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Review article

# Ischemia reperfusion injury as a modifiable therapeutic target for cardioprotection or neuroprotection in patients undergoing cardiopulmonary resuscitation☆,☆☆

Ronson J. Madathil[a], Ravi S. Hira[a], Mathias Stoeckl[b], Fritz Sterz[b], JoAnn Broeckel Elrod[a], Graham Nichol[a,*]

[a] University of Washington, Seattle, WA, United States
[b] Medical University of Vienna, Vienna, Austria

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ABSTRACT

Quick restoration of blood flow is essential in patients who have cardiac arrest or other conditions associated with local or global cessation of blood flow. This restoration of flow is associated with multiple deleterious cellular changes. We sought to review these changes to try to understand whether ischemia-reperfusion injury (RI) is a potentially modifiable therapeutic target for cardioprotection or neuroprotection in patients undergoing cardiopulmonary resuscitation.

Remote ischemic conditioning (RIC) involves brief episodes of non-lethal ischemia and reperfusion applied to an organ or limb distal to the heart and brain. Induction of hypothermia involves cooling an ischemic organ or body. Both have pluripotent effects that reduce the potential harm associated with RI in the heart and brain by reduced opening of the mitochondrial permeability transition pore. Recent trials of RIC and induced hypothermia did not demonstrate these treatments to be effective. Assessment of the effect of these interventions in humans to date may have been modified by use of concurrent medications including propofol. Ongoing research is necessary to assess whether reduction of RI improves patient outcomes.



## Introduction

Quick restoration of blood flow (called reperfusion) is essential to reduce the chance of death after cardiac arrest occurs. While the duration of ischemia affects patient outcome, much of the damaging impact of ischemia is realized during the reperfusion phase. This reperfusion injury (RI) causes release of circulating inflammatory molecules including cytokines (e.g. IL-1ra, IL-6, IL-8, IL-10), changes in coagulation, activation of complement, release of polymorphonuclear leukocytes and cellular injury.[1–5] A myriad of systemic and cellular events occur before, during and after ischemia. In brief, these fluxes are associated with upregulation of DNA endothelial dysfunction, thrombosis, impairment of fibrinolysis, and release of reactive oxygen species (ROS).[1,4,6,7] After cardiac arrest, non-survivors demonstrate plasma IL-6 concentrations 20-fold greater than survivors,[1] which is approximately 50-fold greater than normal human baseline values.[8] Inflammation begins rapidly after restoration of flow.[9–11] The extent of cellular injury correlates with how long a patient was without blood flow, how well they will respond to some treatments, and how likely they are to survive.[12] We sought to review these changes, to try to demonstrate whether ischemia reperfusion injury is a potentially modifiable therapeutic target for cardioprotection or neuroprotection in patients undergoing cardiopulmonary resuscitation. As there are limited data describing the cellular changes associated with RI in global ischemia as in cardiac arrest, we extrapolate from data describing RI in local ischemia such as myocardial infarction or revascularization or traumatic brain injury.

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* Corresponding author.
*E-mail address:* nichol@uw.edu (G. Nichol).

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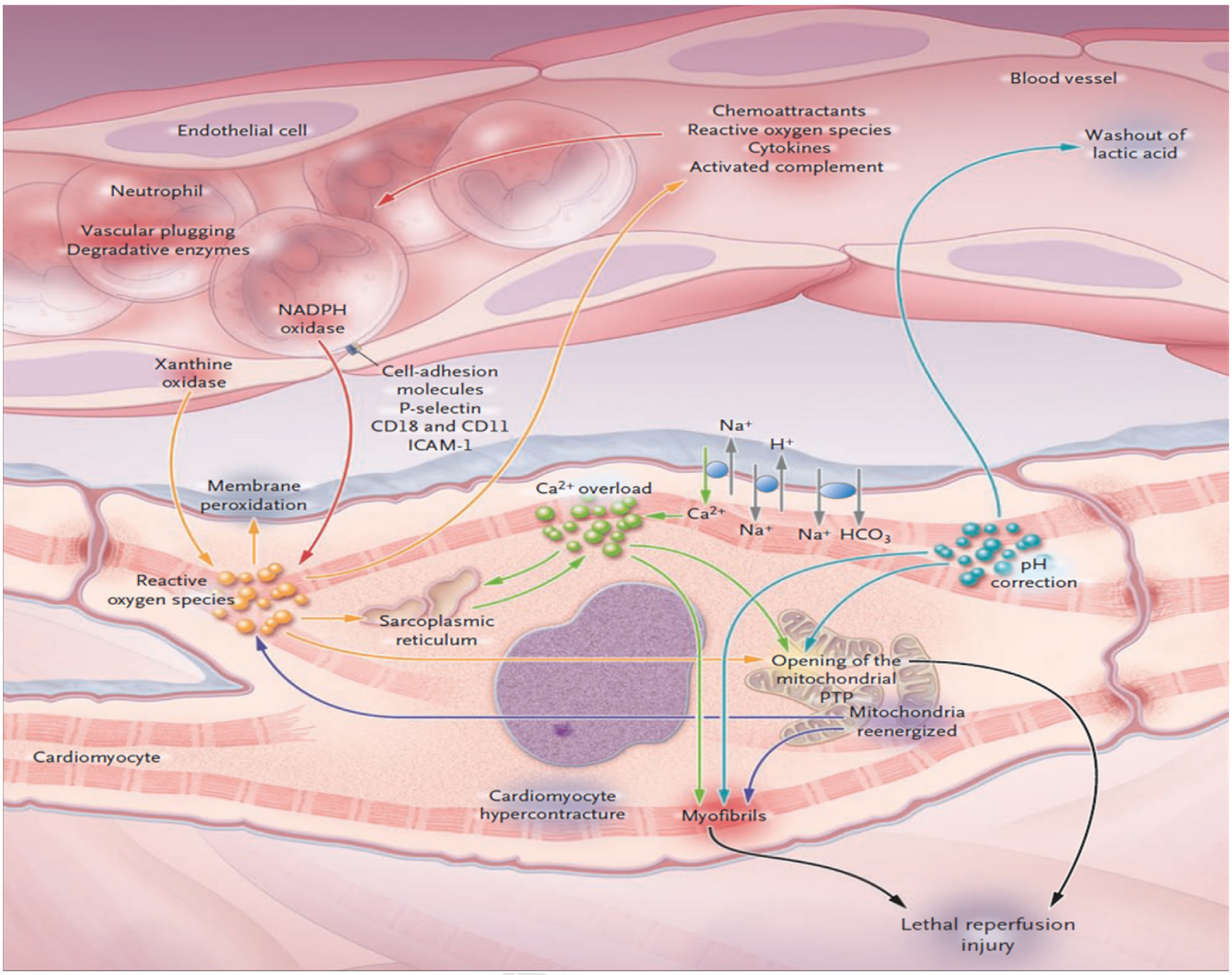


**Fig. 1.** Ischemia-reperfusion injury in heart. Cellular changes during reperfusion of myocardium include mitochondrial re-energization, generation of ROS, intracellular $Ca^{2+}$ overload, rapid restoration of physiologic pH, and inflammation, which all contribute to cardiomyocyte death via opening of the mitochondrial permeability transition pore. Adapted from Ref. 5.

## Reperfusion injury in heart

In the heart, RI is associated with mitochondrial re-energization, rapid restoration of physiologic pH, intracellular calcium influx, release of ROS and free radicals, opening of the mitochondrial permeability transition pore (MPTP). This leads to endothelial dysfunction, impaired oxygen and glucose metabolism, intracellular calcium influx, coagulation and platelet dysfunction, microvascular obstruction, myocardial dysfunction and arrhythmia (Fig. 1).[5]

## Reperfusion injury in brain

In the brain, RI is associated with glutamate release, activation of N-methyl-D-aspartate (NMDA) receptors, intracellular calcium influx, release of ROS and free radicals, and opening of the MPTP. This leads to endothelial dysfunction, impaired oxygen and glucose metabolism, coagulation and platelet dysfunction, seizures (Fig. 2).[13]

Opening of the MPTP results in depolarization of the membrane potential and matrix swelling. This leads to rupture of the outer membrane and release of proteins such as cytochrome C from the intermembrane space into the cytosol. The latter plays a critical role in neuronal and myocardial cell death.[14–16] Importantly many patients with early hemodynamic dysfunction after resuscitation from cardiac arrest survive to have a good neurological outcome.[17,18] Therefore treatments that decrease early mortality related to inflammation and intractable shock could markedly increase the number of survivors of clinical disorders associated with reperfusion injury.

## Conditioning

Conditioning is a term given to multiple strategies that are intended to render an ischemic organ tolerant to the cellular injury that is associated with restoration of flow.

## Timing of conditioning to reduce reperfusion injury

Strategies designed to reduce reperfusion injury by conditioning can be applied during several time periods, as delays in restoration of circulation can occur in all phases of treatment for cardiac arrest. Examples of delays include the initiation of bystander CPR, notification of EMS providers, arrival of EMS providers on scene, application of a monitor/defibrillator, rhythm analysis and defibrillation as indicated, transportation to hospital, and initiation of post-resuscitation care. Preconditioning is applied before the ischemic event. Perconditioning is applied during the event.



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