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RIPC for multiorgan salvage in clinical settings: Evolution of concept, evidences and mechanisms

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ABSTRACT

Ischemic preconditioning is an intrinsic process in which preconditioning ischemia (ischemia of shorter duration) protects the organs against the subsequent index ischemia (sustained ischemia). Remote ischemic preconditioning (RIPC) is an innovative treatment approach in which interspersed cycles of preconditioning ischemia followed by reperfusion to a remote organ (other than target organ) protect the target organ against index ischemia and reperfusion-induced injury. RIPC of various organs to provide multi-organ salvage became a successful approach in numerous species of animals. Consequently, the concept of RIPC evolved in clinical setups, and provided beneficial effects in alleviating ischemia-reperfusion-induced injury in various remote organs, including myocardium. Clinically, RIPC stimulus is generally delivered by inflating the blood pressure cuff tied on the upper arm 20 mm greater than the systolic blood pressure, rendering the forearm ischemic for 5 min, followed 5 min reperfusion by deflating the cuff. This cycle is repeated for 3–4 consecutive periods to precondition the tissue and improve the survival. The institution of RIPC is beneficial in mitigating myocardial injury in patients undergoing various surgical interventions including coronary artery bypass graft surgery, abdominal aortic aneurysm repair, percutaneous coronary intervention, heart valve surgery, drug-eluting stent implantation, kidney transplantation, elective decompression surgery. The involvement of hypoxia inducible factor-1α (HIF-1α), ATP-sensitive potassium channels, signal transducer and activator of transcription (STAT), matrix metalloproteinases, O-linked β-N-acetylglucosamine (O-GlcNAc) levels, autonomous nervous system in mediating RIPC-induced cardioprotective effects has been explored clinically. However, comprehensive studies are required to elucidate the other possible mechanisms responsible for producing multi-organ protection during RIPC.

Contents

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1. Introduction

Ischemia is a vascular disease that is characterized by restriction in blood supply, causing shortage of oxygen and vital nutrients, thus hampering normal cellular metabolism. Establishment of circulation is necessary to resuscitate the tissues and eventually, protect them from cell death after transient absence of oxygen and nutrients in the blood. Prolonged occurrence of ischemia and thereafter, reperfusion results in ischemia-reperfusion-induced injury as a result of release of oxygen free radicals, cytokines and increase in the expression of adhesion molecules (Kukielka et al., 1993; Welbourn et al., 1991). Intraoperative ischemia-reperfusion-induced injury is one of the fundamental causes in the perpetuation of transitory and delayed organ dysfunction (Błogowski et al., 2012; Xie et al., 2012). Therefore, for the sake of providing protection to the organs against ischemia-reperfusion injury, development of a novel therapeutic approach is the need of the hour.

RIPC is a treatment strategy in which alternate cycles of preconditioning ischemia followed by reperfusion are delivered to a remote organ (other than heart) which protects the heart against subsequent index ischemia (sustained ischemia) and reperfusion induced injury (Gho et al., 1996; Przyklenk, 2013). Preclinically, short episodes of occlusion and reperfusion of the arteries such as cerebral, mesenteric, intestinal (Wang et al., 2008), renal (Diwan et al., 2008a, 2008b; Kant et al., 2008), abdominal aorta (Taliyan et al., 2010), skeletal muscle (Liem et al., 2003) produce preconditioning of myocardium against sustained ischemia and reperfusion in various animals like mice, rats etc. However, these approaches may not be directly translated in clinical settings. In clinical setups, the best utilized way for providing myocardial protection is rendering the forelimb (skeletal muscle) ischemic by applying blood pressure cuff on the upper arm. This is advantageous as it is a non-invasive and clinically feasible technique except for surgical procedures. Furthermore, upper limb is more resistant to ischemic insult as even a mild ischemia to vital organs can result in non-reversible cellular injury.

In clinical setup, RIPC is generally initiated by inflating blood pressure cuff tied on the upper arm 20 mm Hg greater than systolic arterial pressure, rendering the forearm ischemic for 5 min followed by 5 min intermittent reperfusion. This cycle may be repeated for three to four consecutive periods (Cheung et al., 2006; D'Ascenzo et al., 2014; Karuppasamy et al., 2011). However, different scientists have made modifications in the protocol to induce ischemia-reperfusion injury of varying degrees. The concept of RIPC came into existence in clinical settings when Cheung et al. subjected 17 children with congenital heart defects to RIPC and this treatment strategy significantly attenuated troponin levels (a chief indicator of myocardial injury) (Cheung et al., 2006). Furthermore, studies conducted by other researchers have reported reduction in neuronal (Gonzalez et al., 2013; Hu et al., 2010), kidney (Er et al., 2013; Walsh et al., 2009; Wu et al., 2014), intestinal and pulmonary injury (Li et al., 2013) in individuals after being subjected to RIPC stimulus (Table 1). RIPC stimulus has also improved the initial distance covered in patients with complaints of intermittent claudication (pain in legs during walking) in the lower limbs (Saes et al., 2013).

The involvement of hypoxia inducible factor-1α (HIF-1α) (Albrecht et al., 2013), ATP-sensitive potassium channels, (K_{ATP} channels) (Loukogeorgakis et al., 2007), signal transducer and activator of transcription (STAT) (Heusch et al., 2012), matrix metalloproteinases (MMPs) (Zitta et al., 2012), O-linked β-N-acetylglucosamine (O-GlcNAc) levels (Jensen et al., 2013), autonomous nervous system (ANS) (Loukogeorgakis et al., 2005) in mediating RIPC-induced cardioprotective effects have been explored clinically (Fig. 1). The present review describes the evidences and possible mechanisms of RIPC-induced multiorgan salvage from ischemia-reperfusion injury in clinical settings.

2. Evolution of concept

Ischemic preconditioning is a therapeutic strategy brought into notice in 1986 by Murry, Jennings and Reimer in order to alleviate ischemia-reperfusion-induced injury (Murry et al., 1986). Murry et al. demonstrated that short ischemic episodes to an organ (in the form of ischemic preconditioning) afford protection against sustained ischemia and reperfusion injury (Murry et al., 1986). This concept has been expanded to include pharmacological preconditioning (Khanna et al., 2008). Remote preconditioning stimulus (repeated cycles of non-lethal ischemia and reperfusion to a distant tissue) can be delivered before, during or after lethal sustained ischemia for RIPC (RIPC) (Kant et al., 2008), remote ischemic perconditioning (Czigany et al., 2013) or remote ischemic postconditioning (RIPostC) (Crimi et al., 2013; Heusch, 2013) respectively. Our own laboratory has demonstrated cardioprotective effects of remote renal preconditioning in rats RIPC (Diwan et al., 2008a, 2008b; Kant et al., 2008). The concept of intracardiac preconditioning came into limelight when Przyklenk et al. demonstrated that 4 cycles of 5 min occlusion and reperfusion of the left circumflex artery led to a reduction in infarct size following sustained occlusion of left anterior descending coronary artery (Przyklenk et al., 1993). This finding led to the emanation of RIPC, which has been explored in numerous species of animals in order to provide multiorgan salvage. Similarly, preclinical studies have been conducted to evaluate the potential of RIPostC and remote perconditioning to alleviate ischemia-reperfusion-induced injury. In clinical settings, RIPostC has provided benefits in attenuating ischemia-reperfusion-induced injury in adults and children undergoing percutaneous coronary intervention/heart surgery (Crimi et al., 2013; Zhong et al., 2013). Likewise, remote ischemic perconditioning is another treatment approach which has led to significant reduction in myocardial injury in patients undergoing valve replacement (Li et al., 2010). However, remote ischemic perconditioning treatment strategy has not been translated extensively into clinical set-ups for reducing ischemia-reperfusion-induced injury.