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Ischaemic Conditioning for Neuroprotection in Stroke (Terence Valenzuela)

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Introduction

Worldwide, stroke remains the second leading cause of death after heart disease. Since the 1970s there has been a 42% decrease in stroke mortality in high-income countries and a 100% increase in low-income countries (Norrving and Kissela 2013). These trends are multifactorial; however, a significant component is due to a less robust infrastructure for tertiary prevention of stroke i.e. rapid diagnostic imaging, thrombolytic medication and endovascular thrombus-removal interventions. These remain largely limited to the 'developed' world. Ischaemic conditioning, a simple, inexpensive, and noninvasive therapy applicable to thrombotic stroke promises to be feasible throughout the world.

Reperfusion Injury and Ischaemic Conditioning

Ischaemia due to impaired blood flow produces within cells a reduction in ATP, an increase in lactate concentration and impairment of cell membrane-based ion transporters. Decreased cytosolic pH, cell and mitochondrial oedema are the sequelae. Cell death and necrosis follow. While reperfusion must occur to salvage ischaemic but potentially viable cells, reperfusion itself causes cell damage distinct from the original ischaemic insult (Hearse et al. 1973).

Ischaemic conditioning is the creation of brief and repeated cycles of non-lethal ischemia alternating with reperfusion in a selected organ or tissue. This 'conditioning' reduces damage from later, prolonged ischemia.

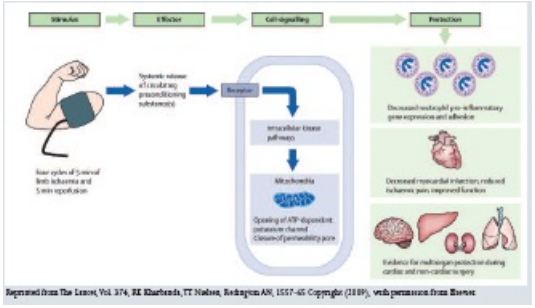

Figure 1. Biological effects of remote ischaemic preconditioning Transient ischaemia of the arm liberates a circulating effector that induces remote cellular adaptation to a subsequent, extended, and potentially lethal period of ischaemia in remote tissues.

Murry and Reimer in 1986 reported a canine model of acute myocardial infarction designed to measure the size of infarction resulting from interruption (forty minutes) of flow in the circumflex coronary artery (LCX). Animals so treated were maintained for four days, sacrificed, and the extent of infarction in the LCX vascular bed measured by histochemical techniques (Murry et al. 1973). An experimental group underwent four cycles of five minute LCX occlusion, each reversed by five minutes of reperfusion, before the prolonged occlusion of the artery. Infarct size in the experimental group was 25% that of dogs that did not receive pulsatile ischemia/reperfusion. This discovery, termed 'ischaemic conditioning', was later extended by Przyklenk in a similar experiment wherein conditioning of the circumflex vascular bed reduced infarct size and contractile dysfunction after subsequent sustained coronary occlusion of the left anterior descending artery (Przyklenk et al. 1993). Ischaemic conditioning

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(IC) thus appeared to generate humoral factors transported in the circulation. Ischaemic conditioning remained an interesting, but not clinically useful, phenomenon until the discovery that ischaemic conditioning of an extremity could induce protection in internal organs such as heart, brain, lung and kidney (Kharbanda et al. 2002). This 'remote' ischaemic conditioning (RIC) effect makes possible the use of an arm or leg for timed pulses of brief ischemia/reperfusion with a standard sphygmomanometer (see Figure 1).

The mechanism of ischaemic conditioning has been intensively studied over the past 25 years and involves humoral, neurogenic, and immune factors (Hess et al. 2013). Moreover, there are two phases to the protection: the first lasts approximately four hours, after which the magnitude of protective effect subsides. This initial phase is likely mediated through 'triggers' - small molecules such as adenosine, bradykinins, opioids, and reactive oxygen species. Dialysate, obtained with a 15 kilodalton- cutoff membrane from the plasma from ischaemic-conditioned human subjects, generated protection against infarction by coronary artery ligation when perfused through isolated rabbit hearts. Partial characterisation of the plasma ischaemic conditioning factor by column chromatography demonstrated a hydrophilic nature (Shimizu et al. 2009). Using proteomic methods, Lang confirmed the humoral factor of ischaemic conditioning to be of small molecular weight (less than 8 kd) (Lang et al. 2006). Subsequent transcription of DNA and protein synthesis produces distinct mediators at 12 to 24 hours (Hausenloy and Yellon 2010; Loukogeorgakis et al. 2005). Research has shown that a significant proportion of the protective effect of RIC is mediated through stabilisation of the mitochondrial permeability transition pore (mPTP) (Hausenloy et al. 2009). In unconditioned tissue reperfusion results in a flooding of small molecules into the mitochondrion followed by subsequent oedema and dysfunction of the organelle.

Ischaemic conditioning may be applied before ischemia (prior to elective procedures such as percutaneous coronary artery stenting), during ischaemia (the interval between onset of thrombotic myocardial infraction or stroke and reperfusion therapy) or after reperfusion. These periods are termed respectively: 'preconditioning', 'perconditioning' and 'postconditioning'.

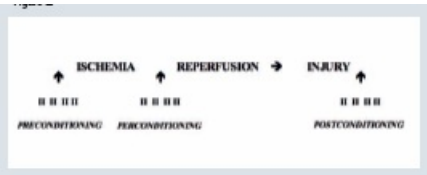

Figure 2

Since the 1980s, large clinical trials have demonstrated rapid thrombolytic therapy to be effective in reducing mortality and morbidity in two major thrombotic emergencies: ST-T segment elevation acute myocardial infarction (STEMI) and acute thrombotic stroke. STEMI established itself first, initially with intravenous thrombolytic drugs (GUSTO investigators 1993), and advancing to percutaneous coronary artery intervention (French et al. 2003). Later, treatment of thrombotic stroke followed a similar path: initial intravenous pharmaceutical thrombolysis to endovascular techniques (Hacke et al. 2004). Both conditions share a similar course: unpredictable initial arterial thrombosis followed by a period of ischaemia then therapeutic restoration of blood flow to the ischaemic organ. In both STEMI and thrombotic stroke, a large number of symptomatic individuals must be screened to identify a genuine acute thrombotic event. Theoretically, the ischaemic interval of both conditions affords an ideal opportunity for application of remote ischaemic conditioning, specifically perconditioning, (see Figure 2) to ameliorate reperfusion injury. Remote ischaemic perconditioning has the additional advantage that personnel with minimal training may administer it prior to a confirmed diagnosis. Finally, the procedure poses a miniscule risk of harm to patients who are not experiencing a thrombotic event.

Bøtker investigated this possibility by randomising symptomatic STEMI patients, transported by ambulance to hospital, for coronary revascularisation. Patients were randomised prehospital to either five cycles of brief ischaemia/ reperfusion, administered to an upper arm by blood pressure cuff, or to no ischaemic conditioning. On arrival, Single Positron Emission Computed Tomography (SPECT) delineated the area of ischaemic myocardium (area at risk). The study called for repeat SPECT thirty days later at which time the area irreversibly infarcted was measured. The primary outcome was the myocardial salvage index defined as (initial ischaemic area of myocardium)/ (initial ischaemic area of myocardium) – (area infarcted at 30 days). Of those completing the study protocol, the median myocardial salvage index in conditioned patients was 0.75 versus 0.55 in the unconditioned group; a difference not statistically significant (Bøtker et al. 2010). In a subgroup analysis of patients with anterior myocardial infarction (therefore, a large area of ischaemic myocardium) from the same study, the investigators suggested a trend toward greater myocardial salvage and long term left ventricular function (Munk et al. 2010; Sloth et al. 2013). Interpretation of these results must take into consideration the large number of randomised patients who did not meet inclusion criteria on hospital arrival, did not return for 3 month imaging or were lost to follow-up. Of 333 randomised patients, only 142 (43%) completed the study protocol, and it was these patients in whom the degree of myocardial salvage could be determined. This study established the feasibility and safety of prehospital conditioning; but did not demonstrate a significant benefit from remote ischaemic perconditioning in clinically relevant outcomes.

Remote Ischaemic Perconditioning and Stroke

The current standard therapy for thrombotic stroke is intravenous tissue plasminogen acti- vator (tPA) (within 3 to 6 hours of symptom onset) to re-establish perfusion. Successful treatment also causes reperfusion injury to the previously ischaemic brain. In a rat model of ischaemic stroke (occlusion of the middle cerebral artery), Hahn studied mice preconditioned and perconditioned with a hind leg tourniquet, The conditioned mice manifested significantly smaller stroke volumes after 120 minutes of cerebral ischemia compared with an unconditioned control group (Hahn et al. 2011; Tropak et al. 2011). Of interest was the observation that perconditioned (conditioning of hind limb during cerebral ischaemia but before reperfusion) developed stroke volumes significantly smaller compared to the preconditioned (conditioning before cerebral ischaemia). Results of the first prospective phase three human trial of remote preconditioning in acute thrombotic stroke were reported by Hougaard and others in 2013. The study design was similar to that of Bøtker, intended to determine whether remote ischaemic conditioning performed as an adjunct to thrombolysis would improve salvage of ischaemic but viable brain during thrombotic stroke. Patients with stroke-like symptoms, en route by ambulance to hospital, were randomised to either perconditioning (administered by blood pressure cuff to the arm) or no perconditioning. Patients whose stroke or transient ischaemic attack were confirmed by MRI and received tPA were enrolled and followed up by MRI 30 days later. One hundred and forty nine subjects completed the 30 day follow- up. The primary endpoint was salvage of ischaemic but viable brain tissue as determined by initial and 30 day MRI (Hougaard et al. 2013). Analysis revealed no significant statistical difference in preservation of ischaemic cerebrum between the two groups. The secondary clinical endpoints of infarct growth from 0-24 hours and on clinical performance

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instruments also did not achieve statistical significance (Meng et al. 2012).

Post Conditioning

Less well understood, but potentially exciting, are reports that post-ischaemic conditioning (five brief cycles of bilateral upper extremity ischemia followed by reperfusion, twice daily for 300 consecutive days after cerebral haemorrhage) with atherosclerotic intracranial arterial stenosis reduced the incidence of recurrent stroke in control subjects at 90 and 300 days from 23.3% and 26.7% respectively, to 5% and 7.9% (p=0.01). Time to recovery was shorter and cerebral perfusion status improved also in the post-conditioned group (Meng et al. 2012).

Ischaemic conditioning is a unique physiologic process that may be seen across species, suggesting that it arose early in evolutionary history. Early prospective human trials have been disappointing; however, increasing knowledge of the bimodal timing of protection - a rapid, short-lived state followed by a later, longer-lasting one - and of the multiple effector pathways offer the hope that combining perconditioning and postconditioning will yield immediate benefit to victims of thrombotic stroke. Ischaemic conditioning for prolonged periods after stroke appears to reduce the rate of reoccurrence and enhance the rapidity and extent of rehabilitation. In any case, the simplicity, low cost, and safety of ischaemic conditioning merit continued clinical study in humans.

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