Remote ischaemic conditioning: building evidence of efficacy

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This editorial refers to 'Improved long-term clinical outcomes in patients with ST-elevation myocardial infarction undergoing remote ischaemic conditioning as an adjunct to primary percutaneous coronary intervention'†, by A.D. Sloth et al., on page 168.

Remote ischaemic conditioning (RIC) is a process by which the conditioning protocol needs to be directly applied to the heart, may be perceived to add to the heart’s ischaemic burden through accruing intermittent occlusion of coronary flow with the total ischaemic time of the injurious insult; is invasive and therefore not without risk of distal atheromatous embolization into the microvasculature; and, as in the case of pre-conditioning, it needs to be instituted prior to an acute myocardial infarction, making it almost impossible to apply in the context of an acute coronary syndrome (ACS). Therefore, unsurprisingly, widespread adoption of classical conditioning has been slow, and it is likely to remain an experimental procedure. The prospective game-changer with regard to clinical application has been the discovery that it is not necessary to condition directly the area of heart being subjected to injurious ischaemia: it is possible to induce protection in the area remotely—be that through transient, intermittent occlusion of a non-culprit artery, or through transient, intermittent ischaemia of a distant organ or tissue bed. Indeed, it has been found that the simple application of a blood pressure cuff to the upper arm and inflating this to 200 mmHg for 5 min, and repeating this three or four times interspersed by 5 min reperfusion periods, is sufficient to trigger significant protection in a variety of organs, not just the heart (Figure 1). Bøtker and colleagues have previously shown that remote ischaemic conditioning can attenuate infarct size following PPCI using gated single photon emission computed tomography (SPECT) to determine the area at risk and extent of infarction, demonstrating a significant increase in mean myocardial salvage from 57% to 69% by remote ischaemic conditioning over controls ($P = 0.0333$) in the 251 patients who consequently proceeded to PPCI. These data were in line with encouraging results from a number of proof-of-concept trials looking at classical direct post-conditioning of the myocardium following successful PPCI. The critical missing piece of the jigsaw necessary to implement ischaemic conditioning in routine clinical practice is convincing clinical outcome data.

The study of Sloth et al. is an important stepping stone to achieving this goal, presenting a follow-up (median 3.8 years) of the 333 patient cohort of the original trial of 2010. Data were accrued for the...
primary endpoint, major adverse cardiovascular and cerebrovascular events (MACCEs): a composite of all-cause mortality, myocardial infarction, readmission for heart failure, and ischemic stroke/transient ischemic attack.\(^1\) In line with the earlier myocardial salvage findings, the authors report significantly fewer MACCEs in the remote ischemia-conditioned group compared with controls (13.5% vs. 25.6%, respectively; giving a hazard ratio (HR) of 0.49, 95% confidence interval (CI) 0.27–0.89, \(P = 0.018\)). The difference in MACCE rate was driven by a difference in all-cause mortality (4.0% vs. 12.0%, HR 0.32, 95% CI 0.12–0.88, \(P = 0.027\)), although there was a generally positive trend for benefit in cardiovascular endpoints in the treatment arm.

The predominant difference in all-cause mortality was the lower rate of cancer deaths in the remote ischemia conditioning group (half of that reported in the placebo group). The authors are rightly cautious in their interpretation of this finding, which is likely to reflect the relatively small patient numbers; the original study was not powered to assess clinical outcomes. Interestingly, however, there is an overlap in the risk factor profile for patients with cardiovascular disease and visceral cancers,\(^1\) and it is not known whether there is a lower mitogenic threshold to ionizing radiation in at-risk cardiovascular patients. However, while PPCI represents a significant exposure to ionizing radiation (estimated to be 136 ± 98 Gy cm\(^{-2}\)), particularly for mediastinal structures,\(^2\) the life-attributable risk of the radiation received as a consequence of PPCI is not estimated to be high.\(^2\) Intriguingly, although data from animal models show that remote ischemia conditioning can attenuate the acute cellular injury associated with ionizing radiation,\(^3\) there is no evidence to suggest that remote ischemia conditioning is an explanation of the reduction in cancer deaths in this study. Recognition of pre-existing malignancy, however, could be very important: recently Velders et al. found that a concomitant diagnosis of cancer was associated with a significantly greater risk of cardiac mortality at 1 year (10.7% vs. 5.4%), largely driven by early mortality (after adjustment at 7 days, HR 3.34, 95% CI 1.57–7.08).\(^4\) Therefore, it may be necessary to consider underlying malignancy as an independent predictor of cardiovascular outcome in future clinical trial design as well as determining potential confounders in all-cause mortality measures.

Although a small study, it is the first to demonstrate a persisting long-term benefit of remote ischemia conditioning in the context of STEMI. In line with the recent data from Heusch’s group, in which 329 coronary artery bypass graft (CABG) patients were randomized to receive either placebo or remote ischemia conditioning,\(^5\) there was a significant improvement in the rates of all-cause mortality and encouraging trends towards a beneficial reduction of cardiac event rates. This study provides grounds for cautious optimism that larger PPCI outcome studies that are currently or about to start recruiting (the Danish Study of Optimal Acute Treatment of Patients With ST-elevation Myocardial Infarction (DANAMI-3, \(n = 2000\); NCT01435408) and the Effect of RIC on Clinical Outcomes in STEMI Patients Undergoing PPCI (CONDII, \(n = 2300\); NCT01857411)) will yield the results to enable routine clinical adoption of what is an extremely simple, low-risk and cost-effective intervention for the benefit of patients undergoing PPCI, utilizing an already familiar piece of equipment: the humble sphygmomanometer.

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References
A very-late migrated coronary stent mimicking aortic root vegetation

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A 77-year-old man developed fever, dyspnoea, and bilateral lung oedema over a 3 days course. Echocardiography found an elongated hyperechoic mass protruding from the aortic wall near left coronary cusp, oscillating in the aortic root (Panel A, Supplementary material online, Video S1). No significant valvular dysfunction or intra-cardiac thrombus was found. The blood cultures grew methicillin-resistant Staphylococcus aureus. Despite of adequate antibiotics coverage, the patient progressed into profound shock. Computed tomography to evaluate infection foci found a metallic material in the aortic root originated from the left main ostium (Panel B). Review of the patient’s history revealed that he had received drug-eluting stents (Promus element, Boston Scientific) implanted from the proximal segment of left circumflex to the left main coronary artery and to the left anterior descending coronary artery 1 year ago (Panel C, left and Supplementary material online, Videos S2 and S3). An urgent operation was taken to explore and correct the aortic root pathology. A metallic stent protruded from the left main coronary ostium was seen, elongated for ≏3 cm into the aortic root (Panel D). The migrated stent was removed and coronary artery bypass grafting was done. The patient succumbed to profound shock but the culture of removed stent was negative for bacteria growth.

Late stent migration of coronary stent was rare. Late stent mal-apposition due to positive remodelling might be the cause of migration. This case reminds physicians a migrated stent to be a possible cause of echogenic material in the aortic root even late after implantation.

(Panel A and B) Image studies before operation. (A) Bed-side echocardiography revealed an oscillating high-echogenic material in the aortic root (white arrow); (B) computed tomography showed a high-Hounsfield unit material (black arrow) protruded into the aortic root.

(Panel C and D) Operative finding and previous coronary angiogram. (C) Coronary angiogram revealed a stent deployed from the proximal left circumflex to the distal left main coronary artery (white arrow); (D) a metallic stent protruded from the ostium of left main coronary artery (white arrow) after the aortic root exposed.

Supplementary material is available at European Heart Journal online.