Myocardial Ischemia Reperfusion Injury: From Basic Science to Clinical Bedside

**Anja Frank, MD[1,2], Megan Bonney, BS[1], Stephanie Bonney, BS[1],
Lindsay Weitzel, PhD[1], Michael Koeppen, MD[1,3], and
Tobias Eckle, MD, PhD[1]**

Abstract

Myocardial ischemia reperfusion injury contributes to adverse cardiovascular outcomes after myocardial ischemia, cardiac surgery or circulatory arrest. Primarily, no blood flow to the heart causes an imbalance between oxygen demand and supply, named *ischemia* (from the Greek *isch*, restriction; and *haema*, blood), resulting in damage or dysfunction of the cardiac tissue. Instinctively, early and fast restoration of blood flow has been established to be the treatment of choice to prevent further tissue injury. Indeed, the use of thrombolytic therapy or primary percutaneous coronary intervention is the most effective strategy for reducing the size of a myocardial infarct and improving the clinical outcome. Unfortunately, restoring blood flow to the ischemic myocardium, named reperfusion, can also induce injury. This phenomenon was therefore termed myocardial ischemia reperfusion injury. Subsequent studies in animal models of acute myocardial infarction suggest that myocardial ischemia reperfusion injury accounts for up to 50% of the final size of a myocardial infarct. Consequently, many researchers aim to understand the underlying molecular mechanism of myocardial ischemia reperfusion injury to find therapeutic strategies ultimately reducing the final infarct size. Despite the identification of numerous therapeutic strategies at the bench, many of them are just in the process of being translated to bedside. The current review discusses the most striking basic science findings made during the past decades that are currently under clinical evaluation, with the ultimate goal to treat patients who are suffering from myocardial ischemia reperfusion–associated tissue injury.

Keywords

ischemic reperfusion injury, heart, myocardial infarction, therapeutic impact, reperfusion injury

Introduction

In the United States alone, approximately 1 million people suffer from myocardial infarction (MI) every year. Additionally, 700 patients undergo cardioplegic arrest for various cardiac surgeries. Despite the different etiologies that lead to the partial or complete arrest of cardiac circulation both patient groups share myocardial ischemia and reperfusion (I/R) injury as a common pathophysiological feature.[1]

Myocardial ischemia and reperfusion injury was first described by Jennings et al[2] in 1960 using a canine heart as a coronary ligation model.[2] The authors of the study observed that reperfusion appeared to accelerate the development of necrosis. The histological changes found after only 30 to 60 minutes of I/R were comparable to the degree of necrosis normally seen after 24 hours of permanent coronary occlusion.

This initial observation kindled a discussion that lasted for decades whether reperfusion itself is responsible for tissue injury. It was not until the discovery of ischemic preconditioning that the independent effects of I/R began to be unraveled from one another. Murry et al[3] reported in 1986 that repetitive short episodes of ischemia followed by a prolonged period of ischemia with reperfusion resulted in a significantly decreased infarct size. The term *ischemic preconditioning* was coined and subsequently

[1]University of Colorado Denver, Aurora, CO, USA
[2]University of Wuerzburg Hospitals, Wuerzburg, Germany
[3]Ludwig-Maximilians-University Munich, Munich, Germany

Corresponding Author:
Tobias Eckle, Department of Anesthesiology, University of Colorado Denver, Room 7121, Research Complex 2, 12700 E 19th Avenue, Mailstop B112, Aurora, CO 80045, USA
Email: tobias.eckle@ucdenver.edu

this phenomenon was confirmed in a number of animal models as well as in humans.[4] It is now well accepted that ischemic preconditioning is an evolutionarily highly conserved mechanism. Subsequent experiments revealed that the reperfusion event is key to the initiation of molecular cascades that have the potential to mediate cardioprotection. Despite the substantial progress in understanding mechanisms of I/R based on models of acute MI, and the associated enthusiasm for translating these findings into patient care, results of clinical studies have been largely disappointing.[1] However, many mechanisms identified at the bench, have not been extensively investigated yet and some larger clinical trials evaluating promising interventions from bench to bedside have just started.

Pathophysiologic Mechanisms of Myocardial Ischemia and Reperfusion Injury

Fifteen to twenty seconds after the occlusion of coronary vessels, anaerobic glycolysis supervenes as the only significant source of new high-energy phosphate. This is sufficient to meet at least the most basic energy demand of cardiomyocytes; however, within 60 to 90 minutes of ischemia, the affected area of the heart develops contracture-rigor.[5] The critical role of anaerobic glycolysis in providing ATP in severe ischemia is dramatically illustrated in experiments in which anaerobic glycolysis was inhibited. As a consequence no glycolytic ATP is formed. In less than 5 minutes, the reserve supplies of energy phosphates are depleted totally and the heart undergoes contracture-rigor.[5]

On reperfusion, mitochondrial oxidative phosphorylation returns to preischemic levels within seconds, however contractile power drags behind and only gradually reaches preischemic values. This phenomenon is termed myocardial stunning.[6,7] Stunned myocardium has relatively excess oxygen consumption for a given rate of contractile work, and thus has a decreased mechanical efficiency. This may, in part, be due to a rapid recovery of the intracellular pH during reperfusion: During ischemia H^+ accumulates intracellularly as a consequence of anaerobic glycolysis. Once perfusion is restored, H^+ is transported into the extracellular space to normalize the pH in exchange for Na^+. The resultant increase in intracellular Na^+ in turn activates the sarcolemmal $2Na^+/Ca^{2+}$ exchanger, resulting in exchange of intracellular Na^+ with extracellular Ca^{2+}. A high rate of $2Na^+/Ca^{2+}$ exchange can finally lead to Ca^{2+} overload and cell death (Figure 1).[8]

Studies in animals have demonstrated that during myocardial reperfusion there is an overshoot in the rate of fatty acid oxidation, impaired pyruvate oxidation, and
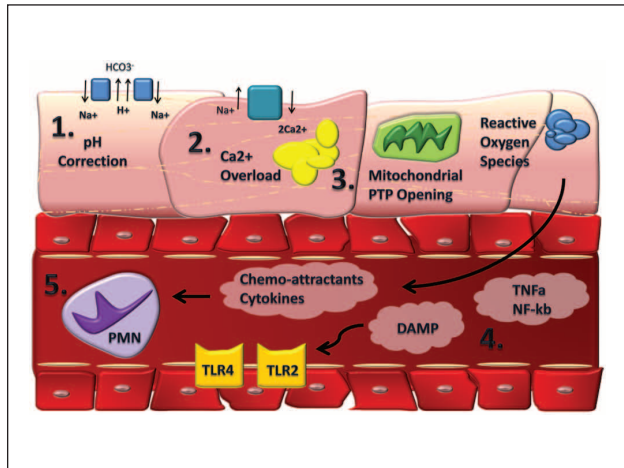

Figure 1. Mediators in myocardial reperfusion injury
During myocardial reperfusion the rapid restoration of physiological pH (1), Ca^{2+} overload (2), and further ATP depletion through opening of the mitochondrial permeability transition pore (mPTP; 3) leads to the generation of reactive oxygen species (ROS). ROS are responsible for the release of pro-inflammatory factors (TNF-α, NF-κB, TLRs, and DAMPs; 4). The release of these chemoattractants leads to the invasion of neutrophils (5).

accelerated anaerobic glycolysis. High rates of fatty acid β-oxidation dramatically inhibit glucose oxidation. This results in a marked imbalance between glycolysis and glucose oxidation. Pyruvate oxidation is likely further inhibited in the clinical situation by the high plasma free fatty acid concentration observed in acute MI. This "uncoupling" is a major source of the net H^+ production in the heart. If glycolysis is coupled to glucose oxidation, H^+ production from glycolysis is 0. However, if glycolysis is uncoupled from glucose oxidation, and pyruvate derived from glycolysis is converted to lactate, there is a net production of $2H^+$ from each glucose molecule, which originates from the hydrolysis of glycolytically derived ATP.[9-11]

Based on these metabolic studies, the important role of the mitochondrial permeability transition pore (PTP), a nonselective channel of the inner mitochondrial membrane becomes a critical determinant of lethal reperfusion injury.[12] Mitochondrial permeability is characterized by permeabilization of an otherwise relatively impermeable mitochondrial inner membrane. During reperfusion, the fate of the cell is determined by the extent of mitochondrial permeabilization. If minimal, the cell may recover; if moderate, the cell may undergo programmed cell death; and if severe, the cell may die from necrosis due to inadequate energy production. Opening the channel collapses the mitochondrial membrane potential and uncouples oxidative phosphorylation, resulting in ATP depletion and cell death. During myocardial ischemia, the mitochondrial

PTP remains closed, only to open within the first few minutes after myocardial reperfusion in response to mitochondrial Ca^{2+} overload, oxidative stress, restoration of a physiologic pH, and ATP depletion. Therefore, the mitochondrial PTP represent an important new target for cardioprotection during reperfusion.[13]

The intracellular changes during ischemia and reperfusion, such as accumulation of H^+ and Ca^{2+} as well as the disruption of mitochondrial membrane potential, lead to the formation of free radical or reactive oxygen species (ROS). ROS accumulation and the subsequent activation of pro-inflammatory pathways play an important role in ischemia reperfusion injury. Therefore a crucial mediator of I/R injury are oxygen derived free radicals, leading to different forms of oxygen species.[14] Reactive oxygen intermediates cause direct damage to cellular DNA, protein, and lipids, in addition to activating pathways of stress response. This nonspecific injury initiates a cytokine-mediated cascade, which results in the production of tumor necrosis factor alpha (TNF-α).[15] Excessive TNF-α expression and subsequent cardiomyocyte TNF receptor type 1 stimulation induce contractile dysfunction, hypertrophy, fibrosis, and cell death.[16] Additionally, the increase in the intracellular Ca^{2+} concentration with the generation of calcium pyrophosphate complexes and the formation of uric acid is a potent stimulator of inflammation. Calcium phosphate complexes and uric acid belong to a group of so called danger signals, and can bind to intracellular protein complexes called inflammasomes.[17] The inflammasomes include different adaptor molecules that mediate an increase of the production and secretion of interleukin-1 (IL-1)β. Furthermore, Toll-like receptors (TLRs) are stimulated through danger signals eventually stimulating the secretion of further pro-inflammatory cytokines and chemokines through the activation of NF-κB.[18]

Finally, the release of chemoattractants draw neutrophils into the infarct zone during the first 6 hours of myocardial reperfusion, and during the next 24 hours they migrate into the myocardial tissue. This process is facilitated by cell adhesion molecules. These neutrophils cause vascular plugging, and release degradative enzymes and more ROS.[8]

As outlined above, a key feature of hypoxia on tissue is the development of metabolic acidosis. As such, these metabolic changes have a direct impact on tissue inflammation, tissue integrity and therefore cell survival. Therefore, it is not surprising that trimetazidine, which acts by inhibiting a mitochondrial enzyme and shifts the preference for energy substrate away from fatty acid metabolism and toward glucose metabolism, reduces I/R damage and tissue inflammation.[19,20] This effect appears to be predominantly caused by a selective block of long-chain 3-ketoacyl-CoA thiolase activity, the last enzyme
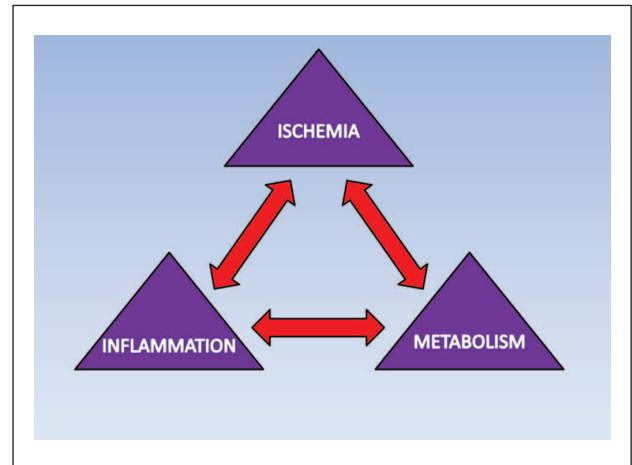

Figure 2. Relationship between ischemia, metabolism, and inflammation
Ischemia and reperfusion leads to significant metabolic changes followed by inflammatory processes. Therapeutic interventions have demonstrated that metabolic modulators have a positive influence on metabolism and heart function with concomitant inhibition of inflammation.

involved in β-oxidation. In fact, a meta-analysis of randomized controlled trials in heart failure revealed that trimetazidine had a significant protective effect for all-cause mortality and cardiovascular events and hospitalization.[21] These recent data once again alerts us to the increasingly unignorable evidence for the benefit of metabolic modulation in myocardial disease and the urgency for a definitive clinical trial.[22]

On the other hand, one may question if anti-inflammatory drugs could also have a beneficial effect on heart metabolism during I/R injury. In fact, it has been shown that IL-6 suppresses myocardial glucose metabolism via inhibition of AMP-activated protein kinase (AMPK).[23] Since AMPK activation and glucose metabolism provide an important source of energy for the heart during I/R,[10] anti-inflammatory agents therefore bear the potential to positively influence cardiac metabolism (Figure 2). However, there is a need for future studies at the bench and the bedside to fully understand the interrelationship between inflammation and metabolism during cardiac I/R injury.

Ischemic Preconditioning

Physicians managing patients with acute coronary syndrome, including severe unstable angina and acute MI, occasionally used to report "the cardiac warm-up phenomenon."[24] This means that patients with at least 1 episode of prodromal angina showed less severe ischemic damage after subsequent exposure to a longer period of

Table 1. Current Clinical Trials on Myocardial Reperfusion Injury (ClinicalTrials.gov)

Mechanism	Current Clinical Trials Studies (Number)	Intervention	Example (Largest Ongoing Clinical Trials)
Preconditioning	5	Remote ischemic preconditioning, levosimendan, nitrate	Remote Ischaemic Preconditioning for Heart Surgery (RIPHeart-Study) No. of enrolled patients: 2070
Postconditioning	9	Remote ischemic postconditioning; erythropoietin, epoetin alpha	DANish Study of Optimal Acute Treatment of Patients With ST-elevation Myocardial Infarction (DANAMI-3) No. of enrolled patients: 2000
Inflammation	4	Acetaminophen, etanercept, adenosine	Myocardial Protection With Adenosine During Primary Percutaneous Coronary Intervention in Patients With STEMI (PROMISE) No. of enrolled patients: 200
Metabolism	14	Melatonin, metformin, dipyridamol, atorvastatin, aminoimidazol–carboxamid–ribonukleotid, glucose–insulin–potassium, 3,5-seco-4-nor-cholestan-5-one oxime-3-ol, exenatide, vitamin C, perhexellin	Melatonins Effect on Ischemia–Reperfusion Injury Following Acute Myocardial Infarction No. of enrolled patients: 60

ischemia. In 1986, Murry et al[3] first documented this phenomenon experimentally through brief intermittent periods of myocardial ischemia, which significantly reduced the size of the infarct from a subsequent total occlusion. This observation was termed *ischemic preconditioning* and has been confirmed repeatedly in various species. For the first time it was shown that infarct size limitation was possible. The observed protective effect was indeed so powerful that this phenomenon has been described by several investigators as "the strongest form of in vivo protection against myocardial ischemic injury other than early reperfusion."[4]

Although direct ischemic preconditioning does reduce reperfusion injury as well as its systemic consequences, its main disadvantage is direct stress to the target organ and mechanical trauma to major vascular structures, which have limited its clinical application. Remote ischemic preconditioning (RIPC) is a novel method where ischemia followed by reperfusion of one organ is believed to protect remote organs either due to release of biochemical messengers in the circulation or due to activation of nerve pathways, resulting in release of messengers that have a protective effect.[25] RIPC was first demonstrated in the myocardium by McClanahan in 1993.[25] He found that ischemia in the kidney followed by reperfusion protected myocardium from ischemia and reduced the infarct size. In animal models, brief ischemia reperfusion of the limb, gut, mesenteric, or kidney reduced myocardial infarct size. In humans, skeletal preconditioning has been used for myocardial

protection with the beneficial effect being attributed to the regulation of endothelial protection.

Since RIPC may be superior over ischemic preconditioning it is not surprising that RIPC, one of the most striking mechanisms identified at the bench, is currently under intense clinical evaluation (Table 1). As such there are several ongoing studies on RIPC in different clinical settings.[26] Although the underlying mechanisms and pathways need further clarification, the close relationship to classical preconditioning makes it a promising approach in a clinical setting (Figure 3).

Nitric oxide (NO), a soluble gas continuously synthesized in endothelial cells by eNOS regulates basal vascular tone and endothelial function, and maintains blood oxygenation via hypoxic pulmonary vasoconstriction. Many studies have implicated the endogenous production of NO, or its therapeutic application in I/R. Administration of NO or NO donors prior to ischemia attenuates the consequences of myocardial I/R injury, and thereby reduces infarct size and endothelial dysfunction.[27] These beneficial effects of NO are related to a pharmacological type of preconditioning.[28] Thus, it is not surprising that there are currently many clinical trials investigating the infusion of nitrates, which is nonenzymatically converted to nitric oxide in the setting of ischemia (Table 1).

Postconditioning

Even though classical preconditioning may work in a clinical setting such as heart surgery, it is not feasible in
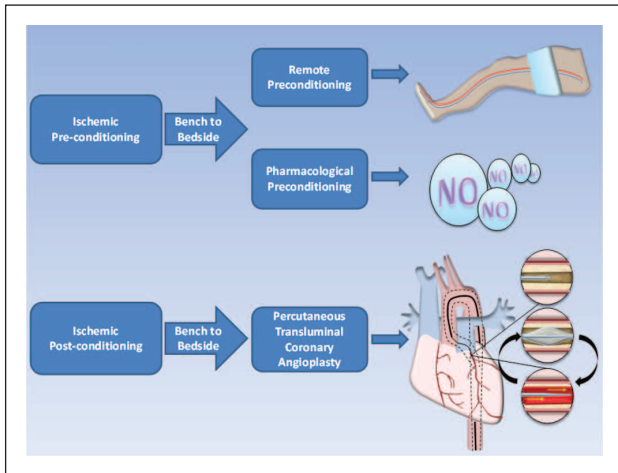
Figure 3. From bench to bedside: Ischemic preconditioning, pharmacological preconditioning, and ischemic postconditioning in the clinical setting
Remote preconditioning can be achieved by intermittent cuff inflation before heart surgery, mimicking ischemic preconditioning, one of the most powerful cardioprotective mechanism found at the bench. Pharmacolgical preconditioning can be achieved by the administration of nitrates prior to surgery, where they are metabolized to NO under ischemic conditions. Ischemic postconditioning during percutaneous transluminal coronary angioplasty is induced by repetitive inflating and deflating of the catheter balloon with the onset of successful reperfusion.

patients with acute MI because the coronary artery is already occluded at the time of hospital admission of the patient. Zhao et al[29] were the first to describethe phenomenon called "postconditioning" in a canine model. Where preconditioning is triggered by brief episodes of I/R performed just before a prolonged coronary artery occlusion, postconditioning is induced by a comparable sequence of reversible I/R but is applied just after the prolonged ischemic insult. Protection by postconditioning was shown to be as potent as that provided by preconditioning, whatever the species and experimental preparation. Unlike preconditioning, the experimental design of postconditioning theoretically allows direct application to the clinical settings, especially during percutaneous transluminal coronary angioplasty. In this case, inflation and deflation of the angioplasty balloon after reopening of the coronary artery can mimic repetitive coronary artery clamping performed in postconditioning animal models (Figure 3). Several clinical studies already suggested that postconditioning by coronary angioplasty protects the human heart during acute MI.[30-34] Based on these promising findings with lower patient numbers, postconditioning is currently investigated in 9 ongoing clinical studies. If the effect is real, the magnitude of the benefit will be remarkably large (35% relative reduction in infarct size), in an era in which it is increasingly difficult to demonstrate additional benefits of new therapies beyond current management because of relatively small infarct size and low mortality of patients with STEMI enrolled in clinical trials.[35] However, to move forward, large multicenter clinical trials of cardiac and remote postconditioning that have adequate statistical power to detect a reduction in clinical end points are needed.[36] Hopefully, studies like the DANish Study of Optimal Acute Treatment of Patients With ST-elevation Myocardial Infarction (DANAMI-3) with 2000 anticipated patient enrollments, will fulfill such criteria (Table 1).

Inflammation

Myocardial I/R leads to an inflammatory response that causes further damage to viable tissue around the infarct, likely through accelerated apoptosis. Acute and chronic immune responses elicited by myocardial ischemia have an important role in the functional deterioration of the heart.[37] Initially, research on modulating the inflammatory response was focused on effector mediators such as leukocytes. However, increasing evidence indicates that various endogenous ligands that act as "danger signals," also called danger-associated molecular patterns (DAMPs), are released on injury and modulate inflammation. Originally described as part of the first-line defense against invading microorganisms, several TLRs on leukocytes and parenchymal cells have now been shown to respond to such signals and to have a pivotal role in noninfectious pathological cardiovascular conditions, such as I/R injury and heart failure. From a therapeutic perspective, DAMPs are attractive targets owing to their specific induction after injury.[37]

Toll-like receptors are implicated in myocardial I/R injury,[38] suggested by the use of the TLR4 antagonist Eritoran in mice that protects against this injurious process (Figure 4).[39] This protective mechanism may be attributed to attenuated inflammation, such as decreased myeloperoxidase activity, leading to smaller infarcts compared with controls. Further studies have suggested that extracellular heat shock cognate protein 70,[39] released by the myocardium during myocardial I/R injury, plays a key role in the postischemic inflammatory response via TLR-4 signaling.[40] TLR-2 also plays a role in myocardial I/R injury, likely related to its modulation of leukocyte activity, which mediates coronary endothelial dysfunction.[41] However, TLR antagonists are still under clinical development and have to be tested in a clinical setting of myocardial I/R injury.[42]

Even though substantial research efforts have been dedicated to identify agents modulating the inflammatory response after MI no promising data from clinical trials have been observed so far. As such a multicenter,
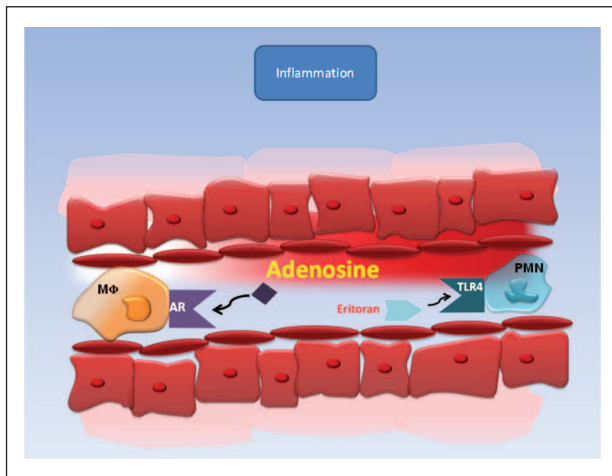
Figure 4. Anti-inflammatory effects of adenosine
Adenosine receptor (AR) or Toll-like receptor (TLR) activation protects the heart from ischemia–reperfusion injury by inactivating the ischemia–reperfusion–induced inflammatory response.

double-blind, placebo-controlled, randomized clinical trial demonstrated that an antibody to CD11/CD18 leukocyte integrin receptor did not reduce infarct size in patients who underwent primary angioplasty.[43] However, multiple studies have suggested that the very old drug "adenosine" is critical for protection against inflammation-mediated I/R injury.[44-47] This mechanism of protection by adenosine includes direct effects on organ parenchymal cells, vasodilatation of coronary arteries, and also inhibition of leukocyte mediated inflammatory response (Figure 4). The protective effect of extracellular adenosine is mediated through 4 adenosine receptors (ARs; Adora1, Adora2a, Adora2b, and Adora3).[48] All ARs have been associated with cardiac tissue protection in different settings. In particular the Adora2b receptor has been implicated in ischemic preconditioning[49] and postconditioning.[50] Although systemic adenosine infusion did not reduce overall mortality in the "famous" AMISTAD-II trial, some effect on infarct size was noted.[50] Based on these findings a multicenter, randomized, placebo-controlled, double-blind study on the safety and efficacy of a brief intracoronary infusion of adenosine applied at the time of reperfusion to limit infarct size is currently being performed (Table 1). In addition, future studies using more specific AR agonists during reperfusion may be necessary to fully elucidate the benefits of adenosine signaling for I/R injury.[49]

Metabolism

Cardiac fatty acid and glucose metabolism, specifically fatty acid β-oxidation and glucose oxidation, are highly regulated processes that meet the majority of myocardial energetic requirements. Cardiac I/R is characterized by complex alterations in fatty acid and glucose oxidation that ultimately have a negative impact on cardiac efficiency and function. Pharmacologically shifting the balance between fatty acid β-oxidation and glucose oxidation by enhancing glucose oxidation at the expense of fatty acid oxidation can improve the efficiency of ATP generation and hydrolysis during reperfusion. Such alterations in energy substrate metabolism can limit the deficits in cardiac efficiency and function that occur during cardiac I/R (Figure 5).[10,11,51]

As the rate-limiting enzyme mediating mitochondrial fatty acid uptake, Carnitine palmitoyltransferase I (CPTI) is an attractive target for inhibiting myocardial fatty acid β-oxidation. Etomoxir, an irreversible inhibitor of CPTI, has been shown to improve myocardial function, concomitant with an increase in glucose oxidation after global ischemia in rat hearts.[52]

Trimetazidine, a partial fatty acid β-oxidation inhibitor that competitively inhibits long-chain 3-ketoacyl-CoA thiolase, is also able to increase glucose oxidation. Results from clinical studies have confirmed the effectiveness of trimetazidine as an anti-ischemic agent.[53] Treatment of angina with trimetazidine has been shown to increase the time to 1-mm ST segment depression.[54]

Ranolazine, another partial fatty acid β-oxidation inhibitor, reciprocally increases glucose oxidation. Clinically, ranolazine has been approved in the United States for the treatment of chronic stable angina. Ranolazine monotherapy has been shown to increase exercise capacity and time to 1-mm ST segment depression, and to reduce the number of weekly angina attacks.[55]

Glucose–insulin–potassium therapy has been shown to increase the rates of glycolysis and also decrease circulating concentrations of free fatty acid.[9] The shift toward glucose utilization decreases infarct size and improves postischemic cardiac function. A number of studies also demonstrate that GIK therapy is beneficial when administered at reperfusion.[56] The Glucose–Insulin–Potassium Study demonstrates a reduction in mortality, although the benefit is limited to patients without heart failure. A more recent Dutch GIK study showed a potentially higher mortality in the GIK group.[57,58] Based on these uncertainties about GIK, currently a clinical trial on the effect of glucose–insulin–potassium solution on myocardial protection during off-pump coronary bypass surgery is underway that will provide more answers to the grade of beneficial effects of this therapeutic approach.

Directly increasing myocardial glucose oxidation represents another approach to improve cardiac function. Dichloroacetate stimulates the mitochondrial PDH complex via the inhibition of the activity of PDK. Improved
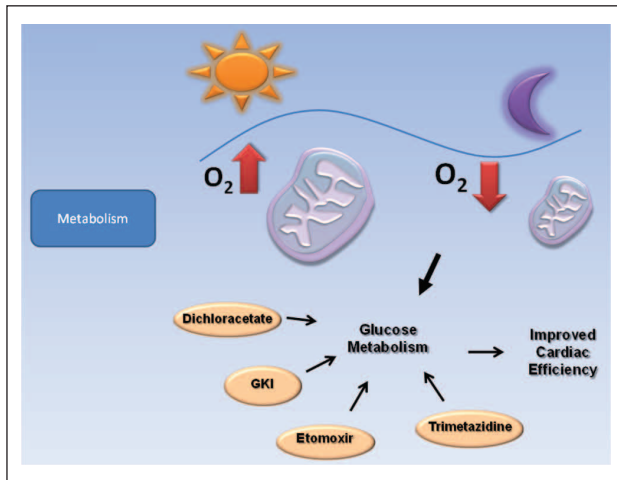
Figure 5. Metabolism as therapeutic target in ischemia and reperfusion injury
Light as a central regulator of circadian rhythmicities may be a novel therapeutic option in the treatment of patients suffering from myocardial infarction by improving cardiomyocyte cell metabolism after myocardial ischemia and reperfusion. Modulators of metabolism like dichloracetate, glucose–potassium–insulin (GKI), etoxomir, and trimetazidine are already used in a clinical setting and can improve cardiac function through shifting cell metabolism from fatty acid β-oxidation to preferred glucose oxidation.

coupling between glycolysis and glucose oxidation contributes to the mechanism(s) by which dichloroacetate exerts its cardioprotective effects.[59] In a small clinical study, where dichloroacetate was given to patients with coronary artery disease via intravenous infusion, improvements in left ventricular stroke volume was observed in the absence of changes in heart rate, left ventricular end diastolic pressure or myocardial oxygen consumption.[60]

As outlined earlier, with the onset of reperfusion after ischemia, the first pathophysiological event is represented by metabolic changes that can lead to cell death and a pro-inflammatory phenotype that further enhances tissue injury. Targeting metabolic events seems to be a promising strategy to reduce ischemia reperfusion injury. In fact, counting the number of ongoing clinical trials with the purpose to target metabolism reveals a total number of 14 studies (Table 1).

Another emerging approach to target metabolism is based on the observation that multiple extracardiac stimuli, such as workload and circulating nutrients (eg, fatty acids), are known to influence myocardial metabolism and contractile function, and to exhibit marked circadian rhythms.[61-67] Thus, it was found that there are circadian rhythmicities in myocardial oxidative and nonoxidative metabolism as well as responsiveness of the rat heart to

changes in workload and fatty acid availability.[67] Almost all living organisms have developed biological rhythms linked to the day/night or light/dark cycles of the sun. The impact that such rhythms exert on a variety of physiological functions in humans has been recognized for a long time. The internal oscillator, or control station regulating the body's circadian clock, is the suprachiasmatic nucleus, located in the hypothalamus, above the optic chiasm. The suprachiasmatic nucleus processes external signals such as ambient light and inputs from the brain to regulate a variety of cyclic functions, including body temperature, sleep/wake cycles, and secretion of hormones such as cortisol, melatonin, thyroxin, and vasopressin.[68-72]

What is clear is that mutations in the *Clock* gene affect metabolism in each genetic background tested, but in different ways.[73] Disruption of another circadian protein, Bmal1, also shows metabolic abnormalities with impaired insulin responsiveness and reduced gluconeogenesis.[74]

Since external signals such as ambient light are central regulators of the circadian rhythm, the question arises if regulated daylight exposure of patients could alter metabolism. The use of daylight and the maintenance of a physiological day/night rhythm in a clinical setting could therefore represent a strategy which may improve cardiac metabolism after myocardial I/R. Indeed, a recent study using red light found acceleration of myocardial contractility recovery and reduction in the amount of molecular products of lipid peroxidation after ischemia.[75] Future studies directed toward the understanding of the circadian rhythm in cardioprotection, therefore, bear the potential to uncover novel, powerful, and easy applicable treatment options to prevent or ameliorate the consequences of myocardial I/R injury in a perioperative setting or in the context of acute MI.

Conclusion

Although translating findings from bench to bedside has been largely disappointing, many striking findings at the bench such as ischemic preconditioning, postconditioning, or remote preconditioning are just under clinical evaluation.

In addition, based on the new understanding of inflammation or metabolism during I/R, the development of new drugs targeting structures such as TLRs or heart metabolism gives hope to implement these strategies into a clinical setting.

Declaration of Conflicting Interests

Funding

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