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Cardiac Postconditioning: An Additional Therapy to Limit Cell Death Following Myocardial Infarction

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1. Introduction

1.1 The concept of lethal reperfusion injury

Following acute myocardial infarction (AMI), early reperfusion therapy with thrombolytic therapy or primary percutaneous coronary intervention therapy (PCI) is the best way to salvage the heart by limiting the infarct size and preserving the left ventricular function. The early survival benefits of reperfusion are probably sustained lifelong and after 20 years, the survival rate of 27% in patients treated with conventional therapy is increased to 37% in patients treated with reperfusion therapy (thrombolytics and/or PCI) (van Domburg *et al.* 2005).

However, the benefits of reperfusion come at a price as restoration of the blood flow in the coronary arteries can paradoxically cause myocardial injury. Lethal reperfusion injury manifests itself clinically as stunned myocardium, arrhythmias and endothelial damage (Yellon and Hausenloy 2007). Although still unclear, the mechanisms behind reperfusion injury involve multiple processes including an increase in oxidative stress (Bolli *et al.* 1989), inflammatory damage (Vinten-Johansen 2004), a change in myocyte osmolarity (Garcia-Dorado and Oliveras 1993), calcium loading (Dong *et al.* 2006, Murphy *et al.* 1987) and a change in pH (figure 1) (Inserte *et al.* 2011).

The rapid return of blood in the ischemic myocardium generates an oxidative stress which itself can mediate myocardial injury (Zweier 1988). The release of reactive oxygen species consecutive to the oxidative stress may generate a degree of myocardial injury superior to ischemia alone, partly due to the reduced bioavailability of the potent vasodilator nitric oxide in the vasculature (Zweier and Talukder 2006). The oxidative stress also contributes to the excessive increase of intracellular calcium inducing cardiomyocyte death by hypercontracture and inadequate opening of the mitochondrial permeability transition pore (mPTP) opening (Piper *et al.* 1998). The opening of this pore leads to uncoupled oxidative phosphorylation , depletion of adenosine triphosphate (ATP) and death (Hausenloy and Yellon 2003). Myocardial ischemia causes a progressive decrease in intra- and extra-cellular pH (Inserte *et al.* 2011). At the onset of reperfusion, the removal of extracellular protons and the correction of intracellular acidosis exerts an adverse effect due, in part, to the intracellular sodium and calcium overload (Piper *et al.* 1996). An upregulation of cell

adhesion molecules during the first hours of reperfusion leads to the accumulation of neutrophils in the infarcted area, causing vascular plugging and the release of more reactive oxygen species (Vinten-Johansen 2004).

According to animal studies, lethal reperfusion injury may represent between 20% and 70% of the total amount of the irreversible myocardial damage, therefore constituting a major therapeutic target. In this regard, the experimental discovery of ischemic pre- and postconditioning (Zhao *et al.* 2003) represents a promising therapy to limit lethal reperfusion injury.

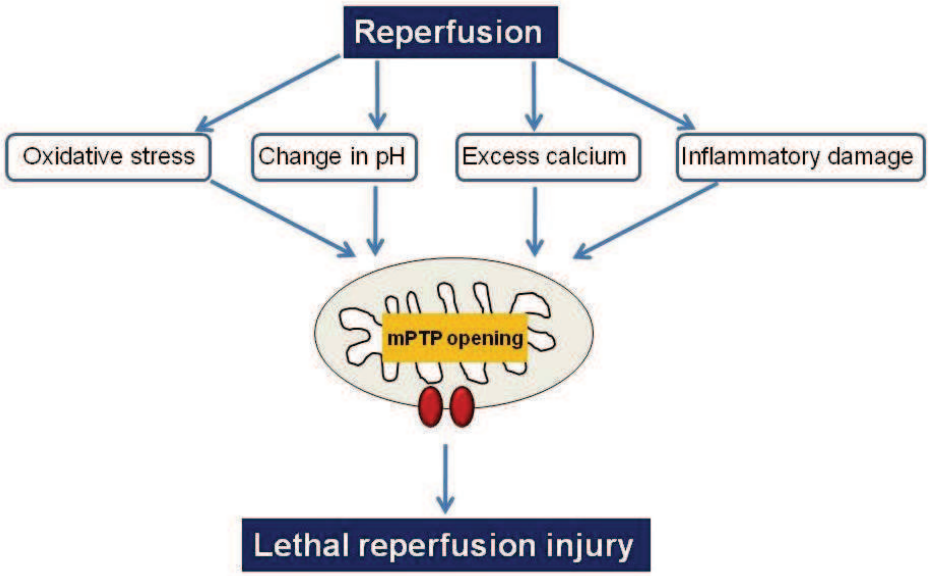

Fig. 1. The concept of lethal reperfusion injury

At the onset of reperfusion, an oxidative stress, a rapid increase in pH, an excess of intra- and extracellular calcium and an inflammatory process facilitate the opening of the mitochondrial permeability transition pore, leading to lethal reperfusion injury.

2. Ischemic preconditioning

2.1 Genesis of an intrinsic cardioprotective solution

In 1986, Murry et al. published a seminal paper describing a phenomenon whereby four cycles of five minutes of coronary artery occlusions with intermittent reperfusion prior to a prolonged 40 minutes occlusion, attenuated infarct size to 25% in the canine myocardium (Reimer *et al.* 1986). Initially, they found that brief periods of ischemia reduced the rate of ATP depletion during subsequent ischemic episodes. Intermittent reperfusion also served to prevent the cumulative effects of ischemic injury by washing out potentially harmful catabolites such as lactate, hydrogen ions (H^+) and ammonia (NH_4). The reduction in ATP depletion was associated with the limitation in infarct size. Given these findings and that

the procedure could be reproduced successfully, this cardioprotective phenomenon was termed 'ischemic preconditioning' (IPC) (Murry *et al.* 1986).

This model of cardioprotection is referred to as 'classic' or early preconditioning and is short-lived, with the preconditioned state lasting for only 1-4 hours (figure 2) (Murry *et al.* 1991). However, within 24 hours of the preconditioning stimulus, a late phase of protection, known as delayed preconditioning or the second window of protection, is evident but is less robust and more prolonged, lasting up to 72 hours after the preconditioning stimulus (Baxter *et al.* 1997). Classic IPC exerts its protective effects via the modification of existing proteins. In contrast, delayed preconditioning allows for the *de novo* synthesis of cytoprotective proteins (Bolli *et al.* 2007). Another distinction between the two phases is that although classic IPC limits infarct size, it does not protect against postischemic myocardial contractile dysfunction or stunning. Conversely, late IPC reduces myocardial cell death and preserves left ventricular function (Bolli *et al.* 2007). These disparities suggest that late IPC would provide greater clinical benefits in terms of greater and longer lasting protection.

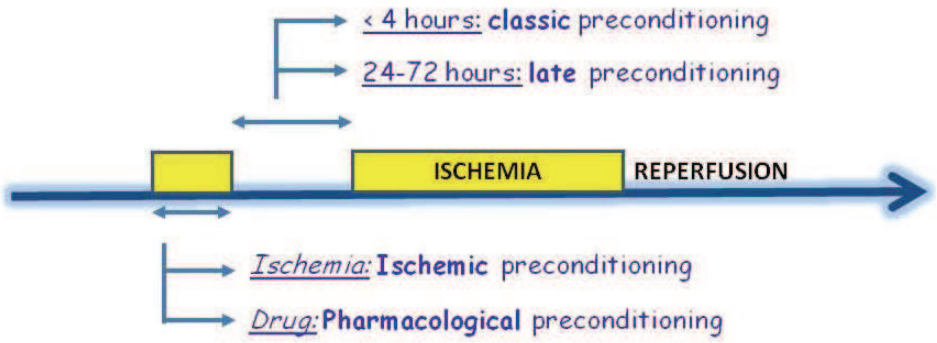

Fig. 2. Schematic representation of classic and delayed postconditioning

2.2 Remote preconditioning

Further research into the development of IPC yielded the discovery that remote ischemia distant to the heart can elicit a similar cardioprotective response as IPC of the local coronary artery. Four brief occlusions of the circumflex branches lasting 5 minutes and interspersed by 5 minutes of reperfusion had a remote infarct reducing effect on the ischemic canine myocardium supplied by the left anterior descending artery (Przyklenk *et al.* 1993). This protective effect was termed remote preconditioning. Subsequent studies have shown that ischemic bursts could be successfully applied to organs such as the intestine (Gho *et al.* 1996), skeletal muscle (Addison *et al.* 2003) and kidney (Pell *et al.* 1998) and as a result, precondition the myocardium.

2.3 Clinical relevance

Although preconditioning is not applicable for patients with AMI, it may serve to alleviate the high risk of myocardial infarction in patients with unstable angina. Furthermore, preconditioning strategies can be applied prior to coronary artery bypass graft (CABG)

surgery to prevent a potentially injurious ischemia insult. A proof-of concept study supporting remote preconditioning of the upper limb in adult patients prior to elective CABG showed significantly reduced serum troponin-T levels (Hausenloy *et al.* 2007). The cardiac remote ischemic preconditioning (CRISP) study implemented remote preconditioning (induced by three 5-minute inflations of a blood pressure to 200 mmHg in the upper arm and followed by three 5-minute reperfusion intervals) before elective PCI in a randomized control trial (Hoole *et al.* 2009). Subject who received the remote IPC had reduced cardiac troponin I release, suffered from less chest pain and ECG ST-segment deviation. In addition, there was a reported improvement in the major adverse cardiac and cerebral event (MACCE) rate. The beneficial use of remote IPC has also been successfully translated to children with congential defects undergoing a cardiopulmonary bypass (Cheung *et al.* 2006).

3. Ischemic postconditioning: A promising therapy to limit reperfusion injury

Discovered in 2003, ischemic postconditioning, achieved by repetitive brief bouts of ischemia at the onset of reperfusion, protects against reperfusion injury and offers a clinical approach in patients with AMI (Zhao *et al.* 2003). Three episodes of 30 secs of reperfusion and 30 secs of ischemia, performed at the onset of reperfusion following a 60 min ischemic insult in dog hearts, protected against reperfusion injury (Zhao *et al.* 2003). Its infarct limiting effect is comparable to ischemic preconditioning and can reduce the infarct size by up to 80% (figure 3) (Zhao *et al.* 2003). Postconditioning has been successful in multiple animal species such as canines, rats, mice and rabbits (Zhao and Vinten-Johansen 2006). Ischemic pre- and postconditioning, used in combination, did not produce any significant benefit over the strategies used separately, which may suggest the activation of similar protective mechanisms by both phenomena (Halkos *et al.* 2004).

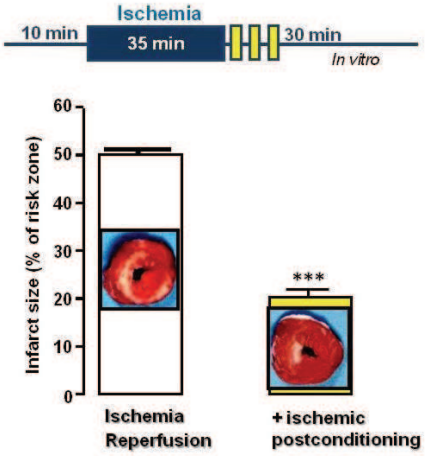

Fig. 3. Ischemic postconditioning decrease infarct size

In animal models subjected to an ischemia-reperfusion insult, ischemic postconditioning performed by short cycles of ischemia-reperfusion at the onset of reperfusion, dramatically reduces the infarct size (dead cells in white).

3.1 Ischemic postconditioning: A rapid translation from bench to bedside

Considering that postconditioning was only discovered in 2003, (Zhao *et al.* 2003) it is remarkable how quickly it made the leap to proof-of-concept clinical trials (figure 4). In 2005, Staat et al published a landmark study whereby postconditioning, applied during the first minutes of reperfusion to AMI patients undergoing emergency PCI, reduced myocardial damage measured through creatine kinase release over 72 hours (Staat *et al.* 2005). After reperfusion by direct stenting, postconditioning simply performed within the first minute of reperfusion by 4 cycles of 1 min inflation/deflation of the angioplasty balloon, reduced the infarct size by 36%. Using more specific endpoints, the same group later confirmed that their postconditioning protocol was associated with a reduction of the infarct size (measured by 201thallium single photon emission computed tomography technique after 6 months) and improved myocardial contractile function (measured by echocardiography) after 1 year (Thibault *et al.* 2008). At 1 year, their pilot study, performed on 38 patients only, showed a 7% increase in the left ventricular ejection fraction in the postconditioned patients (Thibault *et al.* 2008). Animal studies have shown that optimizing the postconditioning protocol is an important process for the success of the therapy (van Vuuren and Lochner 2008). Few human studies seem to confirm this statement. Postconditioning the human heart with three cycles of 30 sec inflation and 30 sec deflation of the angioplasty balloon, within the first 3 min of reperfusion, reduced the infarct size by 27% (Yang *et al.* 2007). In a retrospective analysis of patients undergoing primary angioplasty, the release of creatine kinase in patients who received 4 or more balloon inflations was lower than in patients who received between 1 and 3 balloon inflations (Darling *et al.* 2007).

When measuring the area at risk before reperfusion in patients undergoing primary PCI, the benefit of ischemic postconditioning performed with 4 cycles of 60s reperfusion and 60s reocclusion is not observed in the overall population with ST elevation myocardial infarction but seems to be of value for patients with large areas at risk. Hence, the regression analysis in which the final infarct size was related to the myocardial area at risk showed a significant difference between the control and postconditioning groups (Sorensson *et al.*).

With regards to long term benefit of ischemic postconditioning, a study of 43 patients suggested that the protective effect on cardiac function tends to persist beyond 3 years, but larger studies are needed to confirm its long term effect (Garcia *et al.* 2010).

The benefit of postconditioning can be extended to cardiac surgery. In patients undergoing a valve replacement under cold blood cardioplegic arrest, postconditioning (performed by 3 cycles of 30 sec ischemia and 30 sec reperfusion using aortic clamping) reduced the creatine kinase release, transcardiac neutrophil count and the use of inotropic agents during reperfusion (Luo *et al.* 2008).

Remote postconditioning, whereby the postconditioning protocol applied in one part of the body results in protection of a remote region undergoing ischemia-reperfusion, is successful in animal models (Andreka *et al.* 2007) and may represent a more practical way to protect the human heart than ischemic postconditioning. Recently, remote perconditioning was tested in Danish patients on their way to hospital to receive primary PCI (Botker *et al.*). Remote perconditioning was performed by 4 cycles of 5min inflation/deflation of the blood pressure cuff on the arm of 251 patients. 30 days after reperfusion, the myocardial salvage measured by SPECT imaging was increased by remote perconditioning.

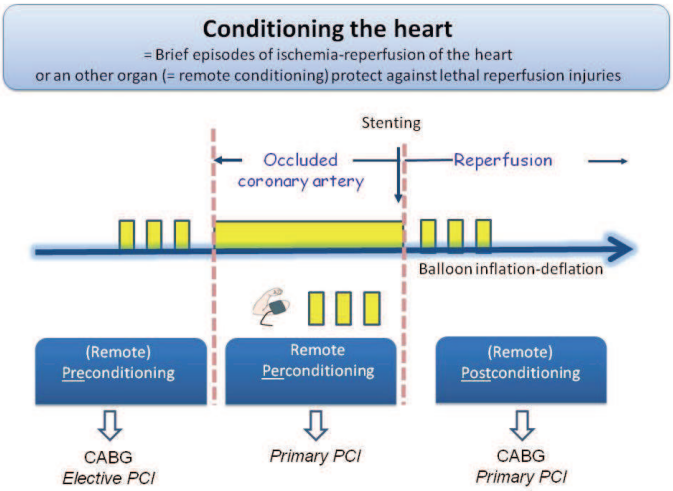

Fig. 4. The concept of conditioning the heart and its clinical applications

3.2 Mechanisms involved in ischemic postconditioning: RISK and SAFE pathways

Following the discovery of ischemic preconditioning in 1986 (Murry *et al.* 1986), intensive research was performed to elucidate the intrinsic prosurvival cascades that can be activated within the heart to limit reperfusion injuries. The delineation of the reperfusion injury salvage kinase (RISK) pathway proved to be a very powerful survival pathway to limit cell death at the onset of reperfusion. More recently, the delineation of another prosurvival signaling cascade termed as the survivor activating factor enhancement (SAFE) pathway and involving the activation of the immune system, offers new potential to limit further reperfusion injury.

3.2.1 RISK pathway

The actual term reperfusion injury salvage kinase (RISK) pathway was first coined in 2002, in a study investigating the signal transduction pathway underlying the infarct-limiting effects of urocortin administered at reperfusion (Schulman *et al.* 2002). Activation of this pathway involves two prosurvival kinases pathways: phosphatidylinositol-3 kinase (PI3K)/Akt and mitogen extraregulated kinase 1/2 (MEK1/2)-extraregulated kinase 1/2 (Erk1/2). Activation of both Erk1/2 and Akt at the onset of reperfusion is generally associated with a reduction of the infarct size and their inhibition with pharmacological agents is often associated with a loss of the infarct sparing effect of many cardioprotective drugs (Hausenloy *et al.* 2011).

In ischemic postconditioning, the RISK pathway is activated at the onset of reperfusion by cell surface receptors including G-protein coupled receptors, cytokine receptors, tyrosine kinase receptors and serine/threonine receptors (Hausenloy and Yellon 2009). Adenosine receptors (Morrison *et al.* 2007) and sphingosine kinase-1 receptors (Jin *et al.* 2008) activate the RISK pathway and it is probable that many other cell-surface implicated as triggers in

ischemic postconditoning, such as bradykinin and opioids receptors, also activate the RISK pathway but this remains to be demonstrated directly.

Activation of Akt and Erk1/2 leads to the activation of endothelial nitric oxide synthase (eNOS) and P70S6Kinase (Tsang *et al.* 2004). There are several other protein kinases that have been implicated in ischemic postconditioning signaling which could also be considered as components of the RISK pathway such as protein kinase C (PKC), protein kinase G, p38 mitogen-activated protein kinase (p38MAPK) and Jun N-terminal kinase MAPK.

3.2.2 mPTP and anti-apoptotic signaling pathways activated by the RISK pathway

There are a number of downstream effectors of the RISK pathway which could be responsible for the cardioprotection elicited by ischemic postconditioning. Many of these terminate on the mitochondria an organelle which occupies an essential role in cardiomyocyte survival and death signaling.

The opening of the mitochondrial permeability transition pore (mPTP) at the onset of myocardial reperfusion is a critical determinant of lethal myocardial reperfusion injury, such that pharmacologically inhibiting its opening at this time can reduce myocardial infarct size by 40-50% in both the laboratory (Argaud *et al.* 2005, Hausenloy *et al.* 2002) and clinical setting (Bolli *et al.* 2004). Although the actual identity of the pore-forming units of the mPTP is unknown, several studies have demonstrated mitochondrial cyclophilin-D (CypD) to be a major regulatory component of the mPTP, such that mice lacking CypD appear resistant to mPTP opening and sustain greatly reduced myocardial infarct sizes (Baines *et al.* 2005, Nakagawa *et al.* 2005). The actual mechanism through which the Akt and Erk1/2 components of the RISK pathway mediate mPTP inhibition is unclear, although potential explanations include: (1) the generation of nitric oxide by endothelial nitric oxide synthase (eNOS), a downstream target of the RISK pathway can inhibit mPTP opening (Kim *et al.* 2004); (2) Akt may modulate mitochondrial morphology thereby rendering mitochondria more resistant to mPTP opening (Ong *et al.* 2010); (3) Akt may modulate intracellular calcium handling- by increasing sarcoplasmic reticulum calcium uptake it may prevent mPTP opening (Abdallah *et al.* 2006); (4) Glycogen synthase kinase (GSK3β), a downstream target of both Akt and extracellular regulated kinase (Erk) 1/2 may act as a point of convergence for a variety of pro-survival signaling pathways resulting in mPTP inhibition (Juhaszova *et al.* 2004, Juhaszova *et al.* 2009).

The possibility of recruiting anti-apoptotic signaling pathways had been one of the original reasons for proposing the RISK pathway as a pro-survival signaling pathway, particularly given the close association of apoptotic cell death with the reperfusion phase (Yellon and Baxter 1999). Interestingly, although a large number of potential anti-apoptotic pathways exist downstream of the RISK pathway, relatively few have actually been investigated in the context of cardioprotection, yet alone ischemic postconditioning. These anti-apoptotic mechanisms include: the phosphorylation and inhibition of pro-apoptotic proteins such as BAD (Bcl-2 antagonist of cell death) (Jonassen *et al.* 2001), BAX (Bcl-2-associated X protein) and the activation of anti-apoptotic proteins such as PIM-1 kinase (Hausenloy and Yellon 2009), the effect of which is preservation of mitochondrial integrity and a favorable increase in the anti-apoptotic proteins such as BCL2 (B-cell lymphoma-2) and BCL-XL (B-cell lymphoma-xl).

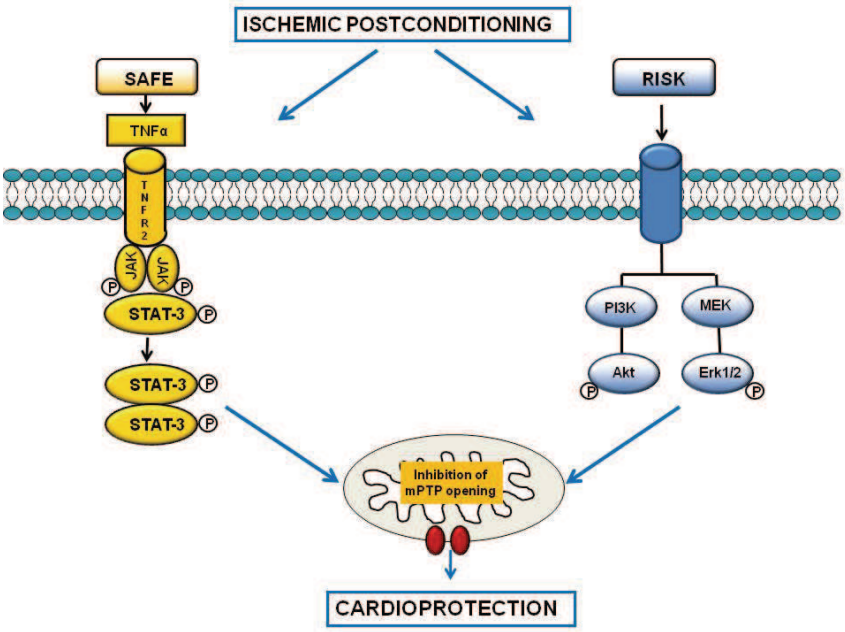

Fig. 5. Prosurvival pathways activated by postconditioning

Ischemic postconditioning activates two powerful prosurvival pathways termed as the SAFE and RISK paths. Both pathways reduce lethal reperfusion injury by limiting the opening of the mitochondrial permeability transition pore (mPTP). SAFE, Survivor Activation Factor Enhancement; TNFα, Tumour Necrosis Factor alpha; JAK, Janus Kinase; STAT-3, Signal Transducer and Activator of Transcription-3, RISK, Reperfusion Injury Salvage Kinase; PI3K, Phosphoinositol 3-Kinase; MEK, Mitogen activated protein kinase Extracellular regulated Kinase; ERK, Extracellular Regulated Kinase.

3.2.3 SAFE pathway

In animal studies, the involvement of the RISK pathway has sparked few inconsistencies, supporting the existence of an alternative prosurvival signal transduction pathway for protecting the ischemic myocardium against lethal reperfusion injury (Lecour 2009b). In this respect, our laboratory has recently described a novel pro-survival pathway, which involves the activation of tumor necrosis factor alpha (TNF) and the transcription factor, signal transducer and activator of transcription 3 (STAT-3), that we have termed as the Survivor Activating Factor Enhancement (SAFE) pathway (figure 5) (Lecour 2009a, b). The SAFE pathway was first discovered in the setting of ischemic preconditioning and its role in ischemic postconditioning has only been recently confirmed.

TNF, a proinflammatory cytokine expressed in all nucleated cell types including cardiomyocytes, exerts its major effects after binding onto its cell surface receptors TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2). The two TFNRs differ in their signal pathways with TNFR1 activating both apoptotic and protective signaling whereas TNFR2,

although poorly studied, seem to convey prosurvival signaling only (Schulz and Heusch 2009). In a dose and time-dependent manner and function to which type of receptor is activated, TNF can be either protective or deleterious. There are now a large number of experimental data supporting the evidence that ischemic postconditionng requires activation of low concentrations of TNF to confer cardioprotection via TNFR2 (Lecour 2009b). Activation of the receptors phosphorylates the janus kinase (JAK) protein, which in turn, can activate the transcription factor STAT-3. In 2006, the role of STAT-3 in ischemic postconditioning was also suggested in an isolated rat heart model whereby the addition of the JAK/STAT-3 inhibitor AG490 at the onset of reperfusion abolished the cardioprotective effect of ischemic postconditioning (Suleman *et al.* 2006). Both ischemic and pharmacological postconditioning with TNF failed to confer an infarct sparing effect in isolated STAT3-deficient murine hearts subjected to ischemia-reperfusion injury (Boengler *et al.* 2008, Lacerda *et al.* 2009). Furthermore, the absence of protection observed in TNF or TNFR2 knockout mice was associated with the absence of STAT-3 phosphorylation (Lacerda *et al.* 2009). Activation of TNF/TNR2/JAK/STAT-3 may be triggered by various mediators including insulin, angiotensin II, bradykinin, adrenoreceptors, opioids, cannabinoids and sphingosine-1 phosphate (Hausenloy *et al.* 2011).

3.2.4 mPTP and anti-apoptotic signaling pathways activated by the SAFE pathway

TNF-induced protection requires the activation of protein kinase C, the mitochondrial ATP-dependent potassium channel and NFκ-B (Lecour *et al.* 2002, Somers *et al.* 2005). In addition, pharmacological preconditioning with TNF is associated with an increase in mitochondrial free radicals and an addition of free radical scavengers such as mercaptopropionyl glycine abolished its cardioprotective effect (Lacerda *et al.* 2006, Lecour *et al.* 2005a). In contrast, neither p38MAPK, Akt, Erk nor GSK3-β seem to be involved in TNF-induced cardioprotection, therefore suggesting that they do not act as the downstream target of the SAFE pathway (Lacerda *et al.* 2009, Lecour *et al.* 2005b, Tanno *et al.* 2003). STAT3 mediates cardioprotection via the phosphorylation and inactivation of the pro-apoptotic factor Bad (Deuchar *et al.* 2007, Lecour *et al.* 2005b) and Bax (Huffman *et al.* 2008). The mitochondrial permeability transition pore (mPTP) is described as an end-effector of ischemic postconditioning and the RISK pathway and there are now strong evidence that the SAFE pathway may also target the mPTP. Hence, STAT3 expression was demonstrated in mitochondria, playing a role in cell respiration (Wegrzyn *et al.* 2009) and mPTP opening (Boengler *et al.* 2010).

3.3 Targeting the RISK and SAFE paths to limit reperfusion injury

Ischemic postconditioning performed by inflation/deflation of the angioplastic balloon is safe, easy to perform, inexpensive but many patients in remote areas do not have a fast access to a PCI performing facility and ischemic postconditioning has never been tested following thrombolysis. The development of pharmacological drugs which can mimic ischemic postconditioning by activating the prosurvival RISK and SAFE pathways would benefit patients undergoing either PCI or thrombolysis and it would certainly be more practical than ischemic postconditioning.

In this regards, the immunosuppressor drug cyclosporine can bind to the mitochondrial cyclophilin D, thereby inhibiting the opening of the mPTP, a downstream target of both the

RISK and SAFE pathways. In a multicenter single-blinded controlled clinical trial, the effect of cyclosporine A was evaluated in 58 patients with acute ST-elevation myocardial infarction who received an intravenous bolus of 2.5mg/kg of cyclosporine immediately before undergoing PCI, significantly reduced the release of creatine kinase by 40% within the first 72 hours. (Piot *et al.* 2008) Infarct size, assessed on day 5 (by measuring the area of hyperenhancement on magnetic resonance imaging) was significantly reduced. Cyclosporine, routinely used as an immunosuppressive agent, is well known for its toxic side-effects, such as renal and hepatic toxicity and increased susceptibility to infections and cancers. A single bolus injection of cyclosporine did not show any of these side-effects, but larger and longer clinical trials are required to prove the safety and efficacy of cyclosporine as a therapeutic agent following AMI.

Two clinical trials have explored the effect of adenosine in patients with acute myocardial infarction (AMISTAD and AMISTAD II) but the results were mitigated by the haemodynamic effect of the drug. (Mahaffey *et al.* 1999, Ross *et al.* 2005) Although adenosine can successfully reduce the infarct size, it has a vasodilatory and negative chronotropic effect, causing hypotension and bradycardia, thus limiting its clinical application. However, recent experimental studies using polyethylene glycol liposomal adenosine in rats protected against ischemia-reperfusion and reduced the hemodynamic effect of adenosine. (Takahama *et al.* 2009) If this protocol can be applied in a clinical setting, it may limit the side effects of adenosine.

Erythropoietin successfully reduced the infarct size in animal models but its clinical application still needs to be confirmed. (Bullard *et al.* 2005)

3.4 Ischemic postconditioning and comorbidities

At the present, little information is available in humans with regards to the success of ischemic postconditioning with different comorbidities and most of the clinical trials have excluded patients with diabetes/metabolic syndrome. Animal studies have shown that various comorbidities affect the protective effect of postconditioning. Rats with obesity, metabolic syndrome or diabetes become more resistant to the infarct limiting effect of ischemic postconditioning and additional cycles of ischemia-reperfusion are required to achieve a beneficial effect (Hausenloy *et al.* 2011). Similarly, hyperglycemia in rabbits abolishes the cardioprotective effect of ischemic postconditioning (Raphael *et al.*). More recently, depressed rats failed to be protected with ischemic postconditioning (Zhuo *et al.* 2011).

4. Conclusion

Ischemic postconditioning is a safe, simple and inexpensive therapy but several factors need to be taken into consideration for its efficacy. Remote ischemic postconditioning and pharmacological postconditioning present the advantage of being applied in AMI patients with or without PCI. However, the severity and duration of ischemia, the presence of collateral circulation and the algorithm of the postconditioning protocol may all affect the protective effect of ischemic postconditioning against lethal reperfusion injury (Hausenloy *et al.* 2010).

Although small clinical proof-of-concept studies suggest that ischemic postconditioning can protect the human heart against lethal reperfusion injuries, larger clinical trials testing

ischemic or pharmacological postconditioning are needed to test the clinical outcome of this phenomenon. In Italy, the POSTAMI trial is currently evaluating the effect of ischemic postconditioning on infarct size (using magnetic resonance imaging) 3 months after ST elevation AMI in 78 patients (Tarantini *et al.* 2010). In Norway, the POSTEMI study is currently evaluating the effect of ischemic postconditioning on infarct size after 4 months by magnetic resonance imaging in 260 patients (Limalanathan *et al.*). Most importantly, the CIRCUS study aims to evaluate whether cyclosporine A, given immediately prior to reperfusion with PCI, can improve clinical outcome in patients with AMI. Conducted in 15 countries and 120 centres, the study will evaluate 1750 patients per group considering cardiac death and hospitalization for in-hospital worsening of heart failure as primary endpoints. The outcome of these larger clinical trials will hopefully conclude that postconditioning should be systematically applied in the management of future patients with AMI.

5. References

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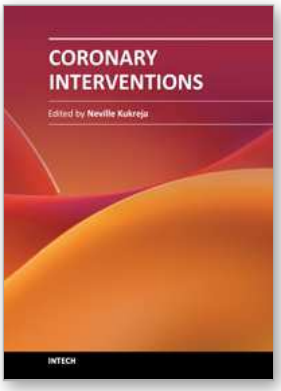

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