Chapter 15
The Effects of Anesthetic Agents on Cardiac Function

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Abstract With the aging population and an increase in health problems such as obesity, diabetes, and coronary artery disease, the perioperative management and induction of general anesthesia in such patients, while providing cardiovascular stability, continues to offer both challenges and new developments in this field. These developments include new anesthesia medications, medical equipment and/or surgical technology, and anesthetic and surgical techniques. The goal of this chapter is to familiarize the reader with commonly employed clinical methodologies and anesthetics, with particular attention to the potential influences on the cardiovascular system.

Keywords Anesthesia · Inhalational anesthetics · Intravenous anesthetics · Anesthesia induction · Cardiac function · Hemodynamics · Cardioprotection · Myocardial preconditioning

15.1 Introduction

Anesthesia is considered necessary for many types of surgeries and procedures. In general, anesthesia may provide analgesia, amnesia, hypnosis, and/or muscle relaxation. The depth of anesthesia varies from minimal sedation to general anesthesia (Table 15.1). Importantly, medications used for general anesthesia can cause significant alterations in hemodynamics, especially during induction of anesthesia. Yet, understanding of anesthetic impact on cardiovascular physiology can allow induction and maintenance of anesthesia with minimal alterations from normal cardiovascular function. Both inhalational and intravenous anesthetics can affect cardiovascular performance; this includes effects on cardiac output, heart rate, systemic vascular resistance, the cardiac conduction system, myocardial contractility, coronary blood flow, and/or blood pressure. The choice of inhalational and intravenous anesthetics is typically associated with the patient's underlying cardiovascular status such as heart failure, cardiac disease, and/or hypovolemia.

15.2 Anesthesia Induction Sequence

A focused patient history and physical is necessary prior to anesthesia to determine the most appropriate anesthetic for that individual. All patients undergoing elective surgery should be nil per os (NPO) of solid foods for at least six hours prior to an anesthetic; this is to minimize the risk of gastric regurgitation and thus aspiration of stomach contents into the lungs during the induction of anesthesia. Past history of any complications or reactions to anesthetics must also be considered. For example, patients with a history of porphyria should not receive a porphyria-inducing agent such as barbiturates or diazepam. Patients with a family history of malignant hyperthermia are at risk of eliciting an episode of malignant hyperthermia when a triggering agent such as succinylcholine or a volatile anesthetic is administered. Therefore, the need for laboratory studies is guided by the preexisting medical condition of each individual patient.

A typical general anesthesia induction sequence for an adult is as follows. After establishing intravenous access and placement of standard American Society of Anesthesiologist (ASA) [1] monitors, a patient is preoxygenated with 100% oxygen. An induction dose of an intravenous medication such as propofol and a muscle relaxant is administered to facilitate smooth induction of anesthesia (JPG 15.1). Once the patient is rendered unconscious and anesthetized, direct laryngoscopy is

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Table 15.1 Continuum of depth of sedation definition of general anesthesia and levels of sedation/analgesia

	Minimal sedation (anxiolysis)	Moderate sedation/analgesia ("conscious sedation")	Deep sedation/analgesia	General anesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful response to verbal or tactile stimulation	Purposeful response following repeated or painful stimulation	Unarousable even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired

ASA Standards, Guidelines and Statements [1].

performed and the trachea is intubated with an endotracheal tube. After confirmation of endotracheal intubation by auscultation of lungs and confirmation of end-tidal carbon dioxide, the patient is placed on an anesthesia ventilator and ventilated with a combination of anesthetic gases, oxygen, and/or air (JPG 15.2). Note, if a total intravenous anesthetic technique (such as propofol and opioid infusion) is chosen, anesthetic gases are not administered. A total intravenous anesthetic technique may be chosen in patients who have reactions to volatile anesthetics such as patients with malignant hyperthermia. The cardiovascular depressant effects of most anesthetics typically become evident during and immediately following induction. Maintaining cardiovascular stability requires: (1) careful titration of medications; (2) knowledge of clinical and basic science in physiology and pharmacology; and (3) diligent monitoring of vital signs (JPG 15.3)

For the induction of general anesthesia in children, one often utilizes a mask induction technique. Since placement of an intravenous catheter preinduction may be traumatic to the child or difficult due to noncooperation, mask induction with halothane, sevoflurane, and/or nitrous oxide is frequently employed; note that in current clinical practice, halothane is rarely used in the United States. After placement of ASA monitors, a high concentration of an inhalational anesthetic such as sevoflurane along with oxygen is administered via a face mask. After the patient becomes unconscious, a peripheral intravenous catheter is placed and a similar general anesthesia and airway management sequence subsequently follows.

It is important to note that direct laryngoscopy and endotracheal intubation can often stimulate the upper and lower airways which, in turn, may cause significant changes in blood pressures and heart rate if airway responses are not blunted. Commonly, titration of anesthetics and opioids are administered to blunt these airways and associated sympathetic responses.

15.3 Inhalational Anesthetics

Commonly used inhalational anesthetics include nitrous oxide, isoflurane, desflurane, and sevoflurane (Fig. 15.1). Each of these inhalational anesthetics has a specific minimum alveolar concentration (MAC) at which general anesthesia is induced (Table 15.2). MAC is defined as the minimum alveolar concentration of an inhaled anesthetic required to prevent movement in 50% of patients in response to a painful stimulus such as a surgical incision. It is important to note that infants and children have a higher MAC requirement than adults, while pregnant women and elderly patients have lower MAC requirements. MAC is additive, that is, 0.5 MAC of nitrous oxide and 0.5 MAC of isoflurane result in 1 MAC total anesthesia. More specifically, the brain anesthetic partial

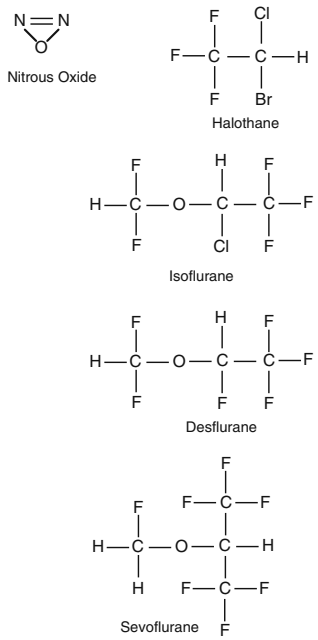

Fig. 15.1 Chemical structure of commonly administered inhalational anesthetics

Table 15.2 Minimal alveolar concentration (MAC) of inhalational anesthetics

Agent	MAC % (% of 1 atmosphere)	Vapor pressure (at 20°C)
Desflurane	6.0	680
Halothane	0.75	243
Isoflurane	1.2	240
Sevoflurane	2.0	160
Nitrous oxide	105	
Xenon	70	

pressure is dependent upon factors such as inspired (F_I) and alveolar (F_A) concentration of anesthetic gas. Brain (F_B) concentration of anesthetic is dependent upon F_A and F_I:

$$F_I \leftrightarrow F_A \leftrightarrow F_B$$

In general, anesthetic uptake is determined by blood solubility, cardiac output, and difference between alveolar to venous partial pressure [2]. The greater the uptake of anesthetic gas into blood, the slower the rate of induction. Inhalational anesthetics with lower blood:gas solubility (i.e., desflurane and sevoflurane) will cause faster induction and emergence from general anesthesia; higher concentrations of these agents are needed for the MAC requirement.

15.3.1 Blood Pressure and Systemic Vascular Resistance

All volatile anesthetics such as isoflurane, desflurane, sevoflurane, and halothane cause dose-dependent effects on cardiovascular function. For example, these agents cause a dose-dependent decrease in mean arterial blood pressure [3–6]. The relative decrease in mean arterial blood pressure is considered due to decreases in systemic vascular resistance, myocardial contractility, sympathetic output, or a combination of the above. In particular, isoflurane, desflurane, and sevoflurane cause greater decreases in systemic vascular resistances when compared to halothane (Table 15.3). Further, increasing doses of halothane result in small changes in system vascular resistance [7], and decreases in mean arterial pressure with halothane administration are associated with decreases in cardiac output. In general, volatile anesthetics decrease systemic vascular resistance by causing peripheral vasodilation and thus increasing blood flow to cutaneous and skeletal muscle tissues [3]. It should be noted that nitrous oxide causes minimal alteration of systemic vascular resistance when administered alone. Typically, an initial drop in blood pressure following induction of anesthesia is associated with a decrease in systemic vascular resistance and preload. Low blood pressure can be increased by administration of intravenous fluids, placing the patient in a Trendelenburg position, and/or by giving peripheral vasoconstrictors such as phenylephrine or ephedrine.

15.3.2 Cardiac Conduction System and Heart Rate

Baroreceptors located near the aortic root, carotid arteries, and other sites detect changes in arterial blood pressure and affect cardiovascular function. A typical baroreceptor reflex from the carotid artery includes the afferent (cranial nerve IX) and efferent (cranial nerve X) nerves. An increase in arterial blood pressure is detected by the baroreceptor, causing reflex decrease in the heart rate. A decrease in arterial blood pressure then causes a reflex tachycardia to maintain cardiac output and organ perfusion. Importantly, volatile anesthetics will cause dose-dependent decreases in baroreceptor reflex activities [8]; hence, hemodynamic compensatory responses are attenuated by volatile anesthetics [9, 10]. It is common that alterations in hemodynamics due to volatile anesthetics may require administration of other pressor medications to offset the attenuation of these normal physiologic protective functions.

Volatile anesthetics may also cause specific cardiac dysrhythmias. Specifically, volatile anesthetics have been reported to both slow the rate of sinoatrial node discharge and increase ventricular and His bundle conduction times

Table 15.3 Cardiovascular effects of inhalational anesthetics

	Heart rate	Blood pressure	Systemic vascular resistance	Cardiac output	Sensitize to epinephrine	Coronary dilation
Desflurane	+	–	– –	0/–	0/+	+
Halothane	0	– –	0/–	–	+++	+
Isoflurane	+	– –	– –	–	0/+	++
Sevoflurane	0	– –	–	0/–	0/+	0
Nitrous oxide	+	0	0	0	0	0

[11], which may increase the development of nodal rhythms. Further, volatile anesthetics may increase ventricular automaticity by altering potassium and calcium ion channels [11]. It has been reported that halothane increases the incidence of ventricular dysrhythmias, especially when coadministered with epinephrine; in contrast, the coadministration of epinephrine with isoflurane, desflurane, or sevoflurane has noted minimal effects on increasing the incidence of ventricular dysrhythmias [12–14]. Furthermore, halothane may blunt the reflex increases in heart rates which typically accompany decreases in blood pressure; it may also slow conduction from the sinoatrial node, resulting in junctional ventricular rhythms. Sevoflurane and desflurane are also known to partially blunt sympathetic baroreflex sensitivity. Importantly, isoflurane is well known to cause significant decreases in systemic vascular resistance, and thus blood pressure. Yet, the baroreceptor response remains partially intact and thus cardiac output is maintained relatively stable with isoflurane by associated increases in heart rate.

In patient populations such as young children and the elderly, it is not uncommon to see decreases in heart rate following induction of anesthesia. An anticholinergic agent such as atropine or glycopyrrolate is frequently administered to prevent and/or treat such bradycardia.

15.3.3 Coronary Blood Flow

In general, volatile anesthetics cause a dose-dependent coronary vasodilation, i.e., with isoflurane having a greater effect than halothane [15, 16]. Increasing the concentration of isoflurane increases coronary blood flow, and this also has the potential to cause "coronary steal" syndrome [17, 18]. Coronary steal is caused by vasodilation of healthy coronary arteries and shunting of blood from myocardium at risk for ischemia to areas not at risk. More specifically, in coronary artery disease, cardiac areas at risk for myocardial ischemia have coronary arteries that are already maximally vasodilated. Desflurane and sevoflurane have not been associated with coronary steal syndrome [19, 20]. Nevertheless, the exact clinical significance of coronary steal in humans remains somewhat unresolved.

15.3.4 Contractility and Cardiac Output

Volatile anesthetics depress myocardial contractility by inducing alterations of calcium ion flux [21]. The mechanism of negative inotropic effects of volatile anesthetics include decreased free Ca^{2+}, decreased Ca^{2+} release from sarcoplasmic reticulum, and/or altered contractile protein response to Ca^{2+} [21, 22]. Halothane diminishes myocardial contractility more than isoflurane, desflurane, and nitrous oxide below 1 MAC. Isoflurane and sevoflurane cause minimal change in contractility and thus allow for better maintained systemic cardiac output [22]. Due to better cardiovascular stability following either isoflurane or sevoflurane administration compared to halothane, the former agents are utilized frequently in patients with congenital heart defects and/or depressed myocardial function.

Due to the simultaneous stimulation of the sympathetic nervous system, the myocardial depressant effects of nitrous oxide are usually not evident in healthy individuals. Yet, in a compromised and failing myocardium, its depressant effects on contractility become much more evident. More specifically, nitrous oxide has been associated with sympathomimetic effects, as it: (1) increases plasma catecholamines; (2) causes mydriasis; and (3) induces vasoconstriction of systemic and pulmonary circulations [23]. When nitrous oxide is administered with opioids such as fentanyl, the sympathomimetic effects are minimized or abolished. Therefore, the combined administration of nitrous oxide and opioids may result in a significant decrease in mean arterial pressure and cardiac output.

The abrupt increase in a patient's desflurane concentration has been associated with a significant increase in sympathetic output, resulting in increased heart rate and mean arterial pressure. A proposed mechanism for this sympathetic stimulation is that it is due to airway and lung irritation with a high concentration of desflurane [24]. A smaller increase in sympathetic output is commonly associated with isoflurane administration, whereas sevoflurane, due to lack of airway irritation with its administration, is not associated with a significant increase in sympathetic output, even with a very rapid increase in concentration. Due to sevoflurane favorable airway properties, it is used frequently for inhalational induction of anesthesia in children; high concentrations of sevoflurane (4–8%) are needed for rapid mask induction and are well tolerated in children.

15.3.5 Pulmonary Blood Flow

Volatile anesthetics are potent bronchodilators and, in some cases, they have been used for the treatment of status asthmaticus. In general, it is considered that volatile anesthetics may cause a mild decrease in pulmonary vascular resistance, whereas nitrous oxide can cause a significant increase in pulmonary vascular resistance. Thus, the administration of nitrous oxide in patients with preexisting pulmonary artery hypertension may exacerbate the strain

on the right heart by increasing pulmonary vascular resistance. This elevated pulmonary vascular resistance may also result in right-to-left intracardiac shunting in susceptible patients (i.e., ventriculoseptal defect). In general, volatile anesthetics also diminish the degree of hypoxic pulmonary vasoconstriction, which may result in hypoxia. It is important that in patients with congenital heart defects (i.e., intracardiac shunts, single ventricle, transposition of great arteries, Tetralogy of Fallot), the properties of select volatile anesthetics may be critical to offer better cardiovascular stability.

15.3.6 Cardioprotection/Preconditioning

The potential for myocardial preconditioning with volatile anesthetics has been extensively studied. Importantly, halogenated volatile anesthetics have been shown to provide cardioprotection against injury associated with ischemia and reperfusion [25–28]**.** The mechanism of cardioprotection seems to be similar to ischemic preconditioning first described by Murray et al. [29], and thus likely ultimately involves the mitochondrial potassium (K_{ATP}) channels [30].

15.3.7 Future Inhalational Anesthetics

Xenon was first used as an anesthetic gas in humans by Cullen and Gross in 1951 [31]. Xenon, an inert gas, has many properties that make it an ideal anesthetic gas; it has very low toxicity and is nonexplosive and nonflammable. The MAC of xenon is approximately 70%. Its very low blood to gas solubility partition coefficient (0.115) provides fast onset and emergence from anesthesia [32]. Recently, preliminary clinical studies with xenon have shown minimal adverse effects on the cardiovascular system and general hemodynamic parameters [32–34]. More specifically, xenon has been shown to induce minimal effects on alterations in heart rate, coronary blood flow, left ventricular pressure, and atrioventricular conduction time [35]. However, factors that may limit the use of xenon as an anesthetic gas are its cost and required unique delivery system; xenon must be extracted from the atmosphere and this process is expensive. Nevertheless, special breathing and delivery systems are in development.

It should be specifically noted that all volatile anesthetics trigger malignant hyperthermia in susceptible patients. Malignant hyperthermia is an inherited pharmacogenetic disorder that affects skeletal muscle and is characterized by a hypermetabolic response when exposed to a triggering agent such as volatile anesthetics and succinylcholine. Disregulation of the ryanodine receptor, the calcium release channel of sarcoplasmic reticulum, is typically involved in this unregulated release of calcium from this storage site. Signs and symptoms of malignant hyperthermia include sympathetic hyperactivity, elevated carbon dioxide production, muscle rigidity, hyperthermia, metabolic acidosis, dysrhythmias, and hyperkalemia. Treatment of malignant hyperthermia requires removal of the triggering agent, intravenous administration of dantrolene, and management of the associated symptoms. For more details on malignant hyperthermia, see http://www.mhaus.org/.

15.4 Intravenous Anesthetics

15.4.1 Barbiturates

In general, barbiturates cause central nervous system inhibition (depression) by enhancing the effects of g-aminobutyric acid (GABA) [36]. Barbiturates bind to the GABA receptor complexes which, in turn, increase chloride channel activities, causing subsequent inhibition of the central nervous system. The GABA receptor complex has binding affinities for GABA, barbiturates, benzodiazepines, propofol, and/or alcohol [23].

Thiopental (3–5 mg/kg) and methohexital (1.5–2 mg/kg) are common barbiturates used for induction of general anesthesia (Fig. 15.2). After intravenous injection of thiopental or methohexital, anesthesia is induced rapidly, within seconds. Yet, the duration of induced anesthesia after a single bolus dose of intravenous barbiturate is short (approximately 5 min) due to rapid redistribution from the brain to other tissues such as muscle and adipose. Importantly, intraarterial injection of thiopental can result in severe vasospasm which may lead to thrombosis, tissue injury, and/or even gangrene. If intraarterial injections do occur, counteractive measures such as sympathetic nerve blocks or administration of papaverine, phenoxybenzamine, or lidocaine may be initiated to decrease induced arterial vasospasm.

The administration of barbiturates is typically associated with decreases in mean arterial pressure which result from both induced vasodilation and decreased myocardial contractility (Table 15.4). Barbiturates have

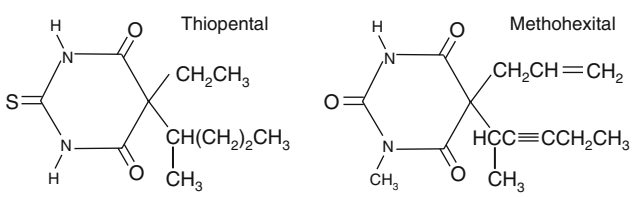

Fig. 15.2 Chemical structure of thiopental and methohexital

Table 15.4 Cardiovascular effects of intravenous anesthetics

	Heart rate	Blood pressure	Systemic vascular resistance	Cardiac output
Thiopental	+	–	–	+
Ketamine	++	++	+	++
Propofol	0/–	– –	– –	–
Etomidate	0	0/–	0	0
Fentanyl	0/–	0	0	0
Morphine	0/–	0/–	0/–	0
Midazolam	0	0	0	0
Methohexital	++	–	–	0/–
Meperidine	++	0/–	0/–	0/+

also been shown to cause dose-related myocardial depression, which is not as pronounced as that associated with volatile anesthetics. Yet, barbiturates may cause a small depression of the carotid and aortic baroreceptors, and therefore, an induced decrease in mean arterial pressure leading to reflex tachycardia. If intravenous barbiturates are administered slowly, relative hemodynamic stability can be maintained [37], especially in patients with normal intravascular volume status. In contrast, a rapid infusion of barbiturates, especially in hypovolemic patients, may result in significant hypotension. Subsequently, typical increases in heart rate upon barbiturate administration are not present if the baroreceptor reflex is not intact, as in heart transplant patients or in isolated heart preparations. Importantly, barbiturates do not generally sensitize the myocardium to the potential arrhythmic effects of administered catecholamines.

15.4.2 Benzodiazepines

Benzodiazepines are considered to produce central nervous system depression by binding to the GABA receptor complex and ultimately increasing chloride channel activities. Benzodiazepines, such as midazolam and diazepam, are often administered as adjuncts to anesthesia for sedation, amnesia, and anxiolysis. Benzodiazepines themselves do not have analgesic properties. Yet, they possess anticonvulsant properties and hence can be utilized in acute management of seizures. Interestingly, the acute administration of benzodiazepines is not associated with significant changes in hemodynamic parameters; blood pressure, heart rate, and systemic vascular resistance are fairly well maintained. However, systemic vascular resistance decreases in a dose-related fashion [38], but a typical dose required for sedation and anxiolysis in adults (1–2 mg intravenous) usually is not associated with any significant hemodynamic alteration.

More specifically, induction of anesthesia with midazolam (0.2–0.3 mg/kg intravenous) is associated with a decrease in systemic vascular resistance, but with minimal effects on cardiac output. Typically, the baroreceptor reflex remains intact and thus a relative decrease in mean arterial pressure will result in a responsive increase in heart rate. It has been reported that diazepam elicits even fewer cardiovascular effects than midazolam; a typical dose required for sedation and anxiolysis in adults usually is not associated with any significant hemodynamic alterations. At most, diazepam administration may cause a minimal change in blood pressure and systemic vascular resistance. Therefore, coadministration of diazepam and nitrous oxide is not associated with significant decreases in cardiovascular function [39]; thus, it is employed in patients where such concerns may be justified.

15.4.3 Opioids

Opioids are analgesics that are commonly administered as adjuncts to anesthesia. Opioids currently used in clinical practice include fentanyl, morphine, meperidine, alfentanil, sufentanil, and remifentanil (Table 15.5). All opioids exert their effect by interacting with opioid receptors (mu_1, mu_2, kappa, or delta; see Table 15.6); they are used as adjuncts to help blunt sympathetic responses to noxious stimuli. Overall, the clinical use of opioids causes minimal changes in cardiac output and blood pressure, yet opioids may generally cause bradycardia due to an increase in vagal tone. Typically at very high doses, opioids may have the following effects on hemodynamics: inhibition of autonomic nervous system, direct myocardial depression, and/or histamine release. More specifically, one *in vitro* study of human atrial myocardium found that fentanyl, remifentanil, and sufentanil did not modify inotropic effects, while alfentanil caused negative inotropy by affecting calcium regulation [40]. Yet, it has also been reported that opioids such as fentanyl may depress rat myocardial contractility by affecting calcium regulation [41]. Finally, it is considered that morphine may cause a decrease in mean arterial pressure by causing

Table 15.5 Opioid agonists commonly used in clinical practice

	Heart rate	Blood pressure	System vascular resistance	Contractility	Histamine
Meperidine	++	–	–	+/–	++
Morphine	0/–	–	–	–	++
Fentanyl	0/–	0	0	0	0
Alfentanil	–	0/–	–	0/–	0
Sufentanil	–	0/–	0/–	0/–	0
Remifentanil	–	0	0	0	0

Table 15.6 Opioid and opioid receptors

Drug	Mu receptor	Delta receptor	Kappa receptor
Morphine	+++	+?	+
Fentanyl	+++	?	
Sufentanil	+++	+	+
Buprenorphine	+		––
Naloxone	–––	–	––
Naltrexone	–––	–	–––
Nalbuphine	––		++
DPDPE		++	
DADLE	+	+++	+?
NorBNI	–	–	–––
DSLET	+	++	
Naltrindole	–	–––	–

Modified from Goodman and Gilman's The pharmacological basis of therapeutics. 10th ed. (Hardman JG, Limbird LE, eds). New York, NY: McGraw-Hill, 2001.

histamine release and bradycardia. It should be noted that high doses of an intravenous opioid such as fentanyl can cause chest wall rigidity, making manual ventilation of nonparalyzed patient difficult.

15.4.4 Ketamine

Ketamine is a phencyclidine derivative (Fig. 15.3) that causes intense analgesia and dissociative anesthesia. Patients who receive ketamine can obtain a cataleptic state with open eyes and/or ocular nystagmus. The typical routes for ketamine administration include intravenous (1–2 mg/kg), intramuscular (3–6 mg/kg), or oral (5–6 mg/kg). In general, ketamine's effects on the central nervous system are considered due to interactions with multiple receptors including *N*-methyl-D-asparate (NMDA), monoaminergic, opioid, and/or muscarinic. Due to interactions with pain receptors, ketamine possesses intense analgesic properties.

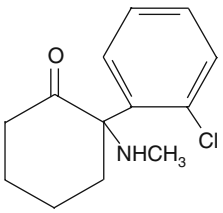

Fig. 15.3 Chemical structure of ketamine

Potential side effects of ketamine administration include the stimulation of the central sympathetic nervous system and thus an increase in circulating epinephrine and norepinephrine. In patients where maintenance of myocardial contractility and systemic vascular resistance is vital (i.e., hypovolemia, trauma, and shock), ketamine may better stimulate the cardiovascular system to maintain cardiac output and blood pressure. More specifically, ketamine causes an increase in heart rate, blood pressure, cardiac output, and myocardial oxygen consumption. Due to stimulation of cardiovascular function, ketamine may not be appropriate in patients with aortic stenosis, coronary artery disease, and/or hypertrophic left ventricle. It should be noted that pulmonary artery pressure may also increase following administration of ketamine. Another important side effect attributed to ketamine administration is its bronchodilating effects; thus, patients with, or at risk for, bronchospasm may benefit from ketamine induction. In contrast, in patients with depleted catecholamine stores, ketamine may cause a serious depression of myocardial function [42]. In other words, the maintenance or elevation of cardiovascular function may not be seen following administration of ketamine in patients with depleted catecholamine stores such as those with sepsis. Furthermore, ketamine may also increase cerebral perfusion and intracranial pressures, and thus should be used carefully in patients with neurovascular disease.

15.4.5 Propofol

Propofol (1% solution) is a 2,6-diisopropylphenol (Fig. 15.4) that is typically administered intravenously for sedation and/or induction of anesthesia. Importantly, intravenous injections of propofol (1.5–2 mg/kg) are associated with rapid loss of consciousness (30–60 s); hence, this has obvious clinical advantages. Furthermore, a general anesthesia maintenance infusion of propofol is typically achieved with 100–200 mcg/kg/min intravenous.

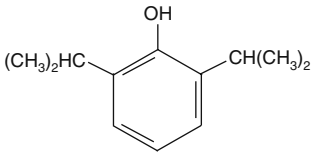

Fig. 15.4 Chemical structure of propofol

Additional advantages of propofol include clear awakening, small cumulative effects, and/or decreased incidence of nausea and vomiting.

Propofol is considered to also interact with GABA receptors and activate them in a similar fashion as barbiturates. Likewise, activation of GABA receptors by propofol increases the conductance of chloride channels, resulting in inhibition of postsynaptic neurons.

Of clinical significance, the administration of propofol commonly causes a decrease in both systemic vascular resistance and cardiac contractility, hence resulting in decreased cardiac output and blood pressure. This reduction in systemic vascular resistance (and vasodilation) is considered due to decreased sympathetic vasoconstrictor activation of vascular smooth muscle [43]. The inhibition of sympathetic tone by propofol is reported to be greater than inhibition of parasympathetic activity; in some patients, this may result in significant bradycardia and even asystole [44–46]. The induced decrease in cardiac contractility is likely due to decreases in calcium uptake into the sarcoplasmic reticulum; decreased reuptake of calcium results in less calcium available for the next activation sequence [47].

Importantly, it should again be noted that in patients with decreased left ventricular function, the administration of propofol may result in severe hypotension and suppressed myocardial contractility. Therefore, the careful titration of propofol and adequate intravascular hydration are important in these types of patients.

15.4.6 Etomidate

Etomidate (Fig. 15.5) is an imidazole compound which is water soluble at lower pH and lipid soluble at physiologic pH. Rapid loss of consciousness is accomplished after intravenous injection of etomidate (0.2–0.4 mg/kg). It is important to recognize that etomidate lacks analgesic properties and does not blunt sympathetic responses to direct laryngoscopy and endotracheal intubation.

Generally, etomidate provides cardiovascular and pulmonary stability; typical induction doses of etomidate result in minimal changes in heart rate and cardiac output. Myocardial contractility is well maintained at doses needed

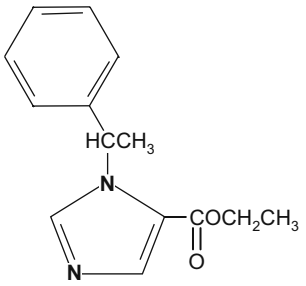

Fig. 15.5 Chemical structure of etomidate

to induce general anesthesia [23] and is considered to produce less myocardial depression when compared to thiopental [48]. Etomidate does not induce significant histamine release, but it does depress adrenocortical function by inhibiting the conversion of cholesterol to cortisol [49]. Specifically, a single induction dose of etomidate can cause adrenal suppression for 5–8 h [50], and a continuous infusion of etomidate will cause further adrenocortical suppression. Typically, there is minimal clinical effect to adrenal suppression following a single induction dose of etomidate.

15.4.7 Nondepolarizing Muscle Relaxants

In general, the majority of nondepolarizing muscle relaxants have minimal effects on cardiovascular and hemodynamic stability. Yet, when induced, nondepolarizing muscle relaxants are believed to elicit cardiovascular effects by stimulating the release of histamine and affecting muscarinic and nicotinic receptors (Table 15.7). For example, pancuronium may cause vagal blockade (antimuscarinic effect) at the sinoatrial node, resulting in elevation of heart rate. The administration of pancuronium is also associated with activation of the sympathetic nervous system [51, 52]. Large doses of atracurium and mivacurium are associated with histamine release which may result in tachycardia and hypotension; such patients may display facial flushing as a result of histamine release. Interestingly, cisatracurium (a stereoisomer of atracurium) is not associated with clinically significant histamine

Table 15.7 Nondepolarizing muscle relaxants

	Histamine release	Vagal blockade
Atracurium	+	0
Cisatracurium	0	0
Mivacurium	+	0
Pancuronium	0	++
Rocuronium	0	0/+
Vecuronium	0	0
Tubocurarine	+++	0
Succinylcholine	0	– –

release. Finally, it is of interest to note that vecuronium and rocuronium are agents that are considered totally devoid of significant cardiovascular effects at clinical doses.

15.4.8 Depolarizing Muscle Relaxant

Succinylcholine is a depolarizing muscle relaxant; it has a similar structure to and mimics acetylcholine by binding to nicotinic cholinergic receptors. The duration of action of succinylcholine is short (min) and is broken down by the abundant pseudocholinesterase enzyme in the plasma. Importantly, the administration of succinylcholine may be associated with cardiac dysrhythmias (i.e., junctional rhythm and sinus bradycardia) by its muscarinic activity at the sinoatrial node. Administration of succinylcholine is associated with hyperkalemia in susceptible patients such as those with malignant hyperthermia, muscular dystrophy, spinal cord injury, and/or burn injury. More specifically, in boys with Duchenne muscular dystrophy, the administration of succinylcholine has been linked to episodes of sudden cardiac death.

15.4.9 Acupuncture

Acupuncture involves stimulation of specific anatomical locations on the skin to alter energy flow patterns throughout the body. The skin can be stimulated by manual or electrical stimulation, or the more typical placement of small metallic needles. Acupuncture has been used in China for thousands of years and, more recently, there has been a surge of interest in these nontraditional methodologies in the United States. Acupuncture has been utilized for treatment and prevention of multiple health conditions such as chronic pain, nausea and vomiting, obesity, substance abuse, and/or asthma. Stress responses and cardiovascular effects of pain have reportedly been attenuated by nonpharmacologic techniques such as acupuncture; it modulates the body's pain system, increases the release of endogenous opioids [53], and decreases postoperative pain [54]. In one study of a feline cardiovascular model, the utilization of electroacupuncture induced improvements in regional cardiac wall motion activity during myocardial ischemia [55]. Furthermore, it was reported that acupressure applied to females undergoing elective cesarean section with spinal anesthesia displayed a reduction in nausea and vomiting [56].

The potential advantages of acupuncture for the treatment of medical conditions continue to be investigated. Interestingly, with initial studies indicating some promising benefits of acupuncture for treatment of multiple medical conditions, the National Institutes of Health Consensus Conference has recommended that acupuncture be included in comprehensive management and may be useful as an adjunct treatment or an acceptable alternative [57]. Finally, limitations in the validation of acupuncture may stem from difficulty creating appropriate randomized, blinded, placebo-controlled clinical studies.

15.4.10 Anesthesia and Temperature Regulation

General and regional anesthesia is often associated with disregulation of body temperature and decreases in core body temperature. During the first hour of anesthesia, it is common for core body temperature to decrease by 0.5–1°C. Most of the body heat lost during anesthesia is via convection and radiation, with some losses due to conduction and evaporation. Principally, anesthetics cause the core body heat to redistribute to the periphery, resulting in a drop in core body temperature [58]. In general, one can consider that, under anesthesia, patients become poikilotherms (minimal ability to thermoregulate). Therefore, multiple modalities to maintain normothermia during surgery have been developed, including forced air warming devices, fluid warmers, ventilator humidifiers, water mattresses and vests, radiant lamps, and warm blankets. Other modalities for warming patients include altering ambient room temperatures and/or the temperatures of irrigation solutions.

Importantly, postoperative hypothermia may be associated with: (1) delayed awakening from general anesthesia; (2) slowed drug metabolism; (3) coagulopathy; (4) vasoconstriction and poor tissue perfusion; (5) increases in blood viscosity; and/or (6) induced shivering. Postoperative shiver may be detrimental in patients with coronary artery disease, as shivering increases oxygen consumption and tachycardia. Currently, meperidine is clinically approved for treatment of excessive shivering in postoperative situations.

15.4.11 Myocardial Preconditioning with Inhalational and Intravenous Anesthetics

Since the initial report by Murray et al. [29] on ischemic preconditioning of dog myocardium, there has been great interest in myocardial preconditioning with pharmacologic agents. This includes myocardial preconditioning with volatile anesthetics such as desflurane [59], isoflurane [60, 61], and sevoflurane [62] as well as intravenous opioid agonists [63, 64]. Pharmacologic preconditioning is not just limited to cardiac tissue; other tissues such as lung, brain,

and skeletal muscle [65] may benefit from preconditioning. In summary, preconditioning with anesthetics may offer life-extending benefits in cardiac, vascular, and/or organ transplantation surgical patients. For more details on this topic, see Chapter 14.

15.4.12 Heart Transplant

With the increasing numbers of individuals surviving heart transplants, the anesthetic management of the patient after a heart transplant procedure requires special considerations. A transplanted heart is initially totally denervated and usually elicits a higher basal heart rate (90–110 beats/min); direct autonomic nervous system effects are absent. Thus, agents such as atropine and glycopyrrolate will not cause an increase in heart rate. Vagal stimulation maneuvers such as carotid massage and oculocardiac reflex are also absent. However, acetylcholinesterase inhibitors such as neostigmine have been associated with severe bradycardia. If bradycardia develops, administration of direct acting cardiac agents such as isoproterenol or epinephrine may be required. The transplanted heart continues to respond to circulating catecholamines, and thus maintenance of cardiac output is aided by increased stroke volume (Frank–Starling relationship); maintaining adequate preload is considered essential in heart transplant patients postoperatively.

15.5 Summary

With the aging population and an increase in health problems such as obesity, diabetes, and coronary artery disease, the perioperative management and induction of general anesthesia in such patients, while providing cardiovascular stability, continues to offer both challenges and new developments in this field. These developments include new anesthesia medications, medical equipment and/or surgical technology, and anesthetic and surgical techniques. Nevertheless, with our growing understanding of inhalational and intravenous anesthetics, the maintenance of stable, physiologic cardiovascular function is common clinical practice today.

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