

Intravenous Anesthesia for the Patient with Left Ventricular Dysfunction

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Patients with heart failure have a diminished cardiac reserve capacity that may be further compromised by anesthesia. In addition to depression of sympathetic activity, most anaesthetics interfere with cardiovascular performance, either by a direct myocardial depression or by modifying cardiovascular control mechanisms. Etomidate causes the least cardiovascular depression. It is popular for induction of anesthesia in cardiac-compromised patients; however, it is not suitable for maintenance of anesthesia because it depresses adrenocortical function. Ketamine has a favorable cardiovascular profile related to central sympathetic stimulation and inhibition of neuronal catecholamine uptake. These counteract its direct negative inotropic effect. In patients with a failing myocardium, however, the negative inotropic effects may be unmasked, resulting in deterioration in cardiac performance and cardiovascular instability. Propofol is the most popular intravenous anesthetic for maintenance of anesthesia. It does have a negative inotropic effect, but the net effect on myocardial contractility is insignificant at clinical concentrations, probably because of a simultaneous increase in the sensitivity of the myofilaments to Ca^{2+} . Propofol protects the myocardium against ischemia-reperfusion injury, an action derived from its antioxidant and free-radical-scavenging properties as well as the related inhibition of the mitochondrial permeability transition pore. For intravenous anesthesia, propofol is always combined with an opioid. Opioids have relatively few cardiovascular side effects and, in particular, do not cause myocardial depression. Indeed, they are cardioprotective, with antiarrhythmic activity, and induce pharmacologic preconditioning of the myocardium by a mechanism similar to the inhalational anesthetics.

The cardiovascular system of a healthy individual has a very large reserve capacity. In contrast, patients with severe left ventricular (LV) dysfunction that results in heart failure function at the very limit of their cardiac reserve. They live on a knife-edge, and any additional stress can easily push them over. Because most anesthetics cause some cardiovascular depression, these patients present anesthesiologists with a very real

challenge. Anesthesia is associated with depression of sympathetic activity, on which many patients with diminished cardiac reserve rely. In addition to this indirect effect, anesthetics interfere with cardiovascular performance, either by a direct myocardial depression or by modifying cardiovascular control mechanisms.

Although heart failure that is due to LV dysfunction is often considered primarily a problem associated with systolic dysfunction, it is now appreciated that diastolic function also significantly influences the overall mechanical performance of the heart. Abnormalities in LV diastolic function can usually be directly linked to systolic dysfunction, but heart failure may result from primary diastolic dysfunction in the absence of, or before the appearance of, systolic dysfunction in a variety of diseases, including ischemic heart disease, hypertrophic obstructive cardiomyopathy, and pressure or volume overload hypertrophy. In fact, many patients with congestive heart failure directly related to diastolic dysfunction have normal systolic performance; therefore, it is important to be aware of the influence of anesthetic drugs on both systolic and diastolic function.

In the healthy heart, cardiac output is regulated primarily by changes in preload LV end-diastolic pressure (LVEDP) and very little by total vascular resistance (afterload). In contrast, the failing heart is much more sensitive to changes in afterload than to preload. As a consequence, arterial vasodilatation improves cardiac output in patients with LV failure, but cardiac output is decreased by venodilators, which include many anesthetics. This effect, coupled with a possible negative inotropic effect by anesthetics, can further deteriorate an already precarious situation. Choosing the anesthetic drug or combination of drugs that minimizes this risk is of the utmost importance in these critically ill patients. This paper reviews the cardiac effects of the most commonly used intravenous anaesthetics.

Etomidate

Etomidate is the intravenous anesthetic that causes the least cardiovascular depression and is a pop-

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ular choice for induction of anesthesia in cardiac-compromised patients. Although in humans etomidate does produce a dose-dependent negative inotropic effect, it is only significant at concentrations considerably in excess of those occurring in clinical practice.^{1,2} De Hert et al³ demonstrated no effect of etomidate on myocardial function in normal or acutely ischemic dog heart segments, and a slight positive inotropic effect of etomidate was reported by Riou et al.⁴ In cardiac muscle that is functionally impaired, etomidate has been studied only in the cardiomyopathic hamster, where there was a slight negative inotropic effect at supra-therapeutic concentrations,⁵ similar to what we have shown for failing human ventricular muscles.

Unfortunately, etomidate is only suitable for use as an induction agent. Etomidate depresses adrenocortical function, by inhibiting the activity of 11- β -hydroxylase, an enzyme necessary for the synthesis of cortisol, aldosterone, and other steroids. Even after a single dose, adrenal suppression persists for 5 to 8 hours. Because of this, the use of etomidate for maintenance of anesthesia is not recommended.

Ketamine

Ketamine, because it maintains hemodynamic stability, is often used for induction of anesthesia in high-risk patients. Unlike most other intravenous anesthetics, ketamine also produces analgesia, and this nociceptive action has led to an increased interest in its use for maintenance of anesthesia in combination with other agents. The favorable cardiovascular profile of ketamine is related to central sympathetic stimulation and inhibition of neuronal catecholamine uptake. These effects counteract the direct negative inotropic effect of ketamine on the myocardium. The net result in a healthy individual is a positive inotropic effect, with an increase in arterial blood pressure, heart rate, and cardiac output. However, the failing myocardium has reduced ability to increase contractility when exposed to ketamine, even in the presence of increased β -adrenergic stimulation.⁶ In such patients, and especially in the presence of adrenoceptor blockade, the negative inotropic effects may be unmasked, resulting in deterioration in cardiac performance and cardiovascular instability.⁷

Ketamine is a chiral compound, and until recently was only available as the racemic mixture.

In Europe the S(+) isomer has been clinically available for a number of years. The advantages of S(+)-ketamine include equivalent hypnosis and analgesia at lower plasma concentrations as well as fewer side effects such as agitated behavior and psychomimetic emergence reactions. This isomer also appears to cause less myocardial depression than the racemate.⁸

Racemic ketamine has been reported to block ischemic preconditioning of the myocardium, but this action was stereospecific, caused by the R(-) isomer, but not by S(+)-ketamine.⁹ In contrast, however, Hanouz et al¹⁰ found that, in vitro, both racemic and S(+)-ketamine preconditioned isolated human myocardium. Ketamine-induced preconditioning involved, at least in part, activation of potassium adenosine triphosphate (K_{ATP}) channels and stimulation of α - and β -adrenergic receptors.

Propofol

Propofol is arguably the most popular intravenous anesthetic for induction and maintenance of anesthesia. In a recent survey, propofol in combination with an opioid was the most popular choice of anesthetic techniques for off-pump coronary artery bypass grafting operations.¹¹ The properties that make it attractive are fast onset and offset of hypnotic action and a short, context-sensitive half time. Although propofol is associated with some degree of cardiovascular depression, manifest mainly by a reduction in arterial blood pressure, current evidence is that this is a result of a decrease in sympathetic tone and a reduction in vascular resistance, and not to reductions in myocardial contractility.^{2,12} Numerous studies have demonstrated that propofol does not cause significant inotropic depression in most species, including humans, at clinically relevant concentrations.^{2,13,14} Although it does have a negative inotropic effect, partly mediated by a decreased uptake of calcium into the sarcoplasmic reticulum, the net effect of propofol on myocardial contractility is insignificant at clinical concentrations, probably because of a simultaneous increase in the sensitivity of the myofilaments to Ca^{2+} .^{13,15,16} The increase in myofilament Ca^{2+} sensitivity involves a protein kinase C pathway.¹⁷

Mather et al¹⁸ compared the direct cardiac effects of thiopental and propofol in awake, instrumented sheep, by infusing increasing doses of the

drugs directly into the left coronary arteries. Both thiopentone and propofol caused rapid, dose-related myocardial depression, as assessed by decreases in dP/dt_{\max} and stroke volume. There were no differences between the enantiomers of thiopentone or between thiopentone and propofol. As expected, drug concentrations in the coronary sinus blood were at least 10 times higher than in arterial blood (which was far lower than those associated with anesthesia. The blood concentrations of propofol decreased more slowly than those of thiopentone, probably caused by the higher heart tissue/blood distribution coefficient of propofol (5.94)¹⁹ compared with thiopentone (0.36).²⁰ However, the negative inotropic effects of both drugs had returned to baseline levels when drug concentrations were still considerably higher than those associated with anesthesia.

The question arises, however, about the effects of propofol in patients with severe LV dysfunction. The experimental evidence in this area is conflicting, possibly reflecting different experimental setups and differences in the species studied. In rabbits with compensated cardiomyopathy, propofol had a negative inotropic effect only at supra-clinical concentrations.²¹ Propofol did not alter myocardial contractility in rats²² or in hamsters with congenital hypertrophic cardiomyopathy,²³ or in isolated human myocardium taken from patients with either failing or nonfailing hearts.¹⁵ In contrast, a study that used left ventricle trabeculae from pigs with pacing-induced congestive heart failure suggested that the myocardial depressive effects of propofol might be greater in the presence of LV dysfunction than in healthy hearts.²⁴

The major hemodynamic consequences of propofol anesthesia in the setting of LV dysfunction due to cardiomyopathy are venodilatation and LV preload reduction.²⁵ This results in a decrease in LVEDP and a reduction in chamber dimensions. Such changes do not appear to compromise global LV performance and indeed may be beneficial.²⁶ Pagel et al²⁶ studied the effects of propofol in dogs with dilated cardiomyopathy induced by continuous pacing at 240 beats/min for up to 3 weeks. Anesthesia was induced with propofol 5 mg/kg and maintained with an hourly infusion of propofol at 25, 50 or 100 mg/kg. Propofol reduced left ventricular preload, afterload and regional chamber stiffness, caused a dose-related direct negative inotropic effect, and impaired early diastolic LV filling. However, the changes in dogs with dilated cardiomyopathy

were similar to those found by the same group in healthy dogs.²⁵ The net result was a decrease in myocardial oxygen consumption as a result of the reduction in LV preload, afterload, and contractility. In intensive care patients, sedation with propofol or midazolam did not alter LV diastolic performance either in healthy patients or in those with pre-existing diastolic dysfunction.²⁷

Extensive experimental data now indicate that volatile anesthetics and opioids protect the myocardium from ischemia and reperfusion injury, as shown by decreased infarct size and a more rapid recovery of contractile function on reperfusion. The mechanism is thought to mimic ischemic preconditioning, a phenomenon whereby subjecting the heart to brief ischemic episodes protects it against the deleterious effects of subsequent prolonged ischemia and reperfusion. The protection resulting from anesthetic drugs has been termed *anesthetic preconditioning*.²⁸⁻³⁰ The most widely held view of the mechanism underlying this protection is adenosine receptor-mediated protein kinase C activation leading to the opening of mitochondrial K_{ATP} channels.

Propofol protects the myocardium against injury by ischemia and reperfusion,³¹⁻³⁴ but does so by mechanisms different from the volatile anesthetics.³⁵ It does not, for example, affect K_{ATP} channels at clinically relevant concentrations,³⁶ although it does inhibit specific subunits of the channel at concentrations 5 to 15 times higher than those encountered during clinical anesthesia.³⁷

Free oxygen radicals and reactive oxygen species are critical mediators of myocardial injury during ischemia and reperfusion.³⁸ Propofol has a chemical structure similar to that of phenol-based free-radical scavengers such as vitamin E. It scavenges free oxygen radicals, reduces disulfide bonds in proteins, and inhibits lipid peroxidation induced by oxidative stress in isolated organelles.³⁹⁻⁴¹ There is experimental evidence that the cardioprotective effects of propofol derive, at least in part, from these antioxidant and free-radical-scavenging properties. Propofol attenuates the mechanical derangements and lipid peroxidation induced by hydrogen peroxide and preserves myocardial ATP content.⁴²

One mechanism by which propofol offers myocardial protection is by inhibiting the mitochondrial permeability transition (MPT) pore.⁴³ The MPT involves the opening of nonspecific pores in the inner mitochondrial membrane under conditions of increased oxidative stress, high intracel-

lular $[Ca^{2+}]$, low levels of ATP, and other conditions associated with ischemia-reperfusion, and is one of the major causes of reperfusion injury.⁴⁴⁻⁴⁷ Opening of the mitochondrial permeability transition pore uncouples mitochondria and interferes with the synthesis of ATP and other mitochondrial functions. Ischemic- and anesthetic-induced preconditioning also involves inhibition of the opening of this pore.^{45,48-50}

Opioids

Opioids are an essential component of general anesthesia. In addition to analgesia, they act synergistically with intravenous anesthetics, allowing a reduction in the doses required. Because they have relatively few cardiovascular side effects, and in particular do not cause myocardial depression, they are especially valuable for patients with compromised ventricular function. In addition convincing evidence exists that opioids have definite cardioprotective actions. They have antiarrhythmic activity, especially in arrhythmias associated with ischemia-reperfusion injury. This is thought to be related to prolongation of the cardiac action potential duration, an action related to δ - and κ -opioid receptors.⁵¹ Morphine also hyperpolarizes the cardiac resting membrane potential by increasing the inwardly rectifying K^+ current (I_{K1}), an action apparently not mediated by opioid receptors.^{52,53}

Morphine and other opioids induce pharmacologic preconditioning of the myocardium.⁵⁴⁻⁵⁶ The underlying mechanism involves K_{ATP} channels, as with the inhalational anesthetics.⁵⁷⁻⁵⁹ Combined administration of isoflurane and morphine enhances the protection against myocardial infarction to a greater extent than either drug alone. This beneficial effect is mediated by mitochondrial K_{ATP} channels and opioid receptors *in vivo*.⁶⁰

Most of the evidence suggests that opioid-induced preconditioning is mediated by δ -opioid receptors, in particular the δ_1 -subtype.⁶⁰⁻⁶² Although morphine is predominantly a μ -receptor agonist, it does have some activity at the δ -opioid receptor. Remifentanyl and fentanyl, even though they have much weaker activity at κ - and δ -opioid receptors than morphine, both induce preconditioning.^{56,63} In rat hearts, the preconditioning by remifentanyl is mediated by cardiac κ - and δ -opioid receptors, which appear to trigger K_{ATP} chan-

nels and protein kinase C, both involved in the final pathway for preconditioning.^{56,64,65} Late cardioprotection induced by morphine seems to involve nuclear transcription factor κB in addition to opioid receptors.⁶⁶

Conclusion

The combination of propofol and an opioid is one of the most popular techniques for intravenous anesthesia for patients with a failing heart caused by left ventricular dysfunction. Although propofol appears to cause minimal myocardial depression in the healthy heart at clinically relevant concentrations, the risk of depression may be greater in the failing heart. Propofol-induced cardiac and peripheral vascular depression is concentration related; therefore, the drug should be administered slowly. This approach also allows the cardiovascular system to compensate for the changes caused by anesthesia.

The combination with opioids, which themselves causes little or no cardiovascular depression, allows for a significant reduction in the dose of propofol required for adequate anesthesia, because of the synergistic interactions between these classes of drugs. This dose reduction decreases further the risk of depression by propofol. The combination of propofol and an opioid has additional potential advantages, especially in patients at risk of ischemia-reperfusion injury. The cardioprotective effects of these drugs rely on different mechanisms, however. Opioids induce preconditioning similar to the volatile anesthetics, whereas the cardioprotective effects of propofol are related to its antioxidant and free-radical-scavenging property.

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