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RNase1 as a potential mediator of remote ischaemic preconditioning for cardioprotection

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Abstract

© The Author 2015. Published by Oxford University Press on behalf of the European Association for Cardio-Thoracic Surgery. All rights reserved. OBJECTIVES: Remote ischaemic preconditioning (RIPC) is a non-invasive and virtually cost-free strategy for protecting the heart against acute ischaemia-reperfusion injury (IRI). We have recently shown that the inhibition of extracellular RNA (eRNA) using non-toxic RNase1 protected the heart against acute IRI, reduced myocardial infarct (MI) size and preserved left ventricular systolic function in rodent animal MI models. Based on this previous work in animals, the role of the eRNA/RNase1 system in cardiac RIPC in humans should be defined. METHODS: Fourteen patients underwent cardiac surgery without RIPC; from each patient, six separate 5 ml blood specimens from radial artery and two blood specimens from coronary sinus at different time points during heart surgery were taken. Six healthy donors received RIPC (4 × 5 min upper limb ischaemia); blood parameters were quantified before and after RIPC. Twelve patients underwent cardiac surgery of which 6 received RIPC, whereas the remaining 6 were exposed to sham procedure. Circulating eRNA was quantified in plasma from arterial and coronary sinus blood obtained from patients undergoing cardiac by standard procedures. Tumour necrosis factor-α (TNF-α) production by heart tissue was assessed by enzyme-linked immuno-sorbent assay; RNase activity was quantified by an enzymatic assay. RESULTS: Before surgery, eRNA levels were similar in both groups (14 ± 6 vs 13 ± 5 ng/ml; P = 0.9967). In patients without RIPC, arterial eRNA levels rose during surgery (87 ± 12 ng/ml) and peaked after (127 ± 11 ng/ml) aortic declamping; accordingly, eRNA levels in coronary sinus blood were significantly higher (206 ± 32 ng/ml; P = 0.0129) than that in radial artery. Moreover, significant elevation of TNF-α (36 ± 6 ng/ml; P = 0.0059) particularly in coronary sinus blood after opening of the aortic clamping was observed. Interestingly, applying a RIPC protocol significantly increased levels of plasma endogenous vascular RNase1 by >7-fold, and the levels of arterial (31 ± 7 ng/ml; P = 0.0024) and coronary sinus (37 ± 9 ng/ml; P < 0.0001) circulating eRNA, as well as circulating TNF-α (20 ± 4 ng/ml; P = 0.0050) levels were significantly reduced. CONCLUSIONS: Upon RIPC, the level of cardioprotective RNase1 increased, while the concentration of damaging eRNA and TNF-α decreased. The present findings imply a significant contribution of the RIPC-dependent (endothelial) RNase1 for improving the outcome of cardiac surgery. However, the exact mechanism of RNase1-induced cardioprotection still remains to be explored.

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Keywords

Acute inflammation, Cardiac surgery, Extracellular RNA (eRNA), Ischaemia-reperfusion, Remote ischaemic preconditioning, Ribonuclease-1 (RNase1), Tumour necrosis factor-α (TNF-α)