10 min after induction, and no reference was made to end-tidal concentrations of anesthetic agents. Girota et al.7 compared 8% sevoflurane with 4% halothane for induction of anesthesia and tracheal intubation in patients with CHD. They observed a 25–26% decrease in systolic blood pressure in the halothane group versus a 15–16% decrease in the sevoflurane group, and a 60% incidence of dysrhythmias in the halothane group versus none in the sevoflurane group. The study was conducted in the first 6 min after induction, and no echocardiographic measurements were reported. High-dose fentanyl has been studied in infants as the sole anesthetic for cardiac surgery, with demonstrated preservation of hemodynamic stability.28,29 The added effect of midazolam on echocardiographic indices of contractility has not been studied; however, increased inotropic support requirements have been documented in infants undergoing cardiac surgery.13 In our study, fentanyl-midazolam significantly depressed HR, blood pressure, and CI, despite preserving contractility, supportive of these findings.

Limitations of the Study

This study was limited by the inability to study load-independent indices of myocardial contractility by wall stress analysis, such as stress-velocity index and stress shortening index.1,2 Although these indices are believed to represent better the isolated effects of the anesthetic agents on myocardial contractility, they are invalid in patients with intracardiac shunts with altered ventricular geometry secondary to volume or pressure overload.14 This study did not include many patients with significant baseline decreases in indices of myocardial contractility; only two patients had a baseline EF or SF below lower limits for age. Patients with a functional single ventricle were also not studied because of the inability to accurately determine myocardial contractility.15 These latter two groups of patients may potentially benefit from three-dimensional echocardiographic evaluation as technology advances. Diastolic function was not analyzed. Newborns were not included in this study. Finally, although this study included a relatively large number of patients, the wide range of ages and diagnoses precluded specific conclusions about lesion- or age group-specific effects of the different agents.

The presence of a right-to-left intracardiac shunt decreases the rate of rise of inhaled anesthetic concentrations in the arterial blood, as a portion of the systemic CO bypasses the lungs and absorbs no new anesthetic, and then dilutes the systemic arterial blood.30 The anesthetic concentration in the blood thus never equals the exhaled concentration. In fact, Huntington et al.30 in a report of six children with right-to-left shunts and average pulmonary-to-systemic blood flow ratio of 0.58, achieved an arterial anesthetic concentration of only 55% of inspired concentration after 15 min during wash-in of 0.8% halothane. This difference between arterial and inspired anesthetic concentration is greater during non-steady states such as induction or washout, greater with less soluble drugs such as sevoflurane, and less with more soluble drugs such as halothane.19 Ten of the 54 patients in our study had right-to-left shunts and a MAC of 1 or 1.5 was not reached in these patients. Although the patients with right-to-left shunts were relatively equally distributed among the four groups, their small number precluded adequate statistical analysis of the effect of this factor on hemodynamic parameters. Similarly, ETCO₂ concentrations with right to left shunts may have significantly underestimated arterial carbon dioxide concentrations.31 An ETCO₂ of 30–35 was chosen in an attempt to account for this factor and ensure an arterial carbon dioxide tension (PaCO₂) within the physiologic range for these patients. Time constraints in this study prevented the use of arterial blood gases to adjust the PaCO₂. Finally, FiO₂ influences pulmonary vascular resistance and the degree of intracardiac shunting in many patients with CHD.32 An FiO₂ of 0.21 was chosen for baseline measurements so the patient would not be agitated by a face mask during the echocardiogram. An FiO₂ of 1.0 was selected for subsequent measurements to replicate common clinical conditions and to make study conditions uniform.

Conclusions

The data in this study may be used to select an anesthetic regimen for patients with CHD. Because patients
were studied before surgery, these findings may also be extended to patients with CHD undergoing non-cardiac surgeries. Sevoflurane and isoflurane maintained systemic CO, with little change in contractility. Isoflurane was also noted to increase HR and lower systemic vascular resistance. Fentanyl and midazolam maintained myocardial contractility, but depressed HR and thus CO. Halothane depressed contractility, CO, MAP, and systemic vascular resistance. Whether this translates into a higher incidence of adverse outcomes with halothane in the population of patients with CHD as a whole, or for specific cardiac diagnoses or age groups, is not known.

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References

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