

The paradoxes of reperfusion in the ischemic heart

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Abstract

Although reperfusion is essential for salvage of the ischemic heart, reperfusion beyond a certain period of ischemia may cause injury to the myocardium. Dramatic changes in contractile function, arrhythmias, and ultrastructure occur in the ischemic-reperfused heart as a consequence of the generation of oxyradicals, loss of cation homeostasis, depletion of energy stores, and changes in subcellular activities. These acute effects of reperfusion appear to be the result of the occurrence of oxidative stress and intracellular Ca^{2+} overload in the heart. Alterations in cardiac gene expression may account for delayed recovery of subcellular organelles in the ischemic myocardium.

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Introduction

Myocardial ischemia occurs when there is a reduction of blood flow as a result of narrowing of the coronary arteries during atherosclerosis, blockage of perfusion as a result of thrombosis, or development of coronary spasm. It is well known that myocardial ischemia results in the loss of contractile function and produces myocardial damage as a consequence of cell death from both necrosis and apoptosis [1–6]. It is therefore essential to restore coronary flow to the ischemic myocardium by interventions such as angioplasty, thrombolytic treatment or coronary bypass surgery [1]. However, if the coronary flow is not restored within a critical period of time, reperfusion itself may cause a wide variety of harmful effects in the ischemic heart – a

phenomenon referred to as “reperfusion injury” [4–6]. For example, reperfusion of ischemic tissue may intensify pathological processes that contribute to the generation of oxyradicals, disturbances in cation homeostasis, and depletion of cellular energy stores, which may elicit arrhythmias, contractile dysfunction, and ultrastructural damage, in addition to endothelial dysfunction and coronary vasoconstriction (*Figure 1*). These paradoxical effects of reperfusion become evident quite rapidly upon the restoration of perfusion [7–11], and may last for periods of several weeks to months. In particular, depressed cardiac function (myocardial stunning) of the ischemic-reperfused heart is commonly seen under chronic conditions after coronary bypass surgery or in patients with a heart transplant.

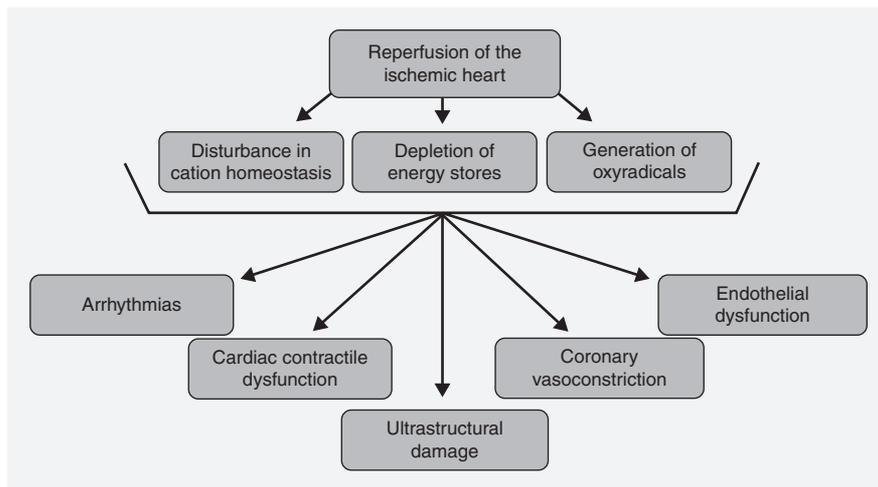


Figure 1. Paradoxical effects of reperfusion in the ischemic heart.

Ischemic injury or reperfusion injury

As ischemia reduces the delivery of oxygen and substrates to the myocardium, the initial process contributing to ischemic injury is a reduction of cellular energy status as a result of compromised mitochondrial production of ATP via impaired oxidative phosphorylation and electron transport [1,2,9,10]. Although there is an increase in anaerobic glycolysis in ischemic hearts, this metabolic change is not sufficient to meet the high energy demands for maintaining cardiac function [1,5,10]. Derangement of the mitochondrial electron transport system also promotes the generation of oxyradicals and development of oxidative stress in the ischemic heart [6,12]. Nonetheless, increased anaerobic glycolysis is considered to result in the accumulation of H^+ , stimulation of the Na^+-H^+ exchanger, activation of the Na^+-Ca^{2+} exchanger in the reverse mode, and development of intracellular Ca^{2+} overload [3,6]. Oxidative stress has also been shown to produce intracellular Ca^{2+} overload, and vice versa.

The degree of oxidative stress and the magnitude of intracellular Ca^{2+} overload in cardiomyocytes seem to be dependent upon the duration of ischemia. In fact, both oxidative stress and intracellular Ca^{2+} overload are considered to be the major mechanisms for the development of ischemic injury, and reperfusion appears to exacerbate the impact of these pathological processes [2,6,7]. Thus it is probable that ischemic injury and reperfusion injury are two facets of the same problem, in which ischemic injury is associated with alterations in myocardial metabolism, including depletion of energy stores, and the reperfusion injury is associated with additional changes, including the development of oxidative stress and the occurrence of intracellular Ca^{2+} overload (Figure 2).

Oxidative stress and the ischemia-reperfusion injury

Reactive oxygen species (ROS) are short-lived oxygen-derived free radicals, which act as signaling molecules at low concentrations, but adversely influence cell function by promoting lipid peroxidation and the oxidation of cardiac proteins when present in high concentrations. The major sources of ROS in the ischemic heart include the enzyme xanthine oxidase, the mitochondrial electron transport chain, and the NADPH oxidase system [8]. Oxidative stress may increase by as much as 100-fold during ischemia and reperfusion, as ROS production is greatly accelerated [8,12,13]. In addition, the cellular conditions associated with ischemia-reperfusion favor the

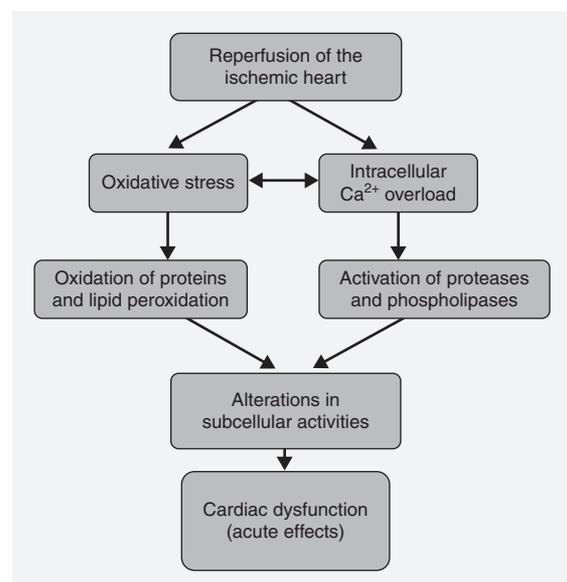


Figure 2. Mechanisms for the acute effects of reperfusion in the ischemic myocardium.

conversion of less reactive oxidants to more reactive species (e.g., the conversion of hydrogen peroxide to hydroxyl radicals or nitric oxide to peroxynitrite) [13,14]. These increases in ROS concentration and potency overwhelm the intracellular free-radical scavenger systems and leads to cellular injury during ischemia-reperfusion.

It has been demonstrated that ROS contribute to altered cation homeostasis through direct effects on membrane proteins involved in the regulation of cation transport and lipid peroxidation, which causes a change in membrane permeability [5] in addition to an increased inflammatory response to ischemia-reperfusion as a result of leukocyte activation. Prolonged oxidative stress also exerts chronic effects, as ischemia-reperfusion has been shown to produce expression of cardiac genes and associated remodeling of subcellular organelles [15,16] (Figure 3). Therapeutic treatments such as the administration of antioxidants or the overexpression of proteins that attenuate oxidative stress have been found to enhance the recovery of contractile function and to reduce infarct size, during ischemia and reperfusion [6,17].

Calcium overload and ischemia-reperfusion injury

Accumulation of intracellular Na^+ and Ca^{2+} during ischemia occurs in response to the loss of energy homeostasis and as a result of changes in the acute regulation of sarcolemmal and sarcoplasmic reticulum cation transport mechanisms. Specifically, ischemia reduces the activity of sarcolemmal Na^+/K^+ -ATPase,

increases the activity of the Na^+-H^+ exchanger, and promotes the activation of the $\text{Na}^+-\text{Ca}^{2+}$ exchanger in a reverse mode. Calcium transport is also affected by ischemia-reperfusion, because oxidative stress adversely influences Ca^{2+} -handling proteins in the sarcoplasmic reticulum (Ca^{2+} pump, sarcoplasmic reticulum Ca^{2+} -ATPase, and the Ca^{2+} release channel) and sarcolemma (sarcolemmal Ca^{2+} pump and the L-type Ca^{2+} channels) [6,18] and thus contributes to the development of an intracellular Ca^{2+} overload.

The pathological effects induced by intracellular Ca^{2+} overload are mediated by Ca^{2+} -induced activation of membrane phospholipases and proteases, and these changes may explain the acute effects of ischemia-reperfusion injury (Figure 2). Mitochondrial dysfunction [19] also contributes to the pathological effects associated with ischemia, because it is known that intracellular Ca^{2+} overload influences the opening of mitochondrial K_{ATP} channels and mitochondrial permeability transition pores, which activate apoptotic pathways [20]. Therapeutic treatments such as Ca^{2+} antagonists [21] and Na^+-H^+ exchange inhibitors [22], which attenuate intracellular Ca^{2+} overload, have been suggested to reduce the size of infarcts resulting from ischemia-reperfusion. Thus the development of intracellular Ca^{2+} overload can be seen to contribute to the acute effects of ischemia-reperfusion injury.

Subcellular remodeling in the ischemic-reperfused heart

During prolonged ischemia-reperfusion, significant changes in expression of cardiac genes occur such that subcellular organelles (eg, mitochondria, myofibrils, sarcolemma, and sarcoplasmic reticulum) are remodeled (Figure 3). As both oxidative stress and intracellular Ca^{2+} overload induced by ischemia-reperfusion are known to produce changes in gene expression, these factors seem to contribute to the remodeling of subcellular organelles and lead to a delayed recovery of contractile function [1,2,6]. These effects are not limited to the cardiomyocyte, as the pathological process may be amplified by the activation of neutrophils, which promote the formation of proinflammatory mediators, oxygen radicals, and the reduction of nitric oxide formation in the endothelium, leading to coronary constriction. Reperfusion-induced functional changes in vascular smooth muscle may also compound the injury process, as altered vascular reactivity may adversely influence the coronary flow and may result in a "no reflow" phenomenon. It may be noted that myocardial stunning, myocardial infarction [9,10,23], and potentially lethal arrhythmias are also associated with reperfusion of the ischemic heart [11]. Although preconditioning,

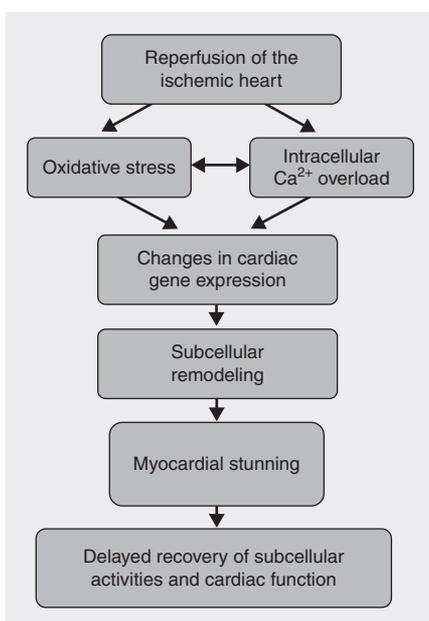


Figure 3. Mechanisms for the chronic effects of reperfusion (myocardial stunning) in the ischemic myocardium.

which is achieved by subjecting the heart to brief periods of ischemia, is known to limit both the size of the infarct and the cardiac dysfunction caused by ischemia-reperfusion [24], it is difficult to use this experimental intervention in clinical settings. Because Ca^{2+} handling by cardiomyocytes from ischemic reperfused heart becomes defective as a consequence of oxidative stress [25], it is to be emphasized that both intracellular Ca^{2+} overload and oxidative stress should be targeted, to avoid the adverse effects of ischemia-reperfusion injury.

Summary

Reperfusion of ischemic myocardium is invariably associated with arrhythmias and cardiac dysfunction as a consequence of the generation of oxyradicals, disturbance in cation homeostasis, and depletion of energy stores. Marked alterations in expression of cardiac genes as a result of ischemia-reperfusion are seen to explain subcellular remodeling and delayed recovery of cardiac function. These paradoxical effects of reperfusion appear to be attributable to the occurrence of oxidative stress and intracellular Ca^{2+} overload in the myocardium. ■

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