Remote Ischemic Conditioning

– From Organs/Tissues to Organs –

Yoshihiko Seino, MD, PhD

Remote ischemic conditioning (RIC) has become a challenging therapeutic strategy for protecting organs or tissues against the detrimental effects of acute ischemia-reperfusion injury. In 1993, Przyklenk et al demonstrated for the first time in a canine model that the application of brief occlusions and reperfusion of the circumflex coronary artery significantly reduced the size of the myocardial infarct arising from sustained occlusion of the left anterior coronary artery.¹ This phenomenon of intramyocardial cardioprotection

across the different coronary territories was then extended beyond the heart such that the latter could be protected by RIC to organs and tissues remote from the heart, and further to protection of other organs such as kidney, brain, lung, liver, and so on. RIC can be applied prior to ischemia (preconditioning: RI-preC), during ischemia (per-conditioning: RI-perC), or at the time of reperfusion (post-conditioning: RI-postC) (**Figure 1**).

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Nippon Medical School Chiba-Hokusou Hospital, Chiba, Japan

Mailing address: Yoshihiko Seino, MD, PhD, Cardiovascular Center, Department of Cardiovascular Medicine, Nippon Medical School Chiba-Hokusoh Hospital, 1715 Kamagari, Inzai, Chiba, Japan. E-mail: y-seino@nms.ac.jp

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Figure 2. Comparison of high-sensitivity troponin T (hs-TnT) release following elective percutaneous coronary intervention (PCI) between the remote preconditioning group and the controls. Although baseline hs-TnT values show no significant difference between the 2 groups, hs-TnT in the RIP group showed significantly lower values ($P < 0.05$) at 6, 12, and 24 h after PCI compared with the control group.

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Arm to Heart

In 2006, Cheung et al² first demonstrated RI-preC in the clinical setting of children undergoing corrective cardiac surgery for congenital heart disease; that is, 4 episodes of 5-min BP-cuff inflations and deflations prior to the surgery reduced perioperative myocardial injury (less troponin I release). In 2010, Botker et al³ reported that RI-preC before hospital admission as complementary to angioplasty in patients with acute myocardial infarction, increased myocardial salvage assessed by myocardial perfusion imaging. A review article last year in this Journal⁴ described the beneficial effect of RIC on myocardial injury assessed by cardiac biomarkers (CK-MB, troponin T/I) in the setting of CABG and PCI, based on their meta-analysis of randomized trials. Meta-analysis of PCI revealed reduced biomarker release for myocardial injury with RI-preC or RI-perC (standardized mean differences: SMD, -0.21 (95% CI: -0.66 to 0.24) compared with controls, while the CABG studies revealed a significant beneficial effect of RI-preC on myocardial injury reduction (SMD, -0.34 , 95% CI: -0.59 to -0.08).³ We have confirmed and presented the cardioprotective effect of RI-preC assessed by high-sensitivity troponin T (Hs-TnT) release-kinetics in patients undergoing elective-PCI.⁵ Prior to elective-PCI, we applied RI-preC consisting of 3 episodes of a 5-min cycle of arm ischemia induced by manual inflations and deflations of the BP-cuff. Our study demonstrated that under similar myocardial stress conditions (equivalent NT-proBNP values in both the RI-preC group and the controls), RI-preC significantly reduced the elevation of Hs-TnT compared with the controls (Figure 2).

Arm to Kidney

Contrast-induced acute kidney injury (CI-AKI) is a common hospital-acquired condition, especially following PCI or coronary angiography (CAG), and is associated with increased morbidity and mortality. The common pathophysiological mecha-

nism for CI-AKI is renal ischemic injury caused by iodinated contrast medium-induced reduction in renal blood flow and glomerular filtration rate, and oxygen free radical-mediated direct tubular toxicity. CI-AKI is universally defined as ≥ 0.5 mg/dl increase in serum creatinine (Cr) or a 25% increase, assessed within 48–72 h after administration of contrast medium. In this issue of the Journal, Igarashi et al⁶ report that RI-preC consisting of intermittent arm ischemia induced by BP-cuff inflations and deflations prior to PCI or CAG alleviated the incidence of CI-AKI defined by their smart and sensitive “L-FABP (liver-type fatty acid-binding protein)-based CI-AKI” criteria. They showed that RI-preC alleviated CI-AKI (26.9% in the controls vs. 7.7% in the RI-preC group, $P=0.038$) defined by a rapidly released more sensitive biomarker, L-FABP, as the L-FABP level $>17.4 \mu\text{g/g}$ Cr or 25% increase within 24 h. In their study, none of the conventional markers, Cr, eGFR and cystatin C, changed significantly 48 h after contrast medium administration in either group. Thus, the universally referred Cr-based CI-AKI was not detected in their study. Their study protocol was almost same as the RenPro trial,⁷ except for the definition of CI-AKI. The RenPro trial demonstrated that RI-preC prevented CI-AKI defined by the universally referred Cr-based CI-AKI (incidence: 40% in the controls vs. 12% in the RI-preC group, $P=0.002$). The clinical implication of L-FABP-based CI-AKI is still obscure. Further investigation should be addressed to clarifying the prognostic and therapeutic implications of a L-FABP-based CI-AKI definition.

Heart to Kidney (RI-PostC)

A recent report by Deftereos et al⁸ describing the renoprotective effect of RI-postC at the heart in patients undergoing PCI is further interesting. They included 225 patients with non-ST-segment elevation MI, and applied RI-postC by cycles of inflation and deflation of the stent balloon during PCI. The Cr-based CI-AKI rate was 12.4% in the RI-postC group vs. 29.5% in the controls ($P=0.002$). Importantly, the 30-day rate of death or rehospitalization was 12.4% in RI-postC group vs. 22.3% in the control group ($P=0.05$). These treatments would be readily

applicable in the clinical setting of PCI in terms of the “win-win” interrelationship.

Possible Mechanisms of RIC

There are 3 pathways considered to underlay the phenomenon of RIC: humoral, neural, and systemic response pathways (Figure 1). There are a number of different signaling mediators, including GPCRs (G-protein cell surface coupled receptors: adenosine, bradykinin, opioids, angiotensin, etc), calcitonin gene-related peptide, activation of the mitochondrial K_{ATP} channel, reactive oxygen species, nitric oxide, heat shock protein, and so on. Igarashi et al⁶ has described that neither the hs-CRP nor the pentraxin-3 level differed significantly between their RI-preC group and the controls, whereas the % changes in ADMA (asymmetrical dimethyl-arginine: endogenous inhibitor of NOS) and DROM (derivatives of reactive oxidative metabolites) were significantly lower in the RI-preC group. Their data suggests that RIC against CI-AKI might be mediated by decreasing oxidative stress, and not necessarily through decreasing the inflammatory response. Shimizu et al⁹ identified circulating humoral factors generated in response to RI-preC of limb to be hydrophobic proteins between 3.5 and 15 kDa. Most recent investigation has revealed that stromal cell-derived factor-1 α (SDF-1 α or CXCL 12), a 10-kDa chemokine induced by hypoxia, recruits stem cells and also exerts direct cardioprotection via its receptor, CXCR4;¹⁰ thus, RIC stimulates SDF-1 α release, which appears to be essential in the process.

Oxygen Pre- (Per- Rather Than Pre-?) Conditioning Also Prevents CI-AKI

Recent study by Sekiguchi et al¹¹ has shown that oxygen administration via nasal cannula at 2 L/min from 10 min before to the end of the procedure (elective PCI or CAG) reduced the incidence of Cr-based CI-AKI (0.6% vs. 5.1%, OR: 0.11, $P=0.01$) compared with the controls. Considering the pathophysiologic mechanisms of CI-AKI as described, oxygen per-rather than preconditioning would oppose renal tissue hypoxia (increase in oxygen demand besides decrease in oxygen supply) caused by acceleration of tissue metabolism accompanied by increased tubular reabsorption, increased oxygen consumption at the renal tubule by microvascular damage, etc and would elicit renoprotection against CI-AKI. Should we apply

remote ischemic conditioning or oxygen conditioning, or both? “Never starve in a cook’s shop.”

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