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REVIEW ARTICLE

Reperfusion Cardiac Injury: Receptors and the Signaling Mechanisms

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Abstract: It has been documented that Ca^{2+} overload and increased production of reactive oxygen species play a significant role in reperfusion injury (RI) of cardiomyocytes. Ischemia/reperfusion induces cell death as a result of necrosis, necroptosis, apoptosis, and possibly autophagy, pyroptosis and ferroptosis. It has also been demonstrated that the NLRP3 inflammasome is involved in RI of the heart. An increase in adrenergic system activity during the restoration of coronary perfusion negatively affected cardiac resistance to RI. Toll-like receptors are involved in RI of the heart. Angiotensin II and endothelin-1 aggravated ischemic/reperfusion injury of the heart. Activation of neutrophils, monocytes, $CD4^+$ T-cells and platelets contributes to cardiac ischemia/reperfusion injury. Our review outlines the role of these factors in reperfusion cardiac injury.

Keywords: Heart, reperfusion injury, Ca^{2+} overload, oxidative stress, inflammation, apoptosis.

1. INTRODUCTION

Despite all the achievements of cardiovascular medicine, the mortality rate in acute myocardial infarction (AMI) remains high [1]. Unfortunately, to date, no drug is available, which could effectively prevent reperfusion injury occurring after the restoration of coronary perfusion in patients with AMI and in patients with cardioplegic arrest [2]. Moreover, according to some investigators, reperfusion injury is responsible for up to 50% of the final size of infarction [3, 4]. Infarct size increased from 6 h (27%) to 24 h of reperfusion (41%) with no further increase at 48 and 72 h of reperfusion after a 60-min coronary artery occlusion (CAO) in dogs [5]. In our opinion, a more detailed understanding of the pathogenesis of myocardial reperfusion injury will greatly facilitate the development of more effective pharmacological interventions for the treatment of myocardial infarction.

Interventions to decrease infarct size will have no effect unless coronary blood flow is restored. It is generally accepted that infarct size can only be affected by the restoration of coronary blood flow. Thus, the death of cardiomyocytes in the ischemic zone is almost complete 6 h after CAO [6]. Therefore, reperfusion only results in positive effects if performed no later than 6 h after the onset of AMI. A few studies indicate that it is possible to limit infarct size without reperfusion [7]. These investigators suggest that the cardioprotective effect can be attributed to their anti-inflammatory action. After the restoration of blood flow in the ischemic myocardium, events develop very quickly. Intravenous administration of the selective $P2Y_{12}$ receptor antagonist cangrelor before cardiac reperfusion reduces infarct size by approximately 50%, while injection of cangrelor 10 min after reperfusion does not affect infarct size in rabbits [8]. Administration of the κ-opioid receptor agonist U50,488 5 min prior to reperfusion can prevent reperfusion cardiac injury in rats [9]. However, U50,488 did not exhibit the infarct-reducing effect if this compound was injected 10 sec after reperfusion. It is our hypothesis that pharmacological agents should be administered prior to reperfusion so that they can penetrate into the ischemic zone before the restoration of coronary perfusion, relying upon collateral blood flow. However, it can also be hypothesized that drugs with the anti-inflammatory effect can initiate the infarct-reducing effect after the restoration of coronary blood flow. When NLRP3 inhibitor was administered 1 h after reperfusion it reduced infarct size in mice [10]. However, the NLRP3 inhibitor had no effect if it was administered after 3 hours of reperfusion. The NLRP3 inhibitor OLT1177 exhibited a

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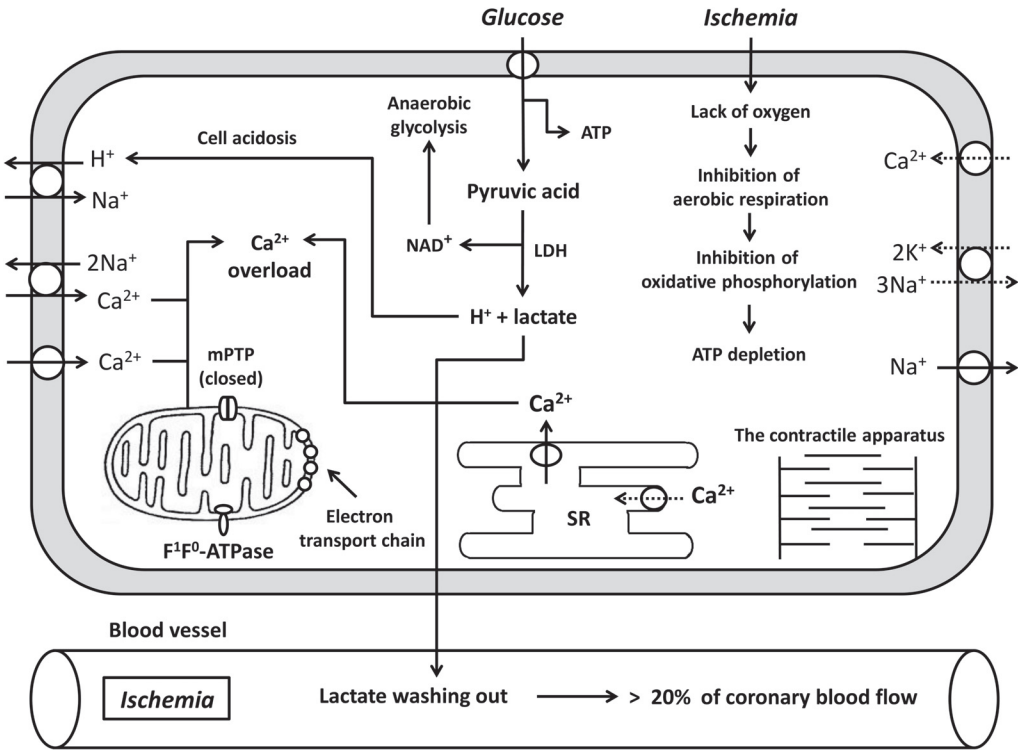

Fig. (1). The main metabolic events that occur during ischemia in cardiomyocytes. SR, sarcoplasmic reticulum; MPTP, mitochondrial permeability transition pore; ROS, reactive oxygen species.

strong infarct-reducing effect if it was administered 1 hour after reperfusion [11]. The infarct-limiting effect was markedly weakened if this inhibitor was administered 2 hours after the restoration of coronary blood flow. This effect completely disappeared when this compound was administered after 3 hours of reperfusion. The aforementioned study indicates the presence of early reperfusion injury of the heart which develops very rapidly (5 - 10 min after the onset of reperfusion) as well as delayed cardiac reperfusion injury which develops in the two - three hours of reperfusion.

2. CA^{2+} OVERLOAD

Reperfusion leads to rapid leaking of protons and lactic acid from the extracellular space. Rapid recovery of extracellular pH stimulates the Na^+/H^+ exchanger and the Na^+/HCO_3^- symporter, which results in extrusion of protons from the cell and rapid normalization of intracellular pH, massive Na^+ influx and intracellular Ca^{2+} overload due to the gain of $2Na^+/Ca^{2+}$ exchange [12]. The importance of the Na^+/H^+ exchanger and the Na^+/HCO_3^- symporter in RI of the heart has been confirmed by Cohen *et al.* [3] and Rodriguez-Sinovas *et al.* [13]. In studies in the isolated rabbit heart, a 90-min CAO and a 2 h-reperfusion were performed [3]. Hypercapnic buffer reperfusion (pH 6.9, 2 min) was demonstrated to decrease the infarct size/area at risk (IS/AAR) ratio by above 60% [3]. In a study that was performed in pigs with CAO and reperfusion [13], it was documented that acidic (Krebs solution at pH 6.4 for the first 3 min of reperfusion) cardiac reperfusion carried out after CAO, resulted in a decrease in the IS/AAR ratio by approximately 30%. These experiments indicate that the Na^+/H^+ exchanger and the Na^+/HCO_3^- symporter may play an important role in reperfusion injury of the heart.

L-type Ca^{2+} channels also play an important role in Ca^{2+} overload (Fig. **1**). Prevention of Ca^{2+} overload by intracoronary administration of the L-type Ca^{2+} channel inhibitor diltiazem during reperfusion resulted in the infarct-reducing effect in pigs [14]. The same effect is caused by the L-type Ca^{2+} channel blocker verapamil administered intravenously 5 min before reperfusion in rats [15]. In a study performed in the isolated perfused rat heart, it was found that hypoxic perfusion causes an increase in $[Ca^{2+}]_i$ 10 min after the onset of hypoxia [16]. It has also been reported that L-type Ca^{2+} channel inhibitors diltiazem and nifedipine may prevent Ca^{2+} overload [16]. The β -adrenergic receptor (AR) blocker esmolol had the same effect. We demonstrated that β -adrenergic receptor antagonists propranolol and nadolol could induce the infarct-reducing effect when they were administered 5 min before reperfusion in rats [15]. The sarcoplasmic reticulum (SR) Ca^{2+}-ATPase inhibitor thapsigargin did not affect Ca^{2+} overload [16]. These investigators concluded that the β-AR-stimulated L-type channel, which mediates Ca^{2+} entry in cardiomyocyte, contributes to hypoxic Ca^{2+} overload. However, the SR is not involved in Ca^{2+} overload during hypoxia of cardiomyocytes [16]. Calcium also can enter cardiomyocytes *via* $2Na^+/Ca^{2+}$ exchange [12].

Recently, evidence has emerged that the cause of Ca^{2+} overload can be the opening of transient receptor potential (TRP) channels [17]. In mice with the deletion of the gene encoding TRPV4, infarct size was smaller than that in wild-type animals [18]. The TRPV4 agonist GSK1016790A, in contrast, increased infarct size. Other studies carried out in the culture of H9C2 cardiomyoblasts have demonstrated the existence of functionally active TRPV4 in cardiac cells [19]. The TRPV4 opener GSK1016790A caused $[Ca^{2+}]_i$ elevation. This effect began at a GSK1016790A concentration of 100

nM. However, the TRPV4 channel blocker HC-067047 (1 μM) eliminated this effect. Hypoxia-reoxygenation of H9C2 cardiomyoblasts caused an increase in $[Ca^{2+}]_i$. Adding GSK1016790A to the incubation medium aggravated this effect, while the TRPV4 inhibitor HC-067047, reduced reoxygenation Ca^{2+} overload. The aforementioned data suggest that TRPV4 is involved in reoxygenation Ca^{2+} overload of cardiac cells.

During I/R Ca^{2+} overload is observed not only in the cytoplasm but also in the mitochondrial matrix via the mitochondrial calcium uniporter (MCU) [20]. Pretreatment with ruthenium red, an inhibitor of MCU, or with Ru360, a highly specific MUC inhibitor, increases tolerance of the isolated rat heart to I/R [21]. In a study performed in the isolated rat heart, a Ca^{2+} chelator BAPTA-AM was used at a concentration that abolished Ca^{2+} overload of both the cytoplasm and mitochondria and ruthenium red at the concentration that abolished Ca^{2+} overload of mitochondria but not the cytoplasm [22]. Both compounds enhanced cardiac resistance to I/R. The cardioprotective effect of ruthenium red and RU360 during I/R of the heart was confirmed by other investigators [23]. It should be noted that ruthenium red also is the transient receptor potential vanilloid (TRPV) channel antagonist [16]. It was documented that the mouse heart lacking MCU is more tolerant to I/R then the heart of wild-type mice [24]. Ruthenium red and RU360 were not used at reperfusion of the heart. Therefore, the role of Ca^{2+} overload of mitochondria in reperfusion cardiac injury remains to be clarified. However, it was documented that Ca^{2+} overload of mitochondria can promote mitochondrial transition pore (MPT pore) opening and cell death as a result of apoptosis [25].

Collectively, these reports indicate that reperfusion Ca^{2+} overload is likely mediated by both L-type Ca^{2+} channels and TRPV4 channel opening. The role of Ca^{2+} overload of mitochondria in reperfusion cardiac injury requires further investigation.

3. NO-SYNTHASE ACTIVATION

Ca^{2+} is required to activate endothelial NO-synthase (NOS3) and neuronal NO-synthase (NOS1), which can then further increase mitochondrial reactive oxygen species (ROS) production [25, 26]. Mitochondrial NO production is catalyzed by mitochondrial NOS (mtNOS), which has been identified as the α-isoform of nNOS [27]. Superoxide radical ($O_2^{\bullet-}$) can interact non-enzymatically with $NO^{\bullet}$ to produce $ONOO^-$ [25]. It is believed that mitochondria are an important source of ROS in cardiomyocytes [26]. It was documented that $NO^{\bullet}$ inhibits complex IV in mitochondria which in turn contributes to an increase in ROS production [28-30]. Complex I can be inhibited when $NO^{\bullet}$ and the high level of matrix Ca^{2+} are present to activate $O_2^{\bullet-}$ production and $ONOO^-$ synthesis which in turn causes S-nitrosylation of complex I [31]. Peroxynitrite anion by itself can also inhibit complex III and V which contributes to respiratory block and additional ROS production [32]. Increased $ONOO^-$ production promotes MPT pore opening [33]. MPT pore opening causes apoptosis and cell death.

Thus, excess $NO^{\bullet}$ production could aggravate cardiac RI. However, moderate $NO^{\bullet}$ formation contributes to increased cardiac tolerance to I/R since $NO^{\bullet}$ stimulates guanylyl cyclase, which synthesizes cGMP activating protein kinase G. This kinase increases cardiac resistance to I/R [34].

4. OXIDATIVE STRESS

The sudden activation of aerobic metabolism upon reperfusion elicits a surge in ROS production. ROS are important mediators of cardiac reperfusion injury. When restoring perfusion, ROS have at least three main sources: the mitochondrial respiratory chain [35-37]; xanthine oxidase, which acts on hypoxanthine and xanthine [36, 37], and NADPH oxidase (Nox) from activated neutrophils and macrophages [38], which enter the myocardial tissue when blood flow is restored. In addition, the source of ROS may be Nox of cardiomyocytes that express Nox1, Nox2, Nox4 [35-37, 39]. It should be noted that xanthine oxidase is absent in the human myocardium [36]. In animals, xanthine oxidase generates $O_2^{\bullet-}$ formation (Fig. **2**).

$$\text{Hypoxanthine} + H_2O + O_2 \rightarrow \text{xanthine} + H^+ + O_2^{\bullet-}$$

$$\text{xanthine} + H_2O + O_2 \rightarrow \text{uric acid} + H^+ + O_2^{\bullet-}$$

NADPH oxidase also catalyzes $O_2^{\bullet-}$ formation

$$NADPH + 2O_2 \rightarrow NADP^+ + H^+ + 2O_2^{\bullet-}$$

Mitochondria are an important source of $O_2^{\bullet-}$. This free radical is formed by complex I and complex III of the respiratory chain [35, 36]. Superoxide radical enters the matrix and intermembrane space of mitochondria [35, 39]. Under normal conditions, NOS catalyzes nitric oxide ($NO^{\bullet}$) formation from L-arginine using tetrahydrobiopterin (BH4) as a cofactor. Under ischemia-reperfusion, BH4 synthesis is impaired. The lack of BH4 leads to uncoupling of NOS, which begins to synthesize $O_2^{\bullet-}$ instead of NO (Fig. **2**) [35, 40].

Under normal conditions, NOS catalyzes the reaction:

$$NADPH + O_2 + \text{arginine} \rightarrow \text{citrulline} + NO^{\bullet} + NADP^+$$

Under ischemia-reperfusion, NOS catalyzes the reaction:

$$NADPH + O_2 \rightarrow O_2^{\bullet-} + NADP^+ + H^+$$

Dismutation of $O_2^{\bullet-}$ occurs either spontaneously or by superoxide dismutase (SOD), causing hydrogen peroxide (H_2O_2) formation. H_2O_2 is relatively stable in vivo compared to other ROS molecules. This compound is lipid-soluble and can freely diffuse across membranes, acting as a physiological signaling molecule by selectively oxidizing target proteins [35, 36].

ROS cause lipid peroxidation, which leads to membrane damage, including sarcoplasmic reticulum membranes that in turn aggravate Ca^{2+} overload [41]. ROS activate and inactivate various enzymes [36]. They damage cellular structures, including DNA [35]. The recovery of neutral pH during reperfusion attenuates the inhibitory effects of H^+ on MPT pore [4]. ROS and Ca^{2+}, present in excess in the cytoplasm, cause MPT pore opening (Fig. **2**) [4, 42]. Release into the cytoplasm of pro-apoptotic proteins cytochrome C and apoptosis inducing factor (AIF) activates apoptotic cascades [43, 44]. In addition, MPT pore inhibition during reperfusion protects the heart from RI [45, 46]. Cytochrome C and AIF are triggers of apoptosis. Therefore, their entry into the cytoplasm induces apoptosis [43, 44]. In addition, MPT pore opening causes a decrease in potential of the inner mito-

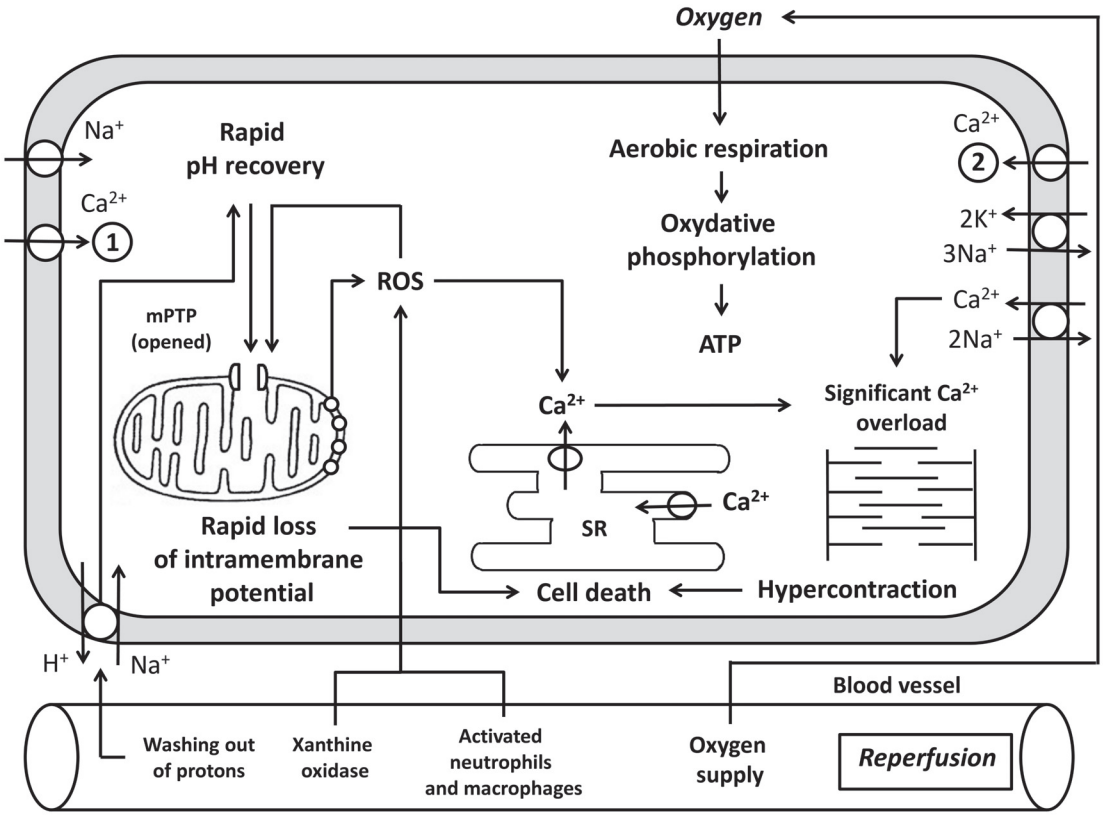

Fig. (2). The main metabolic events that occur during reperfusion in cardiomyocytes. SR, sarcoplasmic reticulum; MPTP , mitochondrial permeability transition pore; ROS - reactive oxygen species; 1. L-type Ca^{2+} channel; 2, TRPV4, transient receptor potential vanilloid channel 4.

chondrial membrane ($\Delta\psi$), which leads to a decrease in ATP synthesis by mitochondria. If this process affects all mitochondria, this can result in cell death due to necrosis [4, 43]. It should be noted that low ROS concentrations serve as intracellular signaling molecules which are involved in the formation of the cardioprotective effect of pre- and postconditioning [36]. It can be hypothesized that some ROS have myocardial damage, while other ROS provide the protective effect of pre- and postconditioning.

5. CALPAINS AND METALLOPROTEASES

Calpains are other targets of Ca2+ overload. Calpains are the family of Ca2+-dependent cysteine proteases [47]. Typically, calpains require Ca^{2+} in μM concentration range which is rarely observed *in vivo* [47]. A possible explanation may relate to the existence of microdomains which have a high Ca^{2+} concentration which is sufficient for calpain stimulation [47]. Pretreatment with a calpain inhibitor A-705253 before CAO and reperfusion reduced infarct size in pigs by 35% [48]. In a study performed in the isolated perfused rabbit heart it was demonstrated that the use of a calpain inhibitor A-705253 at the onset of reperfusion resulted in a decrease in the infarct size/area at risk (IS/AAR) ratio by 32% [49].

Matrix metalloproteinases (MMPs) are not Ca^{2+}-dependent enzymes, but they can be implicated in cardiac I/R injury. However, data on their involvement in cardiac I/R damage is contradictory. It was reported that I/R of the isolated perfused heart caused a decrease in metalloproteinase-2 (MMP-2) activity in the myocardium [50]. According to other investigators [51], the activation of MMP-2 occurred after 15 min of ischemia, but following prolonged ischemia and reperfusion MMP-2 activity declined. Atrial biopsy samples were obtained before cardioplegia and within 10 min after removal of the aortic cross-clamp in patients with coronary artery bypass graft surgery [52]. There was a marked increase in MMP-2 and MMP-9 activity, and a decrease in TIMP-1, an endogenous inhibitor of MMPs, upon reperfusion in cardiac biopsies. It was documented that remote ischemic preconditioning decreases the IS/ARR ratio, reduces MMP-2 and MMP-9 expression, and increases the TIMP-1 level in the myocardium [53]. The broad-spectrum MMP inhibitor ilomastat prevented I/R cardiac injury [50, 54] and reperfusion damage of the heart [54, 55].

It should be noted that not all investigators could demonstrate the infarct-reducing effect of MMP inhibitors [56, 57]. It was found that MMP-8 is involved in the cardioprotective effect of bradykinin [56]. These investigators proposed that bradykinin triggers the protective signalling pathway through MMP-8-dependent transactivation of epidermal growth factor receptor (EGFR) at reperfusion [56].

The aforementioned studies indicated that calpains are involved in ischemic and reperfusion cardiac injury. Thus, it was demonstrated that the activation of MMP-2 and MMP-9 aggravates I/R cardiac injury. Stimulation of MMP-8 promotes an increase in cardiac tolerance to the impact of I/R.

6. DIFFERENT TYPES OF CELL DEATH AND THEIR MECHANISMS

There are three main forms of cell death, which morphologically differ significantly from each other: apoptosis, autophagy and necrosis [58].

6.1. Necrosis

It is possible that necrosis is the most common process of cell death during myocardial reperfusion. Morphologically, necrosis is characterized by an increase in cell volume (oncosis), swelling of mitochondria, activation of lysosomes, rupture of the plasma membrane and release of intracellular contents [58]. The released plasma proteins (troponin I, troponin T, creatine kinase-MB) are used to diagnose acute myocardial infarction. Released intracellular proteins stimulate a strong inflammatory (and immunogenic) reaction, which further enhances cellular damage [59, 60]. Usually, necrosis is understood as an unregulated form of cell death. Occurring at the same time is regulated necrosis which is caused by the MPT pore opening (MPT-driven necrosis) and necroptosis [58], both of which are different and will be detailed below.

A number of mechanisms are known to lead to cell necrosis during reperfusion. These include: (a) oxidative stress, which causes injury to the sarcolemma; (b) increased activity of destructive enzymes, for example, calpains, which are activated during Ca^{2+} overload of cardiomyocytes, cause proteolysis, increase fragility of cellular structures, injury of the cytoskeleton and the sarcolemma [61, 62]; (c) osmotic stress, which is caused by Na^{+}-loading and Ca^{2+}-loading, leads to an increase in the amount of water in the cell and, as a consequence, to their swelling. The aforementioned disruptions of normal cellular processes damage the cytoskeleton leading to osmotic fragility and rupture of the sarcolemma [63].

6.2. Necroptosis

By the 1990s, the consensus of investigators was that cardiomyocytes could die by an uncontrolled process (necrosis) or by programmed cell death (apoptosis). However, in 2000, it was discovered that tumor necrosis factor-α (TNF-α) can induce necrotic-like cell death of fibroblasts in the presence of caspase inhibitors [64]. The aforementioned data suggest the existence of programmed necrosis. This hypothesis was confirmed in 2005 when a group of investigators discovered controlled necrosis, which they called necroptosis [65]. This study was performed in U937 cell culture treated with TNF-α. Simultaneously, evidence was reported that the necroptosis blocker necrostatin-1 was the inhibitor of receptor interaction protein kinase 1 (RIPK1) [65]. Today it has been documented that necroptosis can be caused by the death receptor agonists, such as TNF-α, Fas-ligand and TNF-related apoptosis-inducing ligand (TRAIL) [65-67]. In addition, necroptosis may be induced by activation of Toll-like receptors 3 and 4 (TLR3/4) with bacterial lipopolysaccharide [66-68] or as a result of stimulation of interferon-γ receptors [66]. The activation of these death receptors is followed by autophosphorylation and activation of kinases: RIPK1 and RIPK3 [68]. A complex (necrosome) is formed, containing several phosphorylated molecules of RIPK1 and RIPK3. Necrosome catalyzes phosphorylation of pseudokinase MLKL (mixed lineage kinase domain-like) [68]. Phosphorylated MLKL molecules oligomerize, translocate into the plasma membrane, where they form a pore, which leads to damage to the cell membrane and eventually induces cell death as a result of necroptosis [68]. In 2007, it was demonstrated that intravenous administration of necrostatin-1 at the onset of reperfusion could decrease infarct size in mice [69]. Utilizing a pig model to investigate I/R cardiac damage, it was documented that intravenous administration of necrostatin-1 before reperfusion can reduce infarct size and preserve the function of the left ventricle [70]. The aforementioned studies emphasize the important role of necroptosis in cardiac RI.

6.3. Apoptosis

In 1972, Kerr *et al.* [71] discovered apoptosis, a regulated process of cell death mediated by internal or external stimuli. Apoptosis is regulated caspase-dependent cell death, which is accompanied by a decrease in cell volume, karyopyknosis and karyorrhexis [44, 71]. Cell fragmentation and chromatin condensation are completed by formation of apoptotic bodies surrounded by the cell membrane [71]. Apoptotic bodies are absorbed by phagocytes, thereby avoiding inflammation and indiscriminate cell injury. The aforementioned process prevents indiscriminate release of intracellular components and the subsequent inflammatory response, a hallmark of necrosis and necroptosis [44]. Apoptosis, in contrast to necrosis, is an ATP-dependent process that does not proceed if cellular ATP is severely depleted, as is the case under ischemic conditions. Therefore, apoptosis, which began during ischemia, is enhanced by reperfusion [40, 43]. Apoptosis proceeds by intrinsic and extrinsic pathways. The intrinsic pathway causing apoptosis is MPT pore opening with release to the cytoplasm of apoptotic inducers: apoptosis-inducing factor (AIF) and cytochrome C. The latter participates in apoptosome formation, which requires ATP [44]. The apoptosome includes in its structure cytochrome C, apoptosis protease-activating factor 1 (APAF-1) and procaspase 9, which is proteolytically activated to caspase 9, which, in turn, catalyzes the proteolytic activation of procaspases into caspases-3, -6, -7 [44]. It should be noted that collateral blood flow in the ischemic zone never drops to zero values and can reach 17% of the initial value in dogs [72]. However, some cells in the ischemic zone retain the ability to resynthesize ATP by glycolysis and, therefore, can undergo apoptosis. The extrinsic pathway of apoptosis may be triggered by the activation of death receptors or by the cessation of stimulation of growth factor receptors. Death receptors, which include TNF-α, Fas-ligand (CD95L) and TRAIL [44] play the key role in cell death during ischemia and reperfusion. The same ligands can cause necroptosis under pharmacological blockade of apoptosis [65]. It has now been documented that the apoptosis inhibitor Z-VAD-FMK increases tolerance of the isolated perfused guinea pig heart to I/R [73]. Consequently, apoptosis plays an important role in ischemic and especially in reperfusion injury of the heart.

6.4. Autophagy

Autophagy is another regulated process of cell death, which is characterized by lysosomal degradation of proteins

[74]. Three types of autophagy are recognized. Macroautophagy involves the formation of vesicles which are called autophagosomes that bind cellular proteins, glycosides, lipids and organelles and then deliver them to lysosomes for degradation. Microautophagy refers to a process by which cellular elements are subjected to degradation and are directly absorbed by lysosomes [75]. Chaperone-mediated autophagy is characterized by the binding of proteins containing the KFERQ sequence to the Hsc70 chaperone which transports target proteins into lysosomes with the involvement of lysosomal membrane 2A protein (Lamp2A) [74]. Macroautophagy, which is usually referred to as autophagy, is crucial for the degradation of organelles and adaptation to cell stress, while the other two forms of autophagy are involved in specialized cellular functions [74, 75].

In its initial stage, autophagy is accompanied by phagophore formation, which represents a fragment of the endoplasmic reticular membrane with the involvement of the protein complex Beclin-Vps34 and the protein LC3 (microtubule-associated protein 1 light chain 3), a vesicle called an autophagosome is formed [74, 76]. Autophagy-related genes (Atg) encode more than 30 Atg proteins that participate in formation of autophagosomes [73, 75]. The proteins parkin and p62 play a key role in selective mitophagy [74, 77]. At the final stage of autophagy, autophagosome merges with the lysosome and the autolysosome is formed, in which digestion of intracellular structures takes place. Paradoxically, cell death as a result of autophagy can protect the heart from I/R injury [77]. For example, in pigs exposed to a 45-minute CAO and reperfusion, the putative autophagy inducer chloramphenicol reduced infarct size [78]. Data on the role of autophagy in myocardial RI in humans are contradictory. Autophagy reportedly is activated in the human myocardium after exposure to I/R [79]. However, there is also recent evidence that the cardioprotective phenomenon of remote preconditioning develops without the involvement of autophagy in humans [80].

6.5. Pyroptosis

Pyroptosis is a programmable form of cell death, which is characterized by DNA fragmentation, nuclear condensation and caspase dependence. This process resembles apoptosis but differs from the latter by breaking the cell membrane with subsequent activation of the inflammatory reaction [81]. The term "pyroptosis" was first proposed in 2001 [82]. Pyroptosis is accompanied by caspase-1-dependent pore formation in the cell membrane followed by the disappearance of the cellular ionic gradient, cell swelling and rupture of the cell membrane [83]. Caspase-1 is activated by multiprotein signaling complexes - inflammasomes, which in turn are activated by caspase activation and recruitment domains (CARD) [81].

Inflammasomes are oligomeric protein complexes that cleave to procaspase-1 and to caspase-1 [84, 85].

In addition, inflammasomes are involved in synthesis and secretion of proinflammatory cytokines: interleukin-1β (IL-1β) and interleukin 18 (IL-18) [84], which are involved in pyroptosis. A number of investigators have presented evidence that NOD-like receptor protein (NLRP3) and other components of the inflammasome are not constitutively expressed in cardiomyocytes [84]. A small amount of Nlrp3 mRNA was identified in the myocardium of wild-type mice [86]. NLRP3 inflammasome formation is regulated by nuclear factor-κB (NF-κB) [84]. Pro-inflammatory stimuli such as cytokines, cellular debris or microbial products that bind to TLRs can induce the expression of NLRP3 and other inflammasome proteins in cardiomyocytes, leukocytes, and other cells such as fibroblasts and endothelial cells [84]. Cytokines, cellular debris, and microbial products, collectively termed damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPS) bind to TLRs. The increased expression and activity of the inflammasome peaked after 1 day of reperfusion in the myocardium of mice [84]. Administration of the NLRP3 inflammasome inhibitor (NLRP3inh) at reperfusion did not reduce infarct size at 3 h after reperfusion, while it significantly reduced infarct size at 24 h after reperfusion [10]. It has been reported that OLT1177, a NLRP3 inflammasome inhibitor, administered 1 h after reperfusion dose-dependently reduced the IS/AAR ratio in mice [84]. The aforementioned studies indicate that the NLRP3 inflammasome is involved in reperfusion injury of the heart. This evidence indicates pyroptosis occurs primarily after the first 3 hours of reperfusion. However, there is evidence that stimulation of NLRP3 inflammasome formation may contribute to increased tolerance of the heart to I/R. Accordingly, NLRP3-deficient mice had larger infarctions than wild-type mice [87]. Pretreatment with the TLR2 agonist Pam3CSK4 reduced infarct size in wild-type but not NLRP3 deficient mice [87]. Sandager *et al.* [87] administered the TLR2 agonist before ischemia, while Tondo *et al.* [10, 84] administered the NLRP3 inflammasome inhibitors during reperfusion. It is possible that activation of the NLRP3 inflammasome before CAO enhances cardiac tolerance to I/R. The aforementioned data demonstrate that the NLRP3 inflammasome is involved in cardiac RI. Administration of the caspase-1/4 inhibitor VX-765 (16 mg/kg) 30 min prior to CAO and at reperfusion reduced the IS/AAR ratio by 47% [88]. The same investigators demonstrated that administration of VX-765 (32 mg/kg) prior to reperfusion reduced the IS/AAR ratio by 52% [89]. In addition, VX-765 decreased the serum interleukin-1β level and reduced caspase-1 activity. Consequently, pyroptosis is also involved in reperfusion death of cardiomyocytes.

6.6. Ferroptosis

Ferroptosis is a form of cell death, trigger of which is ferrous ion, which catalyzes the Fenton reaction:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\bullet} + OH^{-}$$

The resulting hydroxyl radical induces lipid peroxidation which induces destruction of the cell membrane and cell death [90]. Thus, ferroptosis is essentially iron-mediated necrosis. Iron chelators, for example, deferoxamine, prevent the occurrence of ferroptosis [90]. It has been reported that deferoxamine increases cardiac resistance to ischemia during cold cardioplegia in rats [91]. Infusion of deferoxamine during coronary artery bypass grafting, which is accompanied by cardioplegic cardiac arrest and myocardial ischemia, reduced the level of lipid peroxidation products which are involved in RI of the heart in human [92]. In contrast, in a study performed on pigs with CAO and reperfusion,

deferoxamine did not limit infarct size [93]. We found that deferoxamine did not affect the IS/AAR ratio in rats [unpublished data]. The reason for these ambiguous findings remains unclear.

Thus, reperfusion promotes cell death as a result of necrosis, necroptosis, apoptosis and, possibly, autophagy and pyroptosis. The role of ferroptosis in reperfusion injury of the heart requires further study.

7. ADRENERGIC SYSTEM

Catecholamines have positive inotropic and chronotropic effects mediated by cyclic AMP, which increases myocardial oxygen demand. Under conditions of limited oxygen delivery during CAO, excessive activation of ARs by catecholamines intensifies hypoxia of the ischemic myocardium, contributing to the expansion of the necrotic zone. The experimental data indicate an increase in the level of norepinephrine circulating in blood in response to CAO in rats and in dogs [94, 95] and an increase in the concentration of interstitial norepinephrine in the area of myocardial ischemia in rats and in rabbits [96, 97]. Fukui *et al.* found that after CAO in rats, the interstitial norepinephrine level increased 200-fold [96]. Circulating catecholamine concentrations were also increased in patients with AMI [98, 99]. The experimental data also indicate an increase in the level of catecholamines circulating in blood. High circulating epinephrine concentration is a predictor of mortality in AMI patients [100]. The ability of the β-AR antagonist propranolol to reduce infarct size in CAO in dogs was first demonstrated by Reimer *et al.* 1973 [101]. Later it was documented that the β-AR antagonists can reduce infarct size when administered just before reperfusion in rats [15]. Based on the aforementioned studies, we hypothesize that β-ARs are involved in RI cardiac injury.

8. HUMORAL FACTORS

The myocardium is impacted by dozens, if not hundreds, of circulating humoral factors. Let us consider only endothelin-1 and angiotensin II. Both of these peptides increase total peripheral resistance and blood pressure [102-104], thereby increasing myocardial afterload. The concentration of angiotensin II in blood and in myocardial tissue increases in response to CAO in rats and in dogs [95, 105]. Angiotensin II receptor blockade has proven to be cardioprotective in rats with CAO [106]. There is also evidence that AMI leads to an increase in the endothelin-1 level in blood plasma of patients with AMI [98, 107]. Endothelin-1 has been found to cause coronary artery vasospasm in rats [108], and its receptor antagonists are cardioprotective when administered at CAO and reperfusion in rats [109].

9. TOLL-LIKE RECEPTORS (TLRS)

TLRs are expressed by leukocytes and play an important role in innate immune responses [110]. These receptors recognize pathogen-associated molecular patterns, for example, TRL4 interacts with bacterial lipopolysaccharide, and TRL2 binds with bacterial lipoproteins [110]. In addition, these receptors interact with endogenous molecules that signal cell damage, for example, heat shock proteins (HSP70 and HSP60), as well as nuclear DNA-binding protein high mobility group box (HMGB-1) [110, 111]. Endogenous TLR's activators belong to the DAMPs. TLRs have also been found in endotheliocytes [112] and cardiomyocytes [111, 113]. When activated, TLRs are involved in the inflammatory response acting through NF-κB translocation into the cell nucleus [111, 114]. Therefore, a number of investigators consider TLR inhibition as a viable approach for the treatment of AMI [111, 115, 116].

Studies in the isolated hearts of wild-type mice and the hearts of TLR2-deficient mice demonstrated that the latter fully restore their contractility after ischemia compared with the hearts of wild-type mice [117]. However, reperfusion creatine kinase (CK) release was the same in both groups. TLR2 deficiency protects coronary arteries from reperfusion endothelial dysfunction in mice [118]. Stimulation of TLR2 causes impaired contractility of murine cardiomyocytes [119]. A comparative study performed on wild-type and TLR4-defective C3H-Tlr4 (LPS-d) mice demonstrated that animals did not differ in the IS/AAR ratio, but in TLR4-defective mice, post-infarction remodeling was less pronounced [120]. Intravenous injection of anti-TLR2 antibodies reduced infarct size in mice by almost 50%, promoted a reduction of post-infarction scar, and improved cardiac contractility 28 days after infarction [117]. Administration of anti-TLR2 antibodies significantly reduced infiltration of neutrophils, macrophages and T-lymphocytes into the infarcted myocardium [117]. Knockout of the gene encoding TLR2 contributes to a decrease in the IS/AAR. Transplantation of bone marrow from wild-type mice to TLR2-null mice increased infarct size to control values [116]. This evidence indirectly indicates that TLR2 of leukocytes rather than TLR2 of cardiomyocytes play a crucial role in reperfusion injury of the heart. It has also been demonstrated that TLR4 is involved in post-infarction cardiac remodeling in pigs [121].

Currently, TLR2 and TLR4 are considered potential targets for the creation of new cardioprotective drugs [111, 116].

10. NEUTROPHILS AND MONOCYTES

Inflammation plays an important role in RI of the myocardium. The number of leukocytes in blood of patients with AMI was significantly correlated with infarct size, which was estimated by the CK, creatine kinase-MB (CK-MB), and troponin-I levels [122].

Neutrophil accumulation in reperfusion zone peaks 24 h after cardiac reperfusion in dogs [5]. Neutrophil adherence to left anterior descending coronary artery segments reaches a peak at 48 h of reperfusion [5]. Myeloperoxidase activity in the area at risk correlated with the extension of infarction during the first 24 h of reperfusion [5]. In 1983, Romson *et al.* [123] found that administration of anti-neutrophil antibodies to dogs before CAO reduced the IS/AAR ratio by 43%. Neutrophils and monocytes express integrin receptor (CD11b/CD18) [124], which enables these cells to adhere to vascular endothelium and invade the tissue parenchyma. Administration of antibodies to CD11b to dogs 45 min after CAO contributes to a 46% decrease in the IS/AAR ratio [125]. Similar findings were obtained by other investigators using monoclonal antibodies to CD11b/CD18 [126]. It was

found that pretreatment with the selective adenosine A_2 agonist CGS-21680 5 min before reperfusion of the heart decreases the IS/AAR by approximately 50% and reduces neutrophil accumulation in the AAR in dogs [127]. In addition, CGS-21680 reduced $O_2^{\bullet}$ production by activated neutrophils [127]. Neutrophils express adenosine receptors [128]. Therefore, it can be hypothesized that CGS-21680 limits accumulation of neutrophils in the myocardium due to the activation of adenosine receptors of these cells.

However, data on the role of neutrophils in RI of the heart is contradictory. It has been documented that neutrophils contain myeloperoxidase (MPO), which synthesizes cytotoxic aldehydes (formaldehyde, acrolein and others) that damage cardiomyocytes [129]. MPO activity in the reperfusion area was increased 5-fold in dogs [130]. Therefore, there is reason to believe that this enzyme is involved in reperfusion cardiac injury. However, a study performed on MPO-null mice demonstrated that infarct size in these mice does not differ from infarct size in wild-type mice [129]. However, postinfarction remodeling of the heart was less pronounced in MPO-null mice [130]. The use of the selective MPO inhibitor PF-1355 did not affect infarct size after transient CAO but prevented postinfarction remodeling in mice [131]. Consequently, MPO is not involved in RI of the heart but in postinfarction remodeling of the heart. The number of circulating neutrophils in AMI patients is significantly higher than in patients with stable angina [132]. In addition, the number of neutrophils correlated with an increase in the plasma CK level [132]. In a multicenter, placebo-controlled study in patients with STEMI, antibodies to CD11b/CD18 were administered before recanalization of the infarct-related coronary artery [133]. Infarct size was evaluated by the CK-MB level and by using SPECT with ^{99m}Tc-sestamibi. The study failed to detect the infarct-reducing effect of the antibodies to CD11b/CD18. The aforementioned data suggest that neutrophils do not play a significant role in RI of the human heart. It is still unclear why the data from animal experiments and the results of clinical studies differ.

Not only neutrophils, but also monocytes/macrophages migrate to the ischemia-reperfusion zone. Their migration is stimulated by chemokine monocyte chemoattractant protein-1 (MCP-1). Studies were performed on wild-type mice and mice deficient in chemokine receptor-2 [38]. Infarct size in mice with genetic deficiency of chemokine receptor-2 was smaller than in wild-type mice. By contrast, macrophage migration inhibitory factor (MIF) inhibits this process. It has now been documented that MIF contributes to a decrease in the IS/AAR ratio in mice with CAO and reperfusion [134]. In mice in which the gene encoding MIF was deleted, the IS/AAR ratio was higher than in wild-type mice [135]. These data clearly indicate that the restriction of migration of monocytes to the ischemic/reperfusion zone contributes to a reduction of RI. However, studies on the isolated hearts of MIF-/- mice have demonstrated that hearts of these mice are also less resistant to I/R than the hearts of wild-type mice [136]. Therefore, the cardioprotective effect of MCP-1 could not be directly associated with restriction of macrophage migration. It should be noted that M2 macrophages can protect isolated neonatal rat cardiomyocytes from the impact of H/R [137].

The aforementioned studies indicate that the migration of neutrophils and monocytes to the ischemic-reperfusion zone may be directly related to cardiac RI. However, strong evidence of involvement of these cells in reperfusion heart damage in humans has not yet been provided.

11. T-LYMPHOCYTES

In 2006, reperfusion was found to promote an increase in neutrophils and $CD3^+$ T-lymphocytes in the murine myocardium [138]. The number of circulating lymphocytes, on the contrary, decreased, apparently due to their sequestration by the myocardium. It was found that the selective adenosine A_{2A} receptor agonist ATL146e administered 5 min before reperfusion reduced T-lymphocyte accumulation and decreased infarct size. In Rag1 knockout mice lacking mature lymphocytes, infarct size was significantly smaller than in wild-type mice but increased to the level of wild-type mice following a transfer of 50 million $CD4^+$ T-lymphocytes delivered from wild-type mice [138]. When mice were depleted of $CD4^+$ T-lymphocytes by monoclonal antibodies, infarct size was significantly smaller than in control mice [138]. T-lymphocytes rapidly decline in the peripheral circulation over the first 90 min following reperfusion in patients with AMI [139] due to sequestration of T-lymphocytes by the myocardium. This fact suggests the possibility of T-lymphocytes' involvement in RI of the human heart.

Consequently, $CD4^+$T-cell accumulation may play an important role in cardiac RI.

12. PLATELETS

Platelets are activated in AMI [131, 132] in parallel with increased P-selectin expression by platelets [140, 141].

In 2002, Mirabet *et al.* tested the hypothesis that the effects of platelets on the myocardium depends on their activation [142]. Pig platelets were obtained 48 min before CAO, 10 min after reperfusion, and after a 60-minute sham operation. The expression of P-selectin platelets was higher in platelets isolated during reperfusion than in platelets isolated before ischemia or after a sham operation. The isolated perfused rat hearts were subjected to global ischemia and reperfusion. Five min before global ischemia, platelets were added to the perfusion medium. Lactate dehydrogenase (LDH) release during reperfusion was similar in hearts perfused with a solution containing platelets isolated before CAO or after a sham operation. LDH release was increased when platelets were isolated from the blood of pigs during reperfusion. Platelet activation by thrombin increased P-selectin expression and LDH release from the isolated rat heart. A close correlation was documented between P-selectin expression and LDH release and platelet accumulation in the myocardium. These investigators concluded [142] that the pathogenic effect of platelets in the reperfused myocardium depends on their activation, which is characterized by P-selectin expression. This expression is enhanced in response to ischemia/reperfusion. These results indicate that platelets play an important role in cardiac RI.

Platelets express GPIIb/IIIa receptor (integrin αIIbβ3) which is the receptor for fibrinogen, von Willebrand factor, fibronectin, and vitronectin [143]. The GPIIb/IIIa receptor

seems to be also involved in reperfusion injury to the heart since blockade of this receptor with MK-0852 reduced the IS/AAR ratio after CAO and reperfusion. However, MK-0852 did not affect the AAR and blood flow in the ischemic zone in dogs [143]. Therefore, there is a reason to believe that MK-0852 not only inhibited platelet aggregation but also prevented the release of substances from platelets that aggravated I/R injury of the heart. With prolonged CAO and reperfusion, inhibition of GPIIb/IIIa receptor by tirofiban contributed to an improvement of microcirculation in the reperfusion zone, thereby preventing the formation of the microvascular obstruction area in dogs [144].

Purinergic $P2Y_{12}$ (adenosine diphosphate agonist) receptor is another receptor which is also expressed in platelets. $P2Y_{12}$ receptor antagonists inhibit platelet aggregation and are used to restore coronary perfusion and prevent recurrent ischemic events in AMI [145, 146]. In recent years, evidence has emerged that the $P2Y_{12}$ receptor antagonist cangrelor cannot only inhibit platelet aggregation, but it can also reduce infarct size in rabbits [8]. Yang *et al.* detected that cangrelor limits infarct size when it is administered intravenously before reperfusion [8], in a situation very similar to the clinical setting. It has been reported that the infarct-reducing effect of cangrelor does not occur in isolated perfused rabbit hearts [8]. This provides indirect evidence of the involvement of platelets in cangrelor's cardioprotective effect. However, the protective effect of cangrelor does not appear to be associated with a change in platelet aggregation, since aspirin, which also inhibits platelet aggregation, did not affect infarct size [8]. The same infarct-limiting effect was exerted by the $P2Y_{12}$ receptor antagonist ticagrelor, when administered to rats 5 min before reperfusion in rats [147]. These studies suggest that the most likely role of platelet $P2Y_{12}$ receptor is regulation of cardiac resistance to reperfusion. In rats receiving the sphingosine kinase inhibitor dimethylsphingosine, cangrelor did not protect the rabbit heart from RI [148]. Thus, the protective mechanism of cangrelor seems to be associated with enhancement of sphingosine-1-phosphate synthesis, which is released from platelets [149] and results in the cardioprotective effect in experiments on the isolated perfused rat heart [150]. Moreover, sphingosine-1-phosphate is able to prevent cardiac RI in vivo in rats [151].

The aforementioned studies indicate that platelets play an important role in cardiac RI.

13. THE MAIN MANIFESTATIONS OF REPERFUSION INJURY OF THE HEART

In experimental studies and in the course of clinical observations, it is difficult to separate RI from ischemic injury. Therefore, in this section we discuss the manifestations of I/R heart's damage. The most characteristic manifestation of I/R of the heart is necrosis and the appearance of markers of cardiomyocyte necrosis in blood: CK-MB, troponin I, and troponin T [152, 153]. It is also the appearance of coronary vascular dysfunction [5, 154-158], ventricular arrhythmias [16, 159-166], myocardial stunning [167], and the no-reflow phenomenon (Table **1**) [168-173].

14. DIAGNOSIS AND TREATMENT OF ISCHEMIC AND REPERFUSION INJURY OF THE HEART

In clinical practice, I/R damage is observed in patients with AMI and also in cardiac surgery patients after cardiopulmonary bypass. ST-segment elevation myocardial infarction (STEMI) can be easily diagnosed by the ST elevation on an ECG. However, it is more difficult to diagnose non-ST-segment elevation myocardial infarction (NSTEMI), which necessitates determination of the levels of myocardial necrosis markers: troponin I, troponin T, and creatine kinase-MB [167, 174, 175]. I/R injury in cardiac surgery patients is documented by increased serum troponin or CK-MB levels [176].

Determination of peak troponin or CK-MB levels allows one to indirectly assess infarct size [167, 174]. Magnetic resonance imaging (MRI) allows one to more accurately detect infract size [177, 178]. MRI and definition of the peak troponin or CK-MB levels are commonly used to assess the effectiveness of drugs in the treatment of AMI. In clinical practice, it is important to diagnose AMI and determine the localization of coronary artery thrombosis. Invasive coronary angiography permits not only correct localization of the site of coronary artery thrombosis but also to lead in stenting of the infarct-related coronary artery. Percutaneous coronary intervention (PCI) still remains the most effective treatment for AMI, since it restores coronary blood flow in 95% of cases [179]. PCI is effective in stopping ischemic damage to the heart, but it frequently results in reoxygenation injury to cardiomyocytes.

One of the most important aims of modern pharmacology is the development of drugs that can slow down the formation of ischemic injury of the heart before PCI and drugs that can prevent reperfusion injury of the heart.

The main cause of death in patients with AMI is cardiogenic shock [180]. The mortality rate is 30 - 70% in patients with AMI and cardiogenic shock [181, 182]. The occurrence of cardiogenic shock is directly dependent on infarct size [183]. Consequently, efforts of cardiologists should be directed towards infarct size reduction and improving cardiac contractility.

Another major problem is the no-reflow phenomenon which is observed in approximately 5% of patients with AMI and PCI [179]. However, even if we could restore coronary blood flow in the main coronary arteries, a problem of microvascular coronary obstruction occurs for which there currently is no effective treatment intervention [184, 185].

Glycoprotein IIb/IIIa inhibitors, $P2Y_{12}$ receptor antagonist, aspirin (in 98% patients), statins (96%), beta-blockers (58%), angiotensin-converting enzyme inhibitors (9%), angiotensin receptor blocker (38%), aldosterone receptor antagonists (17%) are all used for the treatment of AMI in Handan First Hospital (Chine) [186]. The same drugs are used in other clinics for treatment of AMI. However, the ratio of use of these drugs can vary considerably. For example, in the San Francisco Veterans Affairs Health Care System (USA): the following ratio of drugs is used: aspirin (99%), beta-blocker (94%), renin-angiotensin-aldosterone system antagonist (75%), statins (96%), and thienopyridine (94%) [187].

Table 1. The main consequences of myocardial ischemia-reperfusion.

The Main Manifestations of I/R Injury of the Heart	The Mechanisms of Development of the Main Manifestations of I/R Injury	Refs.
Myocardial stunning	The Ca^{2+} overload of cardiomyocytes, activation of the Na^+/H^+ exchanger, $2Na^+/Ca^{2+}$ exchanger and Na^+/HCO_3^- symporter	Cohen M.V. *et al.,* 2007 [3] Piper H.M. *et al.,* 1999 [12] Rodriguez-Sinovas A. *et al.,* 2009 [13] Herzog W.R. *et al.,* 1997 [14] Lishmanov Y.B. *et al.,* 2016 [15] Zhang H. *et al.,* 2013 [16] Neri M. *et al.,* 2017 [153]
Coronary vascular dysfunction	Pyroptosis of endothelial cells, inflammation of endothelial cells, apoptosis and especially autophagy of endothelial cells, damage of the endothelial glycocalyx	Sun W. *et al.,* 2019 [155] Gollmann-Tepeköylü C. *et al.*, 2020 [156] Zhen W. *et al.,* 2020 [157] Araibi H. *et al.*, 2020 [158]
Ventricular arrhythmias	A decrease in repolarizing K^+ currents, an increase in inward Ca^{2+} current, sympathetic nervous system activation, an increase in the cAMP level in cardiac cells, Ca^{2+} overload of cells, excess ROS production, neutrophil invasion in AAR, activation of $2Na^+/Ca^{2+}$ exchange	Zhang H. *et al.,* 2013 [16] Schwartz P.J., Stone H.L., 1980 [160] Bernier M. *et al.,* 1986 [161] Lubbe W.F. *et al.,* 1992 [162] Rosen M.R., 1995 [163] Dhein S. *et al.,* 1995 [164] Antoons G. *et al.,* 2012 [165] van der Weg K. *et al.,* 2019 [166]
The no-reflow phenomenon	Swelling of endothelial cells, aggregation of blood cells in the microvessels, an increase in blood viscosity, impaired endothelium-dependent and endothelium-independent vasodilation	Boag S.E. *et al.,* 2017 [139] Kloner R.A., 1974 [169] Loke K.E. *et al,* 1998 [170] Haiyun L. *et al.,* 2004 [171] Cecchi E. *et al.,* 2009 [172] Ming X. *et al.,* 2012 [173]

CONCLUSION

Cardiomyocyte Ca^{2+} overload and increased production of ROS play pivotal roles in myocardial I/R injury. Necrosis, necroptosis, apoptosis and, possibly, autophagy and pyroptosis are involved in RI of the heart. The role of ferroptosis in I/R injury of the heart requires further investigation. An increase in activity of the adrenergic system during ischemia and the restoration of coronary perfusion negatively affect resistance of the heart to I/R. It has also been reported that neutrophils, monocytes, CD^{4+} T-cells and platelets play an important role in I/R cardiac damage. TLRs, angiotesin II and endothelin-1 are also involved in I/R injury of the heart. The main clinical manifestations of I/R cardiac injury are necrosis, ventricular arrhythmias, contractile dysfunction, and no-reflow phenomenon.

We hypothesize that there are early cardiac RIs that develop within a few minutes (5 - 10 min) after reperfusion, remote injuries that develop within a few hours and 24 to 48 hours after the restoration of coronary blood flow, and late reperfusion injuries that form within a few weeks after the restoration of coronary perfusion. The most studied of these RIs is early reperfusion damage of the heart. Less well documented is the mechanism(s) by which inflammation may play a major role in the remote development of myocardial injury. We know almost nothing about late RI and the extent that it contributes to pathological myocardial remodeling. Our hypothesis is that changes in gene transcription play an important role in the occurrence of post-infarction myocardial remodeling. Future studies should focus on the role of the receptor(s), signaling mechanisms, and inflammation in the pathogenesis of early and remote cardiac RI. The role of gene transcription alterations in the mechanism(s) of postinfarction remodeling also merits further investigation.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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