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Cardioplegia and cardiac surgery: Pharmacological arrest and cardioprotection during global ischemia and reperfusion

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ABSTRACT

Since the start of cardiac surgery in the 1950s, multiple techniques have been used to protect the heart during the surgical requirement for elective global ischemia (and the still, relaxed, bloodless field that this provides the surgeon for repair of the lesion). Most of these techniques have been discarded. The current gold standard, established over 30 years ago, is hyperkalemic (moderately increased extracellular potassium) cardioplegia; this technique revolutionized cardiac surgery, allowing significant surgical advancement with relative safety. Hyperkalemic cardioplegia induces a rapid depolarized arrest that is readily reversible. Recent patient demographic changes, with surgeons operating on older, sicker patients who have more severe and diffuse disease, potentially requires a more prolonged elective ischemia; hence, an improved myocardial protection would be of benefit. Several areas of study have demonstrated that a new concept of myocardial protection—'polarized' arrest—may provide this additional protection. Many pharmacological agents have been shown (in experimental studies), to have the ability to induce a polarized arrest and to provide improved protection. However, the often-overlooked requirements of effect reversibility and systemic safety have meant that these agents usually remain experimental in nature. This review attempts to highlight the cellular components that can be targeted, within the excitation–contraction coupling cascade, to induce cardiac arrest, and to provide an explanation for the mechanism of action of these agents. In this context, the agents are discussed in terms of their clinical potential for use during cardiac surgery, with particular reference to the safety aspects of the agents.

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1. Introduction

During cardiac surgery, the majority of surgeons prefer a relaxed, still (non-beating) heart with a blood-free operating field. The easiest

way to achieve this is to induce a global ischemia to the heart by cross-clamping the aorta (and thereby preventing coronary artery perfusion), with systemic blood circulation transferred to a heart–lung machine. Although convenient for the surgeon, global ischemia of the heart is detrimental; considerable research has been conducted in exploring ways to reduce the damaging effects of surgically-induced ischemia. It is important to realise that ischemia is a progressive process; as the ischemic duration increases, the cellular and molecular changes become more severe such that, without timely reperfusion, they will eventually lead to cell death. Reversible changes occur over

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short periods (seconds to a few minutes) of ischemia, with reperfusion resulting in full recovery (albeit potentially prolonged). However, at some unknown point after a longer ischemic duration, the changes lead to an irreversible injury that will not benefit from reperfusion. In fact, 'reperfusion injury' can occur that may exacerbate the ischemic injury. Hence, it is important during cardiac surgery to initiate cardioprotective procedures so that any ischemic injury is minimized by extending the period of reversible injury, and delaying the onset of irreversible injury for as long as possible.

2. Surgical cardioprotection: a short history

The first open-heart surgery operation (Lewis & Taufic, 1953), in 1952, used whole-body systemic hypothermia (~28 °C) and brief (~6 min) circulatory arrest. At that time, it was known that hypothermia was a protective mechanism that reduced organ oxygen requirement, particularly to the brain. The subsequent development of cardiopulmonary bypass (Gibbon, 1954; Chambers & Hearse, 2001) prevented injury to the brain and other systemic organs, but the extended periods of global ischemia required to repair complex cardiac pathologies leading to increased mortality (often as high as 65%). A common phenomenon was the 'stone heart', the result of maintained and irreversible contracture precipitated by ATP utilization during ischemia (Katz & Tada, 1972). In an attempt to ameliorate this problem, Melrose et al. (1955) introduced the concept of 'elective reversible cardiac arrest' using an intracoronary artery infusion of a high concentration of potassium citrate (77 mmol/L) added to blood. This 'pharmacological arrest' (now termed cardioplegia) induced a cell membrane depolarization, preventing conduction of the action potential and resulted in diastolic cardiac arrest. Reversibility of arrest was easily achieved by washout of the solution. However, this elevated potassium (hyperkalemia) citrate solution was subsequently found to induce focal myocardial necrosis and caused the death of many patients, resulting in the use of hyperkalemic solutions being abandoned for almost 20 years. Over this time period, surgeons used various techniques to protect the heart during ischemia, including continuous or intermittent normothermic perfusion, electrically induced ventricular fibrillation or topical (and profound) hypothermia; surgical results were generally good, but mortality rates were high (around 10–20%).

Interestingly, the concept of pharmacological arrest had been maintained throughout this period by surgeons in Germany, using cardioplegia developed by Bretschneider (1964) and now known as HTK solution. This solution was sodium-poor, calcium-free and contained procaine, a sodium channel blocker; it induced arrest by maintaining a polarized cell membrane and was used routinely with considerable success (Preusse, 1993; Chambers & Hearse, 2001). Unfortunately, however, these advances were not widely known until much later (Bretschneider et al., 1975) due to original publications in the German literature.

In the mid-1970s, to address the continued influence of ischemic injury during cardiac surgery, cardioplegic solutions were reintroduced into surgical practice. These solutions (developed in both the USA and in the UK) were based on an 'extracellular-type' ionic formulation and had moderately elevated potassium chloride concentrations (Hearse et al., 1981b; Chambers & Braimbridge, 1993). Although earlier experimental studies had suggested that the focal necrosis seen in patients resulted from the high citrate concentrations, rather than the high potassium, this was not subsequently confirmed (Tyers et al., 1975). At St. Thomas' Hospital in London, David Hearse (a biochemist) in collaboration with Mark Braimbridge (a cardiac surgeon) developed the St. Thomas' Hospital cardioplegic solutions. These solutions (Hearse et al., 1976; Jynge et al., 1981) were characterized and optimized for each component (based on plasma concentrations) and had potassium concentrations of either 20 or

16 mmol/L (in St. Thomas' Hospital cardioplegic solution No. 1 or 2, respectively), elevated magnesium concentrations of 16 mmol/L, and normal ionized calcium concentrations. St. Thomas' Hospital cardioplegia was first used surgically in 1975 (Braimbridge et al., 1977); within 2–3 years, the use of crystalloid buffer-based cardioplegia became the predominant cardioprotective technique throughout the world, with the St. Thomas' solution being the most widely used crystalloid solution (Robinson et al., 1995). Further development of cardioplegic solutions (from Buckberg's group) used blood as the vehicle for the arresting and protective agents (Follette et al., 1978; Buckberg et al., 1993); blood cardioplegia is now the most commonly used form of hyperkalemic cardioplegia (Robinson et al., 1995; Karthik et al., 2004).

3. The induction of arrest

Cardioplegic arrest remains the current gold standard for cardioprotection during cardiac surgery, and involves the use of a hyperkalemic (elevated potassium) extracellular solution (either crystalloid or blood-based). The principle by which hyperkalemia induces arrest is by establishing a new resting membrane potential which is at a more positive value (ie. is depolarized from normal) and is, therefore, termed 'depolarized' arrest. Despite its almost universal usage, depolarized arrest has disadvantages that make hyperkalemia, potentially, a less than optimal means of inducing arrest. This is important in the present climate of cardiac surgery and the changing population of patients undergoing operations; cardiologists have developed the technique of percutaneous coronary intervention (PCI), which implants vascular stents into diseased coronary arteries, to a sophisticated level. New anti-thrombotic drugs (such as clopidogrel) in combination with conventional aspirin therapy, together with drug eluting stents (that inhibit vascular cell proliferation, and hence stent occlusion), mean that patients with one or two vascular lesions and less diffuse coronary disease who used to receive coronary artery bypass surgery benefit from these recently developed, less invasive, techniques compared to cardiac surgery (Taggart et al., 2008). On the other hand, cardiac surgery remains preferential for either left main coronary artery disease or three (or more) vessels with more diffuse disease and impaired ventricle, because it offers significantly fewer adverse events and prolonged patency (Taggart et al., 2008). This severity of ischemic heart disease, coupled with the increasing age at which patients are undergoing cardiac surgical operations for other conditions such as degenerative valvular disease (Chambers, 2005), means that alternative and more beneficial ways of inducing arrest to enhance cardioprotection are constantly being sought. This is especially relevant to the increase in surgical intervention for patients with impaired ventricles associated with left ventricular hypertrophy and heart failure or urgent revascularization after acute coronary syndrome (ACS) and non-ST-segment elevation myocardial infarction (NSTEMI), where it is generally acknowledged that current methods of myocardial protection are inadequate. Severely hypertrophic hearts have limited metabolic and contractile reserve (Ingwall, 2009), which makes them more susceptible to ischemia and reperfusion injury. Manipulation of the protective strategy for hypertrophic hearts induced by aortic stenosis, by varying the cardioplegia infusion temperature, demonstrated that intermittent antegrade cold blood cardioplegia was better than warm blood cardioplegia (Ascione et al., 2002); however, it was concluded that both cardioplegic techniques conferred sub-optimal protection. Cardioplegic techniques have also been examined in patients undergoing urgent CABG surgery for unstable angina and NSTEMI (Onorati et al., 2005). This study demonstrated that a combination of antegrade and retrograde warm (34 °C) blood cardioplegia administration was superior to antegrade alone, but was also equivalent to off-pump surgery with no ischemia. Similarly, in

patients undergoing emergency CABG surgery for ACS (Rastan et al., 2006), it was shown that beating heart strategies improved hospital outcome and long-term survival compared to cardioplegic arrest (using either HTK solution or hyperkalemic blood cardioplegia). Despite these results, the majority of cardiac surgeons continue to use ischemic cardioplegic arrest in these patients (Ricci & Salerno, 2006); manipulating the conditions of delivery and administration are, essentially, cosmetic changes; real change requires innovation in the concept of myocardial protection to achieve the standard of myocardial protection required for these patients. This review describes the potential disadvantages of depolarized arrest and highlights alternative agents that may possibly be applicable in a clinical setting to induce alternative means of arrest, discussing their potential advantages and disadvantages.

Elective induction of ischemic cardiac arrest forms the cornerstone of myocardial protection for the majority of cardiac procedures (coronary artery bypass surgery and valve surgery) during cardiac operations. Cardioprotection during this ischemia involves the application of a cardioplegic solution to induce rapid myocardial arrest and induce a flaccid diastolic state that allows the surgeon a relaxed non-beating operating field—the induction of ‘cardioplegia’, defined as ‘an elective, rapid and reversible paralysis of the heart during cardiac surgery’. The institution of cardioplegic arrest ensures that myocardial oxygen consumption (MVO_2) is significantly reduced (Buckberg et al., 1977), as is the ATP depletion characteristic of severe ischemia. Cardiac arrest can be induced in a number of ways, by targeting specific processes within excitation–contraction coupling (Fig. 1).

3.1. Targets for arrest within excitation–contraction coupling

The resting membrane potential (E_m) is maintained by selective ionic membrane permeability distribution, predominantly via the potassium gradient (Opie, 2004); in the myocyte E_m is around -85 mV and is therefore close to the potassium equilibrium potential (E_K). During excitation, either by external stimulation (adjacent cell, external pacing and mechanical excitation) or by spontaneous depolarization via the internal pacemaker cells (Purkinje fibres), the membrane potential rapidly depolarizes

triggering the action potential (Fig. 1). This is the net result of a number of ionic currents generated by the activation of various ion channels and pumps in the membrane; these include the fast sodium channel (I_{Na}), the L-type calcium channel ($I_{Ca,L}$), and various potassium channels. These channels are all voltage-gated, and they are of particular interest because they can be pharmacologically targeted to induce myocardial arrest. At onset of the action potential by stimulation of the cell, a rapid depolarization of the membrane potential (to around $+20$ mV) is initiated via opening of the sodium channels (Niedergerke & Orkand, 1966; Opie, 2004). When the membrane potential has depolarized to around -40 to -35 mV, the L-type calcium channels become activated allowing calcium to enter the cell and this maintains the depolarized membrane potential during the plateau phase of the action potential. The membrane permeability to potassium in an outward direction is also decreased during the plateau phase; however, the activation of the potassium channels will generate sufficient outward potassium current to balance the inward current of sodium and calcium entry. The small increase in intracellular calcium via L-type calcium channel activation during the plateau phase leads to activation of intracellular calcium channels (or calcium release channels (Bers, 2002; Opie & Bers, 2004) that form part of a complex known as the ryanodine receptor (RyR) in the sarcoplasmic reticulum (SR). The activation of RyR causes a significant release of calcium from the calcium stores in the SR into the cytosol, a process known as calcium-induced calcium release (CICR). CICR increases the cytosolic calcium concentration (referred to as the calcium transient, which usually increases from around 200 nmol/L to around 1000 nmol/L) and initiates myofilament contraction as a response to the excitation stimulus. The L-type calcium channels are inactivated by the depolarized membrane potentials and by the rapid increase in cytosolic calcium concentration. The membrane potential subsequently becomes repolarized by activation of various potassium channels, returning the membrane potential back to its resting value (Opie, 2004).

Within the excitation–contraction coupling (ECC) cascade (Fig. 1), there are a number of target ionic mechanisms that can be influenced by various pharmacological agents to prevent ECC and induce arrest of the heart. This influence can essentially be divided into two main

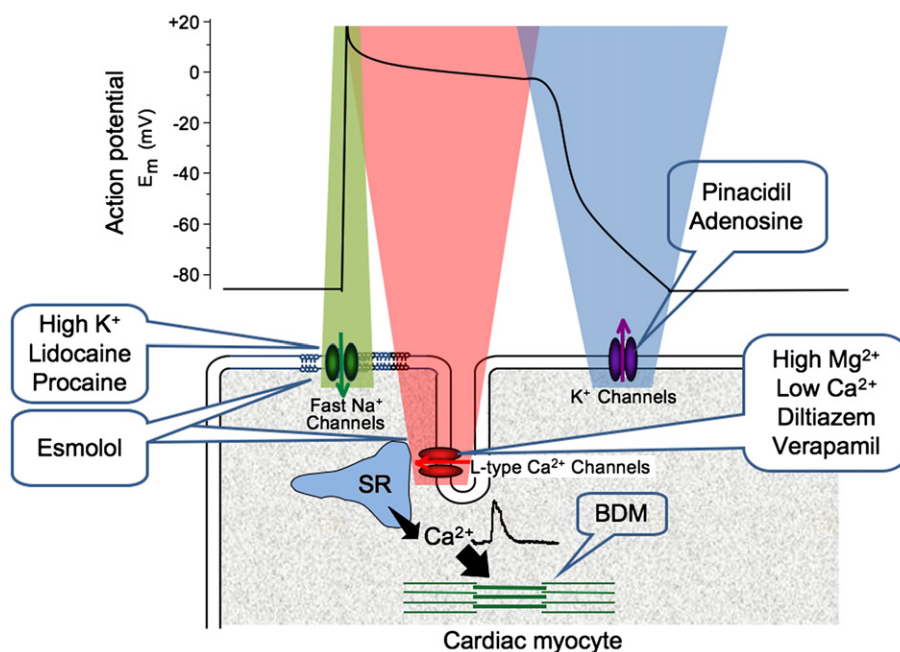


Fig. 1. The cellular targets for cardioplegic arrest and their influence on the action potential with examples of pharmacological agents.

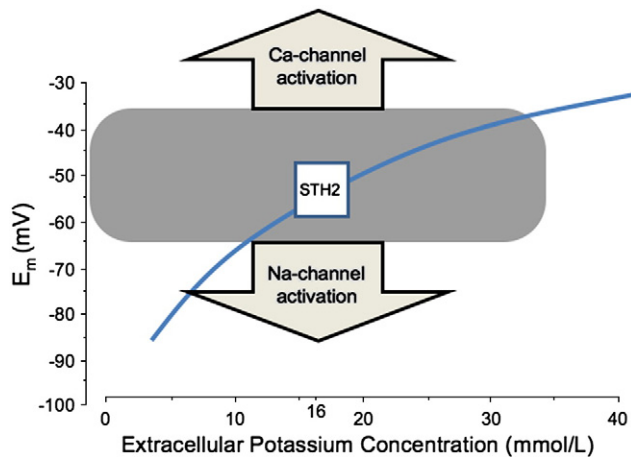


Fig. 2. The relationship between extracellular potassium concentration (mmol/L) and the membrane potential (mV). St. Thomas' Hospital cardioplegia No. 2 (STH2) has a potassium concentration (16 mmol/L) that sits midway between the Na-channel inactivation threshold (around -65 mV) and the L-type calcium channel activation threshold (around -35 mV).

categories. Firstly, agents that target the fast sodium channels can be used to inhibit activity of these channels and prevent the initiation of the action potential. This can be achieved either by: (i) shifting the resting E_m away from the sodium channel activation threshold such that there is (a) an induction of depolarization (ie. to a more positive E_m) by extracellular hyperkalemia (eg. St. Thomas' Hospital cardioplegia) or (b) an induction of hyperpolarization/polarization (ie. at or close to resting E_m) by potassium channel openers (eg. pinacidil and adenosine), or (ii) direct blockade of fast sodium channel activation by induction of polarization (ie. close to resting E_m) by sodium channel blockers (eg. tetrodotoxin (TTX), lidocaine, procaine and esmolol). Secondly, agents that cause an inhibition of calcium-activated mechanisms (to prevent myocyte contraction) are achieved by: (i) hypocalcemia (eg. zero extracellular calcium in Bretschneider solution (Bretschneider et al., 1975)), (ii) direct blockade of sarcolemmal calcium channels (eg. calcium channel blockers—high magnesium, diltiazem, verapamil and esmolol) and (iii) direct myofilament inhibition (eg. calcium desensitization—2,3 butanedione monoxime (BDM)). In addition, it is possible to inhibit multiple cellular targets (which would have the effect of preventing both action potential conduction and myocyte contraction), achieved by direct blockade of sodium and calcium channels (eg. esmolol).

4. Inhibition of the fast sodium channels

4.1. Shifting resting E_m away from sodium activation threshold

4.1.1. Extracellular hyperkalemia (depolarized arrest)

An increase in extracellular potassium will result in depolarization of the normal resting membrane potential (of around -85 mV), and establish a new resting level at a value that is more positive (less negative) and dependent on the extracellular potassium concentration (Fig. 2). Important threshold values are: (i) when the extracellular potassium concentration is ~ 10 mmol/L (equivalent to a membrane potential of approximately -65 mV) the voltage-dependent sodium channel is inactivated, preventing the rapid sodium-induced spike of the action potential initiating diastolic arrest and (ii) at an extracellular potassium level of ~ 30 mmol/L (a membrane potential of around -35 mV) the calcium channel is activated with associated calcium uptake into the myocyte. This has the potential for calcium overload and subsequent ischemia–reperfusion injury (Opie, 2004). Thus, there is a relatively narrow safety range of extracellular potassium concentrations that should be used for hyperkalemic cardioplegic solutions (Fig. 2). Of note, the potassium concentrations used in the St. Thomas' Hospital cardioplegic solutions Nos. 1 and 2 (20 and 16 mmol/L, respectively) fall in the middle of this range (Fig. 2). However, at the membrane potentials induced by this range of potassium concentrations, cellular ionic currents are maintained that can lead to adverse effects. This is best explained by visualizing the activity of the ion channels as being controlled by 'gates'; these 'gates' are either in an activated or inactivated state, depending on the voltage within the action potential. However, the differential activity rates of the 'gates' that control the activation and inactivation of channels (Sperelakis et al., 2001) result in non-inactivating currents ("window" currents) that remain active at these depolarized potentials (McAllister et al., 1975; Attwell et al., 1979), and allow increases in sodium and calcium (Fig. 3) that will contribute to abnormal myocardial cell ionic gradients. In addition, a "persistent" sodium current that is active at membrane potentials of around -50 mV may also contribute to these abnormal sodium gradients in the myocardial cell (Saint, 2006). Attempts to correct these gradients by energy-dependent transmembrane pumps will deplete critical energy compounds (Sternbergh et al., 1989; Hiraoka, 2006), and this in turn may contribute to a reduced myocardial recovery.

Thus, although hyperkalemic cardioplegic solutions remain the most popular and widely used procedure for inducing rapid myocardial arrest, they may not provide optimal cardioprotection. Other agents that induce arrest by alternative means may be beneficial and avoid the adverse effects of hyperkalemia. In patients

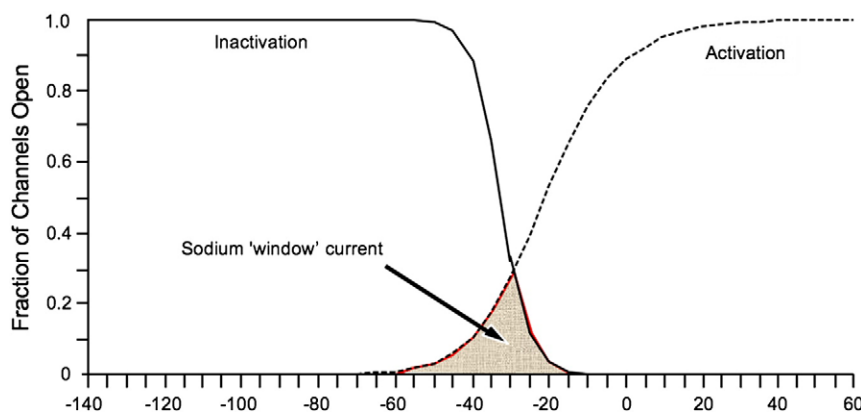


Fig. 3. The sodium 'window' current occurs at membrane potentials between -60 mV and -20 mV. The differential activity rates of the channel 'gates' at these potentials cause non-inactivating 'window' currents. (Modified from McAllister et al., 1975).

currently requiring cardiac surgery, who are older, sicker and who have more severe and diffuse disease, improved myocardial protection is likely to be of significance. An important characteristic of an effective cardioplegic solution is a good systemic safety profile, with minimal adverse effects during acute (or even chronic) reperfusion. Hyperkalemic solutions fulfil these characteristics; they are relatively safe, with little post-operative systemic toxic effects and with rapid cardiac reversibility. Key criteria to take into consideration with regard to developing alternative cardioplegic solutions, and the mechanism of action of their constituent agents, are:

1. Arrest: a rapid diastolic arrest is required to keep the myocardium relaxed and to minimize cellular use of high-energy phosphate compounds (ATP and phosphocreatine).
2. Myocardial protection: should delay the onset of irreversible injury caused by global ischemia and limit the extent of reperfusion injury.
3. Reversibility: arrest should be readily and rapidly reversible on washout for quick resumption of heart function, to enable early weaning off cardiopulmonary bypass.
4. Low toxicity: the cardioplegic agent should have no toxic effects on the heart or other organs after cessation of cardiopulmonary bypass. This is especially important if high concentrations of the pharmacological agent are required to achieve arrest.

Hyperkalemic cardioplegia meets all these criteria, which explains its current monopoly of use in cardiac surgery. Any future alternative cardioplegic solution would be expected to offer a similar safety profile for arrest, reversibility and low toxicity, but with improved myocardial protection.

An alternative to inducing depolarized arrest by hyperkalemia is to induce a hyperpolarized or polarized arrest. This can be achieved by using specific agents that target the cellular components indicated in Fig. 1 to induce arrest at membrane potentials closer to the normal 'resting' membrane potential. A number of benefits should ensue: these include a reduced ionic imbalance leading to reduced energy utilization, and hence improved protection from a cellular perspective.

4.1.2. Hyperpolarization/polarization (potassium channel openers)

The adenosine triphosphate-sensitive potassium channel (K_{ATP} -channel) appears to have a role as a 'metabolic sensor', linking cytosolic energy metabolism to membrane electrical activity in response to stress such as ischemia–reperfusion (Opie, 2004; Jahangir & Terzic, 2005), shortening the action potential and reducing intracellular calcium influx. Opening of K_{ATP} -channels allows an increased potassium flux through the sarcolemma that will act to shift E_m towards the potassium equilibrium potential (E_K), which is normally around -90 mV in myocytes (Opie, 2004). This will induce a more negative E_m (hyperpolarization) and act to keep E_m away from the activation threshold of the fast sodium channel (I_{Na}). High (millimolar) concentrations of K_{ATP} -channel opening drugs can induce arrest by maintaining hyperpolarization. K_{ATP} -channel openers are also potent vasodilators, inducing hyperpolarization on vascular smooth muscle cells (Quast et al., 1994), with some evidence that a 'hyperpolarizing' cardioplegia protects endothelial function compared to a hyperkalemic 'depolarizing' cardioplegia (He & Yang, 1997). Studies from Damiano's group (Maskal et al., 1995; Lawton et al., 1996a; Jayawant et al., 1997), using a variety of K_{ATP} -channel openers (aprikalim, pinacidil and nicorandil) to induce a hyperpolarized arrest, have demonstrated either improved or equivalent myocardial protection to that of hyperkalemic depolarized arrest. However, these studies are not without controversy; we (Walgama et al., 2000a; Walgama et al., 2000b) showed that pinacidil was unable to induce complete arrest during aerobic perfusion, even at very high concentrations (1 mmol/L) over extended periods (30 mins). In addition, E_m measurements indicated that pinacidil alone did not maintain E_m below the sodium channel activation threshold during

ischemia (ie. no hyperpolarization), and required the addition of a sodium channel blocker (procaine, at 1 mmol/L) for complete arrest and improved protection. These drugs also increase the risk of significant post-ischemic arrhythmias (Lawton et al., 1996b); furthermore, the systemic clearance of potassium channel openers is prolonged (Ward et al., 1984) which risks a residual hypotensive effect in patients post-bypass. These limitations make the concept of using a cardioplegia based on K_{ATP} -channel openers as unlikely for future clinical application.

K_{ATP} -channel openers may, however, have a role as an additive protective agent by enhancing the cardioprotection of hyperkalemic cardioplegic solutions. Short pretreatment (at least 3 min) with these drugs before hyperkalemic arrest was shown to improve post-ischemic function (Sugimoto et al., 1994; Dorman et al., 1998; Hebbar et al., 1998), possibly via a preconditioning mechanism (Menasche et al., 1996). Similar improvements were obtained when potassium channel openers were used as additives to hyperkalemic cardioplegic solutions (Hosoda et al., 1994; Qiu et al., 1995; Dorman et al., 1997), but these studies remain controversial since others (Galinaes et al., 1992; Ducko et al., 2000) have been unable to show any benefit. Supplementing hyperkalemic solutions with K_{ATP} -channel openers was shown to prevent increases in intracellular calcium seen with hyperkalemic solutions alone (Lopez et al., 1996; Dorman et al., 1997), which may account for any beneficial effects observed. Such benefits may also be associated with the location of the K_{ATP} -channels; improved protection has been observed with mitochondrial-specific K_{ATP} -channel openers such as diazoxide (McCully & Levitsky, 2003).

Using isolated rabbit sino-atrial (SA) node cells, adenosine (an endogenous purine nucleoside) was shown to induce complete arrest (at 50 μ mol/L) and a hyperpolarization of ~ 12 mV via increased membrane potassium permeability (Belardinelli et al., 1988). It appears to act via an adenosine receptor-activated potassium channel and hence could have similar effects to K_{ATP} -channel openers. This cardioplegic property has been extended to whole hearts, with adenosine used either as an arrest agent (albeit at a high concentration of 10 mmol/L) or as an additive (at 1 mmol/L) to hyperkalemic solutions (Schubert et al., 1989; de Jong et al., 1990; Boehm et al., 1991); addition of adenosine reduced the time to arrest and improved post-ischemic recovery of function compared to hyperkalemic cardioplegia alone. As an additive to hyperkalemic solutions (16 mmol/L potassium), adenosine (1 mmol/L) did not influence the level of depolarization induced by potassium, but did slow the rate of depolarization which reduced the associated intracellular calcium loading (Aleksiev et al., 1996). Additionally, it was shown that 1 mmol/L adenosine (but not 0.1 mmol/L) prevented potassium-induced intracellular calcium loading and that this was associated with a PKC-dependent mechanism but not a K_{ATP} -channel dependent mechanism (Jovanovic et al., 1997). Supplementing St. Thomas' Hospital cardioplegia with adenosine (at concentrations ranging from 0.1 to 20 mmol/L) enhanced protection and increased myocardial content of high-energy phosphates and metabolites at the end of ischemia (Katayama et al., 1997). Interestingly, these effects were temperature-dependent, with hypothermia reducing the benefit; this would limit its usefulness clinically in this context.

Clinical studies using adenosine as an adjunct to hyperkalemic cardioplegic solutions have had equivocal results. Adenosine (at concentrations ranging from 1 to 250 μ mol/L) added to warm antegrade blood cardioplegia was well tolerated up to 25 μ mol/L, but higher concentrations induced hypotension (Fremes et al., 1996). In further studies, adding adenosine (at 15, 50 or 100 μ mol/L) to warm antegrade blood cardioplegia showed no benefit to patient outcome in terms of mortality, function or infarction (Cohen et al., 1998). However, a similar study with adenosine added to cold blood cardioplegia (at higher concentrations of 0.5 or 2.0 mmol/L) showed a tendency to reduce adverse events (Mentzer et al., 1999). The clinical studies leave many unanswered questions regarding the efficacy of

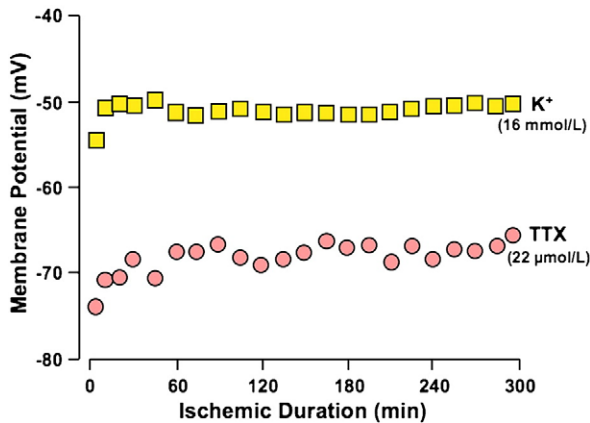


Fig. 4. Myocardial cell membrane potential (E_m), measured by sharp microelectrode, in isolated rat hearts arrested by TTX or K^+ throughout 5 h of cold (7.5°C) storage. [Modified from Snabaitis et al., 1997].

adenosine as an additive to blood cardioplegia; the short half-life of adenosine (~ 30 s) may play a role in these effects, and suggest that it may be more effective when used as a continuous infusion to maintain its effect. Adenosine has been shown to be safe, both experimentally and clinically; its short-acting effect and low potency (requiring relatively high concentrations) is likely to make it more appropriate as an additive to other arresting agents to improve cardioprotection than a cardioplegic agent per se.

4.2. Direct blockade of sodium channel activation (sodium channel blockers)

Direct sodium channel blockade is an effective way to prevent the voltage-activated fast inward sodium-induced depolarization of the action potential (Miller, 1998). Tetrodotoxin (TTX) is a potent and selective blocker of the sodium channel; however, it is also highly toxic (Narahashi, 2008) and has consequently only been used experimentally. TTX binds to sodium channel receptors near the extracellular surface and, as such, can be easily reversible. In experimental studies, TTX has been shown to act as an effective cardioplegic agent, inducing rapid arrest and protecting isolated rat hearts against 60 min of normothermic global ischemia (Tyers et al., 1974). It has been suggested to induce a polarized arrest of the heart, and at a concentration of $25\ \mu\text{mol/L}$ reduced basal metabolic requirements (MVO_2) during ischemic arrest compared to hyperkalemic (depolarized) arrest (Sternbergh et al., 1989). Studies from the authors' laboratory, in which TTX (at an optimally defined concentration of $22\ \mu\text{mol/L}$) was used to induce arrest of isolated working rat hearts subjected to long-term (5–8 h) hypothermic (7.5°C) global ischemic storage, demonstrated significant improvement in protection compared to hyperkalemic ($16\ \text{mmol/L}\ K^+$) arrest (Snabaitis et al., 1997). These studies demonstrated improved post-ischemic function, established that polarized arrest did occur (sharp microelectrode measurements throughout ischemia demonstrated a maintained membrane potential during arrest of around $-70\ \text{mV}$ (Fig. 4)) and confirmed the reduced metabolic requirements by showing that myocardial content of high-energy phosphate compounds (ATP and phosphocreatine) at the end of ischemia were significantly higher in the TTX-arrested hearts. In addition, we showed that polarized arrest reduced the ionic imbalance seen with depolarized (hyperkalemic) arrest (indirectly measured as a reduced efflux of K^+ during ischemia) (Snabaitis et al., 1999). Moreover, the importance of Na^+ and Ca^{2+} overload in the development of myocardial injury was shown (Snabaitis & Chambers, 1999) by the sequential addition to the TTX (polarizing) solution of drugs that induced Na/H exchange inhibition (HOE694), $\text{Na}/\text{K}/2\text{Cl}$ -cotransport inhibition (furosemide) and calcium

desensitization (2,3-butanedione monoxime: BDM) to induce additive protective effects on post-ischemic recovery of function when compared to the St. Thomas' Hospital cardioplegic solution (Fig. 5). Thus, these studies confirmed the concept of polarized arrest as an effective mechanism to induce arrest and improve myocardial protection, but the high toxicity of TTX means that it would be clinically unusable as a cardioplegic agent.

Agents with local anesthetic effects (such as procaine and lidocaine) are, however, available clinically and indeed have been widely used either alone or in combination with other agents to induce cardiac arrest (Hearse et al., 1981a). In contrast to TTX, however, they bind to receptors close to the intracellular end of the channel (Miller, 1998; Narahashi, 2008) giving more prolonged activity with less rapid reversibility. Procaine, used at high (~ 7 – $11\ \text{mmol/L}$) concentrations as a cardioprotective agent, was used in various early cardioplegic solutions developed in Germany, such as the Bretschneider and Kirsch solutions (Kirsch et al., 1972; Bretschneider et al., 1975). However, later systematic characterization of both procaine and lidocaine at various concentrations demonstrated significant detrimental effects when used at high (1 – $20\ \text{mmol/L}$) concentrations (Hearse et al., 1981b). The original St. Thomas' Hospital cardioplegic solution No. 1 includes procaine (at $1\ \text{mmol/L}$) as a membrane stabilizer, but it was removed from the No. 2 solution to enable its use in the USA (procaine is not authorized by the FDA). Although procaine has been demonstrated to control rhythm disturbances post-operatively (Sellevold et al., 1995), this anti-arrhythmic drug may induce cardiac arrhythmia and neurological toxicity due to its narrow safety margin (Brown et al., 1995).

Lidocaine is widely used clinically as a local anesthetic and anti-arrhythmic agent; its mechanism of action is via sodium channel blockade and, as such, would also appear to be a potentially useful cardioplegic agent. Recent studies (Dobson & Jones, 2004) have shown that a combination of $500\ \mu\text{mol/L}$ lidocaine and $200\ \mu\text{mol/L}$ adenosine (AL solution) induces a more rapid arrest (suggested to be a 'polarized' arrest by an estimated calculation of the membrane potential) with improved cardioprotection in rat hearts subjected to prolonged (2 or 4 h) global ischemia compared to a hyperkalemic depolarizing (St. Thomas' Hospital) solution. The calculated membrane potential in these adenosine–lidocaine arrested hearts was

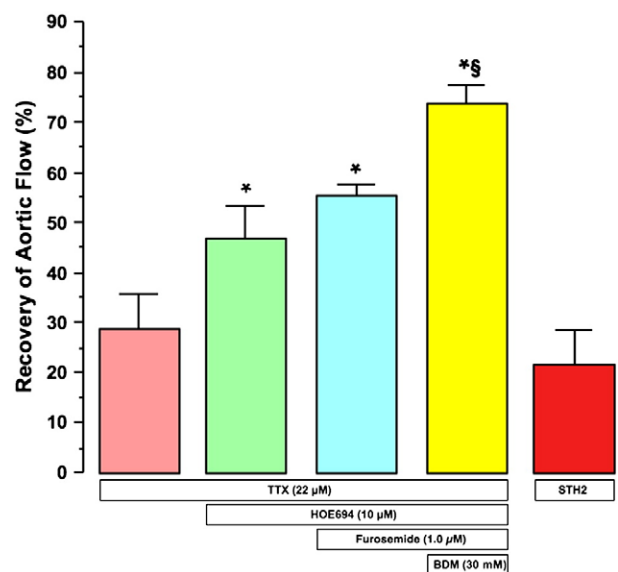


Fig. 5. The synergistic effect of sequential addition to TTX of a Na/H exchange inhibitor (HOE694), a $\text{Na}/\text{K}/2\text{Cl}$ -cotransport inhibitor (furosemide) and a calcium desensitizer (BDM) on cardioprotection (recovery of aortic flow) compared to St. Thomas' Hospital cardioplegia (STH). [Modified from Snabaitis & Chambers 1991].

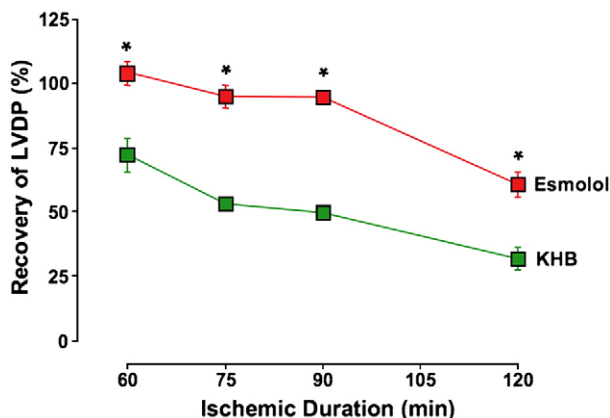


Fig. 6. Effect of multidose esmolol arrest on recovery of LVDP after prolonged normothermic (37 °C) ischemia compared with multidose Krebs Henseleit buffer (KHB). * $p < 0.05$ versus equivalent ischemic duration. [Modified from (Bessho & Chambers, 2002)].

–83 mV, a value similar to that obtained for the resting membrane potential in normal pre-arrest hearts (Kleber, 1983). However, we (Snabaitis et al., 1997) showed that the membrane potential in isolated rat hearts arrested with TTX, measured by sharp electrodes throughout the ischemic period, was maintained at around –70 mV. This would suggest that the calculated values (above) are unlikely, and that some degree of depolarization will be induced during the global ischemia, probably arising from the efflux of potassium from the myocytes. Additional studies from this group (Sloots et al., 2007) and also in rat hearts, showed no differences in myocardial protection between continuous or intermittent AL solution after 40 or 60 min of global tepid (33 °C) ischemia; interestingly, intermittent lidocaine alone was less protective than the AL solution, with increased time to arrest, increased coronary vascular resistance and reduced recovery of function. This would suggest that adenosine, even at the low concentration of 200 $\mu\text{mol/L}$, has a significant additive protective capability. In a more clinically relevant study from the same group (Corvera et al., 2005), it was shown that multidose arrest with a blood-based adenosine–lidocaine (AL-BCP) solution in dogs subjected to cardiopulmonary bypass and global cold (10 °C) or warm (37 °C) ischemia induced similar protection to that of a corresponding blood-based hyperkalemic (20 mmol/L) solution. Interestingly, this AL solution was formulated with higher adenosine (400 $\mu\text{mol/L}$) and lidocaine (750 $\mu\text{mol/L}$) concentrations to that of the original rat study (Dobson & Jones, 2004); despite this, complete arrest was not achieved with cold (10 °C) AL-BCP in all hearts, and quiescence was not maintained. This may indicate a temperature sensitivity of the solution (possibly due to the lidocaine) and suggest that the solution may be more suitable for tepid or warm ischemic arrest.

Whilst a lidocaine-based cardioplegic solution may appear to be a logical option as an alternative to hyperkalemic cardioplegia, with potential for improved cardioprotection, experimental studies have questioned the safety of high concentrations of this drug (despite its clinical use as a local anesthetic and anti-arrhythmic agent, with known side-effects and safety profiles). When used as a blood-based solution, a lidocaine concentration of 1.3 mmol/L (in combination with 5.5 mmol/L magnesium) was shown (Yamaguchi et al., 2007) to be required for effective arrest of dog hearts; efficacy of this solution was equivalent to hyperkalemic cardioplegia. However, systemic concentrations of lidocaine were as high as 20 $\mu\text{g/ml}$ (which is significantly higher than the upper safety margin of ~8 $\mu\text{g/ml}$; this ‘safe’ level was not reached until 60–80 min after initial infusion). This was the first study to examine toxic effects of high doses of a sodium channel blocker when used as a cardioplegic agent (Fallouh & Chambers, 2007). Even using lower concentrations of lidocaine may still have potential risks if large doses of cardioplegia were required in

prolonged procedures, or in patients with liver or renal impairment or heart failure where the half-life of lidocaine (normally about 2 h) could become significantly longer (Thomson et al., 1973). The risk of lidocaine accumulation in the peripheral circulation could cause problems after weaning off cardiopulmonary bypass.

5. Inhibition of calcium-activated mechanisms

The rise in intracellular calcium concentration during each heartbeat (the calcium transient) is a fundamental part of excitation–contraction coupling. Influencing this increase can have profound effects on the heart; reduction (or abolition) of the calcium transient will prevent mechanical contraction and induce a diastolic arrest. Hence, this can be an effective way to induce cardiac arrest; however, caution should be exercised when inhibiting calcium mechanisms as considerable injury can be induced under certain circumstances.

5.1. Hypocalcemia

The complete removal of calcium from an extracellular bathing or perfusion solution of heart muscle effectively prevents calcium influx through the L-type calcium channels and inhibits CICR from the SR, so abolishing excitation–contraction coupling of the myofilaments (Rich et al., 1988; Bers, 2002) and arresting the heart in diastole (Ringer, 1883). However, perfusion of hearts with extracellular solutions containing zero calcium risks induces the ‘calcium paradox’ (Chapman & Tunstall, 1987); this reduction of the calcium driving force leads to calcium efflux and sodium loading via the Na/Ca exchanger during the calcium-free period, which is then replaced by excessive calcium loading when subsequently perfused with calcium-containing solutions, leading to a lethal condition of contracture and massive ultrastructural injury. Despite this, a number of cardioplegic solutions have used zero calcium in their composition. The Bretschneider intracellular-type solution (Bretschneider et al., 1975) contained nominally zero calcium but was combined with low sodium (12 mmol/L) and procaine (7.4 mmol/L); low sodium (and/or high magnesium) will tend to protect against the calcium paradox (Jynge, 1980), as will the conventional hypothermic use of this solution. In reality, there are also often trace contaminants of calcium sufficient to prevent this injury. The low extracellular sodium attenuates the fast sodium current (via the cardiac sodium channel) at the initiation of the action potential; this will tend to maintain membrane potential close to the resting membrane potential, thereby favouring a polarized arrest. Studies comparing the St. Thomas’ Hospital solution (normocalcemic and hyperkalemic) to the Bretschneider solution (Jynge et al., 1977, 1978) demonstrated optimal protection with St. Thomas’ solution at all temperatures; in contrast, Bretschneider solution was only protective at hypothermia. The University of Wisconsin (UW) intracellular-type organ preservation solution (Swanson et al., 1988) is another zero calcium solution; however, for protection of the heart, it has been shown to be infusion- and storage temperature-sensitive (Amrani et al., 1992) with improved protection when calcium and/or magnesium is added (Fremes et al., 1995).

The stoichiometry between calcium and sodium are inextricably linked to the sodium–calcium exchanger; both these ions need to be reduced to ensure relatively safe myocardial protection, but this relationship is extremely complex. As a safer alternative, it may be preferable to use drugs that influence calcium movements.

5.2. Direct blockade of sarcolemmal calcium channels (calcium channel blockers)

Blocking the L-type calcium channel causes a decrease in calcium influx and results in an inhibition of CICR from the SR, which

depresses cardiac function. This can be achieved in a number of ways. Elevated extracellular concentrations of magnesium can induce myocardial arrest (Shattock et al., 1987), and is thought to occur because magnesium acts as a 'natural' L-type calcium channel blocker via displacement of calcium (Iseri & French, 1984). However, these effects are species-dependent; rat myocardium is very sensitive whereas rabbit myocardium is relatively insensitive, possibly reflecting differential sensitivity of the calcium channel to magnesium (Shattock et al., 1987). Effects on human myocardium are thought to be intermediate to rat and rabbit. Hence, magnesium could act as a cardioplegic agent, although it is less effective than potassium and requires higher extracellular concentrations to induce arrest (Hearse et al., 1981a). In fact, magnesium has previously been used as a cardioplegic agent (such as in the Kirsch solution (Kirsch et al., 1972), which had a magnesium concentration of 160 mmol/L, but also a high (11 mmol/L) concentration of the sodium channel blocker procaine). Recently, we (Maruyama and Chambers, 2008b) examined the protective effects of magnesium when used as a cardioplegic agent in a novel perfusion solution (Aqix®). Magnesium was shown to be effective at an optimal concentration of 25 mmol/L, and to provide improved protection (compared to St. Thomas' Hospital solution) when given as multiple infusions, but was less efficacious when used as a single infusion before prolonged ischemia. Despite this evidence for efficacy of magnesium alone as a cardioplegic agent, it is more likely to be used for its anti-ischemic effects as an additive to other cardioplegic solutions.

When used as an additive to hyperkalemic cardioplegia, increased extracellular magnesium (of 10–20 mmol/L) has been shown to protect against calcium overload during ischemia and reperfusion (Hearse et al., 1978; Brown et al., 1991). This improved protection has also been shown in aged hearts (McCully and Levitsky, 1997) and in immature hearts (Kronon et al., 1999). In this context, magnesium is thought to exert its anti-ischemic protective effect by influencing the high-energy phosphate content of the myocardium, resulting in improved ATP availability and reduced ATP utilization (Brown et al., 1991; Tsukube et al., 1997). These metabolic effects are associated with reduced intracellular calcium accumulation (Steenbergen et al., 1990) which is linked to the calcium channel antagonistic effects of magnesium (Iseri & French, 1984; Shattock et al., 1987). Thus, magnesium appears to be a relatively safe additive for cardioplegic solutions, with considerable protective effects associated with an elevated extracellular concentration (Chakraborti et al., 2002).

Drugs have been developed that specifically target the L-type calcium channel and act as antagonists (blockers) of this channel (Fleckenstein & Fleckenstein-Grun, 1988). At high concentrations, these calcium antagonists (calcium channel blockers such as verapamil, diltiazem and nifedipine) can act as cardioplegic agents per se and induce arrest of the heart (Vouhe et al., 1980; Balderman et al., 1992), with comparable protective effects to those of hyperkalemic cardioplegia. However, these agents generally have prolonged negative inotropic effects (such as verapamil with a half-life of >2 h (Popovic et al., 2006)) due to high affinity for the L-type calcium channels (Dillon & Nayler, 1987), and result in a slower recovery (reversibility) than that seen with hyperkalemia. Whilst this may be beneficial, with reduced washout from collateral flow and the potential for reducing calcium overload during reperfusion, the probable prolonged exacerbation of acute stunning leading to low output (Christakis et al., 1986; Breisblatt et al., 1990) would not be acceptable for cardiac surgery patients.

Calcium channel blockers have also been used as additives to hyperkalemic cardioplegic solutions (de Jong, 1986). However, they have been shown to be temperature-sensitive, being unable to provide additional protection under hypothermic conditions (Yamamoto et al., 1985), and shown to be potentially detrimental in patients with severe dysfunction (Christakis et al., 1986). Thus, although calcium channel blockers are known to be cardioprotective during

ischemia, any beneficial effects are likely to be outweighed by the detrimental effects related to dose-dependent, temperature-dependent and time-dependent activities. Consequently, calcium channel blockers could not be recommended for clinical use in cardioplegia.

5.3. Direct myofilament inhibition (calcium desensitization)

An alternative to influencing effects of calcium at the sarcolemmal level via the calcium channel is to inhibit the direct intracellular effect of calcium on contraction of the myofilaments. This can be induced by 2,3-butanedione monoxime (BDM), which causes a myofibril desensitization by inhibiting the force-producing cross-bridge formation between actin and myosin (Gwathmey et al., 1991). BDM, originally developed as an antidote to sarin poisoning, has apparent 'chemical phosphatase' activity. It is a small and uncharged lipophilic molecule and can readily exchange with the intracellular milieu, which makes its effects rapidly reversible; as such, it would appear to be potentially suitable as a cardioplegic agent, and it has been examined in this role in a number of experimental studies. BDM-based cardioplegia (using 30 mmol/L BDM) was compared to Bretschneider's HTK solution in porcine and human heart muscle strips (Vahl et al., 1994; Vahl et al., 1995). It was shown that BDM abolished force development despite maintenance of the calcium transient (to a level of around 60% of control), and complete recovery of function was obtained after ischemic periods of up to 4-fold longer for BDM-based cardioplegia compared to HTK solution. In isolated rabbit hearts, a cardioplegia with 5 mmol/L BDM as the arresting agent produced a similar cardioprotection (after 60 min of global ischemia) to that of the hyperkalemic St. Thomas' cardioplegia, despite maintained electrical activity for around 34 min (Jayawant et al., 1999). Despite these promising experimental results, there have been no clinical studies using BDM as a cardioplegic agent (to our knowledge).

BDM has also been investigated for its efficacy as a protective additive to hyperkalemic cardioplegic or long-term preservation solutions. Using BDM (at 30 mmol/L) as an additive to the UW preservation solution (Stringham et al., 1992) resulted in significantly improved outcome of isolated rabbit hearts stored for 24 h (particularly when calcium was also added) compared to hearts stored in standard UW solution. The addition of BDM prevented contracture formation and reduced high-energy phosphate consumption. Similar studies, investigating the optimal temperature for the UW preservation solution in rat hearts over a 12 hour period (Zhang et al., 1997), showed that addition of 10 mmol/L BDM significantly enhanced protection for the temperature range 0–8 °C. These additional protective effects were also seen in isolated porcine myocytes subjected to hyperkalemia (24 mmol/L potassium) when 30 mmol/L BDM was included over the 2 hour storage period; myocytes had complete recovery compared to significantly reduced recovery in the absence of BDM (Dorman et al., 1996). We (Snabaitis & Chambers, 1999) have also shown similar synergistic cardioprotective effects with BDM (30 mmol/L) when included in a 'polarized' arrest solution (using TTX to induce arrest via sodium channel blockade). Isolated working rat hearts were subjected to 8 h storage; significant additional improvement in recovery was observed when BDM was included compared to the St. Thomas' Hospital cardioplegic solution. In this study, we (Snabaitis & Chambers, 1999) also confirmed a calcium-chelating effect of BDM previously seen by others (Garcia-Dorado et al., 1992); titration of the calcium back to the normal ionic concentrations maintained the protective effect of BDM, indicating that the additional protective effect of BDM was not associated with the hypocalcemia. It is of interest that, although BDM would appear to have considerable cardioprotective properties, it has not (to our knowledge) been used in any clinical solution. This is surprising and may relate to its potential toxic effects (possibly associated with the calcium chelation); however, only temporary neurological effects

have been noted (Zhang et al., 1997), and it should be remembered that it was developed for use in humans as an antidote to poisoning.

6. Inhibition of multiple cellular targets

Although induction of arrest can be achieved by inhibition of each of the cellular ionic mechanisms illustrated in Fig. 1, it is possible that inhibition of multiple targets may act synergistically to improve protection. Alternatively, it might be that lower concentrations of an arresting agent would be needed; this should improve the safety profile of the cardioplegic agents, reduce systemic toxicity during reperfusion and improve the rate of reversibility of the agent(s). One example of this relates to our recent studies concerning the use of esmolol as an arrest agent.

6.1. Direct blockade of both sodium and calcium channels (eg. esmolol)

Esmolol is an ultra-short-acting cardioselective β_1 -blocker (Gorzynski, 1985) that is used clinically for treating hypertension and tachycardia. It has also been shown to be cardioprotective against ischemia and reperfusion in unstable angina patients (Hohnloser et al., 1991) and during cardiac surgery (Boldt et al., 2004). These properties have been exploited in both experimental (Mehlhorn et al., 1996; Geissler et al., 2000; Booth et al., 2002) and clinical (Kuhn-Regnier et al., 1999; Mehlhorn et al., 1999; Kuhn-Regnier et al., 2002) studies. Clinically, it has been used during cardiac surgery as a means of inducing 'minimal myocardial contraction' (profound bradycardia during maintained continuous normothermic myocardial perfusion, thereby avoiding ischemia) to allow coronary artery bypass surgery on the beating heart. These studies also showed that cardioprotection with esmolol compared favourably to conventional cardioplegic solutions; improved protection was suggested to result partly from a reduction in myocardial edema formation associated with the continued perfusion and bradycardia.

In experimental studies, we (Bessho & Chambers, 2001, 2002), and others (Ede et al., 1997), have demonstrated that high concentrations (about 1 mmol/L) of esmolol induce a diastolic cardiac arrest and thus act as a cardioplegic agent. When added to an oxygenated perfusate, esmolol provided superior cardioprotection (improved recovery of function) to isolated rat hearts when compared to cross-clamp fibrillation (Bessho & Chambers, 2001) or St. Thomas' Hospital cardioplegic solution (Bessho & Chambers, 2002) after prolonged periods (up to 2 h) of global normothermic ischemia (Fig. 6). Whilst the β -blocking action of esmolol explains the bradycardia, negative inotropic effect and its induction of arrest (in an isolated heart with no catecholamine background) requires an alternative explanation for this action, especially as it contrasts other β -blockers (such as atenolol) that do not induce a negative inotropy or arrest at equipotent doses. Recent studies have shown that millimolar concentrations of esmolol inhibit the L-type calcium channels (Arlock et al., 2005; Fallouh et al., 2007) and the fast sodium channels (Deng et al., 2006; Fallouh et al., 2008), resulting in a pronounced negative inotropy, prevention of action potential conduction and induction of a diastolic polarized arrest. The short half-life of esmolol (of about 9 min) that results from blood red cell esterase activity (Zaroslinski et al., 1982) gives it independence from renal or hepatic clearance from the systemic circulation, with associated safety profile advantage over some of the other cardioplegic agents described (such as lidocaine, diltiazem, etc). Clinically, the use of relatively high concentrations of esmolol during cardiac surgery (Zaroslinski et al., 1982; Kuhn-Regnier et al., 1999; Mehlhorn et al., 1999; Kuhn-Regnier et al., 2002) has demonstrated its safety. However, prolonged infusion periods in excess of 20 min with esmolol concentrations of around 1.5 mmol/L have suggested that the reversibility may be compromised (Pirk et al., 1999); concentrations of ~0.75 mmol/L were optimal for reversibility which casts some doubt on the clinical potential of these higher

esmolol concentrations as cardioplegic agents per se. Recently, we (Chambers et al., 2009) have shown that a combination of adenosine (at a low concentration of 250 μ mol/L) and esmolol (at the reduced concentration of 600 μ mol/L) still induces arrest, and significantly improved protection against prolonged ischemia (with multiple infusions) compared to St. Thomas' Hospital cardioplegia being observed. This combination might offer the basis of a clinically relevant polarizing cardioplegia.

7. Additional protective strategies: the potential of endogenous mechanisms

Endogenous cardioprotective strategies, termed 'preconditioning' and 'postconditioning', may have a role in cardiac surgery to provide additional protection. Details of both these strategies have been the subject of many recent reviews (Vaage & Valen, 2003; Downey et al., 2007; Ferdinandy et al., 2007; Vinten-Johansen et al., 2007; Venugopal et al., 2009). The elective nature of cardiac surgery, with the known onset of ischemia and reperfusion, lends it to the potential of these strategies. Ischemic preconditioning involves one or more brief episodes of ischemia followed by reperfusion prior to a prolonged ischemia (Murry et al., 1986) and induces a complex cascade of intracellular signalling mechanisms (Downey et al., 2007) that protects the myocardium from the potentially lethal prolonged ischemic duration. Similarly, various pharmacological agents can also induce these mechanisms (Downey et al., 2007). However, the benefit of preconditioning during cardiac surgery is controversial, particularly in the context of cardioplegia (Venugopal et al., 2009). In addition, cardiopulmonary bypass per se (Burns et al., 1995), as well as volatile anesthetics used during surgery (Venugopal et al., 2009), have been implicated in the induction of preconditioning protection, which might account for the lack of additional benefit observed. Recently, remote preconditioning (involving preconditioning another organ to remotely benefit the heart (Przyklenk et al., 1993)) may offer potential in the clinical arena (Kharbanda et al., 2002). The use of limb ischemia to activate hormonal and/or neural stimulation (Hausenloy & Yellon, 2008; Venugopal et al., 2009) may be particularly relevant; however, large-scale randomized clinical trials will be needed to confirm the potential of this interesting technique.

The phenomenon of postconditioning, whereby multiple short episodes of reperfusion and ischemia at the start of reperfusion improves protection, is also a recent development (Vinten-Johansen, 2007) that could be particularly applicable to cardiac surgery. Recent clinical studies (Luo et al., 2008) have demonstrated benefit in patients undergoing cardiac surgery, but we (Maruyama & Chambers, 2008a) were unable to demonstrate efficacy after cardioplegic protection. Thus, whilst these additional protective strategies remain interesting, there are many unanswered questions relating to loss of effect with ageing or patient morbidity (Boengler et al., 2009; Downey & Cohen, 2009), and whether experimental studies in 'healthy' hearts are relevant (Downey and Cohen, 2009).

8. Conclusion

Since the beginning of cardiac surgery in the early 1950s, it has been recognized that protection of the heart was a fundamental requirement to counteract the imposed elective global ischemia used by the surgeon to provide optimal operating conditions. It took about 25 years to develop a consensus method; this was based around a moderate increase in extracellular potassium, and these hyperkalemic cardioplegic solutions provided good myocardial protection, which was relatively safe and easily and rapidly reversible. This technique induces a depolarized arrest, and has been the cornerstone of cardiac protection (albeit with a number of minor alterations—crystalloid or blood solutions, hypothermic or warm, with or without various additives) for over 30 years. However, during this time, the

characteristics of patients who currently undergo cardiac surgery compared to those receiving operations 20–30 years ago, have changed considerably; patients are significantly older and have more severe and diffuse disease, as well as the increasing strategy of operating on high-risk patients with heart failure or acute coronary syndrome. The requirement for optimal, or improved, myocardial protection has never been greater, but this is unlikely to be achieved with current hyperkalemic solutions. New concepts relating to myocardial protection may provide these improvements; these concepts need further examination and investigation to challenge the traditional view that hyperkalemic arrest is best.

There are many agents that can potentially induce cardiac arrest by targeting various components of the excitation–contraction coupling mechanism. However, it is important to ensure that the selected agents have comparable safety profiles to that of hyperkalemia. The concept of polarized arrest has some potential beneficial advantages over hyperkalemia, and recent studies, highlighting a number of agents that can induce polarized arrest, are now being recognized as demonstrating some of these advantages. Not all will be suitable for clinical application, and it is important to continue innovative research studies in this area of myocardial protection. In particular, it is essential to prove clinical efficacy to match experimental promise.

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