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Harnessing the preconditioning phenomenon: does remote organ ischaemia provide the answer?

A Burdess, D Newby



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Despite progress in defining the cellular mechanisms of the ischaemic preconditioning phenomenon, its conversion into convenient clinical practice has been slow. The possibility that an innate mechanism of tissue resistance to ischaemia could be harnessed as a clinical tool is an attractive and enticing prospect

Ischaemic injury to vital organs such as the heart is an extremely common cause of morbidity and mortality. Limiting tissue infarction has been a goal for many years, but, except for rapid reperfusion therapy, there are currently few therapeutic options. With further understanding of the pathophysiology of ischaemia and revascularisation, it is now known that cellular injury and the associated clinical manifestations are the result of a “two pronged attack”: the direct effect of ischaemia, and the subsequent “reperfusion injury”. Preserving tissue viability by making the cells more “resistant” to the ischaemic insult is a novel and potentially important therapeutic approach. It not only has the potential to limit the extent of damage but perhaps to extend the therapeutic window for other interventions such as thrombolysis. Ischaemic preconditioning is a mechanism that can protect tissues from both direct ischaemia and reperfusion injury.

ISCHAEMIC PRECONDITIONING

In a canine model of myocardial infarction, Murry *et al*¹ first described that pretreatment with brief periods of ischaemia paradoxically resulted in a reduction in infarct size. This process, whereby a tissue undergoes adaptive and protective changes in response to a small ischaemic insult, has been termed “ischaemic preconditioning”. This phenomenon appears to be highly conserved and has been described in a variety of different species and tissues.² Both *in vitro*³ and *in vivo*^{4,5} studies have established that this important physiological process also occurs in man.

The process of ischaemic preconditioning exhibits a biphasic pattern of protection. There is an early “classical” period of protection occurring almost immediately after the ischaemic stimulus, followed by a “late preconditioning” phase, starting 12–42 hours later.⁶ The exact mechanisms by which these adaptive changes are mediated remain unknown. Early preconditioning appears to be conducted through a pathway activated by a variety of substances

released during ischaemia and reperfusion, such as adenosine, bradykinin, and opioids. Binding of these mediators to G protein coupled receptors stimulates second messenger pathways, and the translocation of protein kinase C from the cytosol to the membrane.⁶ This phosphorylates an as yet unidentified protein, although candidates such as the mitochondrial adenosine triphosphate dependent potassium channel have been proposed.⁷

In contrast to the early phase, delayed preconditioning is thought to be attributable to alterations in gene expression, creating a hypoxia tolerant phenotype. This includes upregulation of proteins such as growth factors and heat shock proteins that inhibit apoptosis and maintain cellular integrity, respectively.^{6,8}

CLINICAL APPLICATIONS OF ISCHAEMIC PRECONDITIONING

By determining the molecular mechanisms of preconditioning it is theoretically feasible that “preconditioning mimicking agents” could be developed to induce these protective and adaptive pathways, and hence provide a novel therapeutic strategy for preserving ischaemic tissue. A number of agents have been examined including adenosine analogues (acute myocardial infarction study of adenosine; AMISTAD trial)⁹ and stimulators of the mitochondrial K/ATP channel such as nicorandil.¹⁰ Unfortunately the outcomes have been disappointing and inconclusive. This could be due to the timing of administration (agents given after reperfusion rather than before or during ischaemia) or that a single agent may only act on one aspect of a complex multifactorial pathway. Because of this, the translation from experimental observation to therapeutic intervention has to date proven elusive.

Surgical induction of ischaemic preconditioning has been demonstrated. In a study by Yellon *et al*,⁴ myocardial injury was reduced by two 3 minute periods of ischaemic preconditioning induced by aortic cross clamping before coronary artery bypass grafting. Ischaemic preconditioning has also been shown to provide protection for the liver during hepatectomy,⁵ and a reduction in lung injury following lobectomy.¹¹ These studies employ an *in vivo* ischaemic stimulus and therefore activate the preconditioning pathway endogenously. This negates the problem associated with the singular action of a pharmacological mimetic agent. Despite this promising work, direct preconditioning is not routinely used in clinical practice and many clinicians remain to be convinced of its utility. Most studies

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to date involve small numbers of low risk patients where the additional advantages from preconditioning may be marginal. In addition, the end points that have been studied are often an indirect measure of clinical outcome (such as troponin) and have employed diverse and non-standardised surrogate markers. Some have also raised concerns about the practicality and risk of inducing ischaemia, albeit short lived, in a diseased and vulnerable organ.

REMOTE PRECONDITIONING

In addition to local effects, ischaemia followed by reperfusion initiates a systemic inflammatory response that is characterised by the production of proinflammatory mediators and activation of neutrophils. This systemic response is likely to contribute to the multi-organ dysfunction, such as adult respiratory distress syndrome and acute renal failure, associated with the major ischaemic insults of aortic aneurysm repair, hepatic resection, and cardiopulmonary bypass. However, systemic effects of briefer periods of ischaemia can have beneficial protective effects.

Early studies of preconditioning have tended to focus on the local benefits conferred to one particular organ. The paper by Kharbanda *et al*,¹² in this issue of *Heart*, provides further evidence for a remote widespread and systemic benefit from ischaemic preconditioning. The study examined an experimental pig model of cardiopulmonary bypass, where remote ischaemic preconditioning was induced by four 5 minute cycles of lower limb ischaemia. Both cardiac and pulmonary injury and acid-base imbalance were reduced by this remote preconditioning effect. Previous work has also demonstrated that resistance to ischaemia can develop in areas remote to the initial ischaemic stimulus. In a study by Gho *et al*,¹³ prior occlusion and reperfusion of rat mesenteric or renal arteries led to a subsequent reduction in myocardial infarct size, and lower limb ischaemic preconditioning has been shown to limit indices of acute lung injury, and myocardial infarct size in pigs.¹⁴ However these studies have used experimental models of myocardial infarction and the clinical application of such models is limited since the onset of acute myocardial infarction can rarely be predicted and a preconditioning stimulus is not a realistic therapeutic option.

Remote preconditioning presents an exciting clinical concept with the possibility that regional ischaemia of non-vital tissue might protect remote organs. This would avoid the risks associated with inducing direct preconditioning in the vulnerable target organ. A previous investigation by Kharbanda *et al*¹⁵ demonstrated that remote preconditioning can also be induced in man. Ischaemic preconditioning of an upper limb in healthy human volunteers led to in vivo attenuation of neutrophil activation and a reduction in endothelial dysfunction. Normal skeletal muscle is potentially an ideal tissue for the induction of remote preconditioning since it is inherently more resistant to ischaemia than myocardial or neuronal cells, is capable of regeneration, and is readily accessible.

LIMITATIONS OF PRECONDITIONING

Despite the valuable contribution that remote preconditioning may offer as a convenient clinical tool, many questions are still unanswered. The exact mechanisms remain to be elucidated. There has been debate as to whether its effects are mediated via humoral or neurogenic pathways, or a combination of both.¹⁶ There is also the potential for inter-tissue variation, with different systems and mechanisms capable of inducing resistance in some organs but not others.¹⁷

Remote preconditioning faces the same limitations as its direct counterpart. The timing of the preconditioning

stimulus remains a crucial factor with the major benefits seen where the onset of ischaemia is known or predictable, such as cardiopulmonary bypass and organ transplantation. Moreover, repeated ischaemic stimuli fail to prolong the period of protection afforded by either classical or late preconditioning and limits the therapeutic window for this protective technique. This also has implications for patients with ongoing or recurrent ischaemia such as those with stable or unstable angina. The induction of preconditioning may be difficult to establish or have little incremental benefit in patients who have ongoing recurrent or critical ischaemia at presentation. The additive value of additional preconditioning has yet to be established in such clinical settings.

In conclusion, harnessing the potentially powerful and valuable effects of direct and remote preconditioning is an exciting and readily achievable therapeutic option in situations of planned or predictable tissue ischaemia. However, the clinical utility of routine induction of ischaemic preconditioning has yet to be definitively established in clinical practice, particularly in patients with known ischaemic cardiovascular disease or presenting with acute tissue ischaemia.

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