JACC: BASIC TO TRANSLATIONAL SCIENCE
VOL. ■, NO. ■, 2016

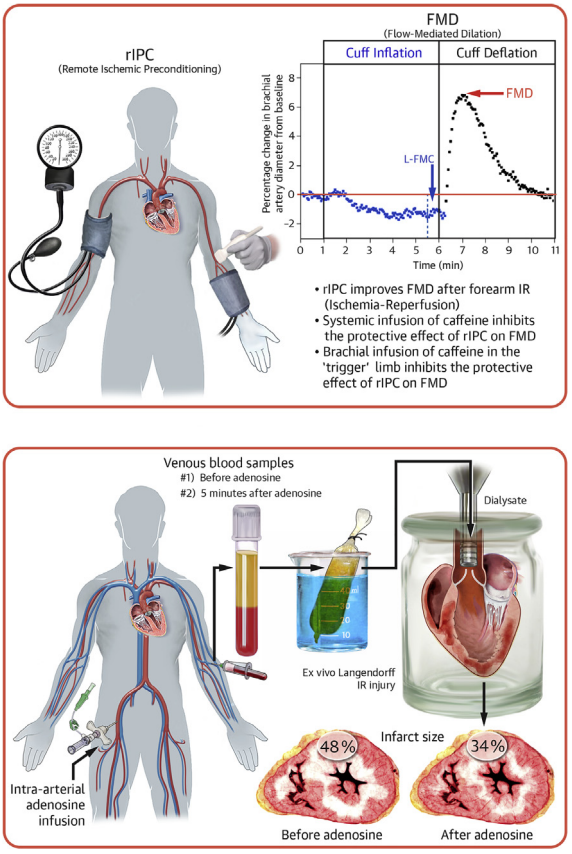
ISSN 2452-302X
http://dx.doi.org/10.1016/j.jacbts.2016.06.002

NEW RESEARCH PAPER

Adenosine Receptor Activation in the "Trigger" Limb of Remote Pre-Conditioning Mediates Human Endothelial Conditioning and Release of Circulating Cardioprotective Factor(s)

Hussain Contractor, MBChB, DPhil,[a] Rasmus Haarup Lie, MD, PhD,[b] Colin Cunnington, MBChB, DPhil,[a] Jing Li, PhD,[c] Nicolaj B. Støttrup, MD, PhD,[b] Cedric Manlhiot, BSc,[c] Hans Erik Bøtker, MD, PhD,[b] Michael R. Schmidt, MD, PhD,[b] J. Colin Forfar, MD, PhD,[a] Houman Ashrafian, MB BChir, DPhil,[a] Andrew Redington, MBBS, PhD,[d] Rajesh K. Kharbanda, MBChB, PhD[a]

VISUAL ABSTRACT



Contractor, H. et al. J Am Coll Cardiol Basic Trans Science. 2016;■(■):■–■.

HIGHLIGHTS

- **Pre-conditioning has emerged as a potentially powerful means of reducing ischemia-reperfusion injury.**
- **Several animal models have implicated adenosine in pre-conditioning pathways, but its role in human physiology is unknown.**
- **In human volunteers, the authors demonstrate that adenosine receptor activation in "trigger" tissue is an important step in initiating a pre-conditioning signal, but adenosine receptor blockade in "target" tissue does not block the protection afforded by pre-conditioning.**
- **The authors also demonstrate that pre-conditioning elaborates a transferrable cardioprotective factor(s) into the serum. This elaboration is prevented by adenosine receptor blockade but can be mirrored by the infusion of exogenous adenosine.**
- **An improved understanding of the physiological effectors of pre-conditioning may allow for better targeted clinical studies of pre-conditioning and pre-conditioning mimetics in the future.**

ABBREVIATIONS AND ACRONYMS

Ach = acetylcholine

ANOVA = analysis of variance

FMD = flow-mediated dilation

GTN = glyceryltrinitrate

IR = ischemia-reperfusion

LV = left ventricular

NMD = nitrate-mediated dilation

rIPC = remote ischemic pre-conditioning

SUMMARY

Remote ischemic pre-conditioning (rIPC) has emerged as a potential mechanism to reduce ischemia-reperfusion injury. Clinical data, however, have been mixed, and its physiological basis remains unclear, although it appears to involve release of circulating factor(s) and/or neural pathways. Here, the authors demonstrate that adenosine receptor activation is an important step in initiating human pre-conditioning; that pre-conditioning liberates circulating cardioprotective factor(s); and that exogenous adenosine infusion is able to recapitulate release of this factor. However, blockade of adenosine receptors in ischemic tissue does not block the protection afforded by pre-conditioning. These data have important implications for defining the physiology of human pre-conditioning and its translation to future clinical trials. (J Am Coll Cardiol Basic Trans Science 2016;■:■–■)

Remote ischemic pre-conditioning (rIPC) induces protection of central (target) organs from ischemia-reperfusion (IR) by brief ischemia of peripheral (trigger) tissue (1,2). Limb ischemia achieves rIPC in humans, and has been tested with positive results in clinical studies (3-10). However, other recent clinical studies also show neutral effects (11-15), and better understanding of the mechanisms of rIPC in humans may lead to maximization of its benefits. The signaling pathway from the trigger limb to target organs is poorly defined, but involves release of circulating factor(s) (16-23) and neural pathways (19,24-26).

In pre-clinical animal models, adenosine antagonists inhibit cardiac rIPC induced by renal and mesenteric ischemia (27,28). Furthermore, femoral arterial (but not femoral vein) adenosine infusion pre-conditioned rat hearts and was inhibited by femoral nerve transection. In a rabbit model, femoral artery (but not femoral vein) infusion of adenosine released humoral cardioprotective factor(s) into the circulation, which reduced infarct size when transferred to a naive Langendorff heart (19). However, a more recent porcine study suggests that adenosine is not involved in rIPC (29). The role of the adenosine pathway in human rIPC remains unknown but clearly warrants further investigation.

The aims of this study were to address: 1) whether adenosine receptor activation is involved in human endothelial rIPC-induced by limb ischemia; 2) whether adenosine receptor activation is involved in the "trigger" or "target" phases of rIPC; 3) its effects on release of circulating cardioprotective factor(s); and 4) whether arterial infusion of adenosine liberates release of a circulating cardioprotective factor(s) in humans.

METHODS

Protocols were approved by the local research ethics committee (refs 08/H0604/152, 09/H0604/118, 10/H0604/28).

EXPERIMENTAL METHODS. Venous occlusion plethysmography. Strain-gauge plethysmography was used to measure forearm blood flow as described previously (30). For each study, the brachial artery of the nondominant arm was cannulated with a 27-gauge needle (Cooper's Needle Works, Birmingham, United Kingdom) under local anesthesia (3 ml of 1% lignocaine). Drugs or normal saline (sodium chloride 0.9% wt/vol) were infused continuously at 1 ml/min. During recording periods, the hands were excluded from the circulation by inflation of wrist cuffs to 200 mm Hg. Responses to both acetylcholine (Ach) (25, 50, and 100 nmol/min) and glyceryltrinitrate (GTN) (4, 8, and 16 nmol/min) were assessed before and after combined rIPC and IR. All recordings and analysis were made using LabChart v.6 (AD Instruments, Chalgrove, United Kingdom).

From the [a]Department of Cardiovascular Medicine, University of Oxford, Oxford, United Kingdom; [b]Department of Cardiology, Skejby Hospital, Aarhus University Hospital Skejby, Aarhus, Denmark; [c]Division of Cardiology, Department of Medicine, University of Toronto, Toronto General Hospital, Toronto, Ontario, Canada; and the [d]Department of Pediatric Cardiology, the Heart Institute at Cincinnati Children's Hospital, Cincinnati, Ohio. This work was supported by Fondation Leducq (06CVD). The Oxford National Institute for Health Research (NIHR) Biomedical Research Centre funded Prof. Kharbanda. Dr. Schmidt is a shareholder in CellAegis Devices. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received May 2, 2016; revised manuscript received June 9, 2016, accepted June 16, 2016.