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ORIGINAL ARTICLES

Ischemic Preconditioning as a Myocardial Protection Strategy in CABG: Evidence from a Prospective Clinical Study

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Abstract

Introduction: Ischemic preconditioning (IP) is a method that may help protect the human heart from injury during cardiac surgery. It is believed that IP prepares the heart for upcoming prolonged ischemia by activating local protective mechanisms.

Objective: This prospective study aims to evaluate the degree of myocardial protection offered by IP compared to standard cold blood cardioplegia (CBC).

Materials and Methods: Fifty patients with stable angina and coronary artery disease (CAD) scheduled for coronary artery bypass grafting (CABG) were randomized into two groups: IP (n=25) and control (n=25). In the IP group, two cycles of 2-minute ischemia followed by 3-minute reperfusion were applied before aortic cross-clamping. Blood samples were collected through a central venous catheter to measure creatine kinase-MB fraction (CK-MB), creatine phosphokinase (CPK), cardiac troponin I (cTnI), and lactate dehydrogenase (LDH). Postoperative cardiac rhythm was also monitored.

Results: The release of cTnI and lactate was significantly lower in the IP group compared to the control group (cTnI $p < 0.0001$, CK-MB $p = 0.005$, CPK $p = 0.005$). However, there was no significant difference in LDH levels between the groups ($p = 0.264$). The need for defibrillation after cardiac arrest was lower in the IP group compared to the control group (18% vs. 40%).

Conclusion: The role of IP in cardiac surgery remains uncertain. However, compared to CBC alone in low-risk CABG patients, IP as an adjunct to CBC reduced levels of cTnI, CK-MB, and CPK, and was associated with a lower incidence of postoperative atrial fibrillation.

Keywords: ischemic preconditioning; coronary artery bypass surgery; myocardial protection

Introduction

Despite advances in anesthesia, protective strategies, and surgical techniques in cardiac surgery, myocardial ischemia–reperfusion injury continues to cause cardiomyocyte death, which can paradoxically diminish the beneficial effects of CABG [1]. In this context, various myocardial protection strategies have been investigated to minimize ischemia–reperfusion injury during cardiac surgery and anesthesia.

Ischemic preconditioning (IP) is a well-recognized method to limit myocardial injury, consisting of brief episodes of reduced blood flow and oxygen delivery to the heart before a major operation. This approach prepares the myocardium by exposing it to controlled cycles of ischemia and reperfusion, thereby enhancing its resilience to the stress of subsequent surgery. This paradoxical protective phenomenon was first described by *Murry et al. [*2, 3, 4]. Over the following decade, extensive studies demonstrated that ischemic preconditioning is among the most potent endogenous cardioprotective mechanisms.

Galinanes et al. reported that combining cardioplegic solution with ischemic preconditioning resulted in superior myocardial protection compared with cardioplegia alone [5].

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Cardiac biomarkers remain the cornerstone for diagnosing myocardial injury. CABG inherently induces the release of these biomarkers, with significant elevations in cardiac troponins and other markers observed even in patients with uncomplicated postoperative courses.

The present study aimed to evaluate the efficacy of ischemic preconditioning in patients undergoing elective coronary revascularization, with particular focus on biochemical markers of ischemic injury and postoperative recovery. Furthermore, we sought to assess whether ischemic preconditioning provides additional protection beyond that afforded by established cardioprotective strategies.

Materials and Methods

This study was approved by the Institutional Review Board of Ankara University Medical School. It was conducted in two distinct phases. The first phase (2003-2005) included 28 consecutive patients scheduled for elective primary coronary revascularization and was carried out at the Department of Cardiovascular Surgery, Ankara University Medical School.

The second phase (2014-2018) included an additional patient cohort and was conducted at the Cardiovascular Surgery Clinic of Istanbul Medicine Hospital in Pristina. Both phases used similar inclusion and exclusion criteria, enabling pooled analysis of ischemic preconditioning and control groups. All participants were fully informed about the study procedures, and written consent was obtained. Demographic data, risk factors, EuroSCORE values, and clinical records were collected.

A detailed cardiovascular history was recorded, including previous myocardial infarction, percutaneous or surgical coronary revascularization, cardiac surgery, and episodes of heart failure. Comorbidities such as peripheral artery disease, cerebrovascular disease, chronic pulmonary disease, and chronic renal impairment were also documented.

Patients were excluded if they met any of the following conditions:

1. Diabetes mellitus treated with sulfonylurea agents,
2. Unstable angina or myocardial infarction within the previous month,
3. Previous cardiac surgery,
4. Chronic hepatic, renal, or pulmonary disease.

Based on power calculations, a target sample size of 50 patients was determined. For blinded randomization, 50 sealed envelopes, each containing the assignment to the ischemic preconditioning (IP) or control group, were prepared. A ward nurse, blinded to the study protocol, distributed one envelope to each patient upon admission for surgery.

Preoperative carotid Doppler ultrasound was performed in all patients; two patients in the IP group who required concomitant carotid endarterectomy were excluded. Ultimately, 30 patients (14 in the IP group and 16 in the control group) were analyzed.

Baseline, intraoperative, and postoperative data were stored prospectively in a dedicated database at the respective clinics. Recorded intraoperative variables included the number of coronary bypass grafts, cardiopulmonary bypass (CPB) time, aortic cross-clamp duration, requirement for inotropic support, and use of blood products.

All patients underwent standardized general anaesthesia. Induction was performed with midazolam (0.05 mg/kg), sufentanil (3 μg/kg), and vecuronium (0.1 mg/kg) intravenously, followed by maintenance with continuous infusion of sufentanil (0.5 μg/kg/h) and vecuronium (0.1 mg/kg/h). Halogenated anaesthetics were avoided to eliminate potential effects on K-ATP channels.

Endotracheal intubation was performed using a single-lumen tube, followed by insertion of a central venous catheter, preferably via the right internal jugular vein.

All operations were performed through a median sternotomy with standard CPB and central cannulation. Moderate hypothermia (28–32 °C) was achieved before aortic cross-clamping. After cross-clamping and antegrade cardioplegia, the left internal mammary artery was anastomosed to the left anterior descending artery; saphenous vein grafts were used as necessary for other target vessels. Proximal anastomoses were performed on the beating heart after removal of the aortic cross-clamp.

Cardioplegia consisted of a crystalloid solution mixed with oxygenated blood (4:1 ratio). Potassium concentration was 21 mmol/L in the initial dose and 9 mmol/L in subsequent doses.

A total of 1 L of antegrade cardioplegia (not exceeding 15 mL/kg) was administered via the ascending aorta immediately after cross-clamping, with maintenance doses repeated every 20 minutes as required.

After completion of central cannulation, full-flow CPB was established, and normothermia was maintained. In the IP group, aortic cross-clamping was applied to induce global myocardial ischemia for 2 minutes, followed by a 3-minute reperfusion period.

This cycle was repeated once more. Thereafter, surgical procedures were performed identically in both groups (Figure 1).

IP Group	2 min ischemia period	3 min reperfusion	2 min ischemia period	3 min reperfusion	Operation
Control Group	10 min car-diopulmonary bypass				Operation

Figure 1. IP protocol applied in our clinic

The effect of ischemic preconditioning on myocardial injury was evaluated by measuring serum levels of CK-MB, CPK, cardiac troponin I (cTnI), and LDH. Blood samples were obtained via the central venous catheter at the following time points: after induction of anaesthesia, at 1, 6, and 12 hours following CPB, and *on postoperative day 1*.

Statistical Analysis

Data are presented as means ± standard deviation. All statistical analyses were performed using SPSS software. Continuous variables are presented as means ± standard deviation. Group comparisons were performed using non-parametric tests (Mann–Whitney U test for continuous variables, and chi-square or Fisher's exact test for categorical variables). A p-value < 0.05 was considered statistically significant.

Results

The two groups were comparable with respect to demographic characteristics and preoperative risk factors (Table 1). No statistically significant differences were observed in CPB duration ($p = 0.398$) or aortic cross-clamp time ($p = 0.554$). The mean number of grafts required for complete revascularization was also similar between groups ($p = 0.574$).

However, ventricular fibrillation requiring defibrillation occurred more frequently in the control group compared with the IP group (40% vs. 20%, respectively) (Table 2).

No significant differences were found between groups regarding intubation time ($p = 0.952$) or length of stay in the intensive care unit. There were no cases of perioperative myocardial infarction or in-hospital mortality in either group. Patients in the IP group required less inotropic support during recovery, although this difference was not statistically significant ($p = 0.395$).

Postoperative atrial fibrillation occurred in four patients: three in the control group and one in the IP group ($p = 0.03$). Except for one IP group patient who responded to the initial amiodarone infusion, all other cases required electrical cardioversion.

Serial measurements of cardiac biomarkers showed similar temporal patterns in both groups (Table 3). Baseline values obtained before CPB and after ICU admission were comparable. However, the control group showed significantly greater elevations at 6 and 24 hours post-CPB. Specifically, troponin I (cTnI) ($p = 0.001$), CK-MB ($p = 0.005$), and CPK ($p = 0.005$) were significantly higher in the control group than in the IP group.

Characteristic	Control Group (n=25)	IP Group (n=25)	*p*-value
Age (years)	61.3 ± 7.2	60.5 ± 6.8	0.74
Male sex, n (%)	18 (75%)	17 (71%)	0.81
BMI (kg/m²)	27.1 ± 3.5	26.8 ± 3.2	0.82
Hypertension, n (%)	14 (56%)	13 (55%)	0.97
Diabetes Mellitus, n (%)	6 (25%)	5 (21%)	0.82
EuroSCORE	3.5 ± 1.2	3.3 ± 1.1	0.68
CPB time (min)	98.2 ± 20.4	95.5 ± 18.7	0.398
Cross-clamp time (min)	63.8 ± 12.6	62.1 ± 13.4	0.554
Number of grafts	3.1 ± 0.7	3.0 ± 0.6	0.574
Ventricular fibrillation, n (%)	10 (40%)	5 (20%)	0.217

Values are expressed as mean ± SD or number (percentage). CPB = cardiopulmonary bypass; IP = ischemic preconditioning.

Table 1. Preoperative and Operative Characteristics of the Study Population

Characteristic	Control Group (n=25)	IP Group (n=25)	*p*-value
Intubation time (hours)	10.2 ± 2.5	10.1 ± 2.3	0.952
ICU stay (days)	2.5 ± 0.8	2.4 ± 0.7	0.71
Inotropic support, n (%)	8 (31%)	5 (21%)	0.395
Atrial fibrillation, n (%)	4 (18%)	2 (7%)	0.03
Requirement for electrical cardioversion, n (%)	3 (12.5%)	0	0.235
Perioperative myocardial infarction, n (%)	0	0	–
In-hospital mortality, n (%)	0	0	–

Values are expressed as mean ± SD or number (percentage). ICU = intensive care unit; IP = ischemic preconditioning.

Table 2. Postoperative Characteristics of the Study Population

Discussion

Ischemia–reperfusion injury remains the most crucial cause of transient myocardial dysfunction following cardiac surgery. This dysfunction manifests across a broad spectrum, ranging from arrhythmias and myocardial stunning to irreversible cell death [6]. Although the exact mechanisms remain incompletely understood, several factors are implicated, including the generation of reactive oxygen species, disturbances in calcium homeostasis, and systemic inflammatory responses [7].

To date, cardioplegic solutions remain the cornerstone of myocardial protection. However, in patients with advanced coronary artery disease, uneven antegrade cardioplegia distribution may limit efficacy, making retrograde delivery a valuable alternative [8, 9].

Cardiac troponin I (cTnI) is a well-established marker with greater prognostic accuracy than CK-MB for predicting survival after myocardial infarction and CABG [10,11]. Moreover, high-sensitivity troponin (hs-cTn) assays are superior to standard cTnI assays and are now recommended by current guidelines for diagnosing myocardial infarction [12].

In our study, the significantly lower rise in cTnI in the IP group during the first 12 postoperative hours strongly supports the endogenous cardioprotective role of ischemic preconditioning.

First described by *Murry et al.* in 1986, ischemic preconditioning (IP) involves brief episodes of ischemia and reperfusion that markedly reduce subsequent ischemic injury, in some cases by up to 75% [13]. This phenomenon has been confirmed across multiple organs, including the liver, kidney, and brain, in both experimental models and clinical studies [14].

Several clinical studies have further shown that IP, when used as an adjunct to CABG, improves postoperative cardiac function, shortens recovery time, and limits myocardial necrosis more effectively than pharmacological preconditioning strategies [15,16].

Our findings indicate that ischemic preconditioning reduces the release of cTnI, CK-MB, and CPK, thereby attenuating ischemic stress during CABG. This is clinically relevant because elevated postoperative cTnI levels are associated with adverse outcomes [17, 18]. (Figure 2)

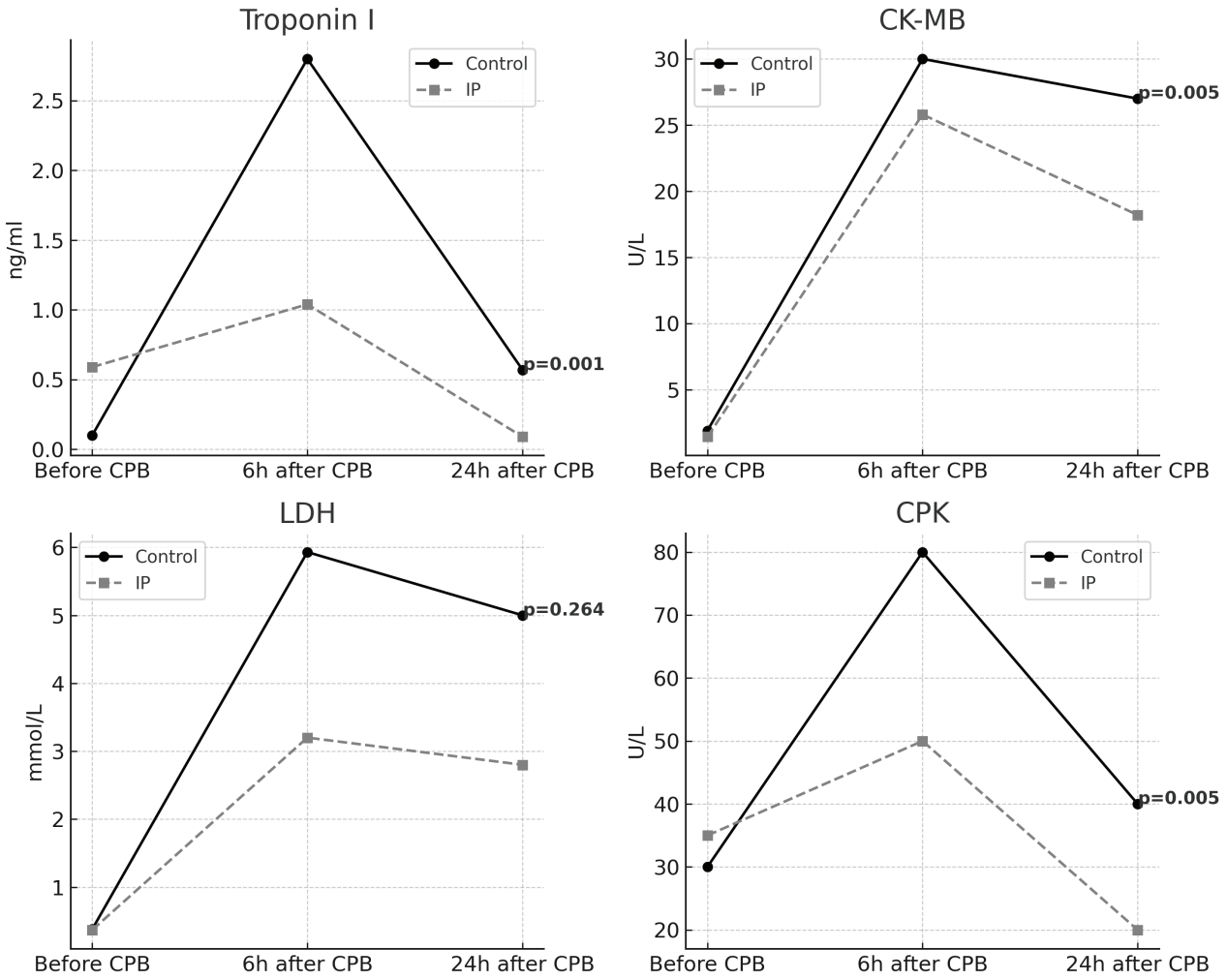

Figure 2. Comparison of Biomarker Levels between Control and IP Groups

Although biomarker elevation after CABG is a well-recognized phenomenon, even uncomplicated cases show marked increases [19], rises exceeding threefold above baseline are explicitly associated with perioperative myocardial infarction [20].

Postoperative arrhythmias are common after CABG and are considered multifactorial in origin; however, inadequate myocardial protection and ischemia remain central contributors [21]. Arrhythmias are therefore often used as clinical markers of reperfusion injury when comparing cardioprotective strategies [22, 23].

In our cohort, spontaneous sinus rhythm after aortic cross-clamp removal was more common in the IP group (82% vs. 40%), with a correspondingly lower defibrillation rate. Furthermore, the incidence of postoperative atrial fibrillation was lower in the IP group than in controls (7% vs. 18.7%; $p = 0.03$). These findings suggest that ischemic preconditioning may suppress both ventricular and supraventricular tachyarrhythmias after CABG.

Although our protocol used direct aortic cross-clamping to induce global ischemia rather than isolated coronary occlusion, the positive effects observed are consistent with those reported in approximately 20 previous studies [24]. Notably, the duration of ischemic intervals has been identified as a key determinant of IP efficacy [25].

Conclusion

Overall, our results support the concept that ischemic preconditioning provides additional myocardial protection beyond that achieved with conventional cardioplegia alone. While no differences in early mortality, hospitalization duration, or significant morbidity were observed, the attenuation of biomarker release and the reduced requirement for inotropic support in the IP group indicate better preservation of myocardial function.

The principal limitations of this study include the relatively small sample size, restriction to low-risk patients, and the inability to obtain histopathological myocardial samples for further validation.

Abbreviations

IP - Ischemic Preconditioning; CBC - Cold Blood Cardioplegia; CABG - Coronary Artery Bypass Grafting; CAD - coronary artery disease; CPK - Creatine Phosphokinase; CK-MB - Creatine Kinase-Myocardial Band; cTnI - cardiac troponin I; LDH - Lactate Dehydrogenase;

COI Statement: This paper has not yet been submitted, presented fully or partially at a meeting, podium, or congress, published, or submitted for consideration beforehand.

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