Review article

Redox-mediated programed death of myocardial cells after cardiac arrest and cardiopulmonary resuscitation

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Besides the fact that prolonged whole-body ischemia causes tissue and organ injury during cardiac arrest, additional damage occurs after the restoration of spontaneous circulation, during which the reperfusion activates a host of intracellular responses. These responses may lead to an increased threshold of oxidant-mediated injury and redox-mediated programed cell death in the stunned myocardium. The aim of this article is to summarize the major intracellular responses occurring from the onset of cardiac arrest until the post-resuscitation period that may lead to redox-mediated programed death of myocardial cells.

Keywords: Cardiac arrest, Ischemia, Post-resuscitation period, Programed cell death, Reperfusion

Introduction

Cardiac arrest is a daunting medical emergency. Characteristically, it has been found that out of every 100 cardiac arrest victims, 30 will achieve restoration of spontaneous circulation (ROSC), but only 5 will survive the post-resuscitation period.[1] Despite recent advances, post-cardiac arrest syndrome remains the main reason for the poor survival of patients who achieve ROSC.

Post-resuscitation myocardial stunning, a component of this syndrome, is the mechanical dysfunction that persists after the ROSC and is characterized by the absence of irreversible damage, as well as by normal or near-normal coronary flow.[2] Although various factors contribute to its emergence, ischemia/reperfusion (I/R) has a central role in the pathogenesis of this phenomenon.

Besides the fact that prolonged whole-body ischemia causes global tissue and organ injury during cardiac arrest, additional damage occurs during cardiopulmonary resuscitation (CPR) (partial-flow reperfusion) and especially after ROSC, a period in which the whole-body I/R activates a host of cellular stress responses. The aim of this review is to summarize the major pathophysiological responses occurring from the onset of cardiac arrest until the post-resuscitation period that may lead to redox-mediated programed death of myocardial cells.

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Cardiac arrest interval

After the onset of cardiac arrest, the intracellular oxygen tension (PO_2), carbon dioxide tension (PCO_2), and pH change due to the shortage of oxygen. Studies have found that following the onset of ventricular fibrillation, intramyocardial PO_2 levels rapidly decrease, whereas PCO_2 and hydrogen ion concentration increase.[3,4] In addition, mitochondrial oxidative phosphorylation stops and adenosine triphosphate (ATP) is depleted, whereas reactive oxygen species (ROS) are formed and inactivate metabolic enzymes, exacerbating the depletion of myocardial energy.[5] As a result, mitochondria depolarize,[6] whereas the breakdown of creatine phosphate and ATP increases the intracellular concentration of P^+.[7]

At the same time, glycolysis is accelerated under anaerobic conditions and the concentration of pyruvate, hydrogen ions, and lactate increase.[2] Although pyruvate increases cytosolic energy and functions as an antioxidant,[8] the prolongation of ischemia will further decrease the intracellular pH. In addition, the cytosolic Ca^{2+} increases and activates various enzymes, causing alterations in contractile proteins and phospholipid degradation.[9] Disturbances in Ca^{2+} homeostasis and other stresses, such as inhibition of glycosylation and oxidative stress, trigger

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the endoplasmic reticulum response, which involves the release of signaling proteins and consists of multiple parallel events, such as the apoptotic pathways of stress-activated protein kinases (SAPKs) 1 and 2.[10,11]

Although the aforementioned factors have a central role in the pathophysiology of post-resuscitation myocardial stunning, the most important intracellular response during this interval is the formation of the large transition pore across the inner and outer mitochondrial membrane. This pore is formed due to the combined effect of oxidative stress, ATP depletion, and sarcolemmal Ca^{2+} increase.[2] The formation of the mitochondrial transition pore (MTP), as well as the mitochondrial ATP-sensitive K^+ channel which opens in response to an influx of K^+, facilitate the influx of water in mitochondria, thereby countering the effect of matrix shrinkage which is deleterious to respiration.[12] However, MTP opening can lead to necrosis through ATP depletion or to apoptosis via cytochrome *c* release.[13] In addition, MTP pore formation can promote autophagy, a regulated process by which a cell carries out lysosomal degradation of its own constituents (Fig. 1).[13]

Redox-mediated responses during CPR

The partial reperfusion of the arrested myocardium and the increased ROS generation by various oxidase systems cause significant changes in oxidant stress and redox state that activate a number of cellular stress responses. In addition, the stunned myocardium is characterized by significant amounts of nitric oxide (NO) which have been generated shortly after the onset of cardiac arrest. Although NO may exert highly protective effects,[14,15] it can also play a deleterious role in I/R injury.[16] During the CPR interval, the mechanism of mitochondrial oxygen sensing involves redox regulation of NO homeostasis in the inner mitochondrial membrane,[17] inhibition of cytochrome *c* oxidase by NO, and superoxide generation,[18] the release of which in the cytosol and the extracellular space is controlled by the mitochondrial membrane and cell membrane anion channels.[19] However, NO can interact with superoxide to form peroxynitrite, exacerbating oxidative stress during this interval.

Post-resuscitation period

After ROSC, I/R is associated with disturbances in metabolic activity, increases in the production of ROS, and various pro-apoptotic pathways.[20–22] Two studies have found that I/R triggers apoptotic cell death through the Fas/Fas ligand pathway and caspase activation.[23,24] Several different caspases are activated in I/R-induced apoptosis via two major pathways, the 'extrinsic' or death receptor-mediated pathway, which is mediated by specific membrane receptors, such as the tumor necrosis factor and Fas receptors, and the 'intrinsic' or mitochondria-mediated pathway, which plays a critical role in the early stages of I/R injury.[25–27]

In addition, after ROSC and a massive burst of ROS production, the already depolarized mitochondria release cytochrome *c*, which has a central role not only in the activation of caspase cascade, but also in the permeabilization of the outer mitochondrial membrane.[28,29] This permeabilization is regulated by the Bcl-2 family proteins, which interact with the outer mitochondrial membrane and disrupt the normal mitochondrial respiratory function.[30] The permeabilized mitochondria, in turn, release the AIF and Endo G factors that translocate to the nucleus and initiate apoptosis through chromatin condensation and deoxyribonucleic acid fragmentation.[31,32]

Besides apoptosis, caspases have been associated with paraptosis, which is another form of programed cell death characterized by cytoplasmic vacuolation and late mitochondrial swelling.[33] Paraptosis has

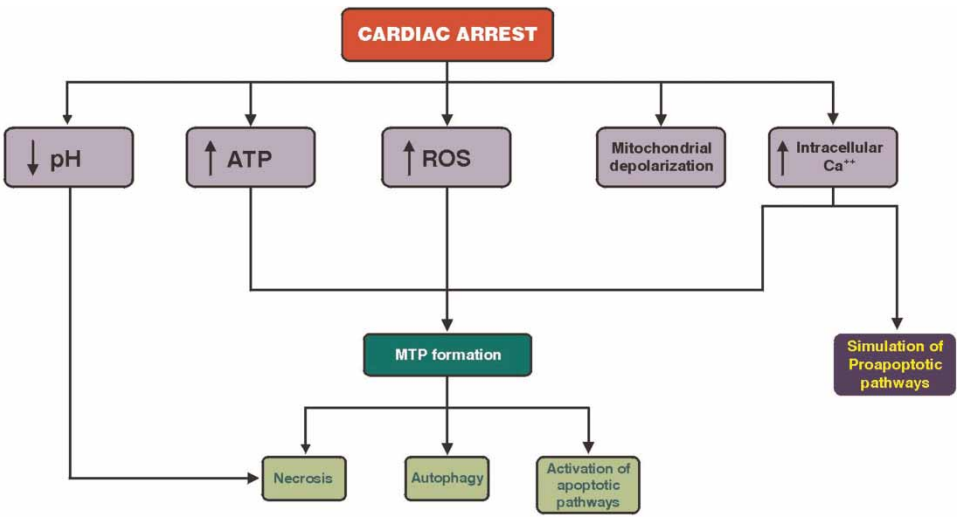

Figure 1 Activation of programed cell-death pathways during the cardiac arrest interval.

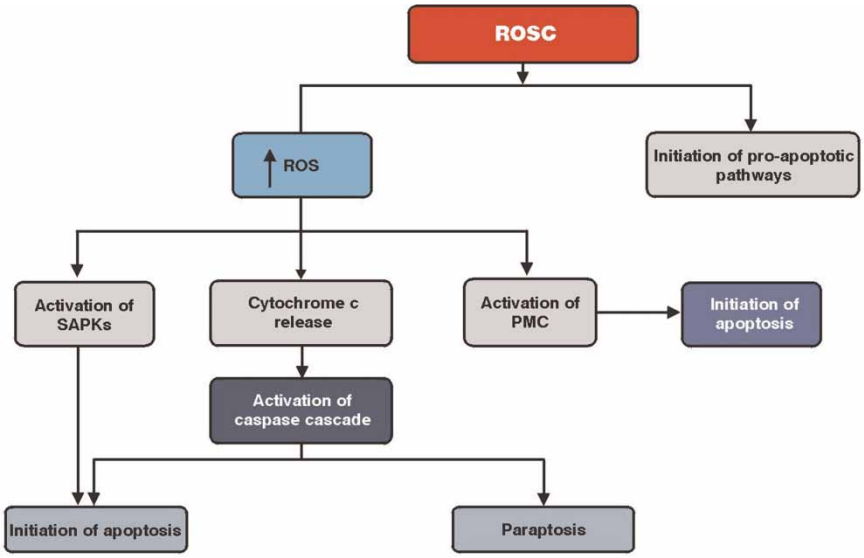

Figure 2 Activation of programed cell death during the post-resuscitation period. PMC, protein kinase C family.

been related to phosphorylation of caspase-9 which, in turn, is associated with I/R-induced cell death.[23,34,35]

Another group of signaling proteins that is strongly activated by ischemia and I/R is the SAPKs, which are closely related to the mitogen-activated protein kinases that regulate cell survival.[36–38] SAPKs are strongly activated by ROS in the myocardium probably through activation of SAPKs kinases or inhibition of phosphoprotein phosphatases.[39,40] It has been found that SAPK1 stimulates the mitochondrial pathway of apoptosis, which is mediated by an adenosine monophosphate-dependent activation of SAPK2.[41,42]

An additional signaling pathway that is activated by I/R is that of the protein kinase C (PKC) family. The PKC family is phospholipid-dependent kinases that are involved in the translation of signaling events (Fig. 2).[43] After ROSC, the PKCs translocate to mitochondria and other subcellular organelles and exert their ROS-mediated pro-apoptotic effects.[44,45] Although the PKC family has been reported to signal preferentially to the SAPK1 and SAPK2 cascades and to potentiate ischemia-induced damage,[46] it has been suggested that translocation of PKC to mitochondria after I/R may induce cell death by stimulating the mitochondrial pathway of apoptosis.[47]

Conclusions

The post-cardiac arrest intracellular stress responses may lead to an increased threshold of oxidant-mediated injury and redox-mediated programed death of myocardial cells. Interestingly, these responses are activated during the cardiac arrest interval and are exacerbated during the CPR interval due to the massive production of ROS. More research is necessary in order to understand the molecular pathophysiology of redox-mediated programed death of myocardial cells during the post-resuscitation period.

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