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Protective effects of limb remote ischemic per-conditioning on the heart injury induced by renal ischemic-reperfusion through the interaction of the apelin with the RAS/iNOS pathway

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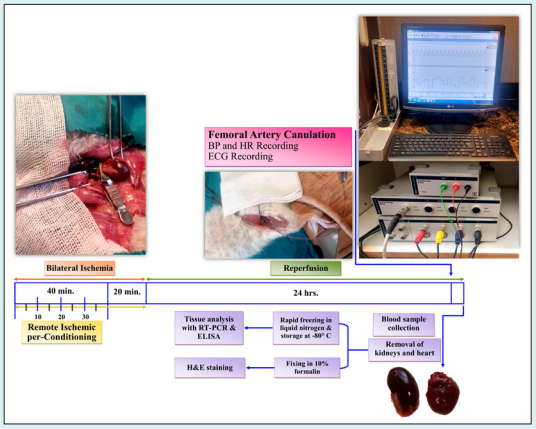
Abstract

Introduction: Remote ischemic conditioning upregulates endogenous protective pathways in response to ischemia-reperfusion injury. This study tested the hypothesis that limb remote ischemic per-conditioning (RIPerC) exerts cardioprotective effects via the renin-angiotensin system (RAS)/ inducible nitric oxide synthase (iNOS)/ apelin pathway.

Methods: Renal ischemia-reperfusion injury (I/R) was induced by bilateral occlusion of the renal pedicles for 60 minutes, followed by 24 hours of reperfusion; sham-operated rats served as controls. RIPerC was induced by four cycles (5 minutes) of limb ischemia-reperfusion along with bilateral renal ischemia. The functional disturbance was evaluated by renal (BUN and creatinine) and cardiac (troponin I and lactate dehydrogenase) injury biomarkers.



Results: Renal I/R injury increased renal and cardiac injury biomarkers that were reduced in the RIPerC group. Histopathological findings of the kidney and heart were also suggestive of amelioration injury-induced changes in the RIPerC group. Assessment of cardiac electrophysiology revealed that RIPerC ameliorated the decline in P wave duration without significantly affecting other cardiac electrophysiological changes. Further, renal I/R injury increased the plasma (322.40±34.01 IU/L), renal (8.27±1.10 mIU/mg of Protein), and cardiac (68.28±10.28 mIU/mg of protein) angiotensin-converting enzyme (ACE) activities in association with elevations in the plasma and urine nitrite (25.47±2.01 & 16.62±3.05 µmol/L) and nitrate (15.47±1.33 & 5.01±0.96 µmol/L) levels; these changes were reversed by RIPerC. Further, renal ischemia-reperfusion injury significantly (P=0.047) decreased the renal (but not cardiac) apelin mRNA expression, while renal and cardiac ACE2 (P<0.05) and iNOS (P=0.043) mRNA expressions were significantly increased compared to the sham group; these effects were largely reversed by RIPerC.

Conclusion: Our results indicated that RIPerC protects the heart against renal ischemia-reperfusion injury, likely via interaction of the apelin with the RAS/iNOS pathway.

Introduction

Renal ischemia-reperfusion (I/R) is a major cause of acute kidney injury (AKI) that is usually induced in some surgeries (kidney transplantation and coronary artery bypass grafting) and multiple clinical situations, including trauma, severe infection, sepsis, and hemorrhagic shock.[1,2] Renal I/R is characterized by sudden restriction of blood supply to the kidney followed by the subsequent restoration of perfusion and re-oxygenation.[3,4]

The consequences of renal I/R injury are local as well as remote organ destruction such as liver,[5] lung,[6,7] and heart.[8] The physiological and pathophysiological

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Research Highlights

What is the current knowledge?

√ Remote ischemic conditioning upregulates endogenous protective pathways in response to ischemia-reperfusion injury.

√ The physiological and pathophysiological interaction between the kidney and the cardiovascular system provides essential indicators for maintaining homeostasis.

What is new here?

√ Limb remote ischemic per conditioning improves the myocardium dysfunction induced by renal ischemia-reperfusion injury through the interaction of the apelin with the RAS/iNOS pathway.

diseases.[55] Apelin depletion progressed the myocardium dysfunction and structural remodeling through angiotensin II pathways.[56] Our data clearly indicated that remote ischemic per-conditioning suppressed the cardiac ACE activity and ACE2 expression.

Conclusion

Remote ischemic per-conditioning is a potential phenomenon to promote endogenous protective pathways against renal I/R injury. The findings of the current study revealed that renal I/R induced kidney and heart structural and functional disturbance by a significant increase in injury biomarkers. Histological damages in the renal and heart tissues were in line with the increased ACE activity and NO metabolites in the tissues and biological samples. On the other hand, the level of apelin mRNA was downregulated, but iNOS and ACE2 genes were upregulated in the renal and heart tissues. In total, our results indicated that RIPerC protects the heart against renal I/R injury, probably through the interaction of the apelin with the RAS/iNOS pathway.

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Authors' Contribution

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Competing interests

The authors declare no conflict of interest.

Ethical Statement

The experimental protocols were approved by the local ethics committee of Shiraz University of Medical Sciences (Approval ID: IR.SUMS.REC.1399.894).

Data Availability Statement

Data reported in this manuscript are available upon reasonable request from the corresponding author.

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