THE EFFECT OF REMOTE ISCHEMIC PRECONDITIONING IN DIABETIC PATIENTS AFTER ELECTIVE PERCUTANEUS CORONARY INTERVENTION

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Background
Experimental and clinical investigations suggest that reperfusion is considered 'a double-edged sword', as reperfusion would restore oxygen and nutrients supply to the ischemic myocardium to improve its functional recovery, but in the other hand reperfusion could augment myocardial ischemic damage, known as myocardial ischemia-reperfusion (I/R) injury. The brief and repeated cycles of I/R given at a distant organ before a sustained ischemia and reperfusion, known as remote ischemic preconditioning (RIPC), would protect the heart from lethal I/R injury.
Objective
The effect of ischemic preconditioning in a diabetic heart is a contradictory whether it could improve or worsen the damage degree of myocardial I/R injury, as reported by some previous studies. These inconsistent reports need further studies.
Methods
Twenty-four diabetic patients with stable CAD undergoing elective percutaneus coronary intervention were randomly assigned to 2 groups: 14 patients submitted to RIPC and 10 patients were control group. We induced RIPC by inflating a blood pressure cuff placed on the upper limb to 20 mmHg above systolic arterial pressure for 5 min and deflating the cuff for 5 min; 4 cycles were performed. All patients had CK-MB level measured at baseline and 18-24 hours after the elective PCI. Myocardial injury was considered when post-PCI CK-MB level rose up to 1-3 fold of the upper normal limit.
Results
A higher proportion in control group (40%) experienced myocardial injury, compared with the group receiving RIPC (0%) ($p = 0.02$). The mean of baseline CK-MB was equal in both control and RIPC groups (19.07 ± 2.84 and 17.5 ± 2.32, respectively; $p = 0.165$). While the mean of post-PCI CK-MB level in two groups differed significantly (34.2 ± 10.43 and 24.42 ± 4.03, respectively; $p = 0.017$).

Conclusions
RIPC lower the incidence of myocardial injury in diabetic patients after elective percutaneus coronary intervention. These data suggest that diabetic patients still gain protection of RIPC.

Introduction

The strategy of reperfusion of ischemic myocardium in patients with coronary artery disease has led to a significant improvement of outcomes. However, reperfusion after a prolonged period of ischemia damages the myocardium, through a process known as

ischemia/reperfusion injury (I/R)[1]. Transient sublethal episodes of ischemia before a prolonged I/R injury, known as ischemic preconditioning (IPC), have been shown to reduce the extent of myocardial infarction (MI). This protection not only acts locally but also can protect distant tissues, a phenomenon known as remote IPC (RIPC), and limits myocardial infarction size in animal models[2]. In humans, RIPC protects against endothelial I/R injury[3] and the extent of MI after adult coronary bypass surgery, pediatric surgery, and noncardiac surgery[4].

Chronic diabetes mellitus remains one of root causes of mortality in developed as well as developing countries with towering prevalence. It has been stated that 23.5 million adults of 20 years or older have had a diagnosis of both coronary artery disease and diabetes mellitus, with an estimation that by 2025, an additional 9% of the total US population will have a diagnosis of a combination of these disorders[5]. Studies have demonstrated preconditioning-mediated cardioprotection in the diabetic myocardium. Moreover, Tatsumi et al.[5] suggested that the diabetic myocardium could rather benefit more from preconditioning stimulus than the normal myocardium, possibly due to diabetes induced reduction in the production of glycolytic metabolites during sustained ischemia and concomitant attenuation of intracellular acidosis. However, it remains a question whether the diabetic myocardium could be protected by the preconditioning stimulus, as considerable numbers of studies paradoxically demonstrated no preconditioning mediated cardioprotection in the presence of chronic diabetes mellitus.

Materials and Methods

Twenty-four diabetic patients with stable CAD undergoing elective percutaneus coronary intervention, and informed written consent was obtained from each patient. Exclusion criteria were patients with pre procedural CK-MB level above normal limit, acute ST-elevation myocardial infarction undergoing primary PCI, acute coronary syndrome less than 7 days before elective PCI, angina pectoris CCS III within the last 24 hours before elective PCI, systolic blood pressure < 90 mmHg, pulmonary oedema or cardiogenic shock, significant renal insufficiency (creatinine level > 2.5 mg/dL that may influence blood enzyme kinetic), target lesion Chronic Total Occlusion (CTO) more than 3 months, with the presence of collateral vessels, symptomatic peripheral arterial disease. The patients were randomly assigned to 2 groups: 14 patients submitted to RIPC and 10 patients were control group.

Remote ischaemic preconditioning (RIPC)

We induced RIPC by inflating a blood pressure cuff placed on the upper limb to 20 mmHg above systolic arterial pressure for 5 min and deflating the cuff for 5 min; 4 cycles were performed, approximately 1 hour before PCI. RIPC was not performed in control group.
This protocol adapted the study conducted by Rentoukas[1], which showed the useful role of RIPC for the prevention of reperfusion injury in patients submitted to primary PCI.

Percutaneus Coronary Intervention

PCI was conducted with the monorail technique and 7F catheters. The selection of coronary balloons and stents was left to the discretion of the interventional cardiologist. Coronary stents were implanted in all patients of both groups after balloon pre-dilatation of the target lesion according to the decision of the operators. All lesions treated were de novo lesions of native coronary arteries.

Blood sampling and laboratory measurements

Venous blood samples for CK-MB level measurements were obtained at baseline and 12-48 hours after the elective PCI. Serum was obtained by centrifugation at 1000 g for 15 min. CK-MB concentrations between 7 and 25 U/l were considered to be within the reference range. Values are expressed as nanograms per millilitre. Myocardial injury was considered when post-PCI CK-MB level rose up to 1-3 fold of the upper normal limit.

Statistical analysis

All data are expressed as mean. For comparisons between the two main groups, Student's t test (unpaired) was used. Significance was taken at a p value of 0.05.

RESULTS

1. Baseline characteristic

Table 1 shows the baseline epidemiological and clinical features of the groups. There were no important differences between the groups. Except for the level of blood glucose, which the mean of RIPC group and control group differed significantly (163.7 ± 41.8 and 124.8 ± 24.5, respectively ; p = 0.015).

Table 1. Baseline Epidemiological and Clinical Features of the Study Population

	RIPC Groups	**Control Groups**	**p value**
Age, mean ± SD	60.5 ± 5.5	58.1 ± 5.4	0.302
Male, n (%)	11 (78.6)	7 (70)	0.615
BMI, mean ± SD	23.6 ± 2.9	23.6 ± 3.1	0.959
Ejection fraction, mean ± SD	54.5 ± 8.8	53.9 ± 8.8	0.871
CAD Risk Factors, n (%)			
Hypertension	11 (78.6)	9 (90)	0.437
Active smoker	2 (14.3)	1 (10)	0.643
Family history	2 (14.3)	0 (0)	0.332
Hypercholesterolemia	3 (21.4)	2 (20)	0.668
Laboratory findings, mean ± SD			
Hb	12.29 ± 1.35	13.54 ± 1.88	0.071
Leukocyte	9142.14 ± 1341	9028 ± 1751	0.858
Platelet	270550 ± 69826	259210 ± 78867	0.714
Ureum	40.7 ± 16.3	30.6 ± 10.6	0.1
Creatinine	1.3 ± 0.2	1.3 ± 0.2	0.66
Blood glucose	163.7 ± 41.8	124.8 ± 24.5	0.015
Total cholesterol	209.7 ± 38.7	188.4 ± 42.5	0.215
HDL	31.1 ± 4.1	29.7 ± 3.3	0.372
Triglyceride	133 ± 55.6	122 ± 33.9	0.599
Medications at enrollment, n (%)			
Beta blockers	6 (42.8)	3 (30)	0.418
Nitrates	8 (57.1)	7 (70)	0.418
Statin	13 (92.8)	10 (100)	0.583
ACE inhibitors	8 (57.1)	7 (70)	0.418
ARB	12 (85.7)	7 (70)	0.332
Trimetazidine	12 (85.7)	9 (90)	0.629

2. Angiographic and Interventional Procedure Characteristic

No differences were observed between the studied groups in angiographic and interventional procedure characteristic in terms of lesion type (ACC/AHA), target vessels, stenosis severity, predilatation type, stenting type, and total stent length, as shown in table 2. In this study, all patients received DES.

Table 2. Angiographic and Interventional Procedure Characteristic

	RIPC Groups	Control Groups	p value
Lesion type (ACC/AHA), n			
A	0	1	0.272
B	12	6	
C	2	3	
Target vessels, n			
1	8	5	0.643
2	5	3	
3	1	2	
Stenosis severity, %, mean±SD	80.71 ± 6.75	85 ± 8.16	0.174
Predilatation time, s, mean±SD	71.5 ± 54.5	71.8 ± 53.3	0.989
Stenting time, s, mean±SD	76.7 ± 50.8	81.6 ± 37.4	0.802
Total stent length, mm, mean±SD	52.1 ± 26.4	61.5 ± 35.2	0.464

3. Baseline and Post-PCI CK-MB Level

Table 3 presents the mean of baseline and post-PCI CK-MB level of the two groups. There were no significant differences between groups in baseline levels of CK-MB (19.07 ± 2.84 and 17.5 ± 2.32, respectively; p = 0.165). While the mean of post-PCI CK-MB level in two groups differed significantly (34.2 ± 10.43 and 24.42 ± 4.03, respectively; p = 0.017). A higher proportion in control group (40%) experienced myocardial injury, compared with the group receiving RIPC (0%) (p = 0.02).

Table 3. Baseline and Post-PCI CK-MB Level

	RIPC Groups	Control Groups	p value
Baseline CK-MB, U/l	19.0 ± 2.8	17.5 ± 2.3	0.165
Post-PCI CK-MB, U/l	24.4 ± 4.0	34.4 ± 10.4	0.017
Myocardial Injury, n (%)	0	4	0.02

DISCUSSION

This study shows that RIPC lower the incidence of myocardial injury in diabetic patients after elective percutaneus coronary intervention, as expressed in the mean of baseline and post-PCI CK-MB level. This finding was consistent with the study of Zhu et al.[6]

conducted in streptozotocin(STZ)-induced diabetic rats. In their study, Zhu et al.[6] demonstrated that non-invasive limb IPC ameliorated ventricular arrhythmia, reduced myocardial infarct size, increased activities of total superoxide dismutase (SOD), manganese-SOD and glutathione peroxidase. It is concluded that non-invasive IPC reduces oxidative stress and attenuates myocardium ischemia-reperfusion injury.

The protective action of ischemic post-conditioning has been known for some time. One study by Tatsumi et al.[5] demonstrated cardioprotective effects of IPC (2 cycles of ischemia and reperfusion of 5 min each) in STZ-induced diabetic rats against myocardial I/R involved preservation of mitochondrial oxidative phosphorylation, inhibition of glycolysis during ischemia, and the simultaneous attenuation of intracellular acidosis in the diabetic heart explaining the possible mechanisms involved. In addition, Ravingerova et al.[7] showed that STZ-induced chronic diabetic rat hearts could be more benefited from IPC (1 cycle of 5-min ischemia and 10-min reperfusion) mediated cardioprotection. Interestingly, Tsang et al.[8] observed cardioprotection by IPC with 3 cycles (5-min global ischemia followed by 10-min reperfusion) in Goto-Kakizaki diabetic rat hearts, while IPC with 1 cycle did not have any cardioprotective effect. This study suggested that induction of Akt phosphorylation could have taken place in multiple cycles of IPC (but not in single cycle of IPC) that could have afforded cardioprotection in diabetic rat hearts. In summary, myocardial Akt phosphorylation, preservation of mitochondrial oxidative phosphorylation, inhibition of glycolysis during ischemia, decreased production of glycolytic metabolites, reduced intracellular acidosis and attenuated oxidative stress could be potential mechanisms involved in IPC-mediated cardioprotection against I/R injury in the diabetic heart[9, 10].

CONCLUSION

RIPC lower the incidence of myocardial injury in diabetic patients after elective percutaneus coronary intervention. These data suggest that diabetic patients still gain

protection of RIPC, possibly due to myocardial Akt phosphorylation, preservation of mitochondrial oxidative phosphorylation, inhibition of glycolysis during ischemia, decreased production of glycolytic metabolites, reduced intracellular acidosis and attenuated oxidative stress.

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