Review Article

Effect of Propofol in the Cardiovascular System and its Related Mechanism Research Progress

X Zhang[1], Ke-Ying Wei[2], D Huang[1]

[1]Department of Cardiology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, [2]School of Medicine, Shanghai Jiao Tong University, Shanghai, China

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Abstract

Propofol is the most widely used short-acting intravenous anesthetic in clinical practice. Existing studies have shown that propofol has many effects on the cardiovascular system in addition to its anesthetic effect. Propofol can antagonize a variety of tachyarrhythmias and reduce the risk of recurrence, regulate autonomic balance of the heart, modulate circulatory dynamics, thereby increasing blood perfusion to vital organs such as the kidney, intestine, and brain, and exert myocardial protection and cerebral protection during ischemia-reperfusion injury. In this paper, we review the potential mechanisms of these effects and provide and ideas for future research and novel drug development of propofol and its derivatives in cardiac electrophysiology and circulatory dynamics.

Keywords: *Autonomic nerves, cardiac arrhythmia, ion channel, myocardial ischemia-reperfusion injury, propofol*

Preface

Propofol role is classic by enhancing central nervous inhibitory receptor gamma aminobutyric acid type A receptor (GABAAR)-mediated chloride current and reduces the excitability of nerve cells and the sedative hypnotic effect. The cardiovascular adverse effects of propofol mainly include bradycardia, hypotension, anaphylactic shock, and propofol infusion syndrome caused by long-term massive infusion. However, existing research has found that the rescue application of propofol quickness arrhythmia may terminate a variety of types of attack and helps to maintain sinus rhythm to reduce the risk of recurrence.[1] It can also reduce reperfusion arrhythmia, reduce myocardial ischemia-reperfusion injury, increase cerebral perfusion, and achieve myocardial and nerve ischemia-reperfusion protection.[2] In the process of operation, propofol can achieve the redistribution of blood and an increase of intestines, brain, and coronary artery perfusion and guarantee the smooth recovery of patients. The above phenomenon involves cardiac ion channels, a myocardial gap junction between heart plexus reflex regulation of autonomic nervous tension, blood pressure, and so on many link mechanisms; these mechanisms in a specific scenario played its positive role in treatment, but the mechanism remains to be elucidated in detail. In this paper, the mechanisms of propofol's anti-arrhythmia, circulatory dynamic regulation, and protective effects on myocardial ischemia/reperfusion injury are reviewed.

Effects of Propofol on Arrhythmia

Antiarrhythmic effects of propofol

Cumulative literature has shown that propofol has a cardioversion effect[3-6] on atrial fibrillation, refractory ventricular tachycardia, torsade de pointes (TdP), and cardiac electrical storm. In the previous reports, however, there is contradictory evidence on the impact of propofol on risk of suffering a TdP. Ellermann *et al.*[5] investigated Q-T interval

Address for correspondence: Dr. D Huang, Department of Cardiology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China.
E-mail: huangdong1004@126.com

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outcomes by administering gradient concentrations of propofol to rabbit cardiomyocytes and found that administration of propofol alone shortened the action potential duration (APD) of cardiomyocytes in a concentration-dependent manner. The results showed that propofol alone could shorten the action potential duration (APD) in a concentration-dependent manner without affecting the spatial dispersion of repolarization. For artificially induced prolonged repolarization, additional administration of propofol could shorten APD, reduce the spatial dispersion, reverse the prolongation of repolarization, eliminate TdP, and facilitate the termination of TdP. An analysis based on a retrospective Mayo Clinic study also showed that the risk of TdP associated with propofol was extremely low (1.93 per 1,000,000) and often accompanied by other risk factors.[7] In conclusion, propofol tends to reduce the risk of TdP episodes, although caution should still be advised in patients with TdP.

Arrhythmogenic effects of propofol

Arrhythmogenic effects of propofol are relatively uncommon within clinical settings. Case reports of occasional arrhythmogenic events, such as bradycardia, atrioventricular block during induction and maintenance of anesthesia, and induction of Brugada electrocardiogram patterns[8-10] after operation, mostly occur in propofol infusion syndrome (PRIS). The majority of patients are children or patients with underlying diseases. With appropriate therapeutic intervention, the prognostic outcomes for patients are favorable.

PRIS mainly occurs in young children, elderly critically ill patients, and patients with neurological diseases or systemic inflammatory stress or severe infection. The main manifestations of PRIS reflected in the cardiovascular system include 1) metabolic acidosis; 2) acute heart failure and renal failure; 3) arrhythmia: ventricular tachyarrhythmia, atrioventricular block, acute refractory bradycardia, and cardiac arrest; and 4) sudden cardiac death. Currently, risk factors for PRIS include inappropriate dose and duration of propofol administration, carbohydrate consumption, severe underlying medical conditions, and concomitant administration with catecholamines and glucocorticoids. The proper management measures mainly include immediate withdrawal of propofol, hemodialysis, hemodynamic support, and extracorporeal membrane oxygenation for refractory cases. Although PRIS mechanism has not yet been fully studied, work has preliminarily revealed the existing with propofol infusion speed, closely related to the dose and duration, so a clinical infusion speed greater than 5 mg/kg/h or a continuous infusion time more than 48 h should be avoided.[11,12]

Propofol Antagonizes the Ion Channel Mechanism of Tachyarrhythmia

Sodium channel

The opening efficiency of inward sodium current (INa) plays an important role in the action potential duration and effective refractory period of working cells. Van't Klooster and others[13] found that propofol can potentiate the inhibitory effect of tropisetron on human myocardial sodium channel Nav1.5 expressed heterologously in HEK293 cells, thereby leading to prolonged total action potential duration. The combination of *in vitro* simulations and *in vivo* experiments in amphibians and prokaryots confirmed that propofol could inhibit the function of Nay channel by binding to Nay channel and promoting its activation coupled inactivation. The specific localization sites of Nay channel may be located at the C terminus of S4 voltage sensor and the N termin[14,15] us of S5 segment.

The hyperpolarization-activated cyclic nucleotide-gated (HCN) channel-mediated pacing current (If) is an important component of autonomous pacing and impulse conduction in the sinoatrial node. Studies have shown that propofol inhibits the If ion channels and transporters and reduce the sinoatrial node distribution of impulse frequency.[16] In patch-clamp studies using isolated sinoatrial node cells from guinea pigs, gradient concentrations of propofol could reversibly reduce the automatic depolarization rate and firing frequency[17] of the sinoatrial node during diastole by slowing the activation kinetics (≥3 μM), converting voltage-dependent activation to hyperpolarizing potential (≥5 μM) and decreasing the maximum conductance (≥10 μM). In addition, the spontaneous activity of pacemaker cells was inhibited. Mice medulla oblongata ventrolateral (RVLM) neurons, according to a study of propofol, were able to inhibit RVLM HCN concentration dependence and neuron membrane hyperpolarization; its inhibitory effect can be associated with increasing age of HCN channel mRNA expression and protein level and enhance its induction.[18] These findings suggest that propofol regulates HCN-gated channel activity as another mechanism involved in regulating autonomic cells to stabilize the heart rate and reduce the risk of downtransmission of tachyarrhythmia to the ventricle.

Calcium ion channels

The inward current dominated by L-type calcium channel (ICa, L) is involved in the plateau phase of myocardial action potential, which is also the key link that transmits the myocardial membrane potential into the cell and triggers the release of calcium from the sarcoplasmic reticulum. T-type calcium channels are closely related to the velocity of depolarization. Is derived from the sinoatrial node cells of guinea pig model confirmed that propofol to ICa, L and ICa, T have inhibition;[17] for *in vitro* atrial muscle in the person of similar experiments, propofol can also be observed by increasing the voltage dependence of inactivation methods priority inhibition of ICa, L.[19] The negative regulation of calcium channels by propofol may be involved in the process of reducing the heart rate, slowing the atrioventricular conduction rate and triggering activity inhibition during surgery.

At present, there is no clear conclusion about the positive or negative inotropic effect of propofol on myocardium. Earlier in the rat myocardial trabecular development in observational studies, the researchers found the influence of propofol on steady-state phonak and pacemaker frequency and calcium ion concentration, when the frequency of pacemaker >0.5 Hz propofol negative inotropic effect, but the pacemaker frequency = 0.1 Hz or Ca^{2+} ion concentration to reduce propofol with positive inotropic effect. The negative inotropic effect of propofol at a normal pacing rate (0.6–1.0Hz) was[20] hypothesized. Other studies have shown[21] that the relaxant effect of propofol on isolated rat pulmonary arteries may involve the inhibition of calcium influx through voltage-operated calcium channels and receptor-operated calcium channels. Therefore, the decrease of cardiac ejection volume or mean arterial pressure induced by propofol may be related to the inhibition of calcium channels in the corresponding tissues.

Potassium channels

Transient outward potassium current (Ito) is closely involved in the early stage of repolarization, which affects the action potential duration and repolarization-related current activation. Propofol can inhibit Ito by blocking K^+ channel opening in a concentration-dependent manner but has no significant[22] effect on its voltage-dependent kinetics or recovery time constant.

Delayed rectifier potassium current (IK) can be divided into at least three different subtypes, super fast rectifier potassium current (IKur), fast rectifier potassium current (IKr), and slow rectifier potassium current (IKs). IKur is specifically distributed in human atrial myocytes, and inhibition of Ikur current is considered to play an anti-AF role. Propofol has been shown to induce concentration-dependent inhibition of IKur current in human atrial myocytes through preferential binding to the open hKv1.5 channel, which is reversible and can be attenuated[23] by serum albumin. Further docking analysis showed that propofol could directly block hKv1.5 channel[24] through binding to Thr480, Val505, and Ile508.

Animal experiments revealed a significant inhibitory effect of propofol on IKs but not[17] on IKr. IKs is composed of a pore-forming subunit of KCNQ1 alpha subunit and an accessory subunit of KCNE1 beta subunit. KCNE1 single-nucleotide polymorphism (D85N) is an existing gene mutation that causes long Q-T syndrome. Kojima *et al.*[25] designed to use the mutations of propofol to inhibit IKs wild type and mutant IKs susceptibility contrast observation to discover KCNE1 beta subunits mediated IKs channel activity and thus speculated that propofol can amplify on the IKs mutations. Some scholars believe that the inhibitory effect of propofol on IKs currents can be used as a compensatory mechanism to offset part of the net negative inotropic effect caused by the inhibition of ICa, L.

Inward rectifying potassium current (IK1) plays an important role in maintaining the resting potential and regulating the excitability of cardiomyocytes. Current studies have shown that propofol has no significant effect[26] on inward rectifier K + current IK1.

In addition, other research shows that, in addition to the heart muscle cells, propofol can activate vascular smooth muscle cells in large conductance calcium activated potassium channels (BKCa), and diastolic mesenteric arterioles, milk, coronary artery, and aortic artery lead to an increase of local organizations and myocardial perfusion amount.[27-30]

Regulation Mechanism of Propofol on Circulatory Dynamics

Parasympathetic/sympathetic nerve tone difference

Propofol regulates the sympathetic and parasympathetic activities of the cardiac plexus in a heterogeneous[31] manner. Heart rate variability (HRV) analysis information can quantitatively assess the tone and balance of cardiac sympathetic and vagal nerve activity and its effect on cardiovascular system activity. The high-frequency component (HF) reflects sympathetic and parasympathetic nerve activity in frequency domain analysis, and the low-frequency component (LF) reflects parasympathetic nerve activity. LF/HF represents the balance between parasympathetic and sympathetic nerve activity. Related studies have shown that propofol

can inhibit the activity of cardiovascular components in the autonomic nervous system, resulting in a decrease in systolic blood pressure. During this period, LF and LF/HF increase and HF decreases; that is, parasympathetic activity is superior[32,33] to sympathetic activity during the same period; however, both of them will achieve a "rebalance"[34] between long-distance and short-distance cortical connectivity with the depth of anesthesia. In order to maintain the stability of blood pressure and heart rate, this compensatory regulation of hemodynamics is more active in the young than in the old.[32] The significant inhibitory[35] effect of propofol on sympathetic nerve activity was also confirmed by tests of skin sympathetic nerve activity and muscle sympathetic nerve activity. It is worth reminding that the results of HRV analysis can be affected by factors such as age, gender, depth of respiratory rate and assisted ventilation, drug combined anesthesia, detection technique, and pain stimulation.

Regulation of baroreflex and vascular endothelial tone

Baroreceptor reflex and the regulation of vascular endothelial tensity are based on the neural, humoral regulation in the vascular tension under the steady state adjust as the negative feedback effect and maintain the balance of the heart blood and blood pressure to normal operation of the circulation system has the vital role. Vanderhaegen, J, *et al.*[36] studied full-term newborn infusion of propofol on systemic hemodynamics and the variability of the covariate assessment and recorded the brain tissue oxygenation index for 3 min, which is reduced, the brief cerebral blood flow perfusion imbalance between supply and demand, a small decrease in heart rate and arterial oxygen saturation that rapidly recovered after 5 minutes, and a decrease in mean arterial pressure that returned to baseline after 1 hour, suggesting short-term effects on cardiovascular hemodynamics, but this study did not specifically assess the cardiovascular benefits or risks of any adverse effects. Ma *et al.*[37] studied blood pressure and hemodynamic changes before and after central infusion and bicuculline in spontaneously hypertensive rats (SHRs) and found that in all anesthetized rats, mean arterial pressure, heart rate, and arterial baroreceptor sensitivity decreased. Gamma-aminobutyric acid can appropriately improve abdominal aortic mean arterial pressure, heart rate, and arterial baroreceptor sensitivity in SHR and then alleviate the fluctuation of heart rate and blood pressure. Since propofol and γ-aminobutyric acid share the same signaling receptors, this study partly projects a positive effect of propofol in maintaining blood pressure levels. Although visible, propofol after entering the body can stress within the circulatory system is short of negative fluctuations and regulating the paralysis, but the overall effect is still in a benefit to the peripheral blood distribution and maintain hemodynamic stability range. For the detailed mechanism of this phenomenon, animal experiments and clinical studies have revealed that propofol can reduce blood perfusion in the renal cortex and medulla, reduce the sensitivity of the baroreflex to renal sympathetic nerve activity in a dose-dependent manner, reduce the responsiveness of perirenal baroreceptors to hypotension, and cause a variety of cardiovascular reflexes, especially the Cushing reflex, to be significantly inhibited.[38,39] The delay of baroreflex counteracts the vasoconstriction during the operation, resulting in a decrease in peripheral resistance and an increase in tissue blood perfusion.

The Regulatory Mechanism of Propofol on Myocardial Protection Induced by Ischemia-Reperfusion Injury

The detailed mechanism of myocardial ischemia-reperfusion injury (MIRI) has not been clearly explained, and it is currently believed to be the result of free radical production, intracellular calcium overload, and activation of white blood cells. Propofol can play a protective role in the ischemic stage of myocardial microcirculation by participating in multiple links in the occurrence and development of MIRI.

Mitochondrial oxidative respiratory chain

Myocardial oxidative stress is considered to be the initial link of MIRI, which is mediated by the mitochondrial oxidative respiratory chain and causes irreversible damage to myocardial cells through free radicals and reactive oxygen species produced. Related studies have shown that propofol through inhibition of the mitochondrial respiratory chain transmission efficiency, changes of mitochondrial membrane permeability transition and mitochondria membrane potential, and inhibiting mitochondrial apoptosis related variety of passing, reduce oxidative stress product synthesis and release and thus play a role in myocardial protection.[40-44] Propofol can also promote the opening of mitochondrial adenosine triphosphate sensitive channel, the activation of nitric oxide synthase, and the stimulation of mitochondrial respiratory chain complex in the early reoxygenation stage of the myocardium and inhibit the ventricular arrhythmia[45] induced by ischemia-reperfusion. However, other related studies have also suggested that the protective effect of propofol is reflected in the toxicity of immature mitochondria. For example, propofol can induce excessive coQ-sensitive leakage in the myocardium of neonatal mice, uncoupling the mitochondria[46] of immature cardiomyocytes and

mediating the toxic mechanism of the developing myocardium. Also, the earlier clinical data showed that the pre-existing mitochondrial diseases or beta oxidation defect was susceptible to PRIS.[47] Together, these findings suggest the reason why children are more susceptible to PRIS.

Intracellular calcium overload

Calcium overload is also an important link in the mechanism of MIRI. Propofol can interfere with the process of calcium overload in a variety of cells, such as inhibiting the calcium influx[48] mediated by TRPV4 channels in cardiomyocytes, inhibiting cellular energy metabolism disorders induced by excessive calcium intake by mitochondria and sarcoplasmic reticulum, and inhibiting the generation of oxygen free radicals mediated by calcium-dependent protease activation. This alleviates cellular acidosis and protects cell membranes and organelle membrane integrity. In addition, propofol also inhibited store-operated calcium channel (SOC) influx in mast cells to reduce tryptase activity, inhibit cardiomyocyte apoptosis, and reduce the expression of myocardial necrosis markers, thereby inhibiting mast cell activation and reducing mast cell degranulation.[49]

Epigenetic regulation

In terms of upstream mechanism research, the current study intends to reveal the detailed mechanism of propofol's myocardial protection and antagonism against reperfusion arrhythmia from multiple regulatory levels. Experiments in human and mouse cardiomyocytes confirmed that the downstream pathways of propofol involved a variety of phenotypes: the activation of Nrf2/gpx4 and AKT/P53 signaling pathways inhibited iron concentration,[50,51] enhancing the synthesis[52] of antioxidative stress products mediated by GSK3β-Nrf2/HO-1 signaling pathway. Inhibition of inflammatory factors released by JAK/STAT pathway can reduce cell apoptosis, alleviate oxidative stress, and inhibit inflammatory response.[53,54] Some studies have also shown that propofol can inhibit myocardial excessive autophagy and apoptosis[55,56] during MIRI through epigenetic modification, such as upregulation of forkhead transcription factor and MicroRNA-30b. The cardioprotective effect of propofol may also involve its protection of myocardial structure and adjacent junctional tissues. Studies in rats have shown that propofol protects the heart against severe ventricular arrhythmias during acute coronary ischemia by preserving ventricular connexin 43, which can be blocked by atropine. This antiarrhythmic effect can be blocked by atropine, which again suggests the close involvement[57] of parasympathetic nervous system in the antiarrhythmic mechanism of propofol. Current studies have provided a certain depth of evidence for the treatment of ischemia-reperfusion with propofol, but there is a lack of multicenter clinical verification and evaluation, and systematic clinical cohort studies are urgently needed.

Summary

Propofol exerts multifaceted effects on the cardiovascular system, with its impact potentially manifesting heterogeneity across different individuals and conditions. The judicious short-term application of propofol can indeed mitigate the risk of certain arrhythmias, stabilize hemodynamics, and offer protection against ischemia-reperfusion injury in the myocardium. These effects may be mediated through the inhibition of ion channels, modulation of the sympathetic and parasympathetic nervous systems' imbalanced inhibition, preservation of gap junctions during myocardial ischemia, and regulation of various signaling pathways to attenuate ischemia-reperfusion injury.

However, it is imperative to acknowledge that the conclusions drawn from previous studies may exhibit inconsistencies due to variations in the species utilized, research protocols, and the altered sensitivity to propofol in patients with specific genetic mutations. Moreover, the use of propofol is not devoid of risks as it may also induce arrhythmias under certain circumstances.

Drawing from the consensus of extensive research, propofol possesses the potential to serve as an antiarrhythmic agent and cardioprotective substance within the context of clinically effective concentrations and in the absence of contraindications in patients. Concurrently, it is imperative to meticulously assess its safety and efficacy across diverse patient populations to avert potential proarrhythmic effects.

In the future, by elucidating the pharmacological targets of propofol, delving deeper into its pharmacodynamic properties, and integrating molecular modifications, it is anticipated that a more personalized therapeutic regimen can be formulated for the treatment of related diseases. This endeavor necessitates not only an in-depth exploration of propofol's antiarrhythmic potential but also a comprehensive evaluation of the risks of induced arrhythmias to ensure the optimization of patient safety and therapeutic outcomes.

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Conflicts of interest

There are no conflicts of interest.

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