Reduction of infarct size by ischaemic post-conditioning in humans: fact or fiction?

Gerd Heusch*

Institut für Pathophysiologie, Universitätsklinikum Essen, Hufelandstr. 55, D-45122 Essen, Germany

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This editorial refers to ‘Ischaemic postconditioning revisited: lack of effects on infarct size following primary percutaneous coronary intervention’, by X. Freixa et al., on page 103

Acute myocardial infarction continues to be a major cause of mortality and morbidity, and infarct size is the major determinant of patients’ prognosis. The only way to reduce infarct size is to restore coronary blood flow; however, reperfusion not only salvages myocardium from infarction, but also brings about additional ‘reperfusion injury’. Ischaemic post-conditioning, i.e. the repeated mechanical brief interruption of coronary blood flow during early reperfusion, attenuates reperfusion injury and reduces the ultimate infarct size. Ischaemic post-conditioning was first characterized in dogs and confirmed in all species tested so far, provided they were young and healthy.

Staat et al. in a landmark proof-of-concept study translated the experimental finding to a small cohort of select patients with acute myocardial infarction; the cumulative creatine kinase (CK) release during reperfusion was reduced by a protocol of four cycles of 1 min angioplasty balloon inflation/1 min deflation before full reperfusion. The cumulative CK release vs. the area at risk, as determined using ventriculography before reperfusion, was not reduced, nor was the relationship of infarct size to area at risk, as determined from coronary angiography using the BARI score. A calculated myocardial salvage ratio was even less with ischaemic post-conditioning. Whereas control patients had a slight improvement of LVEF over 6 months by MRI, patients undergoing an ischaemic post-conditioning protocol did not. These two recent negative studies on ischaemic post-conditioning are disturbing, but also welcome because they challenge and make us critically re-examine the prevailing concept of cardioprotection before its broader translation to clinical practice.

Technically, both negative studies used MRI, although both avoided the Achilles heel of MRI-based infarct size assessment, i.e. the quantification of area at risk from T2 weighted oedema, but used either ventriculography or angiography to this end. Both also found no protection in terms of CK or troponin release, although it is unfortunate that in the study of Freixa et al., the area under the curve for CK was not reported, which would be less dependent than peak CK on release kinetics in the presence of microvascular obstruction. Also, no long-term benefit for LVEF was seen with either echocardiography or MRI in the study of Freixa et al., and therefore the apparent lack of protection in this study and the previous negative study cannot just be ascribed to the use of MRI. One technical issue which remains of concern is the extension of error bars in the myocardial salvage index far into the negative range, reflecting an infarct size larger than the area at risk and emphasizing the limited spatial resolution of this approach; this technical problem was more prominent in the ischaemic post-conditioning group than in the control group.

Biologically, ischaemic post-conditioning as first characterized in animal experiments is a healthy heart phenomenon, and its translation to clinical practice cannot be taken for granted. In fact, a number of conditions have been identified which attenuate or abrogate protection by ischaemic post-conditioning, again using the established algorithm of four cycles of 1 min re-occlusion/reperfusion: CK release was not reduced, and troponin I release was even enhanced. Infarct size, as determined from delayed enhancement MRI, was not reduced, nor was the relationship of infarct size to area at risk, as determined from coronary angiography using the BARI score.

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* Corresponding author. Tel: +49 201 723 4480, Fax: +49 201 723 4481, Email: gerd.heusch@uk-essen.de

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Notably, protection by ischaemic post-conditioning is lost with age. Also, a number of co-morbidities which are frequently present in patients suffering from acute myocardial infarction are related to loss of protection by ischaemic post-conditioning, including hypercholesterolaemia, diabetes, obesity, hypertension, and LV hypertrophy, and some medications, such as β-blockade, statins, or antidiabetic drugs, also interfere with cardioprotection.

However, it is not only the attenuation of protection in the ischaemic post-conditioning group, but also the potential recruitment of protection in the control group which might minimize any difference between ischaemic post-conditioning and control. In fact, a number of medications can recruit cardioprotection, notably adenosine, nitroglycerin, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, AT1-blockers, statins, ivabradine, and dronedarone. Of particular importance for potential differences or the lack thereof between ischaemic post-conditioning and control is the status of the coronary circulation. Coronary microembolization prior to complete coronary occlusion with impending infarction can induce cardioprotection. A potential interference of coronary microembolization with protection by ischaemic post-conditioning has not been studied yet, but is conceivable since embolized myocardium in the absence of reperfusion cannot be protected. Conversely, reperfusion through a residual stenosis, i.e., gentle reperfusion, attenuates reperfusion injury and reduces infarct size as evidenced in pigs. In this respect, the use of direct stenting is of major importance: direct stenting reduces coronary microembolization and establishes immediate full reperfusion. Therefore, direct stenting might abrogate potential protection by reperfusion through a residual stenosis in the control group and eliminates potential interference of coronary microembolization with protection in the ischaemic post-conditioning group, thus maximizing a potential difference.

Considering the above confounders, the much lower use of direct stenting (only in ~50% of patients), the use of adenosine and/or nitroglycerin in many patients, and the slightly higher proportion of diabetics in the present study could easily have cooperated to obscure the protection by ischaemic post-conditioning, which was seen in the original study by Ovize’s group. While such considerations reconcile the existing positive and negative studies without questioning the validity of either one, it raises the concern about the importance of the ischaemic post-conditioning phenomenon and its translation to clinical use. After all, the confounding co-morbidities, co-medications, and interventional procedures are all part of clinical reality. In my view, the mechanical procedure of ischaemic post-conditioning may indeed not become broadly applicable to recruit protection in clinical routine. However, the recognition of its potential and a better understanding of its underlying signal transduction may provide an important paradigm for cardioprotection and its translation to clinical use of pharmacological interventions.

Conflict of interest: none declared.

References


