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REMOTE ISCHEMIC PRECONDITIONING PROTECTS AGAINST ISCHEMIC REPERFUSION INJURY DURING HEART TRANSPLANTATION

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ABSTRACT: *Background: Remote ischemic pre- conditioning (RIPC) is a technique where the application of short, repetitive limb intervals of ischemia and reperfusion would result in the condition of the heart as well as other organs to tolerate the ischemic reperfusion injury. Methods: Many research groups are interested in investigating the mediators, through which this technique works. Many mediators have been suggested to mediate the protective actions of RIPC.Conclusion: This manuscript represents a short review explaining a possible mechanism of action of this technique, through recent published findings, which confirm the ability of the technique to play an important role in the clinical practice of heart transplantation.*

KEYWORDS: Remote Ischemic Preconditioning, Ischemic Preconditioning, Nitric Oxide, Inflammasomes, Inflammatory Cytokines, And Heart Transplantation.

INTRODUCTION

Ischemic preconditioning is a technique where prior application of repeated short cycles of ischemia and reperfusion would be able to attenuate the severity of subsequent ischemic reperfusion injury (IRI). Remote ischemic preconditioning (RIPC) describes the ability of the technique to function through distance. For example, the application of short, repetitive ischemia- reperfusion cycles of the limb would protect distant organs like heart, kidney, brain and liver during subsequent IRI. Both phenomena indicate the involvement of local, paracrine as well as remote, circulating mediators (1).

During limb ischemia, the diminished flow and shearing stress would be associated with cell membrane depolarization and inhibition of the inward driving K^+ channels. The inhibition of KATP channels would lead to the activation of T type Ca^{2+} channels and increased Ca^{2+} influx into endothelial cells. Increased intracellular Ca^{2+} activates Ca^{2+}- dependent endothelial NO synthase (eNOS) (1,2).

Simultaneously, hypoxia and ischemia would result in an increased production of reactive oxygen species (ROS). Hypoxia inhibits oxidative phosphorylation and results in decreased ATP production. Which augments the inhibition of KATP channels and activates xanthine oxidase, leading to increased ROS production. Inhibition of KATP channels and cell membrane depolarization would also result in NADPH oxidase (NOX2) activation, leading to more increase of ROS production (1,3).

Increased production of both NO and ROS might be associated with NO oxidation to produce nitrite (NO_2^-). Several studies documented the important role of NO in mediating the protective effect of IPC and RIPC. While the locally produced NO can exert its action in case of IPC, it can’t be accused for RIPC protective effect because of its short blood half-life (≤ 2 milliseconds) (4). However, it was observed that NO inhalation in human provides protection against IRIs, while being associated with a significant increase in the circulating levels of nitrite. In addition, NO_2^- showed the ability to protect against IRI, to exert cytoprotective effects, and to decrease the infarction size similar to NO (5-12). Moreover, it has recently been confirmed that the application of brachial artery RIPC results in the activation of eNOS and increased plasma NO_2^- levels (13).

In the heart, NO_2^- would be reduced to NO and N_2O_3 by myoglobin (14,15). NO and S-nitrosothiols formed from nitrite would inhibit complex I of the respiratory chain during reperfusion. This would attenuate the increased production of ROS in response to IRI, and would indirectly affect the functionality of complex II (16,17). Being at cross-talking with mitochondrial KATP channels, modification of the functional activity of complex II would influence the activity of mitochondrial KATP channels (18), this might contribute to an improved activity of these channels in response to RIPC, which would inhibit the opening of mitochondrial permeability transition pores and the subsequent release of cytochrome c during reperfusion (17,19).

An important mechanism in the development of the IRI would be the increased production of inflammatory cytokines, which would be responsible for the recruitment of inflammatory cells and initiation of adverse inflammatory reactions (20). In addition to the significant increase of ROS production, IRI activates toll- like receptors (TLRs). Both result in priming of the heart inflammasomes (21).

During ischemia and hypoxia, as well as cold preservation of the heart graft, the associated inhibition of Na^+- K^+ ATPase and or other K^+ channels would result in decreased intracellular K^+ levels. Even with the administration of high extracellular K^+ concentrations (during cardioplegia), this would lead to the closure of K^+ channels (3). The end result would be the drop of intracellular K^+ levels, which activates the primed inflammasomes (22).

Activated inflammasomes activate caspase- 1, which activates proIL1β and proIL18. With IL1β being able to induce IL6, and with a confirmed important role of inflammasomes and TLRs in the establishment of inflammatory reactions and IRI, the above described role of NO and NO_2^- to attenuate ROS production and to improve the activity of KATP channels would interfere with inflammasomes priming and activation in response to IRI. Accordingly, this would contribute to decreased production of inflammatory cytokines, which would ultimately attenuate the immune cell infiltration and the adverse immune reactions generated in response to IRI. (Figure 1)

This mechanism of action of RIPC highlights the importance of inflammasomes inactivation to attenuate the hazards of IRI, though it was reported to the contrary by some studies that the deletion of NLRP3 (which is the most studied inflammasome component) abates the protective effects of IPC due to inhibition of IL6 production and lacking of its signaling (23).
It seems that various inflammatory cytokines are involved in the stimulation of the adverse inflammatory reactions in response to IRI, as well as in protective signaling against subsequent IRI. Accordingly, the above discussed scenario should be confirmed as a whole by experimental studies, to identify whether blocking the release of IL1β and IL18, with the subsequent lack of IL6 induction, would increase or decrease heart protection.

Nevertheless, the augmentation of the above presented scenario at different levels (for example, through NO inhalation, NO_2^- administration, the use of KATP channel agonists) prior to heart transplantation and or other cardiac IRIs was found to (or is expected to) provide a significant degree of protection against the adverse effects of IRI, with an associated better clinical outcome (24).

In conclusion, this manuscript reviews a possible mechanism, through which RIPC would be involved in the attenuation of inflammasomes activation and cytokine production within the heart in response to IRI, especially during transplantation. Further studies should be conducted to confirm this mechanism, and whether it could be also considered for other organs such as lung, kidney and liver.

Conflicts of interest
No special funding was provided to produce this work. The author declares no conflicts of interest.

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Figures

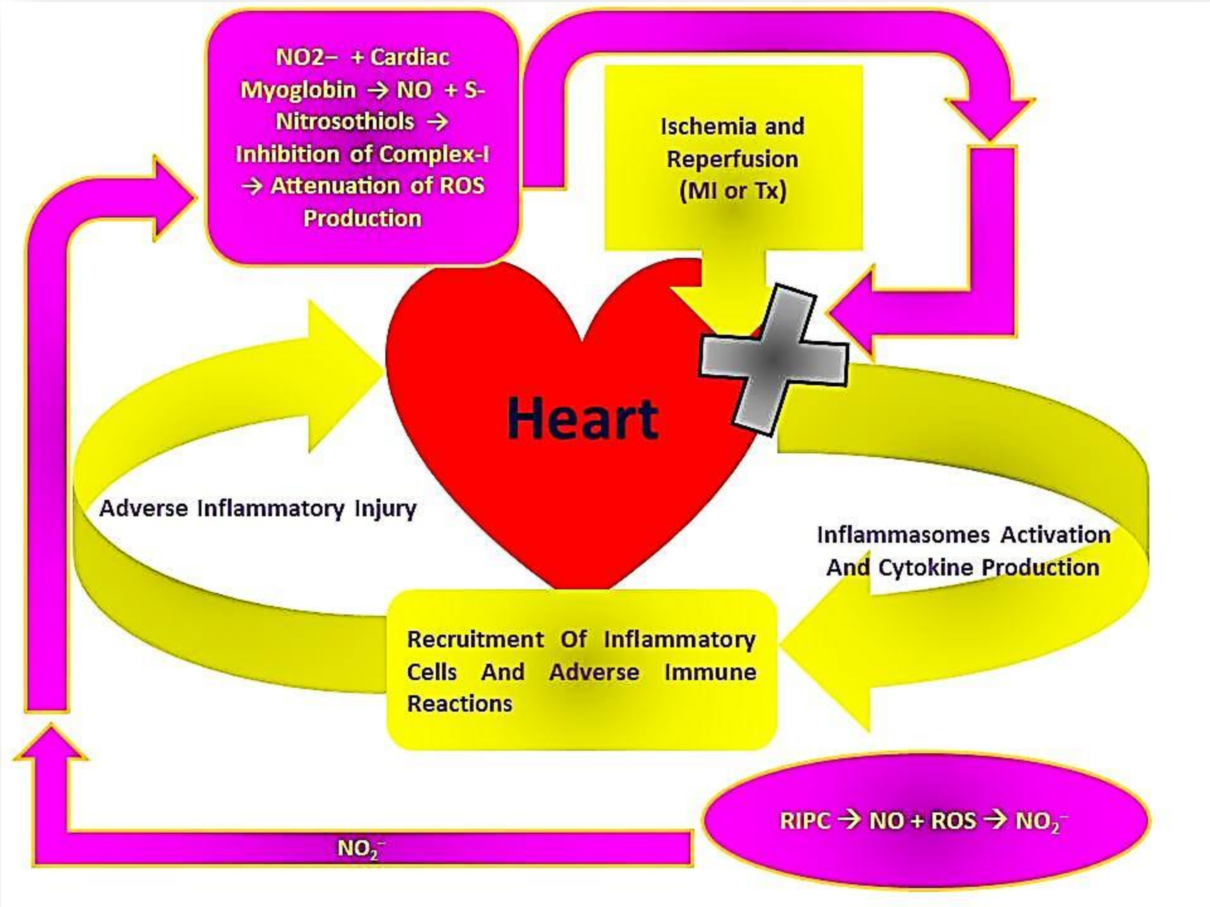

Figure 1; diagrammatic representation of the mechanism, through which RIPC attenuates inflammasomes activation and cytokine production within the heart in response to IRI.