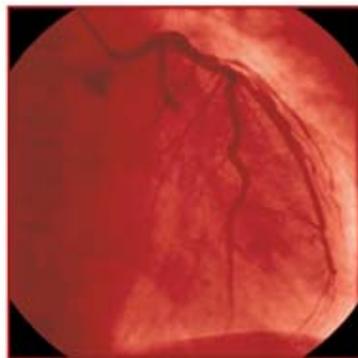


Heart and Metabolism

Number 54 - 2012

Cardiac protection
in acute cardiac syndrome



54

 Springer

EDITORIAL	3
Cardiac protection in acute cardiac syndrome <i>M. Marzilli</i>	
BASIC ARTICLE	5
Magnitude and relevance of reperfusion injury <i>D. J. Hausenloy</i>	
MAIN CLINICAL ARTICLE	9
Pharmacological cardiac protection <i>E. Orsini, M. Marzilli, D. Morrone, P. Capozza, A. Huqi, F. L. Dini, and G. Guarini</i>	
METABOLIC IMAGING	15
Magnetic resonance imaging of the microcirculation in acute coronary syndromes <i>K. De Silva, J. Baker, A. Kidambi, D. Perera and S. Plein</i>	
NEW THERAPEUTIC APPROACHES	20
Postconditioning <i>M. Marzilli, D. Morrone and G. Guarini</i>	
FOCUS ON Vastarel® MR	25
Metabolic cardiac protection <i>G. Guarini</i>	
CASE REPORT	29
Myocardial infarction with contemporary bivasal occlusion: one case, two fates <i>P. Capozza and M. Marzilli</i>	
REFRESHER CORNER	33
Myocytes versus endothelial damage <i>F. L. Dini, E. Orsini, M. Marzilli and G. Guarini</i>	
HOT TOPICS	37
The heart failure and obesity paradox: would you suggest your patients gain weight? <i>A. Huqi</i>	
GLOSSARY	39
<i>G. D. Lopaschuk</i>	



Cardiac protection in acute cardiac syndrome

Mario Marzilli, Cardiac and Thoracic Department, University of Pisa, Pisa, Italy

Correspondence: Professor Mario Marzilli, c/o Dipartimento Cardiotoracico,
Via Paradisa 2, 56100 Pisa, Italy.

Tel: +39 050 996751; fax: +39 050 577239; mobile: þ39 328 729 1353
e-mail: marzilli@med.unipi.it

Editorial

Decades ago, coronary artery occlusion by thrombus formation at the site of a vulnerable atherosclerotic plaque was identified as the precipitating mechanism of acute coronary syndromes. Since then, great efforts have been made in order to design and test strategies for the recanalization of occluded coronary arteries as a strategy to limit infarct size and improve clinical outcomes. Today, over 95% of occluded vessels can be easily reopened in the setting of STEMI. Unfortunately, the clinical impact of these interventions falls short of expectations.

The reduction in mortality, though statistically significant, is of minor entity in absolute terms and limited to patients treated early at tertiary referral centre. From a population point of view, mortality for AMI is still dramatically high, and a large fraction of patients surviving the acute phase is bound to develop heart failure.

Several factors contribute to these disappointing results, including incomplete understanding of the time course of myocardial cell death and underestimation of the contribution of reperfusion injury to final infarct size.

In this issue of *Heart and Metabolism*, experts in ischemia-reperfusion injury, many from my own center, elucidate the mechanisms of ischemic cell death, describe the time course of cellular damage, and discuss the impact of reperfusion on cells previously exposed to ischemia.

The message that can be extrapolated from these contributions is a complex one:

1. Ischemic damage is a time-dependent phenomenon that is completed in a few hours after the occlusion of a coronary vessel. Survival of ischemic tissue may be prolonged by previous exposure to ischemia, or by other interventions, but is certainly shorter than the 12 hours currently accepted as the time limit for primary PCI.
2. Reperfusion injury adds to ischemic injury, but this has appreciable clinical consequences only if flow is re-established when a sizable amount of myocardium is still viable, that is very early, possibly within 2 hours. If flow is re-established later, when the ischemic cell death is completed, reperfusion injury will not impact on final infarct size.
3. Reperfusion injury is triggered by a burst of oxygen free radicals that peaks at 2–5 minutes after restoring flow. Therefore protective agents, to be effective, must be delivered to the target area before restoring flow. •

Magnitude and relevance of reperfusion injury

Derek J. Hausenloy, The Hatter Cardiovascular Institute, University College London, London, United Kingdom.

Correspondence: Derek J Hausenloy, The Hatter Cardiovascular Institute, University College London, 67 Chenies Mews, London, WC1E 6HX, UK.
Tel: +44 203 447 9888 ; Fax: +44 203 447 9505, e-mail: d.hausenloy@ucl.ac.uk

Abstract

Ischemic heart disease (IHD) is the leading cause of death and disability worldwide. For patients presenting with an acute ST-segment elevation myocardial infarction (STEMI, the major cause of which is an acute thrombotic coronary arterial occlusion), the most effective therapeutic strategy for limiting myocardial infarct (MI) size, preserving left ventricular systolic function and improving clinical outcomes, is by timely myocardial reperfusion using primary percutaneous coronary intervention (PPCI) to remove the obstruction. However, restoring blood flow in the infarct-related coronary artery comes at a price, as the process of myocardial reperfusion can in itself paradoxically inflict further injury to the myocardium—a phenomenon which has been termed “myocardial reperfusion injury.” Myocardial reperfusion injury results in myocardial stunning, reperfusion arrhythmias, microvascular obstruction and cardiomyocyte death, and its presence contributes up to 50% of the final MI size. Although the process of myocardial reperfusion by PPCI continues to be improved with recent advances in PCI technology, anti-platelet and anti-thrombotic therapy, there currently exist no effective therapy for preventing myocardial reperfusion injury. Therefore, novel therapeutic interventions, which are capable of reducing myocardial reperfusion injury, are needed to further reduce MI size, prevent the onset of heart failure and improve clinical outcomes in STEMI patients undergoing PPCI. In this article, a brief overview of myocardial reperfusion injury will be provided with special emphasis on its magnitude and relevance to clinical cardiology practice today.

Keywords: myocardial reperfusion injury; primary percutaneous coronary intervention (PPCI); ST-segment elevation myocardial infarction (STEMI)

■ Heart Metab. (2012) 54:5–8

Introduction

Ischemic heart disease (IHD) is the leading cause of death and disability worldwide. The major manifestation of IHD is an acute ST-segment elevation myocardial infarction (STEMI), which is precipitated by the rupture of an unstable atherosclerotic plaque within the coronary artery and the formation of an acute thrombus resulting in complete occlusion and acute myocardial ischemia. For these patients, timely and effective myocardial reperfusion by primary percutaneous coronary intervention (PPCI) is the treatment of choice for limiting myocardial infarct (MI) size, preserving left ventricular (LV) systolic function and improving clinical outcomes. Paradoxically, the process of myocardial reperfusion is a “double-edge sword” [1] and comes at a price, as it can in itself paradoxically inflict further injury to the myocardium—a phenomenon

which has been termed “myocardial reperfusion injury” [1,2]. Although, the process of myocardial reperfusion continues to be optimized with recent advances in PCI technology, anti-platelet and anti-thrombotic therapy, there is currently no effective therapy for reducing myocardial reperfusion injury. Therefore, novel therapeutic interventions, which are capable of preventing myocardial reperfusion injury and which can be administered as adjunctive therapy to PPCI, are needed to improve clinical outcomes in STEMI patients undergoing IHD.

Myocardial reperfusion injury

Over 50 years ago, Jennings et al. [3] first documented in the canine heart, the histological changes which occurred on reperfusing ischemic myocardium. These comprised contracture of myofibrils, disruption of the sarcolemma, and the appearance of intramitochondrial calcium phosphate particles, features which appeared within minutes of myocardial reperfusion and which differed from those induced by myocardial ischemia alone, confirming myocardial reperfusion injury as a distinct pathological entity. However, the significance of these pathological findings only become apparent in the 1980s and 1990s when myocardial reperfusion by thrombolytic therapy and primary PCI was introduced as a therapy for STEMI patients. Clearly, myocardial reperfusion was shown to be essential for myocardial salvage but it soon emerged that the presence of myocardial reperfusion injury diminished the benefits of thrombolysis and PPCI in terms of MI size limitation. The effects of myocardial reperfusion injury include myocardial stunning (a term which describes the “mechanical dysfunction that persists after reperfusion despite the absence of irreversible damage and despite restoration of normal or near-normal coronary flow” and reperfusion arrhythmias, both of which are reversible and are easily managed in the clinical setting) [1,2]. This article will focus on the more serious and irreversible consequences of myocardial reperfusion injury, which are microvascular obstruction and lethal myocardial reperfusion injury.

Microvascular obstruction

Microvascular obstruction (MVO) was first described in 1966 by Krug et al. [4] in the feline heart as the “inability to reperfuse a previously ischemic region.” Its ultrastructural features were later characterized in the

reperfused canine heart by Kloner et al in 1974 [5]. Despite intensive research, the actual cause of the no-reflow phenomenon remains unclear although the major contributory factors are thought to include capillary damage with impaired vasodilatation, external capillary compression by endothelial cell and cardiomyocyte swelling, micro-embolization of friable material released from the atherosclerotic plaque, platelet micro-thrombi, and neutrophil plugging [5,6]. In reperfused STEMI patients it has been reported that the development of the coronary no-reflow phenomenon, the angiographic manifestation of MVO, is determined by several factors which include the extent of myocardial injury [7], the size of the myocardium at risk of infarction [7], the patency of the infarct-related artery [7], the presence of thrombus [8] or a large lipid pool [9] in the culprit lesion. The presence of coronary no-reflow at the time of PPCI is often treated with intracoronary adenosine or nitrates, although the efficacy of these therapeutic agents is unclear. Importantly, up to 60% of STEMI patients with normal coronary flow (TIMI 3) post-PPCI may still have evidence of MVO on cardiac MRI, the presence of which has been associated with a greater MI size, worse LV ejection fraction, adverse LV remodeling, and worse short-term and long-term clinical outcomes [10,11]. Therefore, a large proportion of STEMI patients undergoing may benefit from being administered at the time of PPCI, a therapeutic intervention capable of reducing the incidence and extent of MVO.

Lethal myocardial reperfusion injury

The existence of lethal myocardial reperfusion injury as a distinct entity, which is capable of independently inducing cardiomyocyte death following a sustained episode of myocardial ischemia, has been hotly debated over the years [1,2,12,13]. Part of the problem has been the inability to directly demonstrate that the actual process of reperfusion induces the death of cardiomyocytes, which were viable at the end of the ischemic episode. Indirect evidence for the existence of myocardial reperfusion injury has been provided by the large number of pre-clinical animal studies demonstrating 40–50% reductions in MI size with therapeutic interventions applied at the onset of myocardial reperfusion. This data would suggest that myocardial reperfusion injury may account for 40–50% of the final MI size [2]. The pathophysiology of lethal myocardial

reperfusion injury is closely related to the abrupt effects of myocardial reperfusion on mitochondrial function: the re-energization of the electron transport chain, the production of oxidative stress, mitochondrial calcium and phosphate overload, the rapid restoration of physiological pH, and the opening of the mitochondrial permeability transition pore (mPTP), a critical mediator of cardiomyocyte death in reperfused hearts [14-16].

Clinical relevance of myocardial reperfusion injury

Among many clinical cardiologists, the idea that myocardial reperfusion by thrombolysis or PPCI, which is essential for myocardial salvage in STEMI patients, may actually have detrimental effects on the heart appears implausible. After all, restoring coronary blood flow and maintaining the patency of the infarct-related artery are the major priorities of therapeutic myocardial reperfusion. The evidence that lethal myocardial reperfusion injury exists in man and may actually be relevant to the clinical setting has been recently provided in a small landmark proof-of-concept clinical study published in 2005 by Staat et al. [17]. These authors demonstrated that a therapeutic intervention applied to STEMI patients at the time of PPCI could reduce MI size by 38% (measured by 72 hour area under the curve total CK) [17]. The therapeutic intervention, ischemic postconditioning (IPost), which had been demonstrated in pre-clinical animal studies to reduce lethal myocardial reperfusion injury [18], comprised the interruption of coronary blood flow with four-1 min low-pressure angioplasty balloon inflations/deflations within the infarct-related artery [17]. Subsequent clinical studies have confirmed the beneficial effects of IPost using myocardial nuclear scanning, echocardiography, and cardiac MRI [19,20]. Taken together these clinical cardioprotection studies suggest that in STEMI patients undergoing PPCI, about 40–50% of the final MI is due to lethal myocardial reperfusion injury. Therefore, by applying a therapeutic intervention to prevent lethal myocardial reperfusion injury in STEMI patients at the time of PPCI may result in a further 40–50% reduction in MI size.

Myocardial reperfusion injury as a therapeutic target

Until the discovery of IPost, the translation of a large number of therapeutic interventions proven to be cardioprotective in the pre-clinical animal setting, have failed in the clinical setting. The reasons for this are

many and have been the topic of recent discussion and some of these problems may be overcome in the future with more rigorous testing of novel cardioprotective interventions in the pre-clinical setting and more careful design of the clinical studies [21-23]. However, there are a number of promising therapeutic interventions for reducing myocardial reperfusion injury in the clinical setting including cyclosporin A (an mPTP inhibitor) [24], exenatide (a glucagon-like protein 1 agonist) [25], and remote ischemic preconditioning (four-5 min cycles of upper limb ischemia/reperfusion induced by cuff inflation/deflation) [26], which have been demonstrated in proof-of-concept clinical studies to reduce MI size in STEMI patients when administered prior to PPCI. Large multicenter clinical trials are now required to determine whether preventing lethal myocardial reperfusion injury can improve clinical outcomes in STEMI patients treated with PPCI.

Conclusion

Myocardial reperfusion by PPCI is the treatment of choice for salvaging viable myocardium in patients presenting with a STEMI. However, the full benefits of myocardial reperfusion, in terms of myocardial salvage, are diminished due to the presence of myocardial reperfusion injury, which contributes up to 50% of the final MI size, and for which there currently exists no effective therapy. Therefore, the discovery of novel therapeutic interventions which are able to prevent myocardial reperfusion injury in STEMI patients undergoing PPCI, may allow us to realize the full benefits of myocardial reperfusion with further reductions in MI size, preserved LV systolic function and improved clinical outcomes. •

References

1. Braunwald E, Kloner RA (1985) Myocardial reperfusion: a double-edged sword? *J Clin Invest* 76:1713–1719
2. Yellon DM, Hausenloy DJ (2007) Myocardial reperfusion injury. *N Engl J Med* 357:1121–1135
3. Jennings R, Sommers H, Smyth G, Lack H, Linn H (1960) Myocardial necrosis induced by temporary occlusion of a coronary artery in the dog. *Arch Pathol* 70:68–78
4. Krug A, Du Mesnil dR, Korb G (1966) Blood supply of the myocardium after temporary coronary occlusion. *Circ Res* 19:57–62
5. Kloner RA, Ganote CE, Jennings RB (1974) The “no-reflow” phenomenon after temporary coronary occlusion in the dog. *J Clin Invest* 54:1496–1508

6. Ito H (2006) No-reflow phenomenon and prognosis in patients with acute myocardial infarction. *Nat Clin Pract Cardiovasc Med* 3:499–506
7. Iwakura K, Ito H, Kawano S, Shintani Y, Yamamoto K, Kato A et al (2001) Predictive factors for development of the no-reflow phenomenon in patients with reperfused anterior wall acute myocardial infarction. *J Am Coll Cardiol* 38:472–477
8. Yip HK, Chen MC, Chang HW, Hang CL, Hsieh YK, Fang CY et al (2002) Angiographic morphologic features of infarct-related arteries and timely reperfusion in acute myocardial infarction: predictors of slow-flow and no-reflow phenomenon. *Chest* 122:1322–1332
9. Tanaka A, Kawarabayashi T, Nishibori Y, Sano T, Nishida Y, Fukuda D et al (2002) No-reflow phenomenon and lesion morphology in patients with acute myocardial infarction. *Circulation* 105:2148–2152
10. Gerber BL, Rochitte CE, Melin JA, McVeigh ER, Bluemke DA, Wu KC et al (2000) Microvascular obstruction and left ventricular remodeling early after acute myocardial infarction. *Circulation* 101:2734–2741
11. Kramer CM (2005) The prognostic significance of microvascular obstruction after myocardial infarction as defined by cardiovascular magnetic resonance. *Eur Heart J* 26:532–533
12. Kloner RA (1993) Does reperfusion injury exist in humans? *J Am Coll Cardiol* 21:537–545
13. Piper HM, Garcia-Dorado D, Ovize M (1998) A fresh look at reperfusion injury. *Cardiovasc Res* 38:291–300
14. Crompton M, Costi A, Hayat L (1987) Evidence for the presence of a reversible Ca²⁺-dependent pore activated by oxidative stress in heart mitochondria. *Biochem J* 245:915–918
15. Hausenloy DJ, Yellon DM (2003) The mitochondrial permeability transition pore: its fundamental role in mediating cell death during ischaemia and reperfusion. *J Mol Cell Cardiol* 35:339–341
16. Halestrap AP (2009) Mitochondria and reperfusion injury of the heart—a holey death but not beyond salvation. *J Bioenerg Biomembr* 41:113–121
17. Staat P, Rioufol G, Piot C, Cottin Y, Cung TT, L'Huilier I et al (2005) Postconditioning the human heart. *Circulation* 112:2143–2148
18. Zhao ZQ, Corvera JS, Halkos ME, Kerendi F, Wang NP, Guyton RA et al (2003) Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. *Am J Physiol Heart Circ Physiol* 285:H579–H588
19. Thibault H, Piot C, Staat P, Bontemps L, Sportouch C, Rioufol G et al (2008) Long-term benefit of postconditioning. *Circulation* 117:1037–1044
20. Lonborg J, Kelbaek H, Vejstrup N, Jorgensen E, Helqvist S, Saunamaki K et al (2010) Cardioprotective effects of ischemic postconditioning in patients treated with primary percutaneous coronary intervention, evaluated by magnetic resonance. *Circ Cardiovasc Interv* 3:34–41
21. Ludman AJ, Yellon DM, Hausenloy DJ (2010) Cardiac preconditioning for ischaemia: lost in translation. *Dis Model Mech* 3:35–38
22. Hausenloy DJ, Baxter G, Bell R, Botker HE, Davidson SM, Downey J et al (2010) Translating novel strategies for cardioprotection: the Hatter Workshop Recommendations. *Basic Res Cardiol* 105:677–686
23. Schwartz LL, Kloner RA, Arai AE, Baines CP, Bolli R, Braunwald E et al (2011) New horizons in cardioprotection: recommendations from the 2010 national heart, lung, and blood institute workshop. *Circulation* 124:1172–1179
24. Piot C, Croisille P, Staat P, Thibault H, Rioufol G, Mewton N et al (2008) Effect of cyclosporine on reperfusion injury in acute myocardial infarction. *N Engl J Med* 359:473–481
25. Lonborg J, Vejstrup N, Kelion AD, Botker HE, Kim W, Mathiasen A et al (2011) Exenatide reduces Reperfusion Injury in Patients with ST-Segment Elevation Myocardial Infarction. *Eur Heart J* doi: 10.1093/eurheartj/ehr309.
26. Botker HE, Kharbanda R, Schmidt MR, Bottcher M, Kalltoft AK, Terkelsen CJ et al (2010) Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. *Lancet* 375:727–734

Pharmacological cardiac protection

Enrico Orsini, Mario Marzilli, Doralisa Morrone, Paola Capozza, Alda Huqi, Frank L. Dini and Giacinta Guarini, Cardiovascular Medicine Division, Cardio Thoracic and Vascular Department, University of Pisa, Italy

Correspondence: Giacinta Guarini, Cardiovascular Medicine Division, Cardio Thoracic and Vascular Department, University of Pisa, Via Paradisa, 2, 56100 Pisa, Italy.

Tel.: +393494544161, e-mail: giacinta_guarini@yahoo.it

Abstract

Pharmacological agents administered right at the onset of reperfusion, have the potential to reduce the impact of ischemia reperfusion injury (IRI), and have been proposed as possible strategies to induce cardioprotection (CP) in patients presenting with acute coronary syndromes. Treatment with these agents, mimicking preconditioning, can be instituted at the time of reperfusion obtained by successful coronary angioplasty. In the last two decades, growing body of evidences have elucidated the mechanisms involved in IRI and CP, while several animal and clinical studies have tested different drugs with putative role in CP. In this article we describe first the pathway involved in IRI and in CP; subsequently, while focusing on adenosine, we briefly review other pharmacological agents proposed to induce cardioprotection.

Keywords: ischemia-reperfusion injury; cardioprotection; preconditioning; postconditioning; mitochondrial permeability transition pore; adenosine

■ Heart Metab. (2012) 54:9–14

Introduction

Coronary artery disease accounts for more than 50% of cardiovascular events, and has a significant impact on the global economics as a leading cause of disability and loss of productivity. Acute myocardial infarctions, as well as procedures such as percutaneous coronary interventions (PCI) or cardiac surgeries are associated with ischemia and subsequent ischemia-reperfusion injury (IRI). A systematic study by Reimer et al. [1] confirmed that necrosis progressed in a “wavefront” pattern related to the duration of ischemia, which firmly established the concept that myocardium could be salvaged by initiating reperfusion as early as possible. Jennings et al [2] subsequently recognized and first introduced the concept of IRI. They described significant morphological alterations that appear after the onset of reperfusion, including cardiomyocytes swelling, mitochondrial clarification, amorphous/flocculent densities representing calcium phosphate deposits, hypercontracture, and loss of sarcomere organization. The existence of lethal reperfusion injury is strongly supported by evidence of reduced infarct size achieved by interventions when applied at the onset of reperfusion. Lethal reperfusion injury occurs only after severe ischemic injury and does not take place after fully reversible ischemic episodes. Reperfusion initiates a cascade of events within the first minutes after restoration of flow, and causes injury in a relatively short time (Fig. 1). The mechanisms of IRI have been under intense investigation for several decades, and have been reviewed elsewhere in this issue. Numerous agents and mechanical interventions have demonstrated significant infarct size reduction in experimental studies. Decreasing the burden of ischemia-reperfusion

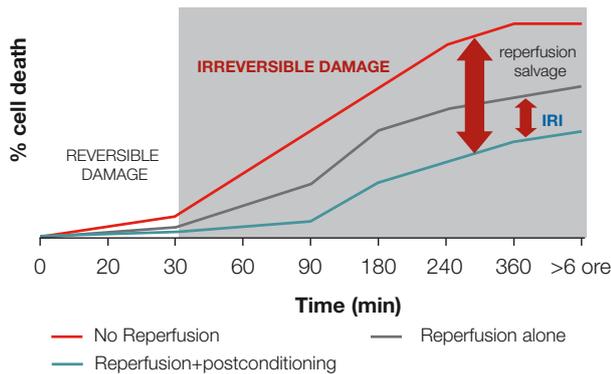


Fig. 1 The concept of lethal reperfusion injury. During ischemia, irreversible cell injury leading to cell death occurs within the ischemic risk zone in a time-dependent manner. In the absence of reperfusion, ischemic injury would progressively, eventually accounting for near total cell death (red line). Reperfusion halts the process of ischemic cell death but in its early stages imposes injury that results in further cell death, beyond that due to the ischemic period: this is lethal reperfusion injury. The net result, however, is that the reperfused tissue sustains less cell death than would occur in ischemic tissue without reperfusion. Hence, targeting cell death due to reperfusion has the potential to maximize cell salvage. Postconditioning applied at the onset of reperfusion limits the extent of reperfusion injury and maximizes reperfusion salvage. The beneficial effects of reperfusion and of adjunctive cardioprotective strategies decrease with longer ischemic time.

injury is a focus of continued research, and it seems that conditioning the heart may become a promising approach that could translate into clinical practice in the near future.

Ischemia reperfusion injury and the role of mPTP

Mitochondria play a crucial role in cell life and death. They provide cells with ATP produced via oxidative phosphorylation under physiological conditions, and initiate cell death through both apoptosis and necrosis in response to severe stress. Oxidative stress accompanied by calcium overload and ATP depletion induces the formation of pathological, non-specific mitochondrial permeability transition pores (mPTP) in the inner mitochondrial membrane. Opening of the mPTP with a high conductance results in matrix swelling ultimately inducing rupture of the mitochondrial outer membrane and releasing pro-apoptotic proteins into the cytoplasm. Cardiac cells undergoing ischemia followed by reperfusion possess exactly the same conditions mentioned above to induce mPTP opening. Due to its critical role in cell death, inhibition of mPTP opening has been accepted as a promising therapeutic approach to protect the heart against IRI. Indeed

emerging studies suggest that cardioprotection (CP) elicited by both ischemic preconditioning and postconditioning may be mediated through the modulation of the mPTP, whose opening uncouple oxidative phosphorylation and induce mitochondrial swelling. Both ischemic preconditioning and postconditioning, and pharmacological preconditioning have been demonstrated to confer cardioprotection in part through the inhibition of the mPTP.

Cardioprotection

The concept of cardioprotection refers to a variety of pharmacological agents or non-pharmacological strategies that applied before or after prolonged ischemia have been shown to reduce the negative impact of ischemia and attenuate the effect of reperfusion injury on the ischemic myocardium. Short episodes of ischemia before the onset of sustained ischemia produce ischemic preconditioning (IPreC). Intermittent reperfusion with repetitive episodes of recurrent ischemia is termed ischemic postconditioning (IPostC). Transient ischemia in a remote organ, which prevents ischemia-reperfusion injury in the heart at distance, is known as remote ischemic conditioning (RPostC). Administration of pharmacological agents able to activate those signaling pathways thought to be involved in cardioprotection is known as pharmacological conditioning. These interventions involve a complex and incompletely understood network of molecular triggering and signaling pathways. Agonist that have shown to provide CP *in vivo* and *in vitro* models (Fig. 2) include adenosine, opioids, nitric oxide, bradykinin, tumor necrosis factor- α , brain natriuretic peptides, and interleukin-6. Putative signaling pathways include opening of sarcolemmal and/or mitochondrial adenosine triphosphate-dependent potassium channels and activation of prosurvival kinases (Akt and ERK-1/2), protein kinase C and G, hypoxia-inducible factor-1, endothelial nitric oxide synthase, and the recently described survivor activating factor enhancement (SAFE) pathway. Blockade of the mPTP is considered a final common pathway. Pharmacological pre and postconditioning may be achieved by administration of agents that activate these cytoprotective pathways (Fig. 3). This review will discuss briefly on pharmacological agents able to induce cardioprotection, focusing most on the role of adenosine.

Adenosine (A1-A3), catecholamines (alfa1), bradikynine (B2), acetylcholine (M2), angiotensin (AT-1), opioids (δ) and others mediators



Inhibition of mPTP opening, activation of mKATP channels, Reduced ROS generation and enhanced glucose oxidation

Cardioprotection from IRI

Fig. 2 Triggers, mediators, and end-effectors proposed to play a role in the mechanism of pre- and post-conditioning. catechol. catecholamine; MAP mitogen-activated protein.

Adenosine in preconditioning and post conditioning

A number of locally acting mediators of cardioprotection, acting in an autocrine–paracrine fashion, have been identified. The best-characterized autacoid that can trigger CP by receptor-mediated mechanisms is adenosine. Downey et al. [3] opened the door to the investigation on mechanisms of preconditioning with a report showing that protection by ischemic preconditioning was abolished by the inhibition of the adenosine receptor before sustained ischemia in vivo. This suggested that adenosine was a trigger of ischemic preconditioning. However, they later reported a conflicting result in vitro. In this study, preischemic treatment with either adenosine or selective adenosine-A1 receptor agonist, 2-chloro-N6-cyclopentyladenosine, exerted minimal protection [4], implying that adenosine was not a candidate for pharmacological preconditioning. This inconsistency was overcome by later reports from other groups showing successful pharmacological preconditioning with selective adenosine-A1 receptor agonists, 2-chloro- N6 cyclopentyladenosine or R-phenylisopropyladenosine, strongly supporting a major role for adenosine receptor activation in ischemic preconditioning [5,6]. In conjunction with other receptors, various membrane adenosine receptors are thought to play an important role in the transduction of extracellular signals, leading to protection by preconditioning, lasting 1–3 hr. Adenosine A1- and A3-receptors mediate inhibition of adenylate cyclase

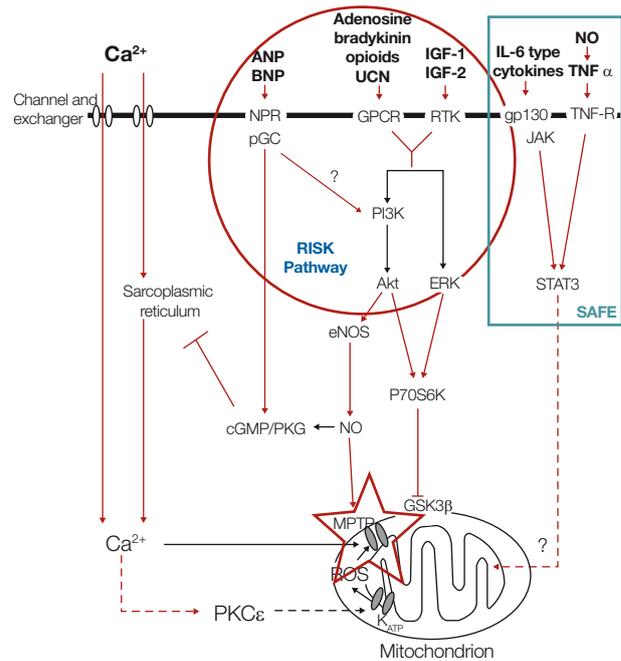


Fig. 3 Proposed mechanisms and effectors involved in cardioprotection. Adenosine, bradykinin, opioid peptides, and other autacoids natriuretic peptides (ANP and BNP), peptide growth factors (IGF-1 and FGF-2), and TNF-alpha could play a role in induce conditioning (pre and/or postconditioning). After binding to cell surface receptors, these autacoids promote the activation of kinase signaling pathways. Evidence from some models implicates the activation of PI3K/Akt and p42/p44 ERKs. This pathway, known as the RISK pathway, is proposed to result in inhibition of mPTP opening at reperfusion, via distal components of the cascade which include NO and inhibition of GSK3 β . Furthermore, it has been proposed that the activation of an intramitochondrial pool of PKC1 might cause opening of the mitochondrial KATP channel (mitoKATP), resulting in a slight increase in reactive oxygen species (ROS) formation which eventually causes mPTP inhibition. An alternative pathway, the so-called SAFE pathway, has been proposed to play a role in ischemic postconditioning. The major components of the SAFE pathway are TNF-a, the kinase JAK, which phosphorylates the transcription factor STAT3. It is proposed that after translocation to the nucleus, STAT3 controls the transcription of factors that confer cardioprotection. Also a mitochondrial localization of STAT3 has been suggested; however, both actions of STAT3 need to be finally proven. eNOS endothelial nitric oxide synthase; GPCR G-protein coupled receptor; GSK3 β glycogen synthase kinase-3 β ; MPTP mitochondrial permeability transition pore; ERK, p42/p44 extracellular regulated kinase; NPR natriuretic peptide receptor; pGC particulate guanylyl cyclase; PKG cGMP-dependent protein kinase; RTK receptor tyrosine kinase; SR sarcoplasmic reticulum; TNF-R TNF receptor. A question mark (?) indicates that the link between those two pathways is not completely understood. Adapted from [30].

via a guanine nucleotide binding inhibitory protein (Gi/o). A2-receptors couple to a comparable stimulatory protein (Gs). Adenosine receptors are found in many tissues, including the heart. A1-receptors are located

on cardiomyocytes and vascular smooth muscle cells, A₂-receptors on endothelial and vascular smooth muscle cells, and A₃-receptors on ventricular myocytes. Ischemic preconditioning by endogenous adenosine takes place through A₁- and A₃-receptors. A_{2A/B}-receptor activation results in vasodilation. Signals from different receptors converge at PKC, reaching a threshold activation of the kinase necessary to induce protection. Tyrosine and mitogen-activated protein kinases may play a role in addition to PKC. However, this hypothesis has been questioned by some studies and reports that have failed to show that preconditioning-induced cardioprotection was associated with an increase in the intramyocardial level of adenosine. Possible reasons for these observations might be due to the sensitivity of the method used for adenosine measurement and, the extremely short biological half-life of adenosine. Conversely, the adenosine hypothesis has been supported by the observation that cardioprotection could be restored by the addition of exogenous adenosine or by extending its biological half-life by either a coadministration with dipyridamole to delay clearance through intracellular uptake [7] or a sustained targeting release using a liposomal envelope [8].

Given the role of adenosine to induce preconditioning, it is logical to assume that administration of adenosine at the time of reperfusion will have a beneficial effect on protecting the heart from IRI. Adenosine has provided to have anti-inflammatory and anti-platelet effects. It is thought that part of the beneficial effect of adenosine involves opening ATP-sensitive potassium channels (mK_{ATP}), whose opening can protect the mitochondria from Ca²⁺ overload and prevent cytochrome c loss [9,10]. It replenishes high-energy phosphate stores in endothelial cells and myocytes. Adenosine inhibits cytokine release from mononuclear cells, oxygen free radical formation, and neutrophils activity and accumulation. It reduces cardiomyocytes apoptosis, improves microvascular function and causes preconditioning responses [11]. The efficacy of adenosine as pharmacological postconditioning drug was clearly documented by Marzilli et al. [12]. In this study, 54 patients with acute myocardial infarction, referred for primary PCI (pPCI) within 3 hour from symptoms onset, were enrolled and received either intracoronary injection of adenosine (n=27, 4 mg of adenosine/2 ml of saline solution) or placebo (n=27, saline solution) at the

time of pPCI. No deaths occurred in the adenosine group while five patients in the saline group died in hospital (p=0.02). The composite end point of recurrent angina, nonfatal MI, heart failure, and cardiac death was present in 5 patients in the adenosine group and in 13 patients in the control group (p=0.03). This proof of concept clinical trial clearly demonstrated that intracoronary administration of high dose of adenosine was well tolerated by patients and effective in inducing cardioprotection. However, three larger randomized trials have reported limited benefits from adenosine in acute myocardial infarction. The Acute Myocardial Infarction Study of Adenosine (AMISTAD) was performed in 236 patients with anterior and inferior infarctions [13]. Patients received thrombolytic therapy plus continuous intravenous adenosine infusion (70 µg/kg per min) together with PCI had a smaller infarct size and a better functional recovery than those without adenosine infusion, especially in the instances of anterior wall infarction and adenosine infusion. The Attenuation by Adenosine of Cardiac Complications (ATTACC) study was a prospective, large-scale, randomized, placebo-controlled study using a low dose of adenosine (10 µg/kg per min) infused intravenously for six hours in patients undergoing thrombolysis. At the six-month follow-up of 292 patients with anterior infarcts, the adenosine group showed a trend for less all-cause mortality (8.4% versus 15.3%; p=0.07) and cardiovascular mortality (8.4% versus 14.6%; p=0.08). In a post hoc analysis of a subgroup with anterior infarcts and severely depressed left ventricle function, the six-month death rate was significantly lower in the adenosine group (2.0% versus 12.1%; p=0.007) [14]. However, the Acute Myocardial Infarction Study of Adenosine II (AMISTAD-II) specifically designed to investigate the role of adenosine in 2,118 patients with anterior STEMI undergoing thrombolysis or pPCI, found no difference in the primary end point of new congestive heart failure, rehospitalization for CHF, or death from any cause within 6 months. Two doses of adenosine were tested: 50 and 70 µg/kg per min [15]. Despite the lack of difference between the two groups in terms of major clinical endpoints, the infarct size tended to decrease in a dose-dependent manner with a marked reduction in infarct size observed in the high-dose group. In a post hoc analysis, among patients receiving reperfusion therapy within three hours of symptoms, adenosine reduced one-month

and six-month mortality rates significantly: 5.2% versus 9.2% ($p=0.014$) and 7.3% versus 11.2% ($p=0.03$), respectively [16].

Statins

Among recent studies using the cardioprotective signaling of postconditioning, the use of 3-hydroxy-3-methylglutaryl-CoA inhibitors (statins) is reported as a readily available, safe, and hopeful option to date. The immediate use of statins either before the onset of ischemia [17] or around the reperfusion period [18], reduced infarct size regardless of hyperlipidemia. This result was also shown in humans [19]; in addition, as shown in the MIRACL trial, administration of statins reduced adverse outcomes when used as late as 24 h after reperfusion. This evidence strongly suggests that cardioprotection induced by statins goes beyond lipid lowering and involves the signaling cascades of postconditioning, such as Akt activation and oxidative stress reduction [20].

Volatile anesthetics

Although the exact signaling pathway is not yet fully understood, the beneficial effect of volatile anesthetic on the heart seems to be mediated by adenosine A1 receptors, G proteins, reactive oxygen species, protein kinase C, and KATP channels [21,22]. The cardioprotective effects of sevoflurane were studied in human volunteers as well as in patients with ischemic heart disease. It seems that a relatively low dose of sevoflurane is sufficient to provide protective effect [23,24]. Sevoflurane administration during cardiac surgery was found to significantly reduce the incidence of myocardial infarction, intensive care unit and hospital stay, time on mechanical ventilation, in-hospital mortality and long term cardiac events [25,26]. The data regarding sedation with sevoflurane in patients not undergoing surgery are limited. In a small study involving patients undergoing elective PCI, low-dose sevoflurane before PCI, had no effect on myocardial damage after PCI [27].

Cyclosporine A

Another emerging target is the use of the mPTP inhibitor cyclosporine A. The role of cyclosporine A was first investigated by Paoletti et al [28] which documented cardioprotection in patients presenting with acute myocardial infarction. Patients were randomized to receive

intravenous bolus of cyclosporine A or normal saline immediately before undergoing pPCI. Administration of cyclosporine was associated with a reduction in infarct size of approximately 40%, measured in terms of CK release, although a not significant reduction in troponin I levels. MRI image on day 5 after infarction confirmed the decrease in infarct size in the cyclosporine group. The findings of protection by cyclosporine are now expanded in endothelial function upon reperfusion in humans [29] but seem still immature and need further confirmation in large-scale clinical trials to establish evidence-based medicine.

Conclusions

Clinical trials on cardioprotective strategies and drugs have given inconsistent results. These may be related to 1) not applying the intervention at the beginning of reperfusion, 2) delaying its application beyond the brief window within which salvage is achievable. Any strategy used to induce cardioprotection is time-sensitive; it can exert beneficial effect only if applied when there are still viable cells that can be salvaged during reperfusion. Therefore, the most striking difference among animal and humans studies is that pharmacological conditioning in animals is applied within few minutes after reperfusion and that, most importantly, reperfusion is initiated 30 minutes to 1 hour after the onset of ischemia. This important concept is well manifested in the study from Marzilli et al. in which they have shown a beneficial effect of adenosine as a pharmacological intervention to induce postconditioning, by using i.c. infusion of adenosine at the onset of reperfusion, including only those patients in which the ischemic time was less than 3 hours.

The controversial results reported about mechanisms involved in cardioprotection can be further explained by the differences between protocols applied to induce ischemia-reperfusion, and by the choice of animal models. Although one of the goals of experimental studies using animals is translational to humans, species differences remain a critical issue that needs to be taken into account. Importantly animal used to study the effect of ischemia-reperfusion had no coexisting comorbidities, and no pharmacological treatment that could attenuate or enhance the expected results from the intervention used to induce cardioprotection. However, animal study remains of

particular importance in order to verify new hypothesis and test the effectiveness of the interventional strategy. •

References

1. Reimer KA, Lowe JE, Rasmussen MM et al (1977) The wave-front phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation* 56(5):786–794
2. Jennings RB, Sommers HM, Smyth GA et al (1960) Myocardial necrosis induced by temporary occlusion of a coronary artery in the dog. *Arch Pathol* 70:68–78
3. Liu GS, Thornton J, Van Winkle DM et al (1991) Protection against infarction afforded by preconditioning is mediated by A1 adenosine receptors in rabbit heart. *Circulation* 84(1):350–356
4. Ganote CE, Armstrong S, Downey JM (1993) Adenosine and A1 selective agonists offer minimal protection against ischaemic injury to isolated rat cardiomyocytes. *Cardiovasc Res* 27(9):1670–1676
5. Miura T, Liu Y, Kita H et al (2000) Roles of mitochondrial ATP-sensitive K channels and PKC in anti-infarct tolerance afforded by adenosine A1 receptor activation. *J Am Coll Cardiol* 35(1):238–245
6. Kitakaze M, Takashima S, Funaya H et al (1997) Temporary acidosis during reperfusion limits myocardial infarct size in dogs. *Am J Physiol* 272(5 Pt 2):H2071–2078
7. Auchampach JA, Gross GJ (1993) Adenosine A1 receptors, KATP channels, and ischemic preconditioning in dogs. *Am J Physiol* 264(5 Pt 2):H1327–1336
8. Takahama H, Minamino T, Asanuma H et al (2009) Prolonged targeting of ischemic/reperfused myocardium by liposomal adenosine augments cardioprotection in rats. *J Am Coll Cardiol* 53(8):709–717
9. Garlid KD, Paucek P, Yarov-Yarovoy V et al (1997) Cardioprotective effect of diazoxide and its interaction with mitochondrial ATP-sensitive K⁺ channels. Possible mechanism of cardioprotection. *Circ Res* 81(6):1072–1082
10. Korge P, Honda HM, Weiss JN (2002) Protection of cardiac mitochondria by diazoxide and protein kinase C: implications for ischemic preconditioning. *Proc Natl Acad Sci U S A* 99(5):3312–3317
11. Stone GW (2008) Angioplasty strategies in ST-segment-elevation myocardial infarction: part II: intervention after fibrinolytic therapy, integrated treatment recommendations, and future directions. *Circulation* 118(5):552–566
12. Marzilli M, Orsini E, Marraccini P et al (2000) Beneficial effects of intracoronary adenosine as an adjunct to primary angioplasty in acute myocardial infarction. *Circulation* 101(18):2154–2159
13. Mahaffey KW, Puma JA, Barbagelata NA et al (1999) 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* 34(6):1711–1720
14. Quintana M, Hjemdahl P, Sollevi A et al (2003) Left ventricular function and cardiovascular events following adjuvant therapy with adenosine in acute myocardial infarction treated with thrombolysis, results of the ATTeNuation by Adenosine of Cardiac Complications (ATTACC) study. *Eur J Clin Pharmacol* 59(1):1–9
15. Ross AM, Gibbons RJ, Stone GW et al (2005) A randomized, double-blinded, placebo-controlled multicenter trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction (AMISTAD-II). *J Am Coll Cardiol* 45(11):1775–1780
16. Kloner RA, Forman MB, Gibbons RJ et al (2006) Impact of time to therapy and reperfusion modality on the efficacy of adenosine in acute myocardial infarction: the AMISTAD-2 trial. *Eur Heart J* 27(20):2400–2405
17. Iliodromitis EK, Andreadou I, Prokavas E et al (2011) Simvastatin in contrast to postconditioning reduces infarct size in hyperlipidemic rabbits: possible role of oxidative/nitrosative stress attenuation. *Basic Res Cardiol* 105(2):193–203
18. Sanada S, Asanuma H, Minamino T et al (2004) Optimal windows of statin use for immediate infarct limitation: 5'-nucleotidase as another downstream molecule of phosphatidylinositol 3-kinase. *Circulation* 110(15):2143–2149
19. Merla R, Daher IN, Ye Y et al (2007) Pretreatment with statins may reduce cardiovascular morbidity and mortality after elective surgery and percutaneous coronary intervention: clinical evidence and possible underlying mechanisms. *Am Heart J* 154(2):391–402
20. Merla R, Ye Y, Lin Y et al (2007) The central role of adenosine in statin-induced ERK1/2, Akt, and eNOS phosphorylation. *Am J Physiol Heart Circ Physiol* 293(3):H1918–1928
21. Riess ML, Kevin LG, McCormick J et al (2005) Anesthetic preconditioning: the role of free radicals in sevoflurane-induced attenuation of mitochondrial electron transport in Guinea pig isolated hearts. *Anesth Analg* 100(1):46–53
22. Riess ML, Stowe DF, Wartier DC. Cardiac pharmacological preconditioning with volatile anesthetics: from bench to bedside? *Am J Physiol Heart Circ Physiol* 286(5):H1603–1607
23. Lucchinetti E, Ambrosio S, Aguirre J et al (2007) Sevoflurane inhalation at sedative concentrations provides endothelial protection against ischemia-reperfusion injury in humans. *Anesthesiology* 106(2):262–268
24. Landoni G, Fochi O, Tritapepe L et al (2009) Cardiac protection by volatile anesthetics. A review. *Minerva Anesthesiol* 75(5):269–273
25. Symons JA, Myles PS (2006) Myocardial protection with volatile anaesthetic agents during coronary artery bypass surgery: a meta-analysis. *Br J Anaesth* 97(2):127–136
26. Jakobsen CJ, Berg H, Hindsholm KB et al (2007) The influence of propofol versus sevoflurane anesthesia on outcome in 10,535 cardiac surgical procedures. *J Cardiothorac Vasc Anesth* 21(5):664–671
27. Landoni G, Zangrillo A, Fochi O et al (2008) Cardiac protection with volatile anesthetics in stenting procedures. *J Cardiothorac Vasc Anesth* 22(4):543–547
28. Plot C, Croisille P, Staat P et al (2008) Effect of cyclosporine on reperfusion injury in acute myocardial infarction. *N Engl J Med* 359(5):473–481
29. Okorie MI, Bhavsar DD, Ridout D et al (2011) Postconditioning protects against human endothelial ischaemia-reperfusion injury via subtype-specific KATP channel activation and is mimicked by inhibition of the mitochondrial permeability transition pore. *Eur Heart J* 32(10):1266–1274
30. Michel Ovize, Gary F. Baxter, Fabio Di Lisa, Péter Ferdinandy, David Garcia-Dorado, Derek J. Hausenloy, Gerd Heusch, Jakob Vinten-Johansen, Derek M. Yellon, and Rainer Schulz (2010) Postconditioning and protection from reperfusion injury: where do we stand? *Cardiovasc Res* 87:406–423

Magnetic resonance imaging of the microcirculation in acute coronary syndromes

Kalpa De Silva¹, James Baker¹, Ananth Kidambi², Divaka Perera¹ and Sven Plein^{2,3}, ¹Cardiovascular Division, Rayne Institute, St. Thomas' Campus, King's College London, UK, ²Multidisciplinary Cardiovascular Research Centre & Leeds Institute of Genetics, Health and Therapeutics, University of Leeds, Leeds, UK, ³Imaging Sciences, Rayne Institute, St. Thomas' Campus, King's College London, United Kingdom

Correspondence: Kalpa De Silva, Cardiovascular Division, Rayne Institute, St. Thomas' Hospital, King's College London, London, SE1 7EH, United Kingdom
e-mail: kd@kalpadesilva.co.uk

Abstract

Microvascular damage is frequently observed in the setting of acute coronary syndromes (ACS). Imaging of the microcirculation is playing an increasingly important role in the risk stratification of patients presenting with acute coronary syndromes, furthering our understanding about coronary microcirculatory patho-physiology in this setting. Of the available imaging methods, cardiac magnetic resonance (CMR) holds particular promise for in vivo detection and assessment of microvascular dysfunction. The CMR methods currently available are described in this review with an overview of how CMR may be used to improve our understanding of microvascular damage in ACS and allow the development of potential cardio-protective measures.

Keywords: microvascular dysfunction; magnetic resonance imaging (MRI); acute coronary syndrome; myocardial infarction

■ Heart Metab. (2012) 54:15–19

Introduction

Myocardial perfusion is controlled by various factors acting to regulate the coronary circulation. The epicardial arteries contribute only 7% to overall coronary resistance, while the microcirculation (arterioles <150 µm in diameter) exerts most control on coronary blood flow and subsequent myocardial perfusion [1]. The microvasculature is hence responsible for the maintenance of coronary vasomotor tone, allowing a dilator stimulus such as ischemia to cause a three- to five-fold increase in coronary flow [2]. This vasodilatory reserve is progressively weakened in the presence of coronary atherosclerosis, as the coronary resistance is redistributed from the microvasculature to the less elastic epicardial circulation. Ultimately, vasodilator reserve is lost, and myocardial hypoperfusion ensues, prolonged periods of which cause irreversible myocardial necrosis. The severity and degree of irreversibility correlate proportionately with the extent of microvascular injury within the boundaries of the infarcted muscle [3].

In clinical practice microvascular dysfunction is frequently observed in the setting of acute coronary syndromes, especially following reperfusion of acute myocardial infarction. Despite

establishing angiographic patency of the infarct-related epicardial artery, myocardial blood flow can remain inadequate, a phenomenon known as “no-reflow” [4]. No-reflow occurs in up to 30% of patients, and is thought to be a consequence of microemboli and subsequent microvascular obstruction (MVO) [5]. The severity of microvascular dysfunction post infarction has been demonstrated to be an important correlate of left ventricular (LV) functional recovery, cardiovascular morbidity and mortality and is proportionate to infarct size [6,7]. Additionally, MVO has been shown to be a powerful independent predictor of adverse outcome [7,8].

Kloner et al. first described the presence of MVO in a canine coronary artery occlusion-reperfusion model, demonstrating a link between angiographic no-reflow phenomenon and severely damaged intramural microvessels with specific histological features of endothelial cell swelling, protrusions, and decreased pinocytotic vesicles [9]. Additional histological changes that have been suggested to occur during the formation of MVO are the production of reactive oxygen species leading to the disruption of endothelial cells, fibrin and platelet deposition, neutrophil activation, and hemorrhagic red cell extravasation following reperfusion. Epicardial thrombi and microvasculature thrombosis may also result from necrotic plaque particulates being showered distally into the myocardium following plaque rupture or as a result of coronary interventional procedures [10–13].

Imaging of the microcirculation is playing an increasingly important role in the risk stratification of patients presenting with acute coronary syndromes, furthering our understanding about coronary microcirculatory patho-physiology in this setting. This may subsequently allow development of potential cardio-protective measures to aid current therapies [14].

Several techniques and modalities have been described to identify microvascular injury following acute MI [6,7,15–18]. Of these, cardiac magnetic resonance (CMR) imaging has become the reference standard for assessment of myocardial injury as it allows accurate assessment of function, perfusion abnormalities, extent of infarction, edema, and myocardial salvage [19] (a composite marker of adverse outcome), as well as delineation of MVO in a single examination [20]. The most frequently used CMR techniques to delineate and differentiate microvascular damage are described in the remainder of this article.

Late-gadolinium enhancement

Most current gadolinium-based contrast media are extracellular agents, with rapid distribution within the intravascular and interstitial space, but exclusion from the intracellular space of intact myocytes. In the context of acute myocardial injury, the cell membranes can no longer exclude the contrast from the intracellular space and injured myocardium therefore takes up and retains more contrast agent than viable myocardium. In addition, clearance of contrast agent from injured myocardium is reduced. The CMR technique of late-gadolinium enhancement (LGE) makes use of the differences in the distribution volume of the contrast agent, and with appropriate imaging parameters depicts acutely infarcted myocardium as an area of hyper-enhanced myocardium compared to regions of non-infarcted myocardium [21]. Due to its high spatial resolution and tissue contrast LGE imaging can accurately depict the extent and transmuralty of myocardial injury after acute myocardial infarction including microinfarcts as low as 1 gram of tissue [22]. In addition, the pattern of hyperenhancement can be used to differentiate infarction from other types of acute injury such as myocarditis [22,23]. In the presence of MVO, MRI contrast media do not reach the infarct core affected by the reperfusion injury. On LGE images, the MVO zone therefore appears as a dark core residing within a hyper-enhanced infarct zone (Fig. 1). The appearance of the MVO on LGE imaging is a highly dynamic process and due to contrast agent diffusion into the infarcted core, the size of the dark MVO core reduces with increasing imaging time from contrast injection. Therefore, images are often acquired 1–2 minutes after contrast administration, when the MVO appears largest (Fig. 2). However, it is not certain, when the optimal

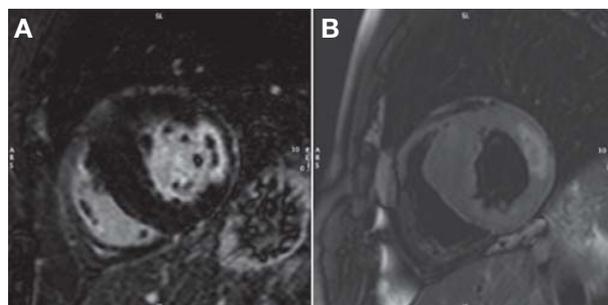


Fig. 1 **A)** Lateral wall LGE with MVO. **B)** T2-weighted image showing edematous region with dark core in area of MVO, suggesting intramyocardial hemorrhage.



Fig. 2 CMR of a patient presenting with an AMI 2 days ago and with ‘no-reflow’ observed during angiography. **A)** First-pass perfusion images acquired at rest show a septal wall defect in the area of MVO. **B)** Early gadolinium enhancement (EGE) acquired 2 minutes after first pass perfusion shows a similar defect caused by MVO. **C)** LGE images acquired 10 minutes later delineate the infarct zone in white and a smaller MVO (due to contrast diffusion into the MVO over time).

time is to image MVO and some studies have suggested that imaging at 10 minutes is most predictive of remodeling [24]. The transmuralty of LGE and the amount MVO present are both inversely related to the eventual left ventricular (LV) ejection fraction and predicts the likelihood of recovery of regional wall motion [25,26].

T2 weighted imaging

One of the patho-physiological consequences of acute ischaemia is an increase in unbound water in the ischemic tissue [27]. T2-weighted CMR (T2w CMR) is sensitive to the water content of tissue and therefore allows the delineation of acutely ischemic myocardium. The area of high signal on T2w CMR has been shown to accurately correlate with the area at risk assessed by microspheres [27]. Additionally, increased myocardial T2 signal may be observed within 30 minutes of ischemia onset—detecting myocardial injury prior to both troponin and LGE [28]. Some controversy remains about the precise mechanism of hyperenhancement on T2w CMR in acute ischaemic injury and T2w CMR methods have lower signal to noise ratio than LGE methods and may be more prone to flow and motion related artifacts [29]. Expertise is therefore needed for the acquisition and interpretation of T2w images. In patients who have severe microvascular dysfunction, reperfusion injury can result in a hemorrhagic transformation of the infarct core, often seen following PCI, which has independent adverse effects on LV remodeling [30]. Hemorrhage present within the myocardium lowers T2 signal, allowing these areas to be identified as a hypointense core within the infarct (Fig. 1) [31].

Myocardial salvage index

Mortality following myocardial infarction is related to several factors, one of which is the amount of myocardium subtended by the infarct-related vessel; the hypoperfused area at risk (AAR) as a result of the ischemic insult [32,33]. Combined, LGE and T2 weighted CMR allow the distinction between infarcted and potentially viable myocardium; LGE delineates the former, whilst T2- imaging determines the latter (Figs. 1 and 3). These CMR methods therefore permit the calculation of a myocardial salvage index (MSI), by correcting the amount of necrotic myocardium for the extent of AAR. From a microcirculatory perspective this index combines information regarding irreversibly damaged microvasculature (LGE) and potentially viable microvasculature (T2w CMR), and if timely reperfusion occurs, the degree of myocardium salvaged is the principal mechanism by which patients with recent myocardial infarction benefit from reperfusion therapies [34]. Reaffirmed by Eitel et al.’s recent prospective demonstration that MSI is a strong independent predictor of both major adverse cardiovascular events

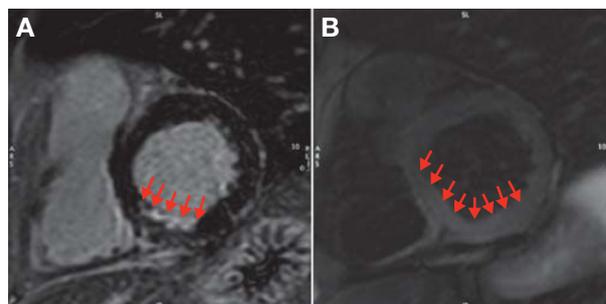


Fig. 3 A) LGE image - subendocardial inferior myocardial infarction. B) T2-weighted image of “area at risk.”

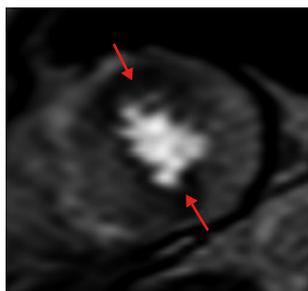


Fig. 4 Dynamic first-pass perfusion image – anterior and inferior ischemia.

and mortality at six months and in the longer term (median of 19 months) following reperfused STEMI [19, 35].

Perfusion CMR

Dynamic contrast-enhanced myocardial perfusion-CMR is based on the monitoring of contrast medium wash-in kinetics into the myocardium. Data can be acquired at rest and during a hyperemic state, which is most frequently pharmacologically induced with a concurrent intravenous adenosine infusion. One of the key advantages of perfusion-CMR over other imaging methods is its high spatial resolution of <3mm or even higher with recent methods, allowing the differentiation of perfusion to the subendocardial and subepicardial myocardial layers (Fig. 4) [36]. In myocardial regions supplied by arteries with hemodynamically significant coronary disease, myocardial perfusion CMR during hyperemia shows delayed and reduced wash-in of contrast agent compared to regions with normal myocardial perfusion [37,38]. In the setting of acute MI, myocardial perfusion CMR can demonstrate areas of MVO during first pass assessment. Subsequent late gadolinium enhancement can be used to confirm the presence of the MVO and assess its change in size over time (Fig. 2) [5].

Conclusion

The coronary microcirculation is critical in the perfusion and mechanical functioning of the myocardium. Increased understanding of the importance of this vascular compartment has allowed improvements in therapeutic strategies in the management of various conditions such as acute myocardial infarction. Non-invasive imaging, particularly with the advent and advancement of CMR, has allowed improved risk

stratification of patients, with greater understanding about possible prognosis and likely recovery in function following ischemic injury. The numerous facets to cardiac magnetic resonance imaging are both valuable, and synergistic to one another, in assessing and differentiating myocardial necrosis from injured but viable myocardium. Further advancement will allow routine quantification of all of these parameters, further enhancing the reproducibility and applicability of CMR in both clinical and research settings. •

References

1. Chilian WM (1991) Microvascular pressures and resistances in the left ventricular subepicardium and subendocardium. *Circ Res* 69(3):561–570
2. Feliciano L, Henning RJ (1999) Coronary artery blood flow: physiologic and pathophysiologic regulation. *Clin Cardiol* 22 (12):775–786
3. Ragosta M, Camarano G, Kaul S, Powers ER, Sarembock IJ, Gimble LW (1994) Microvascular integrity indicates myocellular viability in patients with recent myocardial infarction. New insights using myocardial contrast echocardiography. *Circulation* 89(6):2562–2569
4. Krug A, Du Mesnil de R, Korb G (1966) Blood supply of the myocardium after temporary coronary occlusion. *Circ Res* 19 (1):57–62
5. Mather AN, Lockie T, Nagel E, Marber M, Perera D, Redwood S, Radjenovic A, Saha A, Greenwood JP, Plein S (2009) Appearance of microvascular obstruction on high resolution first-pass perfusion, early and late gadolinium enhancement CMR in patients with acute myocardial infarction. *J Cardiovasc Magn Reson* 11:33
6. Ito H, Maruyama A, Iwakura K, Takiuchi S, Masuyama T, Hori M, Higashino Y, Fujii K, Minamino T (1996) Clinical implications of the ‘no reflow’ phenomenon. A predictor of complications and left ventricular remodeling in reperfused anterior wall myocardial infarction. *Circulation* 93(2):223–228
7. Wu KC, Zerhouni EA, Judd RM, Lugo-Olivieri CH, Barouch LA, Schulman SP, Blumenthal RS, Lima JA (1998) Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. *Circulation* 97(8):765–772
8. Nijveldt R, Beek AM, Hirsch A, Stoel MG, Hofman MB, Umans VA, Algra PR, Twisk JW, van Rossum AC (2008) Functional recovery after acute myocardial infarction: comparison between angiography, electrocardiography, and cardiovascular magnetic resonance measures of microvascular injury. *J Am Coll Cardiol* 52(3):181–189
9. Kloner RA, Ganote CE, Jennings RB (1974) The “no-reflow” phenomenon after temporary coronary occlusion in the dog. *J Clin Invest* 54(6):1496–1508
10. Buja LM (2005) Myocardial ischemia and reperfusion injury. *Cardiovasc Pathol* 14(4):170–175
11. Maxwell SR, Lip GY (1997) Reperfusion injury: a review of the pathophysiology, clinical manifestations and therapeutic options. *Int J Cardiol* 58(2):95–117
12. Engler RL, Dahlgren MD, Morris DD, Peterson MA, Schmid-Schonbein GW (1986) Role of leukocytes in response to

- acute myocardial ischemia and reflow in dogs. *Am J Physiol* 251(2 Pt 2):H314–323
13. Saber RS, Edwards WD, Bailey KR, McGovern TW, Schwartz RS, Holmes DR, Jr (1993) Coronary embolization after balloon angioplasty or thrombolytic therapy: an autopsy study of 32 cases. *J Am Coll Cardiol* 22(5):1283–1288
 14. Yellon DM, Hausenloy DJ (2007) Myocardial reperfusion injury. *N Engl J Med* 357(11):1121–1135
 15. Lepper W, Hoffmann R, Kamp O, Franke A, de Cock CC, Kuhl HP, Sieswerda GT, Dahl J, Janssens U, Voci P, Visser CA, Hanrath P (2000) Assessment of myocardial reperfusion by intravenous myocardial contrast echocardiography and coronary flow reserve after primary percutaneous transluminal coronary angioplasty [correction of angiography] in patients with acute myocardial infarction. *Circulation* 101(20):2368–2374
 16. van 't Hof AW, Liem A, Suryapranata H, Hoorntje JC, de Boer MJ, Zijlstra F (1998) Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Zwolle Myocardial Infarction Study Group. *Circulation* 97(23):2302–2306
 17. Schroder R, Dissmann R, Bruggemann T, Wegscheider K, Linderer T, Tebbe U, Neuhaus KL (1994) Extent of early ST segment elevation resolution: a simple but strong predictor of outcome in patients with acute myocardial infarction. *J Am Coll Cardiol* 24(2):384–391
 18. Kondo M, Nakano A, Saito D, Shimono Y (1998) Assessment of “microvascular no-reflow phenomenon” using technetium-99m macroaggregated albumin scintigraphy in patients with acute myocardial infarction. *J Am Coll Cardiol* 32(4):898–903
 19. Eitel I, Desch S, de Waha S, Fuernau G, Gutberlet M, Schuler G, Thiele H (2011) Long-term prognostic value of myocardial salvage assessed by cardiovascular magnetic resonance in acute reperfused myocardial infarction. *Heart* 97(24):2038–2045
 20. Kim RJ, Chen EL, Lima JA, Judd RM (1996) Myocardial Gd-DTPA kinetics determine MRI contrast enhancement and reflect the extent and severity of myocardial injury after acute reperfused infarction. *Circulation* 94(12):3318–3326
 21. Hillenbrand HB, Kim RJ, Parker MA, Fieno DS, Judd RM (2000) Early assessment of myocardial salvage by contrast-enhanced magnetic resonance imaging. *Circulation* 102(14):1678–1683
 22. Ricciardi MJ, Wu E, Davidson CJ, Choi KM, Klocke FJ, Bonow RO, Judd RM, Kim RJ (2001) Visualization of discrete microinfarction after percutaneous coronary intervention associated with mild creatine kinase-MB elevation. *Circulation* 103(23):2780–2783
 23. Laissy JP, Hyafil F, Feldman LJ, Juliard JM, Schouman-Claeys E, Steg PG, Faraggi M (2005) Differentiating acute myocardial infarction from myocarditis: diagnostic value of early- and delayed-perfusion cardiac MR imaging. *Radiology* 237(1):75–82
 24. Beek AM, van Rossum AC (2011) Cardiovascular magnetic resonance imaging in patients with acute myocardial infarction. *Heart* 96(3):237–243
 25. Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, Klocke FJ, Bonow RO, Judd RM (2000) The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med* 343(20):1445–1453
 26. Kwong RY, Korlakunta H (2008) Diagnostic and prognostic value of cardiac magnetic resonance imaging in assessing myocardial viability. *Top Magn Reson Imaging* 19(1):15–24
 27. Aletras AH, Tilak GS, Natanzon A, Hsu LY, Gonzalez FM, Hoyt RF, Jr., Arai AE (2006) Retrospective determination of the area at risk for reperfused acute myocardial infarction with T2-weighted cardiac magnetic resonance imaging: histopathological and displacement encoding with stimulated echoes (DENSE) functional validations. *Circulation* 113(15):1865–1870
 28. Abdel-Aty H, Cocker M, Meek C, Tyberg JV, Friedrich MG (2009) Edema as a very early marker for acute myocardial ischemia: a cardiovascular magnetic resonance study. *J Am Coll Cardiol* 53(14):1194–1201
 29. Friedrich MG, Kim HW, Kim RJ (2011) T2-weighted imaging to assess post-infarct myocardium at risk. *JACC Cardiovasc Imaging* 4(9):1014–1021
 30. Ganame J, Messalli G, Dymarkowski S, Rademakers FE, Desmet W, Van de Werf F, Bogaert J (2009) Impact of myocardial haemorrhage on left ventricular function and remodelling in patients with reperfused acute myocardial infarction. *Eur Heart J* 30(12):1440–1449
 31. Basso C, Corbetti F, Silva C, Abudurehman A, Lacognata C, Cacciavillani L, Tarantini G, Marra MP, Ramondo A, Thiene G, Iliceto S (2007) Morphologic validation of reperfused hemorrhagic myocardial infarction by cardiovascular magnetic resonance. *Am J Cardiol* 100(8):1322–1327
 32. Lowe JE, Reimer KA, Jennings RB (1978) Experimental infarct size as a function of the amount of myocardium at risk. *Am J Pathol* 90(2):363–379
 33. Christian TF, Schwartz RS, Gibbons RJ (1992) Determinants of infarct size in reperfusion therapy for acute myocardial infarction. *Circulation* 86(1):81–90
 34. Braunwald E (1989) Myocardial reperfusion, limitation of infarct size, reduction of left ventricular dysfunction, and improved survival. Should the paradigm be expanded? *Circulation* 79(2):441–444
 35. Eitel I, Desch S, Fuernau G, Hildebrand L, Gutberlet M, Schuler G, Thiele H (2011) Prognostic significance and determinants of myocardial salvage assessed by cardiovascular magnetic resonance in acute reperfused myocardial infarction. *J Am Coll Cardiol* 55(22):2470–2479
 36. Maredia N, Radjenovic A, Kozerke S, Larghat A, Greenwood JP, Plein S (2011) Effect of improving spatial or temporal resolution on image quality and quantitative perfusion assessment with k-t SENSE acceleration in first-pass CMR myocardial perfusion imaging. *Magn Reson Med* 64(6):1616–1624
 37. Plein S, Radjenovic A, Ridgway JP, Barmby D, Greenwood JP, Ball SG, Sivanathan MU (2005) Coronary artery disease: myocardial perfusion MR imaging with sensitivity encoding versus conventional angiography. *Radiology* 235(2):423–430
 38. Paetsch I, Jahnke C, Wahl A, Gebker R, Neuss M, Fleck E, Nagel E (2004) Comparison of dobutamine stress magnetic resonance, adenosine stress magnetic resonance, and adenosine stress magnetic resonance perfusion. *Circulation* 110(7):835–842

Postconditioning

Mario Marzilli, Doralisa Morrone and Giacinta Guarini, Cardiovascular Medicine Division,
Cardio Thoracic and Vascular Department, University of Pisa, Italy

Correspondence: Mario Marzilli, Cardiovascular Medicine Division, Cardio Thoracic and Vascular Department,
University of Pisa, Via Paradisa 2, 56100 Pisa, Italy.
Tel.: +39050996751, e-mail: mario.marzilli@med.unipi.it

Abstract

Early and successful reperfusion is mandatory to limit infarct size, and reduce morbidity and mortality from acute coronary syndrome. However, reperfusion is a double edge sword, with the potential to induce additional damage to the ischemic myocardium (reperfusion injury). The reperfusion injury may account for up to 50% of final infarct size. By stimulating cardioprotective pathway, postconditioning (ischemic, remote and pharmacological postconditioning) can reduce the negative impact of ischemia and reperfusion on the heart. In the present article, we briefly elucidate the mechanisms involved in cardiac protection and discuss the available supporting data for the use of postconditioning in the clinical scenario.

Keywords: ischemia reperfusion injury; cardioprotection; post-conditioning; remote conditioning

■ Heart Metab. (2012) 54:20–24

Introduction

In the clinical setting, the application of coronary thrombolysis or percutaneous coronary intervention (PCI) for faster recanalization has been shown to improve the outcomes of patients with acute myocardial ischemia. However, even if the ischemic period is short or limited, the functional recovery of a reperfused heart is often less successful than expected due to “reperfusion injury” [1]. Therefore, it is important to fully understand the mechanisms of ischemia-reperfusion injuries and to consider the naturally cardioprotective strategies that the heart uses to attenuates the damage induced by ischemia and subsequent reperfusion (Fig. 1). This concept is supported by the clinical observation that patients experiencing pre-infarctional angina (preconditioning) have better prognosis, and by animal and clinical studies in which a short periods of ischemia, preceding the index ischemia, induce less myocardial damage [2].

Despite increasing data supporting the importance of ischemia-reperfusion injury and therefore cardioprotection, little is known about these phenomena and even less about how to prevent and protect the heart from them.

Preconditioning

Before the concept of ischemic preconditioning (IPreC) arose, cardiologists observed that patients with acute myocardial infarction who had experienced episodes of prodromal angina often exhibited less chest pain, less variation in the ST segment of ECGs, less cardiac dysfunction, and smaller myocardial infarct size. This occurred despite a paradoxical increase in the total ischemic time. This phenomenon was called the “cardiac warm-up phenomenon” [3]. In 1986, Murry et al. [4] confirmed the existence of “preconditioning with ischemia” in a canine

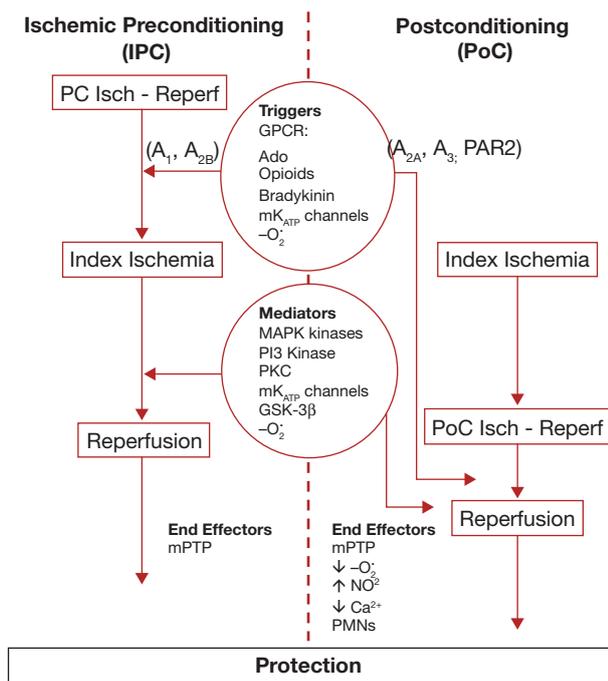


Fig. 1 Common mechanisms thought to be involved in cardioprotection. Differences and similarities between preconditioning and postconditioning pathways. See text for more details. Modified from [19].

model and defined it as a phenomenon where brief periods of ischemia followed by reperfusion just before sustained ischemia exerted 1) a delay in ATP depletion, 2) a reduction in oxygen consumption, 3) a retention of intracellular structure, and 4) a delay or reduction of cellular necrosis due to ATP expiration, finally resulting in delayed progression or reduction of infarct size, despite an increase in the total ischemic period. This is now recognized as a narrow definition of ischemic preconditioning.

It has become clear that the strength of protection by ischemic preconditioning critically depends on the interval between preconditioning ischemia and the onset of index ischemia. Two windows of cardioprotection have been identified, termed “early and late phase” preconditioning. The first period is limited to the initial 3 hours and the second one, associated with the increased expression of cardioprotective heat shock proteins (HSPs), is in the following 24–72 h. These two phases appear to involve different pathways; the former involving reactions that are completed in a short period of time, such as activation of ion channels, phosphorylation/activation of existing enzymes, or rapid turnover/translocation of sub-

stances, the latter involving more time-consuming reactions, such as genomic modulation and expression of channel proteins, receptor proteins, enzymes, molecular chaperone proteins, or immunotransmitters. Multiple, parallel mechanisms seem to induce cardioprotection by preconditioning ischemia, among these adenosine, the activation of alpha and/or beta receptor, G protein-coupled receptor (GPCR) members, opioid receptors, and bradykinin-B2 receptors. However, controversies still exist about the multiple and complicated mechanisms involved in cardiac protection before the onset of prolonged ischemia.

Postconditioning

Because the clinical application of cardioprotection induced by preconditioning is limited by the unpredictable occurrence of acute coronary syndromes, most of the recent translational therapeutic strategies aimed at reducing the damage related to ischemia-reperfusion injury, are applied at the time of reperfusion, after the onset of ischemic insult. Indeed, postconditioning has recently been shown to have potential as a novel cardioprotective intervention against ischemia-reperfusion injury, when applied at the onset of reperfusion following sustained ischemia [5]. This protocol is followed because the “final effectors of preconditioning” share some common pathways with the “contributors of postconditioning” at reperfusion [6]. Three forms of postconditioning: ischemic (IPosC), remote (RPostC), and pharmacological conditioning (discussed in another section of this journal issue) have been explored both in the bench and the bedside.

Ischemic postconditioning

IPosC is defined as brief periods of ischemia alternating with brief periods of re-flow applied at the onset of reperfusion following sustained ischemia. Recently, IPosC has been introduced as mechanical intervention to attenuate reperfusion injury specifically [7]. Similarly to ischemic preconditioning, where brief episode of ischemia preceding prolonged ischemia induce resistance to IRI, ischemic postconditioning effectively reduces myocardial infarct size in all species tested so far, including humans (Fig. 2). IPosC is a simple and safe maneuver, but because reperfusion injury is initiated within minutes of reflow,

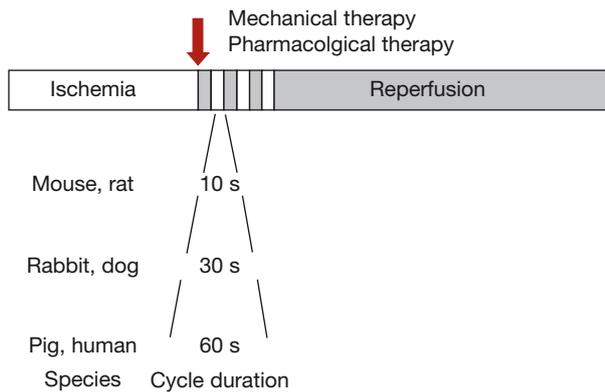


Fig. 2 Ischemic postconditioning protocols used in animal and human studies. Modified from [20].

postconditioning must be applied at the onset of reperfusion. The mechanisms through which postconditioning induces protection include: formation and release of several autacoids and cytokines; maintained acidosis during early reperfusion; activation of protein kinases; preservation of mitochondrial function, most strikingly the attenuation of opening of the mitochondrial permeability transition pore. It has also been documented that IPosC reduces neutrophil accumulation and attenuate endothelial injury. Exogenous recruitment of some of the identified signaling steps can induce cardioprotection when applied at the time of reperfusion in animal experiments, but more recently also cardioprotection was observed in a proof-of-concept clinical trial [8].

Although postconditioning is in its relative infancy as clinical strategy, several studies have shown it to be cardioprotective in both the catheterization laboratory in conjunction with PCI and in cardiac surgery. Studies in patients with an acute myocardial infarction showed a reduction of infarct size and improved left ventricular function when undergoing ischemic postconditioning. In the catheterization laboratory setting, repeated balloon inflations attenuated electrocardiographic changes (ST-segment elevation), lactate release, and left ventricular segmental dysfunction relative to the first balloon inflation suggestive of a preconditioning-like effect. Laskey [9] reported that repetitive 90-s balloon occlusions during angioplasty reduced ST-segment elevations, increased the rate of ST-segment elevation resolution (a marker of improved viability and perfusion) and increased flow velocity reserve in the infarct-related artery.

The beneficial effect of postconditioning have been demonstrated to be persistent, with improved functional recovery and reduced infarct size at 1 year [10]. However, the salvage impact varies among the studies, probably depending on critical requirements in postconditioning maneuvers, and it seems that protocol with fewer cycles or longer intermission [11], or applied after long ischemic time are less protective [11–13]. In cardiac surgery, postconditioning was induced by two 30-s cycles of aortic clamping and declamping at the time of reperfusion (release of the aortic cross-clamp) in children undergoing surgery for congenital malformations. Plasma troponin I levels were significantly less in the postconditioning group compared with no postconditioning. An alternative way to subject the heart to postcondition is to deliver a reperfusate via the cardioplegia line in a cyclical manner, i.e., 30–60 s pulses that mimic the cyclical perfusion pattern of the IPosC. Yellon et al. [14] and Alhulaifi et al. [15] reported that preconditioning the heart by short periods of aortic cross-clamping preceding elective ventricular fibrillation conserved high energy phosphate (i.e., ATP) levels in myocardial biopsy samples, suggestive of a cardioprotective effect. The impact of these observations is limited by the declining use of induced ventricular fibrillation during aorto-coronary artery bypass in favor of some form of chemical cardioplegia and by the hesitation of surgeons to repeatedly cross-clamp aorta that may have some degree of atheromatous plaque and/or adherent thrombi that may dislodge and embolize, particularly in the brain, causing stroke. Alternatively, the heart may be preconditioned remotely, for example by inducing transient limb ischemia before ventricular fibrillation or ischemia. Less CK release, greater myocardial ATP levels, and greater dP/dt values (a soft surrogate measure of function in vivo) suggestive of better contractility upon reperfusion were reported after ischemically preconditioning of patients undergoing chemical cardioplegia and aortic and mitral valve replacement surgery [16]. However, in a study using chemical cardioplegia during surgery, preconditioning was reported to be associated with increased release of CK-MB compared with non-preconditioned patients. All these data need to be verified in largemulticenter-studies that may explore the role of postconditioning in other surgical procedures such as correction of the ascending aortic aneurism, which are associated with high rates of cardiac dysfunction and mortality.

Remote postconditioning

Another step forward, cardioprotection is the discovery that ischemia at a distant site can elicit the same protective effects of ischemic preconditioning. Przyklenk et al. [17] first demonstrated that brief ischemic episodes of the left circumflex coronary artery significantly reduced myocardial infarct size following sustained occlusion of the left anterior descending coronary artery. Following the initial discovery of RPostC in the heart, it was reported that brief, intermittent ischemia of distant organs such as the skeletal muscle, kidney and intestine could also induce protection of the heart against prolonged myocardial ischemia and reperfusion. From a mechanistic standpoint, RPostC very closely resembles traditional IPreC and depends on the very same trigger mechanisms and second messenger signaling pathways to promote cardioprotection. At present, there are three main hypotheses regarding the mechanism responsible for RPostC [18]. The first theory is the neural hypothesis, which proposes that the ischemic remote organ releases endogenous substances (i.e., adenosine, bradykinin) that activate local afferent neural pathways that, in turn, activate efferent neural pathways to trigger target organ protection. A second theory is the humoral hypothesis, which suggests that the target organ releases humoral mediators such as adenosine and bradykinin into the blood stream, which are then transported to the remote organ where the humoral factor directly triggers the intracellular survival pathways. A third theory is termed as the “inflammatory suppression theory,” which proposes that the transient, remote organ ischemia produces a systemic anti-inflammatory phenotype that protects the distant target organ against subsequent ischemia-reperfusion injury. It is not clear which of the three proposed hypotheses accounts for the majority of cardioprotective effects mediated by RPostC. However, it is possible that all three of these hypotheses are correct, and there are interactions between endogenous substances such as adenosine, and local afferent neural pathways that synergize to promote cardioprotection and subsequently produce systemic suppression of inflammation.

Pitfalls of postconditioning

Currently, the most important issue is how to transfer the results of basic research into the clinical scenario

and how to incorporate them in therapeutic strategies. It is unfortunately true that there is an inevitable gap in the scientific approaches used in basic science and in clinical medicine. Clinical science largely relies on statistics because of heterogeneity of disease conditions and individuals, such as age, sex, background diseases, and their comorbidities. It has been suggested that cardioprotection by ischemic and pharmacological postconditioning is attenuated in animal models of left ventricle hypertrophy and it seems to be the same in humans, although few studies have been published on this point. Discrepancy regarding the efficacy of postconditioning has also been reported in animal models of hypercholesterolemia, diabetes and obesity.

Future directions and conclusion remarks

Postconditioning has shown to be an effective and easy strategy to be applied in the clinical setting, and is able to exert protective effects on the heart and reduce the ischemia reperfusion injury. Therefore, we strongly support the use of this approach to protect the heart in addition to other pharmacological agents to further optimize the beneficial effect of reperfusion and revascularization. However, it must be admitted that no definitive results are available regarding the beneficial effect of this strategy in special subset population such as diabetic, obese and hypercholesterolemic patients. More animal and clinical studies are warranted in order to elucidate and encourage the widespread use of this cost-effective technique. •

References

1. Yellon DM, Hausenloy DJ (2007) Myocardial Reperfusion Injury. *N Eng J Med* 357(11):1121–1135
2. Tong H, Chen W, Steenbergen C et al (2000) Ischemic preconditioning activates phosphatidylinositol-3-kinase upstream of protein kinase C. *Circ Res* 87(4):309–315
3. Jaffe MD, Quinn NK (1980) Warm-up phenomenon in angina pectoris. *Lancet*. 2(8201):934–936
4. Murry CE, Jennings RB, Reimer KA (1986) Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation*. 74(5):1124–1136
5. Ovize M, Baxter GF, Di Lisa F et al (2010) Postconditioning and protection from reperfusion injury : where do we stand? *Card Res* doi:10.1093/cvr/cvq129
6. Hausenloy DJ, Yellon DM (2007) Preconditioning and postconditioning: United at reperfusion. *Pharmacology amp. Therapeutics*. 116(2):173–191
7. Zhao ZQ, Corvera JS, Halkos ME et al (2003) Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. *Am J Physiol Heart Circ Physiol* 285(2):H579–588

8. Staat P, Rioufol G, Piot C et al (2005) Postconditioning the human heart. *Circulation*. 112(14):2143–2148
9. Laskey WK (2005) Brief repetitive balloon occlusions enhance reperfusion during percutaneous coronary intervention for acute myocardial infarction: a pilot study. *Catheter Cardiovasc Interv* 65(3):361–367
10. Thibault H, Piot C, Staat P, et al (2008) Long-term benefit of postconditioning. *Circulation* 117(8):1037–1044
11. Iliodromitis EK, Georgiadis M, Cohen MV et al (2006) Protection from post-conditioning depends on the number of short ischemic insults in anesthetized pigs. *Basic Res Cardiol* 101(6):502–507
12. Yang XC, Liu Y, Wang LF et al (2007) Reduction in myocardial infarct size by postconditioning in patients after percutaneous coronary intervention. *J Invasive Cardiol* 19(10):424–430
13. Lonborg J, Kelbaek H, Vejstrup N et al (2011) Cardioprotective effects of ischemic postconditioning in patients treated with primary percutaneous coronary intervention, evaluated by magnetic resonance. *Circ Cardiovasc Interv* 3(1):34–41
14. Yellon DM, Alkhulaifi AM, Pugsley WB (1993) Preconditioning the human myocardium. *Lancet* 342(8866):276–277
15. Alkhulaifi AM, Yellon DM, Pugsley WB (1994) Preconditioning the human heart during aorto-coronary bypass surgery. *Eur J Cardiothorac Surg* 8(5):270–275; discussion 276
16. Lu EX, Chen SX, Yuan MD et al (1997) Preconditioning improves myocardial preservation in patients undergoing open heart operations. *Ann Thorac Surg* 64(5):1320–1324
17. Przyklenk K, Bauer B, Ovize M et al (1993) Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation*. Mar 1993;87(3):893–899
18. Walsh SR, Tang T, Sadat U et al (2007) Cardioprotection by remote ischaemic preconditioning. *Br J Anaesth* 99(5):611–616
19. JakobVinten-Johansen, Zhi-Qing Zhao, Rong Jiang, Amanda J. Zatta, Geoffrey P. Dobson (2007) Preconditioning and postconditioning: innate cardioprotection from ischemia-reperfusion injury. *J ApplPhysiol*103:1441–1448; doi: 10.1152/jappphysiol.00642.2007
20. Granfeldt A, Lefer DJ, Vinten-Johansen J (2009) Protective ischemia in patients: preconditioning and postconditioning. *Cardiovasc Res* 83:234–246

Metabolic cardiac protection

Giacinta Guarini, Cardiovascular Medicine Division, Cardio Thoracic and Vascular Department,
University of Pisa, Italy

Correspondence: Giacinta Guarini, Cardiovascular Medicine Division, Cardio Thoracic and Vascular Department,
University of Pisa, Via Paradisa, 2, 56100 Pisa, Italy.
Tel.: +393494544161, e-mail: giacinta_guarini@yahoo.it

Abstract

Several animal and clinical studies have clearly demonstrated the clinical importance of ischemia reperfusion injury (IRI) in the setting of an acute coronary syndrome (ACS). It is well known that a shift of glucose metabolism from oxidative phosphorylation to substrate level phosphorylation (glycolysis) occurs during prolonged ischemia. As a consequence, protons and lactic acid accumulate within the cells, while ATP, NADH and NAD⁺ dehydrogenase levels decrease. Fatty acid oxidation contribute in the ischemic myocardium to the increased production of reactive oxygen species (ROS), that participate to mitochondrial uncoupling further reducing mitochondrial efficiency and ATP production. These and other changes in cardiac metabolism contribute to the opening of the mitochondrial permeability transition pore (mPTP), responsible for myocytes apoptosis. Varieties of pharmacological approaches have been proposed to minimize IRI and maximize the myocardial salvage, than those achieved by reperfusion alone. This brief review will provide the rationale for the use of metabolic approaches to protect the heart from ischemia and during reperfusion.

Keywords: cardiac ischemia; ischemia/reperfusion injury; cardioprotection; trimetazidine

■ Heart Metab. (2012) 54:25–28

Introduction

The process of restoring blood flow to the ischemic myocardium can induce *per se* injury. This phenomenon, known as myocardial ischemia reperfusion injury (IRI), can paradoxically reduce the beneficial effects of myocardial reperfusion. IRI is defined as injury and death of cardiac myocytes that were viable before reperfusion induced by the restoration of coronary blood flow to an ischemic tissue. Therefore, the IRI decreases the beneficial effects that myocardial reperfusion would have on infarct size and prognosis, by independently inducing cardiomyocyte death.

While investigators have progressively identified multiple mechanisms that participate to the IRI, the concept of metabolic protection of the ischemic myocardium is in continuous evolution. Indeed, it is expected that a clear understanding of the mechanisms responsible for myocytes death during myocardial ischemia, and reperfusion, will provide fundamental knowledge in order to generate successful strategies for the treatment of acute ischemic events.

Cardiac metabolism in normal condition

In normal condition, the heart is able to utilize multiple fuel sources (i.e., fatty acids, glucose, and lactate, ketone bodies) to generate high-energy phosphates (particularly ATP), necessary for the daily demands. Fatty acids (FA) constitute the predominant source of energy in the normal heart, supplying from 60 to 80% of energy. Carbohydrate metabolism is controlled by the

rate of FA oxidation (Randle phenomenon), which strongly inhibits the rate of glucose and lactate uptake and oxidation. This inhibition, determined by elevated FA oxidation levels is mediated by increased ratio of NADH/NAD⁺ and of acetyl co-A/free co-A and enhanced activity of pyruvate dehydrogenase kinase (PDHK), which conversely phosphorylates and inhibits pyruvate dehydrogenase (PHD) activity.

Myocardial ischemia and reperfusion alters cardiac metabolism and cell homeostasis

Myocardial ischemia dramatically alters cardiac metabolism, energy production and cellular homeostasis. During ischemia, due to reduced oxygen level, glucose taken up by the myocardium is not efficiently oxidized into mitochondria but is rather converted to lactate. As a consequence, a switch from lactate consumption to lactate production is observed in the ischemic myocardium. These changes lead to disruption of cell homeostasis, with reduction in ATP content within the cells. Accumulation of lactate and H⁺ induce a fall in intracellular pH and decrease in contractile work. Paradoxically, the ischemic myocardium continues to drive most of its energy (50–70%) from the oxidation of fatty acids despite there being a high rate of lactate production. In this condition high rates of FA oxidation further inhibit glucose oxidation (Fig. 1). FA oxidation in this setting contributes to further reduce mitochondrial efficiency and during reperfusion participate to the generation of the IRI.

Mitochondria use oxygen as a substrate, so by default their respiration is inhibited during ischemia. During ischemia, excess protons due to lactic acidosis drive a cytosolic Na⁺ overload via the Na⁺/H⁺ exchanger (NHE) [1]. This Na⁺ exits via the Na⁺/Ca²⁺ exchanger, causing a cytosolic Ca²⁺ overload. The ischemic lack of ATP prevents adequate management Ca²⁺ by the SERCA pump, and subsequently Ca²⁺ is increased in the cytosol. While some Ca²⁺ uptake into mitochondria can occur during ischemia, it is not sufficient to trigger opening of the mPTP, which is also held closed during ischemia due to the acidic pH [2]. Prompt reperfusion will induce a rapid restoration of substrates essential for the generation of ATP, as well as rapid increase in the oxygen supply, and prompt normalization of the extracellular pH. All these events concur to IRI. Rapid normalization of the extracellular pH will instantly create an extreme H⁺ gradient across the plasma membrane that triggers a robust Na⁺/H⁺ exchange and a massive Na⁺ influx. This Na⁺ gradient triggers the passive, inverted action of the surface Na⁺/Ca²⁺ exchanger, called “reverse mode,” which in turn allows intracellular Ca²⁺ overload. Also at this moment a burst of ROS generation occurs, which together with high mitochondrial Ca²⁺ concentration and re-alkalinization triggers mPTP opening [3], leading to cytochrome c release and cell death [4]. Mitochondrial cytochrome c release also inhibits mitochondrial respiratory function increasing ATP deficiency in the post-ischemic heart [5].

Metabolic targets to induce cardioprotection

The concept of metabolic protection of the ischemic myocardium is in constant evolution and has recently been supported by clinical studies. Historically, enhanced glucose metabolism and glycolysis were proposed as anti-ischemic mechanisms of cardioprotection. The metabolic cardioprotection paradigm includes 1) the benefit of improved coupling of glycolysis to glucose oxidation, 2) a more gradual wake-up of mitochondrial function at reperfusion. Consistent with this hypothesis in cardioprotective mechanisms, some studies have demonstrated that only protocols able to induce a significant delay in pH recovery were able to afford cardioprotection. Furthermore, a close correlation between the delay in pH recovery and the magnitude of myocardial salvage was documented [5]. The beneficial effect of coupling glycolysis to glucose

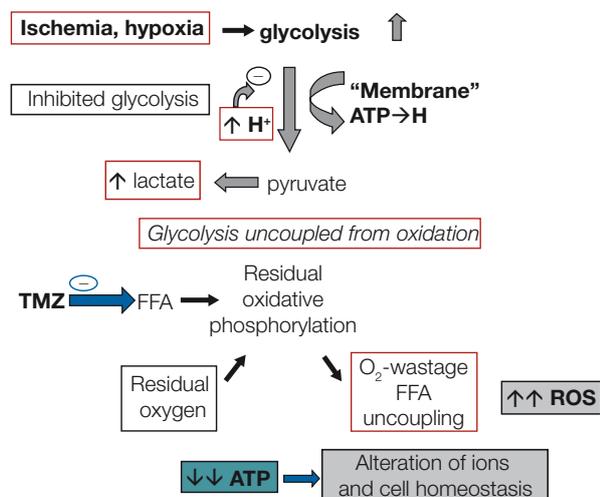


Fig. 1 Ischemia induced alteration in cardiac metabolism. See text for details. Modified from [20].

oxidation explains the efficacy of FA inhibitor such as trimetazidine. This hypothesis is supported by the sub-cellular linkage between key glycolytic enzymes and the activity of two survival-promoting membrane-bound pumps, namely the sodium-potassium ATPase, and the calcium uptake pump of the sarcoplasmic reticulum (SERCA). Indeed, it has been demonstrated that metabolic agents that decrease FA oxidation and increase the rate of glucose and lactate combustion induce enhanced viability after reperfusion. This metabolic strategy affords cardioprotection because glucose oxidation is more “oxygen efficient” than FA oxidation, producing more ATP for mole of oxygen consumed. The same effect might be achieved by administration of insulin-glucose-potassium (GIK) solution, but to date no conclusive results support a wide clinical use of this approach.

Metabolic cardioprotective agents

Mitochondria play a critical role in cardiac function, and are also recognized as crucially involved in signaling cardioprotective pathways. Targets of cardioprotection include Ca²⁺ overload, oxidative stress (ROS), ATP-dependent potassium channels (mK_{ATP}), mechanisms that ultimately lead to disruption of the inner mitochondrial membrane and opening of the nonspecific mitochondrial permeability transition pore (mPTP) complex causing cell death [6].

By increasing NADH and decreasing FAD content, cardiac ischemia conditions mitochondria to be in a relatively reduced state. Consistent with this notion are the observations that during ischemia NADH increases (reduced mitochondria) but on reperfusion NADH decrease and FAD increase, suggesting a more mitochondrial oxidation state [7]. The implications of these results are that a reduced redox state in the cardiac cell could be an important condition for efficient resumption of the H⁺ gradient for ATP synthesis and hence for better functional recovery. Prevention of ATP hydrolysis to maintain mitochondrial membrane $\Delta\Psi$ during ischemia is therefore a valid goal for preserving function. Along with these observations, a recent study has investigated the role of ranolazine in protecting against the IR injury. Its mechanisms of protection are not clearly understood but evidence points to blocking the late Na⁺ current that arises during ischemia, inhibition of mitochondrial complex I activity, or modulating mitochondrial metabolism. Mitochondria isolated from ranolazine-treated

hearts had mild resistance to permeability transition pore (mPTP) opening and less cytochrome c release than control hearts, suggesting that ranolazine was effective in protecting the heart against the IR injury [8]. Other pharmacologic reagents that inhibit complex I activity have now demonstrated to afford protection against IR injury. These include amobarbital [9], rotenone [10], S-nitrosothiols [11], analgesics such as capsaicin [12], volatile anesthetics such as halothane and isoflurane [13], and anti-diabetics such as metformin [14]. Complex I (NADH ubiquinone oxidoreductase) is a key site of electron entry into the respiratory chain in cardiac mitochondria, owing to the heavy reliance of the heart on β -oxidation of fatty acids and subsequent generation of NADH from acetyl-CoA in the Krebs' cycle. In addition to playing a role in cardiac metabolism, complex I is also an important site of ROS generation, and a regulator of NADH/NAD⁺ redox balance in the mitochondrion. Notably, the latter has been shown to be critical in determining the open probability of the mPTP, such that complex I inhibition can directly inhibit pore opening via an increased NADH/NAD⁺ ratio.

Since high fatty acid oxidation rate markedly decreases glucose oxidation, another approach to induce cardioprotection is to increase glucose oxidation, by inhibiting fatty acid oxidation. Pharmacological agents that inhibit fatty acid oxidation include direct beta-oxidation inhibitors. This novel group of compounds includes the 3-ketoacyl-coenzyme A thiolase (3KAT) inhibitor trimetazidine (TMZ). TMZ is a metabolic anti-ischemic agent with cardioprotective properties [15] that selectively inhibits the long chain 3-ketoacyl CoA thiolase (3-KAT) activity. This leads to reduction in fatty acid oxidation and stimulation of glucose oxidation that is independent of any hemodynamic effects that influence myocardial oxygen consumption. Various studies demonstrated that it inhibits mitochondrial oxidation of palmitoyl carnitine, thus only slightly altering oxidation of pyruvate and preserving mitochondrial oxidative functions [16]. It also stimulates PDH activity, the rate-limiting enzyme for glucose oxidation. As a result, TMZ attenuates the adverse effects of free fatty acid-associated oxidative stress [17], lessens oxygen demand by decreasing oxygen consumption [18], and improves mitochondrial metabolism and cardiac performance during ischemia [19]. TMZ has been reported to attenuate neutrophil activation, thereby protecting post-ischemic hearts from

neutrophil-mediated injury. At the cellular level, TMZ conserves ATP production and lowers intracellular acidosis and calcium overload, while maintaining cellular homeostasis. It reduces oxidative damage to the mitochondria and protects the heart from IR induced damage arising from mitochondrial respiration. TMZ has also shown cytoprotective efficacy in several models of myocardial infarction. In addition to its beneficial effects in the treatment of IRI, TMZ has been reported to induce protection in patients experiencing acute periods of ischemia when undergoing PCI. •

References

1. Piper HM, Meuter K, Schafer C (2003) Cellular mechanisms of ischemia-reperfusion injury. *Ann Thorac Surg*. 75(2):S644–648
2. Chen X, Zhang X, Kubo H et al (2005) Ca²⁺ influx-induced sarcoplasmic reticulum Ca²⁺ overload causes mitochondrial-dependent apoptosis in ventricular myocytes. *Circ Res*. 97(10):1009–1017
3. Karmazyn M (1998) The myocardial sodium-hydrogen exchanger (NHE) and its role in mediating ischemic and reperfusion injury. *Keio J Med*. 47(2):65–72
4. Armstrong JS (2006) Mitochondrial membrane permeabilization: the sine qua non for cell death. *Bioessays* 28(3):253–260
5. Borutaite V, Mildaziene V, Brown GC et al (1995) Control and kinetic analysis of ischemia-damaged heart mitochondria: which parts of the oxidative phosphorylation system are affected by ischemia? *Biochim Biophys Acta* 1272(3):154–158
6. Di Lisa F, Canton M, Carpi A et al (2011) Mitochondrial injury and protection in ischemic pre- and postconditioning. *Antioxid Redox Signal* 14(5):881–891
7. Aldakkak M, Stowe DF, Heisner JS et al (2008) Enhanced Na⁺/H⁺ exchange during ischemia and reperfusion impairs mitochondrial bioenergetics and myocardial function. *J Cardiovasc Pharmacol* 52(3):236–244
8. Aldakkak M, Camara AK, Heisner JS et al (2011) Ranolazine reduces Ca²⁺ overload and oxidative stress and improves mitochondrial integrity to protect against ischemia reperfusion injury in isolated hearts. *Pharmacol Res* 64(4):381–392
9. Chen Q, Hoppel CL, Lesnefsky EJ (2006) Blockade of electron transport before cardiac ischemia with the reversible inhibitor amobarbital protects rat heart mitochondria. *J Pharmacol Exp Ther* 316(1):200–207
10. Lesnefsky EJ, Chen Q, Moghaddas S et al (2004) Blockade of electron transport during ischemia protects cardiac mitochondria. *J Biol Chem* 279(46):47961–47967
11. Nadochiy SM, Burwell LS, Brookes PS (2007) Cardioprotection and mitochondrial S-nitrosation: effects of S-nitroso-2-mercaptopyronyl glycine (SNO-MPG) in cardiac ischemia-reperfusion injury. *J Mol Cell Cardiol* 42(4):812–825
12. D'Alonzo AJ, Grover GJ, Darbenzio RB et al (1995) In vitro effects of capsaicin: antiarrhythmic and antiischemic activity. *Eur J Pharmacol* 272(2–3):269–278
13. Hanley PJ, Ray J, Brandt U et al (2002) Halothane, isoflurane and sevoflurane inhibit NADH:ubiquinone oxidoreductase (complex I) of cardiac mitochondria. *J Physiol* 544(Pt 3): 687–693
14. Kawabata H, Ishikawa K (2003) Cardioprotection by metformin is abolished by a nitric oxide synthase inhibitor in ischemic rabbit hearts. *Hypertens Res* 26(1):107–110
15. McClellan KJ, Plosker GL (1998) Trimetazidine. A review of its use in stable angina pectoris and other coronary conditions. *Drugs* 58(1):143–157
16. Fantini E, Demaison L, Sentex E et al (1994) Some biochemical aspects of the protective effect of trimetazidine on rat cardiomyocytes during hypoxia and reoxygenation. *J Mol Cell Cardiol* 26(8):949–958
17. Gambert S, Vergely C, Filomenko R et al (2006) Adverse effects of free fatty acid associated with increased oxidative stress in postischemic isolated rat hearts. *Mol Cell Biochem* 283(1–2):147–152
18. Monteiro P, Duarte AI, Goncalves LM et al (2004) Protective effect of trimetazidine on myocardial mitochondrial function in an ex-vivo model of global myocardial ischemia. *Eur J Pharmacol* 503(1–3):123–128.
19. Kantor PF, Lucien A, Kozak R et al (2000) The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. *Circ Res* 86(5): 580–588
20. Opie LH, Sack MN (2002) Metabolic plasticity and the promotion of cardiac protection in ischemia and ischemic preconditioning. *J Mol Cell Cardiol* 34(9):1077–1089

Myocardial infarction with contemporary bivasal occlusion: one case, two fates

Paola Capozza and Mario Marzilli, Cardiovascular Medicine Division, Cardiac and Thoracic Department, University of Pisa, Pisa, Italy

Correspondence: Paola Capozza, Cardiovascular Medicine Division, Cardiac and Thoracic Department, Via Paradisa, 2, 56124 Pisa, Italy.

Tel.: +39 050 995307, fax: +39 050 995308, e-mail: paola.cap@alice.it

Abstract

A 42-year-old man was admitted to our department with a diagnosis of myocardial infarction with ST-elevation. The coronary angiography showed the thrombotic occlusion of both circumflex and right coronary arteries. Only the dependent territory of circumflex artery, treated before recanalization with adenosine, showed a total recovery.

Keywords: myocardial infarction; adenosine; cardioprotection; microcirculation

■ Heart Metab. (2012) 54:29–32

History

A 42-year-old man was referred to our department for chest pain lasting for three and a half hours. The electrocardiogram (ECG), obtained at the Emergency Department upon arrival, showed a ST-elevation in the inferior leads and in V6 (Fig. 1).

The patient had been asymptomatic until that afternoon. His cardiovascular risk profile included: a family history for coronary artery disease (his mother suffered from a large myocardial infarction); smoking on 20 cigarettes/day; arterial hypertension treated with ACE-inhibitors and β -blockers.

The physical examination showed the patient was suffering, the blood pressure was 160/90 mmHg, the pulse was 90/min, oxygen saturation was 96%. A grade II diastolic murmur was heard together with a third heart sound. The chest and the abdomen examinations were normal; no peripheral edema was found.

The echocardiogram revealed akinesia of the mid-basal segments of the infero-lateral and inferior walls and hypokinesia of the antero-lateral wall with a mild left ventricular systolic dysfunction (EF 46%). In addition, there was a moderate mitral regurgitation.

The patient was treated with oxygen, aspirin, and glycoprotein IIb/IIIa inhibitors, and he was immediately referred to the cardiac catheterization laboratory.

The patient underwent a left ventriculography confirmed the akinesia of the mid-basal inferior wall with normal left ventricular volume and mildly depressed ejection fraction.

On the coronary angiography, the left main coronary artery was free from critical stenosis; the left anterior descending coronary artery (LAD) had a focal stenosis in the proximal segment followed by minor irregularities in the middle tract and a tight stenosis in the distal segment. The circumflex coronary artery (Circ) was occluded at the origin of a large second marginal

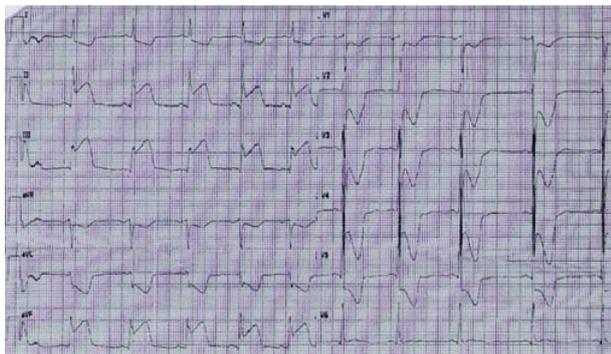


Fig. 1 ECG in the Emergency Department.

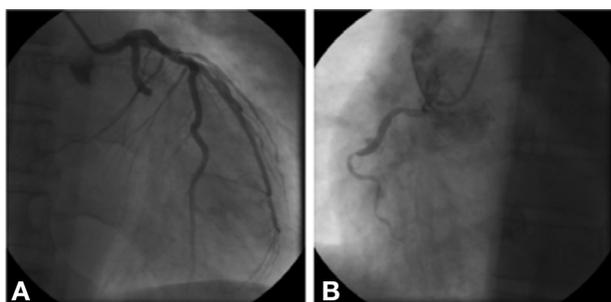


Fig. 2 These coronary frames show the total Circ (panel A) and RCA (panel B) occlusion.

branch (Fig. 2, panel A); another large marginal branch was free of stenosis. The right coronary artery (RCA) was dominant and was occluded in its middle tract (Fig. 2, panel B), immediately after the origin of the marginal branch. So, we found two vessels, the circumflex coronary artery and the right coronary artery, simultaneously occluded; that being so, both arteries could have been considered responsible for the clinical set. Given the technical difficulties of putting the catheter into the right coronary artery, first we decided to treat the Circ; so, in order to prevent the myocardial ischemia/reperfusion injury, a bolus of adenosine was directly injected into the marginal branch (4 mg in 2 ml saline) before performing the percutaneous coronary intervention (PCI) [1]. Then, a bare metal stent was implanted in the second marginal branch. After all we finally performed PCI and stenting of the medium tract of the right coronary artery (RCA).

The patient, returned to the Intensive Coronary Unit, was asymptomatic for chest pain. The ECG revealed a mild ST elevation in the inferior leads and ST depression in V1–V6.

Immediately after the PCI, we repeated the echo examination and we confirmed both the akinesia of the mid-basal segments of infero-lateral and inferior walls and the hypokinesia of the antero-lateral wall. Abciximab was administered for 12 hours after the stenting procedure; the patients also received aspirin, enalapril, metoprolol p.o., high dose of atorvastatin and lansoprazol.

From the second day after the PCI, the echo exam revealed a complete recovery of the prominent hypokinesia at the antero-lateral wall, while the alterations in the infero-lateral and inferior wall continued to be. Besides, we found a moderate to severe mitral regurgitation (eccentric jet, vena contracta width, got in long-axis parasternal view: 0.7 cm; mild dilated left atrial) and a restrictive diastolic pattern (E/A 1.6; DT 120 ms; average lateral and septal Tissue Doppler E': mm; E/E' 18).

Discussion

In animal models, infarct size and subsequent impairment of ventricular function are determined in a non-linear way after coronary occlusion [2]. In dogs, if reperfusion is activated after 5–15 minutes of vessel closure, there is almost complete recovery of the myocardium at risk. A significant recovery is still possible after occlusion lasting up three hours. When the “occlusion time” is extended beyond three hours, reperfusion does not result in recovery of contractile function [3].

Attempts to transfer these concepts on the clinical level have led to conflicting results (4–6). A relatively recent study about the effects of “ischemia time” on some clinical variables demonstrated that the favorable effects of thrombolysis on infarct size and ejection fraction are exclusive to patients who receive the optimal treatment within two hours after onset of symptoms [7]. Nevertheless, numerous studies have shown that status of coronary microcirculation plays a fundamental role in the prognosis of patients after an acute myocardial infarction. Failure to restore myocardial perfusion after recanalization of the artery responsible for infarction, documented by contrast echocardiography, is a strong negative prognostic factor and it is related to worse recovery of contractile function [8].

In a study of 31 patients with myocardial infarction, coronary velocity-flow after angioplasty and stenting

was demonstrated being an important predictor for the recovery of global and regional left ventricular function [9].

In recent times it has been shown that the presence of antegrade flow in the infarct before reperfusion, results in myocardial salvage and a good early functional recovery of stunned myocardium [10]. In the long-term follow-up was observed that patients with evidence of reperfusion before performing primary percutaneous transluminal coronary angioplasty (PTCA) had a more favorable course, with a significantly reduction of cardiogenic shock, with a better result of the procedure, with small size of the myocardial infarct area, and reduction in mortality [11].

Our group has shown that the intracoronary administration of adenosine immediately before reopening the culprit-lesion vessel dramatically improves myocardial perfusion. This reperfusion strategy is associated with an early recovery of contractile function [12]. More recently, Claeys et al. obtained similar results [13]. However, the administration extra-venously of lower adenosine doses did not alter significantly the clinical outcomes of patients with STEMI enrolled nell'AMISTAD-II trial [14], while achieving a reduction in size of the myocardial infarct area.

Several mechanisms contribute to the ischemia-reperfusion injury, including production of oxygen-free radicals, neutrophil activation, endothelial and myocyte edema, loss of antioxidant enzymes, and cardiomyocyte apoptosis [15]. Given this complex pathogenesis, several strategies are currently under investigation to prevent or lessen myocardial damage. Adenosine, an endogenous purine nucleoside, antagonizes many of the biochemical and physiological mechanisms implicated in ischemia-reperfusion injury and has been shown to reduce post-ischemic ventricular dysfunction and myocyte necrosis and apoptosis [16,17]. The exact mechanism of the cardioprotective effect of adenosine is not fully understood, although inhibition of neutrophil activation and prevention of endothelial damage seem to play a major role. Encouraged by this theoretical and experimental framework, we investigated the effects of adenosine as an adjunct to PTCA in acute myocardial infarction (AMI). Given the disappointing results of intravenous adenosine administration [18], we developed a strategy for the selective treatment of the ischemic territory right before the onset of reperfusion.

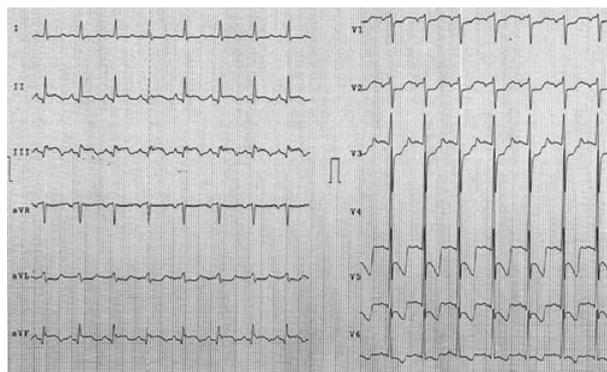


Fig. 3 Post-procedural ECG.

Conclusion

In this case report, we documented the relatively rare occurrence of two coronary arteries both responsible of myocardial infarction, but only one territory was protected with adenosine.

Ischemia and reperfusion both contribute to myocardial damage in AMI. Adenosine has been shown to limit ischemia-reperfusion injury in animal models. In this study, we have shown that adenosine administration in the infarct-related artery is feasible in the setting of primary angioplasty and that this treatment is safe and well tolerated and does not prolong procedural time. In this pilot study, intracoronary adenosine administration was associated with beneficial effects on coronary flow, on ventricular function, and on clinical course (Fig. 3). These observations are consistent with the hypothesis that a component of the ischemia-reperfusion injury can be prevented in humans by adenosine adjunct to primary PTCA. •

References

1. Marzilli M., Orsini E, Marraccini P, Testa R (2000) Beneficial Effects of Intracoronary Adenosine as an Adjunct to Primary Angioplasty in Acute Myocardial Infarction *Circulation* 101:2154–2159
2. Reimer KA, Jennings RB (1979) The "wavefront phenomenon" of myocardial ischemic cell death, II: transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. *Lab Invest* 40:633–644
3. Lavalleye M, Cox D, Patrick TA, Vatner SF (1983) Salvage of myocardial function by coronary artery reperfusion 1, 2, and 3 hours after occlusion in conscious dogs. *Circ Res* 53:235–247
4. Raitt MH, Maynard C, Wagner G et al (1996) Relation between symptom duration before thrombolytic therapy and final infarct size. *Circulation* 93:48–53
5. Newby LK, Rutsch WR, Califf RM et al (1996) for the GUSTO I Investigators. Time from symptom onset to treatment and

- outcomes after thrombolytic therapy. *J Am CollCardiol* 27: 1646–1655
6. Boersma E, Maas AC, Derckers JW et al (1996) Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 348:771–775
 7. Chareonthaitawee P, Gibbons RJ, Roberts RS et al for the CORE Investigators (2000) The impact of time to thrombolytic treatment on outcome in patients with acute myocardial infarction. *Heart* 84:14–28
 8. Ito H, Tomooka T, Sakai N et al (1992) Lack of myocardial perfusion immediately after successful thrombolysis: a predictor of poor recovery of left ventricular function in acute myocardial infarction. *Circulation* 85:1699–1705
 9. Wakatsuki T, Nakamura M, Tsunoda T et al (2000) Coronary flow velocity immediately after primary coronary stenting as a predictor of ventricular wall motion recovery in acute myocardial infarction. *J Am CollCardiol* 35:1835–1841
 10. Lim YJ, Masuyama T, Mishima M et al (2000) Effect of preperfusion residual flow on recovery from myocardial stunning: a myocardial contrast echocardiography study. *J Am Soc Echocardiogr* 13:18–25
 11. Brodie BR, Struckey TD, Hansen C, Muncy D (2000) Benefit of coronary reperfusion before intervention on outcomes after primary angioplasty for acute myocardial infarction. *Am J Cardiol* 85:138
 12. Marzilli M, Orsini E, Marraccini P, Testa R (2000) Beneficial effects of intracoronary adenosine as an adjunct to primary angioplasty in acute myocardial infarction. *Circulation* 101:2154–2159
 13. Claeys MJ, Bosmans J et al (2004) Effect of intracoronary adenosine infusion during coronary intervention on myocardial reperfusion injury in patients with acute myocardial infarction. *Am J Cardiol* 94(1):9–13
 14. Ross AM, Gibbons RJ, Stone GW, Kloner RA, Alexander RW (2005) A randomized, double-blinded, placebo-controlled multicenter trial of adenosine as an adjunct to reperfusion in the treatment of AMI. *JACC* 45:1775–1780
 15. Gottlieb RA, Bureson KO, Kloner RA, Babior BM, Engler RL (1994) Reperfusion injury induces apoptosis in rabbit cardiomyocytes. *J Clin Invest* 94:1621–1628
 16. Olafsson B, Forman MB, Puett DW, Pou A, Cates CU, Friesinger GC, Virmani R (1987) Reduction of reperfusion injury in the canine preparation by intracoronary adenosine: importance of the endothelium and the no-reflow phenomenon. *Circulation* 76:1135–1145
 17. Meldrum DR (1998) Tumor necrosis factor in the heart. *Am J Physiol* 274:R577–R595
 18. Van der Heide RS, Reimer KA (1996) Effect of adenosine therapy at reperfusion on myocardial infarct size in dogs. *Cardiovasc Res* 31:711–718

Myocytes versus endothelial damage

Frank L. Dini, Enrico Orsini, Mario Marzilli and Giacinta Guarini, Cardiovascular Medicine Division, Cardio Thoracic and Vascular Department, University of Pisa, Italy

Correspondence: Giacinta Guarini, Cardiovascular Medicine Division, Cardio Thoracic and Vascular Department, University of Pisa, Via Paradisa, 2, 56100 Pisa, Italy.
Tel.: +39 3494544161, e-mail: giacinta_guarini@yahoo.it

Abstract

Ischemic injury and reperfusion injury have been largely investigated in vitro and in animal models. This wide research body has elucidated several mechanisms involved in the processes. However, clinical applications of this information are limited and scanty. In the present article we attempt to summarize the different time course and the mechanisms involved in ischemic damage versus reperfusion injury. A better understanding of these complex phenomena may help in a more efficient application of cardioprotective and reperfusion strategies. This in turn could ameliorate the clinical outcome in patients with acute coronary syndromes.

Keywords: ischemic injury; reperfusion injury; endothelial damage; cardioprotection

■ Heart Metab. (2012) 54:33–36

Introduction

Reperfusion therapy in acute myocardial infarction (AMI) aims to restore myocardial perfusion in order to salvage jeopardized myocardium. Major advances in interventional techniques and pharmacological adjunctive therapy have made it possible to reopen and maintain patent over 95% of occluded vessels. But, paradoxically, this high recanalization rate has highlighted the limitations of current strategies in regards to restoring adequate tissue perfusion and improving patient prognosis. In fact, although we have observed an overall reduction in mortality, in hospital mortality still approaches 10% and over 25% of patients surviving acute phase are bound to develop heart failure syndrome.

Ischemic injury

Several studies have conclusively demonstrated that survival in the acute phase of myocardial infarction is directly related to the duration of ischemia and to recovery of tissue perfusion. The salvage of jeopardized myocardium is primarily determined by: 1) total ischemic time, 2) microcirculatory perfusion, and 3) myocytes and non-myocytes (endothelial cells and fibroblasts predominantly) preservation after the ischemia–reperfusion sequence [1,2]. This is consistent with animal models of ischemia and reperfusion described by Reimer et al. [3]. Few changes are detectable in the myocytes during the early phase of ischemic injury, while damage becomes evident and irreversible after 30–40 minutes of ischemia. This transition to irreversibility is associated with new ultrastructural changes [4], including diffuse mitochondrial swelling, the appearance of amorphous densities in the matrix space of the mitochondria, virtual absence of glycogen, marked peripheral aggregation of nuclear protein and the appearance of discontinuities in the cell membrane. This holds true in patients with STEMI, as clearly indicated in a recent work by Agati and al. using cMRI [5]. They observed that patients reperfused

within <90 min had a smaller infarct size, showed less severe microvascular damage and greater myocardial salvage after reperfusion, whereas patients reperfused later (>6 hours) presented with larger infarcts and greater microvascular obstruction and limited, if any, myocardial salvage. They also reported that the area at risk reduced over time only in patients reperfused within 90 min while it progressed to irreversible damage when reperfusion was achieved later. These data clearly confirm that the potential for myocardial salvage decrease dramatically with time and that after 90 minutes of ischemia there is limited benefit, if any, in term of infarct size reduction [2].

Reperfusion injury

Ultrastructural images obtained at a different time of coronary occlusion (20–80 minutes) in a dog model of coronary ligation and reperfusion, demonstrated that microvascular damage appears after 60 minutes of occlusion and always lags behind myocardial cell injury, appearing as early as 20 minutes after the beginning of ischemia. Microvascular alterations were consistently located in areas of irreversibly damaged myocytes [6]. The extension of non-reperfused area, within the ischemic zone, was larger after severe and prolonged ischemia and after prolonged reperfusion [7,8]. Additional studies have also confirmed that the area of no reperfusion increases with time, suggesting an independent progression of the reperfusion injury [9,10]. Microvascular damage has been identified as one of the key components of the no-reflow phenomenon. The cardiac no-reflow phenomenon was originally described in 1974 by Klöner et al. [11,12]. When canine myocardium was exposed to short periods of ischemia (<40 min of ischemia), no significant changes were noted in small cardiac vessels. However, when ischemia was maintained up to 90 min, dramatic changes appeared in the endothelial cells at capillary level. Electron microscopy studies revealed severe endothelial damage with capillary swelling and blebs causing intraluminal protrusions. Cellular and interstitial edema were also noted. Manciet et al. [13] demonstrated that ischemia for less than 30 min did not have a significant effect on small vessels. However, when arteries were exposed to ischemia of longer duration, capacity for endothelium-mediated relaxation progressively decreased and was totally lost after 120 min of ischemia. With loss of normal endothelial

function the vascular system lost the metabolic regulation capacity, i.e., lost the capacity to dilate in response to myocardial needs. In addition, intracellular edema and endothelial cell swelling occurred during myocardial infarction [14], resulted in compression of capillaries and small arterioles, further increasing resistance to flow through these dysfunctional vessels [13]. Ambrosio et al. [9] studied canine hearts submitted to 90-minute occlusions followed by reperfusion for either 2 minutes or 3.5 hours. The areas of absent capillary filling were larger after 3.5 hours than after 2 minutes of reperfusion and resulted primarily from intracapillary erythrocyte stasis and marked intravascular neutrophil accumulation. Reperfusion injury is a multifactorial process, including the “endothelial trigger” and “the inflammatory amplification” steps [15]. One of major determinants of endothelial dysfunction [16] is the loss of the endothelial cells capacity to release nitric oxide (NO) [17], which occurs within 2.5–5 min following re-establishment of flow. The reduced release of NO from the ischemic-reperfused endothelium occurs after 2.5–5 min of reperfusion, persists for hours, and appears to be related to superoxide radicals production by the abrupt reoxygenation [18]. Thus, a component of the reduced NO release is due to enhanced quenching of NO by superoxide radicals. This is followed by a dramatic increase in polymorphonuclear cells (PMN) adherence to the reperfused endothelium, becoming highly significant at 20 min post-reperfusion. This enhanced leukocyte adherence to the endothelium leads to capillary plugging and edema formation resulting, in turn, in coronary blood flow reduction. Leukocytes present in the coronary microcirculation at the time of reperfusion play a central role in the no-reflow phenomenon [19]. Following PMN adhesion to the endothelium, transendothelial migration of activated PMNs can occur resulting in PMN accumulation in the myocardium. Even if capillary leucocyte trapping is prominent in the area of no-reflow, the effects of leucocytes are probably not limited to mechanical plugging, but may involve complex interactions with endothelium, platelets, and perhaps with myocytes. Polymorphonuclear cells are able to release ROS, proteolytic enzymes, and lipooxygenase products (leukotrienes) that influence platelet and endothelial function. Endothelial cells can modulate leucocyte function by the expression of adhesion molecules—for example, intercellular

adhesion molecule-1 (ICAM-1) or P-selectin—and by release of soluble factors including nitric oxide, prostacyclin, endothelin, and platelet activating factor. Platelets affect polymorphonuclear cell activation by release of thromboxane A₂, platelet derived growth factor, serotonin, lipooxygenase products, proteases, and adenosine [19].

Latchman et al. [20] have further investigated the specific ways and time of death of endothelial cell (EC) and cardiac myocytes during ischemia and reperfusion in a rat model of ischemia/reperfusion. Apoptosis after ischemia/reperfusion proceeds in a cell- and time-dependent manner. Ischemia alone was not sufficient to complete the apoptotic death of myocyte and non-myocyte cells. Apoptosis of EC was initially visible in small coronary vessels to appear later on also in larger vessels and was associated with a progressively enlarging perivascular cuff of cardiomyocytes apoptosis. After 2 hours of reperfusion, the proportion of apoptotic EC decreased, and apoptotic cardiomyocytes were more homogeneously distributed. This led the authors to suggest that ischemia without reperfusion can initiate the molecular pathway of apoptosis, although reperfusion is required to complete the DNA fragmentation and morphological changes typical of an end-stage apoptotic cell. This requirement for reperfusion in completing the apoptotic program is consistent with previous studies [21,22]. The observation that EC apoptosis precedes that of cardiomyocytes has two important implications. First, mediator(s) generated during the ischemic period, released into the circulation may be necessary to complete the apoptotic process during reperfusion. Second, cardiomyocytes apoptosis may be triggered by the diffusion into the myocardium of soluble apoptogenic mediators derived from damaged EC. Several candidate mediators for this paracrine apoptosis of cardiomyocytes have been postulated, including those that ligate to tumor necrosis factor-alpha or Fas ligand and free radicals. The potential involvement of soluble factors in apoptosis after ischemia/reperfusion injury suggests that strategies based on their scavenging or inhibition may allow endothelial cell rescue and protect the myocardium.

Summary and conclusions

These observations are consistent with the hypothesis that cellular injury at the microvascular level is already

initiated during the ischemic insult, and that injurious mechanism(s) continues to operate, as a vicious cycle, during the reperfusion process. Therefore the final extent of microvascular damage and myocytes death is determined by the processes developing during the occlusion period as well as by the time at which reperfusion is applied. Ischemic damage needs no longer than 30 to 40 minutes to be established and reperfusion damage occurs within minutes from coronary blood flow restoration. These observations have two major consequences. First, they impose to reperfuse as soon as possible in order to reduce infarct size and second, they mandate the use protective strategies at the time of reperfusion to limit myocardial damage. The potential beneficial effect of these cardioprotective strategies is higher when reperfusion occurs early (less than 2 hours), i.e., when significant amount of viable myocardium is still present. Reperfusion damage contributes little to final infarct size when the myocardium is reperfused later after completing ischemic cell death. •

References

1. Stone GW, Dixon SR, Grines CL et al (2007) Predictors of infarct size after primary coronary angioplasty in acute myocardial infarction from pooled analysis from four contemporary trials. *Am J Cardiol* 100(9):1370–1375
2. Brodie BR, Webb J, Cox DA et al (2007) Impact of time to treatment on myocardial reperfusion and infarct size with primary percutaneous coronary intervention for acute myocardial infarction (from the EMERALD Trial). *Am J Cardiol* 99(12):1680–1686
3. Reimer KA, Vander Heide RS, Richard VJ (1993) Reperfusion in acute myocardial infarction: effect of timing and modulating factors in experimental models. *Am J Cardiol* 72(19):13G–21G
4. Jennings RB, Ganote CE (1974) Structural changes in myocardium during acute ischemia. *Circ Res* 35 Suppl 3:156–172
5. Francone M, Bucciarelli-Ducci C, Carbone I et al (2009) Impact of primary coronary angioplasty delay on myocardial salvage, infarct size, and microvascular damage in patients with ST-segment elevation myocardial infarction: insight from cardiovascular magnetic resonance. *J Am Coll Cardiol* 54(23):2145–2153
6. Kloner RA, Braunwald E (1980) Observations on experimental myocardial ischaemia. *Cardiovasc Res* 14(7):371–395
7. Reffelmann T, Hale SL, Li G et al (2002) Relationship between no reflow and infarct size as influenced by the duration of ischemia and reperfusion. *Am J Physiol Heart Circ Physiol* 282(2):H766–772
8. Reffelmann T, Kloner RA (2002) The “no-reflow” phenomenon: basic science and clinical correlates. *Heart* 87(2):162–168
9. Ambrosio G, Weisman HF, Mannisi JA et al (1989) Progressive impairment of regional myocardial perfusion after initial restoration of postischemic blood flow. *Circulation* 80(6):1846–1861

10. Kloner RA (1993) Does reperfusion injury exist in humans? *J Am Coll Cardiol* 21(2):537–545
11. Kloner RA, Ganote CE, Whalen DA, Jr. et al (1974) Effect of a transient period of ischemia on myocardial cells. II. Fine structure during the first few minutes of reflow. *Am J Pathol* 74(3):399–422
12. Kloner RA, Ganote CE, Jennings RB (1974) The “no-reflow” phenomenon after temporary coronary occlusion in the dog. *J Clin Invest* 54(6):1496–1508
13. Manciet LH, Poole DC, McDonagh PF et al (1994) Microvascular compression during myocardial ischemia: mechanistic basis for no-reflow phenomenon. *Am J Physiol* 266(4 Pt 2):H1541–1550
14. Carlson RE, Aisen AM, Buda AJ (1992) Effect of reduction in myocardial edema on myocardial blood flow and ventricular function after coronary reperfusion. *Am J Physiol* 262(3 Pt 2):H641–648
15. Tsao PS, Aoki N, Lefer DJ et al (1990) Time course of endothelial dysfunction and myocardial injury during myocardial ischemia and reperfusion in the cat. *Circulation* 82(4):1402–1412
16. Tsao PS, Lefer AM (1990) Time course and mechanism of endothelial dysfunction in isolated ischemic- and hypoxic-perfused rat hearts. *Am J Physiol* 259(6 Pt 2):H1660–1666
17. Lefer AM, Lefer DJ (1996) The role of nitric oxide and cell adhesion molecules on the microcirculation in ischaemia-reperfusion. *Cardiovasc Res* 32(4):743–751
18. Ma XL, Weyrich AS, Lefer DJ et al (1993) Diminished basal nitric oxide release after myocardial ischemia and reperfusion promotes neutrophil adherence to coronary endothelium. *Circ Res* 72(2):403–412
19. Meisel SR, Shapiro H, Radnay J et al (1998) Increased expression of neutrophil and monocyte adhesion molecules LFA-1 and Mac-1 and their ligand ICAM-1 and VLA-4 throughout the acute phase of myocardial infarction: possible implications for leukocyte aggregation and microvascular plugging. *J Am Coll Cardiol* 31(1):120–125
20. Scarabelli T, Stephanou A, Rayment N et al (2001) Apoptosis of endothelial cells precedes myocyte cell apoptosis in ischemia/reperfusion injury. *Circulation* 104(3):253–256
21. Gottlieb RA, Buleson KO, Kloner RA et al (1994) Reperfusion injury induces apoptosis in rabbit cardiomyocytes. *J Clin Invest* 94(4):1621–1628
22. Fliss H, Gattinger D (1996) Apoptosis in ischemic and reperfused rat myocardium. *Circ Res* 79(5):949–956

The heart failure and obesity paradox: would you suggest your patients gain weight?

Alda Huqi, Cardiovascular Medicine Division, Cardio Thoracic Department, University of Pisa, Pisa, Italy.

Correspondence: Dr. Alda Huqi, Cardiovascular Medicine Division, Cardio Thoracic Department, University of Pisa, Via Paradisa, 2, 56100 Pisa, Italy. And: 423 Heritage Medical Research Center
Tel: +39 32972 56426, e-mail: alda_h@hotmail.com

Hot Topics

Obesity is a well-established risk factor for cardiovascular disease, including hypertension (HTN), heart failure (HF), and coronary heart disease (CHD) [1]. Interestingly, for each increment of 1 unit in body-mass index (BMI), an increase in the risk of heart failure of 5% for men and 7% for women has been estimated [2]. However, once the disease is established, data from clinical cohorts suggest that overweight and obese patients with HTN, HF, and CHD tend to have a more favorable short- and long-term prognosis, a phenomenon termed as “obesity paradox” [3,4]. Although the underlying mechanisms remain elusive, the obesity paradox has led physicians to question whether obesity should be treated when associated with HF.

Obesity paradox clearly represents a controversial area, and this is reflected both in the lack of finite directions from the HF international guidelines, as well in some of the issues regarding data in the literature. First of all, the available data are mostly retrospective in nature and, as such, cannot replace prospective studies. Moreover, although weight loss in chronic HF has consistently been linked to impaired survival [5], there are no data to support that purposeful weight gain improves clinical outcomes of HF patients. In addition, none of the major studies accounted for non-purposeful weight loss (an important phenotype of advance HF patients) or duration of disease. Indeed, over the past 50 years, the prevalence of HF has continuously risen due to improved survival [6]. As a consequence, HF patients present with a longer and a more advanced disease history, which is associated with an increased catabolic state. In this regard, obese patients with HF may represent a patient population with a greater metabolic reserve [5,7] or, in other words, a less advanced disease stage. In fact, obese patients with HF are, on average, younger, have lower natriuretic peptide levels, have more skeletal muscle, better appetite and are less catabolic.

On the other hand, when assessed in other cardiovascular disease setting such as CHD, purposeful weight loss as a result of cardiac rehabilitation program appears to have a favorable impact on long-term outcome, regardless of initial BMI [8]. Moreover, despite the obesity paradox in HF, trials have suggested that weight loss can induce improvements in left-ventricular (LV) mass as well as in systolic and diastolic ventricular function [9–11]. In addition, it has been suggested that, when separately assessed, weight loss and fat loss may have a different impact on mortality rates [12,13].

As outlined, the “weight” of evidence does not support weight gain as a treatment choice in HF patients. Systematic studies on purposeful changes in body composition in HF are warranted to establish the pathophysiology and evidence-driven management of nutritional status in this patient population. •

References

1. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J et al (2009) Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 373(9669):1083–1096
2. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG et al (2002) Obesity and the risk of heart failure. *N Engl J Med* 347(5):305–313
3. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH (2001) The relationship between obesity and mortality in patients with heart failure. *J Am Coll Cardiol* 38(3):789–795
4. Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA (2008) Body mass index and mortality in heart failure: a meta-analysis. *Am Heart J* 156(1):13–22
5. Anker SD, Negassa A, Coats AJ, Afzal R, Poole-Wilson PA, Cohn JN et al (2003) Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. *Lancet* 361(9363):1077–1083
6. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK et al (2002) Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* 347(18):1397–1402
7. Kalantar-Zadeh K, Block G, Horwich T, Fonarow GC (2004) Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. *J Am Coll Cardiol* 43(8):1439–1444
8. Sierra-Johnson J, Romero-Corral A, Somers VK, Lopez-Jimenez F, Thomas RJ, Squires RW et al (2008) Prognostic importance of weight loss in patients with coronary heart disease regardless of initial body mass index. *Eur J Cardiovasc Prev Rehabil* 15(3):336–340
9. Alpert MA, Terry BE, Mulekar M, Cohen MV, Massey CV, Fan TM et al (1997) Cardiac morphology and left ventricular function in normotensive morbidly obese patients with and without congestive heart failure, and effect of weight loss. *Am J Cardiol* 80(6):736–40
10. Artham SM, Lavie CJ, Milani RV, Ventura HO (2011) Value of weight reduction in patients with cardiovascular disease. *Curr Treat Options Cardiovasc Med* 12(1):21–35
11. Lavie CJ, Milani RV, Artham SM, Patel DA, Ventura HO (2009) The obesity paradox, weight loss, and coronary disease. *Am J Med* 122(12):1106–1114
12. Allison DB, Zannolli R, Faith MS, Heo M, Pietrobello A, VanItallie TB et al (1999) Weight loss increases and fat loss decreases all-cause mortality rate: results from two independent cohort studies. *Int J Obes Relat Metab Disord* 23(6):603–611
13. Lavie CJ, De Schutter A, Patel D, Artham SM, Milani RV (2011) Body composition and coronary heart disease mortality--an obesity or a lean paradox? *Mayo Clin Proc* 86(9):857–864

Adenosine

Adenosine is a purine nucleoside comprised of adenine attached to a ribose sugar that plays a key role in cellular processes such as energy transfer and signal transduction.

Akt

Akt, also known as protein kinase B, is a kinase activated upon insulin stimulation that aids in facilitating glucose uptake into insulin sensitive tissues such as the skeletal muscle.

ATP-sensitive potassium channels (K_{ATP})

K_{ATP} are potassium channels gated by ATP present in the sarcolemmal, mitochondrial, and nuclear membranes. Increased ATP levels cause these channels to close, resulting in depolarization.

Cyclosporin A

Cyclosporin A is an immunosuppressive agent that inhibits MPTP opening via binding to cyclophilin D.

Electron transport chain

The electron transport chain encompasses a series of four inner mitochondrial membrane protein complexes that allow electron transfer between electron donors (i.e., NADH/FADH₂) and electron acceptors such as O₂. The transfer of electrons between these complexes causes the transfer of protons from inside the mitochondrial matrix outside into the mitochondrial inner membrane space, which drives an electrochemical proton gradient used to drive ATP synthesis in the process of oxidative phosphorylation.

Exenatide

Exenatide is the synthetic version of the GLP-1 receptor agonist hormone, exendin-4, and is currently used in the treatment of type 2 diabetes due to its ability to enhance glucose-stimulated insulin secretion.

FGF-2 (fibroblast growth factor-2)

FGF-2 exists as low molecular weight (18 kDa) and high molecular weight isoforms (20-34 kDa). It belongs to a large family (FGF-1-FGF23) of highly conserved

heparin binding growth factors that act by binding to and activating cell surface receptors (FGFR1-FGFR4) possessing intrinsic tyrosine kinase activity.

Heat shock proteins (HSPs)

Heat shock proteins are cytoprotective, molecular chaperone proteins, belonging to five families based on molecular weight (kDa)—HSP100, HSP90, HSP70, HSP60, and small HSPs (12-43 kDa).

Insulin-like growth factor-1 (IGF-1)

IGF-1 is a 70 amino acid peptide hormone that is structurally related to insulin, IGF-1 contributes to a wide range of processes including the regulation of cellular growth, differentiation, survival, and energy homeostasis.

Mitochondrial permeability transition pore(MPTP)

The MPTP is a protein pore that forms in the inner mitochondrial membrane during cellular stresses such as ischemia/reperfusion injury, resulting in mitochondrial swelling and subsequent cellular death via either apoptosis or necrosis.

Reperfusion injury salvage kinase (RISK) pathway

The RISK pathway is a cytoprotective kinase signaling pathway comprised of the pro-survival kinases phosphatidylinositol 3-kinase, Akt, and the extracellular regulated mitogen activated protein kinases (ERK1/2). It is implicated in limiting myocardial ischemia reperfusion injury.

Sevoflurane [1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy)propane]

Sevoflurane is a volatile liquid that is utilized as an inhalation anesthetic to induce and maintain general anesthesia.

Survivor activating enhancer (SAFE) pathway

The SAFE pathway is a cytoprotective kinase signaling pathway that requires the activation of signal transducer and activator of transcription 3 (STAT-3) and is implicated in limiting myocardial ischemia reperfusion injury. •