The role of myocardial ischaemic preconditioning during beating heart surgery: biological aspect and clinical outcome

Efstratios Apostolakis, Nikolaos G. Baikoussis* and Nikolaos A. Papakonstantinou

Department of Cardiac Surgery, University of Ioannina, School of Medicine, Ioannina, Greece

* Corresponding author. Tel: +30-697-4201838; fax: +30-265-1099679; e-mail: ngbaik@yahoo.com (N.G. Baikoussis).

Abstract

Short periods of ischaemia consecutive to reperfusion periods before a sustained ischaemic condition, the so-called ischaemic preconditioning (IP), aim to protect myocardial cells against prolonged ischaemia. IP appears as a considerable endogenous cardioprotective mechanism decreasing the infarct size after total occlusion in either experimental models or humans. Angina periods before an acute coronary syndrome limit the myocardial infarction being protective for the myocardium. Our report aims to review the international bibliography of the IP during off-pump coronary artery bypass grafting.

Keywords: Ischaemic preconditioning · Coronary artery bypass grafting · Myocardial infarction · Beating heart cardiac surgery · Off-pump coronary artery bypass

INTRODUCTION

Although cardiopulmonary bypass (CPB) and cardioplegic cardiac arrest with aortic cross-clamping provide an optimal operative field, they are hazardous techniques for myocardial injury and inflammation mediated by the production of free radicals during reperfusion. Moreover, patients having experienced conventional CPB are more prone to neurological disorders because of cerebral microembolism [1].

Nowadays, provided that stabilizing devices and retraction techniques have been implemented, beating heart myocardial revascularization—the well-known off-pump coronary artery bypass grafting (OPCABG)—is getting more and more popular [2], avoiding hypothermia, aortic cannulation and aortic cross-clamping with their deleterious effects [2, 3]. Beating heart cardiac surgery is associated with decreased blood transfusion requirements, shorter hospital stays, decreased organ dysfunction and haemorrhagic complications and lower mortality rates in high-risk patients [4, 5].

Nevertheless, OPCABG provides a less adequate operative field with limited access [5]. Furthermore, the final result of the off-pump surgical method is a beating, normothermic, but regionally ischaemic heart [6] provided that it intrinsically requires short intervals of ischaemia for the vascular anastomosis to be performed which result in regional ischaemia [7]. Even these short-term regional ischaemic periods can lead to myocardial ischaemia/reperfusion injury [1]. Contractile dysfunction, injury of the vascular endothelium and myocardial necrosis are possible to happen [6]. Permanent myocardial injury is favoured in the absence of cardioplegia due to the reduced myocardial tolerance to ischaemia under normothermia [1]. The impact of the damage of these short ischaemic periods on the myocardium depends on the ischaemia duration, the mass and status of the myocardium at risk, the myocardial oxygen consumption balance and the existence of collateral circulation [8]. If the latter is not enough developed, regional hibernation, stunning or even myocardial infarction may occur. Arrhythmias and haemodynamic instability may follow making conversion to CPB necessary [8]. However, brief ischaemic periods are usually well tolerated without signs of major ischaemia and without affecting haemodynamics [9–12]. An ST segment elevation of 1–2 mm happens in up to 40% of OPCABG cases [13, 14]. The percentage of myocardial infarction concerning beating heart surgery is not higher than 1–4.8% in large series [3, 10, 11]. According to van Aarnhem *et al.* [8], ischaemia took place in 10% of cases, but haemodynamics were affected only in 1.4% (5 of 365 anastomoses). Therefore, protection against ischaemia is also needed during beating heart surgery.

Short episodes of ischaemia consecutive to reperfusion periods before a sustained ischaemia period, the so-called ischaemic preconditioning (IP) [15], aim to protect myocardial cells against prolonged ischaemia [16]. IP appears as a considerable endogenous cardioprotective mechanism decreasing the infarct size after total occlusion in both experimental models and humans [17–21]. Angina periods before an acute coronary syndrome limit the myocardial infarction being protective for the myocardium [13]. Elevated creatine kinase levels, fewer Q waves, lower mortality and congestive heart failure rates and more successful thrombolysis have been reported [22–26]. Apart from delaying myocardial injury [1], IP maintains high-energy phosphates, prevents arrhythmias and improves functional recovery after the ischaemia [17, 21]. Decreased lactate generation during the ischaemia due to the depletion of myocardial glycogen is an additional benefit of IP [17, 21]. Therefore, although the efficacy

of IP is doubted [7, 17, 27, 28], it seems to constitute a promising cardioprotective method [1].

METHODS

We searched in the international electronic database PUBMED in order to find studies related to IP during beating heart surgery. Studies included in our paper were published in the aforementioned database from 1984 to 2010. In order to identify these studies, we used the following keywords: ischaemic pre-conditioning, coronary artery bypass grafting, myocardial infarction, OPCAB, beating heart cardiac surgery and off-pump coronary artery bypass. *A priori*, we excluded retrospective studies, case series and studies concerning on-pump cardiac surgery. Our scope was to form a review of more recent studies about the use of IP as a cardioprotective method during OPCAB including both positive and negative data.

IP protocol

Neely and Grotyohann [16] were the first to report the protective impact of brief ischaemia periods against ischaemia-reperfusion injury. Nevertheless, the term 'preconditioning' was established by Murry *et al*. [17] who showed the aforementioned protective effect in canine myocardia.

More than 90 s of coronary occlusion is required for the manifestation of IP effects [29], and repeated cycles of ischaemia and reperfusion are necessary to ensure these protective effects [30]. An ideal IP procedure should offer the maximal heart protection without rendering the main surgical procedure more complicated, so a minimal ischaemic stimulus repeated few times is advisable [1]. Three to five minutes of IP seem to be enough to ensure myocardial protection against ischaemia in patients experiencing OPCABG [31, 32].

Succi *et al*. [15] suggested the occlusion of the anterior descending coronary artery for 2 min, followed by a 1-min reperfusion period as a complete cycle of the IP technique. Two such cycles were performed as the IP method. The IP method applied by van Aarnhem *et al*. [8] contained the alternation of cycles of 5 min of local coronary artery occlusion and of 5 min of reperfusion. Two cycles of 2 min of ischaemia in the left anterior descending (LAD) area followed by 3 min of reperfusion before the vascular anastomosis were performed consisted the Laurikka *et al*. IP method [1].

Finally, Matsumoto *et al*. [33] proposed the simultaneous use of IP with an ATP-sensitive potassium channel (KATP) opener and an oxidative radical scavenger in order to achieve a further decrease in duration and number of cycles of IP, since both of them contribute to the improvement of cardiac dysfunction as well as to the recovery of the myocardial function after the ischaemia.

Benefits gained by IP in experimental models

Although there is the abundance of evidence showing that IP has a potent cardioprotective impact [17, 21, 28], several studies do not report any improvement of short-term myocardial function in animals undergoing IP under off-pump surgery [6, 27]. Nevertheless, even the latter do demonstrate longer-term profits with regard to endothelium-dependent relaxation, endothelial viability, β-adrenergic regulation and post-ischaemic myocardial blood flow that are improved and with regard to neutrophil accumulation that is partially prevented [6, 27].

In a study [2] of 21 pigs undergoing CABG using a left internal thoracic artery conduit, seven pigs were submitted to IP consisted of 5 min of occlusion of the LAD coronary artery followed by 15 min of reperfusion. Post-reperfusion regional myocardial function was not favoured by IP despite limiting the infarct size. A decrease in the infarct size was also demonstrated by other studies when IP was performed in dogs [17] and pigs [34], thus improving post-ischaemic cardiac performance [35, 36] and metabolism [37] after reperfusion. Despite the aforementioned, the benefits of IP concerning global or regional myocardial function after reperfusion are doubted [38–40]. According to another study [41], IP had no impact on regional stunning either. Ten healthy, young pigs without a coronary disease underwent IP, consisted of 10 min of coronary occlusion, followed by 15 min of reperfusion before they experienced 20 min of ischaemia. These pigs were compared with 10 other pigs experiencing only 20 min of ischaemia. After a reperfusion period of 120 min, IP did not influence regional stunning, but the coronary vascular resistance (CVR) during the reperfusion period was significantly greater in the IP group ($P < 0.005$).

Whether the results regarding IP are positive or not, however, the conclusions should not be applied to the patients' human hearts. The reason why this is proposed is that whereas patients undergoing off-pump surgery have obstructed coronary arteries and potential collateral circulation, experimental animals have relatively healthy hearts, so the results concerning the latter are not safe enough for the former [1]. Apart from the aforementioned, comorbidities such as diabetes, hypercholesterolaemia and hypertension which often accompany human patients are notorious for their harmful effects on heart.

Benefits gained by IP in humans

It is established that angina episodes before an acute coronary syndrome are protective for the myocardium [15]. Half of the patients who experience myocardial infarction have symptoms of angina before the event. These patients with pre-infarction angina symptoms are reported to gain lots of benefits in terms of mortality which is less and in terms of ventricular function which is better maintained [22, 42, 43]. This intrinsic myocardial defensive mechanism best reflects the cardioprotective properties of IP [15]. There are several studies that support this protective impact of IP during OPCABG on the myocardium against ischaemia [31, 32], but other ones demonstrate the controversial results [13, 44].

In Malkowski's report [13], 17 patients underwent OPCABG due to more than 70% LAD coronary artery stenosis. A 5-min coronary occlusion followed by a 5-min reperfusion period was performed before a second coronary occlusion during anastomosis. However, regional systolic dysfunction and pulmonary artery hypertension because of ischaemia were not prevented during the second ischaemia episode, so they concluded that repeated cycles of ischaemia and reperfusion do not significantly affect systolic dysfunction. Similar results were also reported by Dupouy *et al*. [45] who demonstrated that short ischaemic episodes due to LAD occlusion are not protective for the preservation of ventricular function.

CORONARY

On the other hand, Yellon *et al.* [46] demonstrated the protective effect of brief ischaemia periods on the human myocardium against sustained ischaemia. Laurikka *et al.* [1] examined 32 patients who underwent OPCABG and were divided into a group submitted to IP and a second one without IP at random. Lower release of post-operative cardiac troponin I (CTnI; *P* = 0.045) and creatine kinase isoenzyme MB (*P* = 0.100) was observed in the IP group. The stroke volume index (SVI) which was significantly higher (*P* = 0.039) along with the heart rate (HR) which was significantly less elevated (*P* = 0.035) in the same group also showed a beneficial effect of IP on the myocardial function recovery.

Moreover, another benefit gained by the IP procedure concerns aortic blood flow acceleration. The maximum acceleration of the aortic blood flow constitutes a marker of myocardial contractility [47]. Sabbah *et al.* [48] showed a strong correlation between the aortic blood flow acceleration and the contractility of the left ventricle as it is evaluated via the ejection fraction (EF). Measuring the blood flow acceleration in the aorta in three groups of patients with different EF, they found that patients with an EF over 60% presented a peak acceleration of 19 ± 5 m/s^2, those with an EF between 41 and 60% had a peak acceleration of 12 ± 2 m/s^2 and the ones with an EF <40% had even lower peak acceleration (8 ± 2 m/s^2). Succi *et al.* [15] performed off-pump myocardial revascularization surgery in 40 patients who were divided into two groups; it depends on the use of IP. Although the ventricular work was similar in both groups, a significant decrease in the aortic blood flow acceleration between the beginning and the end of the procedure was reported in the group without IP. On the contrary, no such change was observed in the IP group where the acceleration was nearly stable, showing that the myocardial contractility was preserved.

Apart from enzymatic and haemodynamic benefits, IP has been reported to prevent from post-operative supraventricular and ventricular arrhythmias [49]. Doi *et al.* [50] also showed these anti-arrhythmic effects of the IP in humans. In their study, 45 patients with LAD disease were submitted to OPCABG. IP led to the minimization of their electrophysiological parameters including anisotropy and QT and JT dispersions [50].

Reasons why IP effects may be underestimated

Despite its benefits, the success of the method of preconditioning depends on the patient's tolerance to the occlusion of the selected coronary vessel. IP can induce an ST-segment elevation or even an atrioventricular block. If such a case occurs, an emergent changeover to an on-pump procedure with extracorporeal circulation is necessary [15].

The underestimation of the effectiveness of IP via LAD occlusion is also possible if collateral circulation in the distal LAD area exists [1]. Collateral circulation itself is able to limit the infarct size, thus participating in the prevention of contractile dysfunction [1, 15]. Furthermore, several anaesthetic agents and inotropic drugs used during cardiac surgeries may have a cumulative result to the IP effects hiding the latter. Therefore, anaesthetic agents and inotropic drugs may be considered responsible for the positive effects of IP [1].

CONCLUSIONS

In conclusion, the cardioprotective effects of IP with regard to the experimental models despite having mostly healthy hearts are controversial. There are both studies favouring the use of IP as a cardioprotective method [17, 21, 28, 34–37] and others that report no profit in terms of post-reperfusion myocardial function after IP [2, 6, 27, 38–41]. However, even the latter do demonstrate a positive impact of IP on the myocardium with regard to endothelium-dependent relaxation, endothelial viability, β-adrenergic regulation and post-ischaemic myocardial blood flow which are improved, in terms of neutrophil accumulation which is partially prevented [6, 27], with regard to the infarct size which is restricted [2] and in terms of the CVR during the reperfusion period which is significantly greater [41]. On the other hand, as far as the human hearts are concerned, the cardioprotective efficacy of the IP under OPCABG is also doubted. There are those who vote for the positive effects of IP regarding cardioprotection [1, 15, 31, 32, 46, 49, 50] and the ones who support that IP does not offer the preservation of the ventricular function under OPCABG [13, 44, 45]. According to the former IP under OPCABG appears to prevent reduction in the left ventricular contractility [15], as well as to be accompanied with significantly lower levels of CTnI and significantly better haemodynamics (SVI and HR), with better recovery of ventricular work [1] and with anti-arrhythmic effects [49, 50]. On the contrary, Malkowski *et al.* [13] and Dupouy *et al.* [45] reported that repeated short ischaemic intervals are not significantly protective against regional systolic dysfunction.

Therefore, IP appears as a promising alternative in myocardial protection under beating heart surgery requiring though more evidence for its beneficial effects. Its additional advantage as a cardioprotective method is the fact that IP mimics an endogenous myocardial mechanism against infarction, the pre-infarction angina [17–22, 42, 43]. As there are both patients who gain and who did not gain from IP, there should be stratification of the patients' demographics in order to be defined which patient's profile can be benefited from IP. A study towards this direction would be really helpful. Finally, more survey on this topic would be absolutely beneficial, as in this way the deleterious CPB-related and cardioplegia-related complications can also be avoided.

Conflict of interest: none declared.

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