Rationale for Propofol Use in Cardiac Surgery
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Propofol is a commonly used intravenous anesthetic agent. Chemically, propofol is a lipophilic, sterically hindered alkylated phenol that is a very weak acid.1-3 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 antiepileptic, 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,5-9 clinical studies have shown that the agent, in combination with an opioid and adequate intravenous fluid supplementation, is a safe option for such procedures.7 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 al15 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 cardiopulmonary 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

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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. 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. A decrease in cardiac function was measured by several hemodynamic parameters, including left ventricular end-systolic pressure, end-diastolic length and systolic shortening, myocardial contractility, and a decrease in mean arterial pressure. Alterations in left ventricular preload, afterload, and regional chamber stiffness with impaired early-diastolic left ventricular filling and wall-thickening fraction of the myocardium also were found.

Direct myocardial and coronary vascular responses to propofol were studied by Stowe et al. They found that propofol moderately depressed cardiac function and markedly attenuated autoregulation by causing coronary vasodilatation. In this experimental in vitro study, at concentrations below 10 μmol/L, no significant changes were observed; beyond 50 μmol/L, propofol caused progressive but differential decreases in heart rate, atrioventricular conduction time (leading to atrioventricular dissociation), left ventricular pressure, +LVdP/dTmax (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 were more pronounced in quantity compared with persons with a preserved cardiac function and lower perioperative risk. Nevertheless, no impact on the requirement for inotropic support at the termination of CPB was found during propofol anesthesia, and the simultaneous administration of calcium chloride during the induction of anesthesia may diminish the negative influence of propofol on cardiac function.

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 calcium inhibition.

In an experimental study on rat papillary muscle, Zhou et al 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-adrenoceptor binding and alteration in receptor responsiveness to catecholamines in a dose-dependent (ranged from 25 to 200 μmol/L) and competitive manner. Lejay et al showed that at a concentration of 45 μmol/L, the agent abolished the positive effect of α- but not β-adrenoceptor stimulation. Supportive data were published by Sprung et al 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.

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.
Electrophysiology

Propofol has an impact on electrophysiologic findings in patients. Numerous studies revealed that during both the induction and maintenance of total intravenous anesthesia, propofol significantly shortened the QT interval. Additional data suggested that propofol infusion may prolong the corrected QT (QTc) interval but only in subjects with a normal QTc interval, whereas it can be shortened in patients with a prolonged QTc interval at baseline. However, the effects of the agent on the QT interval are generally small and to be identified in an intraoperative electrocardiogram. This is consistent with a study that showed no influence of propofol on QTc in healthy children (Table 3).

Propofol infusion is also believed to decrease both heart rate and heart rate variability, predominantly by a reduction in cardiac parasympathetic tone. Wu et al. found in an experimental study that the atrioventricular conduction interval may be lengthened by propofol in a dose-dependent and age-related manner, even at low concentrations (3 μmol/L). At higher concentrations, propofol significantly prolonged the atrioventricular conduction interval (10 μmol/L and more), slowed conduction through the atrial tissue (SA interval) and the His-Purkinje system (HV interval), decreased the spontaneous heart rate, and prolonged the AV Wenckebach cycle length (all at concentrations of 30 μmol/L and higher). These findings are consistent with in vivo studies of Cervigón et al. who reported that anesthesia with propofol may slow atrial fibrillation and Owczuk et al. who revealed a decrease in P-wave dispersion after propofol anesthesia.

Taking the previously described data into account, clinicians should be cautious of propofol’s electrophysiologic influence on patients with delayed or blocked conduction in the heart. Propofol can be a reasonable choice for cardiac surgery patients with atrial fibrillation, but it should be used with caution during cardioversion because of hypotension and an increase in energy required for successful effect of the procedure.3

PROPOFOL AND THE INFLAMMATORY SYSTEM

Cardiopulmonary bypass is one of the acknowledged causes of a complex systemic inflammatory response during cardiac surgery, and it may contribute to postoperative complications and even multiple-organ dysfunction. Inflammation, as a result of cellular oxidative stress and myocardial injury, is mediated by several agents including interleukins 6, 8, and 10; high-sensitivity C-reactive protein; tumor necrosis factor α; and the release of other inflammatory agents. Thus, results suggesting that propofol has antioxidative properties and may be of great importance because of its ability to reduce ischemia-reperfusion injury in coronary artery bypass graft (CABG) surgery patients.

In an experimental study, propofol anesthesia was directly related to a significant decrease in oxidative activity measured by malondialdehyde levels in plasma and pulmonary lavage. In a study by Corcoran et al., it was found that in patients undergoing CABG surgery, clinically relevant concentrations of propofol attenuated free radical-mediated and inflammatory components of myocardial reperfusion injury including modulation of serum concentration of malondialdehyde; systemic concentrations of interleukins 4, 6, 8, and 10; and systemic leukocyte functions. In several investigations, an antioxidative effect of propofol was shown via mechanisms involving decreases in neutrophil infiltration, plasma inflammatory cytokine levels, oxygen free-radicals production, and lipid peroxidation. In vitro studies also showed that propofol depresses the immunologic reaction to bacterial challenge as well as chemoattractive activity.

There are some supplementary data indicating that propofol may also protect erythrocytes against both oxidative and physical stress, suggesting its efficacy and usefulness as an antioxidant. In the latter study, propofol increased erythrocytes’ membrane fluidity, thereby increasing their resistance to physical and hemodynamic stress. Moreover, the protective effect of propofol on oxidation in red blood cell membranes was enhanced by another antioxidant, ascorbic acid.

Hypertriglyceridermia is common in propofol-treated patients, and may be associated with the PRIS occurrence. In a study by Oztekin et al., propofol was found to increase triglycerides and very low-density lipoprotein concentrations, but not glucose concentrations a few hours after CABG surgery. Reported measures of the lipid profile could become a valuable marker for monitoring this side effect.

CARDIOPROTECTIVE EFFECTS OF PROPOFOL

Propofol is believed to possess a cardioprotective effect that derives in part from its antioxidative properties and free radical scavenging properties. These properties were described in several studies. Zou et al. and Xia et al. reported the role of propofol in the reduction of cardiac troponin I concentration in clinical investigations. Myocardial protection by the agent may involve the activation of protein kinase C. It is suggested that propofol increases the sensitivity of myofibrillar actomyosin ATPase to calcium by increasing intracellular pH via the protein kinase C–dependent activation of Na⁺-H⁺ exchange. In diabetic cardiomyocytes, propofol was found to decrease myofilament Ca²⁺ sensitivity via a protein kinase C–nitric oxide synthase–dependent pathway. Supplementary data revealed that infusion of the agent significantly reduced the number of in vitro apoptotic cells or prevented dopamine-induced apoptosis of the heart cells after ischemia in an animal model.

On the basis of registry data from 10,535 surgical procedures comparing the influence of sevoflurane and propofol anesthesia on clinical outcomes, Jakobsen et al concluded that propofol anesthesia may be superior in patients with severe ischemia, cardiovascular instability, or in acute/urgent surgery because of its cardioprotective properties. The 30-day mortality was comparable among all patients from the sevoflurane and propofol groups (2.84% vs 3.3%, p = 0.18) as well as in a subgroup of subjects with unstable angina (5.48% vs 4.8%, p = 0.58) or recent myocardial infarction (4.91% vs 4.72%, p = 0.93). Sevoflurane anesthesia resulted in a decrease in mortality in patients with stable angina and no history of myocardial infarction compared with the propofol group (2.28% vs 3.14%, p = 0.01). In the cited study, propofol anesthesia had its most important beneficial influence on 30-day mortality in urgent CABG procedures (16.23% vs 8.19%, p = 0.03). However, there was no confirmation of a protective effect or
outcome advantage of propofol in a multicenter prospective randomized study in 150 CABG surgery patients by Triapepe et al. The postoperative concentration of troponin I was 2 times higher in anesthetized subjects from the propofol group (median = 5.5 ng/dL) compared with patients from the desflurane group (median = 2.5 ng/dL). Moreover, patients receiving a volatile anesthetic had a reduced need for postoperative inotropic support (32% vs 41.3% in the propofol group, p = 0.04). Consistent findings relating to differences between propofol and sevoflurane anesthesia were shown by De Hert et al in a group of 20 coronary artery surgery patients. They reported that for the sevoflurane group, troponin I concentrations remained below the cutoff value of 2 ng/mL throughout the 36-hour observation period, but, in the propofol group, an elevation in troponin I concentrations was found 12 hours after CPB, with a peak at 24 hours followed by a decrease in the next 12 hours. Kohro et al found that the administration of propofol may also hamper previously reported cardioprotective effects of inhalation anesthetics (eg, isoflurane and sevoflurane) as well.

PROPOFOL AND THE BRAIN

Neurologic deterioration after CPB including complications of stroke, transient ischemic attacks or cognitive dysfunction is frequent. The results of longitudinal assessment of neurocognitive function after CABG surgery revealed that the incidence of cognitive decline occurred in more than half the patients (53%) at discharge and remained after 5 years (46%). Moreover, cognitive function at discharge was a major predictor of cognitive decline at 5 years. The etiology of neuropsychologic deterioration is complex and includes microembolization, altered cerebral perfusion, temperature perturbations, cerebral edema, blood-brain barrier dysfunction, and a generalized or localized inflammatory response.

Proper perioperative management is required to reduce neurologic decline. The current literature describes several potential neuroprotective interventions including perioperative propofol administration. It has been suggested that the neuroprotective effect of propofol is attributed to its global and regional (at brain level) antioxidative properties that were mentioned earlier, however, its role is believed to be beneficial only in limiting the size of cerebral damage rather than the incidence of infarction. The protective role of the decreased cerebral mean arterial pressure caused by vasodilatation has been neglected. Propofol’s protective effect may be mediated by microembolic delivery reduction by way of decreasing cerebral blood flow, but this has not yet been confirmed in clinical trials (Table 4).

The decrease in cerebral metabolic rate and oxygen consumption during propofol infusion on CPB may potentially be of some importance. It was revealed that in patients undergoing CABG surgery, induction with propofol resulted in a 51% decrease in cerebral blood flow, a 36% reduction of cerebral metabolic rate and oxygen consumption, and a 25% decrease in cerebral perfusion pressure. Newman et al described a significant reduction in cerebral blood flow, cerebral oxygen delivery, and cerebral metabolic rate in response to propofol anesthesia during nonpulsatile normothermic and hypothermic phases of CPB. Burst-suppression doses of propofol during moderate hypothermic CPB were also found to decrease cerebral blood flow by 35% and cerebral oxygen consumption by 10%.

Roach et al, however, reported no association between a reduction in cerebral metabolic suppression or a reduction in cerebral blood flow and neurologic or neuropsychologic dysfunction after propofol anesthesia during CPB. By using a battery of neurologic and neuropsychologic tests in 225 patients, they showed that, compared with a sufentanil group, patients in the propofol-sufentanil group tended to have an even higher incidence of adverse neurologic outcomes on postoperative days 1 and 2 (40% vs 25%, p = 0.06) and at 5 to 7 days (18% vs 8%, p = 0.07). These differences resolved after 50 to 70 days (6.2% vs 6.2%, p = 0.8). The incidence of neuropsychologic deficits was comparable between the propofol and sufentanil groups (91% vs 92%, p = 0.73 at days 5-7, and 52% vs 47% at days 50-70, p = 0.58, respectively), and neither the severity nor the prevalence or neuropsychologic outcomes differed among patients.

In view of the previously described information, the clinical relevance of propofol use to prevent cognitive deterioration in cardiac surgery needs to be confirmed in larger prospective studies. The lack of neuroprotection in some studies may be caused by the fact that either propofol has no neuroprotective effects or that appropriate perioperative treatment diminishes any protective impact of the agent significantly (eg, proper oxygenation, glucose control, arterial filters and membrane oxygenators, and concomitant volatile anesthesia). Moreover, the methodology of the cited studies varies significantly and presents a serious limitation to reaching a conclusion.

VASCULAR EFFECTS OF PROPOFOL

From a cardiac surgeon’s point of view, the influence of propofol on the biologic tissues used for vascular grafts (CABG) and vasoregulation is crucial. Early postoperative graft failure attributed to spontaneous contraction or spasm requires improvements in preventative strategies and effective treatment. Thus, the potential vasodilating effect of propofol may be crucial during the perioperative period. Unfortunately, there is still a discrepancy between the number of animal investigations and clinical studies concerning the influence of propofol on systemic vasoregulation.

Animal Studies

The well-known hypotensive effect of propofol may be mediated via multiple mechanisms including its action on peripheral vasculature (arterial and venous vasodilatation) as well as a decrease in myocardial contractility, resetting of baroreflex

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<td>EEG burst suppression ↓</td>
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<td>↓ Cerebral metabolic rate and oxygen consumption</td>
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Abbreviations: ↓, decrease; EEG, electroencephalography.
activity, and inhibition of the sympathetic nervous system outflow. The primary cause of reduction in blood pressure differs between individual studies. Data from the literature raise questions about the molecular background of vasodilatation caused by propofol, and information published about this issue is inconsistent. A number of articles confirm that vasodilatation is endothelium-dependent and uses the activation of numerous endothelial agents. However, some contradictory data revealed that the effect is mediated in an endothelium-independent manner. It was also found that propofol may cause significant vasodilatation in both endothelium-intact and endothelium-denuded tissue. Thus, further investigations focused on potential mechanisms of the anesthetic are needed.

Effects of the agent on arterial and venous tissue showed the changes to be dose dependent. In a study by Stowe et al, propofol, administered at the highest concentration (100 μmol/L), increased coronary flow by 57% ± 10%, decreased myocardial oxygen consumption by 37% ± 5%, and increased oxygen delivery/myocardial oxygen consumption ratio by 150% ± 15%. Between concentrations of 100 μmol/L and 1 mmol/L, coronary flow was maximally increased and myocardial oxygen consumption was maximally decreased by the agent. In endothelium-intact arterial rings precontracted with PGF2α, propofol did not change vascular smooth muscle tone in low concentrations (1 μmol/L-10 μmol/L), but at high concentrations (100 μmol/L-100 mmol/L) it produced a significant relaxation compared to endothelium-denuded rings.

There is some evidence suggesting a quantitative role of vascular diameter during the process of relaxation. Coughlan et al investigated the influence of propofol in canine coronary arteries and showed that small arteries showed greater vasodilatation (at similar concentrations) than larger arteries. Vasodilating properties of propofol were more pronounced in distal than in proximal vessels.

**Human Studies**

The impact of propofol on the vessels seems comparable in animals and humans, but the issue of the underlying mechanism is still controversial. In a study by Klockgether-Radke et al, propofol administered at high concentrations (100 μg/mL) caused an endothelium-independent relaxation on porcine and human coronary artery segments to a similar extent (−32% up to −49% and −11% to −67%, respectively). Wallestedt et al investigated the relaxant effects of propofol on smooth muscle tonus in human omental arteries and veins, and found that propofol induced relaxation of both vessels in an endothelium-independent manner. Contradictory data showed that propofol-related relaxation may be endothelium-dependent in omental and radial arteries and omental veins, and Moreno et al found that the vasodilatation after propofol administration was similar in intact and denuded endothelium mesenteric rings.

**Pulmonary Vasoregulation**

Park et al showed that propofol also promoted marked vasodilatation in pulmonary arteries. In the endothelium-intact aortic and pulmonary artery rings, the initial vasodilatation at the propofol concentration between 30 and 100 μmol/L showed gradual and partial recovery over 15 minutes, and, at a concentration of 300 μmol/L, it caused sustained relaxation. Moreover, endothelium-denuded rings and L-NAME pretreated endothelium-intact rings showed constant and sustained vasodilatation with all propofol concentrations. The propofol vehicle had no dilating effect on vascular rings and indomethacin pretreatment decreased relaxation, the latter suggesting a mediating role of endothelium in the process. Similar findings relating to the underlying mechanism were reported on a canine and rat model. Moreover, the vasorelaxing response to propofol was seen in extrapulmonary but not in intrapulmonary arteries. Contradictory information was revealed by Horibe et al, who found that propofol caused dose-dependent and endothelium-independent pulmonary vasorelaxation.

**CONCLUSIONS**

In summary, for cardiac anesthesia, propofol is useful for the induction and maintenance of anesthesia, and sedation as well, mainly because of its favorable pharmacokinetic properties. However, the benefits of its use are still theoretic, and outcome advantages in cardiac surgical patients are unconvincing. Clinicians should be aware of serious adverse effects of propofol including hemodynamic instability, respiratory depression, and PRIS. Although propofol seems to be a promising vasodilator for the treatment of perioperative spasm of coronary artery grafts, there is a paucity of epidemiologic data regarding cardiac and neuroprotective effects of the agent. Further investigations are required to explore the molecular mechanisms of propofol more precisely and to extend indications for its use in cardiac anesthetic practice.

**REFERENCES**


RATIONALE FOR PROPOFOL USE IN CARDIAC SURGERY