Remote Limb Ischemic Postconditioning Improves Postresuscitation Cerebrovascular Circulation and Survival/Neurological Prognoses via In Situ and Remote Activation of Akt-eNOS-NO Signaling Pathway

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Introduction: Cerebrovascular circulation is usually compromised after cardiac arrest and CPR. Remote limb ischemic post-conditioning (RLIP) is clinically feasible and can potentially mitigate post-resuscitation neurological deficits. Since nitric oxide (NO) is implicated in post-conditioning protection, we aim to investigate if RLIP impacts post-resuscitation cerebral perfusion and prognosis via NO-related mechanism.

Hypothesis: RLIP improves post-CPR cerebral perfusion and prognosis through \textit{in situ} and remote activation of Akt-eNOS signaling.

Methods: Using an established rat model of asphyxia cardiac arrest and CPR, we randomized the rats to the following groups: (1) sham, (2) standard CPR, (3) RLIP 5 min after return of spontaneous circulation (ROSC). RLIP was done by 3 cycles of 5 min of left hind limb ischemia followed by 5 min of reperfusion. Arterial blood was sampled for colorimetric determination of nitrate/nitrite. The cerebral perfusion was continuously recorded by OxyFLO probe. Two hours after ROSC, the brain and left femoral artery were harvested for measuring phosphorylated endothelial NO synthase (p-eNOS at Ser1177) and protein kinase B (p-Akt at Ser473). In a subgroup the survival and neurological outcomes were monitored up to 3 days.

Results: The cerebral perfusion was significantly decreased (0.6-0.8 folds that of baseline) after ROSC in standard CPR group. If RLIP was employed, the cerebral perfusion was significantly augmented (up to 1.6 folds, \( P < 0.001 \)) in the post-resuscitation phase. This was associated with improved survival (log-rank \( P < 0.05 \)) and neurological scores at 6, 24, 48 and 72 h (all \( P < 0.05 \)). Plasma NO as indicated by nitrate/nitrite was significantly increased in the RLIP group (\( P < 0.05 \)). Most of all, p-eNOS and p-Akt were significantly increased not only in left femoral artery but also in brain. If NOS inhibitor \( \text{N}^\omega \)-nitro-L-arginine methyl ester (10 mg/kg) was used, not only the NO increase was reversed, the improvement in survival and neurological outcomes were also abrogated.

Conclusions: RLIP enhances post-resuscitation cerebral perfusion and improves survival and neurological prognoses not only via \textit{in situ} limb artery derived NO but remote activation of Akt-eNOS signaling in the brain.

Disclosure: