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Effects of Lidocaine on Ischemia/Reperfusion Injury in *In vivo* Rabbit Hearts

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Abstract

Objective: The aim of this study was to investigate the cardioprotective effects of lidocaine administered at three different timings, as indexes of hemodynamics, infarct size, antiarrhythmic action, and changing activation time by electrocardiogram in *in vivo* rabbit hearts.

Methods: Thirty two rabbits received regional ischemia by 30 min of left anterior descending coronary artery occlusion followed 3 hours of reperfusion under ketamine and xylazine anesthesia. The animals were randomly assigned to the following 4 treatment groups: a control group, a lidocaine-preconditioned group, a lidocaine-postconditioned group, and a lidocaine-continuous administration group.

Results: The ratio of areas at risk revealed no significant difference among all groups. Mean infarct size of the area at risk was significantly less in a lidocaine-continuous administration group than other 3 groups. The incidence of arrhythmias during myocardial ischemia was no significant difference between a control group and other 3 groups. The incidence of arrhythmias during reperfusion was no significant difference among all groups. However, lidocaine depressed the activation time which was prolonged by ischemia.

Conclusions: It was suggested that lidocaine produced neither preconditioning nor post-conditioning benefits. Lidocaine did not have antiarrhythmic effects during ischemia/reperfusion injury. The clinical implications of this investigation are that lidocaine infusion is no longer recommended for the treatment of ventricular arrhythmias during acute coronary syndrome; however, continuous administration of lidocaine may be effective to make the infarct size small. The prolonged activation time during ischemia was depressed by lidocaine. Thus, it was also indicated that the activation time during ischemia and reperfusion can be normalized by lidocaine.

Keywords: Arrhythmia; Ischemia/reperfusion injury; Lidocaine; Myocardial protection; Preconditioning; Postconditioning

Introduction

Ischemia/reperfusion injury refers to the tissue damage which occurs when blood supply returns to tissue after a period of ischemia [1]. Clinically, patients with coronary artery disease are often subjected to coronary reperfusion after cardiac arrest, interventional recanalization, myocardial infarction, coronary spasm or thorombosis [2]. Recently, myocardial ischemia/reperfusion injury and its prevention have become the focus of considerable attention.

The local anesthetic lidocaine is often used for antiarrhythmic drug which acts as a blocker of fast Na channels, and the effectiveness of lidocaine in the treatment of malignant ventricular arrhythmias during ischemia/reperfusion has been reported [3]. Also, several studies have demonstrated that continuous administration of lidocaine reduces myocardial ischemia-reperfusion injury *in vitro* rat heart [4] and *in vivo* rabbit [5], cat [6], pig [7], mice [8] and dog heart [9].

On the other hand, lidocaine seems to have no proven short- or long-term efficacy in cardiac arrest, and may be considered if amiodarone is not available, according to the American Heart Association (AHA) Guidelines 2010 for cardiopulmonary resuscitation and emergency cardiovascular care [10].

So far, there has been little information about the effects of lidocaine on ischemia/reperfusion injury when administered before ischemia (preconditioning), and during reperfusion (postconditioning). The aim of this study was to investigate the cardioprotective effects of lidocaine administered at three different times, as indexes of hemodynamics, infarct size, the incidence of arrhythmias, and changing activation time by electrocardiogram during ischemia/reperfusion in an *in vivo* rabbit model.

Materials and Methods

The present study was performed in accordance with the guidelines of animal care and use Committee of Kanagawa Dental College.

General surgical preparation

Male New Zealand White rabbits weighting 2.5~3.6 kg were allowed *ad labium* access to standard laboratory stock diet and water. Animals were initially anesthetized with ketamine (35 mg/kg) and xylazine (5 mg/kg) given intramuscularly. 5 ml of 1% lidocaine was subcutaneously injected as an additional local anesthetic during the initial surgical procedures. 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 using a mechanical ventilator (Acoma, PRO-45Va, Tokyo, Japan) and a semi-

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closed breathing circuit (Acoma, NS-5000A, Tokyo, Japan). Inspired and expired anesthetic concentration, inspiratory O_2 percentage and end-tidal CO_2 partial pressures were continuously monitored using a multigas anesthetic monitor (COLIN, BP-508, Tokyo, Japan). The respiratory rate was frequently adjusted to maintain PaO_2 greater than 100 mmHg, $PaCO_2$ at 35-45 mmHg, 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). After all the surgical procedures had been performed, a 15 min period was allowed for stabilization. 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. 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.

An array of 6×6 monopolar electrodes (32 Map) to cover 13×13 mm square (interpolar distance, 2 mm) was put on the LAD of the left ventricle wall around the snare at any point during ischemia and reperfusion (Figure 1). The 32 Map signals recorded were processed by a computer (Unique Medical, HMS-100, Tokyo, Japan).

Study group and experimental protocol

The experimental design used in the current study is illustrated in figure 2. Rabbits were randomized into four groups (n=8, respectively). All the rabbits received regional ischemia by 30 min. of the LAD occlusion followed by 3 hrs of reperfusion K/X anesthesia. In the Group Control, rabbits were subjected to 30 min of LAD occlusion and 3 hrs of reperfusion under K/X anesthesia. Lidocaine-preconditioned group (Group Pre) animals received lidocaine bolus (4 mg/kg, IV) 10 min prior to ischemia. Lidocaine-postconditioned group (Group Post) animals received lidocaine bolus (4 mg/kg, IV) at the beginning of reperfusion. Lidocaine-continuous administration group (Group I+R) animals received continuous infusion of lidocaine (4 mg/kg/hr, IV) from 10 minutes prior to ischemia up to the end of reperfusion.

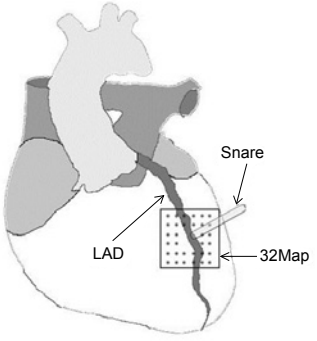

Figure 1: An array was put on the LAD of the left ventricle wall during ischemia and reperfusion.

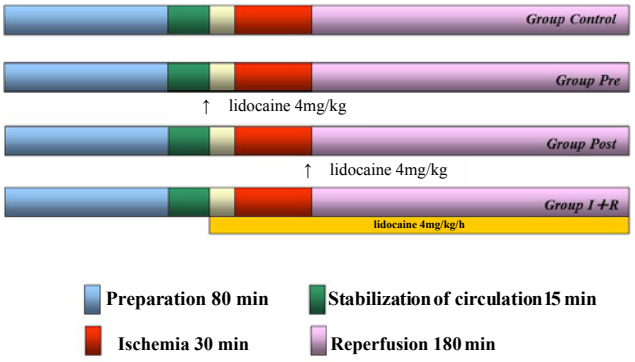

Figure 2: The experimental design used in the current study.

Determination of area at risk and infarct size

The area at risk and infarct size were determined by the standard approach [11,12] as follows. 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 area at risk, infarct area and left ventricle were made with computer aided morphometry. From each section, the ischemic risk area and the infarcted area were outlined and measured by planimetry. The infarct size was expressed both as a percentage of total left ventricle (LV) and as a percentage of the ischemic risk area.

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 and 60 min of reperfusion.

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.

Signal analysis and mapping

Activation time (AT) was defined as the interval from the beginning of QRS to the sharp negative deflection (min dV/dt). Total activation time (TAT) was measured from the maximal difference of AT [13].

Statistical Analysis

Between-group differences in area at risk/left ventricle and infarct size/area at risk and activation time were assessed by Kruskal-Wallis

	Group	Pre Ischemia	29 min after Ischemia	30 min after Reperfusion	60 min after Reperfusion
HR (beats/min)	Group Control	192.7 ± 10.3	198.4 ± 6.9	193.6 ± 7.9	196.5 ± 3.4
	Group Pre	210.7 ± 15.7	207.8 ± 12.4	201.5 ± 9.9	195.9 ± 10.9
	Group Post	214.5 ± 7.8	210.5 ± 8.4	204.6 ± 9.6	194.9 ± 9.4
	Group I+R	185.3 ± 11.1	193.0 ± 8.8	175.6 ± 11.7 §	168.9 ± 12.1
MAP (mmHg)	Group Control	78.9 ± 4.1	78.3 ± 3.8	75.4 ± 3.8	76.1 ± 3.8
	Group Pre	78.6 ± 5.1	65.6 ± 6.5	68.4 ± 5.3	74.0 ± 4.2
	Group Post	78.5 ± 1.9	74.4 ± 3.8	62.6 ± 7.4	66.8 ± 7.7
	Group I+R	76.4 ± 3.1	67.4 ± 7.1	67.8 ± 5.7	71.5 ± 4.2
RPP (mmHg/min)	Group Control	17914.7 ± 1138.9	18597.7 ± 756.3	17581.3 ± 673.4	18176.9 ± 658.6
	Group Pre	19523.6 ± 1 849.4	16319.3 ± 1478.9	16088.9 ± 968.0	16846.6 ± 892.2
	Group Post	20164.5 ± 1 095.8	18596.9 ± 1201.4	l5727.0 ± 1972.0	15955.3 ± 1985.0
	Group I+R	17045.5 ± 1022.5	15770.8 ± 1518.3	14410.4 ± 1010.3	14625.3 ± 814.0*

Table 1: Hemodynamics during ischemia and reperfusion.

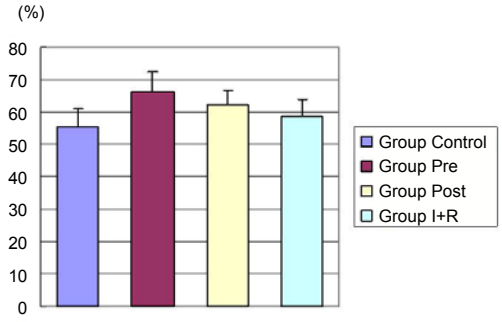

Figure 3: The ratio of areas at risk (R) to left ventricle (L).

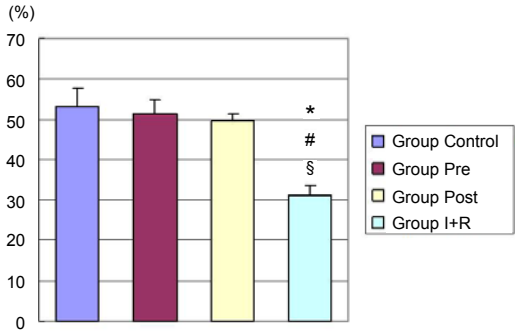

Figure 4: The infarct size expressed as percentage of area at risk in four groups.

test followed by Dunn's procedure as a multiple comparison procedure. Statistical comparisons of individual hemodynamic parameters between groups were made by using one–way analysis of variance (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. The difference in the percentage incidence of arrhythmias was analyzed with a χ^2 test. All data were reported as group mean ± SEM, and were considered statistically significant at a probability value (P) less than 0.05.

Results

Hemodynamics during ischemia and reperfusion are shown in table 1. Mean arterial blood pressure (MAP) did not alter significantly at the data points in all the groups. Heart rate (HR) in Group I+R was significantly less as compared with Group Post at 30 min after reperfusion. As for rate pressure product (RPP), there was significant difference between Group I+R and Group Control at 60 min after reperfusion.

The ratio of areas at risk (R) to left ventricle (L) ranged from 55.4 ± 5.8% to 66.3 ± 5.9% with no significant difference among all the groups (Figure 3). Figure 4 shows the infarct size expressed as percentage of area at risk in four groups. Mean infarct size (I) of the area at risk (R) was significantly less in Group I+R (31.2 ± 2.4%), than those in Group Control (53.0 ± 4.8%), Group Pre (51.3 ± 3.4%), and Group Post (49.6 ± 1.8%).

The incidence of arrhythmias during myocardial ischemia was 50.0% in Group Control and Group Post, 87.5% in Group Pre, and 25.0% in Group I+R respectively (Figure 5). There was no significant difference between Group Control and other 3 groups.

The incidence of arrhythmias during reperfusion was 75.0% in Group Control, Group Pre, and Group Post, and 37.5% in Group I+R respectively (Figure 5). There was no significant difference among all the groups.

Total activation time (TAT) ranged from 6.3 ± 1.0 ms to 7.6 ± 0.6 ms with no significant difference among all the groups before ischemia. TAT at 10 min after ischemia was 15.3 ± 1.2 ms in Group Control and decreased significantly in Group Pre (5.3 ± 0.5 ms) and Group I+R (6.8 ± 0.9 ms). TAT at 10 min after ischemia was 12.0 ± 1.7 min in Group Post and decreased significantly in Group Pre and Group I+R. TAT at 10 min after reperfusion was 16.0 ± 2.9 ms in Group Control and decreased significantly in Group Pre (5.6 ± 0.8 ms), Group Post (8.3 ± 0.9 ms), and Group I+R (6.0 ± 0.7 ms). TAT at 30 min after reperfusion was 12.9 ± 1.4 ms in Group Control and decreased significantly in Group Pre (6.9 ± 0.9 ms), Group Post (8.5 ± 1.0 ms), and Group I+R (6.5 ± 0.9 ms) (Figure 6).

Discussion

Murry et al. [14] first described that brief periods of ischemia before ischemia/reperfusion have powerful cardioprotective phenomenon: a phenomenon called ischemic preconditioning [14]. Recently, volatile anesthetics such as sevoflurane [15,16] and isoflurane [17] as well as ischemia have been proposed as preconditioning agents. And the concept of postconditioning, whereby ischemia or volatile anesthetics are introduced immediately upon reperfusion in an effort to attenuate myocardial ischemia/ reperfusion injury, has garnered increased attention [18].

We tried to test the hypothesis that lidocaine has preconditioning

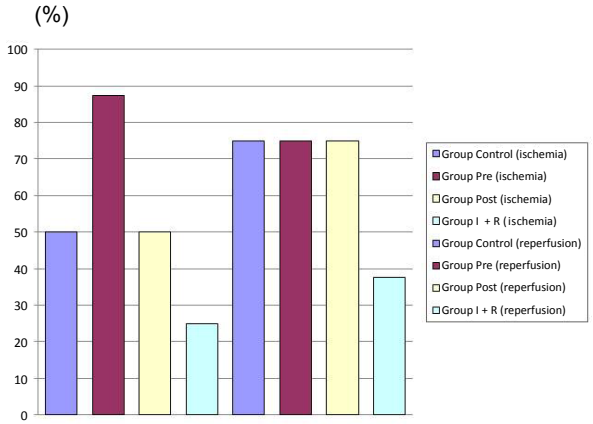

Figure 5: The incidence of arrhythmias during reperfusion.

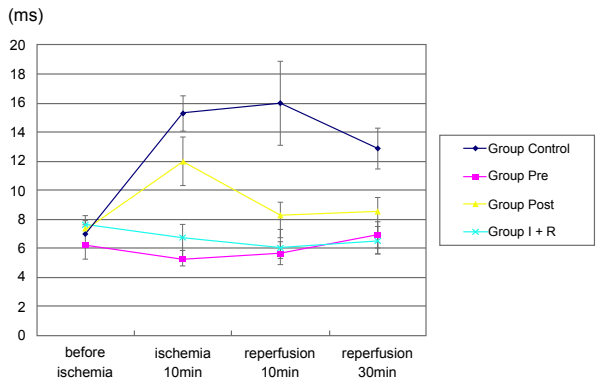

Figure 6: Total activation time (TAT).

or postconditioning effects like volatile anesthetics, since there have been few reference whether lidocaine is related to preconditioning or postconditioning with the exception of one report that administration of lidocaine before ischemia exhibited a potent myocardial protective effect in *in vivo* pig models [19].

Lidocaine is commonly administered as a bolus injection and, because of its short half-life (13 minutes), is continuously infused at the rate of 1-4 mg per minute. A rate of 1-5 mg/kg/h infused intravenously is suggested for therapeutic purposes for human [20,21]. Lidocaine has narrow therapeutic index, with only small difference between therapeutic and potential toxic concentrations [22]. The serum concentration associated with the clinical side effects is considered greater than 6.0 μg/ml [23,24].

In this study, 4 mg/kg of lidocaine was administered as a bolus injection and was continuously infused at the rate of 4 mg/kg/h, considering its side effects, hemodynamics and lower sensitivity to lidocaine in rabbits [2].

In this study, lidocaine administered before ischemia or during reperfusion neither reduced the infarct size nor the incidence of ventricular arrhythmias. These results suggest that lidocaine produced no preconditioning or postconditioning benefits.

Although the mechanisms underlying the cardioprotective effects of preconditioning are fully unknown, the opening of K_{ATP} channels seems to play a pivotal role in the signal transduction cascade in ischemic and volatile anesthetic-induced preconditioning and post conditioning [25,26]. Lidocaine, however, has been demonstrated to inhibit or attenuate the opening of the K_{ATP} channel [27-29]. That might be the reason why lidocaine is unable to produce preconditioning or postconditioning benefits.

On the contrary, continuous administration of lidocaine from 10 minutes prior to ischemia up to the end of reperfusion exerted cardioprotective effects after ischemia reperfusion injury, as shown by a reduction of the infarct area. Therefore, continuous infusion of lidocaine is necessary to limit the size of infarcts. A recent report [8] has shown similar results when lidocaine is infused continuously during ischemia in *in vivo* mice.

In the present investigation, the infarct size was determined by staining with TCC. 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 in animals [30]. TTC staining has been demonstrated to reveal equivalent infarct size values when compared with histologic determination in rabbits and dogs after 2 to 3 hr of reperfusion [31,32]. Similar conditions of ischemia and reperfusion were used in the present study and therefore the lower infarcts observed in this study do not appear to be attributable to technical factors other than lidocaine.

However, infarct size is affected by some factors such as the hemodynamics, the choice of anesthetics, timing of administration of drugs, and collateral blood flow of the animal used. Our results have shown that the rate pressure product, which is one index of myocardial oxygen demand, was significantly less in Group I+R compared with Group Control at 60 min after reperfusion. This suggests that the infarct size limiting effects by continuous infusion of lidocaine partly depends on decreased myocardial oxygen demand and supply. We have previously reported that lidocaine administered 10 minutes prior to and during ischemia and reperfusion can reduce the infarct size under sevoflurane anesthesia [33]. Regardless of the choice of anesthetics, continuous infusion of lidocaine during ischemia/reperfusion produced the infarct size limiting effects. These cardioprotections must be explained by a different mechanism from those of preconditioning and/or postconditioning. In this study, small amount of lidocaine administration before or after ischemia did not establish cardio protection and only continuous lidocaine administration caused infarct-limiting effects. These results may suggest the larger dose of lidocaine contributes to reducing the infarct size.

Although lidocaine might act as a stimulus to increase collateral blood flow to the ischemic area, the beneficial effects of lidocaine in our model is not explained by the enhanced collateral blood flow in rabbits whose coronary collateral blood flow is less than 2% [34,35], which is similar to human hearts.

For evaluation of the dynamics of the epicardial activation process, we used parameters TAT [36]. TAT (total activation time) reflects excitation conduction time to regional myocardia [37]. In the present study, TAT was prolonged in myocardial ischemia, and lidocaine itself did not cause noteworthy alterations of TAT in *in vivo* rabbit hearts. In addition, lidocaine depressed TAT which was prolonged by ischemia. This indicates that lidocaine prevents TAT from being extended by ischemia. In this point, lidocaine has cardio protective effects.

On the contrary, lidocaine produced no antiarrhythmic effect in spite of an infarct size limiting effect in the present study. Generally, the main cause of ischemia-induced arrhythmias is marked accumulation of intracellular Ca^{2+} and extracellular K^{+} with ischemia [38,39], and

the main cause of reperfusion-induced arrhythmias is Ca overload and generation of oxygen radicals [40,41]. Since lidocaine is a potent blocker of sodium channels [42], its antiarrhythmic properties are generally explained by its influence on sodium conductance. However, lidocaine was unable to decrease the incidence of arrhythmias in this study. These data suggests that this dose of lidocaine used in this experiment did not have antiarrhythmic effects during myocardial ischemia and reperfusion. As indicated in the AHA guidelines 2010 for Cardiopulmonary resuscitation and Emergency cardiovascular care [10], one shot of lidocaine administration after cardiac arrest may not be effective for arrhythmias. This would support our results even though the circumstances of this study are a little different from those of the AHA Guidelines.

Conclusions

In conclusion, continuous administration of lidocaine is necessary to limit the size of infarcts, although lidocaine neither produced preconditioning nor postconditioning benefits. Lidocaine did not have antiarrhythmic properties during ischemia/reperfusion injury in *in vivo* rabbit hearts. The activation time prolonged by ischemia was depressed by lidocaine suggesting that it can normalize activation time during ischemia and reperfusion. From these results, the clinical implications are that lidocaine infusion is no longer recommended for the treatment of ventricular arrhythmias during acute coronary syndrome; however, continuous administration of lidocaine may be effective to make the infarct size small. However, additional study regarding the optimal dose of lidocaine and its toxity during continuous infusion will be necessary if applied to humans.

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