Adenosine and high-energy phosphates in cardiac anesthesiology

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Summary. Usage of adenosine and high-energy phosphates in cardiac anesthesiology is widely discussed. Implementation of above substances can be achieved via three possible ways: during the preparation of patients for cardiac surgery, during surgery and after the surgery during intensive postoperative care. Optimum methods for cardiac protection, which could guarantee safe, lasting heart function preservation after the surgery are investigated till now. Advantages and disadvantages of adenosine application during preoperative and postoperative periods as well as in cardiac surgery are presented. Possibilities to use phosphocreatine for cardioprotection will be discussed as well.

Introduction
Appropriate preparation of patients for cardiac surgery, myocardial protection during the surgery and intensive postoperative care is inseparable part of recent studies in cardiac surgery and anesthesiology.

Preoperative preparation of the patients and choice of postoperative tactics is one of the most important factors for improvement of patient prognosis. Postoperative improvement of myocardial function is very important task as well. All these methods influence reduction of postoperative morbidity and mortality.

Application of adenosine (ADO) and high-energy phosphates (HEP) in cardiac anesthesiology will be discussed. ADO (nucleoside) is a precursor of HEP (adenosine monophosphate (AMP), diphosphate (ADP) and triphosphate (ATP)). Due to this reason application of ADO will be discussed together with application of HEP (phosphocreatine).

A great number of ADO effects are conditioned by its interaction with specific receptors. This is very important in perioperative myocardial protection. This problem will be discussed thoroughly in the article.

Problem of ADO and HEP application in cardiac anesthesiology will be discussed in three different aspects:
1. Application of ADO and HEP for diagnostic purposes and in order to prepare patients for surgery,
2. Myocardial protection achieved by application of ADO and HEP during cardiac surgery (not for cardioplegia),

Theoretical preconditions for adenosine and high-energy phosphates application
It is important to mention that importance of ADO and HEP application in cardiac anesthesiology is conditioned by two main mechanisms of action of above substances:
 a) Preservation of energy resources,
 b) Effects conditioned by ADO interaction with specific receptors.

ADO and phosphocreatine are two main substances could be used for “energetic” aspect. As it was mentioned above, ADO is a precursor of AMP, ADP and ATP, at the same time phosphocreatine is a “buffer” of ATP, in the cells where creatine kinase is found [26].


Exogenous ADO can be excreted through kidneys [19]. Main way of ADO metabolism is AMP formation. Formation of inosine is initiated, if great amount of ADO is administered (due to therapeutic reasons). Further inosine is transformed by nucleosidphosphorylase to hypoxanthine, which is transformed to AMP by phosphorylase [19].

It is proven that ADO, inosine, hypoxanthine, adenine are important in preservation of post ischemic ATP and myocardial function [26].

Application of ADO for synthesis of HEP is one of the possible mechanisms of ADO action. Second, specific way of action, is conditioned by adenosine
interaction with specific receptors (A₁, A₂α, A₂β, A₃) [19].

A₁ type receptors, are located on cardiomyocytes. ADO interaction with these receptors reduces formation of cyclic AMP (cAMP), this conditions negative chronotropic and dromotropic effects. As a result this reduces consumption and demand of oxygen. This is important during surgery as well as in postoperative period [10,15,16]. A₁ type receptors are responsible for anaerobic glycolysis activation [1,27].

A₂ type receptors are present on coronary vascular smooth muscle and endothelial cells. Interaction of ADO with the A₂ receptors leads to as stimulation of adenylate cyclase activity and subsequent increase in intracellular cAMP levels. It is reported that ADO interaction with A₂ receptors is associated with reduction of local damage through inhibition of neutrophil endothelial adherence and plugging, reduction of toxic free radical formation by neutrophils or ischemic cells. Recent studies indicate that A₂ receptors are also expressed in adult cardiac tissue, is coupled to phosphoinositide metabolism and mediates positive inotropic action [10,19,21].

Q.Y. Zhou et al. in 1992 identified A₃ receptors (called “new” A₃ receptors), what expected to condition decrease of systemic blood pressure (proven in experimental models) [19].

Important effects for myocardial protection are conditioned by ADO interaction with receptors:
1. Negative chronotropic and dromotropic effects,
2. Positive inotropic action,
3. Anaerobic glycolysis and gluconeogenesis,
4. Dilatation of coronary arteries,
5. Inhibition of thrombocyte aggregation,
6. Hypotension

All above effects can be used in preoperative preparation of patients and during postoperative intensive care.

Effects of ADO action are indicated in Fig. 1, 2.

Precursor of ADO acadesine and inhibitors of ADO transport are explored in order to prolong action of ADO [19].

1 Fig. The role of adenosine in the energy supply-demand balance (according to Mubagwa K., 1996)
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Application of adenosine and high-energy phosphates during preoperative period

ADO has wide spectrum of indications for application during preoperative period in comparison with other substances reviewed in the article. ADO can be administered either for therapeutic or diagnostic purposes [19]. Recent indications for ADO application are limited only for diagnostic and treatment purposes of supraventricular tachycardias [19]. Other indications for ADO administration during perioperative period are discussed as well:

1. Correction of hypertension,
2. Correction of pulmonary hypertension,
3. Increment of cardiac output,
4. Correction of arrhythmias,
5. Reduction of reperfusion injury (myocardial protection),
6. Reduction of myocardial infarction zone [19].

Application of HEP (phosphocreatine) during preoperative period in order to prepare patients for cardiac surgery has been widely discussed [14,22]. In 1984 V. Pedone et al. indicated antiarrhythmic action of phosphocreatine for patients undergoing cardiac surgery due to ischemic heart disease [14,20].

M. Cisowski et al. presented a study, where phosphocreatine was administered in order to prepare pa-

tients for cardiac surgery (CAGB). Phosphocreatine was applied for three days before surgery (cardioplegic solution was enriched with phosphocreatine as well). Statistically significant decrease in requirement of inotropic drugs, reduction of incidence of ventricular arrhythmias was observed; damages of sarcolemma were less expressed during postoperative period [6].

In 1995 Weber P et al. presented research study, where phosphocreatine treatment was applied for patients with acute myocardial infarction. Reduced incidence of angina pectoris, ventricular arrhythmias, decreased ratio of heart failure was observed. Improved psychosomatic status of the patients in comparison with control group was observed as well [29].

Application of adenosine and high-energy phosphates during intraoperative and postoperative periods

H. V. Thourani et al. in 1999 presented experimental model, where possibility to apply ADO was explored in case of severe regional ischemia. Left anterior descending coronary artery was loosely encircled. This produced regional myocardial ischemia. Adenosine was administered in two study groups (third – control one): in first group ADO was added to cardioplegic solution, in second group continuous intravenous infusion of ADO was given together with ADO enrichment of cardioplegic solution. Authors observed reduced zone of myocardial infarction. It was proved that application of ADO guarantees protection of ischemic myocardium [25]. This may condition improved prognosis. Decreased levels of creatine kinase and myeloperoxidase were observed in the group where ADO was administered intravenously in comparison with control group. Authors observed statistically significant difference by comparing zone of myocardial edema in the group, where ADO was applied intravenously with other two groups. This zone was significantly reduced in the group where ADO was used intravenously [25]. Reduced activity of neutrophil adhesion in left anterior descending coronary artery at the time of reperfusion was observed in the second group as well [25].

Enhance of energetic resources is important during postoperative period. Application of HEP is one of possible solutions. Reduction of duration of postoperative intensive care treatment and mortality is main the task of usage of these substances. Such effects were observed, if phosphocreatine was applied during the operation. Other effects such as reduced requirement of inotropic substances, improved contractile function of myocardium was observed as well [2,4,6].

Correction of systemic hypertension is a proven effect of ADO. Continuous infusion of ADO reduces blood pressure down to expected level within 1-3 minutes. Discontinuation of ADO continuous infusion provides restoration of blood pressure level within 1-5 minutes. Due to those specific characteristics of blood pressure correction, ADO can be successfully applied for controlled hypotension during operation, but according to recent studies this effect is handy to achieve postoperative correction of hypertension [30]. Further clinical studies are needed to base indications of ADO administration for correction of blood pressure.

Unfortunately, there is lack of studies to prove advantages and disadvantages of ADO and HEP administration in postoperative period [4].

Discussion

Problem of ADO and HEP application has not been solved yet. Different results of research studies were presented. Some authors observed positive effects of ADO and phosphocreatine application, improving and preserving inotropic function of the heart during whole perioperative period (improved response, reduced requirement of inotropic substances) [14,15]. Application of phosphocreatine reduced occurrence of arrhythmias, number of DC-shocks at the end of operations, decreased requirement of inotropic drugs in postoperative period [2,6].

Alternative opinion supports position that application of ADO in preoperative period doesn’t give any reliable effect [13]. This is based on short stability and rapid disintegration of phosphates in the body. This disadvantage might be improved by administration of continuous infusions, searching specific transport inhibitors of ADO, reducing absorption to the cells.

Conclusions:

1. Positive effects of ADO and HEP application in cardiac anesthesiology for preoperative and postoperative treatment are conditioned by improved preservation of myocardial function during postoperative period.

2. Application of phosphocreatine before the operation can significantly reduce incidence of arrhythmias and requirement of inotropic drugs during postoperative intensive care.

3. Research studies for ADO and HEP application are needed for further usage of these substances during postoperative period.
Adenozino ir didelės energinės vertės fosfatų vartojimas kardioanesteziologijai

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