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Effects of Ischemic and Sevoflurane-induced Preconditioning on Myocardial Infarction and Arrhythmias in Rabbits *In Vivo*

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Abstract

Objectives: The present study aimed to investigate whether ischemic or sevoflurane-induced preconditioning exerts infarct size limiting effects and depresses ischemia-reperfusion arrhythmias through opening of mitochondrial K_{ATP} channels in rabbits *in vivo*.

Methods: Rabbits anesthetized with ketamine and xylazine given intramuscularly underwent 30 min of left anterior descending coronary artery (LAD) occlusion followed by 3 hrs of reperfusion. Before this, rabbits were randomized into one of five groups. Control rabbits received no intervention before 30 min LAD occlusion and 3 h reperfusion (Group-C). The ischemia-preconditioned (IP) rabbits underwent 5 min LAD occlusion followed by 10 min of reperfusion before prolonged ischemia-reperfusion (Group-IP). In the sevoflurane (S)–preconditioned group, 30 min of sevoflurane exposure at a 1.5% end-tidal concentration was followed by 15 min of washout before prolonged ischemia-reperfusion (Group-S). The selective mitochondrial K_{ATP} channel blocker, 5-hydroxy-decanoate (5-HD, 5 mg/kg) was given intravenously 10 min before ischemic preconditioning and sevoflurane exposure, respectively (Group-5-HD-IP, Group-5-HD-S). An electrocardiogram was recorded throughout the experiment *via* lead 2 of the standard electrocardiogram. At the end of the 3 hrs reperfusion period, area at risk (R) and infarct size (I) were measured.

Results: RPP decreased in Group-5-HD-IP and Group-5-HD-S compared with Group-S at 30 min after ischemia. The ratio of R to left ventricular mass showed no significant difference among all groups. I/R values of each group were 51.6 ± 3.0% in Group-C, 33.3 ± 4.7% in Group-IP, 36.6 ± 4.8% in Group-S, 48.9 ± 5.2% in Group-5-HD-IP, 54.8 ± 4.2% in Group-Group-5-HD-S. There was no significant difference in duration of arrhythmias during myocardial ischemia and reperfusion among 5 groups.

Conclusion: Ischemic preconditioning and sevoflurane-induced preconditioning exert infarct size limiting effects through opening of mitochondrial K_{ATP} channels. However, ischemic preconditioning and sevoflurane-induced preconditioning do not have antiarrhythmic effects. This suggests that the opening of mitochondrial K_{ATP} channels does not cause antiarrhythmic effects.

Keywords: Arrhythmia; Ischemia/reperfusion injury; 5-Hydroxy-decanoate; Preconditioning

Introduction

Lethal injury to the heart can be dramatically blunted by brief conditioning periods of ischemia and reperfusion: a phenomenon called ischemic preconditioning [1,2]. And brief exposure to a volatile anesthetic agent such as isoflurane [3] and sevoflurane [4,5] also protects the heart against subsequent ischemia–reperfusion injury. This phenomenon has been recognized as anesthetic preconditioning [6]. To date, numerous studies have investigated the mechanism of cardiac preconditioning, and many crucial components underlying cardioprotection have been identified. Adenosine triphosphate-sensitive potassium (K_{ATP}) channels have long been considered as essential components of cardioprotection by both ischemic and anesthetic preconditioning [7,8]. There are two populations of K_{ATP} channels in cardiac myocytes: the mitochondrial (mitoK_{ATP}) channel located in the inner mitochondrial membrane and the sarcolemmal (sarc K_{ATP}) channel located in the plasma membrane [9]. A role for mitochondrial K_{ATP} channels in ischemic preconditioning has been suggested [10]. As for the role for mitochondrial K_{ATP} channels in anesthetic preconditioning, our laboratory demonstrated that the protective effects by sevoflurane as well as brief ischemia may be mediated by mitochondrial rather than sarcolemmal K_{ATP} channel opening [4].

Although the term "preconditioning" is currently employed primarily to describe a limitation of infarct size, subsequent studies [6,11] have demonstrated that preconditioning can in some models, afford protection against ischemia/reperfusion- induced arrhythmias. It remains to be determined, however, if antiarrhythmic protection is a direct consequence of anti-ischemic protection and if the mechanisms involved are the same as those involved in protection against infarction. Also, it is little known whether ischemic preconditioning and anesthetic preconditioning have antiarrhythmic effects or not, and whether K_{ATP} channels are related to arrhythmias during acute myocardial ischemia and reperfusion especially in rabbit hearts.

The present study, therefore, aimed to investigate whether ischemic or sevoflurane-induced preconditioning exerts infarct size limiting effects and depresses ischemia-reperfusion arrhythmias through opening of mitochondrial K_{ATP} channels in rabbits *in vivo*.

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Materials and Methods

The present study was performed in accordance with the Guidelines of Animal Care and Use Committee of Kanagawa Dental University.

General surgical preparation

Male New Zealand White rabbits weighing 2.7-3.2 kg were allowed *ad libitum* access to standard laboratory stock diet and water. Animals were initially anesthetized with ketamine (35 mg/kg) and xylazine (5 mg/kg) given intramuscularly. Tracheotomy was performed and rabbits were intubated with an uncuffed endotracheal tube (ID 3.5 mm). The animals were ventilated with room air supplemented with additional oxygen. Inspired and expired anesthetic concentration, inspiratory O_2 percentage and end-tidal CO_2 partial pressures were continuously monitored using a multigas anesthetic monitor (Datex, Capnomac, Helsinki, Finland). The respiratory rate was frequently adjusted to maintain P_aO_2 greater than 100 mm Hg, P_aCO_2 at 35-45 mm Hg, pH 7.35-7.45, and Base Excess between -3 and +3. After the left jugular vein was exposed and cannulated with a polyethylene catheter, 0.9% sodium chloride (0.15 ml/min) was continually administered during the experiments. The carotid artery was dissected out and fluid-filled polyethylene tube was placed in it and connected immediately to an electrocardiogram monitor (Nihon-kohden Co, Life scope 11, Tokyo, Japan) *via* pressure transducer (Nihon-kohden Co, TP-400T, Tokyo, Japan) for arterial pressure recording. An electrocardiogram was recorded throughout the experiment *via* lead II of the standard electrocardiogram. Ischemia or reperfusion-induced arrhythmias included premature ventricular contraction (PVC) and ventricular tachycardia (VT). Left thoracotomy was performed and pericardium was opened to expose the heart. A silk thread (K-890H, Ethicon, Somerville, NJ) with taper C-1 needle was passed around the left anterior descending artery (LAD) and the end of the tie were threaded through a small vinyl tube to form a snare. The LAD was occluded by pulling the snare, which was then fixed by clamping the tube with a mosquito hemostat. Myocardial ischemia was confirmed by regional cyanosis, ST segment elevation and decreased blood pressure. Reperfusion was confirmed by reactive hyperemia over the surface after releasing the snare.

Study groups and experimental protocol

Figure 1 presents study groups and experimental protocol. Anesthesia was maintained with ketamine and xylazine solution (ketamine 35 mg/kg/hr, xylazine 5 mg/kg/hr i.m.; k/x) with room air supplemented with additional pure oxygen. After all the surgical procedures had been performed, a 15 min period was allowed for stabilization. All anesthetized open-chest rabbits underwent 30 min of left anterior descending coronary artery (LAD) occlusion followed by 3 hrs of reperfusion. Before this, the animals were randomized into one of the following experimental protocols:

Control rabbits received no intervention before 30 min LAD occlusion and 3 hrs reperfusion (Group-C; n=9). The ischemia-preconditioned (IP) rabbits underwent 5 min LAD occlusion followed by 10 min of reperfusion before prolonged ischemia-reperfusion (Group-IP; n=10). In the sevoflurane (S)–preconditioned group, 30 min of sevoflurane exposure at a 1.5% end-tidal concentration was followed by 15 min of washout before prolonged ischemia-reperfusion (Group-S, n=6). The selective mitochondrial K_{ATP} channel blocker, 5-hydroxy-decanoate (5-HD, 5 mg/kg) was given intravenously 10 min before ischemic preconditioning and sevoflurane exposure, respectively (Group-5-HD-IP; n=6, Group-5-HD-S; n=6). At the end of the 3 hrs reperfusion period, area at risk and infarct size were measured.

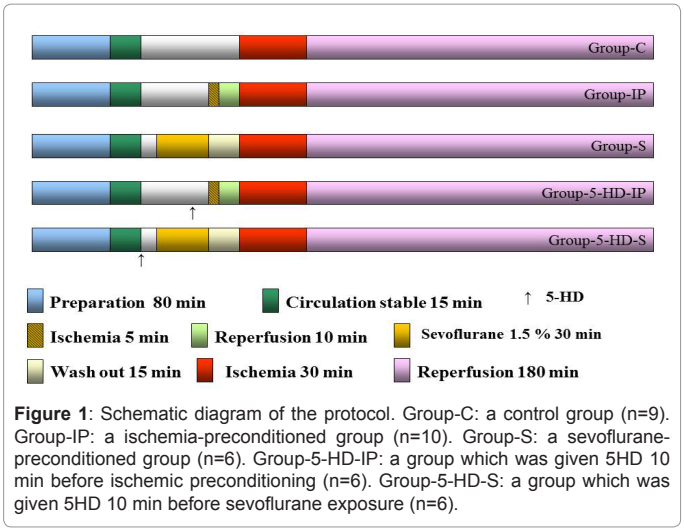

Figure 1: Schematic diagram of the protocol. Group-C: a control group (n=9). Group-IP: a ischemia-preconditioned group (n=10). Group-S: a sevoflurane-preconditioned group (n=6). Group-5-HD-IP: a group which was given 5HD 10 min before ischemic preconditioning (n=6). Group-5-HD-S: a group which was given 5HD 10 min before sevoflurane exposure (n=6).

Hemodynamic measurements

Hemodynamic measurements included systolic, diastolic, mean arterial blood pressures and heart rate. Rate pressure product was calculated as the product of heart rate and peak arterial pressure. Baseline hemodynamic measurements were taken prior to any experimental manipulations. Subsequently, the measurements were taken at 29 min of ischemia and 30, 60 and 180 min of reperfusion.

Determination of area at risk and infarct size

Following completion of experimental protocol, the *in vivo* visualization of the myocardium at risk was accomplished with reocclusion of the coronary artery and injection of 10% Evans blue into the venous cannula until the eyes turned blue. The Evans blue was allowed to circulate for about 30 sec to demarcate the risk and non-risk regions. The hearts were quickly excised under deep anesthesia and frozen. The frozen hearts were then cut into six transverse slices of equal thickness. The area at risk was determined by negative staining with Evans blue. The slices were stained by incubation for 15 min in 1% triphenyl tetrazolium chloride (TTC) in isotonic pH 7.4 phosphate buffer. After staining, the sections were placed in formalin for preservation, and measurements of risk area, infarct area and left ventricle were made with computer aided morphometry. From each section, the ischemic area at risk (unstained by blue dye) and the infarcted area (unstained by TTC) were outlined and measured by planimetry. The area from each region was averaged from the slices. Infarct size was expressed both as a percentage of total left ventricular mass (L) and as a percentage of the ischemic risk area. This method has generally been found to be an accurate measure of ultimate infarct size at 2 to 48 hr of reperfusion when compared with subsequent histologic analysis [12,13].

Rabbits which could not be survived until the end of experiments with lethal arrhythmias such as ventricular fibrillation (VF) have excluded from the data analysis and not considered further.

Statistical Analysis

Statistical comparisons of individual hemodynamic parameters between groups were made using one-way ANOVA followed by Fisher's protected least significant difference. Bartlett's test for equality of variances was used to ensure the validity of statistical comparison using the one-way ANOVA. Statistical comparisons of infarct size/area

at risk, area at risk/left ventricle, and duration of arrhythmias between groups were made using an ANOVA and Kruskal-Wallis test followed Dunn procedure. All data are reported as group mean ± SEM, and were considered statistically significant at a probability value (P) less than 0.05.

Results

Rate pressure product (RPP) is shown in Table 1. RPP decreased in Group-5-HD-IP and Group-5-HD-S compared with Group-S at 30 min after ischemia. The ratio of areas at risk (R) to left ventricular mass (L) ranged from 54.0 ± 4.9% to 66.1 ± 5.3% with no significant difference among all the groups (Figure 2). Figure 3 shows the infarct size (I) expressed as percentage of area at risk (R) in five groups. I/R values of each group were 51.6 ± 3.0% in Group-C, 33.3 ± 4.7% in Group-IP, 36.6 ± 4.8% in Group-S, 48.9 ± 5.2% in Group-5-HD-IP, 54.8 ± 4.2% in Group-Group-5-HD-S. The mean infarct sizes in Group-IP and Group-S were significantly smaller than that of Group-C. Infarct size in Group-IP was significantly smaller compared with that of Group-5-HD-IP. The mean infarct sizes in Group-IP and Group-S were significantly smaller than that of Group-5-HD-S. The duration of arrhythmias during myocardial ischemia were 91.4 ± 37.0 sec in Group-C, 55.7 ± 32.6 sec in Group-IP, 30.1 ± 20.5 sec in Group-S, 42.4 ± 26.8 sec in Group-5-HD-IP, 35.0 ± 22.5 sec in Group-5-HD-S (Figure 4). The duration of arrhythmias during reperfusion were 200.5 ± 39.1 sec in Group-C, 127.4 ± 41.4 sec in Group-IP, 151.0 ± 35.7 sec in Group-S, 153.0 ± 99.4 sec in Group-5-HD-IP, 80.5 ± 38.3 sec in Group-5-HD-S (Figure 5). There was no significant difference in duration of arrhythmias during myocardial ischemia and reperfusion among 5 groups.

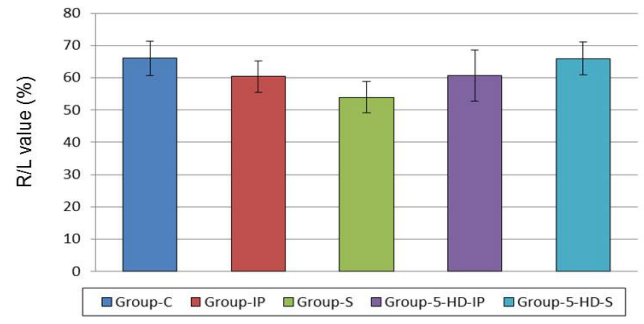

Figure 2: The figure shows R/L value (%), which means the area at risk expressed as percentage of left ventricle. Data are expressed as mean ± SEM. Area at risk revealed no significant difference among all groups, suggesting that the changes in the infarct size observed among the groups did not depend on R/L. Group-C: a control group (n=9). Group-IP: a ischemia-preconditioned group (n=10). Group-S: a sevoflurane-preconditioned group (n=6). Group-5-HD-IP: a group which was given 5HD 10 min before ischemic preconditioning (n=6). Group-5-HD-S: a group which was given 5HD 10 min before sevoflurane exposure (n=6).

Discussion

In the present study, both ischemic and sevoflurane-induced preconditioning also reduced infarct size, and 5-HD, an effective blocker of mitochondrial K_{ATP} channels abolished infarct size limiting effect. Our previous study [14] in the same experimental system and other studies [15-17] have demonstrated that 5-HD alone caused no significant changes in myocardial infarct size and hemodynamics. These results and observations suggest that both ischemic and sevoflurane-induced preconditioning exerted infarct size limiting effect through opening of mitochondrial K_{ATP} channels. Thus, the cardioprotection by ischemic and sevoflurane-induced preconditioning may be mediated, at least in part, by mitochondrial K_{ATP} channel. However, ischemic preconditioning and sevoflurane-induced preconditioning did not have anti-arrhythmic effects. In this experiment, ischemia may result in increased potassium ion (K^+) efflux and accumulation of extracellular K^+, and leads to produce arrhythmias. The mechanisms underlying reperfusion-induced arrhythmias seem to be different from those responsible for the induction of ischemia-induced arrhythmias. These include oxygen free radicals and increased levels of intracellular calcium [18].

Protection of ischemic preconditioning against arrhythmias is somewhat controversial and varies dependent on species [19]. It was reported that ischemic preconditioning decreased incidence of arrhythmias in *in vivo* rats [20-22] and dogs [11,23]. Also, it was suggested that the protective effect of ischemic preconditioning against arrhythmias is not likely to be involved in activation of K_{ATP} potassium channels during ischemia [20]. On the contrary, in *in vivo* dogs, possible mechanism of antiarrhythmic action by ischemic preconditioning is related to opening of mito K_{ATP} channels [22,23].

In the rabbit model, in which collateral flow is negligible [24], protection of ischemic preconditioning against arrhythmias was not observed. And as far as we have investigated, there have been no references that ischemic preconditioning has antiarrhythmic effect during ischemia and reperfusion in *in vivo* rabbit hearts.

As for anesthetic preconditioning, Kevin and Novalija suggested that isoflurane-induced preconditioning reduced the incidence of arrhythmia in in vitro rat hearts [6].

In this study, sevoflurane-induced preconditioning did not reduce ischemia-reperfusion arrhythmias. It may be due to the differences of species, length of ischemia and reperfusion, the choice of anesthetics, timing and concentration of anesthetics exposure and extent of collateral blood flow.

It has been reported that pretreatment with nicorandil and pinacidil, both K_{ATP} channel openers administered just prior to coronary occlusion resulted in protection against ischemia/reperfusion-induced arrhythmias in anesthetized rabbits due to activation of cardiomyocyte mitochondrial K_{ATP} channels. K_{ATP} channel openers may shorten the action potential duration, thereby reducing cellular calcium overload

	Pre-Ischemia	30 min after Ischemia	30 min after Reperfusion	60 min after Reperfusion	180 min after Reperfusion
Group -C	13712.1 ± 864.9	12936.6 ± 455.2	13050.2 ± 840.3	13012.1 ± 788.5	112101.7 ± 733.3
Group -IP	13396.4 ± 987.4	13253.9 ± 845.4	12731.9 ± 924.0	12966.1 ± 863.8	11552.1 ± 793.0
Group-S	13769.3 ± 692.8	14906.7 ± 1071.2	14532.5 ± 1403.8	14151.2 ± 1978.1	10365.0 ± 1868.9
Group -5-HD-IP	12615.0 ± 769.8	12183.2 ± 529.3*	12441.5 ± 498.4	11980.0 ± 442.8	11449.7 ± 654.7
Group-5-HD-S	13501.8 ± 1100.3	11948.5 ± 928.9*	12303.0 ± 922.1	11969.8 ± 758.2	11368.8 ± 853.1

*Significantly different (P<0.05) from Group-S (mean ± SEM)

Table1: Rate pressure product during ischemia and reperfusion.

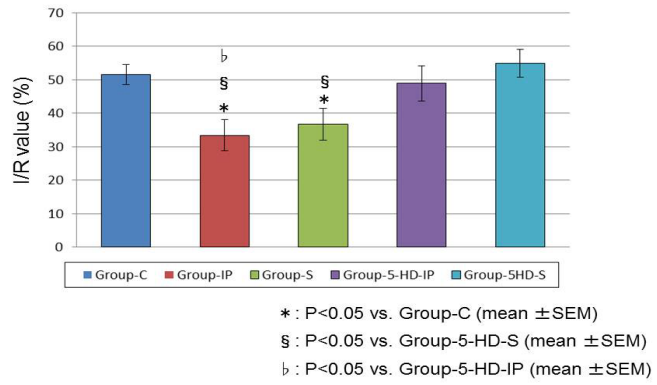

Figure 3: The figure shows I/R value (%), which means the infarct size expressed as percentage of area at risk. Data are expressed as mean ± SEM. *Significantly different (P<0.05) from Group-C, ♭Significantly different (P<0.05) from Group-5-HD-IP, §Significantly different (P<0.05) from Group-5-HD-S. Group-C: a control group (n=9). Group-IP: a ischemia-preconditioned group (n=10). Group-S: a sevoflurane-preconditioned group (n=6). Group-5-HD-IP: a group which was given 5HD 10 min before ischemic preconditioning (n=6). Group-5-HD-S: a group which was given 5HD 10 min before sevoflurane exposure (n=6).

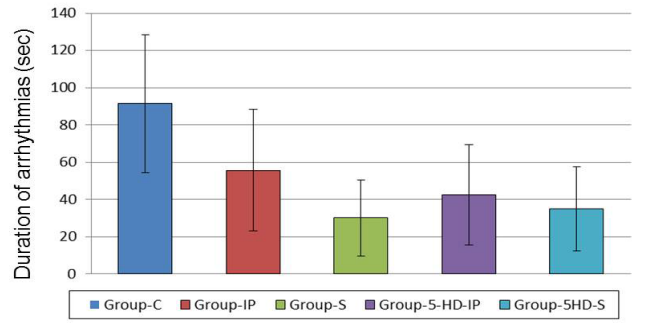

Figure 4: The figure shows duration of arrhythmias during myocardial ischemia. Data are expressed as mean ± SEM. Group-C: a control group (n=9). Group-IP: a ischemia-preconditioned group (n=10). Group-S: a sevoflurane-preconditioned group (n=6). Group-5-HD-IP: a group which was given 5HD 10 min before ischemic preconditioning (n=6). Group-5-HD-S: a group which was given 5HD 10 min before sevoflurane exposure (n=6).

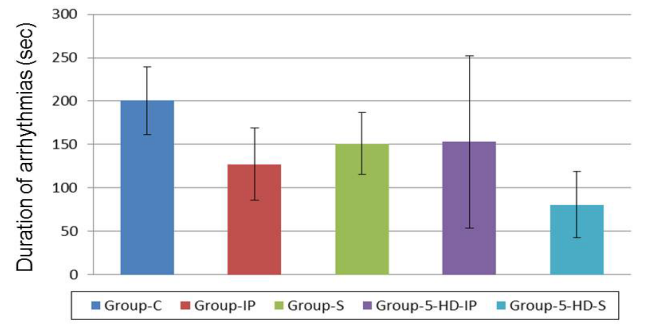

Figure 5: The figure shows duration of arrhythmias during myocardial reperfusion. Data are expressed as mean ± SEM. Group-C: a control group (n=9). Group-IP: a ischemia-preconditioned group (n=10). Group-S: a sevoflurane-preconditioned group (n=6). Group-5-HD-IP: a group which was given 5HD 10 min before ischemic preconditioning (n=6). Group-5-HD-S: a group which was given 5HD 10 min before sevoflurane exposure (n=6).

and preserving viability in ischemic/reperfused myocardium, which was initially proposed as the mechanism for protection of ischemic myocardium [25].

Antiarrhythmic protection must be the manifestation of a preservation of ionic homeostasis, whereas the essential requirements for protection against necrosis may be different. Indeed, from many of the studies, it is clear that it is possible to protect against necrosis without the prevention of arrhythmias and vice versa [26].

In the present investigation, though ischemic and sevoflurane-induced preconditioning reduced infarct size through opening of mitochondrial K_{ATP} channels, it offered no protection against arrhythmias during ischemia and reperfusion.

From these observations, unlike nicorandil and pinacidil, ischemic preconditioning and this dose of sevoflurane might not open K_{ATP} channel enough to exert antiarrhythmic action.

In summary, the present study indicates that ischemic preconditioning and sevoflurane-induced preconditioning exert infarct size limiting effects through opening of mitochondrial K_{ATP} channels. However, ischemic preconditioning and sevoflurane-induced preconditioning do not have antiarrhythmic effects.

This suggests that the opening of mitochondrial K_{ATP} channels by ischemic preconditioning and sevoflurane-induced preconditioning may not be enough to cause antiarrhythmic effects in *in vivo* rabbit hearts even though there is the common mechanism responsible for both infarct limiting and antiarrhythmic effects.

References

1. Murry CE, Jennings RB, Reimer KA (1986) Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation 74: 1124-1136.
2. Liu Y, Sato T, Seharaseyon J, Szewczyk A, O'Rourke B, et al. (1999) Mitochondrial ATP-dependent potassium channels. Viable candidate effectors of ischemic preconditioning. Ann N Y Acad Sci 874: 27-37.
3. Kersten JR, Schmeling TJ, Pagel PS, Gross GJ, Warltier DC (1997) Isoflurane mimics ischemic preconditioning via activation of K(ATP) channels: reduction of myocardial infarct size with an acute memory phase. Anesthesiology 87: 361-370.
4. Ohdachi M, Nishida N, Furuya M, Yoshida K (2005) Sevoflurane does not confer additive cardioprotection on early ischemic preconditioning in rabbit hearts. Circ Cont 26: 314-321.
5. Dai AL, Fan LH, Zhang FJ, Yang MJ, Yu J, et al. (2010) Effects of sevoflurane preconditioning and postconditioning on rat myocardial stunning in ischemic reperfusion injury. J Zhejiang Univ Sci B 11: 267-274.
6. Kevin LG, Novalija E (2008) Anesthetic preconditioning decreases arrhythmias and improves regional conduction in isolated hearts. J Cardiothorac Vasc Anesth 22: 217-224.
7. Jin C, Wu J, Watanabe M, Okada T, Iesaki T (2012) Mitochondrial K+ channels are involved in ischemic postconditioning in rat hearts. J Physiol Sci 62: 325-332.
8. Zaugg M, Lucchinetti E, Spahn DR, Pasch T, Schaub MC (2002) Volatile anesthetics mimic cardiac preconditioning by priming the activation of mitochondrial K(ATP) channels via multiple signaling pathways. Anesthesiology 97: 4-14.
9. Marinovic J, Bosnjak ZJ, Stadnicka A (2006) Distinct roles for sarcolemmal and mitochondrial adenosine triphosphate-sensitive potassium channels in isoflurane-induced protection against oxidative stress. Anesthesiology 105: 98-104.
10. Toller WG, Gross ER, Kersten JR, Pagel PS, Gross GJ, et al. (2000) Sarcolemmal and mitochondrial adenosine triphosphate- dependent potassium channels: mechanism of desflurane-induced cardioprotection. Anesthesiology 92: 1731-1739.
11. Shome S, Lux RL, Punske BB, MacLeod RS (2007) Ischemic preconditioning protects against arrhythmogenesis through maintenance of both active as well as passive electrical properties in ischemic canine hearts. J Electrocardiol 40: 150-159.

12. Horneffer PJ, Healy B, Gott VL, Gardner TJ (1987) The rapid evolution of a myocardial infarction in an end-artery coronary preparation. Circulation 76: V39-42.

13. Fishbein MC, Meerbaum S, Rit J, Lando U, Kanmatsuse K, et al. (1981) Early phase acute myocardial infarct size quantification: validation of the triphenyl tetrazolium chloride tissue enzyme staining technique. Am Heart J 101: 593-600.

14. Salloum FN, Takenoshita Y, Ockaili RA, Daoud VP, Chou E, et al. (2007) Sildenafil and vardenafil but not nitroglycerin limit myocardial infarction through opening of mitochondrial K(ATP) channels when administered at reperfusion following ischemia in rabbits. J Mol Cell Cardiol 42: 453-458.

15. Bai Y, Muqier, Murakami H, Iwasa M, Sumi S, et al. (2011) Cilostazol protects the heart against ischaemia reperfusion injury in a rabbit model of myocardial infarction: focus on adenosine, nitric oxide and mitochondrial ATP-sensitive potassium channels. Clin Exp Pharmacol Physiol 38: 658-665.

16. Chen X, Minatoguchi S, Wang N, Arai M, Lu C, et al. (2003) Quinaprilat reduces myocardial infarct size involving nitric oxide production and mitochondrial KATP channel in rabbits. J Cardiovasc Pharmacol 41: 938-945.

17. Masui K, Kashimoto S, Furuya A, Oguchi T (2006) Isoflurane and sevoflurane during reperfusion prevent recovery from ischaemia in mitochondrial KATP channel blocker pretreated hearts. Eur J Anaesthesiol 23: 123-129.

18. Yoshida K, Takano H, Sawada H, Furuya M, Ohsawa A (2000) Lidocaine protects the ischemic rabbit myocardium from infarction as well as from ventricular arrhythmias. Am J Anesthesiol 27: 419-423.

19. Gross GJ, Peart JN (2003) KATP channels and myocardial preconditioning: an update. Am J Physiol Heart Circ Physiol 285: H921-930.

20. Lu H, Remeysen P, De Clerck F (1993) The protection by ischemic preconditioning against myocardial ischemia- and reperfusion-induced arrhythmias is not mediated by ATP-sensitive potassium channels in rats. Coron Artery Dis 4: 649-657.

21. Kita H, Miura T, Tsuchida A, Hasegawa T, Shimamoto K (1998) Suppression of reperfusion arrhythmias by preconditioning is inhibited by an ATP-sensitive potassium channel blocker, 5-hydroxydecanoate, but not by protein kinase C blockers in the rat. J Cardiovasc Pharmacol 32: 791-797.

22. Matejíková J, Kucharská J, Pintérová M, Pancza D, Ravingerová T (2009) Protection against ischemia-induced ventricular arrhythmias and myocardial dysfunction conferred by preconditioning in the rat heart: involvement of mitochondrial KATP channels and reactive oxygen species. Physiol Res 58: 9-19.

23. Végh A, Parratt JR (2002) The role of mitochondrial K(ATP) channels in antiarrhythmic effects of ischaemic preconditioning in dogs. Br J Pharmacol 137: 1107-1115.

24. Maxwell MP, Hearse DJ, Yellon DM (1987) Species variation in the coronary collateral circulation during regional myocardial ischaemia: a critical determinant of the rate of evolution and extent of myocardial infarction. Cardiovasc Res 21: 737-746.

25. Das B, Sarkar C (2003) Cardiomyocyte mitochondrial KATP channels participate in the antiarrhythmic and antiinfarct effects of KATP activators during ischemia and reperfusion in an intact anesthetized rabbit model. Pol J Pharmacol 55: 771-786.

26. Przyklenk K, Kloner RA, Yellon DM (1994) Ischemic preconditioning: The concept of endogenous cardioprotection. Kluwer Academic Publishers 19-40.