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Cardioprotective Properties Of Xenon

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ABSTRACT

The review presents the main aspects of the cardioprotective properties of the xenon inhalation anesthetic. Based on the analysis of publications, the article discusses modern views on the mechanisms of the protective action of xenon, realized using pre- and post-conditioning mechanisms, shows major molecular targets and their effects. The article presents the results of experimental studies in vivo and in vitro, which showed the protective effect of xenon on the myocardium and the results of recent randomized clinical trials. The analysis of studies demonstrates the ability of xenon to increase myocardial resistance to ischemia and reperfusion and opens up good prospects for its use in clinical practice in patients with a high risk of cardiac complications.

Keywords: xenon, cardioprotection, ischemia-myocardial reperfusion, cardiac arrest, non-cardiac surgery, cardiac surgery

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AC – artificial circulation
ATP – adenosine triphosphate or adenosine triphosphate acid
BP – blood pressure
CABG – coronary artery bypass grafting
CAD – coronary artery disease
CO – cardiac output
COX-2 – cyclooxygenase-2 blocker
HR – heart rate
IL – interleukin
mRNA – messenger ribonucleic acid
PKC – protein kinase C
p38MARK – inhibitor of mitogen - activated protein kinase
RCT – randomized clinical trial
SBP – systolic blood pressure
TIVA – total intravenous anesthesia
Xe – xenon

INTRODUCTION

The search for new technologies to protect the heart from ischemic damage refers to the priority tasks of modern medicine. This is associated both with a large amount of cardiovascular diseases in the world, and a broad implementation methods of treatment, requiring efficient cardioprotection. The most effective method of improving prognosis of life of patients with multivessel stenotic lesion of the coronary arteries at coronary artery disease (CAD) remains the revascularization of the myocardium through coronary bypass [1, 2]. Despite the continuous improvement of surgery and anesthesia procedures, intraoperative mortality even in the leading cardiac centers remains at the level of 2%, and the frequency of the life-threatening complications (intra-operation myocardial infarction, ventricular rhythm disorders) reaches 5% [3].

At the same time, one of the most urgent problems of modern anaesthesiology and resuscitation is cardiac complications during noncardiac surgical interventions in patients with high-risk, particularly among the elderly and senile patients [4]. It is established, that the frequency of these complications may exceed 10%, not only being the cause of in-hospital mortality, but and leading to disability in patients after discharge from hospital, increasing the risk of long-term mortality [5]. Non-fatal damage to the myocardium may serve as a trigger of apoptosis, fibrosis and remodeling of the heart, defining morphological substrate of chronic failure of blood circulation [6].

Therefore it is important to develop methods for cardioprotection with minimal side effects for the cardiovascular system. Inhaled halogenated anesthetics have the ability to affect positively on the oxygen balance of the myocardium, but it is not confined to their ability to protect the myocardium of ischemia [7, 8]. It is about their specific impact on the myocardium, improving resistance of the heart to ischemia, which received the name of "anesthetic preconditioning " [9, 10]. The requirements of the protection of the myocardium from ischemia and reperfusion injury may be met by inhalation anesthetic xenon, which, judging by the large amount of recent experimental data, has not only neuroprotective, but significant cardioprotective properties. Cardioprotection is the ability of therapy to prevent cardiomyocytes from death through suppression of pathogenetic cascade, which leads to their death by apoptosis and necrosis [11].

EXPERIMENTS

In experimental models in various species of animals protective effects of xenon are shown, which are realized with the help of mechanisms of preconditioning and postconditioning [12, 13]. Preconditioning with xenon in models of ischemic injury in rats and rabbits shows a decrease the size of infarction, more than low levels of enzymes of damage [14, 15].

Results of recent studies have shown, that various enzyme systems are involved in the initiation of cardioprotection, such as the phosphatidylinositol 3-kinase (*PI3K)*, protein kinase *C* (*PKC)*, *ERK* - kinase [16].

It was shown, that the protective effect xenon on the myocardium was completely blocked by infusion of an inhibitor of *PKC* or an inhibitor of mitogen - activated protein kinase (*p*38*MAPK)* [17].

It was found, that the xenon increases phosphorylation epsilon isoform *PKC* ε, and this effect is blocked by an inhibitor of *PKC*, but not the inhibitor *p*38*MAPK*, which shows, that *p*38*MAPK is* located above *PKC* in the signal cascade of pharmacological preconditioning induced with xenon [18].

With the help of immunofluorescence staining it was shown, that xenon induced translocation of *PKC* εfrom cytosol to membrane cardiomyocyte. In this way, one can say, that the xenon reduces the size of myocardium through translocation of *PKC* εand depends on the phosphorylation of *MAPK*-kinase.

It is known, that the protein of heat shock (*HSP*27) plays an important role in restructuring of actin network of cytoskeleton. It was shown, that preconditioning with xenon induced phosphorylation of *HSP* 27, which lead to enlargement of *F*-actin fibers [19].

The central role of *PKC* in ensuring the protective effects of various types of preconditioning has been shown in models of ischemia in various animal species, as well as in humans [20, 21].

Lack of activation of *PKC* with pharmacological blockade of mitochondrial adenosine triphosphate (ATP)-dependent potassium channel in the signal cascade pharmacological preconditioning with xenon allows to assume, that the opening of K_{ATP} - channel occurs before activation of *PKC*. There are also other isoforms of *PKC* - *PKC* δ and *PKC* α. However, these isoforms were not involved in the process of pharmacological preconditions of ionization by xenon, which indicates a specific activation of *PKC* ε with xenon [22].

The second gap for cardioprotection occurs after 12-24 hours after ischemia and lasts up to 72 hours. Induced later preconditioning with xenon reduced the size of infarction in rats, subjected to regional ischemia and reperfusion, with 64 to 31% of the area of damaged myocardium. The administration of COX-2 blocker combined with the inhalation of xenon completely neutralized the effect, while after preconditioning, there was no growth of messenger ribonucleic acid (mRNA) expression of COX-2 or protein COX-2 [23].

In addition, the protective properties of xenon may be associated with the effect on the endothelium, which covers the coronary vessels. The surface of the endothelial cells is usually low adhesive, but this property can be changed after ischemia - reperfusion damage. High levels of proinflammatory cytokines increases the expression of molecules of the cell adhesion to the endothelium, the thus ensuring penetration of circulating leukocytes to the site of inflammation. In the experimental work of *N.C. Weber et al*. proinflammatory cytokine TNF-α was used to activate endothelial cells, obtained from umbilical veins in humans, which led to an increased expression of molecules of intercellular (ICAM-1) and vascular (VCAM-1) adhesion [24]. Pre-treatment of endothelium with xenon (exposure with xenon 50% three times for 5 minutes) reduced the expression of mRNA and protein ICAM-1 and VCAM-1, but had no influence on the third molecule of adhesion, E- selectin. Besides that, xenon prevented induced TNF-α induced increase of transcriptional activity of NF-κB. Thus, xenon, most likely, provides protection of the endothelium due to inhibition of the activity of NF-κB and reduction in the level of ICAM-1- and VCAM-1 molecules.

Table 1 shows the experimental works on the cardioprotective properties of xenon *in vivo* and *in vitro*.

Table 1

The results of experimental studies of xenon in vivo and in vitro

Study	Model	Intervention	Results
Baumert J.H., Roehl A.B., Funcke S. et al. (2016) [27]	Pigs, 1 hour occlusion of the left anterior descending artery, 2 hours of reperfusion	Preconditioning Xe 70%	Xenon preconditioning eliminates diastolic dysfunction in myocardial ischemia
Roehl A.B., Funcke S., Becker M.M. et al. (2013) [12]	60 male rats underwent 60 minute coronary artery occlusion and 120 minute reperfusion	Isoflurane, xenon groups and a group with an intraperitoneal injection of ketamine	In the beginning, xenon and isoflurane equally reduced reperfusion injury and the area of myocardial ischemia. Differences appeared in the delayed period in the form of lesser myocardial remodeling and better retention of CO in the xenon group. Hypertrophy, fibrosis, and apoptosis were comparable
Li Q., Lian C., Zhou R. et al. (2013) [14]	Heart of 2 -3 -week-old rabbits, 1 hour of ischemia, 3 hours of reperfusion	Preconditioning Xe 75%	Smaller heart attack compared to control group. Decrease in levels of KPK-MB and LDH in comparison with the control group. Decreased apoptosis. Cardioprotection due to preservation of myocardial mitochondria and opening mitochondrial potassium-dependent ATP-channel (mitoK$_{ATP}$)
Schwiebert C., Huhn R., Heinen A. et al. (2010) [13]	Rats, 25-minute-long coronary artery occlusion followed by 120 minutes of reperfusion	Postconditioning Xe (20%) in combination with hypothermia	The combination of xenon 20% and hypothermia 34° C, used during early reperfusion, reduces the area of myocardial infarction in a rat heart *in vivo*. Xenon and hypothermia have not consistently reduced myocardial infarction area.
Mio Y., Shim Y.H., Richards E. et al. (2009) [15]	Male rats, 30 minutes of myocardial ischemia (occlusion of the left anterior descending artery), 2 hours of reperfusion	Preconditioning Xe 70%	Reducing the area of myocardial infarction Improved phosphorylation of Akt and GSK-3 β
Weber N.C., Frässdorf J., Ratajczak C. et al. (2008) [23]	Rats were subjected to 25 minutes of coronary artery occlusion followed by 120 minutes of reperfusion	Preconditioning Xe 70% Ischemic Preconditioning	Ischemic preconditioning and xenon preconditioning reduces the area of myocardial infarction Inhibitors of COX -2 block cardioprotective effect of xenon
Weber N.C., Stursberg J., Wirthle N.M. et al. (2006) [22]	Rats were subjected to 25 minutes of coronary artery occlusion followed by 120 minutes of reperfusion	Preconditioning xenon	Decreased area of myocardial infarction
Weber N.C., Toma O., Wolter J.I. et al. (2005) [17]	Rat Heart	Preconditioning Xe 70% *in vivo*	The cardioprotective effect of xenon is blocked by a *PKC* inhibitor or *p*38 *MAPK* inhibitor
Weber N.C., Toma O., Wolter J.I. et al. (2005) [18]	Rat Heart	Preconditioning Xe 70% *in vivo*	Xenon increases the phosphorylation of epsilon of the *PKC*ε isoform, and this effect is blocked by a *PKC* inhibitor
Preckel B., Müllenheim J., Moloschavij A. et al. (2000) [28]	Rabbits, 30-minute coronary artery occlusion followed by reperfusion for 120 minutes	Xe inhalation (70%) at the very end of regional myocardial ischemia and during the first 15 minutes of reperfusion (after conditioning)	Decreased area of myocardial infarction

Notes: AKt — Protein kinase B; ATP — adenosine triphosphate or adenosine triphosphoric acid; CO — cardiac output; COX-2 — cyclooxygen-2 blocker; GSK-3 β — glycogen synthase kinase 3 β; KPK-MB — creatine phosphokinase, subunit, isoform of MB — one of the markers of myocardial infarction often used in practice; LDH — lactate dehydrogenase; *PKC* — protein kinase *C*; Xe — xenon

CLINICAL RESEARCH

In clinical practice, the beneficial effects of xenon-based inhalation anesthesia on the myocardium have been shown in a number of studies in patients with cardiovascular diseases in non-cardiac surgery. Two prospective randomized clinical trials (RCTs) have shown greater stability in heart rate and blood pressure compared to isoflurane-based inhalation anesthesia. It is important to note that the study of the contractile function of the heart by transesophageal echocardiography did not reveal changes in the systolic

function of the left ventricle of the heart in patients with coronary artery disease when using xenon-based anesthesia, while isoflurane-based anesthesia led to its decrease [25, 26]. In a prospective RCT in high-risk patients (ASA III – IV) with coronary artery disease, xenon-based inhalation anesthesia provided higher blood pressure and lower heart rate than the propofol-based total intravenous anesthesia (TIVA) group. The study of the contractile function of the heart by transesophageal echocardiography revealed the best function of the left ventricle in the group of patients who received xenon-based anesthesia [29, 30].

A recent meta-analysis of RCTs of 31 studies comparing xenon-based inhalation anesthesia (841 patients) with halogenated vapor-generating inhalation anesthetics (836 patients) and 12 studies comparing xenon-based anesthesia (373 patients) with propofol-based TIVA (360 patients) showed that xenon-based anesthesia provides relatively more stable blood pressure in the intraoperative period, a lower heart rate and faster recovery from anesthesia than compared anesthesia methods [31].

The meta-analysis (2018) of RCTs of 13 studies comparing xenon-based anesthesia with propofol-based TIVA in noncardiac surgery showed similar results [32]. Similar results have been obtained in cardiac surgery. The first study that showed more stable hemodynamic parameters in the xenon group compared to propofol was performed in 2001 [33]. Subsequent studies have confirmed the data on the safety and adequacy of xenon-based anesthesia for CABG [34, 35].

In a recent pilot study in patients who underwent beating heart CABG, the need for intraoperative use of vasopressors was significantly less with inhalation anesthesia with xenon than with anesthesia based on sevoflurane [36]. To date, ischemia-reperfusion myocardial injuries during CABG operations remain an unsolved problem in modern anesthesiology. An increase in the level of troponins I and T reflects the degree of myocardial damage and well predicts long-term adverse outcomes of the disease. The results of recent studies have shown that troponin T levels of more than 0.6 ng / ml in the early postoperative period were an independent predictor of hospital mortality [37].

In 2017, a large multicenter RCT was completed, in which 492 patients underwent CABG with artificial circulation (CI) [38]. Xenon-based inhalation anesthesia was performed in 161 patients, sevoflurane-based anesthesia was performed in 165 cases, and propofol-based TIVA in 166 patients. 24 hours after surgery, the level of troponin I in the blood was 1.14 [0.76–2.10] (ng / ml) in the xenon group, 1.30 [0.78–2.67] (ng / ml) in the sevoflurane group and 1.48 [0.94-2.78] (ng / ml) in the propofol-based TIVA group. Troponin I levels in the xenon group were significantly lower than in the sevoflurane group, and the difference was 0.09 ng / ml (95% CI, -0.30 to 0.11; P = 0.02). The troponin I level 24 hours after the end of the operation was significantly lower in the xenon group than in the TIVA (P = 0.02). The results of this large and well-designed study showed the advantages of xenon-based inhalation anesthesia in patients undergoing CABG with cardiopulmonary bypass compared to sevoflurane-based inhalation anesthesia and propofol-based TIVA in terms of myocardial protection against ischemia and reperfusion, but clinical outcomes the postoperative and hospital periods did not differ in the studied groups.

During the same period of time, Finnish researchers led by O. Arola et al. an RCT was performed in patients with out-of-hospital cardiac arrest who were successfully resuscitated within 45 minutes and were in a coma [39]. According to European studies, hospital mortality in this group of patients is a serious and far from being solved problem and ranges from 41 to 86% [40–42]. Despite the fact that ischemic brain injury is the main cause of hospital mortality after circulatory arrest, myocardial dysfunction and circulatory failure account for the majority of deaths in the first 3 days. The study included 110 patients with out-of-hospital cardiac arrest, who were randomized into two groups upon admission to the intensive care unit. In the first group (control group, 55 patients), hypothermia (33 ° C) for 24 hours was performed in order to protect the brain, in the second (group of inhalation sedation with xenon 40 vol.%) - hypothermia in combination with xenon for 24 hours. The results of the study showed that in the group of inhalation with xenon there was a significant decrease in the level of troponin T 72 hours after cardiac arrest (0.79 ng / ml ± 1.54 in the xenon group) and 1.56 ng / ml ± 1.38 in control group (adjusted mean difference -0.66; 95% CI: from -1.16 to -0.16; P = 0.01), at the same time, significant differences in the periods (24 and 48 hours after stopping) were noted did not have. In the xenon group, the troponin T level was reduced by 44.8%, and in the control group by 11.3% (between 24 and 72 hours after cardiac arrest).

The decrease in 6-month mortality in the xenon group is 27%, compared with 35% in the control group (odds ratio 0.49 [95% confidence interval, 0.23–1.01]) is important, but the difference did not reach statistical significance (P = 0.053).

Table 2 shows clinical data showing the cardioprotective properties of xenon.

Table 2

Clinical studies of xenon inhalation anesthesia

Study	Model	Intervention	Results
Arola O., Saraste A., Laitio R. et al. (2017) [39]	110 patients after out-of-hospital cardiac arrest and successful resuscitation	Xe inhalation (40%) combined with hypothermia (33 ° C) for 24 hours	Inhalation of xenon in combination with mild hypothermia leads to a decrease in myocardial damage compared with hypothermia. A lower troponin T level compared to the control group 72 hours later
Hofland J., Ouattara A., Fellahi J-L. et al. (2017) [38]	492 patients who underwent CABG surgery with AC	Xenon-based inhalation anesthesia was performed in 161 patient, on the basis of sevoflurane — in 165, and the TIVA on the basis of propofol — in 166 patients	24 hours after surgery, the concentration of cardiac troponin I (ng/ml) was 1.14 [0.76 - 2.10] in the xenon group, 1.30 [0.78 - 2.67] in the sevoflurane group and 1.48 [0.94-2.78] in the propofol-based TIVA group. The difference in troponin I release between xenon and sevoflurane was -0.09 ng/ml (95% CI, from -0.30 to 0.11; P=0.02)
Breuer T., Emontzpohl C., Coburn M. et al. (2015) [43]	30 patients after planned CABG	Balanced anesthesia with xenon or sevoflurane	Xenon increased the postoperative increase in IL- 6 and weakened the increase in IL- 10 Alignment with sevoflurane Balanced xenon anesthesia causes pro-inflammatory effects and inhibit the anti-

			inflammatory response in patients undergoing cardiac surgery
Al Tmimi L., Van Hemelrijck J., Van de Velde M. et al. (2015) [36]	42 patients, who underwent planned CABG without AC	Balanced anesthesia with xenon or sevoflurane	Patients who underwent anesthesia with xenon needed lower dosages of norepinephrine to achieve the target of hemodynamic parameters. In the sevoflurane group, a greater number of postoperative delirium was observed. SBP was lower in the sevoflurane group. There were no differences in the level of inflammatory cytokines, troponin T, erythropoietin, and other studied parameters.
Stoppe C., Fahlenkamp A.V., Rex S. et al. (2013) [34]	30 patients undergoing planned CABG	Xenon and sevoflurane groups	No significant differences
Baumert J.H., Hein M., Hecker K.E. et al. (2008) [30]	20 patients with moderate coronary artery disease risk, anesthesia for non-cardiac surgery	Xenon anesthesia versus propofol anesthesia	Higher blood pressure, the lower heart rate in comparison with propofol. Improvement of left ventricular function (according to ultrasound)
Weber N.C., Kandler J., Schlack W. et al. (2008) [24]	Human umbilical vein endothelial cells were isolated from three different drugs. Cells were either left untreated or pretreated with xenon, nitrous oxide, isoflurane or morphine		The expression of vascular cell adhesion molecules was blocked only by inhalation anesthetics, but not by morphine. None of the four agents affected the expression of E-selectin, but had an effect on other adhesion factors.
Wappler F., Rossaint R., Baumert J. et al. (2007) [26]	252 patients without cardiovascular disease for planned surgery	Comparison of hemodynamic parameters in xenon and isoflurane groups	Myocardial contractility was significantly reduced in the isoflurane group and preserved with xenon anesthesia
Lockwood G.G., Franks N.P., Downie N.A. et al. (2006) [35]	16 patients after planned CABG under hypothermia	Gradual increase in xenon concentration during anesthesia	Doppler ultrasound of middle cerebral artery revealed no signs of increased xenon embolism. The levels of troponin T and whey protein S100beta were low
Coburn M., Kunitz O., Baumert J.H. et al. (2005) [29]	160 patients aged 18 to 60 years who underwent planned surgery	Xenon group and propofol anesthesia maintenance group	The two groups were comparable by age, body weight, height, gender, and *ASA* classification . Baseline heart rate and SBP were comparable in both groups. Heart rate decreased to target values only under xenon anesthesia
Rossaint R., Reyle-Hahn M., Schulte Am Esch J. et al. (2003) [25]	224 patients in 6 centers: xenon group, sevoflurane group in combination with nitrous oxide	Anesthesia with xenon and sevoflurane combined with nitrous oxide	A faster recovery after xenon anesthesia was found. The amount of sufentanil did not differ in the two groups. Hemodynamic and respiratory parameters remained stable during the management of both schemes of anesthesia with a slight advantage in the xenon group. Side effects were equivalent

Notes: AC — artificial circulation; ATP — adenosine triphosphate or adenosine triphosphoric acid; CABG — coronary artery bypass grafting; CAD — coronary heart disease; IL — interleukin; SBP— blood pressure; TIVA — total intravenous anesthesia

CONCLUSION

Numerous experimental studies have shown that xenon has the ability to increase myocardial resistance to ischemia due to the effect of pre- and postconditioning, which was an important factor that prompted the beginning of the study of its potential protective properties during coronary artery bypass grafting and in patients with coronary artery disease in noncardiac surgery. The results of recent clinical studies have shown that the inert gas xenon has good prospects for use in surgery not only as a reliable and safe agent for inhalation anesthesia, but also as an anesthetic with high cardioprotective properties. Special attention should be paid to the results of the use of therapeutic anesthesia with xenon in patients with out-of-hospital cardiac arrest, successfully resuscitated and in a coma, which revealed its protective effects on the brain and myocardium. In this regard, further well-organized large clinical studies of the cardioprotective properties of the inert gas xenon are so important as an inhalation anesthetic during operations in patients with high cardiac risk, and as means for inhalation sedation in patients with acute myocardial infarction when performing interventional cardiac surgery.

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