

Myocardial Protective Effect of Lidocaine during Experimental Off-pump Coronary Artery Bypass Grafting

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Off-pump coronary artery bypass grafting (OPCABG) has recently gained popularity. During OPCABG, patients remain vulnerable to ischemic-reperfusion injury due to a temporary coronary occlusion without any active cardioprotection. Some strategies such as ischemic preconditioning (IP) and an intracoronary shunt have been applied with a view to minimizing the effects of ischemia, but the effects of these strategies remain controversial. This study was carried out to investigate the protective effect of lidocaine against myocardial ischemic-reperfusion injury. Twenty-one pigs were assigned to three groups, each consisting of seven pigs. In the control group, using a left internal thoracic artery (LITA) bypass circuit, the left anterior descending coronary artery (LAD) was occluded for 45 min followed by two hours of reperfusion. In the IP group, five min of occlusion followed by 15 min of reperfusion was performed. In the lidocaine group, 2 mg/kg of lidocaine was administered directly into the LAD just before the LAD occlusion. Infarct size expressed as a percentage of the area at risk was significantly smaller in the lidocaine group (2.7±4.2%) than in the control group (79.9±6.0%, p<0.001) or the IP group (57.0±25.9%, p<0.001). Lidocaine exhibited a potent myocardial protective effect in the present OPCABG model. (Ann Thorac Cardiovasc Surg 2003; 9: 36–42)

Key words: off-pump coronary artery bypass grafting, lidocaine, myocardial infarction, ischemia-reperfusion injury

Introduction

The development of retraction techniques and improved stabilizing devices has allowed the successful performance of off-pump coronary artery bypass grafting (OPCABG) which has recently gained popularity. However, hemodynamic deterioration during the procedure of retraction and stabilization, as well as temporary occlusion of an important coronary artery, could occasionally constitute

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This experiment was performed at National Defense Medical College.

a threat to the patients. In acute evolving infarction where blood flow is totally occluded, this temporary coronary occlusion may be superimposed on pre-existing ischemias of varying degrees. In addition, OPCABG has limited the strategies to protect the heart from ischemia or reperfusion injury. When reperfusion occurs, it produces lethal injury to the myocardial cells that are still alive, thus limiting the potential benefit reperfusion has on myocardial salvage. To avoid prolonged ischemia and possible reperfusion injury, the following strategies such as ischemic preconditioning (IP),¹ intracoronary shunts,² perfusion-assisted direct coronary artery bypass grafting (PADCABG)³ or synchronized coronary venous retroperfusion (SVR)⁴ in an experimental model have been applied in order to minimize the effects of ischemia during elective coronary occlusion, especially in multivessel OPCABG. Although many studies have identified effective cardioprotective agents in attenuating is-

chemia-reperfusion injury, a clinically useful strategy to protect the ischemic myocardium has not been developed for OPCABG when extracorporeal circulation and cardioplegia are not available. The use of IP has been advocated as a method for reducing injury from transient coronary occlusion before starting anastomosis.¹⁾ However, the effect of IP on postischemic global or regional myocardial function remains controversial.⁵⁻⁷⁾ Amongst the various cardioprotective drugs, lidocaine is one of the drugs which has been confirmed to be safe in humans and has the potential to protect the myocardium not only against ischemia⁸⁾ but also against reperfusion injury, especially in an experimental model in pigs.^{9,10)}

This study was carried out to investigate whether a selective delivery of lidocaine to a target vessel during OPCABG could attenuate ischemic or reperfusion injury in an OPCABG model.

Materials and Methods

The experimental protocol and methods of animal care were approved by the local ethics committee for animal research, which conforms to the "Guide for the Care and Use of Laboratory Animals", published by the U.S. National Institutes of Health (NIH Publication No. 86-23, revised 1985).

Animal preparation

A total of 24 farm pigs of either sex weighing 34 to 48 kg were premedicated with an intramuscular injection of ketamine hydrochloride 20 mg/kg and atropine 0.1 mg/kg. Anesthesia was induced with sodium pentobarbital (20 mg/kg), injected intravenously via a 22-gauge Teflon catheter which was inserted percutaneously into a marginal ear vein and was maintained by continuous infusion of sodium pentobarbital (2-6 mg/kg/h). The animals were endotracheally intubated and mechanically ventilated by a Harvard respirator (Harvard Apparatus Inc., S. Natick, MA, U.S.A.). The respiratory rate and tidal volume were adjusted to keep an arterial pH of 7.35 to 7.45, Po₂ greater than 100 mmHg, and Pco₂ of 35 to 45 mmHg. Body temperature was maintained at 37.5-38.0°C. Three hundred international units (IU) per kilogram of heparin were given before instrumentation, followed by its supplementation of 100 IU/kg every one hour. A 5 Fr catheter was positioned into the superior cava vein for the administration of drugs and fluids. A 7 Fr catheter was introduced in the common iliac artery via the right femoral artery and was connected to a Statham P23Dp transducer

(P 50, Gould Inc., Oxnard, CA, U.S.A.) for the measurement of blood pressure. A 5 Fr Micro-Tip transducer catheter (Miller Instruments, Houston, TX, U.S.A.) was inserted through the left carotid artery and was positioned in the left ventricle for pressure recordings. A left ventricular (LV) dP/dt was obtained by an electrical derivation. Electrocardiograms (ECG) and all pressures were continuously monitored on a multiple-channel physiologic recorder (Nippon Koden Co., Tokyo, Japan).

Experimental OPCABG model

A median sternotomy was performed, the pericardium was incised, and the heart was placed onto a cradle. A 6 Fr catheter was inserted into the left internal thoracic artery (LITA), which was dissected at approximately 10 cm and then ligated distally. The left anterior descending coronary artery (LAD) was dissected, and an adjustable snare was placed around its distal third. A 20-gauge Teflon catheter was cannulated into the LAD at the exact distal portion to the snare. The LAD was occluded for 45 min by tightening the snare and was then perfused with arterial blood via the ITA through a bypass tube with a continuous monitoring of the blood flow rate by an electromagnetic flow probe (Nippon Koden Co.).

Assessment of left ventricular regional function

Two pairs of 5 MHz piezoelectronic ultrasonic crystals were placed in the anterior myocardium (potential ischemic zone) distal to the planned site of LAD occlusion and to the lateral myocardium in the area of the left circumflex coronary artery. The crystals were positioned in the mid-myocardium of the left ventricles, 10 to 15 mm apart and oriented parallel to the minor axis. Segment lengths were measured with a sonomicrometer (Nippon Koden Co.). Percent systolic segment shortening (%SS) was calculated using the following formula:

$$\%SS = (EDL - ESL) / EDL \times 100$$

where EDL and ESL are the end-diastolic length and the end-systolic length, respectively. EDL was measured just before the onset of max LV dP/dt, whereas ESL was measured 20 ms before min LV dP/dt.

Experimental protocol

Before the 45 min-LAD occlusion, the pigs were randomly assigned to one of the three treatment groups (seven pigs in each group). In the control group, the LAD was occluded for 45 min, followed by two hours of reperfusion via the LITA. In the IP group, the LAD was occluded for five min and reperused for 15 min as IP. Then, the LAD

occlusion and reperfusion were performed in the same manner as for the control group. In the lidocaine group, 2 mg/kg of lidocaine (Fujisawa Pharmaceutical Co., Osaka, Japan) was administered via the Teflon catheter directly into the LAD just before the LAD occlusion. The following steps were the same as the control group.

Sequential hemodynamics and regional myocardial function were recorded in all pigs before LAD occlusion, after 45 min of occlusion, and at 30 min, one hour and two hours after reperfusion except for the IP group in which they were additionally recorded after five min of the LAD occlusion and at 15 min after reperfusion during IP.

Postmortem study

The area at risk was determined by injection of 5% Evans blue dye (0.5 ml/kg) into the left atrium at the termination of reperfusion via the LAD. The heart was then immediately arrested with an injection of potassium chloride (4 mEq/kg) and was excised. Each heart was cut into 8 mm thick slices from the apex to the base parallel to the atrioventricular groove. The slices were photographed in color. The area of non-stained myocardium by Evans blue dye was defined as representing the area at risk. The slices were then incubated in triphenyl tetrazolium chloride, which stains viable myocardium red. The area at risk as well as the area of infarction were identified and calculated on enlarged photographs with a computerized imaging processing system (software package of particle analysis tool, Toshiba Electric Co., Tokyo, Japan).

Randomization procedure

Randomization of the animals was performed using a randomization code. This study was designed to include at least seven pigs completing the protocol in each group. When an animal was excluded, its randomization code was restored to the pool of codes. All measurements, including pathological findings, hemodynamics, and regional myocardial function, were blindly analyzed.

Data and statistical analyses

Data were analyzed by the statistics program package of SPSS version 11.0J (SPSS Inc., Chicago, IL, U.S.A.). One-way analysis of variance (ANOVA) was used for comparison between the three groups while within-group comparisons were performed with two-way ANOVA. If a significant difference was encountered, further analysis was performed with Turkey test in all possible pairwise comparisons. A p value of less than 0.05 was considered

significant. All p values were two-tailed, and all data were presented as "mean±SD".

Results

Three of the 24 pigs (three from the control group) initially instrumented were not resuscitated and died of ventricular fibrillation which occurred in the period 45 min after the LAD occlusion. Therefore, these pigs were excluded from analysis. Data were reported for the remaining 21 pigs (seven pigs in each three groups).

Body weight

The average body weight was comparable in all groups (42.4±3.0 kg in the control group, 39.9±2.8 kg in the IP group, and 41.9±4.9 kg in the lidocaine group).

Hemodynamics

Sequential measurements of the heart rate (HR), mean arterial pressure (MAP), left ventricular end-diastolic pressure (LVEDP), maximum (max) LV dP/dt and minimum (min) LV dP/dt in the experimental groups are listed in Table 1. There were no significant between and within-group hemodynamic differences in the three groups throughout the experiment.

Left ventricular regional function

The effects of the LAD occlusion and reperfusion on %SS are shown in Table 2. Prior to occlusion, baseline %SS was comparable in all three groups. During five min of the LAD occlusion as IP, a severe regional dysfunction occurred, but following 15 min of reperfusion, %SS improved to the baseline level in the IP group. Forty-five minutes of LAD occlusion caused a severe dysfunction in all groups. In the ischemic region, %SS failed to return to the baseline after two hours of reperfusion in all groups. However, in the nonischemic region, %SS did not change in both coronary occlusion and reperfusion in any of the groups.

LITA blood flow rate

The measurement of LITA blood flow are shown in Table 3. The blood flow rate before insertion of the catheter for the bypass to LAD was similar in all groups. There were no significant between and within-group differences in the three groups throughout the experiment.

Table 1. Hemodynamics

Parameter	Group	Baseline	IP		Occlusion	Reperfusion by LITA		
			5 min	After 15 min	45 min	30 min	60 min	120 min
HR (bpm)	Control	128±20			129±21	130±19	130±19	129±20
	IP	121±18	116±16	115±13	124±21	114±9	119±11	123±21
	Lid	115±15			118±13	116±14	115±15	119±18
MAP (mmHg)	Control	88±19			96±22	93±21	96±24	92±26
	IP	96±14	95±15	98±13	99±6	96±10	96±16	94±17
	Lid	90±11			92±7	93±11	89±10	88±13
LVEDP (mmHg)	Control	8±2			7±3	8±3	8±3	8±3
	IP	7±5	6±4	7±3	7±2	7±3	7±3	7±2
	Lid	5±4			6±2	6±4	6±3	6±3
Max LV dP/dt (mmHg/sec)	Control	1,857±458			1,839±412	1,829±295	1,733±506	1,864±612
	IP	2,055±555	1,825±341	1,804±343	1,986±351	1,764±251	1,739±230	1,818±261
	Lid	2,143±595			1,914±636	1,832±662	1,782±572	1,804±658
Min LV dP/dt (mmHg/sec)	Control	-1,761±237			-1,807±283	-1,804±212	-1,800±214	-1,871±547
	IP	-1,829±434	-1,782±273	-1,846±317	-1,893±184	-1,754±192	-1,707±204	-1,700±300
	Lid	-1,789±286			-1,807±230	-1,746±207	-1,721±233	-1,757±273

Values are mean±SD. IP: ischemic preconditioning, lid: lidocaine, HR: heart rate, MAP: mean arterial pressure, LVEDP: left ventricular end-diastolic pressure, LITA: left internal thoracic artery, max LV dP/dt: maximum left ventricular dP/dt, min LV dP/dt: minimum left ventricular dP/dt

Table 2. Regional myocardial function in the left ventricle

%SS	Group	Baseline	IP		Occlusion	Reperfusion by LITA		
			5 min	After 15 min	45 min	30 min	60 min	120 min
Nonischemic region	Control	20.2±4.6			18.0±5.3	18.3±6.1	17.7±5.0	17.7±5.9
	IP	20.4±5.9	18.5±3.0	17.8±3.9	17.3±3.9	17.7±4.3	18.1±4.4	17.6±6.1
	Lid	21.1±7.1			18.4±5.1	17.9±4.6	17.0±3.9	17.5±4.7
Ischemic region	Control	24.2±4.9			-3.4±8.4 ^a	-4.7±7.0 ^b	-3.6±8.9 ^c	-2.0±6.6 ^d
	IP	28.9±7.2	1.8±10.6 ^e	16.5±10.3	-3.4±8.5 ^f	-7.5±10.3 ^g	-4.7±6.9 ^h	-4.1±7.8 ⁱ
	Lid	24.1±10.3			-3.4±8.6 ^j	-4.2±7.4 ^k	-2.9±8.2 ^l	-2.3±6.4 ^m

Values are mean±SD. %SS: the percent systolic segmental shortening, IP: ischemic preconditioning, lid: lidocaine, LITA: left internal thoracic artery

p<0.001 versus baseline (95% confidence interval [CI]: 20.4-34.8^a, 21.8-36.1^b, 20.6-34.9^c, 19.0-33.3^d, 13.7-40.6^e, 19.9-46.9^f, 22.9-49.9^g, 20.1-47.1^h, 19.5-46.5ⁱ, 21.6-35.9^j, 19.9-34.2^k, 19.9-34.2^l, 14.7-29.0^m)

Table 3. Blood flow (ml) in the left internal thoracic artery

Group	Baseline	Reperfusion by LITA		
		30 min	60 min	120 min
Control	64±21	9±2	9±3	11±4
IP	59±20	10±7	10±5	9±2
Lid	68±20	10±6	9±6	10±9

Values are mean±SD.

IP: ischemic preconditioning, lid: lidocaine, LITA: left internal thoracic artery

Postmortem findings

The LV area at risk was similar in all groups (14.6±2.7% in the control group, 15.7±2.5% in the IP group, and 13.7±1.4% in the lidocaine group) (Fig. 1). The infarct size expressed as a percentage of the LV area was significantly smaller in the lidocaine group (0.3±0.5%) than in the control group (11.7±2.5%, p<0.001; 95% confidence interval [CI], -14.8 to -7.8) or the IP group (8.7±3.6%, p<0.001; 95% CI, -11.9 to -4.9). Moreover, the infarct size expressed as a percentage of the area at risk was significantly smaller in the lidocaine group (2.7±4.2%) than in the control group (79.9±6.0%, p<0.001; 95% CI, -98.4

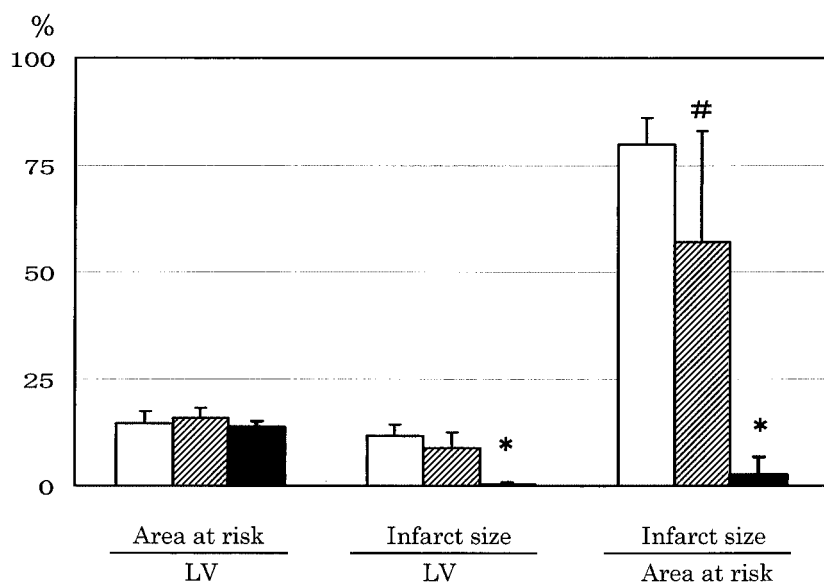


Fig. 1. The area at risk, infarct size expressed as a percentage of the left ventricular (LV) area, and as a percentage of the area at risk are shown in this figure. Data are presented as “mean±SD” for the control (□), IP (▨), and lidocaine (■) groups. *: significant difference versus control and IP groups, #: significant difference versus control group

to -56.0) or the IP group ($57.0 \pm 25.9\%$, $p < 0.001$; 95% CI, -75.5 to -33.1). Similarly, the IP group showed a significantly smaller area than the control group ($p = 0.033$; 95% CI, -44.0 to -1.67).

Discussion

OPCABG has recently gained popularity with the improvement of stabilizers due to its possible effect on avoiding the damage induced by cardiopulmonary bypass with aortic cannulation or aortic cross-clamping, which have side effects as a source of acute inflammatory reactions. The technique limits the application of cardioprotective strategies that have been extensively investigated. During OPCABG, reperfusion after a period of coronary artery occlusion is achieved without any active cardioprotection. For the moment, some strategies such as IP,¹⁾ intraluminal coronary shunt²⁾ or PADCABG³⁾ have been clinically applied for minimizing the effects of ischemic reperfusion injury during elective coronary occlusion, especially in multivessel OPCABG.

IP could reduce the infarct size in dogs¹¹⁾ and pigs,¹²⁾ as it has been widely studied and shown to have a beneficial effect on postischemic cardiac performance^{13,14)} and metabolism¹⁵⁾ after reperfusion. However, the effect of IP on postischemic global or regional myocardial function remains controversial.⁵⁻⁷⁾ The present study showed that IP did not improve regional myocardial function after reperfusion, although the infarct size decreased. Moreover, as it takes several minutes to perform IP, this re-

quires the surgeon to wait prior to coronary anastomosis in OPCABG.

On the other hand, with the aid of an intraluminal device, it enables direct perfusion of the target coronary artery, thereby avoiding ischemia induced by vascular snares in IP.²⁾ The intraluminal shunt, an option that does not require waiting time, has an advantage of saving operation time by letting the target coronary artery be perfused directly, thereby avoiding ischemia induced by vascular snares in IP. However, the intraluminal shunt is not always used as cardioprotection due to the possibility of damaging intima, dislodging atheroma, and causing coronary dissection. Moreover, it interferes with suturing during anastomosis.

The novel PADCABG technique is an acceptable method in terms of both rapid reperfusion and delivery of cardioprotective agents directly into the ischemic-reperfused target area.³⁾ However, it is a complicated system in need of aortic root cannulae and has no cardioprotective effect during the first distal anastomosis.

We have previously established that combined IP and SVR had a significant myocardial protective effect against ischemic and reperfusion injury in an experimental OPCABG model.⁴⁾ However, this device has not been widely spread in hospitals and its blood supply circuit is short due to the bankruptcy of Retroperfusion System Inc. Lidocaine is widely available as an anti-arrhythmic drug in many hospitals. Besides this, it also has the potential of protecting myocardium not only against ischemia,⁸⁾ but

also against reperfusion injury, especially in experimental models in pigs.^{9,10)}

For these reasons, we turned our attention to lidocaine as a cardioprotective agent against ischemic reperfusion injury during OPCABG and also selected a porcine OPCABG model due to its similarities with human coronary circulation. Besides, the chosen 2 mg/kg of lidocaine is thought to be clinically safe dose for human. In this study, the time of occlusion was set for 45 min anticipating the extra time required by a novice cardiac surgeon to anastomose safety. As described in the results, the lidocaine group could remarkably reduce the infarct size of the ischemic region.

Concerning the mechanisms of the cardioprotective effect of lidocaine against ischemic and reperfusion injury, the following five main mechanisms have been suggested,⁸⁾ including sodium channel blocker,¹⁶⁻¹⁹⁾ calcium channel blocker,¹⁸⁾ inhibition of neutrophil adherence,^{20,21)} free radical scavenger,²²⁾ and negative inotropic effect.²³⁾

Myocardial ischemia in particular shows an increase in intracellular sodium concentration that is closely connected to an increase in intracellular calcium through Na⁺/Ca²⁺ exchange.¹⁶⁻¹⁸⁾ Calcium loading is thought to be a major factor not only in ischemic injury but also in reperfusion injury. Lidocaine can reduce ischemic sodium accumulation by blocking the sodium channel following adenosine triphosphate preservation at first,¹⁹⁾ and then reduce ischemic calcium loading by blocking the calcium channel. These findings indicate that the cardioprotection of lidocaine may be as a result of an effect on myocardial reperfusion injury.

Unfortunately, the regional myocardial function in the left ventricle exhibited no remarkable improvement during the two hours of reperfusion despite a marked reduction in myocardial infarction.

It has been known that reperfusion of acutely ischemic myocardium, if initiated in early stages after the onset of ischemia, decreases infarct size.²⁴⁾ However, improvement in cardiac function may be delayed for days or weeks.²⁵⁾ Thus, a longer reperfusion period is necessary to show the functional recovery. This relatively short reperfusion period is a limitation of the present study.

In conclusion, the direct infusion method of lidocaine to the target coronary ischemic region may be clinically feasible in prolonging a coronary occlusion as a particularly easier and quicker method during OPCABG.

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