Progrès en urologie (2014) 24, S56-S61

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Ischemic pre- and post-conditioning: current clinical applications

Pré et post conditionnement ischémique : applications cliniques actuelles

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KEYWORDS
Ischemic conditioning;
Kidney transplantation;
Ischemia-reperfusion injuries

Summary
Ischemic conditioning is a phenomenon through which short sequences of ischemia-reperfusion applied to an organ confer some degree of protection towards future ischemic insults. This phenomenon was first observed in the mid-1980s in cardiac surgery, and has been since widely studied in different settings. Different sort of ischemic conditioning exist: local vs remote, direct or pharmacological, and with different timeframes of protection. Ischemic conditioning seems especially suited to applications in transplantation since schedules of both cold and warm ischemia, as well as reperfusion, are carefully and easily controlled, and the benefits of protecting fragile organs against ischemia-reperfusion injuries might help widen the pool of possible grafts and ensure better graft function and survival. The pathways through which ischemic conditioning work are many, offering both preservation of cell energy, protection against oxidative stress, better blood flow to organs and protection against apoptosis. In the field of pharmacological conditioning, which tries to mimic the protective effects of traditional ischemic conditioning without the potential side-effects associated with vessel clamping, many common-use drugs

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including anesthetics have been shown to be effective. Significant results have been obtained in small animal models, but while ischemic conditioning is successfully used in cardiac surgery, studies in large animal models and human applications in liver and kidney transplantation are still inconclusive.

MOTS CLÉS
Conditionnement ischémique ;
Transplantation rénale ;
Lésions d'ischémie reperfusion

Résumé
Le conditionnement ischémique est un procédé par lequel de courtes séquences d'ischémie-reperfusion appliquées à un organe confèrent un certain degré de protection envers les futures lésions ischémiques. Ce phénomène a été observé pour la première fois dans le milieu des années 1980 en chirurgie cardiaque, et a été depuis largement étudié dans différents contextes. D'autre types de conditionnement ischémique existent: locale ou à distance, directe ou pharmacologique. Le conditionnement ischémique semble particulièrement adapté à une application en transplantation avec des périodes d'ischémie chaude et froide, une reperfusion soigneusement et facilement contrôlé. Les avantages de la protection des organes fragiles contre les blessures d'ischémie-reperfusion pourraient contribuer à élargir le pool de greffons disponibles et à assurer une meilleure fonction et survie du greffon. Les mécanismes d'action du conditionnement ischémique sont nombreux: préservation de l'énergie de la cellule, protection contre le stress oxydatif, meilleure circulation sanguine vers les organes et protection contre l'apoptose. Dans le domaine du conditionnement pharmacologique, qui tente d'imiter les effets protecteurs de conditionnement ischémique traditionnel sans les effets secondaires potentiels associés au clampage vasculaire, de nombreux médicaments d'usage courant, y compris les anesthésiques ont démontré leur efficacité. Des résultats significatifs ont ainsi été obtenus dans des modèles animaux de petite taille. Cependant même si le conditionnement ischémique est utilisé avec succès en chirurgie cardiaque, les études sur des modèles expérimentaux de gros animaux et des applications humaines dans la transplantation hépatique ou rénale ne sont toujours pas concluantes.

Introduction

Organ transplantation face a major challenge in the discrepancy between the number of potential recipients and the number of potential donor, and this challenge has been adressed by widening the scope of potential organ donors to so-called ``extended-criteria donors'' (ECD). These include donors with co-morbidities potentially detrimental to the graft function, such as history of hypertension, vascular disease or diabetes in kidney transplantation, but also non-heart-beating donors (NHBD). Organs from these donors are more fragile than those from ``standard-criteria donors'' (SCD) and thus additional care has to be taken in preserving these organs, so as to minimize the risk of graft dysfunction or failure. Protective measures dealing with organ harvesting techniques, organ preservation and preservation solutions have been described previously in this work. However, another field, already used in human clinic in cardiovascular surgery settings and under evaluation in organ transplantation in both animal models and human clinic shows promising perspectives in organ protection.

Ischemic pre-conditioning (IPC) was first described in the context of heart surgery in the mid-1980s [1]. IPC is a phenomenon by which sequenced short ischemic periods followed by reperfusion confer protection against further ischemic insult to the organ. Studies have shown that this phenomenon is not limited to the heart but also takes place in the kidney, liver, brain and small intestine, and covers different mechanisms and pathways. Time between IPC and ischemic insult should first be taken into consideration: one can then described classic IPC (C-IPC), which typically confers a potent protection against further ischemia but is limited in time, usually 2 to 4 hours after initiation of the procedure [1], and the so called ``second window of protection'' (SWOP); this SWOP happens around 24 hours after the initial IPC procedure but offers more moderate protection. Site of the IPC procedure must also be taken into account, and has led to the description of both local IPC (LIPC) in which the organ vessels are directly clamped and remote IPC (RIPC) where the organ protection is secondary to vessel clamping in a different area [2].

While relatively easy to implement in a controlled, surgical setting such as transplantation or cardiac surgery, IPC is not well-suited to emergency settings, as the onset of myocardiac or brain infarction cannot be anticipated. Therefore of interest is the phenomenon of ischemic post-conditioning (IPoC), which was described subsequently to IPC. Sequential clamping and de-clamping of organ vessels after the ischemic insult can also confer some degree of protection, or higher repair potential to organs. Both local (LIPoC) and remote (RIPoC) IPoC have been described.

Direct clamping of vessels may not always be easily performed or may convey collateral risk to the recipient of surgery. Moreover, ischemic injury may also happen outside of