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Cardioplegic strategies to protect the hypertrophic heart during cardiac surgery

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Abstract

Cardioplegic arrest and cardiopulmonary bypass are key triggers of myocardial injury during aortic valve surgery. Cardioplegic ischaemic arrest is associated with disruption to metabolic and ionic homeostasis in cardiomyocytes. These changes predispose the heart to reperfusion injury caused by elevated intracellular reactive oxygen species and calcium. Cardiopulmonary bypass is associated with an inflammatory response that can generate systemic oxidative stress which, in turn, provokes further damage to the heart. Techniques of myocardial protection are routinely applied to all hearts, irrespective of their pathology, although different cardiomypathies respond differently to ischaemia and reperfusion injury. In particular, the efficacy of cardioprotective interventions used to protect the hypertrophic heart in patients with aortic valve disease remains controversial. This review will describe key cellular changes in hypertrophy, response to ischaemia and reperfusion and cardioplegic arrest and highlight the importance of optimising cardioprotective strategies to suit hypertrophic hearts.

Keywords

hypertrophy; aortic valve surgery; cardioplegia; cardiopulmonary bypass; hypothermia; ischaemia; inflammation; oxidative stress; calcium

Introduction

Cardiopulmonary bypass (CPB) and cardioplegic arrest remain the most popular techniques in clinical intervention during open heart surgery. However, both can directly or indirectly result in cardiac morbidity following surgery[1]. Cardioplegic arrest renders the heart globally ischaemic and, upon reperfusion, triggers myocardial injury[2]. Reperfusion injury is triggered by significant calcium (Ca^{2+}) overload and oxidative stress that leads to mitochondrial permeability transition pore (MPTP) opening. Ischaemia and reperfusion (I/R)-induced oxidative stress may be directly responsible for triggering Ca^{2+} handling defects in myocytes and may, in part, be responsible for the development of Ca^{2+} overload[3]. The myocardial mitochondria are a major source for reactive oxygen species (ROS) production during I/R[4]. Myocardial reperfusion injury also activates neutrophils which trigger an inflammatory response resulting in generation of ROS, cytokine release and complement activation, which are likely to cause more cardiac injury[1]. In addition to the inflammatory

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response generated as a result of tissue reperfusion injury, there is a significant systemic inflammatory response that is triggered by CPB during open heart surgery. The CPB-induced inflammatory response could further contribute to myocardial injury as surgery without CPB appears to be associated with reduced myocardial injury[1]. Formulating strategies to protect the heart during open heart surgery by attenuating reperfusion injury and systemic inflammatory response is essential to improve clinical outcome. This, however, must take into account the fact that different pathologies require different cardioprotective strategies.

Causes of myocardial injury during open heart surgery

Reperfusion injury following cardioplegic arrest

Major advances have been made in the preservation of myocardial function during open heart surgery since the introduction of cardioplegic arrest[5]. However, hyperkalaemic cardioplegic solutions remain the most commonly used technique for protecting the heart against ischaemia during open heart surgery. High potassium protects by arresting the heart and, therefore, reduces energy demands and helps preserving energy substrates during ischaemia. Although cardioplegia does confer protection, human hearts still suffer damage. This is because, under these conditions, the heart is rendered globally ischaemic and, therefore, susceptible to reperfusion injury. During myocardial ischaemia, there is a decrease in the supply of oxygen and nutrients to the heart[2]. This, in turn, provokes a fall in energy production by the mitochondria, which is quickly followed by abnormal accumulation and depletion of several intracellular metabolites (e.g. a fall in adenosine triphosphate (ATP) and a rise in lactate). These metabolic changes lead to a decrease in intracellular pH and an increase in the intracellular concentrations of sodium and Ca^{2+}, which further consumes ATP. Several sarcolemmal ionic pumps and channels are disrupted, leading to membrane depolarization and loss of excitability. If coronary flow is restored quickly, then metabolic and ionic homeostasis is re-established, the plasma membrane repolarises and recovery occurs. However, reperfusion following prolonged ischaemia can result in death of cardiomyocytes. Reperfusion injury is triggered by significant Ca^{2+} overload and oxidative stress that lead to mitochondrial permeability transition pore (MPTP) opening[6]. Oxidative stress during I/R may be directly responsible for triggering Ca^{2+} handling defects in myocytes[7] and may, in part, account for the development of Ca^{2+} overload[3]. It is not surprising, therefore, that the mitochondria, and the MPTP, in particular, have become a major target for protecting the heart against I/R injury. Interestingly, the myocardial mitochondria are a major source for ROS production during I/R[4, 8] and antioxidants, including the mitochondria-targeted ones[9], are currently being investigated for their cardioprotective efficacy(see below).

In addition to the known consequences of I/R injury (e.g. ventricular fibrillation, myocardial stunning and loss of intracellular proteins), the generation of ROS and their release to the extracellular space can further compromise the cardiac function by, amongst other things, promoting an inflammatory response generated by CPB.

Cardiac injury triggered by inflammatory response to cardiopulmonary bypass

Open heart surgery with CPB is associated with an acute inflammatory response which has implications for postoperative recovery and myocardial function[10]. Despite significant changes and improvements in surgical techniques, inflammation remains a significant problem. Therefore, the development of strategies to control the inflammatory response continues to be the focus of extensive experimental research and clinical studies[11]. In addition to CPB, reperfusion injury of the myocardium and the lungs and surgical trauma are also likely triggers of the inflammatory response. Other factors, including anaesthesia,

temperature and genetic predisposal, could also contribute to the inflammatory response. The genetic background and its relation to the inflammatory response during open heart surgery is a recent interesting development[12].

The well established role of CPB in triggering an inflammatory response during open-heart surgery has masked the role of myocardial reperfusion injury as an additional source of inflammatory mediators. Whether oxidative stress is a cause or an effect of myocardial injury during open-heart surgery is not known, but it has been implicated in postoperative complications[13]. The primary source of systemic ROS during open heart surgery on CPB is thought to be the neutrophils[14] which also release several proteolytic enzymes. Neutrophils are activated by agents derived from the systemic circulation, coronary vasculature and myocytes. Cytokines stimulate the up-regulation of adhesion molecules on cardiomyocytes that allow neutrophils to adhere and release ROS and proteolytic enzymes[15]. Neutrophils accumulate in the ischaemically damaged and/or reperfused area of the myocardium.

In addition to CPB, the myocardium generates inflammatory mediators and ROS during ischaemia-reperfusion, which would contribute to cardiac functional depression and apoptosis[16]. In a variety of experimental models, cardiac myocytes, when exposed to ischaemia (hypoxia)-reperfusion or cold crystalloid cardioplegia, have been shown to produce interleukin(IL)-6[17-19] in the coronary bed of patients undergoing coronary artery bypass graft surgery[20]. Other inflammatory cytokines can be produced locally in the heart, including IL-8, which is released in the ischaemic myocardium, which would stimulate the up-regulation of adhesion molecules on different cell types[15]. This, in turn, allows neutrophils to adhere to the myocytes and release ROS and proteolytic enzymes. Other pro-inflammatory and anti-inflammatory cytokines (e.g. IL-10) are also produced by the heart during cardiac insults[21]. It is evident, therefore, that, during stress, the myocardium becomes an additional source of cytokines. Whether cardiac cytokines act on membrane receptors to alter the myocyte response to cardiac insults is not presently known.

Cardioprotective strategies during open heart surgery: key approaches

Anti-inflammatory

Several anti-inflammatory techniques, including leukocyte filtration, corticosteroids, aprotinin, heparin and nitric oxide (NO) donor compounds have been used in recent years in cardiac surgery[22]. Interestingly, these studies have shown evidence of myocardial protection in patients undergoing cardiac surgery on CPB[22]. Whether the cardiac actions of these techniques are directly due to a reduction in inflammatory response is not presently known. For example, there are haemodynamic and osmotic changes which can result in oedema in the heart [23].

Cardioplegic techniques

More recent strategies for myocardial protection include one or more combinations of warm versus cold blood cardioplegia, antegrade versus retrograde delivery, intermittent versus continuous perfusion and the inclusion of various additives that aim at reducing Ca^{2+} overload, provide energy substrates and remove harmful ROS[1,2].

Cardioplegic techniques of myocardial protection are routinely applied to all hearts, irrespective of their pathology. However, the hypertrophic heart has different metabolic demands than other pathologies and, therefore, may have different susceptibility to ischaemia and reperfusion.

Cardiac hypertrophy and vulnerability to reperfusion injury

Cardiac Hypertrophy

Cardiac hypertrophy is an adaptive response to increased workload particularly common in clinical hypertension populations[24,25]. Left ventricular chamber stiffness increases during pressure overload hypertrophy and this is, in part, due to enhanced wall thickness. In general, a good correlation has been reported between myocardial stiffness and collagen content[25]. Interestingly, it is possible to find patients having valvular disease with the same degree of cardiac hypertrophy yet having different chamber and muscle stiffness.

Cardiac hypertrophy is an independent risk factor for the development of sudden death, myocardial infarction and congestive heart failure[26]. Furthermore, the coexistence of cardiac hypertrophy and ischaemia are responsible for creating an arrhythmogenic substrate[27]. Most important is the fact that hypertrophy alters vulnerability to ischaemia and reperfusion[28] (see below).

Cell signalling in cardiac hypertrophy

Pathological hypertrophy signalling can be broadly divided into biomechanical and stretch sensitive signalling, or neurohumoral mechanisms that are associated with the release of cytokines, hormones, chemokines and growth factors. The downstream biochemical signal induces subsequent changes in gene expression, which results in cardiomyocyte hypertrophy.

Neurohumoral signalling—The hormones angiotensin II, endothelin-1, catecholamines and insulin growth factor(IGF)-I bind and activate specific G-protein-coupled receptors (GPCRs). This induces protein kinase C (PKC) activation and production of the signalling molecule inositol-1,4,5-triphosphate ($Ins(1,4,5)P_3$)[29] which, in turn, triggers the release of Ca^{2+} from the sarcoplasmic reticulum. The free Ca^{2+} activates the phosphatase calcineurin, which dephosphorylates nuclear factor of activated T cell (NFAT) transcription factors. This permits the translocation of NFAT to the nucleus where they participate in hypertrophic gene expression. The free Ca^{2+} also activates calmodulin-dependent kinase (CaMK), resulting in histone deacetylase II class inactivation and, as a result, chromatin remodelling[30]. Pathological hypertrophy, through activation of calcineurin or pressure overload, has been associated with enhanced serine phosphorylation of histone deactylase(HDAC)5 and HDAC9 [31]. This has established chromatin regulation as an inducer of the pathological hypertrophic response.

Hypertrophic signalling can also be induced as a result of mitogen-activated protein kinase (MAPK), which is activated via receptor tyrosine kinases (IGF I and fibroblast growth factor receptors) and receptor serine/threonine kinases (transforming growth factor β, cardiotrophin1)[32]. The downstream targets of MAPK include p38, Janus Kinases (JNKs) and extracellular signal-regulated kinases (ERKs), each known to phosphorylate multiple intracellular targets, including transcription factors which induce the hypertrophic gene expression programme within the cardiomyocyte.

Stress signalling—The internal sensory apparatus of myocardial stress can induce pathological hypertrophy. This response is mediated by integrins, which are heterodimeric transmembrane receptors (α and β subunits) that link the extracellular matrix to the intracellular cytoskeleton[33]. Two important proteins that act as stretch sensors in cardiomyocytes are melusin and the LIM domain protein MLP (muscle LIM protein). Melusin has been shown to transduce biochemical stress signals through focal adhesion kinase (FAK)[33], which inactivates GSK-3β through phosphorylation[34]. MLP has been

implicated in a second sensing apparatus at the level of the Z-disc in each sarcomere and induces a stress response through the calcineurin-NFAT signalling pathway[35]. Stress can also be induced at the cell membrane independently of stimulated proteins through the activation of the Angiotensin II GPCR and subsequent activation of Janus kinase 2 (JAK2). This induces the traslocation of G-proteins into the cytosol upon stretch which leads to the activation of ERK and the induction of hypertrophy[36]. Genetic deletion of the stretch sensors (melsulin, MLP, β-integrin and FAK) in mice led to a phenotype representative of pathological hypertrophy[37].

Myocardial metabolic state in cardiac hypertrophy

Heart muscle can adapt to environmental changes by altering the turnover of specific proteins or by changing flux through metabolic pathways. Under severe conditions, energy production can be badly impaired, which will either directly or indirectly induce contractile dysfunction. An example of such conditions is hypertrophy associated with aortic valve disease. An important alteration under these conditions also involves the suppression of the postnatal cardiac gene programme as the heart returns to the foetal gene programme[38]. It has been proposed that these changes in gene expression are an adaptive process, possibly triggered by glucose-derived metabolic signals as the heart uses carbohydrates metabolism in preference to fatty acids for energy production. Whether this adaptation is a survival one remains to be established. What is important is the suggestion that modulation of myocardial metabolism is one key target for therapeutic interventions[39].

Aortic insufficiency is associated with periods of adaptation that include changes in function, metabolism and structure of the left ventricle, culminating in heart failure[40]. Studies involving 31-phosphorous neuclear magnetic resonance (31-PNMR) spectra in patients with left ventricular hypertrophy have shown that heart failure was characterised by a decline in the phosphocreatine/ATP ratio[41]. Work from our unit has provided evidence showing that hypertrophic hearts have a different metabolic state compared to hearts with ischaemic disease, which has implications for energy production, protein turnover and myocardial protection[42].

Susceptibility of hypertrophied hearts to ischaemia/reperfusion

Because of the controversy regarding the metabolic state of the hypertrophied myocardium, it is not surprising that its susceptibility to ischaemic insults remains controversial. The hypertrophied myocardium has a reduced capillary density, which hinders the diffusion of nutrients and oxygen to energy production sites[43]. This is likely to make the heart more vulnerable to ischaemic insults[44]. Others have suggested that ischaemia and reperfusion injury can activate the cardiac renin-angiotensin system, which may be responsible for the increased susceptibility of the hypertrophied myocardium to ischaemia and reperfusion injury[45]. In contrast to the hypertrophic heart, we have shown that hearts with chronic ischaemic disease are more resistant to ischaemia and reperfusion injury compared to normal hearts[46]. It is important to note, however, that there are reports suggesting hypertrophied heart may be more resistant to ischaemia[47]. One reason for this controversy could be related to the severity of hypertrophy as the severely hypertrophied heart is more susceptible to reperfusion injury than the moderately hypertrophied heart[48].

Cardioprotection of the hypertrophied heart

Several signalling pathways have been implicated in cardioprotection of the hypertrophic heart in experimental models. For example, the inhibition of tumour necrosis factor (TNF)-α signalling significantly improves recovery[49]. This effect appears to be related to the type of TNF receptor. In cardiomyocytes, TNF receptor type 1 stimulation induces contractile dysfunction, hypertrophy, fibrosis and cell death, while TNF receptor type 2 stimulation, by

producing a lower TNF-α concentration, is protective.[50]. Inhibition of the sodium/hydrogen exchanger in hypertrophied rat myocardium subjected to cardioplegic arrest was found to confer significant cardioprotection[51]. Increased availability of important cellular substrates (e.g. glutamate and aspartate) is cardioprotective[44,52]. During hypertrophy, there is an increased aspartate[52] and glutamate[44] transporter expression and activity.

Increased vulnerability of the hypertrophic heart to I/R has also been shown to occur when studying cardioprotective effects of cardioplegia[53]. Interventions during cardioplegic arrest have also been shown to be less cardioprotective in the hypertrophic compared to the normal heart. For example, recovery of hypertrophic hearts exposed to pre-ischaemic pharmacological preconditioning and cardioplegic arrest had a lower recovery of hemodynamic parameters compared to normal[54]. Ischaemic post-conditioning attenuates ischaemia/reperfusion injury in isolated hypertrophied rat heart. The cardioprotective effects of ischaemic post-conditioning were partly mediated through the PI3K/Akt/GSK-3β signalling pathway[55].

Strategies to protect the hypertrophic heart of patients during valve replacement surgery

As stated above, myocardial protection techniques have been largely investigated in the clinical setting of coronary revascularisation while relatively little work has been carried out on myocardial protection in patients with left ventricular hypertrophy. One added complication in the relevant studies is the fact that the hypertrophy comes in varying severity and there is a relationship between the degree of hypertrophy and degeneration before ischaemia and the postoperative outcome of the patients[56]. Subsequently, as we shall show in our discussion below, there is significant disagreement as to the characteristic of an optimal cardioplegic technique to protect the hypertrophic heart.

Crystalloid vs. Blood cardioplegia

The choice of the optimal cardioplegic technique to protect the hypertrophic heart during aortic valve surgery remains a significant clinical problem. Issues relating to composition (blood vs. crystalloid), temperature (warm or cold) and delivery (intermittent vs. continuous and antegrade vs. retrograde) of the cardioplegia have not been resolved. Key in myocardial preservation during cardioplegic arrest of a hypertrophic ventricle has been hypothermic perfusion. Hypothermia has been challenged and numerous studies have looked at its role in myocardial protection of the hypertrophic heart. There are reports suggesting that warm blood cardioplegia is good, but its superiority could not be established[57]. Others reported that cold blood cardioplegia is more effective than crystalloid or warm blood cardioplegia[58] and no difference in protection between continuous normothermic and intermittent hypothermic cardioplegia[59,60]. However, antegrade delivery of cold blood cardioplegia has been shown to provide better myocardial protection than cold crystalloid cardioplegia[61]. By and large, these studies have focused on selected clinical outcome measurements and/or release of cardiac proteins. They did not provide an insight into myocardial metabolic changes that are associated with both pathology and cardioplegic ischaemic insult. For many years, our unit has been involved in studies aimed at improving cardioprotection of hypertrophic hearts in patients undergoing aortic valve surgery. Our aim was to correlate intracellular changes in the myocardium with the extent of reperfusion injury and postoperative recovery.

The choice of optimal cardioplegia: the Bristol experience—Following our finding that warm blood cardioplegia is superior to cold blood cardioplegia in patients undergoing coronary artery bypass surgery[62], we decided to investigate both interventions in

patients undergoing aortic valve surgery. In this study, we compared cold versus warm blood cardioplegia and measured left ventricular intracellular metabolites, also monitoring the release of troponin I and clinical outcome. Our data showed that, in contrast to CABG surgery, cold blood conferred better myocardial protection compared to warm blood cardioplegia, as shown by reduced metabolic ischaemic stress and less reperfusion injury. Clinical outcome was also improved. This finding supports our view that, as a result of the metabolic state of hypertrophic hearts being different to those with ischaemic disease[42], different protective strategies are, therefore, required. This is due to metabolic preservation being key in myocardial protection. In spite of the improved recovery with cold blood, the protection remains suboptimal, with significant reperfusion injury. Subsequently, we designed a study to investigate the efficacy of terminal warm blood cardioplegia following cold blood cardioplegic arrest. We found that, for an average cardioplegic arrest time of 70 minutes, the use of retrograde hot-shot is associated with full metabolic recovery in both left (hypertrophic) and right (relatively normal) ventricles. This is supported by the complete preservation of ATP and by the lack of increase of lactate. Interestingly, the use of cold blood cardioplegia alone, although it seems to provide protection for the left ventricle, was associated with a drop in ATP in the right ventricle. Our finding also suggests that retrograde delivery could be better at protecting the right ventricle, as some investigators are concerned that this route may affect distribution of cardioplegia to the right ventricle. In summary, the terminal retrograde hot-shot does not add any extra benefit to antegrade cold blood cardioplegia in preventing left ventricular reperfusion injury in patients undergoing aortic valve replacement. Nevertheless, it appears to reduce metabolic stress in the right ventricle.

Beating heart surgery

Beating heart continuous coronary perfusion has seen a revival as an alternative to cardioplegia for performing complex valvular surgery. However, despite the reported advantages, available evidence for its efficacy is controversial[63]. One study found the beating-heart technique with retrograde coronary sinus perfusion to have shorter CPB and aortic cross-clamp times, but there was more injury (troponin I release) compared to conventional protection[64]. Beating heart valve surgery in patients with a poor ejection fraction yields results similar to conventional surgery using cardioplegia[65]. However, it has been shown that continuous blood cardioplegia required less inotropic and mechanical cardiac support than crystalloid cardioplegia[66]. There is no difference in clinical outcome between on-pump beating heart and hypothermic arrested heart valve replacement surgery [67]. It is evident that further studies are needed to fully evaluate the efficacy of this method of myocardial perfusion, particularly for the high-risk group of patients.

Ischaemic conditioning

Following the discovery of the cardioprotective strategy known as ischaemic preconditioning, other similar interventions applied at different time points or locations (post-conditioning, per-conditioning and remote conditioning) have been described and many of them have been tested in clinical settings. For example, post-conditioning may protect adult the hypertrophic myocardium using cold blood cardioplegic arrest and support the need for further clinical trials to test the efficacy of post-conditioning in cardiac surgery[68]. Remote ischaemic pre-conditioning (RIPC) has been shown to be a powerful protective technique in which brief ischaemia of one organ or tissue (e.g. arm or leg) confers protection of another organ or tissue (e.g. heart) against a sustained ischaemia-reperfusion insult[69]. Several studies have confirmed the cardioprotective efficacy of RIPC in patients undergoing CABG surgery using different techniques of cardioplegic arrest (crystalloid, cold and warm blood)[70-72]. A recent study has tested RIPC in patients admitted for selective valve replacement using intermittent cold blood cardioplegia. RIPC involved three cycles of

4/4 min right lower limb I/R after induction of anaesthesia. In addition, the investigators studied the effect of remote per-conditioning (I/R cycles applied during cardioplegic arrest). Interestingly, the study showed significant improvement with the per- but not pre-conditioning stimulus[73].

Additives to cardioplegia

The addition of procaine to crystalloid cardioplegia in patients undergoing aortic valve replacement surgery did not improve myocardial protection, but had better spontaneous return to sinus rhythm after reperfusion[74]. The addition of insulin to blood cardioplegia was found to improve myocardial protection in patients with left ventricular hypertrophy[75]. Histidine-buffered cardioplegic solution resulted in relatively lower inotropic requirement for left ventricular hypertrophied heart associated with aortic stenosis[76].

Anti-inflammatory interventions

A key strategy in reducing the inflammatory effects on the myocardium is to deplete the leukocytes. This approach has been shown to help protect the hypertrophic heart. For example, leukocyte-depleted reperfusion used as an adjunct to terminal cardioplegia (following crystalloid arrest) reduces reperfusion injury in patients with left ventricular hypertrophy[77]. A similar pattern has been shown when using blood cardioplegia in patients with severe left ventricular hypertrophy[78]. Avoidance or reducing the use of CPB would attenuate the inflammatory response and is likely to confer better protection to the myocardium. Minimal access aortic valve replacement using minimal extracorporeal circulation has been shown to provide excellent clinical results[79]. In fact, mini-sternotomy is considered an excellent approach for aortic valve surgery[80].

Summary

This review has addressed the key issue relating to myocardial protection in patients with left ventricular hypertrophy undergoing open heart surgery. The inflammatory response and reperfusion injury associated with cardiopulmonary bypass and cardioplegic arrest are key triggers of myocardial injury during open heart surgery. The design of cardioprotective strategies must take into account alternatives/improvements in the use of these techniques. Better understanding of metabolic, molecular and structural remodelling during hypertrophy will enable better design of cardioprotective interventions. Finally, the finding that the relatively “normal” right ventricle has different vulnerability to cardiac insults compared to the “conditioned” stressed hypertrophic left ventricle suggests the need for formulating a cardioplegic solution that is optimal for both left and right ventricles.

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