Ischaemic preconditioning during cardiac surgery: systematic review and meta-analysis of perioperative outcomes in randomised clinical trials

Stewart R. Walsha,*, Tjun Y. Tanga, Peter Kullara, David P. Jenkinsb, David P. Dutkac, Michael E. Gaunta

a Department of Vascular Surgery, Cambridge University Hospitals NHS Foundation Trust, UK
b Department of Cardiothoracic Surgery, Papworth Hospital NHS Trust, Cambridge, UK
c Department of Cardiology, Cambridge University Hospitals NHS Foundation Trust, UK

Received 18 March 2008; received in revised form 10 July 2008; accepted 11 July 2008; Available online 9 September 2008

Summary

Numerous small trials have been conducted to confirm the existence of the ischaemic preconditioning (IP) mechanism in the human heart and to clarify whether it can be induced in a clinical situation. The effect on clinical end-points remains unclear. Most of the available trials reported some clinical outcomes. We performed a systematic review and meta-analysis in order to determine whether IP produces any clinical benefit in cardiac surgery. The systematic review identified 22 eligible trials containing 933 patients. All patients undergoing on-pump surgery also received cardioplegia or intermittent cross-clamp fibrillation (ICCF) with or without adjunctive cooling. IP was mainly performed after initiation of cardiopulmonary bypass, before any additional myocardial protection was initiated. Overall, IP was associated with significant reductions in ventricular arrhythmias (pooled odds ratio 0.11; 95% CI 0.04—0.29; p = 0.001), inotrope requirements (pooled odds ratio 0.34; 95% CI 0.17—0.68; p = 0.002) and intensive care unit stay (weighted mean difference 3 h; 95% CI 4.6 to 1.5 h; p = 0.001). These effects persisted when the analyses were restricted to those patients receiving cardioplegia. The effect disappeared when the analyses were restricted to patients receiving ICCF. IP may provide additional myocardial protection over cardioplegia alone, but a large-scale clinical trial may be required to determine the role of IP with any certainty.

#2008 European Association for Cardio-Thoracic Surgery. Published by Elsevier B.V. All rights reserved.

Keywords: Ischaemia/reperfusion; Myocardial protection; Perioperative care; Preconditioning

1. Introduction

It is over 20 years since Murry first described the phenomenon of ischaemic preconditioning (IP) in a canine model [1]. Yellon et al. subsequently demonstrated that the mechanism was preserved in human myocardial tissue [2]. Numerous small trials have been conducted in order to determine whether IP may provide additional myocardial protection during cardiac surgery. Many of these trials were designed primarily to confirm that the IP mechanism was preserved in the human heart and to determine whether it could be induced in a clinically relevant scenario, namely cardiac surgery. Consequently, the trials have been powered to detect differences in biomarkers of myocardial injury but not clinical end-points such as death, myocardial infarction or ventricular arrhythmias. Thus, while IP appears to reduce the level of myocardial injury, its effect on clinical outcomes following cardiac surgery remains unknown. Nevertheless, many of these primary proof-of-concept trials did report some clinical outcomes. Pooling of these available clinical data could provide a useful insight into the potential of direct and remote preconditioning as a perioperative myocardial protective technique. Therefore, we undertook a systematic review and meta-analysis of the available small trials to determine whether IP has any effect on clinical outcome following cardiac surgery.

2. Methods

The systematic review and meta-analysis were conducted in accordance with the QUOROM guidelines [3]. The Medline and Embase databases were searched in October 2007 using the following search terms: ‘ischaemic preconditioning’, ‘ischemic preconditioning’, ‘ischaemic tolerance’, ‘ischemic tolerance’. A supplementary search in June 2008 included an additional search-term (cross-clamp fibrillation) but yielded no additional series. Abstract databases from major cardiovascular meetings (Society of Thoracic Surgeons, Society of
Cardiovascular Anesthesiologists, Society for Cardiothoracic Surgery in Great Britain and Ireland, European Association for Cardiothoracic Surgery, American Society of Anesthesiology) from 2000 to 2007 were manually searched to identify any further trials. Finally, we searched the American Heart Association’s (AHA) online abstract database (www.abstractsonline.com). This archive contains all abstracts presented at major AHA meetings (Scientific Sessions, International Stroke Conference, Arteriosclerosis Thrombosis and Vascular Biology Conference, Basic Cardiovascular Sciences Conference, Quality of Care and Outcomes Research).

The primary outcome for the meta-analysis was perioperative mortality. This was not defined by most of the eligible trials so any death reported was assumed to be perioperative. Secondary outcomes were: numbers of patients with postoperative ventricular arrhythmias requiring inotropic support, sustaining a myocardial infarction (MI), sustaining a cerebrovascular accident and duration of postoperative critical care unit admission. Postoperative MI was not defined by most of the trials so patients were categorised according to their original trial outcome. Studies were eligible for inclusion in the meta-analysis provided that they met the following criteria: randomised controlled trial, patients randomised to IP in addition to standard practice or standard practice alone, at least one clinical end-point reported by the trial authors and trial conducted in adults aged 18 years or older. Two reviewers (SRW and TYT) independently reviewed trial reports to determine eligibility. Trial quality was assessed using the Jadad score, which assigns points for randomisation, double-blinding and reporting of losses due to withdrawals and dropouts (minimum score 0, maximum score 5) [4].

Data from eligible trials were entered into an Excel spreadsheet for analysis. An initial overall pooled analysis

---

**Fig. 1.** Flow diagram of trial detection and inclusion.
Table 1
Characteristics of eligible trials

<table>
<thead>
<tr>
<th>Author, date and country</th>
<th>Patient group</th>
<th>Exclusions</th>
<th>IP stimulus</th>
<th>Timing of IP</th>
<th>Other myocardial protection</th>
<th>Outcomes reported</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ji B 2007 [25], China</td>
<td>40 patients with 3v CAD undergoing primary CABG without valve surgery</td>
<td>EF &lt; 30%; MI in last 2 months; renal, pulmonary or hepatic disease; additional cardiac disease; severe non-cardiac disease; calcified or aneurysmal ascending aorta</td>
<td>2 cycles of 2-min aortic clamping followed by 3 min reperfusion</td>
<td>After initiation of CPB under normothermia; Control group received 10 min normothermic CPB</td>
<td>Antegrade CBC</td>
<td>Deaths: 0</td>
<td>1</td>
</tr>
<tr>
<td>Codispoti HT 2006 [11], United Kingdom</td>
<td>52 patients undergoing primary CABG (92% 3v)</td>
<td>Previous CABG; additional cardiac procedure required; MI in last 7 days; elevated baseline troponin; age &gt; 70 years; patient on sulphonylureas</td>
<td>2 cycles of 3-min aortic clamping followed by 2 min reperfusion</td>
<td>After initiation of CPB; before ICCF; normothermia</td>
<td>ICCF</td>
<td>Deaths: 0</td>
<td>1</td>
</tr>
<tr>
<td>Codispoti HT 2006 [11], United Kingdom</td>
<td>52 patients undergoing primary CABG (92% 3v)</td>
<td>Previous CABG; additional cardiac procedure required; MI in last 7 days; elevated baseline troponin; age &gt; 70 years; patient on sulphonylureas</td>
<td>2 cycles of 3-min aortic clamping followed by 2 min reperfusion</td>
<td>After initiation of CPB; before ICCF; hypothermia (32 °C)</td>
<td>ICCF; systemic cooling (32 °C)</td>
<td>Deaths: 0</td>
<td>1</td>
</tr>
<tr>
<td>Buyukates 2005 [30], Turkey</td>
<td>20 patients undergoing CABG for 2v or 3v</td>
<td>EF &lt; 40%; additional cardiac disease; previous cardiac surgery; diabetes mellitus; peptic ulcer; chronic obstructive airways disease; cerebrovascular disease; steroid use</td>
<td>2 cycles of 3-min aortic clamping followed by 2 min reperfusion</td>
<td>After initiation of CPB; control group received 10 min CPB</td>
<td>Antegrade CBC</td>
<td>Deaths: 0</td>
<td>1</td>
</tr>
<tr>
<td>Laurikka 2002 [43], Finland</td>
<td>32 patients undergoing 1v or 2v off-pump CABG involving the LAD</td>
<td>Not specified</td>
<td>2 cycles of 3-min LAD occlusion followed by 2 min reperfusion</td>
<td>After thoracotomy or sternotomy</td>
<td>None</td>
<td>Deaths: 0</td>
<td>2</td>
</tr>
<tr>
<td>Ghosh ICCF 2003 [26], United Kingdom</td>
<td>40 patients undergoing CABG for stable angina due to 3v</td>
<td>EF &lt; 30%; unstable angina; MI in the previous month; additional cardiac disease; severe non-cardiac disease; diabetes; potassium channel activators</td>
<td>Clamping ascending aorta for 5 min</td>
<td>After initiation of CPB; before first period of ICCF; unclear if IP was at normothermia</td>
<td>ICCF; moderate hypothermia (32 °C)</td>
<td>Deaths: 0</td>
<td>2</td>
</tr>
<tr>
<td>Ghosh CBC 2003 [26], United Kingdom</td>
<td>40 patients undergoing CABG for stable angina due to 3v</td>
<td>EF &lt; 30%; unstable angina; MI in the previous month; additional cardiac disease; severe non-cardiac disease; diabetes; potassium channel activators</td>
<td>Clamping ascending aorta for 5 min</td>
<td>After initiation of CPB; before CBC; unclear if IP was at normothermia</td>
<td>Antegrade CBC; moderate hypothermia (32 °C)</td>
<td>Deaths: 0</td>
<td>2</td>
</tr>
<tr>
<td>Author, date and country</td>
<td>Patient group</td>
<td>Exclusions</td>
<td>IP stimulus</td>
<td>Timing of IP</td>
<td>Other myocardial protection</td>
<td>Outcomes reported</td>
<td>Jadad score</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------</td>
<td>------------</td>
<td>-------------</td>
<td>--------------</td>
<td>-----------------------------</td>
<td>------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Ghosh OPCAB 2003 [26], United Kingdom</td>
<td>40 patients undergoing off-pump CABG for 1v or 2v</td>
<td>EF &lt; 30%; unstable angina; MI in the previous month; additional cardiac disease; severe non-cardiac disease; diabetes; potassium channel activators</td>
<td>5 min occlusion of coronary artery to be grafted followed by 5 min reperfusion</td>
<td>Before first graft</td>
<td>None</td>
<td>Death: 0 MI: 0</td>
<td>2</td>
</tr>
<tr>
<td>Pentilla 2003 [45], Finland</td>
<td>22 patients undergoing off-pump CABG</td>
<td>Ongoing ischaemia; MI in previous month; poorly controlled diabetes; serum creatinine &gt; 150 μmol/l; chronic atrial fibrillation; mitral or aortic valve disease</td>
<td>5 min coronary artery occlusion followed by 5 min reperfusion</td>
<td>One cycle before first graft; further cycle before second graft; no IP before any remaining grafts</td>
<td>None</td>
<td>Death: 0 MI: 1/11 IP vs 0/11 controls Inotropes: 1/11 IP vs 0/11 controls CVA: 1/11 IP vs 0/11 controls</td>
<td>1</td>
</tr>
<tr>
<td>Teoh 2002, United Kingdom [27]</td>
<td>20 patients undergoing elective CABG for 3v with EF &gt; 35%</td>
<td>Age &gt; 80 years; unstable angina; significant left main stem disease; pulmonary, renal or hepatic disease; diabetes; potassium channel agonists within 36 h of surgery</td>
<td>2 cycles of 3-min aortic clamping with rapid epicardial pacing followed by 2 min reperfusion</td>
<td>After initiation of CPB, at normothermia; before first graft</td>
<td>ICCF; first graft at normothermia; remaining grafts at hypothermia (32 °C)</td>
<td>Death: 0 MI: 0 Inotropes: 2/10 IP vs 1/10 controls Arrhythmias: 0 CVA: 0</td>
<td>2</td>
</tr>
<tr>
<td>Wu 2002 [21], Finland</td>
<td>86 stable or unstable angina patients undergoing elective or urgent CABG</td>
<td>Severe calcification of the ascending aorta; MI in the previous 3 months; preoperative atrial fibrillation, additional cardiac disease; severe non-cardiac disease; previous cardiac surgery; emergency surgery; intra- or postoperative death</td>
<td>2 cycles of 2-min aortic clamping followed by 3 min reperfusion</td>
<td>After initiation of CPB, at normothermia Control group received 10 min normothermic CPB</td>
<td>Systemic hypothermia (32 °C); antegrade/retrograde CBC; terminal warm cardioplegia</td>
<td>Death: 0 MI: 0 CVA: 0 Inotropes: 26/43 IP vs 33/43 controls Arrhythmias: 24/43 IP vs 42/43 controls</td>
<td>2</td>
</tr>
<tr>
<td>Fernandes 2001 [12], Brazil</td>
<td>35 patients undergoing CABG for minimum 2v</td>
<td>EF &lt; 30%; unstable angina; acute MI; additional cardiac disease; predicted need for ventriculotomy</td>
<td>2 cycles of 3-min aortic clamping followed by 2 min reperfusion</td>
<td>After initiation of CPB; before first graft but not clear if normothermic or hypothermic</td>
<td>ICCF; systemic hypothermia (32 °C)</td>
<td>MI: 0</td>
<td>1</td>
</tr>
<tr>
<td>Li 2001 [39], China</td>
<td>40 patients with rheumatic heart disease undergoing valve replacement with a mechanical prosthesis</td>
<td>Smokers; previous cardiac surgery; coronary artery disease; major non-cardiac illness; primary pulmonary disease</td>
<td>2 cycles of 3-min aortic clamping followed by 2 min reperfusion</td>
<td>After initiation of CPB; before CBC Controls received 10 min of CPB</td>
<td>CBC</td>
<td>Death: 0</td>
<td>1</td>
</tr>
<tr>
<td>Wei 2001 [9], Finland</td>
<td>22 male patients undergoing primary elective CABG</td>
<td>EF &lt; 30%; unstable angina; valve disease; steroids; aortic cross-clamping time &gt; 2 h; patient requiring urgent re-expploration</td>
<td>2 cycles of 2-min aortic clamping followed by 3 min reperfusion</td>
<td>After initiation of CPB, at normothermia, before CBC Controls received 10 normothermic CPB</td>
<td>Antegrade/retrograde CBC terminal warm blood retrograde cardioplegia</td>
<td>Inotropes: 2/9 IP vs 1/10 controls</td>
<td>2</td>
</tr>
<tr>
<td>Study Year</td>
<td>Country</td>
<td>Study Design</td>
<td>Patient Characteristics</td>
<td>Surgical Procedure</td>
<td>Duration</td>
<td>Temperature</td>
<td>Sedation</td>
</tr>
<tr>
<td>------------</td>
<td>---------</td>
<td>--------------</td>
<td>--------------------------</td>
<td>--------------------</td>
<td>----------</td>
<td>-------------</td>
<td>----------</td>
</tr>
<tr>
<td>Luo 2001</td>
<td>China</td>
<td>90 patients with chronic valve disease undergoing elective prosthetic replacement</td>
<td>None specified</td>
<td>2 cycles of 2-min aortic clamping followed by 3 min reperfusion</td>
<td>After initiation of CPB, at normothermia Controls received 10 min normothermic CPB</td>
<td>Moderate hypothermia (26–28 °C; antegrade CBC; topical saline ice slush; 30 patients randomised to also receive terminal warm cardioplegia</td>
<td>Death: 0/30 IP vs 2/60 controls Inotropes: 12/30 IP vs 32/60 controls</td>
</tr>
<tr>
<td>Wu 2000</td>
<td>Finland</td>
<td>40 patients undergoing 3v CABG for stable angina</td>
<td>EF &lt; 40%; unstable angina; MI in last 3 months; additional cardiac disease; severe non-cardiac disease; calcified or dilated ascending aorta</td>
<td>2 cycles of 2-min aortic clamping followed by 3 min reperfusion</td>
<td>After initiation of CPB, at normothermia Controls received 10 min normothermic CPB</td>
<td>Mild hypothermia (32 °C); antegrade/retrograde CBC; terminal warm cardioplegia</td>
<td>Death: 0/20 IP vs 1/20 controls CVA: 0/20 IP vs 1/20 controls MI: 0 Inotropes: 13/20 IP vs 19/20 controls</td>
</tr>
<tr>
<td>Li 1999</td>
<td>China</td>
<td>40 patients undergoing double valve replacement with mechanical prostheses</td>
<td>None specified</td>
<td>2 cycles 3-min caval occlusion + aortic cross-clamping followed by 2 min reperfusion</td>
<td>After initiation of CPB Controls received 10 min CPB</td>
<td>Moderate hypothermia (actual target temperature not specified); CBC</td>
<td>Death: 0/20 IP vs 1/20 controls CVA: 0/20 IP vs 15/20 controls MI: 0 CVA: 0 Inotropes: 1/20 IP vs 10/20 controls</td>
</tr>
<tr>
<td>Illes 1998</td>
<td>United States</td>
<td>70 patients undergoing cardiac surgery</td>
<td>Previous cardiac surgery</td>
<td>1 min aortic cross-clamping and 5 min reperfusion at normothermia</td>
<td>After initiation of CPB Controls received 6 min normothermic CPB</td>
<td>Hypothermia (32 °C for CABG; 28 °C for valve procedures); antegrade CBC (CABG); antegrade/retrograde CBC (valves)</td>
<td>Death: 0/35 IP vs 1/35 controls CVA: 1/35 IP vs 0/35 controls MI: 0/35 IP vs 1/35 controls Inotropes: 0/35 IP vs 13/35 controls</td>
</tr>
<tr>
<td>Cremer 1997</td>
<td>Germany</td>
<td>14 patients undergoing elective 3v CABG</td>
<td>Significant left main stem stenosis; EF &lt; 50%; previous cardiac surgery; insulin use; sulphonylurea use; hepatic or renal dysfunction</td>
<td>2 cycles 5 min aortic cross-clamping and 10 min reperfusion at normothermia</td>
<td>After initiation of CPB; heart vented and beating empty</td>
<td>Moderate hypothermia (30 °C); antegrade CBC</td>
<td>Death: 0/17 IP vs 1/16 controls CVA: 0/17 MI: 0 Arrhythmia: 0</td>
</tr>
<tr>
<td>Jenkins 1997</td>
<td>United Kingdom</td>
<td>33 patients undergoing 3v primary CABG</td>
<td>Unstable angina; EF &lt; 30%; ventricular aneurysm; valve disease; sulphonylurea use</td>
<td>2 cycles of 3-min aortic clamping with rapid epicardial pacing followed by 2 min reperfusion at normothermia</td>
<td>After initiation of CPB Control patients received 10 min of normothermic CPB</td>
<td>ICCF; normothermia for first graft; moderate hypothermia (32 °C) thereafter</td>
<td>Death: 0/17 IP vs 1/16 controls CVA: 0/17 MI: 0 Inotropes: 0 Arrhythmia: 0</td>
</tr>
<tr>
<td>Kaukoranta 1997</td>
<td>Finland</td>
<td>30 patients undergoing elective CABG</td>
<td>EF &lt; 40%; significant left main stem stenosis; unstable angina</td>
<td>5 min aortic clamping followed by 5 min reperfusion at normothermia</td>
<td>After initiation of CPB</td>
<td>Antegrade/retrograde CBC</td>
<td>Death: 0/15 IP vs 3/15 controls MI: 0 CVA: 0/15 IP vs 0/15 controls</td>
</tr>
</tbody>
</table>
was conducted in order to assess the role of IP in general cardiac surgery. Separate analyses were then conducted for patients undergoing on-pump coronary artery bypass grafting (ONCABG), open valve replacement (OVR), and off-pump CABG (OFFCABG). Finally, analyses were performed restricted to trials using intermittent cross-clamp fibrillation (ICCF) and cardioplegia. Pooled odds ratios were calculated using the random effects model of Der Simonian and Laird, which is considered most appropriate due to the inherent heterogeneity of surgical populations [5]. Weighted mean differences were calculated for continuous variables. Heterogeneity was assessed using the Cochran’s Q-test, a negative hypothesis test in which a value less than 0.05 indicates statistically significant heterogeneity. Bias was assessed by visual inspection of funnel plots and by the Egger test. Significance in the Egger test was set at 10% [6]. For all other tests, the 5% level was considered significant. The statistical analyses were performed using Statsdirect 2.5.7 (Statsdirect Ltd., Altrincham, UK).

3. Results

The search results are presented in Fig. 1. Of 39 potentially relevant citations identified by the systematic review [2,7–46], 22 trials were ultimately eligible for inclusion in the meta-analysis [7,9,11,12,14,17,21,24–27,30,36,37,39,40,42,43,45]. The characteristics of these 22 eligible trials are summarised in Table 1.

Perioperative mortality was reported by 17 trials (374 IP, 402 controls) [7,11,14,17,21,24–27,30,36,37,39,40,42,43,45]. Overall, there were five deaths in the control group and none reported in the IP group (pooled odds ratio 0.33; 95% CI 0.07–1.64; \( p = 0.17 \)). There was no evidence of significant heterogeneity but the Egger test was positive, suggesting inherent bias (Table 2).

Inotrope use was significantly reduced in the overall cardiac surgery group, following valve surgery alone and when cold-blood cardioplegia was used as the primary mode of myocardial protection (Table 2). There was evidence of significant statistical heterogeneity between the trials. In addition, there was evidence of bias in the cardioplegia subgroup. Postoperative ventricular arrhythmias were significantly reduced in the overall pooled cohort, the on-pump CABG subgroup and the cold-blood cardioplegia subgroup. There was no statistical evidence of heterogeneity or bias in these analyses (Table 2). Sufficient data were available to analyse the effect of IP on intensive care unit stay in four groups: the overall pooled cohort, valve surgery, on-pump CABG and those receiving CBC as myocardial protection (Table 3). The duration of ITU stay was consistently reduced in all four groups analysed. There was evidence of heterogeneity in the overall pooled analysis but not in the subgroup analyses.

4. Discussion

Murry’s description of ischaemic preconditioning [1] stimulated considerable interest. However, IP has been slow to translate from an interesting bench observation to a
Cardiac surgery

Death [7, 11, 14, 17, 21, 24–27, 36, 37, 39, 40, 42, 45] 0/174 5/402 0.33 0.07–1.64 0.17 p = 0.18 p = 0.02

MI [7, 12, 14, 17, 21, 24, 25, 26, 27, 36, 42, 43, 45] 5/301 4/301 1.10 0.27–4.54 0.89 p = 0.39 p = 0.85

CVA [7, 14, 17, 21, 24, 27, 36, 42, 43, 45] 2/194 4/193 0.69 0.16–2.93 0.62 p = 0.59 p = 0.34

Ventricular arrhythmias [7, 14, 21, 27, 30, 36, 40, 43] 28/153 65/182 0.11 0.04–0.29 0.001 p = 0.43 p = 0.95

Inotrope use [9, 11, 14, 17, 21, 25, 27, 30, 36, 39, 40, 42, 45] 84/289 157/318 0.34 0.17–0.68 0.002 p = 0.01 p = 0.18

On-pump CABG

Death [7, 11, 14, 17, 21, 24–27] 0/198 2/197 0.83 0.24–2.81 0.76 p = 0.99 p < 0.001

MI [7, 12, 14, 17, 21, 24–26, 30] 4/199 3/199 1.07 0.36–3.22 0.90 p = 0.99 p = 0.32

CVA [7, 14, 17, 21, 24, 27] 0/112 4/111 0.55 0.13–2.42 0.42 p = 0.99 p = 0.002

Ventricular arrhythmias [7, 14, 21, 27, 30] 24/87 47/86 0.15 0.03–0.78 0.03 p = 0.26 p = 0.01

Inotrope use [7, 9, 11, 17, 21, 25, 27, 30] 59/157 75/156 0.56 0.25–1.27 0.16 p = 0.17 p = 0.49

Off-pump CABG

Death [26, 45] 0/31 0/31 1.00 0.06–16.81 0.99 p = 0.99 —

MI [26, 43, 45] 1/47 0/47 1.65 0.19–14.03 0.65 p = 0.87 p = 0.65

CVA [43, 45] 1/27 0/27 2.02 0.16–25.76 0.59 p = 0.65 —

Inotrope use [43, 45] 5/27 7/27 0.64 0.17–2.42 0.52 p = 0.75 —

Valve surgery

Death [36, 37, 39, 40] 0/84 2/113 0.70 0.11–4.38 0.70 p = 0.97 p = 0.004

Inotrope use [36, 39, 40] 20/70 62/100 0.18 0.04–0.77 0.02 p = 0.02 p = 0.11

Trials using CBC

Death [7, 17, 21, 24–26, 36, 37, 39, 40, 42] 0/244 4/273 0.67 0.22–2.04 0.48 p = 0.99 p < 0.001

MI [7, 17, 21, 24–26, 30, 36, 42] 4/190 4/190 0.93 0.29–2.96 0.90 p = 0.87 p = 0.91

CVA [7, 17, 21, 24, 36, 42] 1/140 4/140 0.57 0.14–2.32 0.44 p = 0.86 p = 0.45

Ventricular arrhythmias [7, 21, 30, 36] 26/80 57/80 0.06 0.02–0.21 0.001 p = 0.61 p = 0.85

Inotrope use [9, 17, 25, 21, 30, 36, 40, 42] 62/207 137/238 0.21 0.10–0.46 0.001 p = 0.04 p = 0.08

Trials using ICCF

Death [11, 14, 26, 27] 0/99 1/98 0.72 0.13–3.94 0.70 p = 0.98 p = 0.002

MI [12, 14, 26, 27] 0/64 0/64 1.00 0.14–7.34 0.99 p = 0.99 p = 0.95

CVA [14, 27] 0/27 0/26 0.97 0.06–16.41 0.98 p = 0.98 —

Ventricular arrhythmias [14, 27] 0/27 0/26 0.97 0.06–16.41 0.98 p = 0.98 —

Inotrope use [11, 14, 27] 28/62 23/62 1.43 0.68–3.01 0.35 p = 0.87 —

MI: myocardial infarction; CVA: cerebrovascular accident; POR: pooled odds ratio.

Table 3

Effect of IP on intensive care unit stay

<table>
<thead>
<tr>
<th>Group (trials included)</th>
<th>WMD</th>
<th>95% CI</th>
<th>p</th>
<th>Cochran’s Q</th>
<th>Egger</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac surgery [11, 17, 21, 25, 36, 37, 39, 40, 43]</td>
<td>−3.0 h</td>
<td>−4.6 to −1.5 h</td>
<td>0.0001</td>
<td>p = 0.0001</td>
<td>p = 0.77</td>
</tr>
<tr>
<td>On-pump CABG [11, 17, 21, 25]</td>
<td>−5.0 h</td>
<td>−7.0 to −3.8 h</td>
<td>&lt;0.0001</td>
<td>p = 0.53</td>
<td>p = 0.53</td>
</tr>
<tr>
<td>Valve surgery [36, 39]</td>
<td>−2.6 h</td>
<td>−5.1 to −0.5 h</td>
<td>0.05</td>
<td>p = 0.80</td>
<td>—</td>
</tr>
<tr>
<td>CBC [17, 21, 25, 36, 39, 42]</td>
<td>−3.7 h</td>
<td>−5.2 to −2.2 h</td>
<td>&lt;0.0001</td>
<td>p = 0.10</td>
<td>p = 0.73</td>
</tr>
<tr>
<td>ICCF (Codispoti HT and Codispoti HT pooled)</td>
<td>−0.7 h</td>
<td>−6.6 to 5.1 h</td>
<td>0.81</td>
<td>0.39</td>
<td>—</td>
</tr>
</tbody>
</table>

WMD: weighted mean difference; HT: hypothermia; NT: normothermia.

useful bedside intervention. To date, only a single small trial of remote IP in 82 open abdominal aortic aneurysm patients has demonstrated a significant reduction in clinical end-points, namely postoperative myocardial infarction [47]. Numerous trials of IP have been conducted in cardiac surgery, but it is not widely applied in the clinical setting. Perrault and Menasche commented that there is a fundamental difference between animal models of myocardial ischaemia and cardiac surgery in humans. The animal models generally do not use any additional form of myocardial protection. In open-heart surgery, additional forms of myocardial protection (cardioplegia, systemic and topical cooling) are used routinely. Thus, while IP may show impressive results in otherwise unprotected animals, its role in optimally protected human hearts may be more limited [48].

The magnitude of the preconditioning stimulus has an important bearing on the degree of protection provided. Animal models demonstrate that ischaemic stimuli ranging from 1.25 min to 5 min interspersed with minimum reperfusion periods of 30 s to 1 min provide protection [49]. Furthermore, excessive stimuli may result in loss of protection [50]. The majority of the trials included in the meta-analysis induced IP by cross-clamping the ascending aorta for a two sequential periods of 2–3 min followed by a similar period of reperfusion [9, 11, 12, 14, 17, 25, 30, 36, 37, 39, 40, 43]. This is similar to the protocol used by Yellon et al. when they described a preconditioning effect in the human myocardium [2]. Some of the trials in the meta-analysis used different stimuli, such as a single cross-clamp application of 5 min duration [7, 24, 26], or simultaneous aortic and caval clamping [36, 37]. Illes et al. used a single 1 min period of aortic cross-clamping followed by
5 min of reperfusion [42]. This may not have provided an adequate stimulus. In view of this, we performed a sensitivity analysis on our results, excluding Illes series. There was no change in the outcome of any of the analyses (data not shown).

With the exception of those undergoing off-pump surgery, all patients received additional myocardial protection, with either ICCF or cardioplegia, with or without hypothermia. It has been suggested that IP has little to add to the protection already provided by cardioplegia [48] as the initial ischaemic insult may actually cause more myocardial damage than cardioplegia alone [51]. Moreover, preconditioning reduces infarct size, while the issue in heart surgery is often post-surgery pump dysfunction due to stunning, which preconditioning may not affect [48]. In view of these issues, we undertook subgroup analyses on trials that used cardioplegia as additional myocardial protection (Table 2). In these trials, all patients received some combination of antegrade/retrograde, warm/cold cardioplegia. The IP arm were preconditioned after initiation of bypass, before any cardioplegia. Arrhythmias and inotrope requirements were both significantly reduced, albeit with evidence of heterogeneity and bias. Nevertheless, IP appeared to confer added benefit, over and above cardioplegia alone, with respect to arrhythmias and pump dysfunction requiring inotropic support. Certainly, there was no evidence of harm.

Intermittent cross-clamp fibrillation may itself activate the preconditioning pathway. ICCF is associated with a significant decrease in intra-cellular adenosine triphosphate levels after the first ischaemic stimulus, but ATP is preserved thereafter, fibrillation is reduced and myocardial stunning prevented [52]. This is the same response observed in experiments using preconditioning. Moreover, the protective effect of ICCF in animal models is attenuated by the administration of protein kinase C inhibitors and K-ATP channel antagonists, both of which block key steps in the classical preconditioning pathway [53]. Thus, ICCF acts, in part, through preconditioning. In humans undergoing CABG with ICCF, some patients display a marked reduction in the rate of decrease of myocardial intra-cellular pH over several periods of ischaemia and reperfusion, which may represent the effect of preconditioning during ICCF [54]. However, Dunning’s pH monitoring also revealed that 50% of patients undergoing ICCF displayed poor recovery of pH during periods of reperfusion. This implies that reperfusion may be unpredictable during ICCF. Theoretically, then, formal IP could be of value, even in ICCF. When we restricted our meta-analyses to those series using only ICCF as myocardial protection, we were unable to demonstrate any additional benefit for IP (Table 2). Only five trials used ICCF [11,12,14,26,27], and there were only sufficient data to meta-analyse death and inotrope use, with a maximum of 99 patients in any arm. There is no large benefit to IP as an adjunct to ICCF, but a small additional benefit cannot be excluded.

There was evidence of heterogeneity and bias with respect to a number of outcomes. This is unsurprising, when one considers that the primary trials were generally designed with the intention of confirming the existence of IP in the setting of cardiac surgery. None of them were primarily designed to assess the effect of IP on clinical end-points. While some clinical outcomes were reported, this was done on an ad-hoc basis. The primary trial outcomes were usually serum biomarkers of myocardial injury. It could be argued that it is inappropriate to pool the clinical outcomes reported by these proof-of-concept studies. That said, these trials comprise the only available source of clinical outcome data from cohorts randomised to IP or standard practice. IP and remote IP constitute an attractive means of ameliorating the adverse consequences of perioperative ischaemia-reperfusion injury in a range of clinical settings. It is easily performed, requires little additional equipment and is likely to be highly cost-effective. A large-scale trial would be required to assess the effect of IP or remote IP on clinical outcomes in cardiac or other major surgery. However, a meta-analysis of available data should be undertaken to determine if sufficient equipoise still exists. Our meta-analysis has demonstrated that IP reduces arrhythmias, inotrope requirements and critical care stay following cardiac surgery. However, in view of the caveats regarding study design, bias and heterogeneity, we would contend that clinical equipoise regarding IP in cardiac surgery exists. The mortality rate in the control arm of our meta-analysis was 1.2% (5 deaths from 402 patients). A trial with 80% power to detect a reduction in perioperative mortality following open-heart surgery from 1.2% to 0.6% would require 3800 patients in each arm. The GALA trial in carotid endarterectomy has recruited over 5000 patients, demonstrating that such large-scale surgical trials are feasible [55]. It may require just such an endeavour to determine the role of IP in cardiac surgery.

References


