Time is muscle ... even after reperfusion

EXPERT’S PERSPECTIVE

Michel Ovize*

Inserm U1060 (CarMeN) and Service d’Explorations Fonctionnelles Cardiovasculaires, Hospices Civils de Lyon, Université Claude Bernard Lyon1, Lyon, France

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This editorial refers to an article by H. Kin et al. published in Cardiovascular Research in 2004. It is accompanied by a retrospective editorial by one of the authors of that original article, J. Vinten-Johansen, pp. 183–187, this issue, as part of this Spotlight on Landmark Papers in Cardiovascular Research.

It has long been known that time is a major determinant of tissue damage following a prolonged ischaemic insult. This holds true for all organs in all experimental models. The seminal experimental studies by Reimer et al. have clearly identified the wavefront progression of cardiomyocyte death as a function of the duration of ischaemia. This knowledge has been translated into clinical practice where considerable efforts have been made to limit the duration of ischaemia duration and hasten reperfusion therapy in acute myocardial infarction (MI) patients. As a consequence, the prognosis of ST elevation myocardial infarction (STEMI) patients has improved, and the specific ‘management of time’ represents indeed a wonderful example of a successful transfer from bench to bedside.

Importantly, the crucial importance of ‘time management’ during acute MI is not limited to the ischaemic period. Following his landmark description of the postconditioning phenomenon, Vinten-Johansen’s group completed a second study which clearly identified one major limitation of this protection against lethal reperfusion injury. Kin et al. reported in the in vivo rat model of acute MI that delaying the first brief episode of ischaemia of the postconditioning algorithm by >1 min resulted in the loss of protection, i.e. infarct size reduction. A number of experimental studies have now confirmed, using various algorithms, that application of such cycles of brief ischaemia and reperfusion during the early minutes of reperfusion can dramatically reduce the infarct size. Further, Staat et al. and Thibault et al. demonstrated that this also applied to STEMI patients. Recent evidence, however, suggests that a delayed (30 min) application of the postconditioning intervention may still be protective. Indeed, in a mouse model of myocardial infarction, it has been shown that postconditioning intervention up to 30 min after reflow affords significant infarct size reduction. Yet, delayed postconditioning poses several questions: are the signalling pathways involved here similar to that activated during the first minute of reflow? Can the RISK or SAFE pathways be re-activated or re-inhibited after 30 min of reflow? Are other pathways involved? Additional work is needed to address these important issues. On the other hand, the early and narrow window option allows one to propose a link between known mechanisms occurring at the time of reflow and the postconditioning protection. For example, resumption of normal pH at reperfusion fits well with the timing of protection afforded by postconditioning, as demonstrated by Inserte et al.

Similarly, the opening of the mitochondrial permeability transition pore (PTP) has been shown to occur during the early minutes of reflow, and inhibiting this phenomenon prevents lethal reperfusion injury. Yet, the dynamics of the PTP opening (and closing) after reperfusion and their influence on cell survival is poorly understood.

Importantly, the clinical implications of the Kin et al. study are major. First, it confirms that the timing of application of ischaemic postconditioning is crucial for the treatment of lethal reperfusion injury. This study allowed a major advance contributing to patients’ care by clearly indicating a key prerequisite for the design of clinical trials aimed at determining the protective effects of any treatment against lethal reperfusion injury. It also helped to at least partly understand why some past infarct size reduction studies, in which this question was not taken into account, were negative. Secondly, it poses practical questions as to the application of ischaemic postconditioning...
in clinical conditions. Although protective intervention during the first minute of reflow may be easy to handle in coronary artery bypass grafting, it can be quite difficult to apply during primary percutaneous coronary intervention in STEMI patients. In the initial 2004 Staat et al. study, thrombo-aspiration was not widely used and re-inflation of the same angioplasty balloon was easily performed (upstream of the stent and at low pressure) within 1 min after reflow. Nowadays, most patients undergo coronary thrombectomy in the first place, which can delay the application of the first angioplasty balloon inflation of the postconditioning algorithm beyond the first minute of reflow. Clinical studies are needed to determine whether thrombectomy, now performed in most STEMI patients, might preclude any benefit of angioplasty postconditioning, or whether the window might be larger than expected in the human heart. It is noteworthy that any variation in this time period for applying the first brief ischaemia of the angioplasty postconditioning may be an additional confounding factor for future clinical trials in this field. Hopefully, the window for protection is somewhat different for pharmacological postconditioning. While the downstream limit (1 min after reperfusion) is probably unchanged whatever ischaemic or pharmacological postconditioning is used, the protective drug can be administered before reperfusion (except for an intracoronary route). According to its pharmacokinetics, this drug treatment may then be given to the STEMI patient any time from first medical care up to the first minute after reperfusion, provided there is a sufficient circulating concentration available as soon as the culprit coronary artery is re-opened. Based on this important advantage that favours a clinical application, there is little doubt that pharmacological postconditioning will soon take the lead in ischaemic postconditioning.

At this point, only 8 years after its publication, it should be acknowledged that the Kin et al. paper remains one of the more important contributions to this field, both for its pathophysiological implication and for its clinical impact.

References