Ischemic Preconditioning Influence Ventricular Function in Off-Pump Revascularization Surgery

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Abstract

Background: Ischemic preconditioning is a method that prepares and protects cells to tolerate a long period of ischemia with the least possible injury.

Objectives: Evaluate the influence of ischemic preconditioning over left ventricular function during off-pump myocardial revascularization.

Method: Forty patients with clinical indication for off-pump myocardial revascularization were randomized in two groups, with or without ischemic preconditioning. Ischemic preconditioning was carried out by performing coronary occlusion for two minutes and releasing blood flow for one minute; two cycles were performed. Left ventricular contractility was evaluated through transesophageal Doppler by measuring blood flow acceleration in the descending aorta – Hemosonic 100. The acceleration measurements were performed at the start of the surgery, after heart positioning and five and ten minutes after coronary occlusion.

Results: There was no significant difference in left ventricular contractility between the two groups. At the beginning of the procedure flow acceleration was 9.37 ± 2.9m/s² in the preconditioning group and 12.5 ± 3.1 m/s² in no-preconditioning group (p = 0.23); after positioning of heart, it was 8.47 ± 3.3 and 8.31 ± 3.6 m/s² (p = 0.96); after five minutes - 8.7 ± 4.1 and 7.94 ± 2.9 m/s² (p = 0.80); and after ten minutes – 9.2 ± 4.5 and 7.98 ± 3.4 m/s² (p = 0.71). However, contractility evolution was different throughout time in each group. The preconditioning group maintained left ventricular contractility during the entire procedure, since the beginning (0.52), while the group without ischemic preconditioning presented reduction in left ventricular contractility (p = 0.0034).

Conclusion: Ischemic preconditioning prevented the decrease in left ventricular contractility during off-pump myocardial revascularization surgery. (Arq Bras Cardiol 2010; 94(3):319-324)

Key words: Myocardial contraction; myocardial ischemia; coronary artery bypass, off-pump.

Introduction

The ischemic pre-conditioning (IPC) is defined as brief periods of ischemia, intercalated with reperfusion, that precede a period of sustained ischemia. This procedure is carried out with the objective of preparing and protecting the cell for eventual damage caused by a prolonged period of ischemia[1].

Several authors have demonstrated this protective effect of ischemic pre-conditioning in several body tissues[2-5].

In the myocardium, this effect has been clinically studied and it has been verified that patients with angina symptoms presented a better evolution and lower mortality during a myocardial infarction episode, when compared to those that were asymptomatic before the same event[6].

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The off-pump myocardial revascularization surgery represents, since the 1980s[7], an effective therapeutic alternative in the treatment of coronary failure and it has been regularly used by several Services, presenting advantages in comparison to the conventional surgery in patients with severe clinical morbidities in the preoperative period[8,9].

Additionally, it presents as characteristic of the operative technique, the need for brief periods of coronary occlusion to perform the vascular anastomosis[10].

Taking advantage of this technical characteristic, we carried out a randomized clinical study with the objective of evaluating the influence of ischemic pre-conditioning on left ventricular contractility during off-pump myocardial revascularization surgery.

Methods

Study Population

This study was assessed and approved by the Medical Ethics Committee of Hospital Bandeirantes in Sao Paulo.

Forty patients who had received an indication for the surgical treatment of coronary failure were submitted to off-pump myocardial revascularization surgery. These patients were randomized in two groups, with and without ischemic pre-conditioning. Twenty-seven patients were males and 13 were females; aged ranged from 40 to 88 years, with a mean age of 66.7 years. All patients presented stable angina and used beta-blockers, nitrates and acetylsalicylic acid (ASA); the latter was withdrawn five days before the surgery. The preoperative clinical characteristics are shown in Table 1. There were no significant differences and all patients presented normal ventricular function.

The left internal thoracic artery was used in all patients to revascularize the anterior interventricular artery (anterior descending artery). The right coronary artery and the marginal branches of the circumflex artery were revascularized with grafts from the magna saphena vein.

Only the territory of the anterior interventricular artery was submitted to ischemic pre-conditioning.

Surgical procedure

After patient monitoring and pre-oxygenation, the anesthetic induction was performed with sufentanil up to a dose of 0.5μg/kg and propofol until loss of reflexes was achieved. Muscular relaxation was obtained with pancuronium bromide (0.1 to 0.2mg/kg or atracurium, 0.5mg/kg).

After sternotomy and dissection of the left internal thoracic artery, the surgical team was ready to perform the myocardial revascularization. The two groups were stabilized hemodynamically through the use of volume and/or vasoactive drugs before the start of the procedure. Therefore, the two groups presented the same hemodynamic conditions regarding blood pressure, volemia and heart rate. The heart was positioned in all patients through stitches applied to the pericardium and submitted to traction to expose the anterior interventricular artery. The Octopus vacuum stabilizer was always used, in addition to proximal snaring of the anterior interventricular artery to interrupt blood flow and, therefore, perform the anastomosis of the left internal thoracic artery with the coronary artery.

Ischemic pre-conditioning

The proximal snaring of the anterior interventricular artery for a period of two minutes, followed by the opening of this artery for one minute, was standardized as the ischemic pre-conditioning method. Two cycles were performed using this system and then the anastomosis was initiated.

Evaluation of the left ventricular function

The evaluation of the left ventricular function was carried out through the measurement of the blood flow acceleration in the descending thoracic aorta. That was accomplished using a non-invasive method: a pulsed Doppler of the descending thoracic aorta obtained through a transesophageal equipment (Hemosonic 100).

After the anesthetic induction, the echography and Doppler transducers were introduced by oral route and positioned to obtain the blood flow acceleration in the descending thoracic aorta (Figure 1). This acceleration (Acc) of the blood flow in the descending thoracic aorta

Table 1 – Clinical and angiographic characteristics.

Patients	(N=20) With IPC	(N=20) Without IPC	P
Age (years)	65.6	68.2	NS
Female sex	7 (35%)	6 (30%)	NS
Smoker	12	15	NS
Myocardial infarction (previous)	5	4	NS
Arterial Hypertension	17	18	NS
Diabetes Mellitus	9	8	NS
Unstable Angina	4	5	NS
Biarterial disease	28.18%	24.16%	NS
Triarterial disease	71.82%	75.84%	NS
Number of grafts/patient	2.2	2.1	NS
Ejection fraction (mean)	65.68%	64.58%	NS

IPC - ischemic preconditioning; n – number of patients

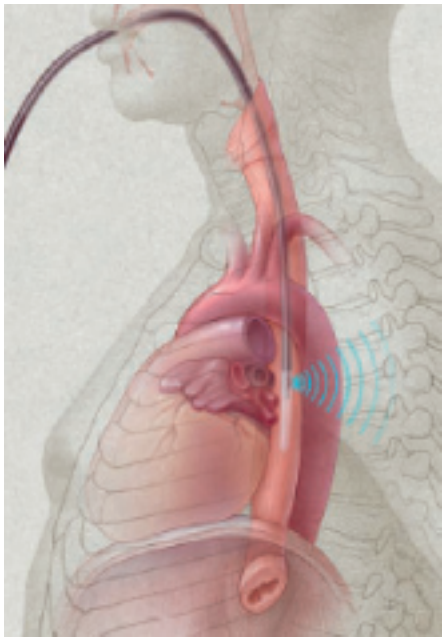

Imagem em baixa resolução

Figure 1 – *Placement of the transesophageal Doppler probe next to the descending aorta.*

provided the analysis of the left ventricular function during the procedure. These measurements were obtained at four different moments: at the start of the procedure, after the positioning of the heart, after 5 minutes of snaring of the coronary artery and after 10 minutes of snaring of the coronary artery, in both groups.

Statistical analysis

The analysis of the qualitative variables in the two groups was carried out through the Chi-square test or Fisher's exact test. The comparison of the quantitative variables between the two groups at the studied moments was carried out with the non-parametric Mann-Whitney test. To evaluate the behavior of the groups throughout time, the non-parametric Friedman's test (analysis of variance) was used. A p value < 0.05 was considered significant for all tests.

Results

There was no mortality in this series, as well as no complications in the postoperative hospital period. The number of performed grafts was similar in the two groups: 2.2 grafts/patient in the group with IPC and 2.1 grafts/patient in the group without IPC (ns).

The analysis of the aortic blood flow showed that the acceleration (Acc) at the start of the procedure and before the positioning of the heart in the group with IPC was 9.37 ± 2.9 m/s², and 12.5 ± 3.1 m/s² (ns) in the group without IPC (Chart 1). When the heart was positioned for the start of the anastomoses, the Acc was 8.47 ± 3.3 m/s² in the group with IPC and 8.31 ± 3.3 m/s² in the group without IPC (ns) (Chart 2).

During the anastomoses, the Acc with 5 and 10 minutes of coronary snaring did not show any difference in the groups with and without IPC, as shown in Charts 3 and 4. Although there was no difference between the groups at the four moments regarding the acceleration of the blood flow, we verified that the behavior was different between the groups throughout time.

The group that received IPC presented maintenance of the blood flow Acc in the descending aorta, whereas the group without IPC presented a significant decrease in the blood flow throughout time (Chart 5).

Table 2 shows the comparative data between the two groups and in each group throughout time, with the respective statistical values.

Discussion

The present study shows that the group that underwent ischemic pre-conditioning maintained the blood flow Acc in the aorta during the surgical procedure, demonstrating sustained myocardial contractility, whereas the patients that did not undergo IPC presented a significant decrease in the blood flow acceleration.

The first studies on pre-conditioning were carried out with analyses of the cardiac muscle[1]. Neely & Grotyohann[1] showed experimentally that short periods of sustained myocardial ischemia produced a protective effect against

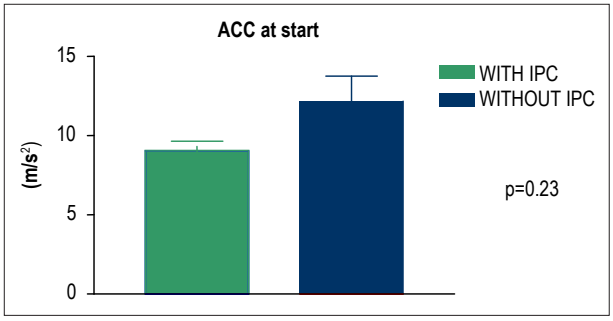

Chart 1 – Acceleration (Acc) of the aortic blood flow at the start of the procedure, before the positioning of the heart in the groups with and without ischemic preconditioning. IPC - ischemic preconditioning.

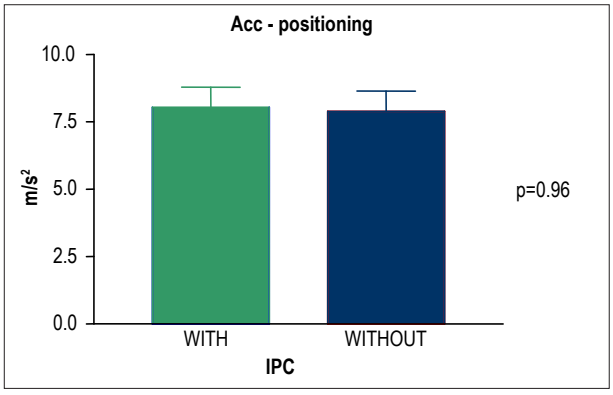

Chart 2 - Acceleration in the Aorta (Acc) after the positioning of the heart to perform the anastomosis of the left internal thoracic artery with the anterior descending artery. IPC - ischemic preconditioning.

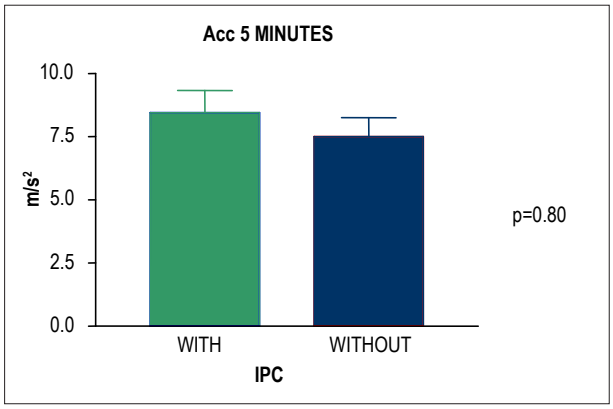

Chart 3 - Values of the blood flow acceleration in the descending aorta in m/s² (meters per square second) in the two groups, with five minutes of snaring, without statistically significant differences. IPC - ischemic pre-conditioning.

ischemia and reperfusion lesions. However, it was Murry t al[11] that documented the protective effect of IPC in the myocardium of dogs and disseminated the term "pre-conditioning".

Subsequently, several organs and tissues to which the pre-conditioning could be applied were studied, as well as its protective benefits in the preservation of cellular

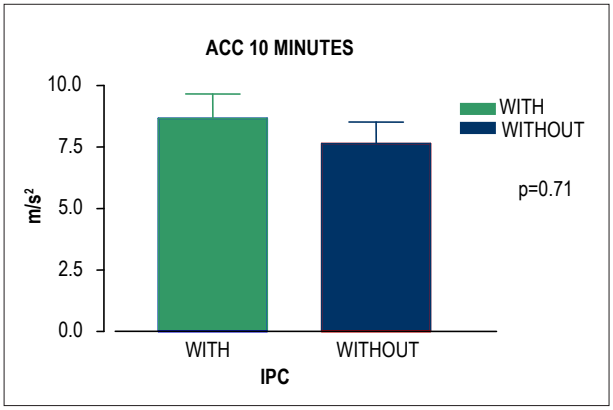

Chart 4 – Values of the blood flow acceleration in the descending aorta in the two groups with 10 minutes of coronary snaring.

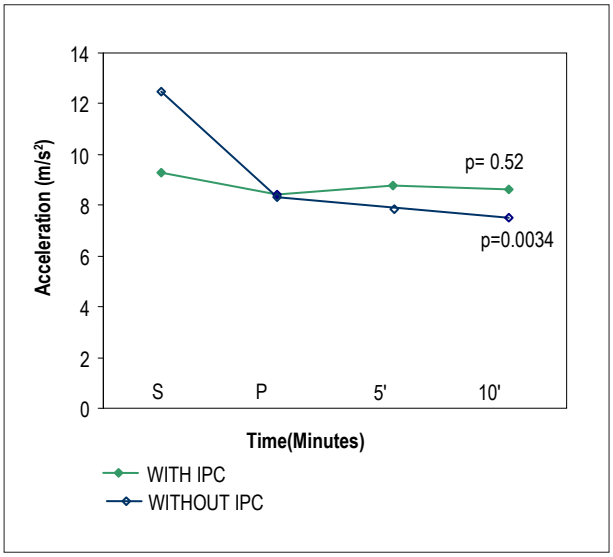

Chart 5 - Acceleration curve of the aortic blood flow (Acc) throughout time in the two groups: S - start, P - positioning of the heart, 5' - five minutes of snaring, 10' - ten minutes of snaring. IPC - ischemic preconditioning.

Table 2 - Comparison of the Acceleration (Acc) of the aortic blood flow in the two groups, at each moment and throughout time in each group (mean and Standard Deviation).

	ACCELERATION (Acc – m/s²)				
T	S	P	5'	10"	p
With IPC	9.37±2.9	8.47±3.3	8.70±4.1	9.2±4.5	0.52
Without IPC	125±3.1	8.31±3.3	7.94±2.9	7.98±3.4	0.0034
With IPC x Without PCI					
p	023	0.96	0.80	0.71	

With IPC - with ischemic preconditioning; Without IPC - without ischemic preconditioning; S - Start; P - positioning of the heart; 5' - five minutes of coronary snaring; 10' - ten minutes of coronary snaring. With IPC X Without IPC: comparison between the two groups at each moment.

integrity[2-5,12-17]. Several mechanisms are involved in the phenomenon of ischemic pre-conditioning.

The ischemia induces the release of chemical mediators that stimulate ATP-sensitive potassium channel receptors on the mitochondrial membrane, leading to the local decrease of Ca++ and the increase in the production of ATP. Some of these mediators are: adenosine, opioids, bradykinin, endothelial factors and free radicals[18]. The maintenance of ATP and creatine-phosphate levels, associated to a decrease in the energy consumption by the cell seems to be one of the pre-conditioning effects in cell respiration[14,19-21]. Additionally, there seems to be a decrease in the glycogen deposits during the ischemia periods of pre-conditioning, as well as a decrease in glycolysis during the sustained ischemia period[22]. This characteristic, associated with the catabolite washout during the reperfusion periods of the IPC, lead to a lower accumulation of lactate and hydrogen ions (H+), decreasing the velocity of ischemic acidosis progression[14].

In clinical cardiology, the protective concept of pre-infarction angina is increasingly disseminated; this apparent paradox is one of the clinical observations that best reflects the protective effect of ischemic pre-conditioning.

Half of the patients that are victims of myocardial infarction have angina symptoms preceding the infarction. Several authors have pointed out a better hospital evolution with lower mortality and better preservation of ventricular function in patients with myocardial infarction that presented previous angina symptoms[6,23,24].

The surgical treatment of coronary failure, specifically in off-pump myocardial revascularizations, which obligatorily needs coronary occlusion for the performance of the vascular anastomoses, has in the concept of ischemic pre-conditioning a large field of research and a condition of immediate applicability of the possible benefits.

Laurikka et al[25] applied the concept of IPC to 32 patients that were submitted to off-pump myocardial revascularization. These patients were randomized in two groups, with and without IPC. The group with IPC presented lower enzymatic release in the postoperative period and better recovery of ventricular work assessed by the Swan-Ganz catheter.

Wu et al[26] randomized 40 patients submitted to myocardial revascularization with and without IPC, with two 2-minute cycles of ischemia and three of reperfusion. There was a decrease in the cardiac index and the right and left ventricular work within the first six postoperative hours in the group without pre-conditioning. The authors did not observe any differences in the levels of CKMB, troponin I, lactate and myoglobin in the two groups.

In our country, studies carried out using the ischemic pre-conditioning through the intermittent clamping of the aorta in surgeries with extracorporeal circulation demonstrated a lower release of CKMB and troponin I[27,28].

In addition to the hemodynamic and enzymatic aspects, a decrease in supraventricular and ventricular arrhythmias was observed in the postoperative period with the use of IPC[29].

The assessment of the cardiac output and left ventricular contractility is usually carried out through the Swan-Ganz

catheter, which is used most of the times in the postoperative period to adequately assess the patient's hemodynamic conditions. However, during the intraoperative period, this method of assessment of cardiac output can be influenced and even impaired by the positioning and manipulation of the heart, which can cause the dislocation of this catheter and hinder the analyses of cardiac output, in addition to being an invasive method. Therefore, to evaluate the influence of ischemic pre-conditioning on ventricular contractility, we used a non-invasive method to identify the possible hemodynamic alterations during the off-pump surgery.

The Hemosonic 100, through Doppler echography, measures the maximum acceleration of the aortic blood flow, which is a parameter of myocardial contractility that correlates with the dp/dt index of the left ventricle obtained at the hemodynamic study[30].

Sabbah et al[31] evaluated the acceleration of the aortic blood flow using echography in three groups of patients and compared it with the ejection fraction (EF) obtained during the hemodynamic study through left ventriculography. In the first group, with an EF > 60%, the peak acceleration was 19 ± 5 m/s^2; in the second, with an EF between 41% and 60%, it was 12 ± 2 m/s^2; and in the third group, with an EF < 40%, the peak acceleration was 8 ± 2 m/s^2. That demonstrates a linear correlation between the blood flow acceleration in the aorta and the EF, which the authors concluded to be an effective, non-invasive method to evaluate left ventricular contractility.

When we analyze the two groups (with and without IPC) moment by moment, we observe no differences in ventricular function; however, the groups present different behaviors throughout time.

We observe that the group with IPC maintained the aorta blood flow acceleration values between the start and the end of the procedure, whereas the group without IPC presented a significant decrease in the acceleration.

It is likely that, as the two groups consist of patients with preserved ventricular function, it was not possible to observe differences between the groups at specific moments. However, this difference could be higher in patients with ventricular dysfunction, and even if that does not occur, the maintenance of the initial conditions and the lack of decrease in ventricular function would already justify the use of the method.

Moreover, when the pre-conditioning is applied, we are also assessing the tolerance to coronary occlusion. Although it did not occur in this series, some patients can present ST-segment elevation or even atrioventricular block and need conversion to emergency extracorporeal circulation.

Another aspect that can influence the results is the anatomical variation of the coronary arteries. Sometimes the anterior descending artery is practically the only one on the anterior wall or gives out more distal diagonal branches, which are involved in the snared region; other times, there are proximal diagonal branches that are not involved in the coronary occlusion and these diagonal branches maintain the perfusion of part of the anterior wall. These anatomical variations can determine heterogeneity in the pre-conditioning area and eventually, influence the left ventricular contractility.

Conclusions

The ischemic pre-conditioning prevented the decrease in the left ventricular contractility during the off-pump myocardial revascularization surgery.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any post-graduation program.

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