Cardioprotection during cardiac surgery

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Abstract   Coronary heart disease (CHD) is the leading cause of morbidity and mortality worldwide. For a large number of patients with CHD, coronary artery bypass graft (CABG) surgery remains the preferred strategy for coronary revascularization. Over the last 10 years, the number of high-risk patients undergoing CABG surgery has increased significantly, resulting in worse clinical outcomes in this patient group. This appears to be related to the ageing population, increased co-morbidities (such as diabetes, obesity, hypertension, stroke), concomitant valve disease, and advances in percutaneous coronary intervention which have resulted in patients with more complex coronary artery disease undergoing surgery. These high-risk patients are more susceptible to peri-operative myocardial injury and infarction (PMI), a major cause of which is acute global ischaemia/reperfusion injury arising from inadequate myocardial protection during CABG surgery. Therefore, novel therapeutic strategies are required to protect the heart in this high-risk patient group. In this article, we review the aetiology of PMI during CABG surgery, its diagnosis and clinical significance, and the endogenous and pharmacological therapeutic strategies available for preventing it. By improving cardioprotection during CABG surgery, we may be able to reduce PMI, preserve left ventricular systolic function, and reduce morbidity and mortality in these high-risk patients with CHD.

Keywords   CABG surgery • Cardioprotection • Ischaemic preconditioning • Ischaemic postconditioning • Peri-operative myocardial infarction • Peri-operative myocardial injury • Remote ischaemic preconditioning

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1. Introduction

Coronary heart disease (CHD) is the leading cause of morbidity and mortality worldwide, accounting for an estimated 7.3 million deaths in 2008 according to the World Health Organisation. For a large number of patients with CHD, coronary artery bypass graft (CABG) surgery remains the preferred strategy for coronary revascularization. Major improvements in myocardial preservation strategies over the last 10–20 years have meant that for many patients, the operative risk of CABG surgery remains low. However, over the last few years, the operative risk has increased as high-risk patients undergo more complex forms of CABG surgery.[1] This may be due to a number of different factors including: (i) the ageing population; (ii) the increasing prevalence of co-morbidities such as diabetes, peripheral vascular disease, obesity, hypertension, and so on; (iii) the greater complexity of coronary artery disease and the need for re-do surgery due to recent advances in percutaneous coronary intervention (PCI) technology; (iv) an increase in the number of patients undergoing CABG with concomitant valve surgery. These high-risk patients are more susceptible to peri-operative myocardial injury and infarction (PMI) and are therefore more likely to require

enhanced inotropic and ventilatory support post-surgery, and are more susceptible to the complications of surgery such as low-output syndrome, acute kidney injury (up to 34% of patients),[2] and stroke (1–3%).[3]

For these high-risk patients, the current myocardial preservation strategies are inadequate to protect the heart against PMI, resulting in worse clinical outcomes in this patient group. Therefore, novel therapeutic strategies are required to protect the myocardium from PMI in order to preserve left ventricular (LV) systolic function and improve clinical outcomes in patients undergoing CABG surgery. In this article, we review the aetiology of PMI during CABG surgery, its diagnosis and clinical significance, and the endogenous and pharmacological therapeutic strategies available for its prevention.

2. A historical overview of myocardial preservation during cardiac bypass surgery

The evolution of myocardial preservation strategies during CABG surgery has had a long and eventful history. Only a brief

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overview can be provided here—for more detailed accounts, the reader is referred to the following review articles.[4,5] In 1954, John Gibbon performed the first atrial septal defect closure using cardiopulmonary bypass (CPB), thereby heralding the era of cardiac bypass surgery.[6] For cardiac bypass surgery to progress from this point, it was essential to create a blood-free and motionless operative field for the surgeon, in order to improve visibility, facilitate the surgical procedure, and prevent air embolism. This was achieved by cross-clamping the aorta (to isolate the heart from the systemic circulation) and inducing electrochemical cardiac arrest (to stop the heart beating), respectively. Myocardial preservation strategies were required to protect the heart from the acute global ischaemic injury induced by cross-clamping the aorta to temporarily isolate the heart from the systemic circulation during intracardiac surgery, and to protect against the subsequent acute global myocardial reperfusion injury induced by unclamping the aorta when restoring circulation to the heart.

In the 1950s, it was demonstrated that total body hypothermia may be a beneficial approach to reducing myocardial oxygen consumption and preserving cardiac function during cardiac surgery.[7] In 1955, Melrose *et al.*[8] were the first to introduce the concept of inducible electrochemical cardiac arrest using potassium citrate, but the high levels of potassium were associated with myocardial necrosis. Over the next 10–20 years, many refinements were made to the crystalloid cardioplegic solution resulting in the formulation of Bretschneider's solution in 1964[9] and subsequently St Thomas Solution (Number 1 in 1976 and Number 2 in 1981),[10,11] both of which are still being used today for myocardial preservation. In 1978, Buckberg and colleagues[12] refined the cardioplegic solution by mixing it with blood and supplementing it with glutamate and aspartate and found that it offered greater myocardial protection than crystalloid cardioplegia alone. In the 1980s, Buckberg also performed a series of experimental studies investigating how altering the conditions of reperfusion impacted on myocardial recovery—this included the use of gentle reperfusion as a cardioprotective strategy,[13,14] a finding which preceded the discovery of ischaemic postconditioning.[15] Based upon previous studies[16] in the UK, cold blood cardioplegia has become the myocardial preservation strategy of choice for most patients undergoing CABG surgery. However, depending on surgical requirements and preference, there exist a number of variations to how the cardioplegic solution is delivered, including intermittent or continuous perfusion in an anterograde (via the aortic root) or retrograde (via the coronary sinus) manner using either cold, tepid, or warm blood cardioplegic solution (reviewed in Nicolini *et al.*[5]). Warm blood cardioplegia is an effective preservation strategy which is used by some surgeons.[17] An alternative approach to myocardial preservation during CABG surgery, which does not require the use of cardioplegia, is hypothermic intermittent cross-clamp fibrillation, a technique which is still used by some surgeons.[18] Over the last few years, off-pump coronary artery bypass (OPCAB) or 'beating-heart' surgery has emerged as the surgical treatment of choice in selected patients, and this avoids CPB, cardioplegic arrest, and the associated acute global ischaemia/reperfusion injury (IRI).[19] Furthermore, OPCAB may be associated with bradycardia, which may in itself be cardioprotective.[20]

However, despite using the most effective myocardial preservation strategy available, in the high-risk patient, the heart is still subjected to significant acute global IRI during cardiac bypass surgery, resulting in increased risk of PMI, impaired LV systolic function, and worsened

morbidity and mortality. There is therefore a need to discover novel therapeutic strategies which enhance myocardial protection in this setting.

3. Peri-operative myocardial injury and infarction

3.1 Causes of peri-operative myocardial injury and infarction

The mechanisms underlying PMI are multifactorial and include those due to early graft failure and include graft occlusion, graft kinking or overstretching, subtotal anastomotic stenosis, or graft spasm (which can be distinguished by the extent of serum cardiac enzyme release),[21] and those due to non-graft causes and include acute global IRI induced by aortic cross-clamping and declamping, systemic inflammatory injury from CPB, distal coronary microembolization,[22] surgical manipulation of the heart, particulate and soluble factors released from surgically manipulated coronary vessels,[23] genetic susceptibility to acute myocardial IRI, and so on.

3.1.1 Genetic predisposition
Genetic susceptibility to the detrimental effects of acute myocardial IRI may be expected to impact on the extent of PMI and clinical outcomes post-CABG surgery. For example, it has been reported that the extent of PMI may be more severe in patients who have certain inflammatory gene variants, presumably because the inflammatory response triggered by the cardiopulmonary response is heightened.[24,25] More recently, genetic variants in chromosome 9p21, which have been previously associated with increased risk of myocardial infarction (MI) in non-surgical settings, have also been associated with higher incidence of PMI during CABG surgery[26] and higher mortality rates at 5-year post-surgery.[27] The mechanisms underlying this increased genetic susceptibility to PMI remain unclear.

3.1.2 Acute global IRI
In order to create a blood-less operative field, the aorta is cross-clamped to isolate the heart from the systemic circulation, a manoeuvre which induces acute global myocardial ischaemic injury, which if prolonged will result in irreversible myocardial injury and cardiomyocyte death. In order to protect the heart from the ischaemic injury and to electrochemically arrest the heart, cardioplegic solution is injected anterogradely into the aortic route or retrogradely via the coronary sinus. After surgical insertion of the grafts, the cross-clamp is removed from the aorta, a process which subjects the heart to acute global myocardial reperfusion injury, which is composed of reversible forms of myocardial injury such as stunning and arrhythmias, and irreversible forms of myocardial injury and cardiomyocyte death. Despite optimal myocardial preservation using cold-blood cardioplegia, a significant amount of acute global myocardial IRI and cardiac dysfunction occurs at this time in high-risk patients. Coronary embolization would be expected to induce a focal area of acute myocardial ischaemic injury.[28] The opportunities for reducing this form of myocardial injury are reviewed in Section 4.

3.1.3 Systemic inflammatory response
In patients undergoing on-pump CABG surgery, the implementation of CPB triggers both a local and systemic acute inflammatory response, which can contribute to PMI. The components of this

response include a consumptive coagulopathy, cytokines, chemokines, vasoactive substances, cytotoxins, reactive oxygen species, and proteases of the coagulation and fibrinolytic systems.[29,30] The main cause of this response is from blood coming into direct contact with the foreign surfaces of the CPB circuitry, but other causes include acute IRI, complement activation, blood loss or transfusion, hypothermia, and direct surgical trauma (reviewed in Raja and Dreyfus[29] and Suleiman et al.[30]).

A number of therapeutic strategies have been investigated in the setting of CABG surgery in an attempt to modulate this inflammatory response. These include surgical strategies for reducing the inflammatory response of CABG surgery such as the use of the Minimized Extracorporeal Circulation (MECC) System, Off-Pump CABG surgery, minimally invasive cardiac surgery, heparin-coated CPB circuits, haemofiltration and leucocyte depletion, and a variety of pharmacological treatment strategies including complement inhibition, anti-oxidants, aprotonin, and cyclo-oxygenase inhibitors.[29,30]

3.2 Indicators of peri-operative myocardial injury and infarction in cardiac surgery

Peri-operative myocardial injury and infarction can be detected by measuring serum biomarkers of myocardial necrosis such as serum creatine kinase MB isoenzyme (CK-MB), troponin T (Trop T; standard and high-sensitive), and Trop I. Cell membrane rupture is required to release these cardiac biomarkers into the bloodstream, with cytosolic CK-MB being released early after myocardial injury. The troponins comprise both a free cytosolic and a structurally bound protein component, and therefore display an early initial release followed by a late more prolonged release. In a recent meta-analysis, it has been reported that for patients undergoing CABG surgery, elevation of CK-MB or Trop I in the first 24 h was associated with increased intermediate (1 year) and long-term (3 year plus) risk of mortality.[31] Because of the wide variability in the definitions used, the incidence of reported peri-operative MI (serum cardiac enzymes at five times the upper limit of normal) is highly variable and depends on the study, but it is in the region of 10−40% (Table 1). However, in the majority of patients undergoing CABG surgery, a degree of peri-operative myocardial injury can occur in the absence of classical infarction.

In order to establish standard criteria for the diagnosis of peri-operative MI, it has been agreed that the definition of a CABG-related MI or a Type V MI is an increase in serum biomarker values '. . . to more than five times the 99th percentile of the normal reference range during the first 72 h following CABG surgery, when associated with the appearance of new pathological Q-waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium'.[32] Therefore, the term peri-operative MI should be restricted to the above definition, and the term peri-operative myocardial injury can be used to denote significant myocardial injury outside of this definition. Cardiac magnetic resonance imaging (MRI) has recently been used to detect new loss of viable myocardium post-CABG surgery, and this non-invasive imaging modality can therefore also be used to detect peri-operative MI.

3.2.1 Creatine kinase MB isoenzyme
One of the first major clinical studies to link the peri-operative elevation of serum CK-MB during CABG surgery with clinical outcomes was the Arterial Revascularization Therapies Study (ARTS) study

published in 2001.[33] In 496 patients undergoing CABG surgery, it was reported that an elevation of serum CK-MB to five times the upper limit of normal was associated with an increase in mortality from 0.5 to 7.0% at 30 days.[33] Since the publication of this study, a number of larger clinical studies have confirmed the association of a peri-operative CK-MB release and in-hospital mortality, short-, medium-, and long-term clinical outcomes (see Table 1 for a summary of the major trials). However, due to the lack of specificity for myocardial injury, more specific biomarkers of myocardial necrosis such as Trop I and T are more often used to assess PMI.

3.2.2 Troponins T and I
Cardiac Trop T and I (Trop T and I) are specific markers of myocardial injury which have been used to detect, characterize, and quantify PMI during CABG surgery. In patients undergoing CABG surgery, Trop T and I will always be detected in the circulation, as these biomarkers of myocardial injury are released even in the absence of overt acute IRI and can become elevated even with surgical manipulation of the heart and aortic cannulation. Kinetic studies have revealed a biphasic pattern of troponin release during CABG surgery with a small peak of troponin at 8−10 h post-surgery indicating non-specific peri-operative myocardial injury, and a second larger peak at 20 h post-surgery indicating PMI due to actual myocardial necrosis.[34−36] The role of high-sensitive Trop T, which has been reported to have increased diagnostic and prognostic yield in patients presenting with acute coronary syndrome,[37] in the setting of CABG surgery as a serum biomarker of PMI is currently unknown.

A number of clinical studies have examined the association of peri-operative release of Trop T and I and clinical outcomes post-CABG surgery (see Table 1 for a summary of the major studies). However, many of these studies were published prior to the Universal definition of CABG-related MI or Type V MI in 2007[32] and used arbitrary definitions to denote PMI. This problem is illustrated in a recent meta-analysis which found that although a post-operative elevation in Trop T or I was associated with a 5.5-fold increase in mortality at 1 year (sensitivity 0.45, specificity 0.87) and a 6.6-fold increase in mortality at 30 days (sensitivity 0.59, specificity 0.82),[38] estimations of actual effect size and cut-off values were difficult given the variability in patient population, timing of the troponin sample, the troponin isoform used, and the actual troponin assay performed.[38] In this regard, further clinical studies are needed to investigate the impact of CABG-related MI or Type V MI on clinical outcomes post-CABG surgery. However, it must also be appreciated that even in CABG patients with peri-operative troponin release in whom the criteria for Type V MI are not met, significant myocardial necrosis arising from the CABG surgery may still be detected and quantified by cardiac MRI,[39] and its presence may still be associated with worse clinical outcomes.

3.2.3 Cardiac MRI
The detection and quantification of PMI can be quite challenging using electrocardiograms (as changes are difficult to interpret following surgery unless there is the appearance of a new Q-wave MI), echocardiography (can be used to detect LV systolic dysfunction or regional wall motion abnormalities which represent myocardial stunning rather PMI), and myocardial nuclear scanning (which will only detect obvious perfusion defects arising from graft or native coronary artery occlusion and again will not detect diffuse PMI). Therefore, cardiac MRI offers a non-invasive radiation-free imaging modality for

Table 1 Major clinical studies investigating the effect of PMI (measured by serum CK-MB, and Trop T and I) on clinical outcomes in adult patients undergoing CABG $\pm$ valve surgery

Study	Patient number	Surgery	Cardiac enzyme	Incidence of myocardial injury	Clinical outcome		
CK-MB							
Costa et al.,[33] ARTS trial	496	CABG	CK-MB at 6, 12, 18 h post-surgery	42.9%, 1−3× ULN 7.5%, 3−5× ULN 11.5%, 5× ULN	Mortality 0.5%, MI 1.4% Mortality 5.4%, MI 2.7% Mortality 7.0%, MI 12.3%* at 30 days		
Brener et al.[123]	3812	CABG	CK-MB at 8 and 16 h post-surgery	10%, ≤1 ULN 50%, 1−3× ULN 22%, 3−5× ULN 11%, 5−10× ULN 6%, >10× ULN	Mortality 7.2% at 3 years Mortality 7.7% at 3 years Mortality 6.3% at 3 years Mortality 7.5% at 3 years Mortality 20.8% at 3 years*		
Gavard et al.,[124] GUARDIAN trial	2332	CABG	CK-MB at 4, 8, 12 and 24 h post-surgery	10%, ≤1 ULN 50%, 1−5× ULN 22%, 5−10× ULN 6%, >10× ULN	Mortality 5.8% at 6 months Mortality 2.8% at 6 months Mortality 5.9% at 6 months Mortality 12.0% at 6 months*		
Domanski et al.,[31] Pooled analysis	18 908	CABG	Variable	10%, <1 ULN 10%, 1−2 ULN 50%, 2−5 ULN 22%, 5−10 ULN 11%, 10−20 ULN 6%, 20−40 ULN	Mortality 0.63% at 30 days Mortality 0.86% at 30 days* Mortality 0.95% at 30 days* Mortality 2.09% at 30 days* Mortality 2.78% at 30 days* Mortality 7.06% at 30 days*		
Troponin T							
Kathiresan et al.[125]	136	CABG	Troponin T 6−12 h and 18−24 h post-surgery		TnT > 1.58 ng/mL at 18−24 h associated with 5.5-fold increased risk of mortality at 12 months		
Lehrke et al.[126] Nesher et al.[127]	2041918	CABG or valve CABG and/or valve	Troponin T at 4 h, 8 h then daily for 7 daysTroponin T (peak levels in 24 h)	55%, <0.46 µg/mL 45%, >0.46 µg/mL 59%, <0.8 µg/mL 41%, >0.8 µg/mL	TnT ≥ 0.46 µg/L at 48 h is associated with 4.9-fold increased risk of mortality at 28 months cTnT > 0.8 µg/L associated with increased MACE (all-cause in-hospital death, low-output syndrome or peri-operative MI)		
Troponin I							
Lasocki et al.[128]	502	CABG ± valve	Troponin I 20 h post-surgery	11.4%, >13 ng/mL	>13 ng/mL at 20 h associated with 6.7× risk of in-hospital death		
Fellahi et al.[129]	202	CABG	Troponin I 20 h post-surgery	86% low TnI (4.1 ng/mL; range, 1.1−12.6) 14% high TnI (23.8 ng/mL; range, 13.4−174.6)	Mortality at 2 years higher in high TnI patients compared with low TnI patients (18 vs. 3%) No difference in in-hospital mortality		
Paparella et al.[130]	230	CABG	Troponin I (peak post-op value)	63.5%, <13 ng/mL 36.5%, >13 ng/mL	In-hospital mortality increased from 0.7 to 9.5%. No difference in 2-year mortality		
Croal et al.[131]	1365	CABG	Troponin I At 2 and 24 h post-surgery	24 h TnI predictive 25% (0−2.19 µg/L) 25% (2.20−4.30 µg/L) 25% (4.31−8.48 µg/L) 25% (8.49−350.81 µg/L)	30 days 0.9 0.3 1.9 4.6	1 year 1.8 2.2 4.0 9.8	3-year mortality (%) 4.6 6.5 8.7 12.9

ULN, upper limit of normal; MI, myocardial infarction; TnI, Troponin I; TnT, Troponin T.
*P < 0.05.

the identification, characterization, and quantification of PMI. Delayed gadolinium contrast enhancement by cardiac MRI (DE-CMR) is the gold-standard imaging technique for visualizing myocardial fibrosis or infarction. Delayed wash-out of the extracellular contrast agent, gadolinium, in areas of increased myocardial interstitial volume can be used to visualize myocardial fibrosis or infarction as areas of enhanced signal intensity on CMR. Several clinical studies have used this non-invasive radiation-free imaging modality to detect, characterize, and quantify new loss of myocardial viability following CABG surgery.

The first clinical study to use DE-CMR to image PMI in patients undergoing elective CABG surgery was by Selvanayagam et al.[40] in 2004. These authors compared the effects of off-pump CABG surgery against on-pump CABG surgery on LV systolic function and peri-operative MI (imaged by DE-CMR).[40] Although, off-pump CABG surgery was associated with improved LV systolic function, there was no difference in the incidence or median mass of peri-operative MI between the two groups (44% and 6.3 g with on-pump CABG vs. 36% and 6.8 g with off-pump CABG, respectively).[40] Later that same year Steuer et al.[41] demonstrated that DE-MRI (performed on days 4–9 following surgery) detected MI in 18 out of 23 patients (a median mass of 4.4 g equal to 2.5% of the LV), a finding which correlated with the rise in serum cardiac enzymes (CK-MB, Trop T and I).[41] The major limitation of this initial study was the inability to be sure that the presence of MI on DE-CMR was actually due to the surgical procedure as a pre-CABG CMR scan had not been performed to exclude the presence of any pre-existing chronic MI. This may explain the unusually high incidence of 'perioperative' MI (78%) reported in that study.[41]

Studies have investigated peri-operative levels of Trop I as a predictive marker of delayed enhancement on cardiac MRI. Analysis of the serum Trop I in first series of patients revealed that a 48 h peak Trop I level of >1.15 μg/L had the best accuracy for the detection of peri-procedural MI in CABG surgery.[42] Another series of 28 patients undergoing CABG surgery published by the same research group suggested that the presence of new hyperenhancement on CMR [observed in nine patients (32%)] was best predicted by a 1 h Trop I level of >5.0 μg/L.[43] Finally, a series of 40 CABG patients suggested that a 24 h Trop I level of >6.6 μg/L best predicted the presence of Type V MI and the presence of new hyperenhancement on CMR [observed in eight patients (20%)] was best predicted by a 1 h Trop I level of >5 μg/L.[39] The relationship between serum Trop T (conventional or high-sensitive) has not yet been compared with a new peri-operative MI detected by DE-CMR.

The appearance of delayed enhancement on CMR may also be able to characterize the peri-operative MI in patients undergoing CABG surgery and this may provide clues to the underlying aetiology of myocardial injury. In this regard, three patterns of DE-MRI have been described:[41,44] (i) a transmural MI (without or without microvascular obstruction) in a coronary artery territory, which may represent an early graft or native coronary artery occlusion; (ii) a subendocardial MI, which may represent distal coronary embolization; and (iii) diffuse patchy areas of myocardial necrosis which may be due to acute global IRI or other causes.

Whether the presence of MI on DE-CMR in patients undergoing CABG surgery is associated with worse clinical outcomes was investigated by Rahimi et al.,[45] who demonstrated that the presence of a new peri-operative and peri-procedural MI on CMR following either CABG or PCI was associated with a 3.1-fold increase risk in major adverse cardiovascular events (death, non-fatal MI, sustained ventricular arrhythmia, unstable angina, or heart failure requiring hospitalization). A recent porcine coronary microembolization model has suggested that late gadolinium enhancement may only be able to detect focal myocardial damage exceeding 5% of the myocardium within the region of interest, demonstrating one of the potential limitations of using CMR.[46]

4. Endogenous therapeutic strategies for cardioprotection

Inadequate cardioprotection during CABG surgery, particularly in high-risk patients, is associated with worse clinical outcomes. Therefore, novel therapeutic strategies are required to reduce PMI and prevent post-surgical complications. In this regard, it is possible to 'condition' the heart to protect itself from the detrimental effects of acute IRI by subjecting it to brief non-lethal episodes of ischaemia and reperfusion.[47] Importantly, the 'conditioning' stimulus may be applied either prior to [ischaemic preconditioning (IPC)],[48] after the onset of (ischaemic perconditioning),[49] or at the end of the index ischaemic event and at the time of reperfusion (ischaemic postconditioning),[15] making it possible to intervene at several different time points during CABG surgery.

4.1 Ischaemic preconditioning

In 1986, Murry et al.[48] first discovered that the heart could be 'conditioned' to protect itself from MI, using brief non-lethal cycles of myocardial ischaemia and reperfusion. In their seminal experimental study, it was demonstrated that subjecting the canine heart to four 5 min cycles of ischaemia and reperfusion [by left anterior descending (LAD) occlusion and reflow] reduced MI size by 75% following 40 min of sustained LAD occlusion and 72 h reperfusion. This phenomenon, which has been termed IPC, has been shown to offer ubiquitous cardioprotection in all animal species tested using a wide variety of experimental in vivo and in vitro IRI models (reviewed in Yellon and Downey[50]).

IPC was the first 'conditioning' strategy to be applied in the clinical setting of CABG surgery. A pioneering clinical study by our research group in 1993[51] first demonstrated that IPC could be reproduced in patients undergoing CABG surgery by clamping the aorta for 2 min and unclamping the aorta for 2 min to induce brief episodes of non-lethal global myocardial ischaemia and reperfusion prior to the sustained global myocardial ischaemia induced by aortic cross-clamping required for CABG surgery. We found that patients randomized to receive IPC at the time of surgery had preserved ATP levels in ventricular biopsies[51] and less peri-operative myocardial injury as evidenced by lower serum Trop-T concentrations.[52] Since these original findings, a number of clinical studies have investigated IPC in the setting of CABG surgery, the results of which have been summarized in a recently published meta-analysis of 22 such studies (933 patients) which concluded that IPC was associated with fewer ventricular arrhythmias, less inotropic requirements, and a shorter intensive care unit stay (see Table 2 for the summary of major studies).[53] Due to the invasive nature of the IPC protocol and the risk of arterial thrombo-embolism from cross-clamping and declamping the aorta, it has been difficult to justify performing a large prospective clinical study to determine definitively whether IPC can improve clinical

outcomes in patients undergoing CABG surgery. In this regard, the phenomenon of remote ischaemic preconditioning (RIC) is more amenable to clinical application as it obviates the need to intervene on the heart directly.

4.2 Remote ischaemic preconditioning

The major disadvantage of IPC as a cardioprotective strategy in patients undergoing CABG surgery is that it requires the 'conditioning' stimulus to be applied directly to the heart, which may not be practical and could actually be harmful. The discovery that the 'conditioning' stimulus could be applied to an organ or tissue away from the heart (a phenomenon termed remote ischaemic conditioning, RIC),[54] and the demonstration that the 'conditioning' stimulus could be applied non-invasively using a standard blood pressure cuff placed on the upper or lower limb[55] has facilitated the translation of RIC into the clinical setting (reviewed in Hausenloy and Yellon[56]). The actual mechanism underlying RIC is currently unclear but has been attributed to either a humoral or neurohormonal pathway which links the remote organ or tissue to the heart.[56–59]

The first attempt to investigate RIC in the clinical setting of CABG surgery was a small pilot clinical study by Gunaydin *et al.*[60] in 2000. Eight patients were randomized to receive RIC (a cuff was placed on the upper arm and inflated to 300 mmHg for 3 min and deflated for 2 min, a cycle which was repeated three times in total) prior to CABG surgery. There was no difference in serum CK-MB 5 min following declamping of the aorta, although at this time point, lactate dehydrogenase was higher in the RIC-treated group. However, given the small size of the study, and the failure to examine serum cardiac enzymes beyond 5 min of aortic declamping, the results are difficult to interpret. The first successful clinical application of RIC was in children undergoing corrective cardiac surgery for congenital heart disease by Redington's group in 2006.[61] In this small proof-of-concept study, 37 children were randomized to receive either RIC (three 5 min inflations/deflations of a blood pressure cuff placed on the thigh to 15 mmHg above systolic blood pressure) or control (a deflated blood pressure cuff placed on the thigh for 40 min) 5–10 min prior to going on cardiac bypass. Those children who received the RIC treatment had a lower inotropic score, lower airway pressures, and less peri-operative myocardial injury (measured by 24 h area under the curve Trop I) when compared with those children who were randomized to the control arm.

Our research group was the first to successfully apply RIC to adults undergoing elective CABG $\pm$ valve surgery.[62] Fifty-seven patients undergoing planned CABG $\pm$ valve surgery were randomized to receive RIC (three 5 min inflations/deflations of a blood pressure cuff placed on the upper arm to 200 mmHg) or control (a deflated blood pressure cuff placed on the upper arm for 30 min) after induction of anaesthesia but prior to surgery. Peri-operative myocardial injury as measured by the 72 h area-under-the-curve serum Trop-T concentration was reduced by 43% in those patients treated with RIC prior to surgery when compared with the control group. Subsequently, a number of clinical studies have been performed by different research groups, although not all the studies have been positive[63–65] (*Table 2*). The reasons for this discrepancy are unclear but may relate to a number of factors: (i) the RIC protocol itself—the RIC stimulus may have been submaximal or incorrectly applied. It is interesting to note that in the negative study by Rahman *et al.*,[64] the RIC stimulus was initiated after skin incision, whereas in the majority of studies,

the RIC stimulus was applied after the induction of anaesthesia and prior to skin incision; (ii) concomitant medication—patients may have been administered volatile anaesthetics or nitrates during surgery, which are known to protect the heart against IRI during cardiac bypass surgery.[65–67] In both the negative RIC CABG studies, all patients received volatile anaesthetics, whereas in most of the other studies, a proportion of the patients received intravenous anaesthesia. Furthermore, in the negative study by Karuppasamy *et al.*,[65] all patients received both isoflurane and propofol, anaesthetics agents which may have a synergistic cardioprotective effect.[68] Finally, a recent study has demonstrated that RIC was effective in those patients receiving isoflurane but not propofol at the time of CABG surgery[67]; (iii) patient selection—whether high-risk patients are more or less amenable to RIC is unclear; (iv) the characteristics of the surgery itself—whether the duration of aortic cross-clamp or cardiac bypass time impacts on the efficacy of RIC is unclear; and (v) it has been postulated that the human myocardium may already be preconditioned by going on CPB, although this view is contentious.[69] A large multicentre randomized controlled clinical trial is required to investigate the cardioprotective effects of RIC in cardiac bypass surgery. In this regards, whether RIC can improve clinical outcomes in adult patients undergoing CABG surgery is unknown and is currently being investigated in two ongoing multicentre clinical trials called the ERICCA (The Effect of Remote Ischemic preConditioning on Clinical outcomes in patients undergoing Coronary Artery bypass graft surgery: NCT01247545)[70] and the RIPHeart (Remote Ischemic Preconditioning for Heart Surgery: NCT01067703) studies. Further clinical studies are required to characterize the RIC stimulus and to investigate the patient population which is most likely to benefit from this therapeutic strategy.

4.3 Ischaemic postconditioning

In 2003, Zhao *et al.*[15] first demonstrated that the ischaemic canine heart could be 'conditioned' at the onset of myocardial reperfusion, by interrupting coronary reflow with short-lived episodes of LAD occlusion and reflow. The mechanistic pathways underlying ischaemic postconditioning (IPost) cardioprotection are complex and some of them are similar to those utilized by IPC and are the subject of several recent reviews.[71,72] Ischaemic postconditioning has been recently applied in the setting of CABG surgery, at the time of aortic cross-clamp removal, when the patient comes off cardiac bypass and the heart is subjected to a period of global reperfusion. Luo *et al.*[73] were the first to demonstrate the beneficial effect of IPost in the setting of cardiac surgery. Twenty-four children undergoing cardiac surgery for Tetralogy of Fallot were randomized to receive IPost, which comprised unclamping the aorta for 30 s and then re-clamping the aorta for 30 s, a cycle which was repeated two times in total, and resulted in a lower 2 h level of CK-MB and Trop-T.[73] Clearly, the risk of clamping the aorta in younger patients with relatively non-atherosclerotic aortas is not as great when compared with adult patients undergoing CABG $\pm$ valve surgery. A number of subsequent clinical studies have confirmed the cardioprotective effects of IPost in the setting of cardiac surgery for Tetralogy of Fallot[74] and aortic valve replacement[75] and have reported beneficial effects on peri-operative myocardial injury, inotropic requirements, intensive care unit (ITU) stay, and ventilation time. Again, whether this invasive cardioprotective strategy can impact on clinical outcomes in patients undergoing cardiac surgery remains to be determined.

Table 2 Clinical studies investigating potentially novel endogenous cardioprotective strategies in patients undergoing cardiac bypass surgery

Study	Patient number	Surgery	Intervention	Effect of treatment	Notes
Ischaemic preconditioning					
Walsh et al.[53] (meta-analysis of 22 studies)	933	CABG ± valve	Various protocols of intermittent aortic cross-clamping	Fewer ventricular arrhythmias (OR 0.11), less inotropic requirements (OR 0.34) and a shorter intensive care unit stay (by 3 h)	Benefit of IPC only observed in presence of cardioplegia. Intermittent cross-clamping of the aorta to induce IPC in the adult patient is invasive and may increase risk of thrombo-embolism from an atherosclerotic aorta
Remote ischaemic preconditioning					
Hausenloy et al.[62]	57	CABG ± valve	3 × 5 min arm cuff	43% reduction in 72 h AUC TnT	Benefit observed in patients receiving both cross-clamp fibrillation and cold blood cardioplegia
Venugopal et al.[132]	45	CABG ± valve	3 × 5 min arm cuff	42% reduction in 72 h AUC TnT	Benefit observed in patients receiving cold blood cardioplegia alone
Thielmann et al.[63]	53	CABG	3 × 5 min arm cuff	45% reduction in 72 h AUC TnI	Benefit observed in patients receiving crystalloid cardioplegia alone
Ali et al.[133]	100	CABG	3 × 5 min arm cuff	Reduction in CK-MB at 8, 12, 24, and 48 h	
Wagner et al.[134]	101	CABG	3 × 5 min arm cuff 18 h before surgery	Reduction in TnI at 8, 16, and 24 h	Benefit observed in patients receiving crystalloid cardioplegia alone. First study to investigate SWOP
Rahman et al.[64]	162	CABG	3 × 5 min arm cuff applied after skin incision	No difference in 48 h AUC Trop T	Unstable angina patients included. All patients received cold blood cardioplegia, iv GTN, sevoflurane/enflurane
Li et al.[135]	81	Valve	3 × 4 min leg cuff RIPC prior surgery RIPerC after AXC	RIPerc reduced peak TnI by 40%. RIPC no effect	RIPerC more effective than RIPC
Hong et al.[136]	130	Off-pump CABG	4 × 5 min arm cuff	Non-significant 26% reduction in 72 h AUC TnI	Study under-powered
Choi et al.[137]	76	CABG ± valve	3 × 10 min leg cuff	27% reduction in 24 h CK-MB peak level	No protection from acute kidney injury observed
Karuppasamy et al.[65]	54	CABG	3 × 5 min arm cuff	No difference in 48 h AUC Trop I	All patients received isoflurane and propofol. Patients either received cold blood cardioplegia or cross-clamp fibrillation
Kottenberg et al.[67]	72	CABG	3 × 5 min arm cuff	50% reduction in 72 h AUC TnI in patients receiving isoflurane. No significant reduction in patients receiving propofol	Only non-diabetic patients. All patients received crystalloid cardioplegia. Benefit only observed in those patients receiving isoflurane anaesthesia
Ischaemic postconditioning					
Luo et al.[73]	24 children	Tetralogy of Fallot	2 × 30 s cycles of aortic cross-clamping	Reduction in TnI and CK-MB at 4 h post-IPost	First study to show efficacy with IPost in cardiac bypass surgery
Luo et al.[75]	50 adults	Aortic valve surgery	3 × 30 s cycles of aortic cross-clamping	Reduction in CK-MB but not TnI	IPost also resulted in a reduction in inotropic requirement
Li et al.[74]	99 children	Tetralogy of Fallot	2 × 30 s cycles of aortic cross-clamping	Reduction in TnI at 4 h post-IPost	IPost also resulted in a 44% reduction in ventilation time and 40% reduction in inotropic requirement

MI, myocardial infarction; TnI, Troponin I; TnT, Troponin T; IPost, ischaemic postconditioning.

5. Pharmacological strategies for cardioprotection

The opportunities for administering a pharmacological cardioprotective strategy to protect the acute global IRI include administering the cardioprotective agent prior to aortic cross-clamping, adding the pharmacological agent to the cardioplegic solution, or giving the cardioprotective agent at the time of aortic cross-clamp removal or a combination of these different approaches. Over the years, a large number of pharmacological strategies have been investigated as potential cardioprotective agents but only the major ones will be reviewed here, including some which mimic the cardioprotective effects of ischaemic conditioning.

5.1 Anaesthesia and cardioprotection

5.1.1 Volatile anaesthetic agents

Volatile anaesthetic agents depress cardiac function and reduce myocardial oxygen consumption during cardiac bypass surgery. However, in addition to this beneficial effect, there is experimental evidence supporting a direct cardioprotective role for volatile anaesthetic agents in animal models of IRI.[76] Furthermore, a number of clinical studies have been performed, demonstrating beneficial effects with volatile anaesthetic agents in the setting of CABG surgery (reviewed in Symons and Myles[77] and Yu and Beattie[78]).

One of the first pre-clinical studies to demonstrate a cardioprotective effect with a volatile anaesthetic agent was in 1985 by Freedman *et al.*[79] who discovered that pre-treatment with enflurane could improve functional recovery of the isolated rat heart subjected to IRI. A number of experimental studies have confirmed the cardioprotective effects of volatile anaesthetic agents (predominantly isoflurane, desflurane, enflurane, and sevoflurane) in a variety of *in vitro* and *in vivo* animal models of MI (reviewed in Kato and Foex[76]). These anaesthetic agents, which have been reported to mimic the cardioprotective effects of IPC and ischaemic postconditioning, have also been shown to recruit the intracellular signal transduction pathways which are known to underlie these endogenous cardioprotective strategies.[80]

One of the first clinical studies to investigate the cardioprotective effects of volatile anaesthesia in patients undergoing CABG surgery was by Belhomme *et al.*[81] in 1999, who reported reduced levels of serum Trop I and CK-MB in patients randomized to receive isoflurane anaesthesia when compared with intravenous anaesthetics. The cardioprotective effect of volatile anaesthetic agents in the clinical setting of CABG surgery has been assessed in several recent meta-analyses. A meta-analysis of 27 clinical trials comprising 2979 patients by Symons and Myles[77] in 2006 compared the effects of volatile anaesthetic agents with non-volatile intravenous anaesthetic agents on clinical outcomes post-cardiac surgery. They found that, compared with those patients receiving intravenous anaesthesia, patients who had received volatile anaesthetic agents (isoflurane, sevoflurane, desflurane and enflurane) had better cardiac function and less requirement for inotropic response, experienced less peri-operative myocardial injury (lower serum Trop I levels), required a shorter duration of mechanical ventilation (by 2.7 h), and a shorter hospital stay (by 1 day).[77] However, there was no difference in the incidence of MI, intensive care unit stay, or in-hospital mortality.[77] A subsequent meta-analysis of 32 studies (2841 patients) by Yu and Beattie[78] found that the volatile anaesthetic agents, sevoflurane and desflurane,

were associated with smaller serum Trop I concentrations at 6, 12, 24, and 48 h after operation. Another meta-analysis by Landoni *et al.*[82] of 22 studies (1922 patients) found that the use of desflurane and sevoflurane anaesthesia was associated with decreased incidence of peri-operative MI, less post-operative Trop I, a shorter ITU and hospital stay, less inotropic and ventilation requirements, and a reduction in mortality, when compared with intravenous anaesthesia.

These meta-analyses were limited by their analysis of the small number of clinical studies which had actually investigated meaningful clinical outcomes post-surgery, and as such, although the use of volatile anaesthetic agents (particularly desflurane and sevoflurane) may appear to offer myocardial protection during CABG surgery when compared with intravenous anaesthetics, whether they reduce mortality in this setting remains to be determined in an adequately powered randomized controlled prospective clinical trial.

5.2 Sodium–hydrogen exchange inhibitors

During myocardial ischaemia, the absence of oxygen promotes anaerobic glycolysis resulting in intracellular acidosis which in turn drives the sodium–hydrogen (Na^+–H^+) ion exchanger to extrude protons from the cell in exchange for sodium resulting in an elevation in intracellular sodium and a rise in intracellular calcium, the effect of which is detrimental for cardiomyocyte survival. Treatment with the Na^+–H^+ ion exchange inhibitor, cariporide, prevents the accumulation of intracellular sodium and calcium during myocardial ischaemia and has been reported in experimental animal studies to reduce MI size if administered prior to the index ischaemic insult.[83] The GUARd During Ischemia Against Necrosis (GUARDIAN) trial published in 2000 demonstrated in 1477 high-risk patients undergoing CABG surgery that pre-treatment with cariporide (120 mg) resulted in less peri-operative CK-MB release and a 25% reduction in risk of death and non-fatal MI when compared with placebo at 36 days (16.2 vs. 12.2%; $P < 0.027$). The beneficial effect of cariporide was maintained at 6-month post-surgery (18.6 vs. 15.0%; $P < 0.033$).[84] The subsequently published larger Na^+/H^+ Exchange inhibition to Prevent coronary Events in acute cardiac condition (EXPEDITION) clinical trial confirmed the reduction in the primary endpoint of death and MI at day 5 from 20.3 to 16.6%.[85] However, the incidence of MI alone was reduced from 18.9% in placebo to 14.4% with cariporide treatment, whereas mortality was paradoxically increased from 1.5% in the placebo group to 2.2% with cariporide, an unexpected finding which was associated with an increase in cerebrovascular events.[85] This unfortunate off-target effect of cariporide on cerebrovascular events has prevented any further application of this therapeutic cardioprotective strategy in CABG patients.

5.3 Pharmacological preconditioning strategies

A number of pharmacological agents have been investigated based on their ability to mimic the cardioprotective effects of IPC. Adenosine was shown to mimic the infarct-limiting effects of IPC in 1993 and has been reported in several clinical studies to reduce peri-operative myocardial injury and improve cardiac indices in the setting of CABG surgery when administered either as an intravenous therapy or when added to the cardioplegic solution.[86–88] However, not all the clinical studies have been positive[89,90] and its haemodynamic effects have precluded any further investigation of this cardioprotective strategy.

Acadesine, a modulator of endogenous adenosine that increases the availability of adenosine locally in ischaemic tissues, was investigated as a cardioprotective treatment strategy in patients undergoing CABG surgery and showed initial benefits.[91,92] However, in a subsequent large multicentre randomized controlled clinical trial (Acadesine 1024), pre-treatment with acadesine had no effect on the primary endpoint of cardiac death, MI, or stroke at 4 days.[93] In a subsequent study, however, in the small proportion of patients who had a peri-operative MI (3.7%), pre-treatment with Acadesine was reported to reduce mortality by 4.3-fold.[93]

Another important preconditioning mimetic is bradykinin which has also been investigated in the setting of CABG surgery, but it only demonstrated a weak anti-inflammatory cardioprotective effect at the expense of significant haemodynamic compromise.[94,95] The same research group also demonstrated that the putative mitochondrial ATP-dependent potassium channel opener, diazoxide, administered in the setting of cardioplegia improved functional recovery following CABG surgery, although it did not reduce peri-operative myocardial injury as measured by CK-MB release.[96,97]

Most patients undergoing CABG surgery will be on angiotensin-converting enzyme-inhibitor (ACE-I) therapy, but whether ACE-I treatment is beneficial when administered solely as a preconditioning agent at the time of CABG surgery is unknown. Although, a subgroup analysis of the QUO VADIS trial reported beneficial effects with starting an ACE-I prior to surgery,[98] recent studies have shown that starting it early after CABG surgery may not be beneficial and could be harmful.[99]

5.4 Anti-inflammatory therapeutic strategies

Pro-inflammatory effects of CPB may contribute to peri-operative myocardial injury in CABG patients through the activation of complement. The production of terminal complement activation products of C5 cleavage, C5a (a potent anaphylatoxin) and C5b-9 (membrane attack complex), can induce cardiomyocyte death, thereby contributing to the pro-inflammatory component of peri-operative myocardial injury experienced by CABG patients. Experimental animal studies have demonstrated that terminal complement inhibition using pexelizumab, a terminal complement inhibitor which prevents the production of C5a and C5b-9, can reduce inflammation and myocardial necrosis in animal models of MI and CPB.[100]

The Pexelizumab for Reduction in Infarction and Mortality in Coronary Artery Bypass Graft surgery (PRIMO-CABG I) trial demonstrated in 2476 patients, with one or more pre-defined risk factors, that treatment with pexelizumab resulted in a non-significant 18% reduction in the primary combined 30-day endpoint of death and non-fatal MI in patients undergoing CABG surgery alone (11.8% with placebo vs. 9.8% with pexelizumab; $P = 0.07$). Based on these clinical findings, the PRIMO-CABG II trial was organized to investigate pexelizumab in 4254 patients with two or more pre-defined risk factors undergoing CABG, but this had no effect on its primary endpoint of death and MI.[101] However, a *post hoc* analysis of the combined PRIMO-CABG I and II trials did find a significant reduction in 30-day mortality from 8.1% with placebo to 5.7% with pexelizumab treatment.[101]

5.5 Statin therapy

The benefits of 'statin' therapy for the primary and secondary prevention of cardiovascular disease is well established. However, in addition to its LDL cholesterol-lowering effects, statins have beneficial pleiotropic effects in the cardiovascular system which include a direct protection of the myocardium from the detrimental effects of acute IRI. Pre-clinical animal studies have shown that statin therapy can limit MI size when administered either prior to ischaemia or even at the onset of myocardial reperfusion (reviewed in Ludman *et al.*[102]). Retrospective analyses and prospective studies have reported beneficial effects in patients taking statin therapy prior to elective CABG surgery.[103,104] A recent meta-analysis of pre-operative statin therapy in CABG surgery comprising 30 000 patients reported significant benefits with pre-operative statin use on early post-operative all-cause mortality, atrial fibrillation, and stroke but conferred no benefit on post-operative MI or renal failure.[105] Given that most CHD patients will be on statin therapy prior to CABG surgery probably precludes this therapeutic approach as a novel strategy for cardioprotection. From previous animal studies[106] and recent PCI clinical studies,[107,108] there had been the suggestion that high-dose statin therapy may be more effective that standard statin therapy but we were unable to find any benefit in terms of reducing peri-operative myocardial injury with a higher dose of statin in the setting of CABG surgery.[109]

5.6 Erythropoietin therapy

Erythropoietin, a haematopoietic cytokine which is used in the treatment of chronic anaemia, has been reported in a number of pre-clinical animal studies to reduce MI size when administered at high doses prior to myocardial ischaemia and at the onset of myocardial reperfusion (reviewed in Riksen *et al.*[110]). However, its clinical translation into the clinical setting as a cardioprotective therapy has been hugely disappointing with lack of benefit in the setting of both acute MI[111,112] and CABG surgery.[113]

6. Improving the translation of novel cardioprotective strategies

A recurring theme in the field of cardioprotection has been the discordancy between the number of potential cardioprotective strategies discovered in the pre-clinical animal setting and the number which has actually been translated into the clinical setting. This issue has been extensively discussed elsewhere.[114–118] The reasons for the failure to translate novel cardioprotective strategies into the CABG setting may be attributed to a number of factors including: (i) the subject: the juvenile healthy animal is a poor representation of the typical CHD middle-aged CABG patient with co-morbidities such as diabetes, hypertension, and hyperlipidaemia, all of which may interfere with cardioprotection.[119,120] The presence of these co-morbid conditions can attenuate the efficacy of cardioprotection observed in the normal heart by modifying key mediators of cardioprotection such as mitochondrial function, biochemical pathways, and intracellular signalling pathways.[120] There are diabetic, hypertensive, and hyperlipidaemic animal models available which should be used to test potentially novel cardioprotective strategies in the pre-clinical setting; (ii) the inadequacy of the animal IRI models; many of the animal models investigating novel cardioprotective strategies in the pre-clinical setting are based on regional acute coronary artery occlusion and reflow, a model which does not accurately reproduce the conditions of global acute IRI (in the presence of cardioplegia) experienced during CABG surgery. There are rat, canine, and

porcine models of CPB which closely simulate CABG surgery,[121,122] but these are infrequently used; (iii) the novel cardioprotective strategy itself; the pre-clinical studies should demonstrate conclusive cardioprotection in a variety of *in vivo* animal models in different laboratories. In this regard, the NIH have implemented the Caesar Cardioprotection Consortium of research centres to test a particular novel cardioprotective agent in the murine, rabbit, and porcine MI models in a randomized controlled fashion;[118] (iv) concomitant medication: the effect of concomitant medication on cardioprotection is rarely tested in pre-clinical animal studies, although patients will normally been on a variety of cardiac medication. In addition, there are the effects of anaesthetic drugs on cardioprotection to consider; (v) the timing of the intervention: clearly, the timing of the therapeutic strategy (prior to ischaemia, during ischaemia, or at the onset of reperfusion) should match that used in the pre-clinical experimental studies wherever possible; (vi) clinical endpoints: relevant clinical endpoints should be used in the design of the clinical study. Surrogate markers such as PMI measured by serum cardiac enzymes, and LV systolic function may be used in proof-of-concept clinical studies. In terms of clinical outcomes, a potential cardioprotective agent may be expected to impact on PMI, LV systolic function, the onset of heart failure, and cardiovascular death and is unlikely to influence coronary revascularization and MI.

7. Summary and conclusions

High-risk patients are undergoing CABG surgery, putting them at greater risk experiencing PMI, resulting in increased operative risk and worse morbidity and mortality. The current myocardial preservation strategies may be inadequate at protecting the myocardium from the acute global IRI which occurs on aortic cross-clamping and declamping during on-pump CABG surgery. Therefore, novel therapeutic strategies are required to protect the heart against IRI and reduce the extent of PMI so as to preserve LV systolic function and improve clinical outcomes in these high-risk patients undergoing CABG surgery. The process of translating potentially novel cardioprotective strategies from the pre-clinical studies to setting of CABG surgery needs to be improved. Several therapeutic strategies have shown promising beneficial effects in the setting of CABG surgery, including pharmacological agents such as acadesine and volatile anaesthetics and endogenous cardioprotective strategies such as remote ischaemic preconditioning and ischaemic postconditioning. Large multicentre prospective randomized controlled clinical trials are needed to investigate whether these therapeutic interventions can improve clinical outcomes in patients undergoing CABG surgery.

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