REVIEW ARTICLE

Myocardial ischemic conditioning: Physiological aspects and clinical applications in cardiac surgery

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Ischemia–reperfusion is a major determinant of myocardial impairment in patients undergoing cardiac surgery. The main goal of research in cardioprotection is to develop effective techniques to avoid ischemia–reperfusion lesions. Myocardial ischemic conditioning is a powerful endogenous cardioprotective phenomenon. First described in animals in 1986, myocardial ischemic conditioning consists of applying increased tolerance of the myocardium to sustained ischemia by exposing it to brief episodes of ischemia–reperfusion. Several studies have sought to demonstrate its effective cardioprotective action in humans and to understand its underlying mechanisms. Myocardial ischemic conditioning has two forms: ischemic preconditioning (IPC) when the conditioning stimulus is applied before the index ischemia and ischemic postconditioning when the conditioning stimulus is applied after it. The cardioprotective action of ischemic conditioning was reproduced by applying the ischemia–reperfusion stimulus to organs remote from the heart. This non-invasive manner of applying ischemic conditioning has led to its application in clinical settings. Clinical trials for the different forms of ischemic conditioning were mainly developed in cardiac surgery. Many studies suggest that this phenomenon can represent an interesting adjuvant to classical cardioprotection during on-pump cardiac surgery. Ischemic conditioning was also tested in interventional cardiology with interesting results. Finally, advances made in the understanding of mechanisms that underlie the cardioprotective action of ischemic conditioning have paved the way to a new form of myocardial conditioning which is pharmacological conditioning.

Keywords: Ischemia–reperfusion injury, Ischemic preconditioning, Ischemic postconditioning, Remote ischemic preconditioning, Cardiac surgery

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Contents

Introduction

Postoperative myocardial dysfunction is still common in patients undergoing cardiac surgery [1,2]. It is one of the leading causes of postoperative morbidity and mortality. Ischemia–reperfusion injury is the most decisive factor in myocardial impairment in such patients. Developing new strategies to reduce ischemia–reperfusion injury is currently one of the main goals of research in cardioprotection. In this context, myocardial ischemic conditioning has recently been proposed as an interesting adjuvant to classical cardioprotection during cardiac surgery. Myocardial ischemic conditioning is a powerful endogenous cardioprotective phenomenon. It was first described in animals in 1986 [3]. During the last thirty years, myocardial ischemic conditioning has been the subject of much research concerning both its underlying mechanisms and its clinical applications. Several clinical trials in cardiac surgery and interventional cardiology have therefore sought to demonstrate its effectiveness in clinical settings.

The aim of this article is to review the different types of myocardial ischemic conditioning, its underlying mechanisms, and its clinical applications in cardiac surgery.

Abbreviations

IPC	ischemic preconditioning
RIPC	remote ischemic preconditioning
mPTP	mitochondrial permeability transition pore
mK_{ATP}	mitochondrial ATP-dependent potassium channels

Physiological aspects of ischemic conditioning

Ischemic preconditioning (IPC)

In 1986, Murry et al. [3]. discovered that by applying 40 min of occlusion of the circumflex coronary artery in dogs, the myocardial infarct size resulting from this sustained ischemia was reduced by 75% if the dogs were previously exposed to brief episodes of ischemia–reperfusion. Ischemia–reperfusion consisted of four five-minute cycles of intermittent occlusion of this same coronary artery. This ability of the myocardium to tolerate sustained ischemia after short episodes of ischemia–reperfusion was named ischemic preconditioning (IPC). This powerful cardioprotective phenomenon was found thereafter in all species including humans [4]. During IPC, protection occurs in two phases. An early phase of protection, known as classical ischemic preconditioning, begins immediately after the preconditioning stimulus and lasts for 2–4 h. A delayed phase of protection begins after 12–24 h, lasts 2–3 days, and is known as the second window of protection [5]. The classical ischemic preconditioning likely involves preformed factors. It has a powerful protective effect against myocardial necrosis but does not protect against stunning [6]. The second window of protection is likely related to the synthesis of neoformed factors. It protects against myocardial stunning but is less effective against necrosis [6].

Ischemic preconditioning involves several factors that are usually divided into three groups: triggers, mediators, and effectors. The signaling pathways are complex and not yet fully understood. Brief episodes of ischemia result in the release of initiating factors such as adenosine, bradykinin, and endorphins [7].

During the early phase, these initiators bind to their specific receptors coupled to G proteins resulting in message transduction. Two signaling