Anesthetic agents and their cardiovascular effects

Dean B. Andropoulos

Introduction

A wide variety of anesthetic regimens is used for patients with congenital heart disease (CHD) undergoing cardiac or non-cardiac surgery, procedures in the cardiac catheterization laboratory, or other diagnostic or therapeutic procures such as magnetic resonance imaging. The goal of all of these regimens is to produce general anesthesia or adequate sedation, while preserving systemic cardiac output (CO) and oxygen delivery. Many of these patients have limited cardiac reserve, and if a cardiac arrest or other adverse cardiac event occurs, successful resuscitation is less frequent than in patients with normal hearts. Thus, intelligent selection of regimens and dosage, with the patient’s unique pathophysiology of their cardiac lesion in mind, along with requirements for the particular procedure they are undergoing, is essential. This chapter reviews the effects on hemodynamics and myocardial contractility of anesthetic agents and muscle relaxants commonly used for patients with CHD.

Volatile agents

In vitro studies of effects on contractility in isolated adult human atrial fibers indicate that direct myocardial contractility depression is greatest with halothane and that sevoflurane is equal to isoflurane and desflurane (Fig. 4.1). These studies of myocardium reveal that differences among these agents occur primarily from differing effects on calcium flux through L-type Ca\(^{2+}\) channels, both trans-sarcolemmal, and in the sarcoplasmic reticulum (SR) (Fig. 4.2). Halothane reduces Ca\(^{2+}\) flux through the sarcolemma more than isoflurane, with the net result that there is less intracellular Ca\(^{2+}\) available to bind to the troponin–actin–myosin complex which produces myocyte contraction. Another mechanism of myocardial depression is that halothane, but not isoflurane, directly activates ryanodine-sensitive SR Ca\(^{2+}\) channels, thereby reducing Ca\(^{2+}\) storage in the SR and making less available for release during contraction. The effects of sevoflurane and desflurane on Ca\(^{2+}\) flux are similar to isoflurane.

The effects of volatile anesthetic agents on myocardial contractility and hemodynamics in children with normal hearts reveal halothane to have a greater myocardial depressant effect than the other agents at every MAC. Reproduced with permission from Hanouz JL, Massetti M, Guesne G. In vitro effects of desflurane, sevoflurane, isoflurane, and halothane in isolated human right atria. Anesthesiology 2000; 92: 116–24.
and also compared Doppler-derived cardiac indices. In both studies, halothane caused a significantly greater decrease in contractility than sevoflurane at 1.0 and 1.5 minimum alveolar concentration (MAC). In the latter study, cardiac index (CI) was preserved with sevoflurane, but was significantly decreased with halothane. Isoflurane’s effect has been studied echocardiographically in infants and young children with normal hearts, and found to have a similar profile to halothane, namely a decrease in CI and systolic and mean blood pressure. It is important to note that infants from the newborn period up to an age of approximately 6 months exhibit an exaggerated degree of depression of myocardial contractility and blood pressure in response to all volatile agents, but especially halothane (Fig. 4.2). This is likely due to the immaturity of the Ca$^{2+}$ release and reuptake system, necessitating higher levels of free cytosolic Ca$^{2+}$ to be available to bind to the troponin–actin–myosin complex to produce myocyte contraction. Recent evidence supports this theory. Sevoflurane, and to a greater extent, halothane, interfere with both L-type Ca$^{2+}$ channel and Na$^{+}$–Ca$^{2+}$ exchanger Ca$^{2+}$ flux at the plasmalemmal membrane more in neonatal than adult rat myocytes. The volatile anesthetics interfered with Ca$^{2+}$ release from the SR more in adult rat myocytes. This information provides a mechanism for what is commonly observed clinically.

In a recent report of the Pediatric Perioperative Cardiac Arrest Registry halothane alone or in combination was deemed to be responsible for 67% of the medication-related cardiac arrests. Isoflurane was responsible for none, and sevoflurane for 4% of the medication-related cardiac arrests.

In a study of 40 preterm neonates (mean post-conceptual age 32 weeks) undergoing a variety of procedures (9 patent ductus arteriosus ligations), Friesen et al. found that after atropine and pancuronium (which increased heart rate [HR] 8–12%), both halothane and isoflurane maintained HR, and decreased systolic blood pressure by 25% and 30% respectively. The effects of volatile agents on systemic vascular resistance (SVR) as measured by arterial blood pressure differ between agents. Ca$^{2+}$ flux in the smooth muscles of arterioles is reduced by all of these agents, resulting in less resting tone and thus lower blood pressure and vascular resistance. Halothane exhibits the most pronounced reduction of blood pressure, due to the combination of reduction in arterial tone, as well as the more pronounced depression of myocardial contractility. Isoflurane and sevoflurane lower pressure primarily through reduction in SVR.

In patients with CHD halothane also appears to have the most pronounced reduction in blood pressure. Glenski et al. used echocardiography to compare the effects of iso- and halothane on M-mode derived measures of contractility and showed that contractility was preserved with iso- and depressed with halothane (Fig. 4.3). A study using transthoracic echocardiography comparing halothane, iso-, and sevoflurana in 54 children with CHD (Table 4.1) reported that at 1.0 and 1.5 MAC there was significant myocardial depression from halothane, resulting in a decline in mean arterial pressure (MAP, decline of 22% and 35%), ejection fraction (EF, decline of 15% and 20%) and CO (CO decline of 17% and 21%) in patients aged from 1 month to 13 years with two ventricles undergoing cardiac surgery. Sevoflurane maintained both CO and HR, and had less profound hypotensive (MAP decrease 13% and 20% at
Halothane, isoflurane, and sevoflurane did not change $Q_p : Q_s$ as measured by echocardiography. Russell et al. compared halothane with sevoflurane in the pre-bypass period in 180 children with a variety of cardiac diagnoses, including 14 with single-ventricle physiology. The incidence of significant hypotension, bradycardia, and arrhythmia requiring drug treatment with atropine, phenylephrine, epinephrine, or ephedrine was higher with halothane (two events per patient vs. one). Serum lactate also increased slightly with halothane.

In normal children desflurane commonly produces tachycardia and hypertension during the induction phase, followed by a slight reduction in HR and systolic blood pressure during steady state at 1 MAC anesthetic level. There are no reports of its hemodynamic profile in patients with CHD. In a study of 47 children, mean age 12.8 years, undergoing electrophysiological study for supraventricular tachycardia (SVT), desflurane allowed induction of the SVT in all patients, and demonstrated no clinically important differences in any electrophysiological measurement compared to a fentanyl-based anesthetic. The arrhythmogenic potential of desflurane has been demonstrated to be similar to that of isoflurane.

Twenty-three to forty-eight percent of children with normal cardiac anatomy develop arrhythmias from the use of halothane, with up to 40% of these arrhythmias being ventricular in origin. This compares to an incidence of 6–12% in patients exposed to sevoflurane. A study performed in infants, mean age 7.5 months, found sevoflurane induction caused a 20% incidence of junctional bradycardia (< 80 beats/minute). Isoflurane, when utilized in children for electrophysiologic studies and radiofrequency ablation for supraventricular tachycardia, does not affect sinoatrial or atrioventricular node conduction, and all arrhythmias were easily induced.

Few studies to date have addressed the effects of the different anesthetics on two important groups of pediatric patients with congenital or acquired heart disease: patients with a single functional ventricle, and patients with cardiomyopathy or significantly decreased systolic ventricular function. Diastolic function with halothane and isoflurane has been studied in animal models of cardiomyopathy. The two agents differ with halothane producing negative lusitropic effects, while isoflurane conserves or may even improve diastolic function. There are no reports of diastolic function in response to anesthetic agents in patients with CHD.

Some practitioners consider halothane to be indicated for use in patients with ventricular outflow tract obstruction, such as tetralogy of Fallot (TOF) or hypertrophic cardiomyopathy (HCM), where depressed contractility and maintenance of baseline HR is desirable to allow for a longer ejection time to reduce obstruction to outflow. This theoretical advantage of halothane may well be offset by a greater decrease in MAP, which could increase right-to-left shunting in TOF, or the gradient across the left ventricular outflow tract in HCM. Loss of sinus rhythm, more likely with halothane, is poorly tolerated by many of these patients. However, halothane has been used for TOF with success, and no controlled studies have addressed this question.

Of the three most commonly used volatile agents isoflurane and sevoflurane are most likely to maintain cardiovascular stability (contractility, CO, maintenance of normal sinus rhythm [NSR]) in biventricular patients with CHD. Halothane poorly preserves myocardial function in
this patient population. Halothane and sevoflurane cause minimal airway irritation and thus are preferable for inhaled induction of anesthesia; however, there is little evidence for the continued use of halothane for this purpose in patients with CHD. Isoflurane has even less effect on contractility and hemodynamics than sevoflurane, and thus is considered by many to be the best maintenance agent, especially in light of its lower cost.

**Nitrous oxide**

Despite its ubiquitous use as an adjunct to anesthetic induction and maintenance in patients with CHD, information regarding the effect of nitrous oxide on hemodynamics in patients with CHD is very limited. Its use may be relatively contraindicated where increased $F_{O_2}$ is indicated, or where enlargement of enclosed air collections is possible, such as in any intracardiac or intrathoracic surgery. Reports of increased pulmonary vascular resistance ($PVR$), sympathetic stimulation, or significantly decreased CO in response to $N_2O$ are limited. In adult patients, $N_2O$ has not been substantiated in children with or without cardiac disease.

In infants and small children with normal hearts, Murray et al. $^{31}$ found that addition of 30% and 60% $N_2O$ to 1 MAC halothane or isoflurane resulted in a decreased HR and CI, without changing EF and stroke volume measured echocardiographically. These authors also demonstrated that when 0.6 MAC halothane or isoflurane was substituted for 60% $N_2O$ during 0.9 MAC isoflurane or halothane anesthesia, HR, MAP, and CI were unchanged. $^{32}$

In 14 patients with CHD recovering from surgery, Hickey et al. $^{33}$ administered 50% $N_2O$ and observed a decrease of 9% in HR, 12% in MAP, and 13% in systemic CI. However, mean pulmonary artery pressure ($PAP$) and $PVR$ were not significantly changed in these well-ventilated patients with a $P_{aCO_2}$ of 34–35, and pH of 7.47–7.49, even in patients with elevated $PVR$ at baseline. This single report represents the total number of patients with CHD in which $N_2O$ administration has been carefully studied. Despite this paucity of information, extensive clinical experience has demonstrated $N_2O$ to be safe and effective, particularly as an adjunct to inhaled induction of anesthesia for congenital heart surgery.

**Xenon**

Xenon, a noble gas, has anesthetic properties and a blood : gas partition coefficient even lower than $N_2O$ (0.14 vs. 0.47). $^{34}$

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**Table 4.1** Hemodynamic changes in response to four anesthetic regimens in 54 children with congenital heart disease with two ventricles.

<table>
<thead>
<tr>
<th>Agent</th>
<th>MAC (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/m²)</th>
<th>SVRI (dyne · s · cm⁻⁻ · m²)</th>
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<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>1425 ± 622</td>
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<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>1331 ± 529</td>
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<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>1132 ± 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>1014 ± 653</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>58 ± 10*</td>
<td>39 ± 9</td>
<td>46 ± 26</td>
<td>35 ± 14</td>
<td>5.78 ± 3.06</td>
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<tr>
<td>Isoflurane</td>
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<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>
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<td>1</td>
<td>125 ± 16*</td>
<td>54 ± 9*</td>
<td>62 ± 8</td>
<td>37 ± 4</td>
<td>39 ± 17</td>
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<td>4.82 ± 2.20</td>
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<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>
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<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>
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<td>42 ± 30</td>
<td>47 ± 25</td>
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<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>1559 ± 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, sevoflurane, and isoflurane at 1.0 and 1.5 MAC. CI, systemic cardiac index; EF, ejection fraction; HR, heart rate; LVEDVI, left ventricular end-diastolic volume index; MAP, mean arterial pressure; SF, shortening fraction; SVI, stroke volume index; SVRI, systemic vascular resistance index.

In clinical studies in adults, it reliably produces general anesthesia with very rapid induction and emergence, and is virtually devoid of cardiovascular effects. Dogs with induced cardiomyopathy demonstrate minimal effects on systemic and pulmonary hemodynamics, as well as systolic or diastolic left ventricular function, from inhalation of xenon. The major drawbacks are a MAC of 70%, and high cost. Xenon also increases oxygen consumption, probably by directly stimulating the cellular metabolic rate. No reports have been published about the use of xenon in pediatric patients, however the favorable hemodynamic and pharmacokinetic characteristics of this anesthetic would be ideal for patients with CHD, particularly those with compromised myocardial characteristics of this anesthetic would be ideal for patients with CHD, particularly those with compromised myocardial function undergoing procedures where other volatile agents, N₂O or large doses of narcotics are undesirable.

**Opioids and benzodiazepines**

Fentanyl and sufentanil have been studied as a sole anesthetic in patients with CHD. Hickey and Hansen et al. provided the basis for this technique with a series of studies in neonates and infants less than 1 year of age undergoing complex repairs ranging from the Norwood operation to complete repair of biventricular lesions. Fentanyl doses of 50–75 µg/kg, and sufentanil doses of 5–40 µg/kg, administered with pancuronium 0.1–0.15 mg/kg, provided excellent hemodynamic stability with minimal changes in HR and blood pressure throughout the surgery. The increase in PAP and resistance in response to suctioning in infants recovering from cardiac surgery was eliminated with 25 µg/kg fentanyl. Moore et al. demonstrated that 5, 10, or 20 µg/kg sufentanil in children 4–12 years of age had no effect on EF as measured by echocardiography, in patients undergoing repair of biventricular lesions. Increases in HR, blood pressure and stress hormones were more effectively blunted by the higher doses. Glenski et al. reported M-mode echocardiographic measures of contractility, blood pressure, and HR response using fentanyl (at 100 µg/kg) or sufentanil (at 20 µg/kg) in children from 6 months to 9 years of age. Measurements were made at three different times: after a premedication with morphine and scopolamine, after induction, and after tracheal intubation. These opioids decreased both EF and shortening fraction after induction, but they returned to or above baseline after intubation (Fig. 4.3).

Midazolam is often added to fentanyl anesthesia to provide sedation and amnesia, as a substitute for low dose volatile anesthetic agent, particularly in hemodynamically unstable patients and young infants, where the myocardial depressant effects of volatile agents are more pronounced. Fentanyl and midazolam combinations have been studied in two different clinically utilized dose regimens (15–30 µg/kg fentanyl and 0.29–0.45 mg/kg midazolam) for induction and the pre-bypass period in congenital heart surgery in biventricular patients. Vecuronium was used for muscle relaxation in order to isolate the effects of the other two agents on hemodynamics. Measurements of CO and contractility were made by echocardiography. Fentanyl/midazolam caused a significant decrease (22%) in CO despite preservation of contractility. That was predominantly due to a decrease in HR. Coadministration of a vagolytic agent such as atropine or pancuronium would likely preserve CO. The added effect of midazolam on echocardiographic indices of contractility has not been previously reported; however, increased inotropic support requirements have been documented in infants undergoing cardiac surgery with the addition of midazolam bolus totaling 0.3 mg/kg, and infusion of 0.1 mg/kg/hour intraoperatively. The stress response to major cardiac surgery in infants and children has been the subject of considerable interest. Anand and Hickey reported the use of high dose sufentanil at a total mean dose of 37 µg/kg as a sole anesthetic for complex neonatal surgery. The sufentanil was continued by infusion for 24 hours postoperatively. This regimen was compared to halothane plus morphine (mean dose of 0.35 mg/kg) intraoperatively, followed by intermittent morphine and diazepam postoperatively. Stress response, as measured by changes in adrenal hormones, cortisol, glucose, and lactate was significantly reduced in the sufentanil group, and mortality and major complications such as sepsis and necrotizing enterocolitis were also significantly reduced. A more recent study from the same institution of 45 infants averaging 3 months of age undergoing biventricular repair was reported. A fentanyl total dose 100 µg/kg, either given as intermittent boluses of 25 µg/kg, or as boluses plus infusion, either with or without midazolam, resulted in a significant endocrine stress response to cardiac surgery. Despite this, outcome was excellent in all groups with no adverse outcomes related to the anesthetic technique nor to stress response. The sole hemodynamic difference between the regimens was a lower MAP during cooling on bypass in the group who received midazolam. Finally, Duncan et al. reported a dose-response study of 2, 25, 50, 100, and 150 µg/kg fentanyl before bypass in 40 children averaging 13 months and 8.5 kg. The 2 µg/kg group had significant increases in pre-bypass norepinephrine, glucose, and cortisol, and significantly higher HR and blood pressure than all other groups. Doses of 25 µg/kg or higher eliminated changes in these parameters for the duration of the surgery. It is difficult to interpret the significance of these stress-response studies because they evaluated by different age groups and lesions. Also there was more than one decade between reports with improvements in surgical, bypass, and postoperative management. If any group of patients had benefited from attenuation of the stress response, it would appear to be neonatal patients undergoing complex surgery.

In choosing between fentanyl and sufentanil, there appear to be few if any specific differences between the agents. Cost considerations and familiarity lead most practitioners to select...
fentanyl as the basis for most high or moderate complexity congenital heart surgeries.

Remifentanil is a synthetic ultra-short acting narcotic agent metabolized by plasma esterases with half-life 3–5 minutes that is independent of the duration of infusion.\(^4^7\) It is particularly useful for short non-cardiac procedures with intense stimulation where narcotic-based anesthesia and its hemodynamic stability would be desirable, yet where rapid emergence is also important. Remifentanil at 0.25 \(\mu g/\text{kg/minute}\) provides equivalent analgesia and a similar hemodynamic profile to epidural bupivacaine when used with \(\text{N}_2\text{O}/\text{isoflurane}\) anesthesia for major abdominal or lower extremity surgery in children.\(^4^8\) Donmez \textit{et al.}\(^4^9,5^0\) reported a series of 55 children undergoing cardiac catheterization with a remifentanil infusion of 0.1 \(\mu g/\text{kg/minute}\). This regimen maintained excellent cardiovascular stability, with minimal changes in heart rate, blood pressure or oxygen saturation. Fifty-eight percent of patients required additional sedation with midazolam or ketamine. Apnea was infrequent, and the time to recovery score of five (10-point scale) was only 2–4 minutes. Patients undergoing long cardiac catheterization procedures could potentially benefit from this agent. Its use has been reported for atrial septal defect repair, where patients are extubated in the operating room (OR).\(^5^1\) It apparently does not bind to the cardiopulmonary bypass (CPB) circuit,\(^5^2\) and its clearance in children before and after CPB appears to be predictable within a narrow range, making it a potentially useful agent for “fast-track” anesthesia and early extubation for simple surgical procedures. Despite these advantages, nausea/vomiting and bradycardia/hypotension,\(^4^8\) as with other synthetic \(\mu\)-receptor agonists, are a prominent feature of the adverse event profile.

**Propofol**

Propofol has become a popular agent for sedation and general anesthesia for cardiac catheterization procedures and for postoperative intensive care unit (ICU) sedation to facilitate early tracheal extubation. In plasma concentrations found in routine clinical use, propofol has minimal negative inotropic effects in isolated animal cardiac preparations,\(^5^3\) or in human adult atrial muscle strips.\(^5^4\)

In children with normal hearts on induction propofol consistently decreases systolic and MAP by 5–25%,\(^5^5\) without changing HR. There has been one published study using echocardiography to assess myocardial contractility and CO in infants with normal hearts induced with propofol.\(^5^5\) The shortening fraction or CI was not changed, SVR decreased by 14% and 27% at 1 and 5 minutes after induction. Load independent measures of contractility (stress-velocity index and stress-shortening index) decreased significantly from baseline at 5 minutes after induction with propofol.

Williams \textit{et al.}\(^5^6\) measured the hemodynamic effects of propofol in 31 patients aged 3 months to 12 years at a dose of 50–200 \(\mu g/\text{kg/minute}\) undergoing cardiac catheterization (Fig. 4.4). They found that propofol significantly decreased MAP and SVR; however, systemic CO, HR, and mean PAP, as well as PVR, did not change. In patients with cardiac shunts, the net result was a significant increase in the right-to-left shunt, a decrease in the left-to-right shunt, and decreased Qp : Qs, resulting in a statistically significant decrease in PaO\(_2\) and Sao\(_2\), as well as reversal of the shunt from left-to-right to right-to-left in two patients. In another study of patients undergoing cardiac catheterization, Lebovic \textit{et al.}\(^5^7\) demonstrated that patients could experience a 20% decrease in HR or MAP.

Zestos \textit{et al.}\(^5^8\) studied patients undergoing congenital heart surgery with CPB who were selected for early extubation in the ICU (\(n = 26\)). A propofol infusion at 50 \(\mu g/\text{kg/minute}\) was begun after CPB, and compared to a placebo control group who received intralipid. The infusions were discontinued upon leaving the OR, and morphine was given as needed for pain. Both the time to tracheal extubation (33 vs. 63 minutes) and the number of morphine doses (1.0 vs. 2.3) were significantly less in the propofol group. No hemodynamic

![Fig. 4.4](image-url) Changes in intracardiac shunting in response to propofol induction and infusion in children undergoing cardiac catheterization. Group 2, patients with net left-to-right cardiac shunting; Group 3, patients with net right-to-left cardiac shunting. Qp : Qs decreased significantly in both groups. Reproduced with permission from Williams GD, Jones TK, Hanson KA, Morray JP. The hemodynamic effects of propofol in children with congenital heart disease. Anesth Analg 1999; 89: 1411–16.
depression was observed in this study. Another recent study with a similar protocol for propofol infusion after weaning
from bypass demonstrated that 70% of children undergoing
simple and complex surgery were extubated within 9 hours
of ICU admission.59

Propofol has no significant effect on sinoatrial or atrio-
ventricular node conduction, or on the ability to induce
supraventricular tachycardia, and therefore is desirable as a
primary agent during electrophysiologic studies and radio-
frequency ablation.25,60 However, ectopic atrial tachycardia
may be suppressed by propofol.61

Although propofol is very useful for cardiac catheteriza-
tion, short, stimulating procedures, and short term sedation
after cardiac surgery, its use long term as an ICU sedative
is controversial, with a report of unexplained metabolic
acidosis and myocardial failure after long term (> 48 h) high
dose use in pediatric patients.62,63

In summary, propofol can be utilized in patients with
adequate cardiovascular reserve who can tolerate a mild
decrease in contractility and HR, and a decrease in SVR.
Propofol may cause an increased intracardiac right-to-left
shunt, and reversal of shunt in some patients (i.e. acyanotic
TOF), and thus hemodynamic data obtained in the cardiac
catheterization laboratory should be interpreted accordingly.

### Ketamine

The general anesthetic and analgesic effects of ketamine are
thought to be mediated by its interaction with N-methyl
D-aspartate receptors in the brain.64 It increases HR, blood
pressure, and CO through central nervous system mediated
sympathomimetic stimulation and inhibition of the reuptake
of catecholamines. It has been shown that ketamine is a direct
myocardial depressant when studied in isolated myocyte
preparations,65 and in adult human failing atrial and ventric-
ular muscle trabeculae (Fig. 4.5).66 The direct myocardial
depression caused by ketamine may be unmasked when
administered to patients whose sympathomimetic responses
are already maximally stimulated from cardiomyopathy, or
other conditions leading to poor myocardial reserves, because
further increase in catecholamine release is limited. Similarly,
if the patient is chronically receiving β-adrenergic agonists,
catecholamine receptors may be downregulated, resulting in
a diminished response to endogenously generated catechol-
amines, again allowing the myocardial depressant effects of
ketamine to predominate.

The mechanism of myocardial depression is by inhibition
of L-type voltage-dependent Ca\(^{2+}\) channels in the sarcolemmal
membrane. An increased extracellular Ca\(^{2+}\) concentration
may enhance this effect.65 This direct myocardial depression
effect is greater than that produced by etomidate.54 In
a patient with end-stage cardiomyopathy awaiting heart trans-
plant, hemodynamic collapse occurred after the induction of
anesthesia with ketamine.67 In a study of ketamine vs. sufen-
tanil for induction of anesthesia in patients undergoing car-
diac transplant, whose average EF was 14%, and who were all
receiving inotropes and vasodilators preoperatively found
that ketamine increased MAP, central venous pressure, and
PAP significantly, and decreased stroke volume index and
left ventricular stroke work index.68 Cardiac index decreased
slightly but not to a statistically significant degree. Systemic
vascular resistance and HR were higher. The sum total of the
hemodynamic effects of ketamine induction in these patients
was less myocardial work at the expense of a higher myocard-
ial wall tension. Sufentanil induction did not change any of
these parameters from baseline.

Other well-recognized untoward effects associated with
ketamine use do not differ among patients with CHD. These
include emergence reactions, excessive salivation, and an
increase in cerebral metabolism, intracranial pressure, cere-
bral blood flow and cerebral oxygen consumption.64

Despite the adverse effects of ketamine that are delineated
above, this drug has been a mainstay of induction of general
anesthesia in patients with CHD.69,70 It can be administered
intravenously or intramuscularly; and it will reliably main-
tain HR, blood pressure, and systemic CO at an induction
dose of 1–2 mg/kg i.v., or 5–10 mg/kg i.m., and a mainten-
ance dose of 1–5 mg/kg/hour in patients with a variety of

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**Fig. 4.5** Developed tension over time (+dT/dt) in cardiac muscle trabeculae in explanted hearts from adults undergoing cardiac transplantation in response to increasing ketamine concentrations. The upper limit of clinical concentration is 44 μM after 2 mg/kg induction dose. A, atrial muscle; buffer, Krebs–Henseleit buffer control; ISO, change with addition of 1 μM isoproterenol; V, ventricular muscle; Vehicle, control solution without ketamine. Numbers in parentheses represent numbers of muscle strips/number of patients, respectively. Reproduced with permission from Sprung J, Schuetz SM, Stewart RW et al. Effects of ketamine on the contractility of failing and nonfailing human heart muscles in vitro. Anesthesiology 1998; 88: 1202–10.
CHDs, including TOF (Fig. 4.6). The question about exacerbation of pulmonary hypertension has been addressed in two important studies. Morray et al. demonstrated that in cardiac catheterization patients, 2 mg/kg ketamine caused a minimal (<10%) increase in mean PAP, and ratio of PVR to SVR (Rp : Rs), with no change in direction of shunting or Qp : Qs. Hickey et al. studied postoperative cardiac surgery patients with normal PaCO₂ and demonstrated that ketamine 2 mg/kg had no effect on PAP or calculated PVR, either in patients with normal or elevated baseline PVR. There have been two cardiac catheterization laboratory studies reporting increases in PVR in some patients; however, these studies were both performed at 5000 feet altitude, which contributed to these confounding results.

Ketamine, supplemented with small doses of midazolam and/or morphine, has been used for interventional cardiac catheterization procedures and for postoperative analgesia after cardiac surgery in children. Hemodynamic stability has been excellent, with few complications. The most notable adverse effect was transient apnea in 10% of spontaneously breathing newborns undergoing balloon atrial septostomy in the catheterization laboratory.

Intramuscular induction of anesthesia may be achieved with ketamine 5 mg/kg, succinylcholine 4 mg/kg, and atropine 20 μg/kg mixed in the same syringe. This regimen is useful for small patients who present to the OR without intravenous access in whom the inhalational induction of anesthesia may produce undesirable hemodynamic effects. Endotracheal intubation can usually be achieved in 3–5 minutes, and attention can be turned to establishing intravenous access with the airway secure and a stable hemodynamic state.

In summary, ketamine is an attractive choice for intravenous or intramuscular induction of anesthesia in patients with CHD with good or moderately limited hemodynamic reserve, including those with pulmonary hypertension or cyanosis. However, care must be taken in patients with severely limited cardiac reserve and depressed myocardial contractility. Such patients may be chronically receiving β-adrenergic or similar agents, or their own endogenous sympathomimetic system is maximally stimulated because of a low CO state. The myocardial depressant properties of ketamine may be unmasked and lead to hemodynamic compromise.

**Etomidate**

Etomidate is an imidazole derivative introduced into clinical practice in 1972. It is thought to produce its hypnotic effects (without analgesia) by interaction with γ-aminobutyric acid receptors. Besides having a desirable lack of effect on hemodynamics, etomidate reduces cerebral blood flow and cerebral metabolic rate for oxygen consumption (30–50%), and intracranial pressure. It has little effect on ventilation, does not release histamine, and does not change airway smooth muscle tone. Of all of the available intravenous induction agents, etomidate consistently demonstrates the smallest amount of direct myocardial depression in several *in vitro* models. Two well-designed studies using adult human atrial and ventricular tissue demonstrated no effect of etomidate on myocardial contractility in concentrations seen in clinical use (Fig. 4.7). In the same model, ketamine showed slight, and thiopental strong, negative inotropic effects in clinical concentration ranges. This was true even in abnormal myocardial samples of ventricular tissue taken from hearts removed for cardiac transplantation.

All of these beneficial effects of etomidate are offset by a number of undesirable effects. Etomidate is water insoluble and thus is formulated in propylene glycol, and commonly produces pain on injection, which may be ameliorated by pretreatment with lidocaine, and 1 : 1 dilution with sterile water. Myoclonic movement, hiccoughs, and nausea and vomiting are frequent. It should be noted that, as in adults, a single dose of etomidate used for induction in pediatric patients undergoing cardiac surgery with CPB suppresses the usual increase in plasma cortisol levels by inhibiting 11-β-hydroxylase, the enzyme that converts 11-deoxycortisol to cortisol. Cortisol levels returned to normal 24 hours later.

There are few published reports of the hemodynamic effects of etomidate in children with CHD. Twenty patients with a variety of congenital defects were studied in the cardiac catheterization laboratory. These authors found that etomidate at 0.3 mg/kg bolus followed by an infusion of 26 μg/kg/minute had similar effects as ketamine 4 mg/kg.
followed by an infusion of 83 µg/kg/minute, namely a slight increase in HR but no change in MAP during induction or the 60-minute infusion. Sarkhar et al. studied etomidate bolus 0.3 mg/kg in 12 children undergoing cardiac catheterization for device closure of atrial septal defect, or radiofrequency ablation of atrial arrhythmias. There were no significant changes in any hemodynamic parameter, including HR, MAP, filling pressures, vascular resistances, Qp : Qs, or mixed venous oxygen saturation. A case report of stable hemodynamics in a pediatric patient with end-stage cardiomyopathy receiving a second anesthetic 4 weeks after cardiovascular collapse with ketamine induction (see above) demonstrates the utility of the drug in this population. Etomidate has been utilized for induction of anesthesia in adults with congenital cardiac conditions such as ruptured aneurysm of the sinus of valsalva, and cesarean section in a patient with uncorrected coronary artery to pulmonary artery fistula, and has been demonstrated to be devoid of cardiovascular effects in these patients.89

Thus it would appear that etomidate is best utilized in patients with the most limited cardiac reserve. It seems to be particularly useful in teenagers or adults with poorly compensated palliated CHD presenting for cardiac transplantation, or revision of previous surgeries. New water soluble preparations, or other formulations of etomidate may eliminate the troubling side effects of pain on injection and phlebitis.

Barbiturates

An induction dose of thiopental was studied with transthoracic echocardiography to determine cardiovascular responses in infants with normal hearts. In contrast to propofol, thiopental did not alter systolic or MAP, or SVR. Shortening fraction decreased significantly, and there was a mild decrease in load-independent measures of contractility as well. The HR and CI did not change significantly. Another study comparing thiopental and propofol for induction in children found thiopental produced a decrease in MAP of 14–21%, and a 10–15% reduction in CO, which was possibly influenced by the inhalation of N2O and halothane.

The rapid acting barbiturates, including thiopental, are direct myocardial depressants. A recent study using adult human atrial muscle strips, found a reduction in contractility of 25–50% after exposure to thiopental at clinically relevant concentrations. Thiopental also causes venodilation and pooling of blood in the periphery. The mechanism for these cardiovascular effects is related to both an interference of Ca2+ flux across the sarcolemmal membrane, and an alteration of the nitric oxide synthase pathway.

Hemodynamic homeostasis is mediated by baroreceptor reflex-induced sympathetic stimulation. Patients with limited reserves, and maximally stimulated sympathetic responses or downregulated β-adrenergic receptors will likely experience significant hypotension with barbiturate anesthetic inductions.

In summary, the intravenous induction of anesthesia with barbiturates in patients with CHD should be reserved for those patients with good cardiac reserves and intact baroreceptor reflexes, who can tolerate a reduction in contractility, and a possible reduction in arterial pressure.

Special conditions effecting anesthetic pharmacokinetics and pharmacodynamics in congenital cardiac anesthesia

Intracardiac shunts

The presence of a right-to-left intracardiac shunt decreases the rate of rise of the concentration of inhaled anesthetic in the arterial blood, as a portion of the systemic CO bypasses the lungs and then dilutes the anesthetic concentration in the systemic arterial blood. The anesthetic concentration in the blood thus never equals the exhaled concentration. Huntington et al. studied six children with right-to-left shunts from a fenestrated Fontan operation whose average pulmonary to systemic blood flow ratio was 0.58. These
patients achieved an arterial anesthetic concentration \((F_a)\) of only 55% of inspired halothane concentration \((F_i)\) after 15 minutes during washin of 0.8% halothane. After closure of the right-to-left shunt (occlusion of Fontan fenestration in the cardiac catheterization laboratory), the arterial concentration of halothane equaled the inspired concentration. This difference between \(F_a\) and \(F_i\) is greater during induction or washout; and greater with less soluble drugs such as sevoflurane, desflurane, and nitrous oxide, than with less soluble drugs such as halothane.

In the face of significant right-to-left intracardiac shunting, intravenous agents given by bolus may pass directly into the left side of the heart with less dilution by systemic venous blood and passage through the pulmonary vascular system. This may result in transient high arterial, brain, and cardiac concentrations of drugs such as lidocaine. Intravenous induction agents and muscle relaxants may also achieve sufficient arterial and brain concentrations more rapidly with right-to-left intracardiac shunts.

Left-to-right intracardiac shunts have little effect on the speed of induction with inhaled anesthetic agents. The recirculation of blood through the lungs results in increased uptake of anesthetic and in a higher blood anesthetic concentration in the pulmonary capillaries, which in turn reduces the anesthetic concentration gradient between the alveolus and the pulmonary capillary blood, reducing anesthetic uptake. The two effects cancel each other. Only in the case of severe congestive heart failure from left-to-right shunt, with significant interstitial and alveolar edema, would left-to-right intracardiac shunting be expected to slow inhalation induction, from the combined effects of diffusion limitation and ventilation-perfusion mismatch resulting alveolar deadspace ventilation in which no new anesthetic agent is taken up.

**Cardiopulmonary bypass**

The onset of CPB affects plasma levels of intravenous drugs by a number of different mechanisms. Hemodilution of the patient’s blood volume by a factor of 50% to 300%, depending on the size of the patient and the priming volume of the circuit, causes an immediate reduction in plasma levels. Many drugs also bind to the membrane oxygenator and other components of the bypass circuit, resulting in a further decrease in plasma levels. This effect is variable, and is dependent on the drug, the type of bypass circuit used (i.e. silicone vs. polypropylene), the age and size of the patient, and the plasma and bypass prime albumin concentrations. Hypothermia slows the metabolism of all drugs by reducing the rate of reaction of all enzymes involved in drug metabolism, whether they are in the liver (cytochrome P450 system), kidney, or plasma. Rewarming significantly increases the rate of metabolism of intravenous agents.

A constant, stable fentanyl plasma level can be achieved in most children through the administration of a loading dose of 30–50 µg/kg followed by an infusion of 0.15–0.30 µg/kg/minute. Plasma fentanyl levels decrease by 70–75% immediately upon institution of CPB with a silicone membrane oxygenator. After cooling to 18–25°C, fentanyl metabolism decreases considerably and free drug concentrations change very little, even without added drug. Metabolism then increases and drug levels decline in the plasma as rewarming proceeds. Data concerning common anesthetic adjuvants such as midazolam suggest similar changes in plasma concentrations. Thus, without supplementation of intravenous agents such as fentanyl and midazolam, either just before or at the initiation of bypass, there is an increased risk of awareness. A similar risk would appear to be true during the final phases of the rewarming period. Indeed, this concept is borne out by recent studies using the bispectral index (see below) as an indicator of depth of sedation in children undergoing bypass with mild hypothermia.

Neuromuscular blocking agents have an enhanced effect during hypothermic bypass, both from decreased metabolism and clearance, and because of the effects of hypothermia to potentiate the pharmacodynamic effects of the drugs at the neuromuscular junction. These effects rapidly reverse themselves during rewarming. These drugs have a small volume of distribution and thus few tissue stores from which to re-equilibrate plasma levels. Thus, plasma levels would be expected to decline in proportion to the hemodilution factor of the pump prime, subject to changes in protein binding. This may be offset by reductions in the patient’s plasma volume on bypass due to vasoconstriction. The action of these drugs in response to bypass is accordingly more variable than other commonly used intravenous anesthetic agents.

There is limited pediatric information available. Monitoring of neuromuscular blockade with a twitch monitor is recommended if early reversal is desired. Volatile agents may be used during bypass to supplement anesthetic depth, or as vasodilators. Isoflurane is most commonly utilized at a concentration of 0.5–2.0% inspired into the sweep gas of the bypass circuit. Multiple adult studies have demonstrated the effectiveness and relatively rapid washin of this agent. However, pediatric data is limited, and because sweep gas flow rates are often less than 1 L/minute, uptake is probably much slower and it cannot be assumed that the desired blood anesthetic level is rapidly reached when volatile anesthetic agents are administered through the bypass circuit to infants and small children. Washout of volatile agents is also slower at low sweep gas rates, and volatile agents should be discontinued early during the rewarming period to avoid the myocardial depressant effects of these agents while attempting to wean the patient from bypass.

**Hypothermia**

Studies performed on animal models reveal hypothermia reduces the MAC of volatile anesthetics.
Monitoring anesthetic depth and awareness

Until recently, the only means available to the clinician to monitor anesthetic depth and assess the risk of awareness was through a general knowledge of the pharmacokinetic and pharmacodynamic properties of anesthetics, along with measurement of the end-tidal anesthetic concentrations and clinical signs of depth of anesthesia. The clinical signs of inadequate anesthesia in the paralyzed cardiac surgical patient include autonomic signs such as papillary dilation, tearing, and tachycardia/hypertension. These signs are often unreliable, given the hemodynamic derangements common in this population, manipulation by the surgeon causing activation of baroreceptor reflex responses, and the use of vasoactive and chronotropic drugs, or drugs that block the autonomic response. Recently the BIS, a highly processed electroencephalogram, has become available. Available pediatric data suggest that this modality correlates with end-tidal levels of volatile anesthetics and with MAC awake levels, with better correlation in children over 1–2 years of age, although interpatient variability is significant. Studies in both infants and older children undergoing congenital heart surgery with CPB, demonstrate that the index (a dimensionless number 0–100) decreases with lower nasopharyngeal temperature, and increases during the rewarming phase. However, BIS did not correlate with hemodynamic, metabolic, or hormonal indices of light anesthesia. BIS has been demonstrated to be more sensitive to changes in the levels of volatile anesthetics and propofol, and less sensitive to narcotics and benzodiazepines. In our experience, we commonly find that BIS increases during rewarming on bypass to levels in the range for risk of awareness despite large doses of fentanyl and midazolam. Pediatric studies of BIS during cardiac surgery are limited, and larger prospective studies are needed to demonstrate the validity and utility of device.

Neuromuscular blocking agents and antagonists

Succinylcholine

Succinylcholine is rarely indicated for anesthesia for CHD because of its association with the development of malignant hyperthermia, hyperkalemic cardiac arrest, and bradycardia after intravenous bolus administration. Succinylcholine will produce a more rapid onset of muscle relaxation than non-depolarizing muscle relaxants, and we have limited its use to full-stomach emergency indications, i.e. cardiac transplant, to treat laryngospasm, and as part of an intramuscular induction. Infants and children frequently exhibit bradycardia, nodal rhythm, ventricular premature beats, and rarely, asystole, after intravenous dosing of 1–2 mg/kg without atropine pretreatment. The frequency of all of these arrhythmias increases with a second dose. A dose of 4 mg/kg i.m., either alone, or with atropine 20 µg/kg, and ketamine 5–10 mg/kg in the same syringe, rarely causes bradycardia.

Pancuronium

Pancuronium is frequently used in doses of 0.1–0.3 mg/kg for initial relaxation for CHD and is particularly desirable in many small infants and young children because of the vagolytic and mild sympathomimetic effects, which preserve or increase HR, especially in the face of concomitant bradycardia from high dose narcotic anesthesia.

Vecuronium

Vecuronium is devoid of cardiovascular effects in children. It is a useful agent when increases in HR are undesirable, e.g. HCM. When no uncertainties about ability to manage the airway are evident, it is a useful alternate to succinylcholine in a dose of 0.3–0.4 mg/kg for modified rapid sequence induction.

Rocuronium

Rocuronium is a moderately rapid onset intermediate duration non-depolarizing neuromuscular blocker that is useful at a dose of 0.6–1.2 mg/kg i.v. At the upper dose ranges it is an acceptable substitute for succinylcholine for modified rapid sequence induction. Cardiovascular effects are minimal, however, because it causes pain on injection, or because it is a weak vagolytic medication, an increase in HR is often observed after injection. This agent may be utilized for intramuscular administration in doses of 1.8–2.0 mg/kg, and when injected into the deltoid will produce suitable intubating conditions in 3–4 minutes.

Atracurium and cisatracurium

These agents are non-organ dependent for elimination and are attractive choices in the face of significant hepatic and renal dysfunction. Atracurium at high dosages frequently causes histamine release, resulting in hypotension when injected rapidly, making it undesirable for many patients
with CHD. Cisatracurium is a stereoisomer of atracurium, also degraded by Hoffmann elimination, does not release histamine, and like vecuronium, is devoid of cardiovascular effects even when administered rapidly. 103

Antagonists

The muscarinic effects of neostigmine must be blocked by atropine or glycopyrrolate to prevent potentially serious decreases in HR. Because the onset of cardiovascular effects of neostigmine and glycopyrrolate are similar, a most useful regimen is to utilize neostigmine and glycopyrrolate in the same syringe in a 5 : 1 ratio of neostigmine : glycopyrrolate (i.e. 75 µg/kg : 15 µg/kg) injected slowly to minimize the small risk of arrhythmia with neostigmine.

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