Remote ischaemic conditioning and ischaemic heart disease

As clinical evidence builds regarding the efficacy of remote ischaemic conditioning's ability to attenuate myocardial injury arising from acute coronary syndromes and cardiac surgery, this article describes the conditioning phenomenon, current clinical evidence and how ischaemic conditioning may be used in future clinical practice.

Introduction

Despite the undeniably significant improvements in prevention and management of acute coronary syndromes over the last two decades, ischaemic heart disease nonetheless remains a leading cause of mortality and morbidity in the western world, and worryingly it is becoming an ever-more prevalent problem the developing nations (Murray and Lopez, 1997). Optimizing medical care of patients presenting with acute coronary syndromes or undergoing coronary artery bypass surgery therefore remains as prescient today as it ever has.

Emergency management of acute myocardial infarction involves the rapid restoration of blood flow through the occluded 'culprit' epicardial coronary artery: myocardial cell death, or necrosis, progresses rapidly with the persistence of myocardial ischaemia, leading to the oft-repeated mantra that 'time is muscle'. The great paradox of myocardial reperfusion is the phenomena of 'lethal reperfusion injury': the rapid re-introduction of oxygenated blood to formerly ischaemic tissue leads to intracellular free-radical generation, calcium overload and restoration of intracellular pH, a particularly lethal combination of conditions leading to myocardial necrosis which is estimated to contribute up to 50% of the final infarct size (Yellon and Hausenloy, 2007).

Lethal reperfusion injury

Lethal reperfusion injury is thought to be primarily mediated through the disruption of mitochondria. Loss of mitochondria and high-energy phosphates might in itself be bad enough for the viability of the injured cell, but failure of mitochondrial volume homeostasis leads to membrane disruption and release of constituents that initiate cell death (apoptotic) signalling cascades. These frequently progress to necrosis under the pathophysiological conditions of injurious ischaemia and reperfusion (for review see Bell and Yellon (2011)).

In current medical practice, little is done to modify the progression of lethal reperfusion injury, but this area could be at the cusp of change with the emergence of various cardioprotective regimens, and particularly a phenomenon known as remote ischaemic conditioning.

Ischaemic conditioning

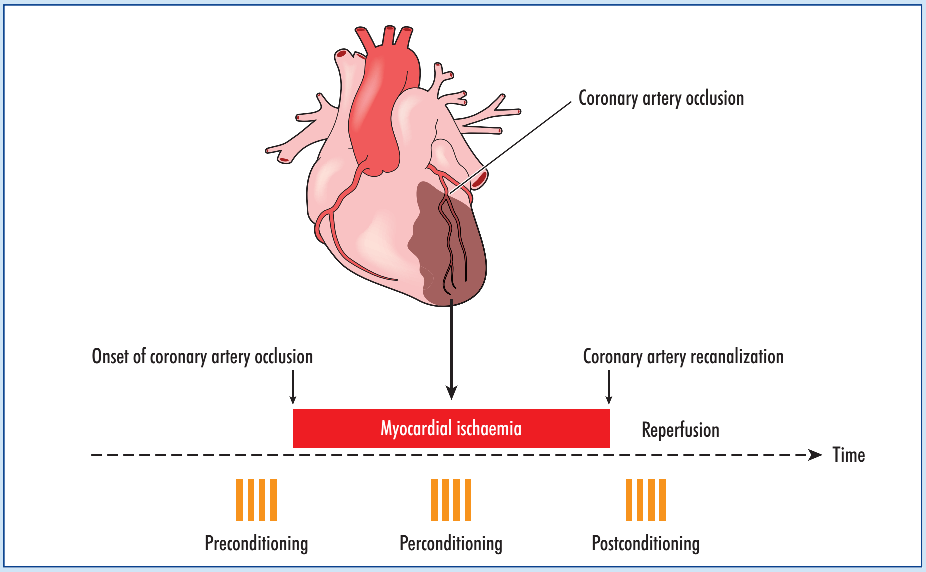
Ischaemic conditioning has been on a 'slow burn' from translation from laboratory bench to the clinical bedside, from powerful experimental phenomena to a practical clinical intervention. First described in dogs in 1986 (Murry et al, 1986), and found in every mammalian species since studied, ischaemic conditioning is an extremely complex phenomenon.

Conditioning requires a sufficient ischaemic stimulus to be protective – which can vary depending on individual patient factors such as age or the presence of comorbidities such as diabetes or hypertension (reviewed in Ferdinandy et al (2007)). Moreover, the time course of protection is finite and occurs in two phases: an immediate phase of protection that lasts 2–3 hours, and then a later, delayed phase of protection that starts 12–24 hours after the conditioning stimulus and then persists for a further 72 hours (Bell et al, 2007).

Getting these factors right is instrumental for extracting the maximum benefit from ischaemic conditioning, but the key for widespread clinical applicability is an easy method of administration that avoids direct invasive instrumentation of the heart (or other organ system being studied).

There are three forms of ischaemic conditioning, named according to the timing of the ischaemic treatment intervention relative to the onset and recovery from the injurious ischaemic insult: preconditioning, perconditioning and postconditioning (*Figure 1*).

Figure 1. Schema of ischaemic conditioning. Occlusion of coronary flow results in the onset of ischaemia within the territory of myocardium served by the occluded vessel until the blood flow is restored and the myocardium is reperfused. The extent of myocardial injury can be limited by ischaemic conditioning. Cycles of transient, non-injurious ischaemia followed by reperfusion can be applied either directly to the heart or remotely, before the onset of injurious ischaemia (preconditioning), during the time of injurious ischaemia (perconditioning) or after the onset of reperfusion (postconditioning).



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Ischaemic preconditioning – whereby pre-emptive, short periods of ischaemia, induced by transient coronary artery occlusion and reperfusion, lead to significant attenuation of myocardial infarction following an injurious ischaemic insult – has been extensively studied and demonstrated to attenuate myocardial injury in the context of coronary artery bypass surgery (Thielmann et al, 2013).

The self-evident limitation of preconditioning is that it is a pre-emptive cardioprotective intervention: it simply is not practical to administer preconditioning for innately unpredictable acute coronary syndrome presentations because injurious ischaemia is invariably well established by the time of clinical presentation to medical professionals. However, as has been already alluded to, preconditioning is not the only ischaemic conditioning regimen available in the arsenal against lethal reperfusion injury: perhaps surprisingly, cycles of short reperfusion and ischaemia administered during the early reperfusion phase after injurious ischaemia also significantly ameliorate myocardial necrosis.

So-called ischaemic postconditioning, like ischaemic preconditioning, is effective in humans: clinical trials where the angio-plasty balloon was re-inflated periodically following the restoration of coronary flow have shown significant improvements in terms of myocardial salvage determined by a variety of different outcome measures (reviewed by Zhou et al (2012)).

Perhaps the main barrier to widespread adoption of ischaemic conditioning has been the invasiveness of the technique required to trigger the protection: the heart itself has to be subjected to further ischaemia over and above that of the presenting ischaemic injury in order to realize protection. Not only is this contrary to the clinician's instinctive desire to reduce the heart's ischaemic burden as far as possible, but the methods used to occlude the coronary vasculature may themselves have undesirable effects, not least the potential for embolization of atheromatous material into the distal microvasculature. Unsurprisingly therefore, much interest has centred on targeted pharmacological interventions as an alternative to ischaemic conditioning to attenuate reperfusion injury. The interested reader is encouraged to read a number of reviews on this approach to myocardial protection (Cour et al, 2011).

Remote ischaemic conditioning

The conditioning protocols discussed above can be grouped as 'direct' ischaemic conditioning methodologies – making the heart transiently ischaemic to protect the heart. However, this is not the sole approach available to the clinician to imbue protection against lethal reperfusion injury: conditioning one vascular bed, tissue or organ remarkably results in the protection of another organ distant to the intervention site – a phenomenon termed 'remote' ischaemic conditioning, or conditioning at a distance.

First identified by Przyklenk et al (1993), who noted that ischaemic conditioning of one coronary territory led to protection in another, unconnected vascular territory within the heart, it has subsequently been shown that inflation of a simple blood pressure cuff on a limb (typically over three or four cycles and for 5 minutes at a time; Kharbanda et al, 2002) can result in significant myocardial protection against lethal ischaemia and reperfusion injury (for review, see Hausenloy and Yellon (2008)).

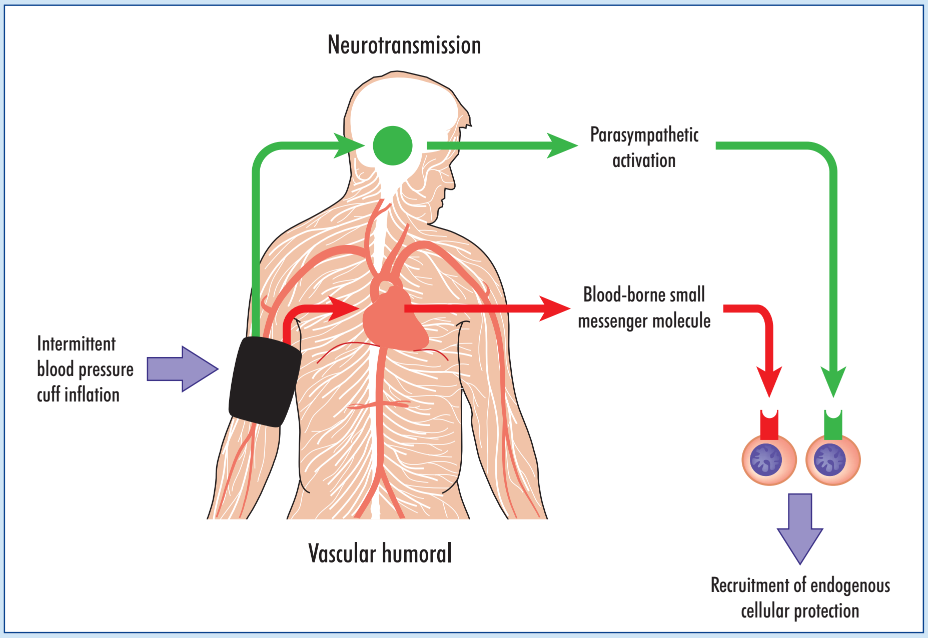
In fact, the protection elicited by remote ischaemic conditioning is not restricted to the heart – protection can also be shown in lung, kidney, liver and brain (Hausenloy and Yellon, 2008). It appears that all organ systems are interconnected, and an insult to one leads to resistance to injury in all.

The mechanism underlying this protection currently remain elusive, but two, potentially complimentary hypotheses are proposed (*Figure 2*):

1. A small-molecule humoral factor (<30 kDa) is released into the blood stream and is then able to recruit endogenous cytoprotective signalling in the distal organ (Breivik et al, 2011)
2. A neural pathway, likely via the parasympathetic nervous system, leads to protection through acetylcholine receptor activation and consequent induction of cytoprotective signalling (Mastitskaya et al, 2012).

Identifying the precise nature of the remote ischaemic conditioning pathway is clearly important (*Figure 3* summarizes the proposed cardioprotective mechanisms), but while the basic science is worked out, clinical experience has been accumulating with a technique that appears safe, cheap and practical, requiring only an individual

Figure 2. The proposed model of remote ischaemic conditioning. Administration of periods of upper limb ischaemia through inflation of a blood pressure cuff to 200 mmHg leads to the release of either a vascular humoral signalling molecule or the activation through neural transmission of the parasympathetic nervous system. Downstream of this is the activation of cell-surface receptors on the target organ, which when activated leads to the activation of endogenous cellular protection – likely through the activation of the kinases Akt and ERK and downstream inhibition of the mitochondrial permeability pore.



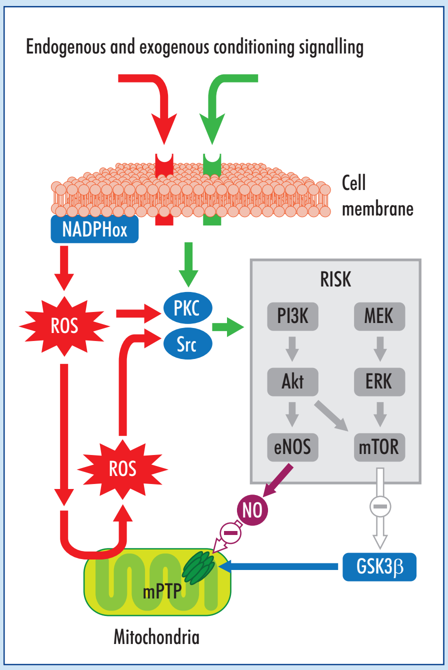
trained to inflate a blood pressure cuff to 200 mmHg for the prerequisite period of time and number of cycles.

Clinical efficacy of remote ischaemic conditioning

Remote ischaemic conditioning offers a number of potential advantages over other forms of ischaemic conditioning, an important one being the flexibility of the timing of its application. The remote ischaemic conditioning stimulus can be applied either before (preconditioning) or during (perconditioning) the injurious ischaemic insult, or immediately upon its resolution (postconditioning) (*Figure 1*).

Preconditioning is ideal for when the onset of myocardial injury is predictable – such as in cardiac surgery or elective percutaneous coronary intervention, whereas perconditioning and postconditioning lend themselves to emergency situations where myocardial ischaemia has already started at the time of clinical presentation.

Figure 3. Simplified diagram of the current model of cardioprotective conditioning signalling. Ischaemic conditioning results in the mobilization of signalling molecules, such as adenosine (from ATP breakdown), bradykinin, opioids; from neuronal signalling, such as acetylcholine, or a so-far unidentified humoral small molecule implicated in remote ischaemic conditioning. These occupy cell surface receptors and lead to activation of downstream signalling that current dogma suggests converge to inhibit the mitochondrial permeability transition pore (mPTP) to prevent disastrous mitochondrial injury and induction of cellular death pathways.



Remote preconditioning and cardiac surgery

The first demonstration of the efficacy of remote ischaemic conditioning was for on-pump (cardiopulmonary bypass) congenital cardiac surgery in children (Cheung et al, 2006), a result soon repeated in adult on-pump coronary artery bypass surgery (Hausenloy et al, 2007). These and other proof-of-concept trials have shown consistent reduction of myocardial injury end points, such as attenuated release of cardiac enzymes and other surrogate clinical end points (D'Ascenzo et al, 2012; Hausenloy et al, 2012a). The data in support of remote ischaemic conditioning against off-pump cardiac surgical procedures are less clear, in part because of the potentially smaller ischaemic or reperfusion injury that this technique may enjoy (Hong et al, 2010). Nonetheless, the clinical data have so far been extremely encouraging, but as yet there is insufficient evidence to yield significant change to clinical practice. This will require the demonstration of improvement in the clinically relevant end points of morbidity and mortality.

Tantalisingly a recent study by Thielmann et al (2013) (*n*=329 enrolled) revealed not only a significant diminution of cardiac troponin-I (cTnI) release following coronary artery bypass as its primary end point, but also a significant benefit in attenuating the rate of all-cause mortality at 1 year. Therefore there is cause for cautious optimism that the two larger, phase 3 trials, RIPHeart (*n*=2070; NCT01406678) (Meybohm et al, 2012) and ERICCA (coronary artery bypass±valve; *n*=1610; NCT01247545)(Hausenloy et al, 2012b), currently recruiting and powered to determine the critical and clinically important end points of morbidity and mortality, are likely to show important and practice-changing results. The outcomes of these two important studies should be known within the next 18 months.

Remote ischaemic conditioning in primary percutaneous intervention

The landmark, proof-of-concept trial of remote ischaemic conditioning in acute ST elevation myocardial infarction was undertaken in Denmark, with the conditioning regimen undertaken in the ambulance on the way to the primary percutaneous intervention centre (Bøtker et al, 2010). The primary outcome was myocardial salvage determined by myocardial perfusion imaging as the proportion of the area at risk salvaged by treatment, which in the treatment arm of the study was significantly improved by 30%.

These findings, demonstrating limitation of myocardial injury by remote ischaemic conditioning, have subsequently been repeated in further small scale studies (reviewed by Schmidt et al (2012)), using pre-, per- and postconditioning. As with remote ischaemic conditioning in cardiac surgery, larger clinical trials are mandated to show improvements of clinical outcomes. The first of these, the 'Effect of Remote Ischaemic Conditioning on Clinical Outcomes in STEMI Patients Undergoing Primary PCI' (CONDI2, *n*=2300; NCT01857414), was due to start recruiting in September 2013 but has not yet begun recruitment.

Remote conditioning and elective percutaneous intervention

Invasive coronary interventions have the potential to induce peri-procedural (type 4a) myocardial infarction. This myocardial injury, mediated by coronary occlusion through inflation of an intra-coronary balloon and stent deployment, is potentially amenable to amelioration by remote ischaemic preconditioning regimen.

A body of evidence is now accumulating to demonstrate the efficacy of remote ischaemic preconditioning to reduce myocardial cellular death and enzyme release (Hoole et al, 2009; Ahmed et al, 2013; Luo et al, 2013), an attenuation of injury that appears to translate into a long-term benefit against major adverse cardiovascular events (Davies et al, 2013). However, as found in all the paradigms of cardioprotection, the presence of comorbidity impacts upon the efficacy of the conditioning modality (Xu et al, 2013), and perhaps a more robust remote ischaemic conditioning intervention, with four rather than three ischaemia and reperfusion cycles, may be required to trigger the protection required in the general cardiovascular patient cohort.

Conclusions

Clinical trial data so far have been encouraging with the use of remote ischaemic conditioning in ischaemic heart disease. While outside the scope of this article, the ability of remote ischaemic conditioning to protect other organ systems may be of great benefit in dealing with potential complications of angiography, percutaneous intervention and cardiac surgery in other organ systems. Amelioration of acute kidney injury in both arenas is one such example (Venugopal et al, 2010; Er et al, 2012), and thus the anticipated cardioprotective benefit of remote ischaemic conditioning is an amalgam of protection in multiple organ systems.

At present, remote ischaemic conditioning is at an important and exciting threshold: with results of potentially definitive clinical outcome trials pending, we may yet see a future where the humble blood pressure cuff undergoes a transformation from simple haemodynamic monitoring technique to a powerful, multi-organ protective intervention in the settings of both coronary artery bypass and valvular surgery and elective and emergent percutaneous intervention. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Although great progress has been made in recent years in the management of ischaemic heart disease, there are still further advances to be made in the management of those presenting with acute coronary syndrome or for those undergoing coronary artery bypass surgery.
- Rapid revascularization of the ischaemic myocardium remains paramount, but it carries the penalty of 'lethal reperfusion injury' that may contribute up to 50% of the final infarct size.
- Ischaemic conditioning is a powerful phenomenon that recruits endogenous cardioprotective signalling to attenuate ischaemia and reperfusion injury.
- Remote ischaemic conditioning can condition the heart, and other organs from a distance, to reduce cell death resulting from injurious ischaemia and reperfusion.
- Large, multicentre, double blind, randomized control trials are currently recruiting, the results of which could lead to widespread application of remote ischaemic conditioning in the next 2 years.