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Review

'Conditioning' the heart during surgery☆,☆☆

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Summary

Coronary heart disease (CHD) is the leading cause of death worldwide. Coronary artery bypass graft (CABG) surgery remains the procedure of choice for coronary artery revascularisation in a large number of patients with severe CHD. However, the profile of patients undergoing CABG surgery is changing with increasingly higher-risk patients being operated upon, resulting in significant morbidity and mortality in this patient group. Myocardial injury sustained during cardiac surgery, most of which can be attributed to acute myocardial ischaemia—reperfusion injury, is associated with worse short-term and long-term clinical outcomes. Clearly, new treatment strategies are required to protect the heart during cardiac surgery in terms of reducing myocardial injury and preserving left ventricular systolic function, such that clinical outcomes can be improved. 'Conditioning' the heart to harness its endogenous cardioprotective capabilities using either brief ischaemia or pharmacological agents, provides a potentially novel approach to myocardial protection during cardiac surgery, and is the subject of this review article.

Keywords: Cardioprotection; Cardioplegia; Intermittent cross-clamp fibrillation; Ischaemic preconditioning; Pharmacological preconditioning; Remote ischaemic preconditioning; Ischaemic postconditioning

1. Introduction

Coronary heart disease (CHD) is the leading cause of death and morbidity worldwide. Coronary artery bypass graft (CABG) surgery is one of the most established procedures for the treatment of patients with severe CHD. About 20,000 first time CABG operations are performed in the United Kingdom each year with an average mortality of 1.6% according to the latest healthcare commission report in the United Kingdom. However, the risk profile of patients being referred for cardiac surgery continues to change with factors such as the aging population, the increasing incidence of diabetes and more complex percutaneous coronary interventions, resulting in higher-risk patients being operated upon [1]. These patients are at a greater risk of sustaining peri-procedural myocardial injury, experiencing a perioperative myocardial infarction, and requiring inotropic support post-surgery [2]. It has been estimated that the predicted operative risk has increased by 30% over the past decade [3]. One of the important causes of myocardial injury during cardiac surgery is acute ischaemia—reperfusion injury resulting from cross-clamping of the aorta. Despite modern techniques of myocardial protection there remains a clinical need to further reduce myocardial injury during CABG surgery.

'Conditioning' the heart to render it more resistant to an episode of acute myocardial ischaemia—reperfusion injury is an endogenous cardioprotective strategy which can be readily applied to the clinical setting of CABG surgery, to reduce myocardial injury and preserve LV systolic function [4]. This article will provide an overview of 'conditioning' as a strategy for cardioprotection and its emergence as a potential clinical therapy for patients undergoing cardiac surgery.

2. An historical perspective of myocardial preservation during cardiac surgery

Cardiac surgery has come a long way since the inception of open heart surgery by Gibbon in 1953 [5], a surgical procedure which was associated with a significant risk of air embolism and was hampered by a blood-filled operative field. In order to circumvent these issues, cardiac standstill, achieved by cross-clamping the aorta, was introduced, but this procedure rendered the heart globally ischaemic, resulting in worse patient outcomes. Because of this, the concept of myocardial protection or preservation during cardiac surgery with the development of treatment strate-

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gies such as hypothermia with or without circulatory arrest, as a means of reducing the impact of global myocardial ischaemic injury was introduced (reviewed by Cordell [6]). Subsequently, potassium citrate was used to induce elective cardiac arrest for the first time by Melrose and colleagues [7]. The term 'cardioplegia' was first introduced by Sealy's group [8], to refer to the use of a variety of substances for inducing cardiac standstill. However, the high concentrations of potassium in these solutions led to focal myocardial necrosis, resulting in cardioplegia falling out of favour in the 1960s [6].

2.1. Intermittent cross-clamp fibrillation

Meanwhile, the use of hypothermia with continuous myocardial perfusion was enjoying great success [8], and hypothermic ventricular fibrillation was being commonly used during cardiac surgery. The use of ventricular fibrillation with continuous perfusion resulted in reduced subendocardial blood flow and myocardial ischaemic injury, an effect which could be offset by the cross-clamping of the aorta to induce global ischaemia [9]. Conversely the use of aortic cross-clamping alone in normothermic hearts resulted in ischaemic contractures and the so-called 'stone-heart' [10]. Thus the method of intermittent cross-clamp fibrillation with moderate topical hypothermia became a popular method of myocardial preservation during cardiac surgery.

2.2. Cardioplegia

The concept of using a cardioplegic solution to induce cardiac standstill was later revived in the 1970s and 1980s with the development of a variety of cardioplegic solutions [11—14]. The seminal work of Hearse and colleagues [14] resulted in the development of the St. Thomas Cardioplegia solution 1 which heralded the era of crystalloid cardioplegia. Further refinement of the crystalloid cardioplegia solutions was undertaken to achieve maximum myocardial protection with the use of amino acids, adenine nucleotides, oxygen radical scavengers and nitric oxide donors (reviewed in [15]). However, David Hearse's elegant summary of the three general principles of cardioplegia remain true even today: (1) energy conservation through the rapid induction of diastolic arrest, (2) slowing metabolic and degenerative processes through the induction of hypothermia and (3) selective prevention or reversal of unfavourable ischaemic changes by using substrate enhancement [16].

A study by Follette and colleagues [17] brought into vogue the use of blood as a cardioplegic medium with alterations in calcium, potassium, pH and osmolality, as well as substrate enhancement using glutamate and aspartate amongst other additives, for the enrichment of the energy-depleted myocardium. Blood is considered a better medium for cardioplegia because of its greater oxygen carrying capacity, superior buffering capacity, antioxidant and oncotic properties [17,18]. Cold blood is now the standard cardioplegic vehicle world-wide, although there have been some advocates for the beneficial effects of total warm blood cardioplegia [19]. The latter strategy has been reported to better preserve cellular enzymes and a 'terminal hot-shot' of potassium-enriched warm normothermic blood has been demonstrated to improve the functional recovery of stunned myocardium at the end of cardiopulmonary bypass [20]. The cardioplegic solution can be administered either antegradely through the aortic route and/or retrogradely through the coronary sinus. Compared to the antegrade route which may not allow perfusion of myocardium distal to complete coronary occlusions especially if coronary collateralisation is poor, the retrograde route may provide more homogenous myocardial preservation [21].

2.3. Intermittent cross-clamp fibrillation versus cardioplegia

Today there are two major methods of myocardial preservation in use for on-pump CABG surgery: cold blood (or less commonly, crystalloid) cardioplegia and intermittent cross-clamp fibrillation both of which are performed under moderate hypothermia (28—32 °C). Among cardiac surgeons who use cardioplegia, the preferred route of administration is the antegrade one, with a small proportion of surgeons using the retrograde route. An even smaller proportion use warm cardioplegia or the so called 'terminal hot-shot' [22].

Advocates of the cardioplegic method focus on its cellular protective benefits and the consequent additional comfort it provides the surgeon. Meanwhile there are some clear benefits of cross-clamp fibrillation, the most important of which being its simplicity and that the ischaemic times are reportedly significantly shorter than with cardioplegia [23—25]. Moreover there are three specific situations in which cross-clamp fibrillation may be useful [26]. Firstly, there is a lower incidence of postoperative conduction defects with this technique and is therefore more suitable for patients with preoperative conduction abnormalities. Secondly, in patients with a cardiac pacemaker, electromechanical activity is automatically terminated by the fibrillatory stimulus whereas the pacemaker has to be disconnected in the setting of cardioplegia. Thirdly, in the presence of cold agglutinins, which are a significant problem in the developing world, cardiac surgery has to be performed in the normothermic setting and the shorter ischaemic times of cross-clamp fibrillation are especially useful.

2.4. Off-pump CABG surgery

More recently, attention has been focused on minimally invasive CABG surgery and 'beating heart' or off-pump coronary artery bypass (OPCAB) surgery. Since OPCAB does not require the use of an extracorporeal circuit it avoids the potential detrimental effects of cardiopulmonary bypass such as the systemic inflammatory response. Importantly, since the aorta is not cross-clamped to cause cardiac standstill and only individual coronary arteries are clamped or partially occluded during the insertion of the grafts the ischaemic insult to the myocardium is only regional and not global as in conventional on-pump CABG surgery. OPCAB has thus been found to be associated with reduced hospital stay, a lower incidence of renal failure, less blood loss and reduced requirement for blood transfusion and myocardial injury as compared to conventional CABG surgery [27].

Two surveys of current practice in the United Kingdom have provided valuable insights into the changing practice in myocardial protection strategies in cardiac surgery. Izzat and

colleagues in 1994 [28] reported from a questionnaire-based survey that 72% of surgeons preferred cardioplegia while 28% preferred cross-clamp fibrillation. OPCAB was not established in clinical practice at that time. Whilst a survey in 2004 [22] indicates that about 50% of surgeons perform on-pump CABG, 10% perform OPCAB whereas the remaining 40% could perform either. Among those surgeons performing on-pump CABG surgery, 85% use cardioplegia, with most surgeons preferring antegrade cold blood cardioplegia; and 15% use cross-clamp fibrillation. A similar pattern emerges in the United States with 25% of surgeons performing only OPCAB [27], while a report from Japan claims that 60% of coronary artery grafting is performed using the OPCAB technique [29].

3. Perioperative myocardial injury sustained during cardiac surgery

3.1. Mechanisms of myocardial injury

Myocardial injury sustained during cardiac surgery can be attributed to several different mechanisms, with acute myocardial ischaemia–reperfusion injury being the most important. Other causes include the inflammatory response to the extraneous substances in the cardiopulmonary bypass circuit, left ventricular over-distension, coronary atheroembolism, increased cardiac workload during the intra-operative period and direct myocardial injury due to retraction and handling of the heart [30]. Myocardial injury can be minimised by cardiac decompression, careful management of blood pressure, heart rate and systemic vascular resistance intra-operatively and by exercising caution during manipulation of the heart and aorta.

Acute myocardial ischaemia–reperfusion injury during conventional on-pump CABG surgery results from the intermittent aortic cross-clamping required to undertake the attachment of each distal coronary anastomosis, resulting in cumulative episodes of global myocardial ischaemia. In patients undergoing a cardioplegic strategy, the cardioplegic solution is administered initially and repeated during each episode of aortic cross-clamping; or a continuous cardioplegia strategy may be used. In the technique of cross-clamp fibrillation an alternating current is applied to the myocardium to induce ventricular fibrillation. Ventricular fibrillation during perfusion results in an increase in the left ventricular end-diastolic pressure (LVEDP) causing subendocardial hypoperfusion [31], however this rise in LVEDP does not occur during ischaemia [9]. Therefore aortic cross-clamping and ventricular fibrillation appear to obviate the detrimental effects of each other. Overall however, the total time of aortic cross-clamping and fibrillation (approximately 30 min) equates to a significant myocardial ischaemic insult [25]. Several studies have compared clinical outcomes and the extent of myocardial injury in cross-clamp fibrillation and cardioplegia [23,24,32–34] and have found the two techniques to be comparable.

In contrast to on-pump CABG surgery, the acute myocardial ischaemia–reperfusion injury encountered during OPCAB surgery is regional rather than global as discussed above. The coronary artery is partially occluded or coronary blood flow is shunted away from the artery of interest in order to perform the distal bypass graft anastomosis. Therefore the propensity for myocardial injury is much less than with conventional CABG surgery. Indeed a prospective randomised study by Alwan and colleagues [35] has demonstrated less myocardial injury following OPCAB surgery, when compared to conventional on-pump CABG surgery. Several short-term clinical outcomes have been shown to be improved with OPCAB surgery, including blood-loss and transfusion requirement, neurocognitive outcomes, post-operative arrhythmias and the duration of hospital stay [27,36]. However prospective randomised controlled studies have reported no reduction in major adverse cardiac events with OPCAB when compared to standard CABG surgery [37–39].

The profile of patients undergoing CABG surgery is changing over the years with increasingly higher-risk patients being operated upon [1]. The favourable metabolic effects of cardioplegia have encouraged more surgeons to adopt this technique in their practice although comparable clinical outcomes have been achieved with cross-clamp fibrillation [40]. Recent studies have shown that OPCAB surgery can also be successfully used in high-risk patients [41,42].

3.2. Significance of perioperative cardiac enzyme release

Cardiac-specific markers such as troponin-T, troponin-I and CK-MB have been used to quantify the myocardial injury sustained during cardiac surgery. Lehrke and colleagues [43] reported in a case series of 204 patients undergoing elective CABG surgery that perioperative troponin-T release was associated with worse clinical outcomes, such that a 48 h post-surgery serum troponin-T level of $\geq$0.46 μg/l was associated with the greatest risk as evidenced by a 4.9-fold increase in long-term risk for subsequent cardiac death. Other clinical studies have correlated troponin-T [2], troponin-I [44], and CK-MB [45] with worse short- and long-term outcomes post-cardiac surgery. Indeed the recent new universal definition of myocardial infarction has recognised the importance of postoperative cardiac enzyme release with associated ECG changes and has defined this as Type 5 myocardial infarction, the presence of which is associated with poorer clinical outcomes. [46]

4. 'Conditioning' during cardiac surgery

4.1. Ischaemic preconditioning in cardiac surgery

Ischaemic preconditioning (IPC) refers to the resistance to acute myocardial ischaemia–reperfusion injury induced by prior application of one or brief episodes of non-lethal myocardial ischaemia and reperfusion [47]. Planned cardiac surgery as a clinical setting is readily amenable to the clinical application of an IPC protocol, which by definition demands a cardioprotective strategy being instituted prior to the myocardial ischaemic insult (see Table 1).

In 1993, our research group was the first to demonstrate cardioprotection using IPC in patients undergoing CABG surgery. In patients undergoing CABG using intermittent cross-clamp fibrillation, we found that two $\times$ 3 min cycles of aortic cross-clamping separated by 2 min of reperfusion

Table 1
Clinical studies of ischaemic preconditioning in cardiac surgery.

Study	No.	Intervention	Myocardial preservation	Outcomes
Yellon et al. (1993) [48]	14	Two cycles of 3 min/2 min I/R	Cross-clamp fibrillation	Increased ATP levels in ventricular myocardium
Perrault et al. (1996) [50]	20	One cycle of 3 min/2 min I/R	Warm cardioplegia	Increased CK-MB/lactate release
Jenkins et al. (1997) [49]	33	Two cycles of 3 min/2 min I/R	Cross-clamp fibrillation	Less troponin-T release
Lu et al. (1997) [55]	30	Two cycles of 2 min/3 min I/R	Cold crystalloid cardioplegia	Improved myocardial ATP levels. Less CK-MB released. Improve myocardial contractility.
Kaukoranta et al. (1997) [52]	41	One cycle of 5 min/5 min I/R	Normothermic retrograde cardioplegia	No difference in CKMB or troponin-T release
Cremer et al. (1997) [51]	14	Two cycles of 5 min/10 min I/R	Cold blood cardioplegia	No difference in CK-MB, troponin-T release or inotrope use
Illes et al. (1998) [53]	70	One cycle of 1 min/5 min I/R	Cold blood cardioplegia	Improved postoperative cardiac index and less inotrope use
Li et al. (1998) [54]	40	Two cycles of 3 min/2 min I/R	Cold blood cardioplegia	Reduced CKMB release, and improved postoperative cardiac function
Szmagala et al. (1998) [117]	56	One cycle of 4 min/6 min I/R	Cold blood cardioplegia	Less troponin-T at 1 h
Wu et al. (2000) [56]	40	Two cycles of 2 min/3 min I/R	Cold blood cardioplegia	Improved LV function but no difference in troponin-I or CK-MB
Wu et al. (2001) [118]	40	Two cycles of 2 min/3 min I/R	Cold blood cardioplegia	Improved LV function
Laurikka et al. (2002) [119]	32	Two cycles of 2 min/3 min I/R applied to LAD	Off-pump	Improved LV function Less troponin-I but no difference in CK-MB
Teoh et al. (2002) [25]	30	Two cycles of 3 min/2 min I/R	Cross-clamp fibrillation and cardioplegia	Less troponin-T at 72 h
Wu et al. (2002) [59]	86	Two cycles of 2 min/3 min I/R	Cold blood cardioplegia	Less VF/VT and lower inotrope score
Wu et al. (2003) [120]	21	Two cycles of 2 min/3 min I/R	Cold blood cardioplegia	Improved LV/RV function but no difference in myocardial apoptosis.
Ghosh et al. (2003) [61]	120	One cycle of 5 min/5 min I/R	Cross-clamp fibrillation versus cold blood cardioplegia versus off-pump	Less troponin-T only in patients undergoing off-pump surgery.
Wu et al. (2005) [121]	86	Two cycles of 2 min/3 min I/R	Cold blood cardioplegia	Less heart rate variability
Codispoti et al. (2006) [122]	104	Two cycles of 3 min/2 min I/R	Cross-clamp fibrillation ± hypothermia	Reduced troponin-I irrespective of temperature
Ji et al. (2007) [123]	40	Two cycles of 2 min/3 min I/R	Cold blood cardioplegia	Less troponin-I at 6 and 12 h post-surgery

CK: creatine kinase; CK-MB: creatine kinase-MB fraction; ATP: adenosine tri-phosphate; I/R: ischaemia/reperfusion times referring to the preconditioning protocols; VF: ventricular fibrillation; VT: ventricular tachycardia.

resulted in higher ATP levels in ventricular biopsy specimens taken at the end of the first 10-min episode of cross-clamp fibrillation [48]. The results suggested for the first time that the human myocardium could be preconditioned in the setting of CABG surgery. Following this, we demonstrated a reduction in myocardial injury as indicated by a significant reduction in troponin-T release [49].

The results of IPC in the setting of cardioplegia are more controversial. An early study by Perrault and colleagues [50] reported an increase in creatine kinase release and lactate production in patients who underwent a single short (3 min ischaemia/2 min reperfusion) preconditioning protocol before the institution of cardiopulmonary bypass and cardioplegic arrest. Longer preconditioning protocols used by Cremer et al. [51] (5 min ischaemia/10 min reperfusion) and Kaukoranta et al. [52] (5 min ischaemia/5 min reperfusion) either showed increased myocardial injury or no difference between groups. However several other studies have also shown positive results with cardioprotection in the setting of both crystalloid and cold-blood cardioplegia during CABG as well as valve surgery using myocardial injury, inotrope use and postoperative cardiac function as outcome measures [53–55]. A study from our group has also compared the cardioprotective effects of IPC, cardioplegia and cross-clamp fibrillation and found that IPC exerts similar effects in the presence of either cardioplegia or cross-clamp fibrillation [25]. In a series of important studies, Wu and colleagues have established the utility of IPC in the setting of cardioplegia. Two short cycles (2 min ischaemia/3 min reperfusion) of aortic cross-clamping improved early postoperative left [56] and right ventricular function [57], reduced the incidence of postoperative atrial fibrillation [58] and ventricular tachycardia and fibrillation [59] in the early reperfusion period and also 24 h after surgery. The latter results suggest that both classic and delayed IPC can be induced in the setting of CABG surgery.

The discrepancy in the results in the setting of cardioplegia can be attributed to two reasons. Firstly, there are several differences in the practice of cardioplegia: antegrade versus retrograde or both, blood versus crystalloid, warm versus cold versus a terminal hot-shot and the variable use of substrate enhancement. It is possible that the different methods of administering cardioplegia interact differently with IPC. Secondly, the preconditioning protocols used are not consistent and the discrepant results of these studies may reflect these differences.

One potential explanation cited for the lack of benefit with IPC is that cardiopulmonary bypass may itself have a preconditioning effect. Burns et al. showed in sheep, that cardiopulmonary bypass (CPB) alone elicited a similar protective effect as non-CPB IPC and that this effect was abolished by $\alpha 1$ adrenoceptor and adenosine receptor blockade [60]. In a recent study, Ghosh and Galinanes [61] compared the effects of IPC on patients undergoing cross-clamp fibrillation, cardioplegia and OPCAB and reported that only OPCAB patients undergoing surgery without CPB could be protected. They also harvested right atrial tissue samples

in the on-pump surgery group before and after the institution of CPB and showed that the samples obtained before CPB could be preconditioned by an in-vitro hypoxia-reoxygenation protocol while those obtained after CPB already had improved cell viability indices such that the preconditioning protocol could not elicit any further protection. The authors have indirectly derived that CPB itself may have a preconditioning effect. However as discussed earlier, cardiopulmonary bypass has been associated with detrimental pro-inflammatory effects as evidenced by increased cytokine production from the heart [62] and therefore further clarification is required of this so-called preconditioning effect. The multitude of studies showing the cardioprotective effects of IPC in conventional CABG surgery imply that CPB definitely does not preclude the preconditioning potential and that the myocardium can be further protected.

A recent meta-analysis of 933 patients from 22 clinical trials examining the clinical efficacy of ischaemic preconditioning reported that IPC was associated with significant reductions in ventricular arrhythmias, inotrope requirements and intensive care unit stay [63]. However, it was interesting that the beneficial effects of IPC were maintained in patients receiving cardioplegia alone but not in those receiving cross-clamp fibrillation. Clearly, large multicentred clinical trials will be required to determine the actual effect of IPC on clinical outcomes in patients undergoing cardiac surgery.

Despite these clinical studies reporting beneficial effects with IPC in cardiac surgery, the routine application of IPC in cardiac surgery has not materialised [22]. The reasons for this have been summarised in a review by Vaage and Valen [64]. Firstly surgeons have been reluctant to apply an invasive preconditioning protocol that may prolong the duration of surgery; secondly the preconditioning effects of volatile anaesthetics (see below) and CPB and the resistance of an increasingly elderly population to IPC, suggest that IPC may provide 'no further gain'; thirdly, there is a lack of clarity on the frequency and number of preconditioning cycles required to elicit cardioprotection in humans and myocardial enzymes are inadequate as predictors of outcome, the measurement of which requires large sample sizes and multicentre trials. In addition, the application of an invasive preconditioning protocol by aortic clamping and de-clamping has inherent atherothrombotic risks.

These issues could be circumvented in part by pharmacological agents that are capable of recapitulating the cardioprotection elicited by IPC, thereby obviating the need

Table 2
Clinical studies of pharmacological preconditioning in cardiac surgery.

Study	No.	Intervention	Myocardial preservation	Outcomes
Lee et al. (1995) [68]	14	Adenosine infusion	Cold blood cardioplegia	Improved postoperative cardiac function
Mentzer et al. (1997) [70]	61	Adenosine added to the cardioplegia solution	Cold blood cardioplegia	Improved postoperative cardiac function
Mentzer et al. (1999) [124]	253	Adenosine added to the cardioplegia solution	Cold blood cardioplegia	Less MI/death, less inotrope use
Teoh et al. (2002) [125]	30	Adenosine A1 receptor agonist GR79236X	Cross-clamp fibrillation	No difference in troponin-T release at 72 h
Shalaby et al. (2008) [126]	40	Adenosine (250 μg/kg bolus)	Cold blood cardioplegia	No difference in CK-MB release, LV function or myocardial apoptosis
Mangano et al. (2006) [72]	2698	Acadesine infusion (0.1 mg/kg min; 7 h).	Cardioplegia with added acadesine (5 μg/ml)	Improved post-PMI survival in 100 (3.7%) patients who had PMI. No difference in non-PMI patients
Wei et al. (2004) [73]	41	Bradykinin infusion (25 μg over 7 min)	Cold blood cardioplegia	No difference in troponin-I release but reduced CK-MB. Significant hypotensive effect
Wang et al. (2008) [74]	41	Bradykinin infusion (25 μg over 7 min)	Cold blood cardioplegia	No difference in troponin-I release but reduced CK-MB and anti-inflammatory effect
Boyce et al. (2003) [78]	2918	Cariporide	Cold blood cardioplegia	Reduced mortality and MI at 36 days and at 6 months
Mentzer et al. (2008) [79]	5761	Cariporide	Cold blood cardioplegia	Reduced mortality and MI at 5 days but not at 6 months- associated cerebrovascular events
Wang et al. (2003) [76]	40	Diazoxide (1.5 mg/kg over 1.5 min)	Cardioplegia	Improved LV function. Non-significant decrease in CK-MB
Wang et al. (2004) [75]	40	Diazoxide (1.5 mg/kg over 1.5 min)	Cardioplegia	Anti-inflammatory effect only
Tritapepe et al. (2006) [81]	24	Levosimendan	Cold blood cardioplegia	Less troponin-I release and improved LV function
Ranasinghe et al. (2006) [127]	440	GIK/T3	Cold blood cardioplegia	Better LV function. T3 reduced troponin-I
Alexander et al. (2008) [128]	3023	MC-1 250 mg/day for 30 days	Cold blood cardioplegia	No difference in 30-day MI/death. MC-1 increased in-hospital mortality
Verrier et al. (2004) [82]	3099	Pexelizumab (2 mg/kg IV bolus then 0.05 mg/kg h for 24 h).	Cold blood cardioplegia	No effect on 30-day death/MI in CABG. Less 30-day death/MI in CABG ± valve
Symons and Myles (2006) [129]	2979 27 trials	Meta-analysis of volatile anaesthetics	Cold blood cardioplegia and cross-clamp fibrillation	Better LV function, less troponin-I, less inotrope use, shorter ventilation time/ hospital stay. No effect on PMI or death
Yu et al. (2006) [95]	2841 32 trials	Meta-analysis of volatile anaesthetics	Cold blood cardioplegia and cross-clamp fibrillation	Less myocardial injury but no impact on clinical outcomes

CK: creatine kinase; CK-MB: creatine kinase-MB fraction

Table 3
Clinical studies of remote ischaemic preconditioning and ischaemic postconditioning in cardiac surgery.

Study	No.	Intervention	Myocardial preservation	Outcomes
Remote ischaemic preconditioning using brief limb ischaemia/reperfusion				
Gunaydin et al. (2000) [130]	8	Two cycles of 3 min/2 min Limb I/R	Cold blood cardioplegia	No effect on LDH
Cheung et al. (2006) [102]	37	Three cycles of 5 min/5 min Limb I/R	Cold blood cardioplegia	Less troponin-T release, less inotrope requirement and improved airway resistance
Hausenloy et al. (2007) [103]	58	Three cycles of 5 min/5 min Limb I/R	Cold blood cardioplegia and cross-clamp fibrillation	Less troponin-T release over 72 h
Ali et al. (2007) [104]	82	Three cycles of 5 min/5 min Limb I/R	Elective aortic aneurysm repair	Less troponin-T release and improved renal function
Ischaemic postconditioning using brief episodes of aortic clamping				
Luo et al. (2007) [107]	24	Two cycles of 5 min/5 min I/R	Repair of Tetralogy of Fallot	Less troponin-I release.
Luo et al. (2008) [109]	50	Three cycles of 5 min/5 min I/R	Valve surgery with cold blood cardioplegia	Reduction in CK-MB but not troponin-I. Less inotropic support required
Luo et al. (2008) [108]	40	Two cycles of 5 min/5 min I/R	Congenital heart disease with cold blood cardioplegia	Less troponin-I release and less inotrope support required

CK: creatine kinase; CK-MB: creatine kinase-MB fraction.

for an invasive myocardial preconditioning protocol. The elucidation of the mechanistic pathways underlying IPC has identified various pharmacological targets for preconditioning (Table 2).

The signal transduction pathways underlying IPC are complex and only a brief overview can be provided here; for a more comprehensive account the reader is directed to several reviews [65,66]. The ischaemic preconditioning stimulus generates autacoids such as adenosine, bradykinin and opioids which bind to their respective G-protein coupled receptors on the cardiomyocyte surface. This results in the activation of a variety of pro-survival signal transduction pathways most of which comprise protein kinase cascades such as the PI3K-Akt, MEK1/2-Erk1/2, cGMP-PKG, which then terminate on the mitochondria. At the mitochondria, reactive oxygen species (ROS) are generated which then activate other protein kinases such as PKC, which mediate the 'memory' effect of IPC. The mechanism for mitochondrial ROS production is unclear but it has been attributed to the inhibition of the electron transport cycle and potential opening of the ATP-dependent mitochondrial potassium channel. The end-effector of cardioprotection is currently unknown, although mounting evidence suggests that the inhibition of mitochondrial permeability transition pore (mPTP) at the onset of myocardial reperfusion is critical to the cardioprotective effect [66]. The mPTP is a non-selective channel of the mitochondrial inner membrane which mediates cardiomyocyte death by uncoupling oxidative phosphorylation and causing mitochondrial swelling, on its opening in the first couple of minutes of myocardial reperfusion [67].

4.2. Pharmacological preconditioning

Adenosine was one of the first agents to be studied as a pharmacological preconditioning mimetic in the setting of CABG surgery. As demonstrated initially by Lee and colleagues [68] and subsequently confirmed by other studies [69,70], adenosine pretreatment was able to reduce myocardial enzyme release and improved cardiac indices postoperatively. However the haemodynamic effects of adenosine have made it a difficult drug to administer in the clinical setting. Pharmacological preconditioning using an adenosine A1 receptor agonist in patients undergoing elective CABG surgery had no beneficial effects [71]. In a large multi-centred randomised controlled study, acadesine, a modulator of endogenous adenosine, was found to improve survival in the small proportion of patients (3.7%) who experienced a postoperative myocardial infarction (PMI), although there was no difference in outcomes in those patients which did not sustain a PMI [72].

Another important preconditioning mimetic is bradykinin, which in the setting of CABG surgery demonstrated only a weak anti-inflammatory cardioprotective effect but at the expense of significantly greater haemodynamic compromise [73,74]. The same group also demonstrated that the purported mitoK_{ATP} channel opener, diazoxide, administered in the setting of cardioplegia improved functional recovery following CABG and had an inflammatory effect, although it did not reduce myocardial necrosis as measured by CK-MB release [75,76].

Reducing cardiomyocyte sodium and calcium accumulation during myocardial ischaemia using pharmacological inhibitors of the Na^+—H^+ exchanger (NHE) has been demonstrated in experimental studies to reduce myocardial infarct size if administered prior to the index ischaemic insult [77]. Although the initial GUARDIAN clinical study reported beneficial effects with the NHE inhibitor, cariporide, in terms of reduced all-cause mortality and myocardial infarction at 36 days and at 6 months [78], the subsequent larger EXPEDITION trial confirmed the early cardioprotective benefits of cariporide but not the 6-month outcomes and in addition there was an associated increase in mortality from cerebrovascular events [79]. Levosimendan, a calcium sensitiser used in the treatment of heart failure, has been reported to have preconditioning effects in animal models (reviewed in [80]) and was found to reduce myocardial injury in the setting of CABG surgery in a pilot study [81].

A recent large multicentred clinical study has examined an anti-inflammatory approach to myocardial protection. Inhibition of the complement cascade using Pexelizumab was found to benefit patients undergoing CABG with or without valve surgery but not in patients undergoing CABG alone, in terms of 30-day death and myocardial infarction [82].

Studies are currently underway to evaluate the effects of pharmacological activating pro-survival protein kinases using erythropoietin or high-dose atorvastatin, and cyclosporine, an mPTP inhibitor, which has been recently reported to reduce myocardial infarct size when administered as an adjunct to primary PCI [83,84].

4.3. Volatile anaesthetic agents as pharmacological preconditioning agents

The protective anti-stunning and anti-inflammatory effects of volatile anaesthetics were first recognised before the concept of anaesthetic preconditioning was introduced. The anti-necrotic effect of anaesthetic preconditioning was first demonstrated in experimental studies by Toller and colleagues [85] who reported a 40% reduction in myocardial infarct size with sevoflurane in barbiturate-anaesthetised dogs undergoing acute left anterior descending artery occlusion.

The mechanisms underlying anaesthetic preconditioning appear to be similar to those which are activated by IPC and include the phosphorylation of Akt [86], the translocation of PKC [87] and the inhibition of mPTP [88]. In addition, reactive oxygen species have been ascribed an important role for ROS as triggers and mediators of anaesthetic preconditioning [89].

Clinical studies of preconditioning using volatile anaesthetics have yielded inconsistent results with respect to the reduction of myocardial enzyme release [75,90,91], although several other studies [92,93] have demonstrated consistent anti-stunning effects as measured by higher postoperative cardiac index, less incidence of low-output states necessitating inotrope support and shorter duration of intensive care. The cardioprotective effects of sevoflurane preconditioning have also been demonstrated in OPCAB surgery [94].

A recent meta-analysis of 2979 patients in 27 clinical trials found that volatile anaesthetics were associated with better LV function, less troponin-I release, less inotrope use, shorter ventilation time and shorter hospital stay, although there was no effect on perioperative myocardial infarction or death [92,93]. A subsequent meta-analysis of 32 clinical studies comprising 2841 patients found that volatile anaesthetics are able to reduce myocardial injury but no beneficial effect was observed on clinical outcomes [95]. Therefore, a large multicentred clinical study is required to determine whether or not volatile anaesthetics can impact on clinical outcomes post-cardiac surgery.

4.4. Remote ischaemic preconditioning in cardiac surgery

Another strategy for harnessing the 'conditioning' capabilities of the heart and also avoiding an invasive myocardial preconditioning protocol is to apply the preconditioning protocol to an organ or tissue distant from the heart; a concept termed remote ischaemic preconditioning (RIPC) (reviewed in [96]). This intriguing phenomenon was first described by Przyklenk and colleagues [97] when they observed that the myocardial infarct size generated by an acute coronary occlusion in the left anterior descending coronary artery territory of canine hearts could be substantially reduced by preconditioning with brief ischaemia and reperfusion in the left circumflex artery territory. Cardioprotection at a distance was subsequently demonstrated with the preconditioning protocol applied to the kidney [98], the intestine [99], and the limb [100]. The actual mechanism underlying RIPC induced protection is unclear, although the mechanisms underlying the myocardial endogenous protective pathways are probably the same as those recruited by IPC. The mechanism through which the cardioprotective signal is transferred from the preconditioning remote organ or tissue to the heart is unresolved, but has been attributed to either a neural and/or hormonal pathway [96].

The ability to precondition the heart using brief ischaemia and reperfusion in the limb was subsequently characterised as a non-invasive procedure in human volunteers by MacAllister's research group [101]. It is readily applicable in the clinical setting of cardiac surgery, where brief upper and lower limb ischaemia and reperfusion was first reported to reduce myocardial injury in children undergoing corrective cardiac surgery [102]. We have since shown that RIPC induced by three $\times$ 5 min cycles of upper limb ischaemia and reperfusion mediated a 43% reduction in absolute troponin-T release in patients undergoing elective CABG surgery [103] (see Table 3).

RIPC has been shown to have beneficial effects on multiple organ systems. In this respect, Ali and colleagues [104] used an invasive lower limb preconditioning protocol to reduce myocardial and renal injury in patients undergoing elective aortic aneurysm repair. One could speculate that limb preconditioning may be expected to confer protection against acute ischaemia–reperfusion injury sustained in other organs such as the intestine, brain and liver. Clearly, further multicentred clinical studies are required to determine whether RIPC impacts on clinical outcomes post-cardiac surgery.

4.5. Ischaemic postconditioning in cardiac surgery

In 2003, Zhao and colleagues [105] first introduced the concept of ischaemic postconditioning (IPost), as a cardioprotective strategy which could be applied at the onset of myocardial reperfusion making it clinically applicable to patients presenting with an acute myocardial infarction and undergoing myocardial reperfusion therapy. Interrupting the normal myocardial reperfusion process with three or more short-lived episodes of myocardial ischaemia has been reported to reduce myocardial infarct size in AMI patients undergoing primary PCI [106]. Its use in the setting of cardiac surgery has been recently reported in three different clinical studies from the same research group [107–109]. Experimental studies suggest that similar mechanistic pathways underlie cardioprotection induced by IPost, including cell surface receptor signalling, pro-survival kinases cascades and mitochondrial involvement with respect to the mitochondrial permeability transition pore and the mitochondrial K_{ATP} channel [66,110].

IPost in cardiac surgery requires a series of aortic clamping and declamping applied at the time of aortic declamping following coronary artery bypass. In 24 children undergoing repair for tetralogy of Fallot, Luo and colleagues [107] examined the beneficial effects of a surgical postconditioning protocol comprising re-clamping the aorta for 30 s and

declamping it for 30 s, a process which was repeated twice. This invasive treatment protocol was found to reduce myocardial injury as evidenced by less perioperative troponin-T and CK-MB release and smaller inotrope requirements post-surgery. However, in common with IPC, the invasive nature of this treatment strategy and the inherent risks of arterial thromboembolism, is likely to limit its clinical application.

5. Clinical application of 'conditioning'

From the discussion so far, it is clear that the beneficial effect of the various myocardial 'conditioning' interventions on clinical outcomes needs further confirmation in large-scale studies. These beneficial effects may be more difficult to measure in the setting of low-risk, 'routine' CABG where operative mortality is low. However more complex procedures like redo CABG, multi-valve surgery with or without CABG, high-risk CABG in the setting of NSTEMI or more rarely NSTEMI are associated with longer ischaemia times and therefore produce more ischaemia—reperfusion injury. Inclusion of these high-risk patients in larger randomised trials may demonstrate the beneficial long-term effects of 'conditioning' and indeed identify a subset of patients who may especially benefit from these interventions.

Another area of interest is the use of myocardial 'conditioning' to improve the survival of the donor heart in cardiac transplantation. Both crystalloid and blood cardioplegia have been used to preserve the donor heart with comparable effect on long-term outcomes although blood cardioplegia has been associated with better post-operative right heart function and a smaller incidence of arrhythmias [111]. The use of pharmacological, remote or invasive ischaemic preconditioning to improve the survival of the donor heart is an exciting prospect to improve clinical outcomes in this field. Ischaemic preconditioning has been demonstrated to improve donor graft survival in kidneys and liver in pre-clinical studies (reviewed in [112]). Furthermore, ischaemic preconditioning [113] and ischaemic postconditioning [114] have been demonstrated to protect donor grafts in animal models of cardiac transplantation, while remote preconditioning of the recipient has been shown to improve survival of the denervated allograft [115]. The use of 'conditioning' to improve cardiac allograft survival may enable us to use normothermic preservation techniques thereby reducing the detrimental effects of static cold preservation in cardiac transplantation [116].

6. Conclusion

Despite recent developments in the technique of myocardial preservation and the evolution of newer techniques such as off-pump coronary artery bypass surgery, patients undergoing cardiac surgery continue to experience significant morbidity and mortality, particularly in those higher-risk patient groups. Acute ischaemia—reperfusion injury is the predominant cause of myocardial injury sustained during cardiac surgery. It is possible to 'condition' the heart using brief episodes of ischaemia and reperfusion applied to the heart or an organ or tissue remote from the heart, the latter of which is more clinically amenable and can be applied non-invasively to either the upper or lower limb. Huge progress has been made in elucidating the mechanistic pathways underlying 'conditioning' cardioprotection, and have resulted in the identification of novel targets for pharmacological preconditioning. Many of the promising clinical trials have been single-centred proof-of-concept. Clearly, larger multicentred randomised placebo-controlled studies are required to determine whether these novel 'conditioning' treatment strategies are able to impact on short-term and long-term clinical outcomes post-cardiac surgery.

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