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Chapter

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

John G. Kingma

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 ($P2Y_{12}$ 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 perconditioning (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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References

[1] Jennings RB. Historical perspective on the pathology of myocardial ischemia/reperfusion injury. Circulation Research. 2013;**113**(4):428-438. DOI: 10.1161/CIRCRESAHA.113.300987

[2] Reimer KA, Jennings RB. The "wavefront phenomenon" of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. Laboratory Investigation. 1979;**40**(6):633-644

[3] Vinten-Johansen J, Weiss HR. Oxygen consumption in subepicardial and subendocardial regions of the canine left ventricle. The effect of experimental acute valvular aortic stenosis. Circulation Research. 1980;**46**(1): 139-145. DOI: 10.1161/01.res.46.1.139

[4] Hoffman JI, Buckberg GD. The myocardial oxygen supply: Demand index revisited. Journal of the American Heart Association. 2014;**3**(1):e000285. DOI: 10.1161/JAHA.113.000285

[5] Hoffman JI. Determinants and prediction of transmural myocardial perfusion. Circulation. 1978;**58**(3 Pt 1): 381-391. DOI: 10.1161/01.cir.58.3.381

[6] Ganote CE. Contraction band necrosis and irreversible myocardial injury. Journal of Molecular and Cellular Cardiology. 1983;**15**:67-73

[7] Reimer KA, Jennings RB, Tatum AH. Pathobiology of acute myocardial ischemia: Metabolic, functional and ultrastructural studies. The American Journal of Cardiology. 1983;**52**:72A-81A

[8] Kloner RA, Darsee JR, DeBoer LWV, Carlson N. Early pathologic detection of acute myocardial infarction. Archives of Pathology & Laboratory Medicine. 1981;**105**:403-406

[9] Galluzzi L, Bravo-San Pedro JM, Vitale I, Aaronson SA, Abrams JM, Adam D, et al. Essential versus accessory aspects of cell death: Recommendations of the NCCD 2015. Cell Death and Differentiation. 2015;**22**(1):58-73. DOI: 10.1038/cdd.2014.137

[10] JG K. Acute myocardial injury: A perspective on lethal reperfusion injury. Cardiovascular Pharmacology: Open Access. 2017;**6**:8. DOI: 10.4172/2329-6607.1000216

[11] Ganote C, Armstrong S. Ischaemia and the myocyte cytoskeleton: Review and speculation. Cardiovascular Research. 1993;**27**:1387-1403

[12] Steenbergen C, Hill ML, Jennings RB. Cytoskeletal damage during myocardial ischemia: Changes in vinculin immunofluorescence staining during total in vitro ischemia in canine heart. Circulation Research. 1987;**60**(4):478-486

[13] Jennings RB, Hawkins HK, Lowe JE, Hill ML, Klotman S, Reimer KA. Relation between high energy phosphate and lethal injury in myocardial ischemia in the dog. The American Journal of Pathology. 1978;**92**(1):187-214

[14] Jennings RB, Reimer KA, Steenbergen C. Myocardial ischemia revisited. The osmolar load, membrane damage, and reperfusion. Journal of Molecular and Cellular Cardiology. 1986;**18**:769-780

[15] Downey JM, Cohen MV. Reducing infarct size in the setting of acute myocardial infarction. Progress in Cardiovascular Diseases. 2006;**48**(5):363-371. DOI: 10.1016/j.pcad.2006.02.005

[16] Goel K, Pinto DS, Gibson CM. Association of time to reperfusion with

left ventricular function and heart failure in patients with acute myocardial infarction treated with primary percutaneous coronary intervention: A systematic review. American Heart Journal. 2013;**165**(4):451-467. DOI: 10.1016/j.ahj.2012.11.014

[17] Braunwald E, Kloner RA. Myocardial reperfusion: A double-edged sword? The Journal of Clinical Investigation. 1985;**76**:1713-1719

[18] Heusch G. Cardioprotection: Chances and challenges of its translation to the clinic. Lancet. 2013;**381**(9861):166-175. DOI: 10.1016/S0140-6736(12)60916-7

[19] Bernink FJ, Timmers L, Beek AM, Diamant M, Roos ST, Van Rossum AC, et al. Progression in attenuating myocardial reperfusion injury: An overview. International Journal of Cardiology. 2014;**170**(3):261-269. DOI: 10.1016/j.ijcard.2013.11.007

[20] Kloner RA, Ganote CE, Jennings RB. The "no-reflow" phenomenon after temporary coronary occlusion in the dog. The Journal of Clinical Investigation. 1974;**54**(6):1496-1508. DOI: 10.1172/JCI107898

[21] Willerson JT, Powell WJ Jr, Guiney TE, Stark JJ, Sanders CA, Leaf A. Improvement in myocardial function and coronary blood flow in ischemic myocardium after mannitol. The Journal of Clinical Investigation. 1972;**51**(12):2989-2998. DOI: 10.1172/JCI107126

[22] Camilleri JP, Joseph D, Fabiani JN, Deloche A, Schlumberger M, Relland J, et al. Microcirculatory changes following early reperfusion in experimental myocardial infarction. Virchows Archiv. A, Pathological Anatomy and Histology. 1976;**369**(4):315-333. DOI: 10.1007/bf00432452

[23] Ambrosio G, Weisman HF, Mannisi JA, Becker LC. Progressive impairment of regional myocardial perfusion after initial restoration of postischemic blood flow. Circulation. 1989;**80**(6):1846-1861

[24] Jeremy RW, Links JM, Becker LC. Progressive failure of coronary flow during reperfusion of myocardial infarction: Documentation of the no reflow phenomenon with positron emission tomography. Journal of the American College of Cardiology. 1990;**16**(3):695-704

[25] Kloner RA, Rude RE, Carlson N, Maroko PR, DeBoer LWV, Braunwald E. Ultrastructural evidence of microvascular damage and myocardial cell injury after coronary artery occlusion: Which comes first? Circulation. 1980;**62**:945-952

[26] Cobb FR, Bache RJ, Rivas F, Greenfield JC Jr. Local effects of acute cellular injury on regional myocardial blood flow. The Journal of Clinical Investigation. 1976;**57**:1359-1368

[27] Kloner RA. No-reflow phenomenon: Maintaining vascular integrity. Journal of Cardiovascular Pharmacology and Therapeutics. 2011;**16**(3-4):244-250. DOI: 10.1177/1074248411405990

[28] Vinten-Johansen J. Involvement of neutrophils in the pathogenesis of lethal myocardial reperfusion injury. Cardiovascular Research. 2004;**61**(3):481-497. DOI: 10.1016/j.cardiores.2003.10.011

[29] Bresnahan GF, Roberts R, Shell WE, Ross J Jr, Sobel BE. Deleterious effects due to hemorrhage after myocardial reperfusion. The American Journal of Cardiology. 1974;**33**(1):82-86. DOI: 10.1016/0002-9149(74)90742-5

[30] Rezkalla SH, Dharmashankar KC, Abdalrahman IB, Kloner RA. No-reflow phenomenon following percutaneous coronary intervention for acute myocardial infarction: Incidence,

outcome, and effect of pharmacologic therapy. Journal of Interventional Cardiology. 2010;**23**(5):429-436. DOI: 10.1111/j.1540-8183.2010.00561.x

[31] Rezkalla SH, Kloner RA. Coronary no-reflow phenomenon: From the experimental laboratory to the cardiac catheterization laboratory. Catheterization and Cardiovascular Interventions. 2008;**72**(7):950-957. DOI: 10.1002/ccd.21715

[32] Becker LC, Ambrosio G. Myocardial consequences of reperfusion. Progress in Cardiovascular Diseases. 1987;**30**:23-44

[33] Reimer KA, Hill ML, Jennings RB. Prolonged depletion of ATP and of the adenine nucleotide pool due to delayed resynthesis of adenine nucleotides following reversible myocardial ischemic injury in dogs. Journal of Molecular and Cellular Cardiology. 1981;**13**(2):229-239. DOI: 10.1016/0022-2828(81)90219-4

[34] Kloner RA, DeBoer LW, Darsee JR, Ingwall JS, Hale S, Tumas J, et al. Prolonged abnormalities of myocardium salvaged by reperfusion. The American Journal of Physiology. 1981;**241**(4):H591-H599. DOI: 10.1152/ajpheart.1981.241.4.H591

[35] Rahimtoola SH. The hibernating myocardium. American Heart Journal. 1989;**117**(1):211-221

[36] Feigl EO. Coronary physiology. Physiological Reviews. 1983;**63**:1-205

[37] Heyndrickx GR, Baig H, Nellens P, Leusen I, Fishbein MC, Vatner SF. Depression of regional blood flow and wall thickening after brief coronary occlusions. American Journal of Physiology. Heart and Circulatory Physiology. 1978;**234**:H653-H6H9

[38] Heyndrickx GR, Millard RW, McRitchie RJ, Maroko PR, Vatner SF. Regional myocardial functional and electrophysiological alterations after brief coronary artery occlusion in conscious dogs. The Journal of Clinical Investigation. 1975;**56**:978-985

[39] Chatterjee K, Swan HJ, Parmley WW, Sustaita H, Marcus HS, Matloff J. Influence of direct myocardial revascularization on left ventricular asynergy and function in patients with coronary heart disease. With and without previous myocardial infarction. Circulation. 1973;**47**(2):276-286. DOI: 10.1161/01.cir.47.2.276

[40] Benz DC, von Dahlen AP, Huang W, Messerli M, von Felten E, Benetos G, et al. No differences in rest myocardial blood flow in stunned and hibernating myocardium: Insights into the pathophysiology of ischemic cardiomyopathy. European Journal of Nuclear Medicine and Molecular Imaging. 2019;**46**(11):2322-2328. DOI: 10.1007/s00259-019-04440-2

[41] Bolli R. Postischemic myocardial stunning: Pathogenesis, pathophysiology, and clinical relevance. In: Yellon DM, Jennings RB, editors. Myocardial Protection: The Pathophysiology of Reperfusion and Reperfusion Injury. 1st ed. New York: Raven Press; 1992. pp. 105-149

[42] Bolli R. Myocardial 'stunning' in man. Circulation. 1992;**86**(6):1671-1691

[43] Benz DC, Gaemperli O. The right timing for post-ischemic stunning. Journal of Nuclear Cardiology. 2017;**24**(4):1302-1304. DOI: 10.1007/s12350-016-0473-8

[44] Canty JM Jr, Fallavollita JA. Hibernating myocardium. Journal of Nuclear Cardiology. 2005;**12**(1):104-119. DOI: 10.1016/j.nuclcard.2004.11.003

[45] Heusch G, Schulz R, Rahimtoola SH. Myocardial hibernation:

A delicate balance. American Journal of Physiology. Heart and Circulatory Physiology. 2005;**288**(3):H984-HH99. DOI: 10.1152/ajpheart.01109.2004

[46] Camici PG, Rimoldi OE. Myocardial blood flow in patients with hibernating myocardium. Cardiovascular Research. 2003;**57**(2):302-311

[47] Camici PG, Wijns W, Borgers M, De Silva R, Ferrari R, Knuuti J, et al. Pathophysiological mechanisms of chronic reversible left ventricular dysfunction due to coronary artery disease (hibernating myocardium). Circulation. 1997;**96**(9):3205-3214. DOI: 10.1161/01.cir.96.9.3205

[48] Heusch G, Schulz R. Perfusion-contraction match and mismatch. Basic Research in Cardiology. 2001;**96**(1): 1-10. DOI: 10.1007/s003950170072

[49] Heusch G. Hibernating myocardium. Physiological Reviews. 1998;**78**(4):1055-1085

[50] Ross JJ. Myocardial perfusion-contraction matching. Implications for coronary heart disease and hibernation. Circulation. 1991;**83**(3):1076-1083

[51] Manning AS, Hearse DJ. Reperfusion-induced arrhythmias: Mechanisms and prevention. Journal of Molecular and Cellular Cardiology. 1984;**16**:497-518

[52] Majidi M, Kosinski AS, Al-Khatib SM, Lemmert ME, Smolders L, van Weert A, et al. Reperfusion ventricular arrhythmia 'bursts' in TIMI 3 flow restoration with primary angioplasty for anterior ST-elevation myocardial infarction: A more precise definition of reperfusion arrhythmias. Europace. 2008;**10**(8):988-997. DOI: 10.1093/europace/eun123

[53] Akar JG, Akar FG. Regulation of ion channels and arrhythmias in the ischemic heart. Journal of Electrocardiology. 2007;**40**(6 Suppl):S37-S41. DOI: 10.1016/j.jelectrocard.2007.05.020

[54] Curtis MJ, Pugsley MK, Walker MJ. Endogenous chemical mediators of ventricular arrhythmias in ischaemic heart disease. Cardiovascular Research. 1993;**27**(5):703-719. DOI: 10.1093/cvr/27.5.703

[55] van der Weg K, Prinzen FW, Gorgels AP. Editor's choice-reperfusion cardiac arrhythmias and their relation to reperfusion-induced cell death. European Heart Journal Acute Cardiovascular Care. 2019;**8**(2):142-152. DOI: 10.1177/2048872618812148

[56] Bernier M, Hearse DJ, Manning AS. Reperfusion-induced arrhythmias and oxygen-derived free radicals: Studies with "anti-free radical" interventions and a free radical-generating system in the isolated perfused rat heart. Circulation Research. 1986;**58**:331-340

[57] Balke CW, Kaplinsky E, Mickelson EL, Naito N, Dreifus LS. Reperfusion ventricular tachyarrhythmias: Correlation with antecedent coronary artery occlusion, tachyarrhythmias and duration of myocardial ischemia. American Heart Journal. 1981;**101**:449-456

[58] Sommers HM, Jennings RB. Ventricular fibrillation and myocardial necrosis after transient ischemia. Effect of treatment with oxygen, procainamide, reserpine, and propranolol. Archives of Internal Medicine. 1972;**129**(5):780-789

[59] Tanaka K, Hearse DJ. Reperfusion-induced arrhythmias in the isolated rabbit heart: Characterization of the influence of the duration of regional ischemia and the extracellular potassium concentration. Journal of Molecular and Cellular Cardiology. 1988;**20**(3):201-211. DOI: 10.1016/s0022-2828(88)80053-1

[60] Gersh BJ, Stone GW, White HD, Holmes DR Jr. Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction: Is the slope of the curve the shape of the future? Journal of the American Medical Association. 2005;**293**(8):979-986. DOI: 10.1001/jama.293.8.979

[61] Sharma V, Bell RM, Yellon DM. Targeting reperfusion injury in acute myocardial infarction: A review of reperfusion injury pharmacotherapy. Expert Opinion on Pharmacotherapy. 2012;**13**(8):1153-1175. DOI: 10.1517/14656566.2012.685163

[62] Kloner RA. Current state of clinical translation of cardioprotective agents for acute myocardial infarction. Circulation Research. 2013;**113, 4**:451-463. DOI: 10.1161/CIRCRESAHA.112.300627

[63] Bulluck H, Yellon DM, Hausenloy DJ. Reducing myocardial infarct size: Challenges and future opportunities. Heart. 2016;**102**(5):341-348. DOI: 10.1136/heartjnl-2015-307855

[64] Ibanez B, Heusch G, Ovize M, Van de Werf F. Evolving therapies for myocardial ischemia/reperfusion injury. Journal of the American College of Cardiology. 2015;**65**(14):1454-1471. DOI: 10.1016/j.jacc.2015.02.032

[65] Boyle DM, Barber JM, McIlmoyle EL, Salathia KS, Evans AE, Cran G, et al. Effect of very early intervention with metoprolol on myocardial infarct size. British Heart Journal. 1983;**49**(3):229-233. DOI: 10.1136/hrt.49.3.229

[66] Kudoh Y, Maxwell MP, Hearse DJ, Downey JM, Yellon DM. Inability of metoprolol to achieve a sustained limitation of infarct size 24 h after coronary artery embolization in the closed chest dog. Journal of Cardiovascular Pharmacology. 1984;**6**(6):1201-1209

[67] Ibanez B, Cimmino G, Prat-Gonzalez S, Vilahur G, Hutter R, Garcia MJ, et al. The cardioprotection granted by metoprolol is restricted to its administration prior to coronary reperfusion. International Journal of Cardiology. 2011;**147**(3):428-432. DOI: 10.1016/j.ijcard.2009.09.551

[68] Garcia-Prieto J, Villena-Gutierrez R, Gomez M, Bernardo E, Pun-Garcia A, Garcia-Lunar I, et al. Neutrophil stunning by metoprolol reduces infarct size. Nature Communications. 2017;**8**:14780. DOI: 10.1038/ncomms14780

[69] Antoniucci D. Block the ischemia and reperfusion damage: An old adjunctive drug for a new reperfusion strategy. Journal of the American College of Cardiology. 2014;**63**(22):2363-2364. DOI: 10.1016/j.jacc.2014.03.015

[70] Kim MH, Gorouhi F, Ramirez S, Granick JL, Byrne BA, Soulika AM, et al. Catecholamine stress alters neutrophil trafficking and impairs wound healing by beta2-adrenergic receptor-mediated upregulation of IL-6. The Journal of Investigative Dermatology. 2014;**134**(3):809-817. DOI: 10.1038/jid.2013.415

[71] Shen YT, Wiedmann RT, Lynch JJ Jr, Gould RJ. Platelet glycoprotein IIb/IIIa receptor inhibitor preserves coronary flow reserve during progressive coronary arteriostenosis in swine. Arteriosclerosis, Thrombosis, and Vascular Biology. 2000;**20**(10):2309-2315

[72] Rendu F, Brohard-Bohn B. The platelet release reaction: Granules' constituents, secretion and functions. Platelets. 2001;**12**(5):261-273. DOI: 10.1080/09537100120068170

[73] Yuan X, Xiang Y, Zhu N, Zhao X, Ye S, Zhong P, et al. Salvianolic acid a protects against myocardial ischemia/reperfusion injury by reducing platelet activation and inflammation. Experimental and Therapeutic Medicine. 2017;**14**(2):961-966. DOI: 10.3892/etm.2017.4619

[74] Yang XM, Cui L, Alhammouri A, Downey JM, Cohen MV. Triple therapy greatly increases myocardial salvage during ischemia/reperfusion in the in situ rat heart. Cardiovascular Drugs and Therapy. 2013;**27**(5):403-412. DOI: 10.1007/s10557-013-6474-9

[75] Yang XM, Liu Y, Cui L, Yang X, Liu Y, Tandon N, et al. Platelet P2Y(1)(2) blockers confer direct postconditioning-like protection in reperfused rabbit hearts. Journal of Cardiovascular Pharmacology and Therapeutics. 2013;**18**(3):251-262. DOI: 10.1177/1074248412467692

[76] Nanhwan MK, Ling S, Kodakandla M, Nylander S, Ye Y, Birnbaum Y. Chronic treatment with ticagrelor limits myocardial infarct size: An adenosine and cyclooxygenase-2-dependent effect. Arteriosclerosis, Thrombosis, and Vascular Biology. 2014;**34**(9):2078-2085. DOI: 10.1161/ATVBAHA.114.304002

[77] Ye Y, Birnbaum GD, Perez-Polo JR, Nanhwan MK, Nylander S, Birnbaum Y. Ticagrelor protects the heart against reperfusion injury and improves remodeling after myocardial infarction. Arteriosclerosis, Thrombosis, and Vascular Biology. 2015;**35**(8):1805-1814. DOI: 10.1161/ATVBAHA.115.305655

[78] Vilahur G, Gutierrez M, Casani L, Varela L, Capdevila A, Pons-Llado G, et al. Protective effects of Ticagrelor on myocardial injury after infarction. Circulation. 2016;**134**(22):1708-1719. DOI: 10.1161/CIRCULATIONAHA.116.024014

[79] Wang K, Zhou X, Huang Y, Khalil M, Wiktor D, van Giezen JJ, et al. Adjunctive treatment with ticagrelor, but not clopidogrel, added to tPA enables sustained coronary artery recanalisation with recovery of myocardium perfusion in a canine coronary thrombosis model. Thrombosis and Haemostasis. 2010;**104**(3):609-617. DOI: 10.1160/TH09-12-0823

[80] Armstrong D, Summers C, Ewart L, Nylander S, Sidaway JE, van Giezen JJ. Characterization of the adenosine pharmacology of ticagrelor reveals therapeutically relevant inhibition of equilibrative nucleoside transporter 1. Journal of Cardiovascular Pharmacology and Therapeutics. 2014;**19**(2):209-219. DOI: 10.1177/1074248413511693

[81] van Giezen JJ, Sidaway J, Glaves P, Kirk I, Bjorkman JA. Ticagrelor inhibits adenosine uptake in vitro and enhances adenosine-mediated hyperemia responses in a canine model. Journal of Cardiovascular Pharmacology and Therapeutics. 2012;**17**(2):164-172. DOI: 10.1177/1074248411410883

[82] Willerson JT, Golino P, McNatt J, Eidt J, Yao S-K, Buja LM. Role of new antiplatelet agents as adjunctive therapies in thrombolysis. The American Journal of Cardiology. 1991;**67**:12A-18A

[83] Kingma JG Jr, Plante S, Bogaty P. Platelet GPIIb/IIIa receptor blockade reduces infarct size in a canine model of ischemia-reperfusion. Journal of the American College of Cardiology. 2000;**36**(7):2317-2324

[84] Kingma JG. Effect of platelet GPIIb/IIIa receptor blockade with MK383 on infarct size and myocardial blood flow in a canine reocclusion model. Journal of Cardiovascular Pharmacology and Therapeutics. 2018;**24**(2):182-192. DOI: 10.1177/1074248418808389

[85] Boengler K, Lochnit G, Schulz R. Mitochondria "THE" target of myocardial conditioning. American Journal of Physiology. Heart and Circulatory Physiology. 2018;**315**(5):H1215-H1H31. DOI: 10.1152/ajpheart.00124.2018

[86] Argaud L, Gateau-Roesch O, Raisky O, Loufouat J, Robert D, Ovize M. Postconditioning inhibits mitochondrial permeability transition. Circulation. 2005;**111**(2):194-197. DOI: 10.1161/01.CIR.0000151290.04952

[87] Argaud L, Gomez L, Gateau-Roesch O, Couture-Lepetit E, Loufouat J, Robert D, et al. Trimetazidine inhibits mitochondrial permeability transition pore opening and prevents lethal ischemia-reperfusion injury. Journal of Molecular and Cellular Cardiology. 2005;**39**(6):893-899. DOI: 10.1016/j.yjmcc.2005.09.012

[88] Gomez L, Thibault H, Gharib A, Dumont JM, Vuagniaux G, Scalfaro P, et al. Inhibition of mitochondrial permeability transition improves functional recovery and reduces mortality following acute myocardial infarction in mice. American Journal of Physiology. Heart and Circulatory Physiology. 2007;**293**(3):H1654-H1661. DOI: 10.1152/ajpheart.01378.2006

[89] Gibson CM, Giugliano RP, Kloner RA, Bode C, Tendera M, Janosi A, et al. EMBRACE STEMI study: A phase 2a trial to evaluate the safety, tolerability, and efficacy of intravenous MTP-131 on reperfusion injury in patients undergoing primary percutaneous coronary intervention. European Heart Journal. 2016;**37**(16):1296-1303. DOI: 10.1093/eurheartj/ehv597

[90] Lincoff AM, Roe M, Aylward P, Galla J, Rynkiewicz A, Guetta V, et al. Inhibition of delta-protein kinase C by delcasertib as an adjunct to primary percutaneous coronary intervention for acute anterior ST-segment elevation myocardial infarction: Results of the PROTECTION AMI randomized controlled trial. European Heart Journal. 2014;**35**(37):2516-2523. DOI: 10.1093/eurheartj/ehu177

[91] Ottani F, Latini R, Staszewsky L, La Vecchia L, Locuratolo N, Sicuro M, et al. Cyclosporine a in reperfused myocardial infarction: The multicenter, controlled, open-label CYCLE trial. Journal of the American College of Cardiology. 2016;**67**(4):365-374. DOI: 10.1016/j.jacc.2015.10.081

[92] Piot C, Croisille P, Staat P, Thibault H, Rioufol G, Mewton N, et al. Effect of cyclosporine on reperfusion injury in acute myocardial infarction. The New England Journal of Medicine. 2008;**359**(5):473-481. DOI: 10.1056/NEJMoa071142

[93] Alburquerque-Bejar JJ, Barba I, Inserte J, Miro-Casas E, Ruiz-Meana M, Poncelas M, et al. Combination therapy with remote ischaemic conditioning and insulin or exenatide enhances infarct size limitation in pigs. Cardiovascular Research. 2015;**107**(2):246-254. DOI: 10.1093/cvr/cvv171

[94] Hauerslev M, Mork SR, Pryds K, Contractor H, Hansen J, Jespersen NR, et al. Influence of long-term treatment with glyceryl trinitrate on remote ischemic conditioning. American Journal of Physiology. Heart and Circulatory Physiology. 2018;**315**(1):H150-H1H8. DOI: 10.1152/ajpheart.00114.2018

[95] Candilio L, Malik A, Ariti C, Barnard M, Di Salvo C, Lawrence D, et al. Effect of remote ischaemic preconditioning on clinical outcomes in patients undergoing cardiac bypass surgery: A randomised controlled clinical trial. Heart. 2015;**101**(3):185-192. DOI: 10.1136/heartjnl-2014-306178

[96] Kleinbongard P, Thielmann M, Jakob H, Peters J, Heusch G, Kottenberg E. Nitroglycerin does not interfere with protection by remote ischemic preconditioning in patients with surgical coronary revascularization under isoflurane anesthesia. Cardiovascular Drugs and Therapy. 2013;**27**(4):359-361. DOI: 10.1007/s10557-013-6451-3

[97] Kingma JG. Inhibition of Na(+)/H(+) exchanger with EMD 87580 does not confer greater cardioprotection beyond preconditioning on ischemia-reperfusion injury in Normal dogs. Journal of Cardiovascular Pharmacology and Therapeutics. 2018;**23**(3):254-269. DOI: 10.1177/1074248418755120

[98] Heusch G, Kleinbongard P, Skyschally A, Levkau B, Schulz R, Erbel R. The coronary circulation in cardioprotection: More than just one confounder. Cardiovascular Research. 2012;**94**(2):237-245. DOI: 10.1093/cvr/cvr271

[99] Babu GG, Walker JM, Yellon DM, Hausenloy DJ. Peri-procedural myocardial injury during percutaneous coronary intervention: An important target for cardioprotection. European Heart Journal. 2011;**32**(1):23-31. DOI: 10.1093/eurheartj/ehq393

[100] Skyschally A, Walter B, Heusch G. Coronary microembolization during early reperfusion: Infarct extension, but protection by ischaemic postconditioning. European Heart Journal. 2013;**34**(42):3314-3321. DOI: 10.1093/eurheartj/ehs434

[101] Heusch G, Kleinbongard P, Bose D, Levkau B, Haude M, Schulz R, et al. Coronary microembolization: From bedside to bench and back to bedside. Circulation. 2009;120(18):1822-1836. DOI: 10.1161/CIRCULATIONAHA.109.888784

[102] Giglioli C, Cecchi E, Sciagra R, Baldereschi GJ, Meucci F, Valente S, et al. COmparison between COronary THrombus aspiration with Angiojet(R) or export(R) catheter in patients with ST-elevation myocardial infarction submitted to primary angioplasty: The COCOTH study. International Journal of Cardiology. 2016;**203**:757-762. DOI: 10.1016/j.ijcard.2015.03.158

[103] Svilaas T, Vlaar PJ, van der Horst IC, Diercks GF, de Smet BJ, van den Heuvel AF, et al. Thrombus aspiration during primary percutaneous coronary intervention. The New England Journal of Medicine. 2008;**358**(6):557-567. DOI: 10.1056/NEJMoa0706416

[104] Brodie BR. Facilitated percutaneous coronary intervention. Heart. 2005;**91**(12):1527-1529. DOI: 10.1136/hrt.2005.064618

[105] Brodie BR, Stuckey TD, Hansen C, Muncy D. Benefit of coronary reperfusion before intervention on outcomes after primary angioplasty for acute myocardial infarction. The American Journal of Cardiology. 2000;**85**(1):13-18

[106] Kingma JG. Myocardial infarction: Perspectives on cardiac regeneration and cardiac remote conditioning interventions to limit cellular injury. World Journal of Cardiovascular Diseases. 2020;**10**:188-207. DOI: 10.4236/wjcd.2020.104019

[107] Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: A delay of lethal cell injury in ischemic myocardium. Circulation. 1986;**74**:1124-1136

[108] Rosenberg JH, Werner JH, Moulton MJ, Agrawal DK. Current modalities and mechanisms underlying cardioprotection by ischemic conditioning. Journal of Cardiovascular Translational Research.

2018;**11**(4):292-307. DOI: 10.1007/s12265-018-9813-1

[109] Hausenloy DJ, Barrabes JA, Botker HE, Davidson SM, Di Lisa F, Downey J, et al. Ischaemic conditioning and targeting reperfusion injury: A 30 year voyage of discovery. Basic Research in Cardiology. 2016;**111**(6):70. DOI: 10.1007/s00395-016-0588-8

[110] Przyklenk K. Ischaemic conditioning: Pitfalls on the path to clinical translation. British Journal of Pharmacology. 2015;**172**(8):1961-1973. DOI: 10.1111/bph.13064

[111] Kingma JG. Conditioning strategies limit cellular injury? World Journal of Cardiovascular Diseases. 2014;**4**:539-547

[112] Ovize M, Thibault H, Przyklenk K. Myocardial conditioning: Opportunities for clinical translation. Circulation Research. 2013;**113**(4):439-450. DOI: 10.1161/CIRCRESAHA.113.300764

[113] Vander Heide RS, Steenbergen C. Cardioprotection and myocardial reperfusion: Pitfalls to clinical application. Circulation Research. 2013;**113**(4):464-477. DOI: 10.1161/CIRCRESAHA.113.300765

[114] Tsang A, Hausenloy DJ, Mocanu MM, Carr RD, Yellon DM. Preconditioning the diabetic heart: The importance of Akt phosphorylation. Diabetes. 2005;**54**(8):2360-2364. DOI: 10.2337/diabetes.54/8/2360

[115] Kingma JG. The myocardial microcirculation: A key target for salvaging ischemic myocardium? World Journal of Cardiovascular Diseases. 2013;**3**:8-16. DOI: 10.4236/wjcd.2013.35A002

[116] Yellon DM, Downey JM. Preconditioning the myocardium: From cellular physiology to clinical cardiology. Physiological Reviews. 2003;**83**(4):1113-1151

[117] Downey JM, Davis AM, Cohen MV. Signaling pathways in ischemic preconditioning. Heart Failure Reviews. 2007;**12**(3-4):181-188. DOI: 10.1007/s10741-007-9025-2

[118] Hausenloy DJ, Yellon DM. Preconditioning and postconditioning: Underlying mechanisms and clinical application. Atherosclerosis. 2009;**204**(2):334-341. DOI: 10.1016/j.atherosclerosis.2008.10.029

[119] Dawn B, Bolli R. Role of nitric oxide in myocardial preconditioning. Annals of the New York Academy of Sciences. 2002;**962**:18-41

[120] Hausenloy DJ. Signalling pathways in ischaemic postconditioning. Thrombosis and Haemostasis. 2009;**101**(4):626-634

[121] Przyklenk K, Bauer B, Ovize M, Kloner RA, Whittaker P. Regional ischemic preconditioning protects remote virgin myocardium from subsequent coronary occlusion. Circulation. 1993;**87**:893-899

[122] Bromage DI, Pickard JM, Rossello X, Ziff OJ, Burke N, Yellon DM, et al. Remote ischaemic conditioning reduces infarct size in animal in vivo models of ischaemia-reperfusion injury: A systematic review and meta-analysis. Cardiovascular Research. 2017;**113**(3):288-297. DOI: 10.1093/cvr/cvw219

[123] Weber C. Far from the heart: Receptor cross-talk in remote conditioning. Nature Medicine. 2010;**16**(7):760-762. DOI: 10.1038/nm0710-760

[124] Dickson EW, Tubbs RJ, Porcaro WA, Lee WJ, Blehar DJ,

Carraway RE, et al. Myocardial preconditioning factors evoke mesenteric ischemic tolerance via opioid receptors and K(ATP) channels. American Journal of Physiology. Heart and Circulatory Physiology. 2002;**283**(1):H22-HH8

[125] Przyklenk K, Darling CE, Dickson EW, Whittaker P. Cardioprotection 'outside the box'—The evolving paradigm of remote preconditioning. Basic Research in Cardiology. 2003;**98**(3):149-157

[126] Kingma JG, Simard D, Voisine P, Rouleau JR. Role of the autonomic nervous system in cardioprotection by remote preconditioning in isoflurane-anaesthetized dogs. Cardiovascular Research. 2011;**89**(2):384-391. DOI: 10.1093/cvr/cvq306

[127] Jensen RV, Stottrup NB, Kristiansen SB, Botker HE. Release of a humoral circulating cardioprotective factor by remote ischemic preconditioning is dependent on preserved neural pathways in diabetic patients. Basic Research in Cardiology. 2012;**107**(5):285. DOI: 10.1007/s00395-012-0285-1

[128] Li J, Rohailla S, Gelber N, Rutka J, Sabah N, Gladstone RA, et al. MicroRNA-144 is a circulating effector of remote ischemic preconditioning. Basic Research in Cardiology. 2014;**109**(5):423. DOI: 10.1007/s00395-014-0423-z

[129] Davidson SM, Selvaraj P, He D, Boi-Doku C, Yellon RL, Vicencio JM, et al. Remote ischaemic preconditioning involves signalling through the SDF-1alpha/CXCR4 signalling axis. Basic Research in Cardiology. 2013;**108**(5):377. DOI: 10.1007/s00395-013-0377-6

[130] Kudej RK, Shen YT, Peppas AP, Huang CH, Chen W, Yan L, et al. Obligatory role of cardiac nerves and alpha1-adrenergic receptors for the second window of ischemic preconditioning in conscious pigs. Circulation Research. 2006;**99**(11):1270-1276

[131] Haessler R, Wolff RA, Chien GL, Davis RF, Van Winkle DM. High spinal anesthesia does not alter experimental myocardial infarction size or ischemic preconditioning. Journal of Cardiothoracic and Vascular Anesthesia 1997;11(1):72-79. DOI: 10.1016S1053-0770(97)90257-3

[132] Dickson EW, Lorbar M, Porcaro WA, Fenton RA, Reinhardt CP, Gysembergh A, et al. Rabbit heart can be "preconditioned" via transfer of coronary effluent. American Journal of Physiology. Heart and Circulatory Physiology. 1999;**277**(6):H2451-H24H7

[133] Ma XJ, Zhang XH, Li CM, Luo M. Effect of postconditioning on coronary blood flow velocity and endothelial function in patients with acute myocardial infarction. Scandinavian Cardiovascular Journal. 2006;**40**(6):327-333. DOI: 10.1080/14017430601047864

[134] Laskey WK, Yoon S, Calzada N, Ricciardi MJ. Concordant improvements in coronary flow reserve and ST-segment resolution during percutaneous coronary intervention for acute myocardial infarction: A benefit of postconditioning. Catheterization and Cardiovascular Interventions. 2008;**72**(2):212-220. DOI: 10.1002/ccd.21583

[135] Bolognese L, Carrabba N, Parodi G, Santoro GM, Buonamici P, Cerisano G, et al. Impact of microvascular dysfunction on left ventricular remodeling and long-term clinical outcome after primary coronary angioplasty for acute

myocardial infarction. Circulation. 2004;**109**(9):1121-1126. DOI: 10.1161/01.CIR.0000118496.44135.A7

[136] Dwivedi G, Janardhanan R, Hayat SA, Lim TK, Greaves K, Senior R. Relationship between myocardial perfusion with myocardial contrast echocardiography and function early after acute myocardial infarction for the prediction of late recovery of function. International Journal of Cardiology. 2010;**140**(2):169-174. DOI: 10.1016/j.ijcard.2008.11.052

[137] Dwivedi G, Janardhanan R, Hayat SA, Swinburn JM, Senior R. Prognostic value of myocardial viability detected by myocardial contrast echocardiography early after acute myocardial infarction. Journal of the American College of Cardiology. 2007;**50**(4):327-334. DOI: 10.1016/j.jacc.2007.03.036

[138] Przyklenk K. Reduction of myocardial infarct size with ischemic "conditioning": Physiologic and technical considerations. Anesthesia and Analgesia. 2013;**117**(4):891-901. DOI: 10.1213/ANE.0b013e318294fc63

[139] Loukogeorgakis SP, Panagiotidou AT, Broadhead MW, Donald A, Deanfield JE, MacAllister RJ. Remote ischemic preconditioning provides early and late protection against endothelial ischemia-reperfusion injury in humans: Role of the autonomic nervous system. Journal of the American College of Cardiology. 2005;**46**(3):450-456

[140] Hausenloy DJ, Candilio L, Evans R, Ariti C, Jenkins DP, Kolvekar S, et al. Remote ischemic preconditioning and outcomes of cardiac surgery. The New England Journal of Medicine. 2015;**373**(15):1408-1417. DOI: 10.1056/NEJMoa1413534

[141] Meybohm P, Bein B, Brosteanu O, Cremer J, Gruenewald M, Stoppe C, et al. A multicenter trial of remote ischemic preconditioning for heart surgery. The New England Journal of Medicine. 2015;**373**(15):1397-1407. DOI: 10.1056/NEJMoa1413579

[142] Ghaemian A, Nouraei SM, Abdollahian F, Naghshvar F, Giussani DA, Nouraei SA. Remote ischemic preconditioning in percutaneous coronary revascularization: A double-blind randomized controlled clinical trial. Asian Cardiovascular & Thoracic Annals. 2012;**20**(5):548-554. DOI: 10.1177/0218492312439999

[143] Zaugg M, Lucchinetti E, Behmanesh S, Clanachan AS. Anesthetic cardioprotection in clinical practice from proof-of-concept to clinical applications. Current Pharmaceutical Design. 2014;**20**(36):5706-5726. DOI: 10.2174/1381612820666140204120829

[144] Landoni G, Greco T, Biondi-Zoccai G, Nigro Neto C, Febres D, Pintaudi M, et al. Anaesthetic drugs and survival: A Bayesian network meta-analysis of randomized trials in cardiac surgery. British Journal of Anaesthesia. 2013;**111**(6):886-896. DOI: 10.1093/bja/aet231

[145] Schmidt MR, Smerup M, Konstantinov IE, Shimizu M, Li J, Cheung M, et al. Intermittent peripheral tissue ischemia during coronary ischemia reduces myocardial infarction through a KATP-dependent mechanism: First demonstration of remote ischemic perconditioning. American Journal of Physiology. Heart and Circulatory Physiology. 2007;**292**(4):H1883-H1890. DOI: 10.1152/ajpheart.00617.

[146] Yellon DM, Ackbarkhan AK, Balgobin V, Bulluck H, Deelchand A, Dhuny MR, et al. Remote ischemic conditioning reduces myocardial infarct size in STEMI patients treated by thrombolysis. Journal of the American College of Cardiology.

2015;**65**(25):2764-2765. DOI: 10.1016/j.jacc.2015.02.082

[147] Rentoukas I, Giannopoulos G, Kaoukis A, Kossyvakis C, Raisakis K, Driva M, et al. Cardioprotective role of remote ischemic perconditioning in primary percutaneous coronary intervention: Enhancement by opioid action. JACC. Cardiovascular Interventions. 2010;**3**(1):49-55. DOI: 10.1016/j.jcin.2009.10.015