



Go with the flow

Michael Marber
Cardiovascular Division, King's College, London, UK

Correspondence: Dr Michael Marber, Department of Cardiology, The Rayne Institute, St Thomas' Hospital, London SE1 7EH, UK.
E-mail: mike.marber@kcl.ac.uk

Reperfusion is essential and urgent. In ST-segment elevation myocardial infarction (STEMI), this urgency is recognized by dedicated emergency plans and the medical student mantra, "time is muscle". It seems rather strange, therefore, to dedicate an issue of *Heart and Metabolism* to such an obvious necessity.

Reperfusion is the only means by which myocardium that remains viable within the ischemic zone can survive. The only exceptions to this rule are the 25% of individuals with sufficient collateral support to maintain resting myocardial blood flow despite acute obstruction of an epicardial coronary artery [1]. However, it is likely that such individuals never present with STEMI, but may instead have stable angina resulting from a collateral dependent circulation with abnormal flow reserve [2]. For the remaining 75%, with acute coronary artery occlusion, reperfusion is mandatory. So what are the controversies to which this issue is dedicated?

The prime controversy underpinning the Basic Article by Reffelmann and Kloner, Refresher Corner by Dhalla and Duhamel, and the discussion of New Therapeutic Approaches by Thibault and colleagues is the concept of reperfusion injury. The premise that underlies this concept is that myocardium maybe viable at the very onset of reperfusion, but dies subsequently; moreover, this death is not "predestined" by events occurring during ischemia, and hence can be prevented by manipulations during reperfusion. Despite more than two decades of intense debate, the arguments as to whether reperfusion injury even exists rage on. One of the authors of the Basic Article, Robert Kloner, helped originally publicize the dual role of reperfusion as both slayer and saviour, or double-edged sword [3]. However, it is clear from his Basic Article that he remains sceptical as to its existence. One of the difficulties with the concept of reperfusion injury is that it is very difficult to measure myocardial infarction, even histologically,

without reperfusion. Thus the arguments as to its existence revolve around the events that are known to accompany reperfusion and, in particular, the ionic fluxes, mitochondrial depolarization, and cell rupture with release of creatine kinase and troponin – events that are succinctly summarized in Refresher Corner. However, for the concept of reperfusion injury itself to be viable, and not die in the ensuing debate, there needs to be evidence that myocardial salvage can be enhanced by interventions after ischemia. There is now ample evidence from the basic laboratory that agents added to the reperfusate (eg, insulin, adenosine, opioids, and cyclosporin), and not present during ischemia, can reduce ultimate infarction. The only way this can occur is that an injurious component of reperfusion is attenuated. Thus, by definition, they are proof of the existence of reperfusion injury.

The presence and manipulation of reperfusion injury is of direct therapeutic importance, because it is clinically accessible. One of the fundamental problems with most cardioprotective therapies is the need, for maximal effect, for the protective agent to be present at the moment of coronary occlusion [4]. Unfortunately, for most patients, STEMI is unheralded and, for those with premonitory symptoms resulting in admission to hospital, efforts focus on preventing occlusion, rather than allowing occlusion and then alleviating its consequences. However, as pointed out by Thibault and colleagues, the increase in primary percutaneous coronary intervention (PCI) for STEMI provides an unprecedented opportunity to manipulate the moment of reperfusion and, thus, not only terminate ischemic injury, but also prevent subsequent injury during reperfusion. The seminal proof of concept of this strategy was originally reported by Ovize's group [5] and appears in detail within their New Therapeutic Approaches article in this issue. This group harnessed the concept of post-conditioning, which is also explained in detail in

Refresher Corner and the Basic Article. In essence, postconditioning is the slowing/interruption of the hyperemic phase of reperfusion to ease the accompanying chaos. By simply re-inflating the angioplasty balloon to obstruct flow immediately after successful primary PCI, Ovize's group were able to reduce infarction by 30% on average. Thus the concept of injury at early reperfusion has been translated, from laboratory observations made just 4 years [6] ago, into an intervention that may benefit patients.

Despite reperfusion injury being a focus of research in the laboratory, for the jobbing interventional cardiologist, the focus remains the attainment of prompt and high-quality reperfusion for all. Hence the Clinical Article by Webb and Redwood describes techniques for measuring the quality of reperfusion in the catheter laboratory. The premise underlying these techniques is that, because low reflow is associated with a poor outcome, it needs to be improved. Unfortunately, it is not clear which interventions will improve flow in the treated and unobstructed infarct-related artery. Furthermore, as Reffelmann and Kloner point out, low-reflow is most probably a manifestation of substantial infarction, rather than its cause. Thus it seems unlikely that agents to improve reperfusion will have a substantial impact. What about agents to worsen reperfusion? In view of the

findings of the study by Ovize et al [5], perhaps it is time to realize that there may be circumstances in which too much flow during the first minute or two of reperfusion should be avoided. I wonder if we will ever be measuring flow during primary PCI in order to prevent it being too good? For the time being, at least, we should definitely "go with the flow". ■

REFERENCES

1. Pohl T, Seiler C, Billinger M, et al. Frequency distribution of collateral flow and factors influencing collateral channel development. Functional collateral channel measurement in 450 patients with coronary artery disease. *J Am Coll Cardiol*. 2001;38:1872–1878.
2. Vanoverschelde J-LJ, Wijns W, Depre C, et al. Mechanisms of chronic regional posts ischemic dysfunction in humans. New insights from the study of noninfarcted collateral-dependent myocardium. *Circulation*. 1993;87:1513–1523.
3. Brunwald E, Kloner RA. Myocardial reperfusion: a double edged sword. *J Clin Invest*. 1985;76:1713–1719.
4. Avkiran M, Marber MS. Na(+)/H(+) exchange inhibitors for cardioprotective therapy: progress, problems and prospects. *J Am Coll Cardiol*. 2002;39:747–753.
5. Staat P, Rioufol G, Piot C, et al. Postconditioning the human heart. *Circulation*. 2005;112:2143–2148.
6. Zhao ZQ, Corvera JS, Halkos ME, et al. Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. *Am J Physiol Heart Circ Physiol*. 2003;285:H579–H588.