Cardiac protection takes off

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Protecting the heart from ischaemia- and reperfusion-induced injury represents the greatest challenge of cardiology, since myocardial infarction is the major cause of mortality in industrialized countries. Research on cardiac protection has a long history in the discovery of new principles of protection, replete with triumphs but also broken dreams with respect to their clinical application. Treatment of acute myocardial infarction nowadays commences with a rapid opening of the occluded coronary vessel by percutaneous coronary intervention (PCI). When recanalization is achieved, ischaemia is followed by reperfusion. Even though reperfusion restores blood flow, oxygen, and nutrient supply to the cardiac muscle, it does not simply put an end to the cellular disturbance and injury elicited by the period of ischaemic malsupply of the affected myocardium; reperfusion may also aggravate damage to the myocardium beyond that occurring during the preceding period of ischaemia. Therefore, cardiac malfunction and manifest tissue damage after ischaemia–reperfusion may be due to events during ischaemia as well as additional ones during reperfusion, and different routes of protection need to be considered for the (pre)ischaemic or post-ischaemic period. The known mechanisms of protection include targets in specific intracellular signalling pathways, functions of intracellular organelles such as sarcoplasmic reticulum and mitochondria, and control of intracellular ion homeostasis.

In this Spotlight issue, many of the current concepts for myocardial protection during ischaemia and reperfusion are discussed. Most of these concepts have originated from experimental studies, ranging from cell cultures in vitro to the heart in vivo in various animal models. Inserte et al.1 discuss promising targets for protection identified in such studies that have not (yet) reached clinical application. A better understanding of these targets, however, is certainly important for our mechanistic insight into the complex pathways of ischaemia–reperfusion injury. Research aiming at the identification of receptor-activated protective pathways in the heart is discussed by Hausenloy and Yellon,2 who make particular reference to growth factors, as these represent natural cardioprotective agents with promising pharmacology. NO is also an endogenous agent with cardioprotective potential. The paper by Calvert and Lefer3 reviews the evidence that not only NO itself but also its oxidative breakdown product nitrite can provide myocardial protection. Pathways that activate guanylyl cyclase and thereby increase cellular cGMP levels are known to provide cardiac protection. cGMP levels may be influenced therapeutically by pharmacological inhibition of phosphodiesterase-5. The cardioprotective potential of this class of inhibitors is discussed by Reffelmann and Kloner.4

Mitochondria play a central role in the pathophysiology of ischaemia and reperfusion. Obviously, lack of oxidative energy production contributes to cell injury in ischaemia. Less apparent is the fact that the recovery of energy production in reperfused myocardium can also lead to myofibrillar contracture in post-ischaemic cells, as long as they are still exposed to a cytosolic Ca2+ overload. But mitochondrial function/malfunction may also contribute, by a different mechanism, to injury via the intracellular events following the opening of mitochondrial permeability transition pores (mPTP). Regulation of mPTP and its implication for cell pathology are discussed by Zorov et al.5 The review by Gomez et al.6 shows that mPTP opening contributes to cardiac pathophysiology specifically during reperfusion. These insights have already been translated to the treatment of patients with reperfused acute myocardial infarction.

Ischaemic preconditioning and ischaemic postconditioning, i.e. the application of brief episodes of ischaemia shortly before or after the prolonged ischaemic period, provide marked protection to the myocardium. Mechanistically, several of the cytoprotective principles mentioned above are involved. Pre- and postconditioning have been successfully applied to the clinical setting, as discussed by Granfeldt et al.7 The clinical effectiveness of cardioprotection provided by pre- and postconditioning, however, can be limited by many factors. The age of the individual is an important determinant, as has been learnt from animal studies. The loss of cardioprotection by ageing is reviewed by Boengler et al.8 In cardiac surgery, both pre-ischaemic and post-ischaemic protocols of cardioprotection, such as pre- and postconditioning, are easily applicable. In spite of all experimental evidence that controlled reperfusion has great influence on the outcome of a sequence of ischaemia and reperfusion, as occurring during many myocardial surgical interventions, the use of specific reperfusion strategies...
in surgery is still limited. Beyersdorf\(^9\) discusses the reasons for this in his contribution.

In view of the acute changes in the ischaemic-reperfused myocardium, protective interventions must be applied early on. In ischaemia, the best protection is achieved if these means are applied prior to ischaemia, as in preconditioning. Apart from cardiac surgery, however, pre-ischaemic treatment of the myocardium is clinically of limited relevance, since acute myocardial infarction is normally an unforeseen event. Of much greater clinical interest are methods to protect the heart during reperfusion, i.e. in conjunction with PCI. In reperfusion, the first seconds to minutes have the most significant impact on 'acute' reperfusion injury, as shown in many experimental studies. This does not exclude that interventions applied later may also provide some benefit. There is indeed an ongoing debate about whether delayed reperfusion of the myocardium, i.e. after hours or days, may also improve prognosis after acute myocardial infarction, as discussed by Takemura et al.\(^10\)

A few years ago, protection of the heart against acute myocardial infarction in the clinical setting seemed elusive. This was because protection during reperfusion was under investigation by only a few researchers. In contrast, in the current perspective described by the articles in this Spotlight issue, cardioprotection has now taken off.

References