

LETTER TO THE EDITOR

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# Possible involvement of a single common mechanism in the cardioprotective effects of pre-/per-/postconditioning

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**Keywords:** Ischemia reperfusion injury, Postconditioning with lactate-enriched blood, Revascularization, ST-segment elevation myocardial infarction

## To the Editor

Clinical translation of pre-/per-/postconditioning has long been attempted, with no substantial success so far. The precise mechanisms underlying the cardioprotective effects of these approaches remain to be elucidated. Knowledge of the precise mechanisms may help determine when and whom to apply these approaches and how to achieve maximal cardioprotective effects.

My colleagues and I recently reported a modified ischemic postconditioning protocol, postconditioning with lactate-enriched blood (PCLeB) (Koyama et al. 2013,2014). PCLeB comprises intermittent reperfusion and timely coronary injections of lactated Ringer's solution (Fig. 1), aimed at increasing the delay in recovery from intracellular acidosis by impeding lactate washout. Through this modification, we specifically targeted reperfusion-induced hypercontracture, which develops within minutes of reperfusion of the ischemic myocardium. The strong mechanical force generated by hypercontracture disrupts the cell skeleton, leading to irreversible cell injury. The higher tissue lactate concentrations achieved by PCLeB during reperfusion may impede interactions between myofilaments and attenuate hypercontracture development. Despite the small-scale nature of the study, good long-term outcomes associated with reduced plasma NT-proBNP levels have been reported in patients

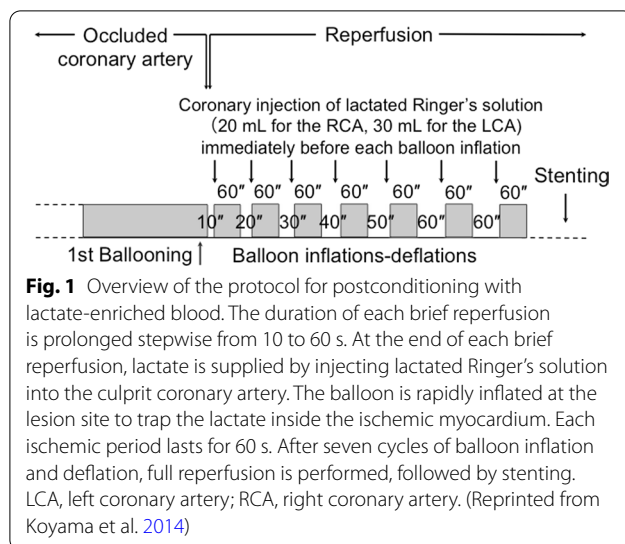
with ST-segment elevation myocardial infarction treated using PCLeB (Koyama et al. 2020).

Remote ischemic preconditioning (McLeod et al. 2017) appears to create a condition similar to that created by PCLeB in reperfused ischemic myocardium. Intermittent limb ischemia releases tissue lactate, which is locally produced and accumulated during limb ischemia, into the systemic circulation. Thus, remote ischemic preconditioning can be regarded as a maneuver that enables reperfusion of the ischemic myocardium with "lactate-enriched blood."

Instead of attenuating force generation, force dispersion may be another approach. Pacing postconditioning is a procedure in which ventricular pacing is implemented during reperfusion (Babiker 2016). Pacing-induced dyssynchrony may disperse the force generated by hypercontracture because the timing of the peak systole differs between cells, and the force generated by myocardial contraction cannot be fully integrated, which may weaken the shear force imposed on each myocardial cell.

Regarding ischemic preconditioning, I previously reported the possibility that its cardioprotective effects may reside in the delayed onset of reperfusion injury (Koyama 2021). In other words, a longer duration of prolonged ischemia may be needed for reperfusion injury to occur in preconditioned hearts. If this is true, a large difference in infarct size observed between the control and preconditioned hearts is determined by whether reperfusion injury has occurred. Preconditioning has been demonstrated to delay the increase in intracellular  $Ca^{2+}$

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concentrations ( $[Ca^{2+}]_i$ ) during subsequent prolonged ischemia (Dekker et al. 1996). Therefore, prolonged ischemia may take longer to achieve the threshold level of  $[Ca^{2+}]_i$  for developing hypercontracture after reperfusion in the preconditioned hearts because hypercontracture develops with elevated  $[Ca^{2+}]_i$  and re-energization of myofilaments by adenosine triphosphate production after reperfusion. When prolonged ischemia is terminated relatively early, myocardial injury caused by reperfusion-induced hypercontracture would occur in control hearts but not in preconditioned hearts; thus, a large difference in the infarct size was observed between the two (Murry et al. 1986).

In conclusion, the cardioprotective effects of pre-/per-/postconditioning may be explained using a single common key concept, reperfusion-induced hypercontracture.

#### Abbreviations

$[Ca^{2+}]_i$ : Intracellular  $Ca^{2+}$  concentrations; PCLeB: Postconditioning with lactate-enriched blood.

#### Acknowledgements

I would like to thank Editage [<http://www.editage.com>] for editing and reviewing this manuscript for English language.

#### Authors' contributions

Not applicable because this is a single-author paper.

#### Funding

None.

#### Availability of data and materials

Not applicable.

#### Declarations

#### Ethics approval and consent to participate

Not applicable.

#### Consent for publication

Not applicable.

#### Competing interests

The author declares no competing interest relevant to this work.

Received: 25 May 2021 Accepted: 14 July 2021

Published online: 19 July 2021

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