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Renal and hepatic protection due to remote ischemic conditioning in coronary artery bypass grafting

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ARTICLE INFORMATION

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Acronyms
CABG: coronary artery bypass grafting
CPB: cardiopulmonary bypass
RIC: remote ischemic conditioning

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ABSTRACT

Introduction: Short periods of distant ischemia can limit myocardial damage caused by ischemia/reperfusion.
Objectives: To identify the effect of remote ischemic preconditioning in relation to the postoperative behavior of creatinine, glutamic transaminase, pyruvic and oxaloacetic levels.
Method: A quasi-experimental, explanatory, comparative study with historical control was carried out in two groups of 247 patients each; all candidates for coronary artery bypass grafting. A blood-pressure cuff was placed on the right arm in the study group alternating three inflations with three deflations of five minutes at 200 mmHg. This procedure was performed prior to during and after the major ischemic episode caused by the coronary artery impingement.
Results: A significant decrease in the values of creatinine, pyruvic glutamic transaminase and glutamic oxaloacetic transaminase was achieved.
Conclusions: Remote ischemic conditioning is an important tool to take into account for renal and hepatic protection in coronary artery bypass grafting.
Keywords: Remote ischemic preconditioning, Reperfusion injury, Myocardial revascularization, Enzymes, Creatinine, Transaminases

Protección renal y hepática por condicionamiento isquémico a distancia en la revascularización miocárdica quirúrgica

RESUMEN

Introducción: Breves períodos de isquemia a distancia pueden limitar el daño miocárdico producido por la isquemia/reperfusión.
Objetivo: Identificar el efecto del condicionamiento isquémico a distancia con fines de protección renal y hepática, relacionado al comportamiento postoperatorio de los niveles de creatinina y transaminasas glutámico-pirúvica y glutámico-oxalacética en la revascularización miocárdica quirúrgica.
Método: Se realizó un estudio cuasiexperimental, explicativo, comparativo con control histórico, en dos grupos de 247 pacientes cada uno, propuestos para revascularización miocárdica quirúrgica. Se colocó un torniquete en el brazo derecho, en el grupo estudio, alternando 3 insuflaciones (con una presión de 200 mmHg) con 3 desinsuflaciones, durante cinco minutos cada una. Este procedimiento se realizó previo, durante y después de la mayor isquemia inducida, provocada por

el pinzamiento de la arteria coronaria.
Resultados: Se logró una disminución significativa en los valores de creatinina (p< 0,001), transaminasa glutámico-pirúvica (p<0,001) y transaminasa glutámico-oxalacética (p<0,05).
Conclusiones: El condicionamiento isquémico a distancia es una importante herramienta a tener en cuenta para la protección renal y hepática en la revascularización miocárdica quirúrgica.
Palabras clave: Precondicionamiento isquémico a distancia, Daño por reperfusión, Revascularización miocárdica, Enzimas, Creatinina, Transaminasas

INTRODUCTION

More than 17 million North Americans have some sort of cardiac problem. From them, 11 million suffer from coronary artery disease, 5 million have valvular heart disease and 1 million have congenital heart disease[1]. The coronary disease is the more frequent cause of death among adults in that country and consumes more health resources than any other disease[1].

Approximately one third of patients who are treated for some type of surgery have a coronary disease or risk of having it. From the 72 million surgical procedures performed, approximately 0.7 million are primary cardiac[2].

In Cuba, cardiovascular diseases are the leading cause of death and among them, the ischemic heart disease accounts for 75%. This disease is suffered by almost 20% of the population over 60 years old[3].

The myocardial ischemia is usually secondary to the obstruction of coronary arteries by atheromatous plaques, which are a consequence of abnormal lipid deposition in the vascular intima, favored by multiple risk factors. The phenomenon leads to endothelial dysfunction and, in general, of the entire arterial wall, whose corollary is a clinical state of acute or chronic low coronary flow[4].

The mechanisms through which the ischemia/reperfusion phenomenon injures the heart are complex and there is intense debate about the contribution of the individual components of this process. Some authors, such as Balakumar y Sharma[5] state that the reperfusion process is twice as harmful to the myocardium as the ischemic lesion itself[2,5,6]. If the heart is damaged by ischemia/reperfusion, its function will also be affected and, therefore, the proper function of vital organs such as liver and kidneys, dependent entirely of an appropriate cardiac output.

The phenomenon of "post-reperfusion injury" in the ischemic heart disease, in return for the benefit of generalized revascularization procedures in recent years, has become of interest for identifying strategies that can counter it. The ischemic preconditioning in animals was described more than 30 years ago, by showing that short periods of ischemia, induced experimentally on the myocardium, limit the size of the resulting infarction after a subsequent coronary occlusion[7].

In 1986 , Murry *et al*[7] developed the first research on ischemic preconditioning in experimental animal models (dogs) and they observed that the production of four cycles of five minutes of ischemia followed by reperfusion for another five minutes, by occlusion and the repermeabilisation of the circumflex artery, immediately before a long-term event of sustained myocardial ischemia produced an experimental acute myocardial infarction (40 minutes of occlusion of that artery), paradoxically, it decreased, by 25%, the infarction's size compared to individuals not treated with the ischemic preconditioning protocol[2,7].

In the 1990s, Przyklenk *et al*[8] published –for the first time in the history of ischemic conditioning– that the ischemia induced in another area of the heart, or in another tissue away from this organ, could also condition the response of the myocardium, in front of a further ischemic insult. Thus, the concept of remote ischemic conditioning (RIC), or at distance, was developed. The first was carried out in 1993 by that author[8], who explains how a protocol of ischemic preconditioning applied by cycles of occlusion and reperfusion of the circumflex artery in dogs could reduce the size of subsequent myocardial occlusion of another coronary artery, the anterior descending; therefore, the protective effect of conditioning can be exerted outside the myocardial territory that will subsequently suffer an infarction. Then, there are works, including controlled clinical trials[8,9], in which the protective effect of ischemic

preconditioning is exerted from outside the heart itself, such as skeletal muscle tissues of the upper or lower extremities.

Generally, the RIC, in its two fundamental forms, pre- and post-conditioning, is an easy procedure to perform, safe, without adverse reactions or demonstrated complications, and it can be applied for protection against ischemia in several organs of our body[10]; among them, the most studied because of its importance is the heart, but others have also been focused, where the RIC is effective as well: brain, kidneys, gastrointestinal system (liver, small and large intestine, pancreas, skeletal muscle) and lungs[10]; the latter, much less affected than the rest due to the double arterial irrigation system that it has, which makes it less susceptible to presenting events of ischemia.

The objective of this study was to identify the effect of RIC for the purpose of renal and hepatic protection, related to the behavior of creatinine levels and glutamic-pyruvic and glutamic-oxaloacetic transaminases in the postoperative stage of the coronary artery bypass grafting (CABG).

METHOD

An explanatory, quasi-experimental study was conducted, with 247 patients (study group) proposed for cardiac surgery of CABG, which were compared with an equal number of patients already operated (control group). The patients of the second group (historical control) were analyzed retrospectively, and the study group, where the RIC was applied, was evaluated prospectively; in both cases according to the order of arrival to the Surgical Unit of the Cardiocentro Ernesto Che Guevara of Villa Clara, Cuba.

Inclusion criteria

The patients who present for elective CABG in a period of one year and (the ones of the study group) expressed their agreement to participate in the research by signing the informed consent. The patients of the control group were already operated, in them, the RIC was not applied and only the data of the clinical history were used, without using their personal data; in addition, there was the approval of the Research Ethics Committee of the center where the study was conducted.

Exclusion criteria

There were excluded the patients who, besides the CABG, were performed procedures of intraoperative ablation of arrhythmic foci, valve implantation or aortic or other grafts, presence of an arteriovenous fistula or lymphedema of the right arm in the case of the study group, previous endovascular or conventional cardiac surgery, urgency or emergency surgery, renal failure and previous neurological dysfunction.

Exit criteria

Patients who died during the perioperative period and the first week after surgery.

Main variables

Liver enzymes: Serum values (in units/liter [U/L]) of glutamic-pyruvic (normal value 7-41 U/L) and glutamic- oxaloacetic (normal value 12-38 U/L) transaminases were evaluated.

Creatinine: Expressed in micromoles per liter (μmol/L); there was considered a normal value up to 132.6 μmol/L.

The serum determinations of these variables were obtained fasting, before (during preoperative check-up) and after surgery (first seven days after surgery), and processed in the clinical laboratory of the hospital where the research was conducted.

Others: Other variables were evaluated, but they were not a primary objective for this article. Among them are: age, sex, number of coronary vessels with lesions angiographically significant, number of revascularized coronary vessels and duration of the cardiopulmonary bypass (CPB).

Anesthetic protocol and of the RIC

The anesthesia was induced with intravenous administration, single dose of lidocaine 2% 1 mg/kg of body weight, fentanyl 5 μg/kg, propofol 2 mg/kg and bromide vecuronium 0.1 mg/kg; then the orotracheal tube was placed. The mechanical pulmonary ventilation was performed with a Fabius GS ventilator, the initial tidal volume was calculated at 7 ml/kg, with respiratory rate of 12 to 16 cycles per minute and a FiO_2 of 50%; a deep venous catheter was then placed in the right internal jugular vein (intermediate route) to monitor the central venous pressure, and two centimeters below, an 8F introducer was

placed to insert a catheter into the pulmonary artery (Swan-Ganz), with which the cardiac index and the systemic vascular resistance were measured. The maintenance of anesthesia was performed with isoflurane between 1 and 1.5 of minimum alveolar concentration.

After stabilizing the patient and the anesthetic instrumentation, the next step was to place, in the study group, a blood-pressure cuff on the right arm (pre-RIC), which was insufflated to a pressure of 200 mmHg and it was kept for five minutes; then, it was deflated to allow reperfusion of the limb for five minutes, then, this cycle was repeated twice.

Once the coronary artery was clamped for its revascularization (major ischemic event), the procedure of insufflate/deflate the cuff (pre-RIC) was repeated and subsequently, upon closing, it was performed by the third and last time, as well as the procedure (post-RIC). After the surgery was completed, the patient was transferred to the surgical intensive care unit (ICU), where he was treated according to the protocol established by the cardiovascular surgery service.

Processing of information

The information obtained was grouped in a database in Microsoft Excel 2010 and processed with the statistical program SPSS version 20. The qualitative variables were summarized by absolute numbers and percentages, the quantitative variables with the mean and their standard deviation. For the comparison of the groups studied, the Chi square test (χ^2) was used for the qualitative variables, and the Student's t-test for the quantitative ones.

RESULTS

Two groups of 247 patients each (representative sample of the study population) were formed, and no significant differences (p>0.05) were found with respect to the set of variables representing the initial state of the patients: age, sex, left ventricle ejection fraction, family medical history of ischemic heart disease, presence of diabetes mellitus, high blood pressure, dyslipidemia or chronic obstructive pulmonary disease, duration of the CPB, extracardiac or peripheral artery disease, number of vessels with significant an-giographic lesions, number of revascularized vessels, functional class according to NYHA, myocardial infarction new/old, unstable angina, smoking habit and treatment, which ensured the homogeneity of the groups and allowed make comparisons among them.

Concerning the creatinine (**Figure 1**), it was noted that, before surgery, no significant differences were found among the groups (p>0.05); however, when each of the first seven postoperative days were analyzed, in the patients of the study group, there were actual significant differences (p<0.001), with higher figures than in the control group.

Similar results were obtained when analyzing the glutamic-pyruvic (**Figure 2**) and glutamic-oxaloacetic (**Figure 3**) transaminases, since there was no statistical difference before surgery (p>0.05) and very significant differences were demonstrated in the first postoperative week (p<0.001), in favor of the group where the RIC was used.

DISCUSSION

Although nowadays reperfusion is considered to be essential in order to save the ischemic myocardium

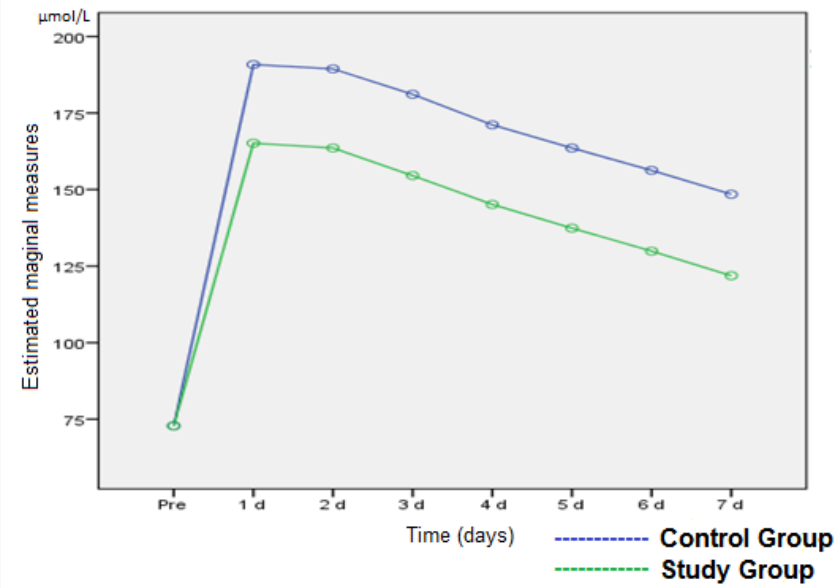

Figure 1. Serum creatinine means according to time and groups studied.

against necrosis, paradoxically, reperfusion itself may produce or increase myocardial injury[2,5]. Therefore, in recent decades the need to improve myocardial protection against ischemia has been intensified, in order to minimize the injury caused by the phenomenon of ischemia/reperfusion. Not less important is the renal and hepatic protection, dependent entirely of the proper cardiac function, because in this type of surgery –CABG with use of CBP–, the perfusion pressures of these organs can be affected and can cause ischemic injury. Moreover, an inadequate cardiac output due to post-CABG myocardial ischemia results in an impairment of renal and hepatic functions because of the decreased myocardial function (low cardiac output), without these organs to be directly affected.

The parameters studied, such as creatinine and glutamic-pyruvic and glutamic-oxaloacetic transaminases decreased significantly in the group where the RIC was applied, suggesting that the procedure could also protect other vital organ systems, not only the heart, such as: kidneys[11-14], liver[10,11,15], brain[11,20,21], and lungs[21], among the most important and essential in the rapid recovery of the patient, and which are very affected by the systemic inflammatory response syndrome, which is triggered during the CBP, a strategy used in most cardiovascular surgeries. However, other authors[16-19] expose that the RIC does not protect the renal system. Nonetheless, an interesting article by Zimmerman and other North American nephrologists[22], where 118 patients were studied divided into two groups, during the postoperative stage of a cardiac surgery, found that from the total sample, prior risk stratification and no significant pre-surgical differences (p=0.43), 12 patients in the study and 28 of the control had acute renal dysfunction, with highly significant statistical differences (p=0.004); this demonstrated the effectiveness of the RIC in the prevention of acute renal damage, especially after one of the main risk factors for this complication in cardiac surgery, the use of CBP.

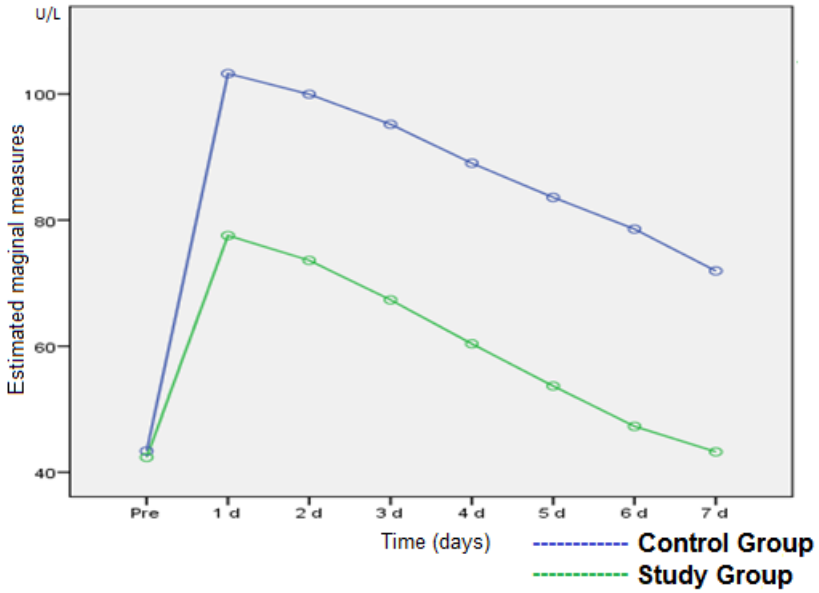

Figure 2. Means of glutamic-pyruvic transaminase according to time (days) and groups studied.

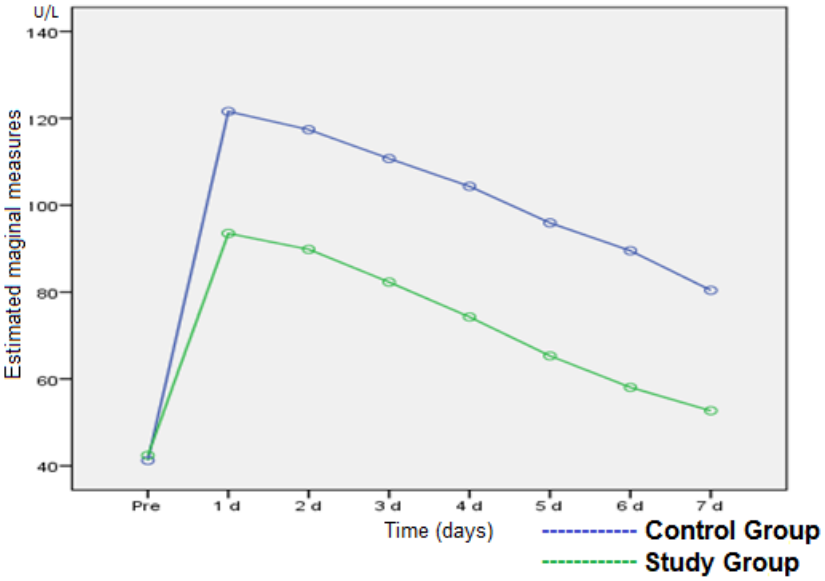

Figure 3. Means of the glutamic-oxaloacetic transaminase according to time (days) and groups studied.

CONCLUSIONS

The remote ischemic conditioning is a useful method for renal and hepatic protection during the coronary artery bypass grafting, evidenced by a significant decrease in the serum values of creatinine, as well as in the glutamic-pyruvic and glutamic-oxaloacetic transaminases.

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