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# Limb ischemic per-conditioning ameliorated myocardial injury induced by renal ischemia/reperfusion in rats: the role of Klotho

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## Abstract

**Background** Renal ischemic/reperfusion (I/R) injury leads to acute kidney injury with multiple organ damage. Klotho has anti-inflammatory and antioxidant capacities and protects the heart and kidneys against I/R injury. This study aimed to determine whether Klotho is involved in the cardioprotective effect of limb ischemic per-conditioning (LIPerC) during renal I/R injury.

**Methods** Sprague-Dawley rats were randomly divided into three groups: Sham, I/R underwent bilateral occlusions of the renal pedicles for 60 min followed by reperfusion for 24 h, and LIPerc + I/R, which underwent cyclic I/R of the left femoral artery performed during renal ischemia. After 24 h, plasma, urine, and kidney and heart tissue were collected. Renal and cardiac functional biomarkers, soluble Klotho, oxidative stress, and inflammatory mediators were assessed.

**Results** Renal I/R injury caused a decrease in soluble Klotho and increased blood urea nitrogen, creatinine, troponin I, and LDH ($p < 0.01$). Moreover, it established oxidative stress and histopathological changes in the kidney and myocardium. The levels of *TNF-α* and *NF-κB* were upregulated, and *Klotho* ($p < 0.01$) was downregulated in the post-I/R cardiac tissue. LIPerC improved the histopathological changes and suppressed the oxidative status and inflammation. LIPerC could not compensate for the *Klotho* expression in the heart tissue. However, correlations between plasma levels and heart expression of Klotho with oxidative and inflammatory signals could confirm the role of Klotho in the healing effect of LIPerC on remote cardiac injury.

**Conclusion** LIPerC may potentially ameliorate the remote cardiac dysfunction induced by renal I/R injury by modulating oxidative and inflammatory signals associated with the Klotho protein.

**Keywords** Heart injury, Inflammation, Klotho, Oxidative stress, Renal ischemic/Reperfusion injury

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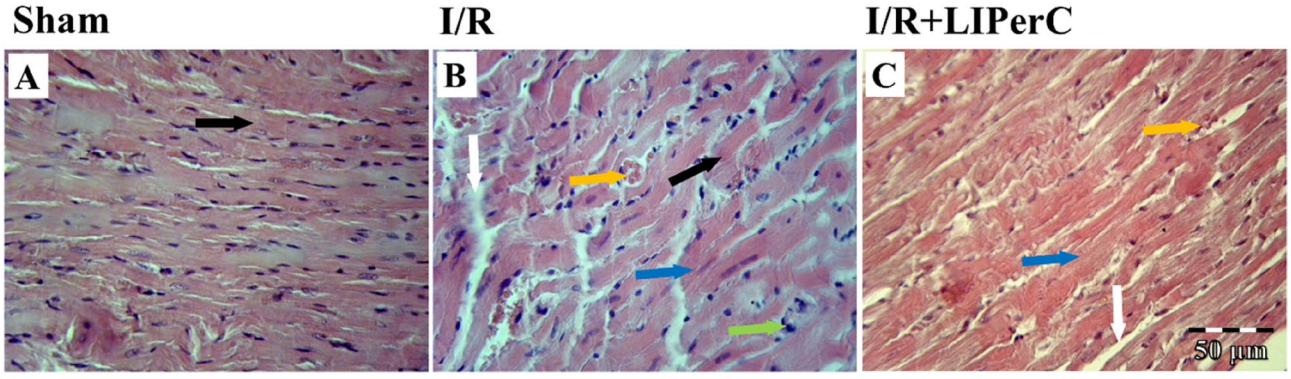


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| Parameters | | Sham | I/R | I/R+LIPerC |
|---|---|---|---|---|
| Heart structural changes | Interstitial edema | No change | Moderate | Mild |
| | Congestion | No change | Mild | Mild |
| | Leukocyte infiltration | No change | Mild | No change |
| | Wavy fiber | No change | Moderate | Mild |

**Fig. 5** Effects of Limb ischemic per-conditioning on the pathological changes of the heart 24 h after renal ischemia-reperfusion injury ($n=5$). Light microphotographs (H&E, ×400, scale bar 50 µm). (A) sham, (B) I/R, (C) I/R + LIPerC, and (D) quantitative score of damages [no change, mild (< 30%), moderate (31–60%), and severe (61–100%)]. Muscle fiber (black arrow), interstitial edema (white arrow), wavy fiber (blue arrow), vascular congestion (orange arrow), and leukocyte infiltration (green arrow). Abbreviations: I/R; ischemic reperfusion, LIPerC; limb ischemic per-conditioning

not capture long-term changes in Klotho dynamics or cardiac remodeling. Second, we did not employ genetic or pharmacological Klotho manipulation, which would provide stronger mechanistic evidence. Third, only male rats were studied, and sex-related differences in response to renal I/R and LIPerC cannot be excluded. Finally, while rodent models provide important mechanistic insights, translation to human AKI and cardiorenal syndrome must be made cautiously.

Further studies should therefore evaluate longer reperfusion periods, employ Klotho gain and loss-of-function strategies, and investigate whether pharmacologic agents or exercise can synergize with LIPerC to enhance cardioprotection. Translational studies in patients with AKI-associated cardiac injury are also needed to confirm the relevance of these findings.

## Conclusions

The present study demonstrates for the first time that cardiac *Klotho* expression is down-regulated following renal I/R. Although LIPerC did not restore myocardial *Klotho* expression, it significantly attenuated renal and cardiac injury, oxidative stress, and inflammation. Our correlation analyses further suggest that soluble Klotho levels are inversely associated with oxidative stress indices and inflammatory mediators, indicating that systemic Klotho availability may contribute to the cardioprotective effects of LIPerC. These findings support the concept of Klotho as a key cardio–renal protective factor and suggest that modulation of oxidative and inflammatory pathways is central to its role. Elucidating these mechanisms in longer-term and translational studies could provide novel therapeutic strategies for preventing cardiorenal complications in patients with AKI.

## Supplementary Information

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Supplementary Material 1.

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**Authors' contributions**

"Z.K.and S.J. designed and supervised the project. Z.K. performed animal surgery and collected samples. F.M. designed primers and performed molecular and ELISA assays. Z.K. analyzed the results, managed the database, performed the statistical analysis, and drafted the manuscript. All authors contributed to the data interpretation and read and edited the final manuscript."

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**Data availability**

No datasets were generated or analysed during the current study.