Chapter

Acute Myocardial Infarction: Perspectives on Physiopathology of Myocardial Injury and Protective Interventions

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Abstract

Diffuse coronary artery injury produces a host of physiopathological, structural and metabolic changes in cardiocytes that, if not rectified, result in significant loss of functional myocardium to cause cardiac contractile dysfunction. Restoration of blood perfusion to the infarct-related artery helps to limit the acute effects of myocardial infarction; however, cardiocyte injury may be exacerbated because of the restoration of blood perfusion to the ischemic zone (i.e. reperfusion injury). Various manifestations of reperfusion injury include no-reflow, myocardial stunning or hibernation and ventricular arrhythmias. Consequently, reperfusion of an infarct related artery is often viewed in the context of being a “double-edged sword.” Pharmacologic and non-pharmacologic interventions have been investigated in pre-clinical and clinical studies in the hunt to develop strategies to protect cardiomyocytes against the long-term effects of ischemia, or delay development of necrosis (resulting from ischemia or reperfusion). This book chapter will update current thinking on cardioprotective strategies to improve clinical outcomes in patients with coronary artery disease.

Keywords: acute myocardial infarction, cardioprotection, ischemic conditioning, myocardial ischemia, reperfusion injury

1. Introduction

Physiopathological mechanisms responsible for myocardial cell death (necrosis, apoptosis, autophagy, etc.) caused by coronary artery disease have been abundantly discussed over the past several decades. Acute myocardial infarction is a leading cause of sudden cardiac death among urban dwellers in North America and Europe. Clinical treatment of patients with coronary artery disease is focused on limiting the deleterious consequences that follow coronary artery occlusion; however, to do so it is fundamental to understand the mechanisms, at the molecular and cellular level, that are involved in cell death and survival. Existing knowledge has progressed massively over the years and useful clinical interventions, both pharmacologic and non-pharmacologic, are currently available to limit, but not abrogate, effects of ischemia. An important question that remains concerns the existence of “reperfusion-induced injury”; many adhere to the notion that significant cellular
death can occur once blood flow is restored to an infarct-related artery. While definitive proof is lacking myocardial stunning, vascular no-reflow (perfusion deficit) and ventricular arrhythmias are often attributed to this form of cardiomyocyte loss after ischemia. The objective of the present chapter is to update current thinking on the question of lethal reperfusion injury and to summarize current treatments used to limit overall effects.

1.1 Acute myocardial infarction

Myocardial ischemia is defined as the condition where coronary blood flow across the ventricular wall is insufficient to conserve steady-state metabolism. Acute disruption of the blood supply to any region of the heart causes cardiomyocyte injury and eventually cellular death depending on the duration of perfusion deficit. Cardiac cell injury is characterized to be either reversible (if reperfusion of the infarct-related artery can be instituted rapidly, ≤15 minutes), or irreversible (poor, or no, cellular survival even if blood flow is restored). Cardiomyocyte necrosis progresses as a transmural gradient across the ventricular wall, from endocardium to epicardium, in most animal models studied [1, 2]. Early development of necrosis in the subendocardium is probably related to higher oxygen requirements (due to greater contribution to myocardial contraction) of that layer compared to the subepicardium [3–5]; myocardial perfusion is coupled to myocardial oxygen consumption. Although we agree that progression of coronary heart disease and symptom phenotypes may differ in relation to sex this subject is beyond the scope of this review.

Myocardial ischemia initiates multiple changes in cardiomyocyte structure including marked swelling, development of contraction bands, mitochondrial calcification and membrane disruption; the pathobiology of cellular changes produced by ischemia have been characterized in earlier studies [6–8]. Different modes (apoptosis, autophagy, oncosis, and necrosis) of cellular injury have been described [9] and are discussed elsewhere [10]. The cardiomyocyte cytoskeleton (i.e. structure needed to maintain cellular morphology and physiology) is markedly altered by biochemical changes caused by disruption of oxygen and nutrient supply [11]. Cardiomyocyte death occurs with disruption of the cellular membrane and subsequent leakage of intracellular components into the extracellular fluid [12–14]. Irreversibly injured cardiomyocytes display small breaks in the plasmalemma along with cellular swelling and sarcolemmal blebbing [1]. Necrosis in non-cardiac cells is not well described but it is clear that other cell types within the myocardium (i.e. vascular endothelial and smooth muscle cells, nervous system cells, etc.) are affected by ischemia.

Restoration of blood flow to the perfusion bed of the infarct-related artery can limit damage to cardiomyocyte as long as reperfusion is instituted within a reasonable period. Indeed, this is the basis for widespread use of percutaneous coronary interventions for relief of symptoms in patients with coronary artery disease and is responsible for manifest reduction in mortality. Thousands of studies have examined the physiopathology of ischemia-reperfusion injury over the past half-century with the aim to elucidate pathways leading to cellular necrosis; increased knowledge gained from these studies has led to the realization that this is a complex and multifaceted scenario.

1.2 Lethal reperfusion injury

It is clear that restoration of blood flow to ischemic myocardium is the most effective treatment against myocyte necrosis [15, 16]. Timely opening of an infarct-related artery is essential as the amount of myocardium salvaged rapidly decreases
when reperfusion interventions are delayed. Furthermore, reperfusion may itself cause further cellular damage; thus it is often viewed in the context of being a “double-edged sword” [17]. Studies have confirmed that reperfusion triggers abrupt metabolic, electrophysiologic, morphologic and functional changes. The term “lethal reperfusion injury” designates damage to viable cardiomyocytes caused after successful restoration of blood flow to the ischemic perfusion bed. Several possible forms of reperfusion injury such as coronary artery no-reflow, myocardial hibernation, myocardial stunning, ventricular arrhythmias, etc. have been advanced [18, 19]; however, definitive proof that reperfusion injury exists remains to be established. With that in mind, we believe that reperfusion might accelerate expression of injury produced by ischemia but does not itself cause de novo cardiomyocyte injury.

Physiopathological mechanisms that produce reperfusion injury are complex and multifactorial; no specific mechanism has been shown to take precedence over others. In experimental animal models, the release of an acute coronary occlusion produces a prolonged hyperemic response particularly in the deeper myocardial layers (subendocardium > subepicardium); hyperemic responses vary depending on the duration of ischemia [20–22]. Reperfusion of the ischemic myocardium depends on arterial driving pressure and extravascular compressive forces; this is particularly important for the function of coronary collateral vessels that supply much needed oxygen and nutrients to surviving cardiomyocytes post-ischemia. As such, restoration of coronary blood flow in the infarct-related artery does not guarantee homogeneous perfusion of blood across the ventricular wall. Indeed, areas where blood flow is less than normal (i.e. no-reflow) are mostly associated with myocardial regions where injury is irreversible.

1.2.1 No-reflow

No-reflow is caused by injury at the structural level (i.e. cell swelling, membrane gaps, etc.) [23, 24]; microvessels might be more resistant to short periods of ischemia compared to cardiomyocytes because their endothelial oxygen requirements are modest and they are in close proximity to oxygen supply. No-reflow does not precede tissue damage but follows it; furthermore, it does not expand myocardial infarct size (role in pathogenesis of tissue damage is considered to be minor) [25, 26]. However, it has been suggested to contribute to infarct expansion, ventricular dilatation and remodeling by limiting access of inflammatory cells to the ischemic zone to initiate cardiac repair [27, 28]. Microvessel damage is also manifest as hemorrhage due to abnormalities in vessel permeability [29].

No-reflow occurs in patients with cardiovascular disease [30, 31]; pharmacotherapy appears to normalize ischemic zone perfusion and reduce mortality.

1.2.2 Myocardial stunning and hibernation

Reperfusion injury is associated with depletion of high-energy phosphate stores, cellular swelling, increases in capillary permeability and reduced microvessel reactivity [32–34]. Restoration of blood flow to the ischemic myocardium mitigates myocardial injury; however, restoration of contractile function is not necessarily immediate. When blood supply to the heart is limited, myocardial contraction is restricted as described for the “smart heart theory” [35]. In normal myocardium, increases in metabolic demand due to intensification of myocardial work are met by regional increases in blood flow as well as increases in oxygen extraction [36]. Post-ischemic myocardial stunning and myocardial hibernation have been described in animals [37, 38] and patients [35, 39] and designate viable but chronically
dysfunctional states [40]. Myocardial stunning refers to persistent (but reversible) contractile dysfunction [41, 42] produced by a relatively brief ischemic period [43]. Myocardial hibernation, on the other hand, refers to viable but chronically dysfunctional myocardium that may be related to poor resting perfusion [35], or general absence of perfusion abnormalities [44, 45] but the latter has not been clearly established [46, 47]. Recent findings suggest that repetitive ischemia, chronic stunning and hibernation are linked as a continuum [40]; in other words, stunned myocardium can progressively transform into hibernating myocardium. For both dysfunctional myocardial states, downregulation of contractile function might be a cellular adaptive mechanism to facilitate preservation of myocardial integrity and viability [35]. Perfusion-contraction matching may be key to myocardial hibernation but this may not be so for myocardial stunning; a number of review articles on this subject are available [48–50]. Whether contractile dysfunction can be reversed by improved revascularization in stunned or hibernating myocardium is moot after the formation of scar [40].

1.2.3 Ventricular arrhythmias

Development of life threatening ventricular arrhythmias, which range from ventricular premature beats with long coupling intervals to ventricular fibrillation early after onset of reperfusion, also represent a form of reperfusion injury [51, 52]. Although the physiopathology causing ventricular arrhythmias during reperfusion is ill understood they are known to be initiated by complex cellular changes with regard to electrophysiological, metabolic and structural properties [53]; potential chemical mediators of arrhythmogenesis have been presented [54, 55]. In rat hearts subject to brief coronary artery occlusion (~5 minutes) followed by reperfusion severe ventricular arrhythmias occur [56]. However, in larger animal species, incidence of lethal ventricular arrhythmias increases when reperfusion is instituted within 30 minutes after coronary occlusion [57]. The overall incidence of ventricular arrhythmias decreases significantly when reperfusion follows longer durations of ischemia [58, 59].

2. Cardioprotection strategies

Strategies designed to protect against myocardial injury caused by ischemia, or reperfusion have been extensively studied. In animal models reduction of infarct size is reported with the use of single, or multiple pharmacologicals; however, translation of cardioprotection to patients remains disappointing. Efficacy of interventions is dependent on a host of factors that include time of administration of treatment (i.e. during ischemia, at reperfusion, late reperfusion), duration of occlusion, reperfusion status, species, cell types and end targets (i.e. molecular, biochemical, etc.). In patients, cellular protection is more difficult; however, multi-target studies continue to attempt to limit cardiomyocyte injury. The presence of comorbidities also affects the cardioprotective capability of different treatments. Development of reliable interventions (i.e. pharmacologic, non-pharmacologic) remains an ongoing challenge; findings from basic science and clinical studies on understanding of mechanisms involved in cellular injury and death have been significant but more work is necessary.

2.1 Pharmacologic strategies

For more than 50 years a host of pharmacologic interventions have been employed to limit the extent of myocardial necrosis in animal models and clinical
studies. Some cardioprotection has been reported for different manifestations of ischemic injury but no long-lasting protection has yet been afforded by any drug. Many different exogenously administered compounds, which act at different levels (i.e. cell membrane receptors, intracellular signaling pathways, platelet aggregation pathways, inflammation, etc.), have been tested, but results are highly variable. In patients with coronary artery disease/acute myocardial infarction, a “golden window of opportunity” may exist after onset of symptoms to attenuate ischemic injury [60]; however, to date most pharmacologic strategies to delay progression of ischemic injury have not shown great promise with regard to clinical outcomes. Potential reasons include problems regarding timing of drug administration and drug dosage as well as the heterogeneity of comorbidities within patient populations [61]. Recent studies have focused on use of pharmaceuticals that target molecular mechanisms and signal transduction at different cellular levels (i.e. cell membrane, mitochondria, etc.); however, translation of protection with pharmaceuticals that act by stimulating intracellular signaling pathways remains a challenge [62, 63]. While numerous pharmacologic compounds have been tested in animal models and humans to date, none offers protection greater than that afforded by ischemic conditioning (cf. below).

Current pharmacologic interventions targeting ischemia-reperfusion injury include use of beta-blockers; these drugs were among the first reported to delay progression of ischemic injury more than 40 years ago [64–67]. Infarct limiting properties were mostly attributed to reductions in myocardial energy and oxygen consumption. More recently, the selective β1-adrenergic receptor antagonist, metoprolol, administered before reperfusion has been shown to inhibit neutrophil-platelet interactions and protect ischemic myocardium in patients [68]; other elements (i.e. neutrophil trafficking, formation of neutrophil-platelet co-aggregates, etc.) associated with neutrophil dynamics might also be involved [69, 70]. The role of neutrophils in ischemia-reperfusion injury is well established. Protection by metoprolol could be due to reduced microvessel plugging, or microvascular obstruction, by neutrophil-platelet plugs, or other inflammatory cell aggregates. Additionally, metoprolol could directly affect platelet aggregation but this remains to be proven.

Platelet aggregation is a crucial factor for post-ischemic vessel re-occlusion in patients with coronary artery disease even after successful percutaneous coronary interventions. Activated platelets release potent chemotactic factors that stimulate formation of thrombus and microaggregates, which can cause microvascular obstruction underperfusion of the ischemic myocardium [71–73]. Anti-platelet and anti-thrombotic interventions provide significant protection against ischemic injury; though poorly understood, protection is probably mediated through pathways that are similar to those activated by ischemic conditioning [74, 75]. In animal studies, platelet aggregation inhibitors such as ticagrelor (P2Y12 receptor blocker) markedly reduce myocardial infarct size that effectively translates to improved cardiac contractile function [76–78]. However, this is not necessarily true for drugs such as clopidogrel (thienopyridine—class of platelet aggregation blockers) which efficiently limits platelet aggregation but does not influence ischemic myocardial injury [75, 79]. Protection probably occurs through adenosine-related mechanisms more than anti-platelet aggregation actions [80, 81]. Other classes of platelet activation blockers (i.e. glycoprotein 2b/3a blockers, etc.) have also reported significant anti-necrosis and anti-arrhythmic effects [82, 83]; however, cardioprotective efficacy of these agents may be limited with extended ischemic durations [84].

Mitochondria are considered an important target for reduction of ischemia-reperfusion injury [85]; mitochondria are responsible for generation of high-energy phosphates and contribute to ion homeostasis, formation of reactive oxygen species
and Ca\(^{2+}\) handling. Myocardial ischemia-reperfusion markedly alters mitochondrial function that can ultimately lead to cell death. Recent studies have focused on a large conductance pore of the mitochondrial membrane—mitochondrial transition pore (mPTP) located in the inner mitochondrial membrane, which opens at onset of reperfusion leading to osmotic swelling and a decrease in oxidative phosphorylation. In the heart, mPTP inhibitors have been studied in animal models of ischemia-reperfusion injury; several have been reported to be cardioprotective [86–88]. In clinical studies, pharmacologicals that target mitochondrial function have not had positive results with respect to limiting ischemic injury [89–92].

To date, no single pharmacologic compound has achieved a level of cardioprotection greater than that obtained by ischemic conditioning. In an attempt to enhance protection, new initiatives have begun to examine the efficacy of combined treatments (i.e. drug plus ischemic conditioning) that target different cellular mechanisms (i.e. insulin signaling, energy metabolism, etc.) affected by ischemia and reperfusion. For instance, combined glucose-insulin-potassium-exenatide with remote conditioning reduced infarct size in a large animal model [93]. In a combined basic science and clinical study from Hauerslev’s laboratory, it was shown that treatment with glyceryl trinitrate (nitric oxide donor) in combination with remote conditioning abolished the individual protective effects obtained with either intervention alone [94]. Similar results have been reported in patients [95] but not all data are consistent [96]. In a canine study from our laboratory, we reported that ischemic conditioning (classic and delayed) significantly reduced ischemic injury; however, combined treatment with EMD 87580 (NHE1 blocker) and ischemic conditioning did not affect the level of cardioprotection [97]. These findings suggest that the level of protection possible with any intervention is limited (i.e. not additive). Underlying explanations for these controversial findings need to be resolved with further investigation.

### 2.2 Non-pharmacologic strategies

In the clinical setting, percutaneous coronary interventions (PCI) remain the benchmark to restore perfusion in the infarct related artery; however, efficacy of these interventions is variable. An unfortunate aspect of PCI that is often underestimated is the release of micro particulate debris and platelet micro-aggregates that can cause additional myocardial injury downstream at the level of the microvasculature [98–100]. As a result, mechanical thrombectomy (i.e. passive aspiration, active mechanical catheters, etc.) is being developed to limit untoward effects of distal embolization by atherothrombotic debris [101–103].

Keeping in mind that “time is muscle” it is clear that any delay in onset of treatment considerably influences overall success. Combined pharmacotherapy with mechanical reperfusion (i.e. facilitated PCI) is being tested to improve clinical outcomes [104, 105].

Cardiac regeneration therapies (i.e. cardiomyocyte transplantation, biocompatible matrices, etc.) to repair damaged myocardium is another promising intervention to restore post-ischemic cardiac dysfunction (cf. recent review from Kingma [106]). Basic studies designed to better understand underlying mechanisms are ongoing; however, many limitations (i.e. rejection of transplanted cells, presence of scar, poor vascularization, tumor formation, myocardial location, etc.) underscore initial optimism afforded to these interventions for improvement of ventricular function.

Cardiac conditioning (also organ conditioning) is a promising intervention that may eventually prove to be useful for protection of ischemic myocardium (or other organs) in patients; this intervention was first described as ischemic
preconditioning more than 30 years ago [107]. Since then, more than 8000 studies have consistently reported protection against necrosis, ventricular dysrhythmias and myocardial contractile dysfunction in experimental animal and in clinical studies [108–111]. At the moment, the clinical usefulness of ischemic conditioning as a preventive strategy for tissue protection remains controversial; the presence of multiple comorbidities may be important [112, 113] but their effect may be overcome depending on the scale of stimulus that is used to trigger cytoprotective pathways [114].

In the original ischemic preconditioning study by Murry and colleagues, dog hearts were exposed in situ to brief, repetitive non-lethal cycles of ischemia-reperfusion prior to a prolonged ischemic event [107]. Development of myocardial necrosis was initially delayed and protection was transient depending on the duration of coronary occlusion. An essential requirement for protection against ischemic injury by this intervention is reperfusion of the ischemic region [18]. Publication of this landmark paper paved the way for numerous studies not only with respect to the heart on potential contributory endogenous cellular protection pathways. To date, anesthetic drugs, other pharmacologic or remote interventions, have all demonstrated ischemic conditioning (pre-, per-, post-conditioning) mediated protection. A cross-tolerance phenomenon could also be involved since many triggers for intracellular signaling pathway-mediated protection are similar [115–117]. Prospective contributory mechanisms to conditioning mediated protection have been reviewed elsewhere [109, 118–120].

The principal difficulty with ischemic conditioning strategies is the inability to translate success in animal models to the clinical setting to improve overall outcomes. A major liability is the requirement to physically apply an ischemic conditioning intervention prior to onset of acute ischemia (incapacity to determine its occurrence). The observation that remote ischemic conditioning could provide robust protection against ischemic injury is promising [121]. In their initial canine cardiac ischemia-reperfusion injury study, Przyklenk and coworkers pretreated a region of the heart with brief non-lethal cycles of repetitive ischemia and reperfusion and showed marked protection (i.e. reduced infarct size) of a distant adjacent region in the same heart. Since the publication of this study, others have reported significant limitation of different manifestations of ischemic injury in various experimental models [122]. A crucial question concerns the mechanism(s) by which cytoprotective signals are transported from conditioned tissue to the distant target tissue. Blood or perfusate-borne humoral factors, neuronal stimulation and transmission as well as systemic alteration of circulating immune cells have all been proposed [123–125]. Findings, in animal models, from our laboratory tend to favor the humoral hypothesis; in dogs subject to acute ischemia-reperfusion injury, protection was not reversed after either pharmacologic or surgical decentralization of the intrinsic cardiac nervous system [126]. On this basis we hypothesized that inter-organ crosstalk did not require an intact autonomic nervous system. Stimulation of the nervous system, either locally or within cardiac ganglia could potentially stimulate release of cardioprotective substances (chemokines, leukotrienes, microRNA, etc.) into the bloodstream to initiate downstream effects [109, 127–129]. Interestingly, activation of the sympathetic nervous system is not required for classical ischemic conditioning, however, it is essential for second-window, or delayed, conditioning [130, 131].

A key element for protection by remote conditioning is restoration of blood flow to affected tissues [111, 132]; without it transfer of triggering mediators would be constrained. In humans, it is not clear that conditioning strategies afford significant protection (against endothelial dysfunction, increased permeability, structural alterations, etc.) at the level of the microcirculation in the
deeper myocardial tissue layers [115, 133, 134]. Nonetheless, improved myocardial perfusion with remote conditioning may occur based on findings of higher TIMI (thrombosis in myocardial infarction) scores, myocardial blush grade and coronary reserve in cardiac patients. Restoration of blood flow to the deeper layers of the myocardial wall is a crucial risk factor for ventricular remodeling and major adverse cardiac events [135–137].

In the clinical setting, results with this intervention (i.e. repeated arm or leg ischemia-reperfusion) are mixed; studies report either manifest cardioprotection [138, 139], no benefit [18, 140, 141] or exacerbation of injury [112, 142]. Failure to provide protection by remote conditioning in patients may be associated with the use of anesthetics such as propofol that abrogates protection [18]; volatile anesthetics are mostly recommended for at-risk cardiac patients [143, 144]. In proof-of-concept studies, other forms of remote conditioning, such as remote ischemic preconditioning (intervention performed during evolving myocardial infarction) have reported protection against tissue injury, ST-segment resolution and biomarker release in animal models and patients [145–147].

3. Concluding comments

Pathogenesis of lethal reperfusion injury remains to be established; the principle that reperfusion injury contributes to post-ischemic myocardial dysfunction is generally accepted but definitive evidence for its existence is lacking. While evaluation of the nature of cellular changes produced by ischemia and subsequent reperfusion has produced significant novel insights it is unclear that cardiomyocytes are the only cell types (within the myocardium) that are at risk of further injury. Of principle importance is that interventions to limit myocardial injury be instituted at the time of, or in conjunction with other reperfusion strategies. Pharmacologic compounds currently being used in the clinical setting delay, at best, short-term progression of cellular injury; long-term effects of these treatments in large animal ischemia-reperfusion injury models have not been properly investigated. The concept of a “magic bullet” intervention remains utopic, at present, considering the complexity of physiopathological mechanisms involved in cell death and myocardial remodeling. Utilization of exogenous interventions such as ischemic conditioning in combination with pharmacologic treatments remains a significant challenge. Further investigations into combination therapy, particularly in longer-term studies should be envisaged; consideration should also be paid to the existence of comorbidities within the patient population since overall efficacy of any treatment option will be affected.
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