Published in final edited form as:
Am J Cardiol. 2010 August 1; 106(3): 360–368. doi:10.1016/j.amjcard.2010.03.032.

Pathogenesis of Myocardial Ischemia-Reperfusion Injury and Rationale for Therapy

Aslan T. Turer, MD, MHS[a,c] and **Joseph A. Hill, MD, PhD**[a,b]

[a]Department of Internal Medicine (Cardiology), University of Texas Southwestern Medical Center, Dallas, TX

[b]Department of Molecular Biology, University of Texas Southwestern Medical Center, Dallas, TX

Abstract

Since the initial description of the phenomenon by Jennings *et al* 50 years ago, our understanding of the underlying mechanisms of reperfusion injury has grown significantly. Its pathogenesis reflects the confluence of multiple pathways, including ion channels, reactive oxygen species, inflammation, and endothelial dysfunction. This complexity should not deter our efforts to intervene in this process, however, since nearly 2 million patients annually undergo either spontaneous (in the form of acute myocardial infarction) or iatrogenic (in the context of cardioplegic arrest) ischemia-reperfusion. The purpose of this review is to examine our current state of understanding of ischemia-reperfusion injury and highlight recent interventions aimed at this heretofore elusive target.

Keywords

coronary artery bypass graft surgery; ischemia; myocardial infarction; reperfusion injury

Each year in the United States, there are approximately 1 million myocardial infarctions (MI) and 700,000 patients undergoing cardioplegic arrest for various cardiac surgeries.[1] Minimizing ischemic time in both of these clinical scenarios has appropriately received a great deal of attention owing to the long-established relationship between duration of ischemia and the extent of myocardial injury. Once coronary flow is restored, however, the myocardium is susceptible to another form of insult stemming from reperfusion of the previously ischemic tissue. Given that cardiac ischemia is either unpredictable (MI) or inevitable (in the operating room), there is great interest in developing strategies to minimize reperfusion-mediated injury.

Historical perspective

The seminal observation that reperfusion following ischemia was associated with myocardial injury was made in 1960 by Jennings and colleagues.[2] Their report was based on experiments with canine hearts subjected to coronary ligation in which reperfusion appeared to accelerate

[c]Corresponding author: Telephone: (214) 645-7558, Fax: (214) 645-7501, aslan.turer@utsouthwestern.edu, 5323 Harry Hines Blvd, Dallas, TX 75230-9047 .

Conflicts of Interest Disclosures
None

the development of necrosis. For example, the authors noted that the histological changes seen following only 30-60 minutes of ischemia/reperfusion (I/R) were comparable to the degree of necrosis normally seen after 24 hours of permanent coronary occlusion.[2]

Whether reperfusion is independently responsible for tissue injury, or simply hastens the demise of cells otherwise destined for necrosis, remained a matter of debate for some years. Evidence for direct myocardial reperfusion-dependent injury was summarized in 1985 in the classic editorial by Braunwald and Kloner.[3] However, it was not until the discovery of ischemic preconditioning that the independent effects of ischemia and reperfusion began to be unraveled from one another.

In 1986, Murry and Reimer described a process whereby repetitive short bouts of ischemia preceding a prolonged period of ischemia with reperfusion resulted in significantly decreased infarct size in dogs.[4] Subsequently, this “ischemic preconditioning” was confirmed in a number of animal models, including humans, highlighting it as an evolutionarily conserved mechanism. Subsequent experiments revealed that the reperfusion event is key to the initiation of a molecular cascade leading to cardioprotection,[5] thereby serving to solidify the important distinction between ischemia and subsequent reperfusion.

Mechanisms of I/R injury

Molecular and cellular events underlying I/R injury are complex, representing the confluence of divergent biological pathways. Further, the extent to which each of these pathways is relevant to human disease remains unclear, as animal models do not always faithfully recapitulate the I/R disease process in humans. These limitations notwithstanding, several key pathophysiologic features of clinically relevant I/R have emerged (Table 1).

Ischemia induces accumulation of intracellular sodium, hydrogen, and calcium ions, culminating in tissue acidosis. Reperfusion, in turn, elicits rapid alterations in ion flux, and some evidence suggests that rapid renormalization of pH paradoxically leads to enhanced cytotoxicity.[6,7] Sodium-dependent pH regulatory mechanisms, including the Na^+-H^+ exchanger and the Na^+-HCO_3^- transporter, are activated, which consequently lead to intracellular sodium accumulation. High sodium concentrations, in turn, drive increases in sarcoplasmic reticular Ca^{2+} via the Na^+-Ca^{2+} exchange.[8] Enhanced Ca^{2+} entry via sarcolemmal L-type Ca^{2+} channels[9,10] and a deficient import of cytosolic Ca^{2+} into the sarcoplasmic reticulum by the SERCA Ca^{2+-}ATPase[11,12] further promote Ca^{2+} overload. The result is myofibrillar hypercontractility, ATP depletion, ultrastructural damage to mitochondria, and myocardial stunning.[13-15]

Cardiac myocytes consume large quantities of energy. To accommodate this requirement, these cells host a high density of mitochondria. Thus, it is not surprising that these complex, energy-generating organelles, filled with reactive intermediates and pro-apoptotic signals, are intimately involved in I/R injury. As part of this, the mitochondrial permeability transition pore (mPTP) has been the center of a growing amount of attention. The inner mitochondrial membrane, responsible for maintaining mitochondrial transmembrane potential, is normally impermeable to ions and proteins. Dissipation of the electrical potential across this membrane is termed “permeability transition”, a process thought to be mediated through the mPTP. Although the constituent protein components of the pore remain unknown, formation of the pore creates a non-selective channel between the inner membrane of the mitochondrion and the sarcoplasm. This results in loss of the electrochemical gradient, release of reactive oxygen species (ROS), and apoptosome formation. Triggers for mPTP include Ca^{2+} overload,[16] rapid normalization of pH,[17] and oxidative stress.[17-19]

Generation of free radicals through incomplete reduction of oxygen during I/R has been well described. These oxygen species are highly reactive and can quickly overwhelm the cell's endogenous free radical scavenging system. This, in turn, triggers cellular injury by reactions with lipids, proteins, and nucleic acids. The enzyme, xanthine oxidase, has been particularly implicated as a generator of free radicals in the reperfused heart, as its substrates (xanthine and hypoxanthine) accumulate during ischemia.[20,21] In addition to damaging nuclear and cytosolic elements, ROS can trigger the opening of the mPTP.[22] This results in a positive feedback loop of additional free radical release from the mitochondria ("ROS-induced ROS release").[23]

Not only is I/R injury dependent on events occurring within cardiomyocytes, but the endothelium is an active participant as well. The endothelium is the major source of the evanescent molecule, nitric oxide (NO). Under normal conditions, NO generation elicits vasodilation, which has beneficial, protective effects during I/R, likely by influencing oxygen consumption,[24] platelet aggregation,[25] leukocyte adhesion,[26] and free radical scavenging.[27] Paradoxically, in high concentrations, NO may potentiate ROS-mediated toxicity by promoting the formation of highly reactive species, such as peroxynitrite.[27,28] Beyond NO, the coronary endothelium has several other pathophysiological roles in I/R, such as serving as a source of vasoactive substances and by activating the immune system through expression of cytokines, chemokines, and adhesion molecules.

Recent work has implicated autophagy, an evolutionarily ancient mechanism of controlled cellular cannibalism, in the pathogenesis of I/R.[29,30] Time will tell whether this mechanism is a suitable target for therapeutic manipulation in this and other heart disease–related contexts.

Endothelial activation and injury increase vascular permeability and recruitment of inflammatory cells. Cellular adhesion molecules elicited by the injured endothelium (eg, ICAM-1, VCAM-1, E-selectin) promote tissue invasion by inflammatory cells. These infiltrating cells, including (and in particular) neutrophils, are directly toxic to the myocardium by secreting proteases, generating ROS, and occluding the microvasculature. Other components of the innate immune system, such as Toll-like receptors,[31] mannose-binding lectin,[32] and the complement cascade,[33] also appear to participate in the pathogenesis of I/R stress. Additionally, there is a growing appreciation of the role of cell-mediated immunity (ie, T-cells and macrophages) in the pathogenesis of myocardial damage after reperfusion.[34,35]

I/R in acute MI

Although reperfusion injury in the most general sense refers to that component of the infarction process related to restoration of epicardial patency and anterograde blood flow, in the catheterization laboratory, I/R injury is often synonymous with the "no-reflow" phenomenon. The term was first applied to myocardial ischemia following coronary ligation in dogs.[36] Regarded as a dreaded complication of acute MI intervention, it is estimated to occur in more than 30% of cases and is associated with adverse prognosis.[37-40] No reflow is thought to be related in-part to microvascular plugging by vasoactive debris. While dramatic, no-reflow is probably just the most angiographically apparent form of I/R injury in acute MI, and it should be recognized that significant reperfusion injury occurs even without the obvious "hang-up" of contrast dye.

Deciphering the contribution of I/R to myocardial infarct size in humans is more challenging than in animal models. Acute MI in humans is generally associated with thrombotic occlusion of an epicardial coronary, and this prothrombotic and proinflammatory event is not well captured in models involving surgical ligation of the artery. This may be particularly important as microvascular plugging with leukocytes and platelet "debris" has been implicated as an important component of the I/R process.[41,42] Another complexity relates to patient comorbidities that influence the myocardial substrate during I/R. Factors such as left

ventricular hypertrophy,[43,44] diabetes mellitus,[45-47] and chronic ischemia preceding artery total occlusion (ie, recapitulating ischemic preconditioning),[48,49] potentially influence sensitivity to I/R injury. The resulting heterogeneity in the human myocardial phenotype renders analyses of experimental models challenging and limits the degree to which the findings can be extrapolated to the human case. Finally, the emergent nature of most acute MI cases (ST-segment elevation MI, in particular) makes it challenging, often both ethically and logistically, to study these patients, as issues arise of informed consent and seeming coercion during the race to achieve vessel patency. Nonetheless, these limitations have not precluded the testing of a series of therapeutic interventions in patients over the last three decades.

Therapeutic interventions targeting I/R injury in acute MI

Despite the substantial progress in understanding mechanisms of I/R based on models of acute MI, and the associated enthusiasm for translating these findings into patient care, results of clinical studies have been largely disappointing. Whether this reflects our still incomplete understanding of the biology of I/R, or just a naïve belief that a single intervention could be protective against a process involving multiple major pathophysiological components, is not clear. Initial pilot successes have been met with subsequent failures in larger confirmatory trials. The results of these trials have been summarized elsewhere,[50] but interventions have included a spectrum of targets, including oxidant, inflammatory, sodium-hydrogen exchange, NO metabolism, and metabolic pathways (Table 2).

Despite these setbacks, investigation continues in this field. Erythropoietin (EPO), for instance, is currently undergoing investigation in clinical studies[51-53] of acute MI following the discovery of EPO receptor expression in the myocardium.[54] EPO has anti-apoptotic activity,[55,56] positive effects on remodeling,[57-59] and recruits endothelial progenitor cells.[60] It is hoped that this drug may exert positive effects by one or more of these pathways. Other therapeutic strategies currently in clinical trials include the IL-1-receptor antagonist, anakinra[61,62] and glucagon-like peptide-1 analogues.[63,64]

Although most pharmacologic interventions have been administered systemically, the availability of primary percutaneous coronary revascularization has allowed for direct administration of drug to the coronary endothelium and myocardium. One well-studied drug is adenosine. Adenosine, in addition to its well-known vasodilating properties, is intimately involved with both pre-[65] and post-conditioning[66-67] (see below), as well as inhibition of mPTP opening.[68] Although systemic adenosine infusion did not reduce overall mortality in the AMISTAD-II trial, some effect on infarct size was noted.[69] Subsequent smaller scale investigation into the potential adjunctive role of intracoronary (IC) administration has demonstrated some benefit with regards to electrocardiographic and angiographic endpoints in the setting of acute MI.[70-71] Similarly, there has been some enthusiasm, though muted somewhat by the small-scale nature of the studies, for IC nitroprusside in the treatment of no-reflow.[72-74] This direct NO-donor may be of particular benefit when co-administered with IC adenosine.[75]

Ischemic post-conditioning, a process wherein the myocardium is subjected to repetitive bouts of iatrogenic I/R during the course of an on-going acute MI, is also under clinical investigation. This procedure involves several short intracoronary balloon inflations after primary vessel patency has been re-established. Data from animal models suggest that final infarction size is diminished by this strategy,[76-78] and some preliminary data in humans appear promising.[79-81] The mechanism of benefit is unclear, but it may involve induction of a more gradual pH shift in the myocardium or decreasing ROS and Ca^{2+}-induced mPTP opening.[77,82-84]

There is an evergrowing focus on the role of mPTP in I/R. This structure, as outlined previously, appears to be the common effector of a series of upstream intracellular signals and, therefore,

has obvious appeal as a target of therapy. Recently, results of a pilot study of intravenous cyclosporine A (CSA), a non-specific inhibitor of the mPTP, during STEMI were reported.[85] Although a small study, the results were promising, suggesting that inhibition of mPTP may be of benefit in larger trials.

I/R injury during cardiac surgery

I/R stress resulting from cardiac surgery is distinctly different from that occurring during spontaneous MI. Ischemia is induced artificially by aortic cross-clamping, and myocardial preservation strategies are employed throughout this ischemic period. Cardioplegia is achieved via hyperkalemic, hypothermic cardiac arrest and maintained with the intermittent use of a glucose-containing cardioplegic solution (usually mixed with blood) delivered anterograde in the aortic root and/or retrograde via the coronary sinus. These maneuvers are designed to minimize myocardial metabolic activity and consequent oxygen demand during this period of myocardial vulnerability.

Once surgery has been completed, the aortic cross-clamp is released, and the heart is suddenly and globally reperfused with blood that is fully anticoagulated, immunologically primed by exposure to the cardiopulmonary bypass circuit, and characterized by a very high partial pressure of oxygen. As a result, the post-cardiac surgery myocardium is exposed to dramatic extremes of ischemia and reperfusion. And, again, it is important to recognize that hearts undergoing cardiac surgery are highly heterogeneous, ranging across a spectrum of comorbidities, hypertrophy, and contractile function. Patients undergoing aortic arch surgery may have essentially normal hearts, while other patients may be chronically ischemic with severe contractile dysfunction. These tissue substrates would be expected to react differently to such extremes of environmental stress.

Clinically, I/R injury after cardiac surgery can manifest as arrhythmia, myocardial stunning, low cardiac output, and perioperative myocardial infarction. In patients dying soon after coronary artery bypass surgery (CABG), histologic evidence of I/R on autopsy is detected in 25%-45% of patients.[86-88] Furthermore, biochemical evidence of myocardial injury (eg, elevated levels of circulating CK-MB and/or troponin) has been clearly linked with adverse events after cardiac surgery.[89,90]

Interventions targeting I/R injury after cardioplegic arrest

Although the operating theater may appear daunting given the number of personnel, environmental factors, and pieces of equipment needed to successfully manage a patient through cardiac surgery, it is, in many ways, an ideal place to perform research. Duration of ischemia is known, electrolytes and glucose concentrations are meticulously regulated, and hemodynamics can be followed throughout the procedure, including the pre- and post-operative phases. Furthermore, local drug delivery, as opposed to systemic therapy, can be administered reliably via the cannulated coronary circulation.

The cornerstone of cardioprotection in cardiac surgery has been the cardioplegia solution. These solutions typically contain potassium, mannitol, and glucose. By arresting and cooling the heart, the metabolic demands of the myocardium are minimized. However, despite decades of experience with cardioplegia, there has been surprisingly little change in these formulations except for, perhaps, the adoption of blood cardioplegia. And despite the use of cardioplegia, I/R injury still occurs.

There are some small studies supporting the use of metabolic additives, such as pyruvate[91] and glutamate/aspartate.[92,93] The goal of such metabolic supplementation is to provide the arrested myocardium with energy substrates with favorable characteristics (e.g., avoidance of fatty acid

oxidation), and to replete the cell with anaplerotic substrates. However, evidence to date supporting the use of these agents have not been sufficiently convincing to lead to widespread clinical use.

The concept of ischemic preconditioning has also been applied during cardiac surgery. Either before or just following establishment of cardiopulmonary bypass, the aorta is cross-clamped for several minutes, released for several minutes and then once again cross-clamped for cardioplegia. Several groups have utilized this technique, and some benefit has been seen in small studies. A recent meta-analysis concluded that this form of pre-conditioning decreased post-operative ventricular arrhythmias and inotrope use and translated into shorter ICU stays[94]. These suggestive findings await prospective testing in patients.

Given the association of immune system activation with I/R injury, together with the marked systemic inflammation elicited by surgery and by exposure to the bypass circuit, a number of investigators have focused their attention on modulating immune responses. Leukocyte filters,[95-97] steroids,[98-100] and specific volatile anesthetics[101-103] have all been tested in small studies with no clear signal of benefit. Initial data on the anti-C5a antibody, pexelizumab, appeared promising and prompted two large randomized clinical trials. PRIMO-CABG[104] demonstrated a strong trend toward decreasing death or MI, but these results were not confirmed in the larger follow-up PRIMO-CABG II study.[105] Finally, aprotinin, an antifibrinolytic protein with anti-inflammatory properties, was documented to have favorable effects on myocardial I/R in human and animal studies, but was later taken off the market because of clear evidence for harm associated with its use.[106-108] In aggregate, results of inhibiting the inflammatory response occurring in cardiac surgery have been disappointing.

The naturally occurring pyridoxine metabolite and purinergic receptor antagonist, pyridoxal-5′-phosphate (MC-1), was studied in two large CABG clinical studies. MC-1 was found to prevent intracellular Ca^{2+} overload and appeared promising for mitigating I/R injury.[109] Indeed, phase II data from the MEND-CABG I study suggested lower post-procedural infarct sizes.[110] Based on this result, a larger phase III study was undertaken. Disappointingly, however, MEND-CABG II failed to find any difference in infarct size and reported a slight early increase in mortality with MC-1 (1.0% vs 0.3%, P=0.03).[111]

Another strategy to prevent intracellular Ca^{2+} overload is antagonism of the sodium-hydrogen exchanger. Cariporide, a potent inhibitor of this transporter, was first evaluated in the GUARDIAN trial, a catch-all study of patients with non-ST segment elevation acute coronary syndrome (NSTE-ACS) or planned elective revascularization with either percutaneous coronary intervention (PCI) or CABG.[112] An efficacy signal was noted for the CABG subset,[113] and the drug was subjected to a larger trial dedicated to CABG.[114] The primary endpoint in EXPEDITION (death or MI) was lower in the cariporide arm as compared with placebo (16.6% vs 20.3%, P=0.0002), the first time a phase III clinical study of myocardial protection had met its primary endpoint. However, whereas the composite endpoint was driven by a significant reduction in perioperative MI (18.9% vs 14.4%, P<0.0001), there was a paradoxical increase in overall mortality (2.2% vs 1.5%, P=0.02), which appeared to be driven by an increase in cerebrovascular events. Indeed, there was a significant increase in stroke and altered mental status associated with the drug.

Perhaps the most thoroughly studied drug in surgical ischemia-reperfusion is acadesine, a purine analog that increases tissue adenosine levels in energy-deprived tissues.[115,116] A potent cardioprotective role has been ascribed to stimulation of adenosine receptors in I/R via modulation of mPTP opening.[68,117] Acadesine, given as an additive in cardioplegia solution, has been investigated in a number of smaller studies,[118-120] as well in as the ~2,700 patient phase III Acadesine 1024 Trial.[121] Although the largest study failed to show a statistically

significant difference in the primary outcome of peri-procedural MI (3.4% vs 4.0%, *P*=0.24 in favor of acadesine), a subsequent meta-analysis of all available data on acadesine suggested a 27% reduction in MI (3.6% vs 4.9%, *P*=0.02) and a 26% decrease in the combined outcome of stroke/MI/cardiac death (7.6% vs 4.6%, *P*=0.04).[122] Acadesine is currently undergoing study in the Reduction in cardiovascular Events by acaDesine in subjects undergoing CABG (RED-CABG) trial, which plans to enroll 7,500 high-risk subjects.[123]

Acknowledgments

The author would like to thank Lynne Isbell, PhD, at Discovery Chicago for editorial support, which was funded by Schering-Plough Corporation.

Source of Funding

This work was supported by grants from the NIH (HL-075173, HL-080144, HL-090842), AHA (0640084N), ADA (7-08-MN-21-ADA), and the AHA-Jon Holden DeHaan Foundation (0970518N).

References

1. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J. Heart Disease and Stroke Statistics--2010 Update. A Report From the American Heart Association. Circulation 2009;121:e1–e170.
2. Jennings RB, Sommers HM, Smyth GA, Flack HA, Linn H. Myocardial necrosis induced by temporary occlusion of a coronary artery in the dog. Arch Pathol 1960;70:68–78. [PubMed: 14407094]
3. Braunwald E, Kloner RA. Myocardial reperfusion: a double-edged sword? J Clin Invest 1985;76:1713–1719. [PubMed: 4056048]
4. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation 1986;74:1124–1136. [PubMed: 3769170]
5. Hausenloy DJ, Tsang A, Mocanu MM, Yellon DM. Ischemic preconditioning protects by activating prosurvival kinases at reperfusion. Am J Physiol Heart Circ Physiol 2005;288:H971–976. [PubMed: 15358610]
6. Bond JM, Herman B, Lemasters JJ. Protection by acidotic pH against anoxia/reoxygenation injury to rat neonatal cardiac myocytes. Biochem Biophys Res Commun 1991;179:798–803. [PubMed: 1898402]
7. Lemasters JJ, Bond JM, Chacon E, Harper IS, Kaplan SH, Ohata H, Trollinger DR, Herman B, Cascio WE. The pH paradox in ischemia-reperfusion injury to cardiac myocytes. EXS 1996;76:99–114. [PubMed: 8805791]
8. Tani M, Neely JR. Role of intracellular Na+ in Ca2+ overload and depressed recovery of ventricular function of reperfused ischemic rat hearts. Possible involvement of H+-Na+ and Na+-Ca2+ exchange. Circ Res 1989;65:1045–1056. [PubMed: 2551525]
9. Bush LR, Romson JL, Ash JL, Lucchesi BR. Effect of diltiazem on extent of ultimate myocardial injury resulting from temporary coronary artery occlusion in dogs. J Cardiovasc Pharmacol 1982;4:285–296. [PubMed: 6175813]
10. du Toit EF, Opie LH. Modulation of severity of reperfusion stunning in the isolated rat heart by agents altering calcium flux at onset of reperfusion. Circ Res 1992;70:960–967. [PubMed: 1568304]
11. Krause S, Hess ML. Characterization of cardiac sarcoplasmic reticulum dysfunction during short-term, normothermic, global ischemia. Circ Res 1984;55:176–184. [PubMed: 6146409]
12. Kaplan P, Hendrikx M, Mattheussen M, Mubagwa K, Flameng W. Effect of ischemia and reperfusion on sarcoplasmic reticulum calcium uptake. Circ Res 1992;71:1123–1130. [PubMed: 1394874]
13. Kusuoka H, Porterfield JK, Weisman HF, Weisfeldt ML, Marban E. Pathophysiology and pathogenesis of stunned myocardium. Depressed Ca2+ activation of contraction as a consequence

of reperfusion-induced cellular calcium overload in ferret hearts. J Clin Invest 1987;79:950–961. [PubMed: 3818956]

14. Nayler WG. The role of calcium in the ischemic myocardium. Am J Pathol 1981;102:262–270. [PubMed: 7008622]
15. Zimmerman ANE, Daems W, Hulsmann WC, Snijder J, Wisse E, Durrer D. Morphological changes of heart muscle caused by successive perfusion with calcium-free and calcium-containing solutions (calcium paradox). Cardiovasc Res 1967;1:201–209.
16. Orrenius S, Zhivotovsky B, Nicotera P. Regulation of cell death: the calcium-apoptosis link. Nat Rev Mol Cell Biol 2003;4:552–565. [PubMed: 12838338]
17. Kim JS, Jin Y, Lemasters JJ. Reactive oxygen species, but not Ca2+ overloading, trigger pH- and mitochondrial permeability transition-dependent death of adult rat myocytes after ischemia-reperfusion. Am J Physiol Heart Circ Physiol 2006;290:H2024–2034. [PubMed: 16399872]
18. Rajesh KG, Sasaguri S, Suzuki R, Maeda H. Antioxidant MCI-186 inhibits mitochondrial permeability transition pore and upregulates Bcl-2 expression. Am J Physiol Heart Circ Physiol 2003;285:H2171–2178. [PubMed: 12816747]
19. Schild L, Reiser G. Oxidative stress is involved in the permeabilization of the inner membrane of brain mitochondria exposed to hypoxia/reoxygenation and low micromolar Ca2+ FEBS J 2005;272:3593–3601. [PubMed: 16008559]
20. Thompson-Gorman SL, Zweier JL. Evaluation of the role of xanthine oxidase in myocardial reperfusion injury. J Biol Chem 1990;265:6656–6663. [PubMed: 2157706]
21. Xia Y, Zweier JL. Substrate control of free radical generation from xanthine oxidase in the postischemic heart. J Biol Chem 1995;270:18797–18803. [PubMed: 7642530]
22. Zorov DB, Juhaszova M, Yaniv Y, Nuss HB, Wang S, Sollott SJ. Regulation and pharmacology of the mitochondrial permeability transition pore. Cardiovasc Res 2009;83:213–225. [PubMed: 19447775]
23. Zorov DB, Filburn CR, Klotz LO, Zweier JL, Sollott SJ. Reactive oxygen species (ROS)-induced ROS release: a new phenomenon accompanying induction of the mitochondrial permeability transition in cardiac myocytes. J Exp Med 2000;192:1001–1014. [PubMed: 11015441]
24. Loke KE, McConnell PI, Tuzman JM, Shesely EG, Smith CJ, Stackpole CJ, Thompson CI, Kaley G, Wolin MS, Hintze TH. Endogenous endothelial nitric oxide synthase-derived nitric oxide is a physiological regulator of myocardial oxygen consumption. Circ Res 1999;84:840–845. [PubMed: 10205152]
25. Radomski MW, Palmer RM, Moncada S. Endogenous nitric oxide inhibits human platelet adhesion to vascular endothelium. Lancet 1987;2:1057–1058. [PubMed: 2889967]
26. Ma XL, Weyrich AS, Lefer DJ, Lefer AM. Diminished basal nitric oxide release after myocardial ischemia and reperfusion promotes neutrophil adherence to coronary endothelium. Circ Res 1993;72:403–412. [PubMed: 8418991]
27. Beckman JS, Beckman TW, Chen J, Marshall PA, Freeman BA. Apparent hydroxyl radical production by peroxynitrite: implications for endothelial injury from nitric oxide and superoxide. Proc Natl Acad Sci U S A 1990;87:1620–1624. [PubMed: 2154753]
28. Wang P, Zweier JL. Measurement of nitric oxide and peroxynitrite generation in the postischemic heart. Evidence for peroxynitrite-mediated reperfusion injury. J Biol Chem 1996;271:29223–29230. [PubMed: 8910581]
29. Matsui Y, Takagi H, Qu X, Abdellatif M, Sakoda H, Asano T, Levine B, Sadoshima J. Distinct roles of autophagy in the heart during ischemia and reperfusion: roles of AMP-activated protein kinase and Beclin 1 in mediating autophagy. Circ Res 2007;100:914–922. [PubMed: 17332429]
30. Wang ZV, Rothermel BA, Hill JA. Autophagy in hypertensive heart disease. J Biol Chem. 2010 In Press.
31. Chao W. Toll-like receptor signaling: a critical modulator of cell survival and ischemic injury in the heart. Am J Physiol Heart Circ Physiol 2009;296:H1–12. [PubMed: 19011041]
32. Busche MN, Pavlov V, Takahashi K, Stahl GL. Myocardial ischemia and reperfusion injury is dependent on both IgM and mannose-binding lectin. Am J Physiol Heart Circ Physiol 2009;297:H1853–1859. [PubMed: 19749170]

33. Shernan SK, Collard CD. Role of the complement system in ischaemic heart disease: potential for pharmacological intervention. BioDrugs 2001;15:595–607. [PubMed: 11580303]
34. Yang Z, Day YJ, Toufektsian MC, Xu Y, Ramos SI, Marshall MA, French BA, Linden J. Myocardial infarct-sparing effect of adenosine A2A receptor activation is due to its action on CD4+ T lymphocytes. Circulation 2006;114:2056–2064. [PubMed: 17060376]
35. Kobara M, Sunagawa N, Abe M, Tanaka N, Toba H, Hayashi H, Keira N, Tatsumi T, Matsubara H, Nakata T. Apoptotic myocytes generate monocyte chemoattractant protein-1 and mediate macrophage recruitment. J Appl Physiol 2008;104:601–609. [PubMed: 18048593]
36. Kloner RA, Ganote CE, Jennings RB. The “no-reflow” phenomenon after temporary coronary occlusion in the dog. J Clin Invest 1974;54:1496–1508. [PubMed: 4140198]
37. Brosh D, Assali AR, Mager A, Porter A, Hasdai D, Teplitsky I, Rechavia E, Fuchs S, Battler A, Kornowski R. Effect of no-reflow during primary percutaneous coronary intervention for acute myocardial infarction on six-month mortality. Am J Cardiol 2007;99:442–445. [PubMed: 17293180]
38. Henriques JP, Zijlstra F, van ’t Hof AW, de Boer MJ, Dambrink JH, Gosselink M, Hoorntje JC, Suryapranata H. Angiographic assessment of reperfusion in acute myocardial infarction by myocardial blush grade. Circulation 2003;107:2115–2119. [PubMed: 12695301]
39. Gibson CM, Cannon CP, Murphy SA, Marble SJ, Barron HV, Braunwald E. Relationship of the TIMI myocardial perfusion grades, flow grades, frame count, and percutaneous coronary intervention to long-term outcomes after thrombolytic administration in acute myocardial infarction. Circulation 2002;105:1909–1913. [PubMed: 11997276]
40. Niccoli G, Burzotta F, Galiuto L, Crea F. Myocardial no-reflow in humans. J Am Coll Cardiol 2009;54:281–292. [PubMed: 19608025]
41. Okamura A, Ito H, Iwakura K, Kawano S, Inoue K, Maekawa Y, Ogihara T, Fujii K. Detection of embolic particles with the Doppler guide wire during coronary intervention in patients with acute myocardial infarction: efficacy of distal protection device. J Am Coll Cardiol 2005;45:212–215. [PubMed: 15653017]
42. Ito H. No-reflow phenomenon and prognosis in patients with acute myocardial infarction. Nat Clin Pract Cardiovasc Med 2006;3:499–506. [PubMed: 16932767]
43. Attarian DE, Jones RN, Currie WD, Hill RC, Sink JD, Olsen CO, Chitwood WR Jr, Wechsler AS. Characteristics of chronic left ventricular hypertrophy induced by subcoronary valvular aortic stenosis. I. Myocardial blood flow and metabolism. J Thorac Cardiovasc Surg 1981;81:382–388. [PubMed: 6450857]
44. Anderson PG, Allard MF, Thomas GD, Bishop SP, Digerness SB. Increased ischemic injury but decreased hypoxic injury in hypertrophied rat hearts. Circ Res 1990;67:948–959. [PubMed: 2145092]
45. Ferdinandy P, Szilvassy Z, Baxter GF. Adaptation to myocardial stress in disease states: is preconditioning a healthy heart phenomenon? Trends Pharmacol Sci 1998;19:223–229. [PubMed: 9666713]
46. Feuvray D, Lopaschuk GD. Controversies on the sensitivity of the diabetic heart to ischemic injury: the sensitivity of the diabetic heart to ischemic injury is decreased. Cardiovasc Res 1997;34:113–120. [PubMed: 9217880]
47. Di Filippo C, Marfella R, Cuzzocrea S, Piegari E, Petronella P, Giugliano D, Rossi F, D’Amico M. Hyperglycemia in streptozotocin-induced diabetic rat increases infarct size associated with low levels of myocardial HO-1 during ischemia/reperfusion. Diabetes 2005;54:803–810. [PubMed: 15734859]
48. Neckar J, Ostadal B, Kolar F. Myocardial infarct size-limiting effect of chronic hypoxia persists for five weeks of normoxic recovery. Physiol Res 2004;53:621–628. [PubMed: 15588130]
49. Chen C, Chen L, Fallon JT, Ma L, Li L, Bow L, Knibbs D, McKay R, Gillam LD, Waters DD. Functional and structural alterations with 24-hour myocardial hibernation and recovery after reperfusion. A pig model of myocardial hibernation. Circulation 1996;94:507–516. [PubMed: 8759096]
50. Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. N Engl J Med 2007;357:1121–1135. [PubMed: 17855673]
51. Clinical study to examine the effects of erythropoietin on left ventricular function after acute myocardial infarction (HEBEIII). [Accessed January 5, 2010]. Available at: http://clinicaltrials.gov/ct2/show/NCT00449488

52. EPOMI study: ErythroPOietin in Myocardial Infaction. [Accessed January 5, 2010]. Available at: http://clinicaltrials.gov/ct2/show/NCT00648089
53. REVEAL: Reduction of Infarct Expansion and Ventricular Remodeling With Erythropoeitin After Late Myocardial Infarction. [Accessed January 5, 2010]. Available at: http://clinicaltrials.gov/ct2/show/NCT00378352
54. Wright GL, Hanlon P, Amin K, Steenbergen C, Murphy E, Arcasoy MO. Erythropoietin receptor expression in adult rat cardiomyocytes is associated with an acute cardioprotective effect for recombinant erythropoietin during ischemia-reperfusion injury. FASEB J 2004;18:1031–1033. [PubMed: 15059965]
55. Tramontano AF, Muniyappa R, Black AD, Blendea MC, Cohen I, Deng L, Sowers JR, Cutaia MV, El-Sherif N. Erythropoietin protects cardiac myocytes from hypoxia-induced apoptosis through an Akt-dependent pathway. Biochem Biophys Res Commun 2003;308:990–994. [PubMed: 12927817]
56. Gao E, Boucher M, Chuprun JK, Zhou RH, Eckhart AD, Koch WJ. Darbepoetin alfa, a long-acting erythropoietin analog, offers novel and delayed cardioprotection for the ischemic heart. Am J Physiol Heart Circ Physiol 2007;293:H60–68. [PubMed: 17384131]
57. Calvillo L, Latini R, Kajstura J, Leri A, Anversa P, Ghezzi P, Salio M, Cerami A, Brines M. Recombinant human erythropoietin protects the myocardium from ischemia-reperfusion injury and promotes beneficial remodeling. Proc Natl Acad Sci U S A 2003;100:4802–4806. [PubMed: 12663857]
58. Toma C, Letts DP, Tanabe M, Gorcsan J III, Counihan PJ. Positive effect of darbepoetin on peri-infarction remodeling in a porcine model of myocardial ischemia-reperfusion. J Mol Cell Cardiol 2007;43:130–136. [PubMed: 17597149]
59. Schneider C, Jaquet K, Malisius R, Geidel S, Bahlmann E, Boczor S, Rau T, Antz M, Kuck KH, Krause K. Attenuation of cardiac remodelling by endocardial injection of erythropoietin: ultrasonic strain-rate imaging in a model of hibernating myocardium. Eur Heart J 2007;28:499–509. [PubMed: 17242014]
60. Prunier F, Pfister O, Hadri L, Liang L, Del Monte F, Liao R, Hajjar RJ. Delayed erythropoietin therapy reduces post-MI cardiac remodeling only at a dose that mobilizes endothelial progenitor cells. Am J Physiol Heart Circ Physiol 2007;292:H522–529. [PubMed: 16997893]
61. Abbate A, Salloum FN, Vecile E, Das A, Hoke NN, Straino S, Biondi-Zoccai GG, Houser JE, Qureshi IZ, Ownby ED, Gustini E, Biasucci LM, Severino A, Capogrossi MC, Vetrovec GW, Crea F, Baldi A, Kukreja RC, Dobrina A. Anakinra, a recombinant human interleukin-1 receptor antagonist, inhibits apoptosis in experimental acute myocardial infarction. Circulation 2008;117:2670–2683. [PubMed: 18474815]
62. Anakinra to prevent post-infarction remodeling (VCU-ART). [Accessed January 5, 2010]. Available at: http://clinicaltrials.gov/ct2/show/NCT00789724
63. Nikolaidis LA, Mankad S, Sokos GG, Miske G, Shah A, Elahi D, Shannon RP. Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. Circulation 2004;109:962–965. [PubMed: 14981009]
64. Pharmacological postconditioning to reduce infarct size following primary PCI (POSTCON II). [Accessed January 5, 2010]. Available at: http://clinicaltrials.gov/ct2/show/NCT00835848
65. Liu GS, Thornton J, Van Winkle DM, Stanley AWH, Olsson RA, Downey JM. Protection against infarction afforded by preconditioning is mediated by A1 adenosine receptors in rabbit heart. Circulation 1991;84:350–356. [PubMed: 2060105]
66. Yang X-M, Philipp S, Downey JM, Cohen MV. Postconditioning's protection is not dependent on circulating blood factors or cells but involves adenosine receptors and requires PI3-kinase and guanylyl cyclase activation. Basic Res Cardiol 2005;100:57–63. [PubMed: 15614590]
67. Kin H, Zatta AJ, Lofye MT, Amerson BS, Halkos ME, Kerendi F, Zhao Z-Q, Guyton RA, Headrick JP, Vinten-Johansen J. Postconditioning reduces infarct size via adenosine receptor activation by endogenous adenosine. Cardiovasc Res 2005;67:124–133. [PubMed: 15949476]
68. Ki J, McIntosh R, Shen X, Lee S, Chanoit G, Criswell H, Zvara DA, Xu Z. Adenosine A2a and A2b receptors work in concert to induce a strong protection against reperfusion injury in rat hearts. J Mol Cell Cardiol 2009;47:684–690. [PubMed: 19695259]

69. Mahaffey KW, Puma JA, Barbagelata NA, DiCarli MF, Leesar MA, Browne KF, Eisenberg PR, Bolli R, Casas AC, Molina-Viamonte V, Orlandi C, Blevings R, Gibbons RJ, Califf RM, Granger CB. Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction: results of a multicenter, randomized, placebo-controlled trial: the Acute Myocardial Infarction STudy of ADenosine (AMISTAD) trial. J Am Coll Cardiol 1999;34:1711–1720. [PubMed: 10577561]
70. Assali AR, Sdringola S, Ghani M, Denkats AE, Yepes A, Hanna GP, Schroth G, Fujise K, Anderson HV, Smalling RW, Rosales OR. Intracoronary adenosine administered during percutaneous intervention in acute myocardial infarction and reduction in the incidence of “no reflow” phenomenon. Catheter Cardiovasc Interv 2000;51:27–31. [PubMed: 10973014]
71. Stoel MG, Marques KM, de Cock CC, Bronzwaer JG, von BC, Zijlstra F. High dose adenosine for suboptimal myocardial reperfusion after primary PCI: a randomized placebo-controlled pilot study. Catheter Cardiovasc Interv 2008;71:283–289. [PubMed: 17985384]
72. Pasceri V, Pristipino C, Pelliccia F, Granatelli A, Speciale G, Roncella A, Pironi B, Capasso M, Richichi G. Effects of the nitric oxide donor nitroprusside on no-reflow phenomenon during coronary interventions for acute myocardial infarction. Am J Cardiol 2005;95:1358–1361. [PubMed: 15904643]
73. Wang HJ, Lo PH, Lin JJ, Lee H, Hung JS. Treatment of slow/no-reflow phenomenon with intracoronary nitroprusside injection in primary coronary intervention for acute myocardial infarction. Catheter Cardiovasc Interv 2004;63:171–176. [PubMed: 15390241]
74. Amit G, Cafri C, Yaroslavtsev S, Fuchs S, Paltiel O, Bu-Ful A, Weinstein JM, Wolak A, Ilia R, Zahger D. Intracoronary nitroprusside for the prevention of the no-reflow phenomenon after primary percutaneous coronary intervention in acute myocardial infarction. A randomized, double-blind, placebo-controlled clinical trial. Am Heart J 2006;152:814–887.
75. Barcin C, Denktas AE, Lennon RJ, Hammes L, Higano ST, Holmes DR Jr, Garratt KN, Lerman A. Comparison of combination therapy of adenosine and nitroprusside with adenosine alone in the treatment of angiographic no-reflow phenomenon. Catheter Cardiovasc Interv 2004;61:484–491. [PubMed: 15065143]
76. Lie RH, Hasenkam JM, Nielsen TT, Poulsen R, Sloth E. Post-conditioning reduces infarct size in an open-chest porcine acute ischemia-reperfusion model. Acta Anaesthesiol Scand 2008;52:1188–1193. [PubMed: 18823456]
77. Kin H, Zhao ZQ, Sun HY, Wang NP, Corvera JS, Halkos ME, Kerendi F, Guyton RA, Vinten-Johansen J. Postconditioning attenuates myocardial ischemia-reperfusion injury by inhibiting events in the early minutes of reperfusion. Cardiovasc Res 2004;62:74–85. [PubMed: 15023554]
78. Zhao ZQ, Corvera JS, Halkos ME, Kerendi F, Wang NP, Guyton RA, Vinten-Johansen J. Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. Am J Physiol Heart Circ Physiol 2003;285:H579–588. [PubMed: 12860564]
79. Laskey WK. Brief repetitive balloon occlusions enhance reperfusion during percutaneous coronary intervention for acute myocardial infarction: a pilot study. Catheter Cardiovasc Interv 2005;65:361–367. [PubMed: 15945105]
80. Staat P, Rioufol G, Piot C, Cottin Y, Cung TT, L’Huillier I, Aupetit JF, Bonnefoy E, Finet G, Andre-Fouet X, Ovize M. Postconditioning the human heart. Circulation 2005;112:2143–2148. [PubMed: 16186417]
81. Laskey WK, Yoon S, Calzada N, Ricciardi MJ. Concordant improvements in coronary flow reserve and ST-segment resolution during percutaneous coronary intervention for acute myocardial infarction: a benefit of postconditioning. Catheter Cardiovasc Interv 2008;72:212–220. [PubMed: 18546233]
82. Vinten-Johansen J, Zhao ZQ, Jiang R, Zatta AJ, Dobson GP. Preconditioning and postconditioning: innate cardioprotection from ischemia-reperfusion injury. J Appl Physiol 2007;103:1441–1448. [PubMed: 17615276]
83. Cohen MV, Yang XM, Downey JM. The pH hypothesis of postconditioning: staccato reperfusion reintroduces oxygen and perpetuates myocardial acidosis. Circulation 2007;115:1895–1903. [PubMed: 17389262]
84. Cohen MV, Yang XM, Downey JM. Acidosis, oxygen, and interference with mitochondrial permeability transition pore formation in the early minutes of reperfusion are critical to postconditioning’s success. Basic Res Cardiol 2008;103:464–471. [PubMed: 18626679]

85. Piot C, Croisille P, Staat P, Thibault H, Rioufol G, Mewton N, Elbelghiti R, Cung TT, Bonnefoy E, Angoulvant D, Macia C, Raczka F, Sportouch C, Gahide G, Finet G, Andre-Fouet X, Revel D, Kirkorian G, Monassier JP, Derumeaux G, Ovize M. Effect of cyclosporine on reperfusion injury in acute myocardial infarction. N Engl J Med 2008;359:473–481. [PubMed: 18669426]

86. Weman SM, Karhunen PJ, Penttila A, Jarvinen AA, Salminen US. Reperfusion injury associated with one-fourth of deaths after coronary artery bypass grafting. Ann Thorac Surg 2000;70:807–812. [PubMed: 11016314]

87. Moore GW, Hutchins GM. Coronary artery bypass grafts in 109 autopsied patients. Statistical analysis of graft and anastomosis patency and regional myocardial injury. JAMA 1981;246:1785–1789. [PubMed: 6974250]

88. Bulkely BH, Hutchins GM. Myocardial consequences of coronary artery bypass graft surgery. The paradox of necrosis in areas of revascularization. Circulation 1977;56:906–913. [PubMed: 303553]

89. Klatte K, Chaitman BR, Theroux P, Gavard JA, Stocke K, Boyce S, Bartels C, Keller B, Jessel A. Increased mortality after coronary artery bypass graft surgery is associated with increased levels of postoperative creatine kinase-myocardial band isoenzyme release: results from the GUARDIAN trial. J Am Coll Cardiol 2001;38:1070–1077. [PubMed: 11583884]

90. Costa MA, Carere RG, Lichtenstein SV, Foley DP, de Valk V, Lindenboom W, Roose PC, van Geldorp TR, Macaya C, Castanon JL, Fernandez-Avilez F, Gonzales JH, Heyer G, Unger F, Serruys PW. Incidence, predictors, and significance of abnormal cardiac enzyme rise in patients treated with bypass surgery in the arterial revascularization therapies study (ARTS). Circulation 2001;104:2689–2693. [PubMed: 11723020]

91. Olivencia-Yurvati AH, Blair JL, Baig M, Mallet RT. Pyruvate-enhanced cardioprotection during surgery with cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2003;17:715–720. [PubMed: 14689411]

92. Uyar I, Mansuroglu D, Kirali K, Erentug V, Bozbuga NU, Uysal G, Yakut C. Aspartate and glutamate-enriched cardioplegia in left ventricular dysfunction. J Card Surg 2005;20:337–344. [PubMed: 15985134]

93. Modi P, Suleiman MS, Reeves B, Pawade A, Parry AJ, Angelini GD, Caputo M. Myocardial metabolic changes during pediatric cardiac surgery: a randomized study of 3 cardioplegic techniques. J Thorac Cardiovasc Surg 2004;128:67–75. [PubMed: 15224023]

94. Walsh SR, Tang TY, Kullar P, Jenkins DP, Dutka DP, Gaunt ME. Ischaemic preconditioning during cardiac surgery: systematic review and meta-analysis of perioperative outcomes in randomised clinical trials. Eur J Cardiothorac Surg 2008;34:985–994. [PubMed: 18783958]

95. Fabbri A, Manfredi J, Piccin C, Soffiati G, Carta MR, Gasparotto E, Nardon G. Systemic leukocyte filtration during cardiopulmonary bypass. Perfusion 2001;16(Suppl):11–8. [PubMed: 11334202]

96. Koskenkari J, Rimpilainen J, Biancari F, Surcel HM, Kaukoranta P, Kiviluoma K, Ala-Kokko T, Juvonen T. Leukocyte depleting filter attenuates myocardial injury during elective coronary artery bypass surgery. Scand Cardiovasc J 2005;39:358–368. [PubMed: 16352489]

97. Leal-Noval SR, Amaya R, Herruzo A, Hernandez A, Ordonez A, Marin-Niebla A, Camacho P. Effects of a leukocyte depleting arterial line filter on perioperative morbidity in patients undergoing cardiac surgery: a controlled randomized trial. Ann Thorac Surg 2005;80:1394–1400. [PubMed: 16181877]

98. Liakopoulos OJ, Schmitto JD, Kazmaier S, Brauer A, Quintel M, Schoendube FA, Dorge H. Cardiopulmonary and systemic effects of methylprednisolone in patients undergoing cardiac surgery. Ann Thorac Surg 2007;84:110–8. discussion 118-119. [PubMed: 17588396]

99. Fillinger MP, Rassias AJ, Guyre PM, Sanders JH, Beach M, Pahl J, Watson RB, Whalen PK, Yeo KT, Yeager MP. Glucocorticoid effects on the inflammatory and clinical responses to cardiac surgery. J Cardiothorac Vasc Anesth 2002;16:163–169. [PubMed: 11957164]

100. Tassani P, Richter JA, Barankay A, Braun SL, Haehnel C, Spaeth P, Schad H, Meisner H. Does high-dose methylprednisolone in aprotinin-treated patients attenuate the systemic inflammatory response during coronary artery bypass grafting procedures? J Cardiothorac Vasc Anesth 1999;13:165–172. [PubMed: 10230950]

101. De Hert S, Vlasselaers D, Barbe R, Ory JP, Dekegel D, Donnadonni R, Demeere JL, Mulier J, Wouters P. A comparison of volatile and non volatile agents for cardioprotection during on-pump coronary surgery. Anaesthesia 2009;64:953–960. [PubMed: 19686479]

102. Meco M, Cirri S, Gallazzi C, Magnani G, Cosseta D. Desflurane preconditioning in coronary artery bypass graft surgery: a double-blinded, randomised and placebo-controlled study. Eur J Cardiothorac Surg 2007;32:319–325. [PubMed: 17574858]

103. Julier K, da Silva R, Garcia C, Bestmann L, Frascarolo P, Zollinger A, Chassot PG, Schmid ER, Turina MI, von Segesser LK, Pasch T, Spahn DR, Zaugg M. Preconditioning by sevoflurane decreases biochemical markers for myocardial and renal dysfunction in coronary artery bypass graft surgery: a double-blinded, placebo-controlled, multicenter study. Anesthesiology 2003;98:1315–1327. [PubMed: 12766638]

104. Verrier ED, Shernan SK, Taylor KM, Van de Werf F, Newman MF, Chen JC, Carrier M, Haverich A, Malloy KJ, Adams PX, Todaro TG, Mojcik CF, Rollins SA, Levy JH. Terminal complement blockade with pexelizumab during coronary artery bypass graft surgery requiring cardiopulmonary bypass: a randomized trial. JAMA 2004;291:2319–2327. [PubMed: 15150203]

105. Testa L, Van Gaal WJ, Bhindi R, Biondi-Zoccai GG, Abbate A, Agostoni P, Porto I, Andreotti F, Crea F, Banning AP. Pexelizumab in ischemic heart disease: a systematic review and meta-analysis on 15,196 patients. J Thorac Cardiovasc Surg 2008;136:884–893. [PubMed: 18954626]

106. Shaw AD, Stafford-Smith M, White WD, Phillips-Bute B, Swaminathan M, Milano C, Welsby IJ, Aronson S, Mathew JP, Peterson ED, Newman MF. The effect of aprotinin on outcome after coronary-artery bypass grafting. N Engl J Med 2008;358:784–793. [PubMed: 18287601]

107. Schneeweiss S, Seeger JD, Landon J, Walker AM. Aprotinin during coronary-artery bypass grafting and risk of death. N Engl J Med 2008;358:771–783. [PubMed: 18287600]

108. Fergusson DA, Hebert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, Teoh K, Duke PC, Arellano R, Blajchman MA, Bussieres JS, Cote D, Karski J, Martineau R, Robblee JA, Rodger M, Wells G, Clinch J, Pretorius R. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med 2008;358:2319–2331. [PubMed: 18480196]

109. Kandzari DE, Dery JP, Armstrong PW, Douglas DA, Zettler ME, Hidinger GK, Friesen AD, Harrington RA. MC-1 (pyridoxal 5'-phosphate): novel therapeutic applications to reduce ischaemic injury. Expert Opin Investig Drugs 2005;14:1435–1442.

110. Tardif JC, Carrier M, Kandzari DE, Emery R, Cote R, Heinonen T, Zettler M, Hasselblad V, Guertin MC, Harrington RA. Effects of pyridoxal-5'-phosphate (MC-1) in patients undergoing high-risk coronary artery bypass surgery: results of the MEND-CABG randomized study. J Thorac Cardiovasc Surg 2007;133:1604–1611. [PubMed: 17532963]

111. Alexander JH, Emery RW Jr, Carrier M, Ellis SJ, Mehta RH, Hasselblad V, Menasche P, Khalil A, Cote R, Bennett-Guerrero E, Mack MJ, Schuler G, Harrington RA, Tardif JC. Efficacy and safety of pyridoxal 5'-phosphate (MC-1) in high-risk patients undergoing coronary artery bypass graft surgery: the MEND-CABG II randomized clinical trial. JAMA 2008;299:1777–1787. [PubMed: 18381567]

112. Theroux P, Chaitman BR, Danchin N, Erhardt L, Meinertz T, Schroeder JS, Tognoni G, White HD, Willerson JT, Jessel A, Guard during ischemia against necrosis (GUARDIAN) Investigators. Inhibition of the sodium-hydrogen exchanger with cariporide to prevent myocardial infarction in high-risk ischemic situations. Main results of the GUARDIAN trial. Circulation 2000;102:3032–3038. [PubMed: 11120691]

113. Boyce SW, Bartels C, Bolli R, Chaitman B, Chen JC, Chi E, Jessel A, Kereiakes D, Knight J, Thulin L, Theroux P. Impact of sodium-hydrogen exchange inhibition by cariporide on death or myocardial infarction in high-risk CABG surgery patients: results of the CABG surgery cohort of the GUARDIAN study. J Thorac Cardiovasc Surg 2003;126:420–427. [PubMed: 12928639]

114. Mentzer RM Jr, Bartels C, Bolli R, Boyce S, Buckberg GD, Chaitman B, Haverich A, Knight J, Menasche P, Myers ML, Nicolau J, Simoons M, Thulin L, Weisel RD. Sodium-hydrogen exchange inhibition by cariporide to reduce the risk of ischemic cardiac events in patients undergoing coronary artery bypass grafting: results of the EXPEDITION study. Ann Thorac Surg 2008;85:1261–1270. [PubMed: 18355507]

115. Mullane K. Acadesine: the prototype adenosine regulating agent for reducing myocardial ischaemic injury. Cardiovasc Res 1993;27:43–47. [PubMed: 8458030]

116. Gruber HE, Hoffer ME, McAllister DR, Laikind PK, Lane TA, Schmid-Schoenbein GW, Engler RL. Increased adenosine concentration in blood from ischemic myocardium by AICA riboside. Effects on flow, granulocytes, and injury. Circulation 1989;80:1400–1411. [PubMed: 2553298]

117. Forster K, Paul I, Solenkova N, Staudt A, Cohen MV, Downey JM, Felix SB, Krieg T. NECA at reperfusion limits infarction and inhibits formation of the mitochondrial permeability transition pore by activating p70S6 kinase. Basic Res Cardiol 2006;101:319–326. [PubMed: 16604438]
118. Leung JM, Stanley T III, Mathew J, Curling P, Barash P, Salmenpera M, Reves JG, Hollenberg M, Mangano DT, SPI Research Group. An initial multicenter, randomized controlled trial on the safety and efficacy of acadesine in patients undergoing coronary artery bypass graft surgery. Anesth Analg 1994;78:420–434. [PubMed: 7818622]
119. Menasche P, Jamieson WR, Flameng W, Davies MK, Multinational Acadesine Study Group. Acadesine: a new drug that may improve myocardial protection in coronary artery bypass grafting. Results of the first international multicenter study. J Thorac Cardiovasc Surg 1995;110:1096–1106. [PubMed: 7475138]
120. Multicenter Study of Perioperative Ischemia (McSPI) Research Group. Effects of acadesine on the incidence of myocardial infarction and adverse cardiac outcomes after coronary artery bypass graft surgery. Anesthesiology 1995;83:658–673. [PubMed: 7574044]
121. Mangano DT, Miao Y, Tudor IC, Dietzel C. Post-reperfusion myocardial infarction: long-term survival improvement using adenosine regulation with acadesine. J Am Coll Cardiol 2006;48:206–214. [PubMed: 16814669]
122. Mangano DT, The Multicenter Study of Perioperative Ischemia (McSPI) Research Group. Effects of acadesine on myocardial infarction, stroke, and death following surgery. A meta-analysis of the 5 international randomized trials. JAMA 1997;277:325–332. [PubMed: 9002496]
123. The effect of acadesine on reducing cardiovascular and cerebrovascular adverse events in coronary artery bypass graft (CABG) surgery (Study P05633AM1)(RED-CABG). [Accessed January 5, 2010]. Available at: http://clinicaltrials.gov/ct2/show/NCT00872001
124. Venugoapl V, Hausenloy DJ, Ludman A, Di Salvo C, Kolvekar S, Yap J, Lawrence D, Bognolo J, Yellon DM. Remote ischaemic preconditioning reduces myocardial injury in patients undergoing cardiac surgery with cold-blood cardioplegia: a randomised controlled trial. Heart 2009;95:1567–1571. [PubMed: 19508973]
125. Faxon DP, Gibbons RJ, Chronos NA, Gurbel PA, Sheehan F, HALT-MI Investigators. The effect of blockade of the CD11/CD18 integrin receptor on infarct size in patients with acute myocardial infarction treated with direct angioplasty: the results of the HALT-MI study. J Am Coll Cardiol 2002;40:1199–1204. [PubMed: 12383565]
126. APEX AMI Investigators. Armstrong PW, Granger CB, Adams PX, Hamm C, Holmes D Jr, O'Neill WW, Todaro TG, Vahanian A, Van de Werf F. Pexelizumab for acute ST-elevation myocardial infarction in patients undergoing primary percutaneous coronary intervention: a randomized controlled trial. JAMA 2007;297:43–51. [PubMed: 17200474]
127. Zeymer U, Suryapranata H, Monassier JP, Opolski G, Davies J, Rasmanis G, Linssen G, Tebbe U, Schröder R, Tiemann R, Machnig T, Neuhaus KL, ESCAMI Investigators. The Na(+)/H(+) exchange inhibitor eniporide as an adjunct to early reperfusion therapy for acute myocardial infarction. Results of the evaluation of the safety and cardioprotective effects of eniporide in acute myocardial infarction (ESCAMI) trial. J Am Coll Cardiol 2001;38:1644–1650. [PubMed: 11704395]
128. Boden WE, van Gilst WH, Scheldewaert RG, Starkey IR, Carlier MF, Julian DG, Whitehead A, Bertrand ME, Col JJ, Pedersen OL, Lie KI, Santoni JP, Fox KM. Diltiazem in acute myocardial infarction treated with thrombolytic agents: a randomised placebo-controlled trial. Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis post-Thrombolysis (INTERCEPT). Lancet 2000;355:1751–6. [PubMed: 10832825]
129. Umemura S, Nakamura S, Sugiura T, Tsuka Y, Fujitaka K, Yoshida S, Baden M, Iwasaka T. The effect of verapamil on the restoration of myocardial perfusion and functional recovery in patients with angiographic no-reflow after primary percutaneous coronary intervention. Nucl Med Commun 2006;27:247–254. [PubMed: 16479244]
130. Vijayalakshmi K, Whittaker VJ, Kunadian B, Graham J, Wright RA, Hall JA, Sutton A, de Belder MA. Prospective, randomised, controlled trial to study the effect of intracoronary injection of verapamil and adenosine on coronary blood flow during percutaneous coronary intervention in patients with acute coronary syndromes. Heart 2006;92:1278–84. [PubMed: 16449518]

131. Guan W, Osanai T, Kamada T, Hanada H, Ishizaka H, Onodera H, Iwasa A, Fujita N, Kudo S, Ohkubo T, Okumura K. Effect of allopurinol pretreatment on free radical generation after primary coronary angioplasty for acute myocardial infarction. J Cardiovasc Pharmacol 2003;41:699–705. [PubMed: 12717099]

132. Ishii H, Ichimiya S, Kanashiro M, Amano T, Imai K, Murohara T, Matsubara T. Impact of a single intravenous administration of nicorandil before reperfusion in patients with ST-segment-elevation myocardial infarction. Circulation 2005;112:1284–8. [PubMed: 16116055]

133. Guffin AV, Kates RA, Holbrook GW, Jones EL, Kaplan JA. Verapamil and myocardial preservation in patients undergoing coronary artery bypass surgery. Ann Thorac Surg 1986;41:587–91. [PubMed: 3487296]

134. Weinstein GS, Rao PS, Tyras DH. Reduction of myocardial injury with verapamil before aortic cross-clamping. Ann Thorac Surg 1990;49(3):419–23. [PubMed: 2310248]

135. Seitelberger R, Hannes W, Gleichauf M, Keilich M, Christoph M, Fasol R. Effects of diltiazem on perioperative ischemia, arrhythmias, and myocardial function in patients undergoing elective coronary bypass grafting. J Thorac Cardiovasc Surg 1994;107:811–21. [PubMed: 8127110]

Table 1
Pathophysiologic Mechanisms of Myocardial I/R Injury

- Ion accumulation
  - Intracellular calcium overload
  - Increased intracellular sodium
  - Drop in pH with rapid normalization upon reperfusion
- Dissipation of mitochondrial membrane potential
  - Mitochondrial permeability transition pore (mPTP)
- Free radical formation/reactive oxygen species (ROS)
  - Generation from Xanthine oxidase
  - Release of reactive mitochondrial intermediates
  - Neutrophil infiltration
  - ROS-induced ROS
- Dysregulated nitric oxide (NO) metabolism
  - Loss of NO-vasodilation
  - Accumulation of reactive peroxynitrite
- Apoptosis and autophagy
- Endothelial dysfunction
  - Cytokine and chemokine signaling
  - Expression of cellular adhesion markers
  - Impaired vasodilation
- Platelet aggregation and microembolization
- Immune activation
  - Innate immunity (e.g. complement activation, expression of Toll-like receptors)
  - Neutrophil accumulation
  - Cell-mediated damage (macrophage and T-cell)

Table 2

Some notable therapeutic interventions which have been used (with variable success) to mitigate I/R injury in acute MI and CABG

Acute MI

- Anti-inflammatory
  - Inhibition of leukocyte accumulation, e.g. anti-CD11/CD18[125]
  - Complement inhibition, e.g. pexelizumab[126]
- Increasing local adenosine concentrations
  - Systemic infusions[69]
  - Intracoronary bolus dose[70,71]
- Inhibition of mPTP
  - Cyclosporine[85]
- Ischemic post-conditioning
  - Repetitive balloon inflations[79-81]
- Nitric oxide metabolism
  - Nitroprusside[72-75]
- Prevention of intracellular calcium overload
  - Inhibition of Na^+-H^+ exchange, e.g. cariporide,[112] eniporide[127]
  - Calcium channel blockers[128-130]
- Reducing ROS
  - Inhibition of xanthine oxidase, e.g. allopurinol[131]
- Vasodilation
  - Potassium-channel opening, e.g. nicorandil[132]

Cardiac Surgery

- Metabolic additives in cardioplegic solutions
  - Pyruvate[91]
  - Amino acids[92,93]
- Ischemic pre-conditioning
  - Remote pre-conditioning[124]
  - Repetitive aortic cross-clamping[94]
- Volatile anesthetics[101-103]
- Anti-inflammatory
  - Leukocyte filters[95-97]
  - Steroids[98-100]
  - Complement inhibition[104,105]
- Prevention of intracellular calcium-overload
  - Pyridoxal-5′-phosphate (MC-1) [110,111]
  - Calcium-channel blockers[133-135]

- Inhibition of Na^+-H^+ exchange, e.g. cariporide[113,114]

- Increase local adenosine levels
  - Acadesine[118-122]