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Remote ischaemic preconditioning: essential part of the "Great Game" to reduce myocardial injury after PCI

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"Go up the hill and ask. Here begins the Great Game" - Kim, Kipling, 1901

We read with great interest the paper of Kumar et al[1] published in the present edition of AsiaIntervention, as this is the first randomised clinical trial demonstrating the benefit of remote ischaemic preconditioning (RIPC) on the reduction of periprocedural myocardial infarction (PMI) after a percutaneous coronary intervention (PCI) in Indian patients.

Two main considerations may arise from the present work: 1) RIPC is not affected by ethnicity; 2) the benefit offered in patients undergoing PCI for stable angina seems consistent with data already reported in the literature.

Some animal studies that date back to almost twenty years ago have already postulated the beneficial effect of a "brief ischaemia", both in the heart and in the non-cardiac tissues[2,3]. Recently, some steps towards clarifying the mechanism responsible for remote ischaemic preconditioning have been taken[4-6]. The signals seem to be transferred to the peripheral target organs through different pathways, involving both the somato-sensory and the autonomous nervous systems[4]. Both of them might carry the central inputs to the downstream extracellular specific receptors, and then, by intracellular signal transduction molecules, may cause changes in mitochondrial function[4,5], as shown in **Figure 1**. Adenosine, bradykinin, and calcitonin gene-related peptide are probably important mediators in the afferent loop of this reflex[2,3,6,7]; however, the exact nature of the signal transduction from the remote tissue to the target organs remains to be fully clarified.

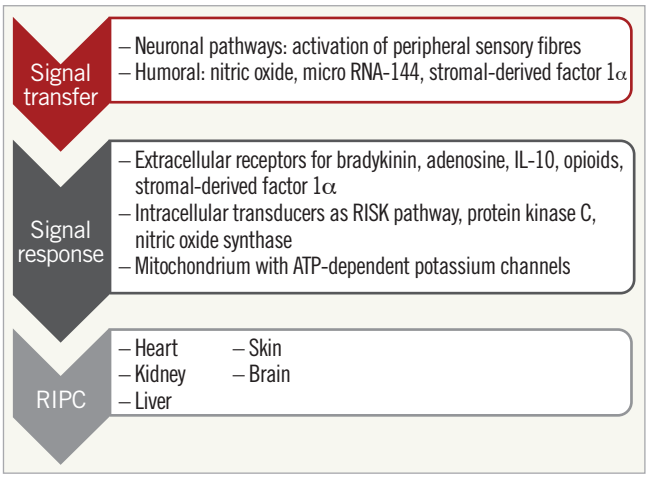

Figure 1. *RIPC exerts its function through different pathways.*

The impact of these experimental models in clinical practice has been largely debated. A meta-analysis of randomised controlled trials (RCTs) of patients undergoing coronary surgical revascularisation showed a reduced release of troponin after the intervention in those treated with RIPC, especially in the presence of multivessel coronary disease[8]. Interestingly, among the nine selected trials, one[9] focused on Asian patients, showing consistent benefit of RIPC in terms of myocardial protection.

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Similarly, another meta-analysis has shown a reduction in terms of PMIs for patients treated with PCI[10], despite heterogeneity of definition[11]. In that paper, two RCTs enrolling Asian patients were included, one from Egypt and the other from Iran[12,13]. These trials showed conflicting results, but when pooling them together with the present study a significant reduction of PMIs was shown (OR 0.29 [0.16-0.53]) **(Figure 2)**.

Moreover, this paper opens new horizons for future research. Kumar et al[1] have found a trend towards a lower incidence of TIMI flow <3 during the procedure in the RIPC group, postulating a positive effect of the remote preconditioning in the setting of acute coronary syndrome, as shown in the work of Bøtker et al[14]. Certainly, in this clinical context the inflammatory response to the plaque rupture and the individual stress response to the event are significant confounding factors that might influence the clinical response to RIPC. However, it is precisely these patients, who lack collateral circulation systems, who could benefit more from remote preconditioning.

Finally, like Kipling's Kim, now is the time to leave the research laboratories and to go on up the hill in the interventional cathlabs to "ask" patients if RIPC may exert positive effects after interventional procedures.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Kumar S, Krishna A, Kapoor A, Tewari S, Garg N, Kumar Goel P. Role of remote ischaemic preconditioning on myocardial injury in stable patients undergoing percutaneous coronary intervention: a randomised case-control study. *AsiaIntervention.* 2015;1:116-23.

2. Gho BC, Schoemaker RG, van den Doel MA, Duncker DJ, Verdouw PD. Myocardial protection by brief ischemia in noncardiac tissue. *Circulation.* 1996;94:2193-200.

3. Pell TJ, Baxter GF, Yellon DM, Drew GM. Renal ischemia preconditions myocardium: role of adenosine receptors and ATP-sensitive potassium channels. *Am J Physiol.* 1998;275:H1542-7.

4. Heusch G, Bøtker HE, Przyklenk K, Redington A, Yellon D. Remote ischemic conditioning. *J Am Coll Cardiol.* 2015;65:177-95.

5. Heusch G. Molecular basis of cardioprotection: signal transduction in ischemic pre-, post-, and remote conditioning. *Circ Res.* 2015;116:674-99.

6. Leung CH, Wang L, Nielsen JM, Tropak MB, Fu YY, Kato H, Callahan J, Redington AN, Caldarone CA. Remote cardioprotection by transfer of coronary effluent from ischemic preconditioned rabbit heart preserves mitochondrial integrity and function via adenosine receptor activation. *Cardiovasc Drugs Ther.* 2014;28:7-17.

7. Jensen RV, Stottrup NB, Kristiansen SB, Bøtker HE. Release of a humoral circulating cardioprotective factor by remote ischemic

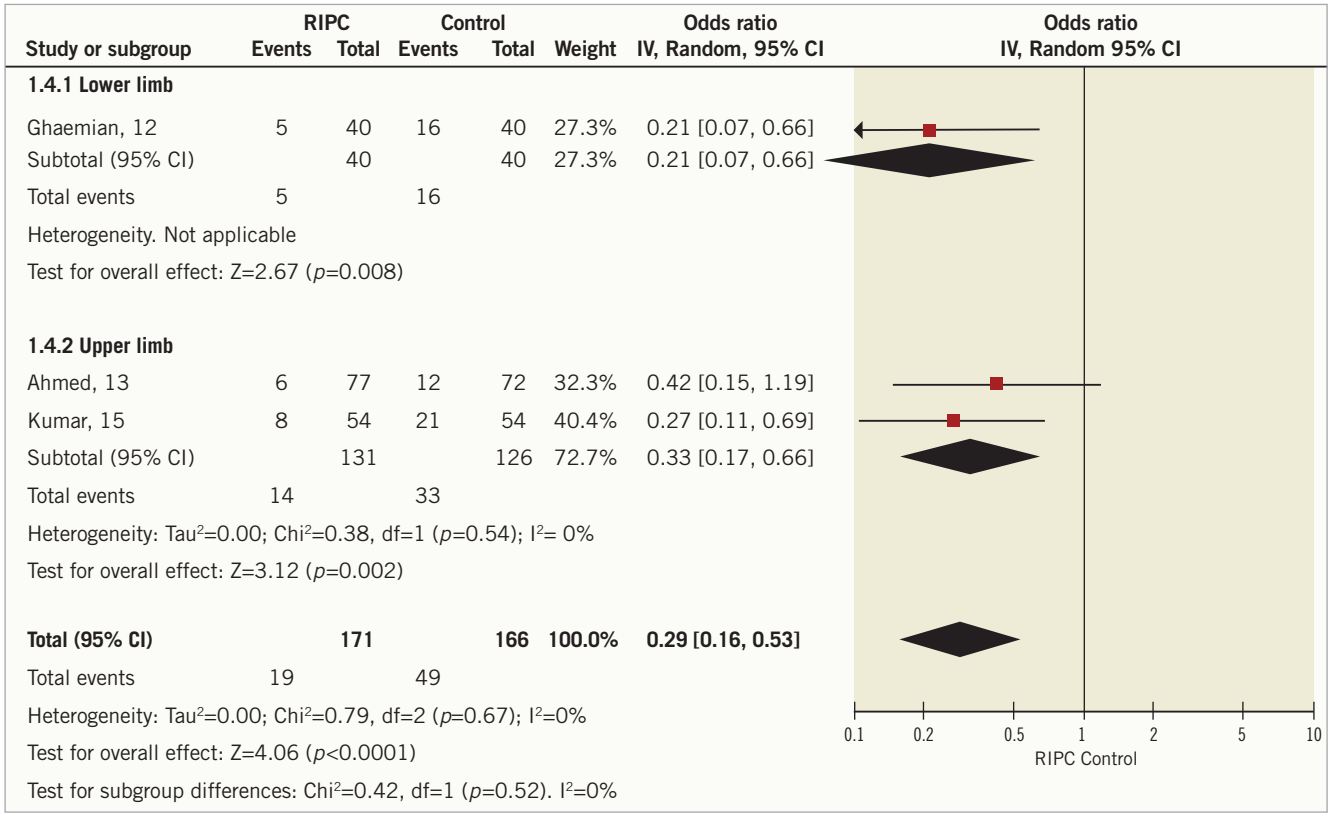

Figure 2. *Benefit of RIPC in Asian patients to reduce periprocedural myocardial infarctions.*

preconditioning is dependent on preserved neural pathways in diabetic patients. *Basic Res Cardiol.* 2012;107:285.

8. D'Ascenzo F, Cavallero E, Moretti C, Omedè P, Sciuto F, Rahman IA, Bonser RS, Yunseok J, Wagner R, Freiberger T, Kunst G, Marber MS, Thielmann M, Ji B, Amr YM, Modena MG, Zoccai GB, Sheiban I, Gaita F. Remote ischaemic preconditioning in coronary artery bypass surgery: a meta-analysis. *Heart.* 2012;98:1267-71.

9. Hong DM, Mint JJ, Kim JH, Sohn IS, Lim TW, Lim YJ, Bahk JH, Jeon Y. The effect of remote ischaemic preconditioning on myocardial injury in patients undergoing off-pump coronary artery bypass graft surgery. *Anaesth Intensive Care.* 2010;38:924-9.

10. D'Ascenzo F, Moretti C, Omedè P, Cerrato E, Cavallero E, Er F, Presutti DG, Colombo F, Crimi G, Conrotto F, Dinicolantonio JJ, Chen S, Prasad A, Biondi Zoccai G, Gaita F. Cardiac remote ischaemic preconditioning reduces periprocedural myocardial infarction for patients undergoing percutaneous coronary interventions: a meta-analysis of randomised clinical trials. *EuroIntervention.* 2014;9:1463-71.

11. Gili S, D'Ascenzo F, Moretti C, Cerrato E, Cavallero E, Er F, Presutti DG, Colombo F, Crimi G, Conrotto F, Dinicolantonio JJ, Chen S, Prasad A, Biondi Zoccai G, Gaita F. Impact on prognosis of periprocedural myocardial infarction after percutaneous coronary intervention. *J Interv Cardiol.* 2014;27:482-90.

12. Ahmed RM, Mohamed EH, Ashraf M, Maithili S, Nabil F, Rami R, Mohamed TI. Effect of remote ischemic preconditioning on serum troponin T level following elective percutaneous coronary intervention. *Catheter Cardiovasc Interv.* 2013;82:E647-53.

13. Ghaemian A, Nouraei SM, Abdollahian F, Naghshvar F, Giussani DA, Nouraei SA. Remote ischemic preconditioning in percutaneous coronary revascularization: a double-blind randomized controlled clinical trial. *Asian Cardiovasc Thorac Ann.* 2012;20:548-54.

14. Bøtker HE, Kharbanda R, Schmidt MR, Bottcher M, Kaltoft AK, Terkelsen CJ, Munk K, Andersen NH, Hansen TM, Trautner S, Lassen JF, Christiansen EH, Krusell LR, Kristensen SD, Thuesen L, Nielsen SS, Rehling M, Sørensen HT, Redington AN, Nielsen TT. Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. *Lancet.* 2010;375:727-34.