Acute myocardial infarction: new protagonists and new challenges

Since the observation that acute myocardial infarction is associated with coronary artery occlusion, various mechanical and pharmacological approaches have been developed to restore vessel patency, assuming that vessel recanalization would result in myocardial reperfusion. Several options are now available to recanalize an occluded coronary artery, including thrombolytic agents, percutaneous coronary angioplasty, and cardiac surgery. Large scale clinical studies have demonstrated the efficacy of these strategies and have concluded that early vessel recanalization significantly reduces in-hospital mortality. So, early vessel recanalization is the primary goal of therapy in acute myocardial infarction.

Unfortunately, it has emerged that re-establishing vessel patency does not necessarily result in effective myocardial reperfusion. In experimental animals it has long been known that reperfusion of ischaemic myocardium, while preventing or reducing necrosis, is associated with detrimental morphological and functional changes known as reperfusion injury. Several mechanisms contribute to reperfusion injury, including oxygen free radical production, neutrophil activation, cellular and interstitial oedema. Myocardium still viable at the end of the ischaemic period may therefore lose viability as a consequence of reperfusion.

Today these events are no longer confined to the experimental laboratory, but are part of our clinical routine. Although a clear distinction in man between reperfusion injury and ischaemic damage is difficult, we do face prolonged post-ischaemic depression of ventricular function, the so-called ‘stunned myocardium’ as well as progressive increase in microcirculatory resistance to flow, the so-called ‘no-reflow phenomenon’.

Both adverse events have been repeatedly reported after successful coronary revascularization by thrombolysis or primary PTCA. In prospective studies, evidence of impaired myocardial perfusion after a successful PTCA has been found in one third of the patients and was consistently associated with adverse prognosis.[3] And few experiences are as frustrating for the interventional cardiologist as rushing an acute patient to the cath lab to successfully dilate the occluded vessel, only to see, a few minutes later, the flow progressively slowing down, the ST segment rising again, and re-exacerbation of chest pain.

So far, the attention of investigators and clinicians has been focused on ‘myocardial ischaemia’. Morphological, metabolic, and mechanical reactions of myocardial cells to ischaemia have been explored in depth and treatments have been proposed based on these observations. It is becoming increasingly clear that this approach is no longer adequate and may...
actually represent a severe underestimation of the problem.

We should just consider that:
(1) Isolated ischaemia is probably a rare event in the natural history of ischaemic heart disease. Most episodes of absolute or relative reduction of blood flow are followed, sooner or later, by restoration of flow and sometimes by hyperaemic flow. Thus, the vast majority of the ‘ischaemic’ episodes are indeed ‘ischaemia–reperfusion’ episodes. And we know that both contribute to damage and are relevant to prognosis.

(2) Ischaemia in man is never limited to myocardial cells. A variety of cells and tissues are present in the exposed territory, including endothelial cells, vascular smooth muscle cells, circulating elements, interstitial cells, etc., and they are all affected by the ischaemia–reperfusion sequence.

A better understanding of the sequence of events and of their effects on the variety of cell populations present in the affected territory appears necessary to develop more effective therapeutic strategies and improve short- and long-term prognosis of reperfused myocardial infarction patients.

Based on these considerations, the therapeutic goals should be enlarged to provide protection against the combined effects of ischaemia and reperfusion and to protect not only the myocites but all the tissues and cells that are present in the area exposed to the ischaemia–reperfusion sequence. The accomplishment of these goals requires a better understanding of the reactions of various cell types to the ischaemia–reperfusion sequence and the identification of specific treatment strategies. At present, it is conceivable that some of the drugs shown to be beneficial in acute myocardial infarction, including beta-blockers and ACE inhibitors, may exert part of their therapeutic action on the endothelium and on coronary microvasculature, but we lack treatments specifically aimed at the protection of endothelial cells or other types of cells from ischaemia–reperfusion injury.

In this issue, Karila-Cohen and co-workers report on the protective effect of pre-infarction angina in acute myocardial infarction[4]. Pre-infarction angina is known to be associated with reduction of infarct size, improved left ventricular function, and a better prognosis. Karila-Cohen and co-workers confirm these observations and propose an original and stimulating hypothesis to explain the beneficial effects of preconditioning. By using myocardial contrast echocardiography, they have been able to demonstrate that pre-infarction angina protects against microvascular reperfusion injury and observe a convincing relationship between preservation of microvascular integrity and recovery of ventricular function.

Pre-conditioning has been previously shown to protect coronary endothelial cells against ischaemia–reperfusion injury in animal models[5]. The paper by Karila-Cohen et al. suggests that this may occur also in humans and provides an additional mechanism for the beneficial effects of pre-infarction angina.

In conclusion, this paper[4] adds to the existing evidence, suggesting a major impact by post-ischaemic microcirculatory dysfunction on the prognosis of acute myocardial infarction. Unfortunately, at the moment, the occurrence of no-reflow following early vessel recanalization in acute myocardial infarction is difficult to predict and almost impossible to reverse. Attempts to protect against ischaemia–reperfusion injury in conjunction with primary PTCA have given conflicting and disappointing results, with the possible exception of intracoronary adenosine given as an adjunct to PTCA directly into the ischaemic territory and prior to reperfusion[6].

Large scale studies are needed to confirm these results and to explore therapeutic strategies that can be applied to a broader population than that undergoing direct PTCA.

However, a greater awareness of the need to protect a variety of cells and tissues from ischaemia–reperfusion injury in order to optimize the beneficial effects of early coronary recanalization should be the first step in the development of specific therapeutic strategies. Karila-Cohen et al. have to be acknowledged for their contribution to these objectives.

M. MARZILLI
M. MARIANI
Cardiothoracic Department, Pisa University Medical School, Pisa, Italy

References