Reducing the impact of myocardial ischaemia/reperfusion injury

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It seems surprising that more than five decades of intense biochemical and molecular research on a leading cause of death and disability globally— ischaemic myocardial injury/myocardial infarction—and the spending of huge sums of money have achieved relatively little in the prevention of cell death secondary to ischaemia. The greatest progress has been made in methods to mechanically or chemically re-open acutely occluded coronary arteries and in increasingly better logistics of pre-hospital treatment and patient transport to hospitals providing this kind of therapy. This has resulted in a very important reduction in mortality among patients with acute myocardial infarction. The understanding of the pathological mechanism of ischaemic cell injury in the heart has also grown impressively, but much of this knowledge concerns the initiation of cell injury as a result of oxygen and energy deprivation, accumulating cellular ion imbalance, proteolytic activation, cell swelling, and similar mechanisms. The effects on ischaemic cell injury of a very effective protective regimen that is provided by the procedure of preconditioning applied prior to ischaemia are also impressive. But apart from the limited applicability of this therapeutic wisdom in cardiac surgery, nothing practical has come out of this knowledge as the much more frequent clinical situation is the one in which cardiac ischaemia is already manifest at the time the patient seeks medical help. Today, however, it is clear that ischaemic and pharmacological conditioning at the time of reperfusion may also be protective, but the impact of these approaches on clinical practice is negligible.

Having made this point, we think it is fortunate that researchers have not given up early on analysing the cellular and subcellular changes in ischaemic myocardial cells. As it turned out, many different mechanisms play a role in cardiomyocyte injury when the ischaemic tissue is reperfused. This is not a trivial finding, since it has been difficult to gain the understanding that after prolonged ischaemia, reperfusion creates a pathophysiological scenario of its own. We first needed hard-to-obtain evidence that even prolonged ischaemic myocardial injury may be reversible by specific interventions at the time of reperfusion. The reversal requires first preventing the deleterious effects of late reperfusion, hereafter termed ‘reperfusion injury’. The possibility that the myocardium can be protected during the acute phase of reperfusion has long remained overlooked, mainly because the window of time for protection is short and therefore easy to miss.

Myocardium acutely salvaged from irreversible damage during ischaemia and early reperfusion may end up largely functional. However, secondary effects of tissue damage, such as inflammatory responses or scar formation, may cause progressive failure of myocardial contractile function. Heart failure is, in fact, the most prominent outcome of ischaemia/reperfusion. It is well established that the risk of heart failure increases with the loss of viable tissue in ischaemia/reperfusion. For this reason, the well-known motto ‘first things first’ also applies to the clinical strategies for treating ischaemic and reperfusion injury: namely to start as early as possible with protective measures during reperfusion.

The first of the reviews in the present Spotlight Issue on Reducing the Impact of Myocardial Ischaemia/Reperfusion Injury provides insight into the role of intracellular Ca2+ in cardiomyocyte death during ischaemia/reperfusion.1 While it has long been known that the level of cytosolic Ca2+ rises in ischaemic cells, it has often been debated whether this is merely a sign of a healthy cell’s ability to maintain an intra-/extracellular Ca2+ gradient. Today, however, it is clear that Ca2+ signalling in the ischaemic and reperfused myocardial cell is intimately intertwined with other signalling mechanisms and contains several targets for protective interference. Important intracellular organelles orchestrating the signalling of cellular Ca2+ are the sarcoplasmic reticulum (SR) and the mitochondria. These constituents of signalling pathways are therefore important targets for reperfusion therapy.

Along these lines, the original paper by Cai et al.2 investigates the importance of a down-regulation of junctin and triadin, regulatory proteins of the SR Ca2+ release mechanism. They show that their down-regulation contributes to the post-ischaemic contractile failure and seems to be caused by a previous Ca2+ overload-induced activation of the protease calpain.

The role of mitochondria in the pathogenesis of ischaemia/reperfusion injury of the myocardium is addressed by the reviews of Miura and Tanno3 and Ong and Gustafsson.4 It is a relatively recent insight that mitochondria contribute to the development of myocardial cell failure and death not only by the inability to produce ATP under
hypoxic conditions; mitochondria also play a decisive role because they actually represent a switchboard for several signalling pathways regulating cellular life or death. One important switch is the mitochondrial permeability transition pores (mPTP), which, when open, remove the otherwise tightly regulated ionic barrier between the mitochondrial matrix and the cytosolic space. mPTP opening can cause cellular necrosis or apoptosis. These structures are regulated by several biochemical pathways that are disturbed in ischaemia/reperfusion. The review by Miura and Tanno focuses on four of these pathways containing hexokinase II, glycogen synthase kinase-3B, STAT3, and SIRT3. Since mitochondria are so central to healthy cell function, many attempts have been aimed at preserving or, once disturbed, restoring their normal function. Approaches towards this aim are discussed in the review paper by Ong and Gustafsson. One of the routes by which Ca\(^{2+}\) may enter the mitochondrial matrix space, and cytosolic Ca\(^{2+}\) overload may thereby spread into mitochondrial Ca\(^{2+}\) overload, is via the mitochondrial Ca\(^{2+}\)-uniporter. In an original article, Thu et al. describe the effect of a new compound, NecroX-5, which acts as a mitochondrial Ca\(^{2+}\)-uniporter inhibitor, on mitochondrial functions under simulated in vitro conditions of ischaemia and reperfusion.

From a living cell, damaged mitochondria and other organelles and macromolecules are disposed of by the process of autophagy. Autophagy is highly regulated, and must be, as too much as well as too little activity may destroy a cell. The review by Przyklenk et al. discusses the possibilities of providing protection to the myocardium injured by ischaemia/reperfusion by modulating the autophagic process. As described above, mitochondria play a central role in the various protective mechanisms, now commonly called pre-, per- or post- and remote conditioning. The ‘conditionings’ seem to be evolutionarily very old, endogenous mechanisms of protection that are based on the principle that a brief, initial episode of ischaemia activates protective signalling mechanisms in the affected organ or even in remote organs. Shi and Vinten-Johansen have contributed to the present spotlight issue with a comprehensive review on this topic. Apart from the common type of initiator, i.e. brief ischaemia, it seems also common that the various signalling mechanisms involved converge on the mitochondria. The heart is not unique to this kind of protection, but possibly the organ best investigated.

Vincent et al. report in an original article on the role of the pro-apoptotic gene Zac1, which had been found to be down-regulated under conditions of pre- and postconditioning in myocardial tissue. They now show that this down-regulation plays an important role for protection against ischaemia/reperfusion injury in vivo. There have been many studies in the past indicating that a modulation of myocardial metabolism prior to ischaemia can affect the heart’s tolerance for ischaemia. The original work by Ussher et al. reports that a reperfusion-targeted direct stimulation of glucose oxidation via the activation of pyruvate dehydrogenase, or secondary to inhibition of malonyl CoA decarboxylase, reduces infarct size and improves cardiac functional recovery during reperfusion following ischaemia. Another original article by Rui et al. addresses the question of why the vulnerability of the diabetic heart to ischaemia/reperfusion injury might be increased. The results indicate that a reduction in the myocardial cytokine interleukin-33 in diabetes, which leads to a sustained activation of PKCβII, is the cause. A classical way to achieve tissue protection during surgery is mild hypothermia. It is generally assumed that mild hypothermia acts protectively because many energy-consuming processes are slowed down with a lowering of temperature, and thus, the lack of energy supply in ischaemia can be tolerated for a longer time. Upon taking a closer look, we see that for various reasons, it is not as simple as that. One is that hypothermia may also cause cellular disturbances in ion homeostasis, which may jeopardize cell survival. This, however, may only be a problem for hypothermia at temperatures lower than 25°C. The review by Tissier et al. summarizes the present knowledge on mild hypothermia at 32–35°C. It is argued that the protection afforded by mild hypothermia is not due to diminished energy utilization but rather to the activation of protective cellular signalling pathways. It is argued that the protection by mild cooling and pre- and postconditioning might be additive, as the biochemical mechanisms seem to involve different pathways. Protective interventions applied in experimental settings may be difficult to apply in the patient. This is particularly relevant for reperfusion therapy, as it has to be applied very rapidly with the onset of reperfusion. Ischaemic tissue is heterogeneous and this also causes heterogeneity in reperfusion. The review by Hinkel et al. gives an overview of the various technical approaches for the application of reperfusion therapy directly to the heart.

Malfunction or outright failure of the coronary circulation in transporting oxygen and nutrients to the myocardium is the cause of ischaemia. The condition of the coronary vascular bed in large and small vessels determines the chances for successful re-supply of the heart tissue with blood, the washout of ischaemic waste products, and, possibly, the delivery of specific therapeutic agents to the ischaemically stressed cells. The coronary circulation is therefore also a target for protection. The review by Heusch et al. is focussed on the role of the coronary circulation in ischaemia/reperfusion.

The reason why clinical studies directed specifically at protection during reperfusion have been so long in coming is discussed in the review by Morel et al. As explained, it took a long time for clinical medicine to accept that reperfusion injury exists also in the human heart. Presently, several small studies have been completed and larger ones are underway.

In heart surgery, the number of patients with complex conditions of coronary disease is constantly increasing. These patients have a high risk of peri-operative myocardial infarction. Novel therapeutic strategies applicable in heart surgery are therefore highly desirable. The review by Hausenloy et al. puts new strategies for protection in perspective within the background of more traditional recipes for intra-operative cardiac protection.

In clinical studies aimed at reperfusion therapy, reliable determinations of myocardial salvage are of crucial importance. ‘Measuring cardiac salvage’ is the title of a review contributed by Bøtker et al. It addresses the present technical possibilities used to measure the ratio between infarct size and area at risk in patients.

Myocardial injury may occur in ischaemia, in the acute phase of reperfusion, and also in a delayed fashion following an episode of ischaemia/reperfusion. The activation of the innate immune response can play a major part in the delayed development of myocardial injury. At the same time, this response is also required for scar formation, which represents a beneficial aspect of the ‘healing’ process after the loss of viable tissue. This topic is reviewed by Timmers et al. Scar formation, loss of myocardial cells, hypertrophy of the remaining cells, and angiogenesis are all parts of the post-ischaemic remodelling process. In all of these processes of adaptation and growth, which lead either to a stabilization of the heart as a functional organ or to the progressive deterioration of this organ’s pumping
function, microRNAs are now known to play a regulatory role. As these signalling molecules may either be effectors of therapy or indicators of the activation of specific regulatory pathways, they are receiving widespread attention in the analysis of the ischaemic–reperfused myocardium as reviewed by Zhu and Fan.\(^\text{18}\)

In an original paper, Wang et al.\(^\text{19}\) demonstrate along these lines the role of miR-144/451 in protection by preconditioning.

After ischaemia/reperfusion, the heart is a traumatized organ, containing a wound in which mechanisms of cell death, inflammation, fibroblast proliferation and degradation, and de novo synthesis of extracellular matrix all take place under the influence of numerous local and remote signals. Haemodynamically adverse remodelling is a major cause of morbidity and mortality following acute myocardial infarction. The review by Fraccarollo et al.\(^\text{20}\) is focused on the present understanding of wound healing in post-infarct remodelling and gives an outlook towards therapeutic options based on this premise.

Remodelling of the heart after ischaemia/reperfusion can be modulated by the activity of nitric oxide synthase expressed in cardiomyocytes by cGMP-dependent and -independent mechanisms. The review by Manoury et al.\(^\text{21}\) analyses the signalling effectors involved and the perspectives for using this knowledge for future therapy directed at the prevention of heart failure.

In their review, Ravassa et al.\(^\text{22}\) elucidate the potential of glucagon-like peptide-1 (GLP-1), which plays an increasing role in the therapeutic strategies for the treatment of patients with type 2 diabetes mellitus and which is also known to exert cardioprotective effects. It is argued that GLP-1 represents a promising therapeutic target in the ischaemic and reperfused myocardium with beneficial effects on myocardial remodelling and heart failure.

Finally, post-ischaemic scar formation and changes in the texture of myocardial tissue both change the electrical wave propagation in cardiac tissues and are therefore a cause of arrhythmias. Sudden death is a major cause of mortality in patients with post-infarct myocardial tissue both change the electrical wave propagation in cardiac tissues and are therefore a cause of arrhythmias. Sudden death is a major cause of mortality in patients with post-infarct myocardial infarction. Ablation of junctin or Rac-1. Ablation of junctin or Rac-1.

Unfortunately, interventions aimed at controlling risk factors of coronary atherothrombosis, surgical or percutaneous revascularization, and strategies to rapidly restore coronary blood flow in acutely occluded arteries will not remove ischaemic heart disease from among the top ranking of diseases with the greatest mortality and morbidity during the next decades. A large community of investigators is currently pursuing the use of cell therapy and other approaches to stimulate cardiac regeneration and repair as a last resort in hearts with large fibrotic scars. To reduce the extent of myocardial necrosis through interventions aimed at preventing cell death at the time of reperfusion appears to be a logical line of defence against the deleterious effects of acute ischaemia. The present issue of Cardiovascular Research provides an updated overview of pre-clinical and clinical evidence showing the promise of this approach to reducing the impact of ischaemia/reperfusion injury on the heart.

**Conflict of interest:** none declared.

**References**


