

Reperfusion – the good, the bad, and the ugly

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Abstract

Reperfusion is mandatory to salvage ischemic myocardium from impending infarction. However, reperfusion also causes additional irreversible injury, not only to the myocardium, but also to the coronary microcirculation. Such reperfusion injury is the target of cardioprotective conditioning strategies. Such strategies include brief cycles of ischemia/reperfusion before (preconditioning), during (perconditioning), or after (postconditioning) the sustained myocardial index ischemia, either locally in the coronary circulation or remotely in limbs or other organs. Reperfusion injury is also the target of pharmacological cardioprotection therapies, eg, cyclosporine A, exenatide, or metoprolol, which engage parts of the signal transduction pathways involved in conditioning strategies. Acute myocardial stunning—fully reversible contractile dysfunction—during reperfusion after shorter episodes of myocardial ischemia is more paradigmatic than clinically relevant; however, long-term repetitive stunning initiates hibernation, ie, a state of prolonged contractile dysfunction, though with preserved viability such that contractile dysfunction is reversible upon eventual revascularization. Reperfusion arrhythmias are frequently observed, but are only rarely a clinical problem. ■ *Heart Metab.* 2016;70:4-7

Keywords: cardioprotection; myocardial ischemia; reperfusion

The good: reperfusion is mandatory for myocardial salvage

In acute myocardial infarction, myocardial ischemia results from the coronary occlusion resulting from the rupture of an atherosclerotic plaque in an epicardial coronary artery with superimposed thrombosis. The duration of coronary occlusion that the myocardium can tolerate before irreversible injury occurs differs between species and depends largely on the residual/collateral blood flow and on heart rate. In larger mammals, infarction begins to develop after a 20- to 40-minute coronary occlusion and spreads in

a wavefront transmurally from the inner to the outer layers and laterally to the borders of the area at risk; infarction is more or less complete after 6 hours of coronary occlusion. Humans, like other primates, are relatively resistant to infarction such that even after 12 hours of coronary occlusion, parts of the ischemic myocardium survive and can still be rescued by interventional reperfusion. Reperfusion precipitates the morphological signs of irreversible injury, but is absolutely mandatory to salvage ischemic myocardium from impending infarction. The final infarct size after myocardial ischemia/reperfusion depends on (i) the size of the area at risk—ie, the coronary perfusion

territory—that undergoes ischemia and reperfusion; (ii) the duration of coronary occlusion (see above); (iii) the severity of myocardial ischemia or, conversely, the amount of residual blood flow through collateral vessels; (iv) the myocardial temperature; and (v) the hemodynamic situation, notably heart rate.¹ Myocardial infarction is largely the result of a necrotic mode of cell death, but other modes of cell death—such as apoptosis, necroptosis, and autophagy—have also been reported to contribute to myocardial infarction in a number of experimental studies.¹ Collapse of mitochondrial function and structure, activation of intracellular proteolysis (calpain, caspases), intracellular sodium and calcium overload with subsequent edema, and excessive and uncoordinated contractile activity secondary to calcium cycling between sarcoplasmic reticulum and cytosol causally contribute to cell death. The resulting infarct size determines the process of post-myocardial infarct remodeling, the progression to heart failure, and ultimately, a patient's prognosis.² A reduction in infarct size via reopening of an occluded coronary artery was first reported in dogs in 1972,^{3,4} and this approach was relatively quickly translated to humans, first in the form of thrombolysis and now preferably in the form of percutaneous coronary intervention, including stent implantation. Today, the need for reperfusion to salvage ischemic myocardium from impending infarction is obvious and is no longer under scientific debate; the discussion is rather about logistics and implementation. Also, all adjunctive cardioprotective strategies known so far only work in conjunction with reperfusion.¹

The bad: reperfusion injury to myocardium and coronary microcirculation

Whether or not reperfusion only precipitates signs of irreversible injury or causes injury per se has been a matter of a long-lasting debate, because the precipitation of signs of injury with reperfusion could not be distinguished from true causation of injury by reperfusion.⁵ However, with the recognition of the postconditioning phenomenon—ie, the reduction in infarct size resulting from several cycles of brief reocclusion and reperfusion of a coronary artery during the early moments of reperfusion after a prolonged coronary occlusion⁶—it is now unequivocally clear that reperfusion per se causes irreversible injury and contributes to infarct size.⁷ Such reperfusion injury affects not only the cardiomyocytes,

but also the coronary microcirculation such that myocardial infarction and coronary “no-reflow”⁸ are closely associated in reperfused myocardial infarction.⁹ The amount of reperfusion injury largely depends on the duration of the preceding ischemia and displays a typical maximum (Figure 1).¹⁰ Both ischemia and reperfu-

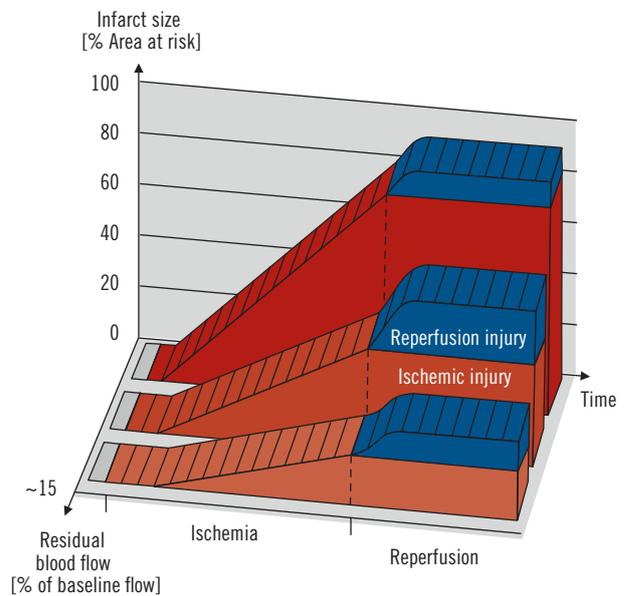


Fig. 1 Ischemia and reperfusion contribute to final infarct size. Reperfusion injury depends on the duration and severity of myocardial ischemia and displays a maximum.

After reference 10: Heusch. *Compr Physiol.* 2015;5(3):1123-1145. © 2015, American Physiological Society.

sion contribute to final infarct size. Reperfusion injury is the prime target of all cardioprotection therapies.¹¹ Brief cycles of ischemia/reperfusion, either locally in the coronary circulation¹² or remotely in the limbs or other parenchymal organs^{13,14}—before (preconditioning),¹² during (perconditioning),¹⁵ or after (postconditioning)⁶ the sustained index myocardial ischemia—activate a molecular cardioprotective program,¹⁶ which when combined with reperfusion reduces myocardial infarct size and attenuates coronary microvascular injury.¹⁷ Cardioprotective signal transduction is highly complex: neuroendocrine transmitters (eg, norepinephrine), autacoids (eg, adenosine, bradykinin), and cytokines (eg, tumor necrosis factor α) activate sarcolemmal receptors, which then initiate cytosolic signal transduction cascades, involving a protein kinase C (PKC)–nitric oxide synthase (NOS)–protein kinase G (PKG) system, the reperfusion injury salvage kinase (RISK) system (involving Akt [or protein kinase B], extracellular signal-regulated kinase [ERK], and glycogen synthase kinase-3 β [GSK-3 β]), and the survival activating factor enhancement system (SAFE: signal transducer and activator

of transcription 3 [STAT3]). These signal transduction cascades converge at the mitochondria, activate mitochondrial adenosine triphosphate (ATP)-dependent potassium channels, which interact with mitochondrial connexin 43, and ultimately inhibit mitochondrial permeability transition pore opening.^{18,19} It is still unclear what mediator(s) transfers the cardioprotective signal from an ischemic/reperfused limb or parenchymal organ to the heart; however, neuronal and humoral mediators, including nitrite, stromal-derived factor-1, and microRNA 144 have been proposed.¹⁴

Reperfusion injury is also attenuated through gentle, as opposed to abrupt, reperfusion—ie, with reduced perfusion pressure or slow restoration of coronary blood flow.²⁰ Finally, there are a number of drugs that engage parts of the signal transduction pathways of the mechanical conditioning strategies and reduce infarct size; examples include cyclosporine A,²¹ enenatide,²² and metoprolol,²³ each of which have reduced infarct size in proof-of-concept clinical trials. In pig experiments, the selective heart rate-reducing agent ivabradine also reduced infarct size even when given only shortly before reperfusion.²⁴ The ischemia/reperfusion-induced coronary microvascular injury, manifesting as edema and microvascular obstruction during reperfusion, is multifactorial in origin. Each of the following contribute: embolization of particulate atherosclerotic debris from the epicardial culprit lesion, aggregation of platelets and of platelets/leukocytes, intense vasoconstriction in response to mediators released from the culprit vessel, extravascular coronary compression by the edema, and physical destruction of the capillaries with luminal obstruction.^{1,25} Ischemic pre- and postconditioning not only reduce infarct size, but also attenuate the damage to the coronary microcirculation such that myocardial edema is reduced.^{6,26} Cardiomyocyte necrosis/myocardial infarction is closely related to coronary microvascular injury,⁹ but microvascular injury is probably not causal for infarction.

The ugly: stunning and reperfusion arrhythmias

Even myocardial ischemia without irreversible injury leaves the myocardium stunned, ie, in a state of fully, but only slowly, reversible contractile dysfunction.²⁷ The pathomechanisms of stunning involve excess reactive oxygen species formation and calcium overload which, in close interaction, impair excita-

tion-contraction coupling and, ultimately, contractile function. Acute stunning per se rarely causes clinical problems; it predominantly affects diastolic left ventricular function and is probably more paradigmatic than clinically important.²⁸ However, long-term repetitive stunning causes hibernation, ie, a persistent state of contractile dysfunction, but with preserved viability such that contractile dysfunction is reversible upon eventual revascularization. Hibernating myocardium has molecular and morphological features of both adaptation and degeneration.²⁹ Reperfusion arrhythmias are frequently observed, but only rarely are a clinical problem. ■

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