

Rationale for Propofol Use in Cardiac Surgery

Lukasz J. Krzych, MD, PhD,* Dariusz Szurlej, MD, PhD,† and Andrzej Bochenek, MD, PhD*

PROPOFOL IS A COMMONLY USED intravenous anesthetic agent. Chemically, propofol is a lipophilic, sterically hindered alkylated phenol that is a very weak acid.^{1,2} Pharmacokinetic and pharmacodynamic properties make propofol a useful drug in everyday anesthesia with rapid and clear emergence, precise control of the level of sedation, and lack of cumulative effects even after prolonged administration.¹⁻⁴ Although the terminal half-life of propofol is long, recovery is rapid because of the slow mobilization from the highly lipophilic tissue compartment.¹⁻⁴

The indications for propofol use include the induction and maintenance of anesthesia for most surgical procedures, and it can be extended into the postoperative setting or intensive care unit for sedation. Rapid redistribution and elimination make propofol valuable for short procedures and ambulatory surgery.¹⁻⁴ Moreover, the agent possesses antiemetic, antipruritic, and anticonvulsant properties.¹⁻⁴

Propofol is also widely used in subjects with cardiac disease.^{3,4} An anesthetic drug for cardiac surgery should provide intraoperative amnesia, analgesia, and hemodynamic stability with minimal direct myocardial depression and rapid recovery; ideally, with weak inotropic support.⁴ Pharmacokinetic properties of propofol favor its use in clinical practice in cardiac surgery patients.³⁻⁵ The induction of anesthesia with an opioid-benzodiazepine/etomidate combination followed by a maintenance infusion of propofol supplemented with an inhalation agent or opioid analgesic or both as needed are considered acceptable for patients undergoing routine cardiac surgery.³ Apart from general anesthesia, major indications for propofol use are sedation during painful procedures (eg, cardioversion), sternal wound debridement, central venous catheter insertion, and transesophageal echocardiography (Table 1).^{3,4}

Propofol is safely administered to patients with cirrhosis and renal failure, with no impairment in its clearance.¹ However, in comparison with other agents, the induction dose of propofol has a relatively higher prevalence of respiratory depression, short-lived apnea, and arterial blood pressure (estimated even at

30%-40%) decrease.¹⁻³ Although propofol has a negative impact on systemic blood pressure in cardiac surgery patients,⁶⁻⁹ clinical studies have shown that the agent, in combination with an opioid and adequate intravenous fluid supplementation, is a safe option for such procedures.⁵ The other unpleasant effect of propofol is pain on injection, which can be dealt with either by a prior injection of a small amount of local anesthetic (eg, lidocaine) or by mixing it in the same syringe.¹⁻⁴ The previously mentioned effects are age, but not sex, dependent; the dose should be reduced in elderly patients and increased in children.^{1-5,10} Obesity has no influence on the clinical duration of the effects of propofol (Table 2).²

A major concern is the propofol infusion syndrome (PRIS), which is rare but may be fatal if not identified early.¹¹⁻¹⁴ The review by Wysowski and Pollock¹¹ reported 36 cases of PRIS, including 15 pediatric and 21 adult patients, described in the literature from 1989 to 2005; and Kam and Cardone¹² found 61 patients with PRIS, 32 pediatric and 29 adult cases, described up to 2006. PRIS is characterized by metabolic acidosis, lactic plasma, hepatomegaly, rhabdomyolysis, and electrocardiographic changes (eg, right bundle-branch block, acute bradycardia leading to asystole, and other cardiac arrhythmias), with no structural cardiac lesions or abnormalities in contractility on echocardiography.^{1-5,12,13} Vasile et al¹⁴ suggested 2 groups of mechanisms directly related to the occurrence of PRIS, namely priming and triggering factors. The first group stems from severe critical illness (eg, multiple-organ failure) and central nervous system activation, resulting in the production of catecholamines and glucocorticosteroids.^{12,13} PRIS is believed to be triggered by a dose of propofol exceeding 4 mg/kg/h, time of infusion longer than 48 hours, and implementation of concomitant infusions of endogenous catecholamines and steroids.^{12,13} PRIS should be considered a potential serious adverse effect in high-risk cardiac surgery patients who often require catecholamine support and prolonged mechanical ventilation with long-lasting sedation.

Propofol has been suggested as a useful adjunct to cardioplegic solutions because of its potential protective effect on the heart mediated by a decrease in ischemia-reperfusion injury in clinically relevant concentrations.¹⁵ Nevertheless, clinicians should be aware that cardiopulmonary bypass (CPB) alters its concentration by hemodilution, reduces clearance caused by changes in renal and hepatic blood flow, changes in unbound compared with bound drug, absorption by CPB apparatus, and hypothermia.^{6,7,15}

Therefore, the authors have attempted to describe a rationale for propofol use in cardiac surgery. The aim of the article is to summarize data from the literature regarding the impact of the

From the *1st Department of Cardiac Surgery and †Department of Cardiac Anesthesia and Postoperative Intensive Care, Medical University of Silesia, Katowice, Poland.

Address reprint requests to Lukasz J. Krzych, MD, PhD, 1st Department of Cardiac Surgery, Medical University of Silesia, 47 Ziolkowa Street, 40-635 Katowice, Poland. E-mail: l.krzych@wp.pl

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Table 1. Indications for Propofol Use in Cardiac Patients

Fast-track anesthesia; induction and maintenance	Sedation in cardiac ICU patients
Sedation during transesophageal echocardiography	Arterial/venous catheterization
Sedation for cardioversion	Sternal (other) wound debridement

Abbreviation: ICU, intensive care unit.

agent on the heart, vessels, and blood, including the inflammatory system.

PROPOFOL AND THE HEART

Myocardial Contractility

The influence of propofol on the heart has been investigated in several studies. Its negative effect on myocardial contractility and hemodynamic status has been revealed both in animal and human (in vitro) models.¹⁶⁻²⁶ The negative inotropic impact was found in nonfailing (nonischemic) and failing (acute ischemic) myocardium in a dose-dependent manner, but only at concentrations higher than those typically used in clinical practice.^{24,25} A decrease in cardiac function was measured by several hemodynamic parameters, including left ventricular end-systolic pressure, end-diastolic length and systolic shortening,²⁴ myocardial contractility, and a decrease in mean arterial pressure.²⁵ Alterations in left ventricular preload, afterload, and regional chamber stiffness with impaired early-diastolic left ventricular filling²⁶ and wall-thickening fraction of the myocardium also were found (Table 3).²⁶

Direct myocardial and coronary vascular responses to propofol were studied by Stowe et al.²⁷ They found that propofol moderately depressed cardiac function and markedly attenuated autoregulation by causing coronary vasodilatation. In this experimental in vitro study,²⁷ at concentrations below 10 $\mu\text{mol/L}$, no significant changes were observed; beyond 50 $\mu\text{mol/L}$, propofol caused progressive but differential decreases in heart rate, atrioventricular conduction time (leading to atrioventricular dissociation), left ventricular pressure, $+LVdP/dT_{\text{max}}$ (change in the maximal positive derivative of left ventricular pressure), percent oxygen extraction, and myocardial oxygen consumption of isolated hearts.

The adverse effects of propofol in elderly and high-risk patients or those with impaired left ventricular ejection fraction are more pronounced in quantity compared with persons with a preserved cardiac function and lower perioperative risk.^{22,28} Nevertheless, no impact on the requirement for inotropic support at the termination of CPB was found during propofol anesthesia,^{29,30} and the simultaneous administration of calcium

Table 2. Side Effects of Propofol

Vasodilatation with arterial blood pressure decrease	PRIS
Respiratory depression with apnea	Histamine release
Pain on injection	Venous thrombosis/phlebitis
Excitatory phenomena	Hypertriglyceridemia

Table 3. Propofol and the Cardiovascular System

Myocardial contractility	Negative inotropic effect ↓ Left ventricular loading (↓ LVESP, ↓ LVEDP, ↓ SF, ↓ WT) ↓ HR
Electrophysiology	No impact on QTc interval ↓ HR and ↓ HRV (↓ SA conduction) Atrial fibrillation inhibition (↓ AV conduction, His-Purkinje system inhibition)
Molecular mechanisms	↓ Sympathetic activity α - and β -adrenoceptor response modification L-type calcium cardiac inhibition Receptors' sensitivity modulation
Cardioprotective effects	↓ Oxidative stress (↓ plasma inflammatory cytokine levels, ↓ oxygen-free radicals, ↓ lipid peroxidation, ↓ chemotactic activity, ↓ leukocyte infiltration) ↓ Ischemia-reperfusion injury ↓ Cardiac troponin I concentration
Vessels	Arterial dilatation (pulmonary and peripheral) Venous dilatation (pulmonary and peripheral)

Abbreviations: ↓, decrease; LVESP, left ventricular end-systolic pressure; LVEDP, left ventricular end-diastolic pressure; SF, shortening fraction; WT, wall thickening; HR, heart rate; HRV, heart rate variability; AV, atrioventricular; SA, sinus atrial; QTc, control QT interval.

chlorate during the induction of anesthesia may diminish the negative influence of propofol on cardiac function.³¹

Molecular Mechanisms

Previous observations depicted multiple possible biologic mechanisms linking propofol with cardiac depression including a decrease in sympathetic activity, vasodilatory effect, and modifications of α - and β -adrenoceptor binding and L-type calcium cardiac inhibition.³²⁻³⁶ In an experimental study on rat papillary muscle, Zhou et al.³² found that propofol acted as a calcium channel blocker and had a direct impact on calcium channel proteins to diminish voltage-dependent L-type calcium current. Another explanation for propofol's impact on the heart included the antagonism of β -adrenoreceptor binding and alteration in receptor responsiveness to catecholamines in a dose-dependent (ranged from 25 to 200 $\mu\text{mol/L}$) and competitive manner.³³ Lejay et al.³⁴ showed that at a concentration of 45 $\mu\text{mol/L}$, the agent abolished the positive effect of α - but not β -adrenoreceptor stimulation. Supportive data were published by Sprung et al.³⁵ who found that the impact of propofol was reversible with β -adrenergic stimulation and mediated by reduced calcium uptake into the sarcoplasmic reticulum. As far as adrenergic-receptor competition is concerned, the addition of propofol to dopamine may prevent dopamine-induced apoptosis while maintaining positive inotropy by improving dopamine-mediated diastolic function after ischemia.³⁶

Besides the above results from in vitro studies, the clinical evidence for propofol use in cardiac surgery patients is limited. The small number of in vivo studies, especially in humans, is a serious limitation. However, propofol has shown no significant negative inotropic effect in the clinically used concentrations.^{34,37}

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