



PATHOPHYSIOLOGY, CLINICAL SIGNIFICANCE AND POSSIBILITIES OF CARDIOPROTECTION IN MYOCARDIAL STUNNING, HIBERNATION AND PRECONDITIONING

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Abstract

The prolonged acute myocardial ischemia was once thought to result in irreversible cellular damage. Nevertheless, it is now demonstrated that in cardiac tissue under the stress of oxygen and substrate deprivation endogenous mechanisms of cell survival may be activated. Hibernating myocardium is a state of persistently impaired myocardial function at rest due to reduced coronary blood flow owing to residual stenosis that can be restored toward normal by revascularization. The success of revascularization procedures depends on the presence of dysfunctional but viable myocardium. The pattern of cell survival elicited by ischemia in myocardial stunning, hibernation and preconditioning results in the activation of cytoprotective mechanisms that will protect the heart against further ischemic damage. The basic mechanisms underlying stunning and hibernation are still a matter of intense research, which includes the discovery and characterization of new survival genes not revealed in the heart before, the unraveling of new cellular processes, such as autophagy, and study of metabolic biochemical disturbances. Therefore, understanding pathways of molecular adaptation of the cardiac myocyte during stress maintains its survival in these states and might help defining novel mechanisms of endogenous myocardial salvage in order to expand the conditions of preserved cellular viability and function of ischemic myocardium. Basic, clinical aspects and opportunities of therapeutic approaches in these types of cardiac dysfunctions are reviewed in this paper.

Keywords: *myocardial stunning, myocardial hibernation, myocardial preconditioning, coronary artery disease, cardiac dysfunction.*

During the last decades the definition of non-specific types of coronary artery disease were clinically and pathologically determined, which enabled myocardium to adapt and preserve the ability to stressful states by up-regulating its protective systems, which can defend it from subsequent injury. These phenomena are revealed by different pathological and clinical states and known as myocardial hibernation, preconditioning and stunning [Bollig R., 1990; Schawrz E.R. et al., 1996; Bollig R., Marban E., 1999; Ross J.Jr., 1991; Bonow R.O., 2002]. These myocardial

protective mechanisms opened new horizons for the study of the mechanisms for myocardial protection and opportunities of therapy.

Stunning protects a myocardial injury that persists after reperfusion, despite the absence of irreversible damage and restoration of normal coronary flow. Stunning may be triggered by short-term episodes of ischemia due to reduced coronary flow or inability of flow to insure increasing myocardial demands. Primary factor thought to be responsible is the cytosolic calcium overload during reperfusion due to the increased calcium entry into the cell and decreased uptake by the sarcoplasmic reticulum, oxygen-derived free radicals release [Bollig R., 1996]. Transient

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ischemia occurs in the catheterization laboratory followed by reperfusion, angioplasty. Peroxidation of free fatty acids in membranes may alter Na–Ca pump function, resulting calcium influx and cellular calcium overload [Kloner R.A. *et al.*, 1989]. This may result in proteolysis of troponins [Suzuki S. *et al.*, 1974; Bolli R., 1996]. These two mechanisms overlap in the pathologic damage of cellular membrane.

As showed by B.L. Gerber and co-authors, noninfarcted, dysfunctional human myocardium mostly presents with a perfusion-contraction mismatch, consistent with stunning [Gerber B.L. *et al.*, 2008]. By contrast, dysfunctional myocardium presenting with a perfusion-contraction match is always associated with significant amounts of necrosis. It has to be mentioned that stunning should not be considered as primary pathologic process, but it is a possible cardio-protective response, which needs to be restored. The early diagnosis of stunning process may clarify the possible reversible contractile dysfunction.

From the clinical point, stunning is characterized as prolonged myocardial contractile dysfunction with a gradual restoration of contractile activity and represented by persistent regional dysfunction at a time when chest pain, ST segment abnormalities and regional perfusion have recovered [Bolli R., Marban E., 1999; Billinger M., 2002]

The concept of reperfusion injury, although firstly recognized from animal studies, is now recognized as a clinical phenomenon that may result in microvascular damage, no-reflow phenomenon, myocardial stunning, myocardial hibernation, and ischemic preconditioning. The final consequence of this event is left ventricular (LV) systolic dysfunction leading to increased morbidity and mortality. The typical clinical case of reperfusion injury occurs in acute myocardial infarction (MI) with ST segment elevation in which an occlusion of a major epicardial coronary artery is followed by recanalization of the artery [Ross J.Jr., 1991; Gerber B.L. *et al.*, 2008]. This may occur either spontaneously or by means of thrombolysis and/or by primary percutaneous

coronary intervention (PCI) with efficient platelet inhibition by aspirin (acetylsalicylic acid), clopidogrel and glycoprotein IIb/IIIa inhibitors. Although the pathophysiology of reperfusion injury is complex, the major role that neutrophils play in this process is well known. Neutrophils generate free radicals, degranulation products, arachidonic acid metabolites, and platelet-activating factors that interact with endothelial cells, inducing endothelial injury and neutralization of nitrous oxide vasodilator capacity [Baxx J.J. *et al.*, 1997]. Adenosine, despite its multi-targeted pharmacological actions, is able to inhibit some of the above-mentioned detrimental effects. The next protective effect of adenosine in in vivo models of reperfusion injury is the reduction of the infarct size, the improvement of the regional myocardial blood flow and the regional function of the ischemic area. Additionally, adenosine preserves the post-ischemic coronary flow reserve, coronary blood flow and the post-ischemic regional contractility. In small-scale studies in patients with acute MI, treatment with adenosine has been associated with smaller infarcts, less no-reflow phenomenon and improved LV function. During the elective PCI adenosine reduced ST segment shifts, lactate production and ischemic symptoms. During the last years, three relatively large placebo-controlled clinical trials have been conducted: Acute Myocardial Infarction Study of Adenosine Trial (AMISTAD) I and II and Attenuation by Adenosine of Cardiac Complications (ATTACC). In the AMISTAD trials, the final infarct size was reduced and the LV systolic function was improved by adenosine treatment, mainly in patients with anterior MI localization [Barbagelata A. *et al.*, 2005]. However, morbidity and mortality were not affected. In the ATTACC study, the LV systolic function was not affected by adenosine, however, trends towards improved survival were observed in patients with anterior MI localization. The possibility of obtaining a Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow in the infarct-related artery in up to 95% of patients with acute MI (increasing the occurrence of

reperfusion injury) has turned back the interest towards the protection of myocardial cells from the impending ischemic and reperfusion injury in which adenosine alone or together with other cardio-protective agents may exert important clinical effects [Ross A.M. et al., 2005; Forman M.B., Jackson E.K., 2007].

The other type of specific cardiac adaptation to pathologic state in coronary artery disease represents hibernating myocardium. Hibernating myocardium is the impaired myocardial regional function due to chronically reduced coronary blood flow, which may be restored after successful revascularization. It is the type of adaptation of myocardium, when myocardium reduces its contractility to meet reduced perfusion, thereby preserving cellular viability [Calhoun W.B. et al., 1996]. Revascularization has provided an effective treatment of depressed left ventricular function in patients with chronically ischemic and “viable” myocardium. Assessment of viable myocardium can be achieved by several noninvasive techniques including dobutamine stress echo or radionuclides such as flurideoxyglucose (F18DG). F18DG uptake studies are based on the assumption that enhanced glucose uptake in areas of diminished blood flow provides evidence of viable myocardium [Gerber B.L. et al., 1996; Baxx J.J. et al., 1997]. Positron Emission Tomography (PET) has the excellent sensitivity to reveal hibernating viable myocardium in patients with left ventricular dysfunction. In comparative studies, PET showed highest predictive accuracy of all imaging methods in detecting dysfunctional myocardium that will improve after revascularization [Marinho N.V. et al., 1996]. The diagnosis of this type dysfunction has clinical importance because revascularization can improve myocardial function, decrease the symptoms of heart failure [Depre C. et al, 1995; Bonow R.O., 2002]. Hibernating myocardium can cause abnormal systolic or diastolic ventricular function or both. Symptoms of heart failure in hibernating myocardium may be inappropriately interpreted to myocardial necrosis, when the symptoms may, in fact, be reversed after the

chronic ischemia and relieved by coronary revascularization. In areas of hibernation, myocytes appear differentiated, resembling the fetal cardiomyocyte phenotype with the development of fibrosis. The increase of intracellular matrix proteins is observed in areas of hibernation. Despite the loss of contractile elements, biochemically cardiomyocytes are preserved [Depre C. et al., 1995]. The process of apoptosis is identified in biopsies from hibernating myocardium [Schawrz E.R. et al., 1996].

A large body of literature has supported the theoretical benefit of revascularization in recruiting hibernating or stunned myocardium [Calhoun W.B. et al., 1996; Gerber B.L. et al., 1996]. This has been supported by recent registry and population-based studies demonstrating a survival benefit after revascularization in patients with heart failure and coronary artery disease independent of angina. Some studies have suggested that coronary artery bypass grafting may be superior to percutaneous coronary intervention in a selected group of patients [Bonow R.O., 2002]. To date no randomized clinical trials have addressed the role of revascularization in this patient cohort [Shanmugam G. Legare J.F., 2008].

Several studies showed that chronic but reversible ischemic dysfunction is associated with almost normal resting myocardial perfusion, with maintained FDG uptake, and with recruitable inotropic reserve [Ross J. Jr., 1991]. These data support the contention that chronic hibernation is not the consequence of a permanent reduction of transmural myocardial perfusion at rest.

Ischemic preconditioning refers to the reduction of infarct size resulting from prolonged ischemia by one or more preceding short episodes of ischemia. Several studies suggest that the late phase of ischemic preconditioning is due to the synthesis of stress proteins and antioxidant enzymes. Indeed ischemic preconditioning represent as cardioprotective effect increasing protection to subsequent ischemia [Bolli R., 1996]. In clinical practice, ischemic preconditioning phenomenon is relied in warm up angina [MacAlpin R.N., Kattus A.A., 1965; Edwards R.J. et al., 2002].

Patients with CAD undergoing exercise stress test may have increased resistance to ischemia at the second test, performed after 15 min. The increased resistance is reflected by the reduction of symptoms, ST-segment depression and oxygen consumption at corresponding rate pressure products on second time compared with the first test [Williams D. et al., 1985]. It is now established that ischemic preconditioning may have biphasic course, with a first window of protection developing within minutes and lasting 1-2 hours and second window of protection between 12-24 hours [Bolli R., 1996; Zhai X. et al., 1996]. Ischemic preconditioning reduces energy utilization and the rate of glycogenolysis during regional ischemia, which leads to the sparing of high energy phosphates, less catabolite accumulation, which contributes to the improved recovery of oxidative metabolism. There are several data that heat shock protein increases the resistance of the heart to the ischemia and offer an endogenous route to myocardial protection [Gordon J.L., 2000; Krause S., Hess M.L., 2001].

Over the last two decades, it has become increasingly clear that oxidant and oxygen radical formation is greatly increased in the post-ischemic heart and serves as a critical central mechanism of post-ischemic injury. This oxidant formation is generated through a series of interacting pathways in cardiac myocytes and endothelial cells and triggers subsequent leukocyte chemotaxis and inflammation. Nitric oxide (NO) production and NO levels are also greatly increased in ischemic and post-ischemic myocardium, and this occurs through NO synthase (NOS)-dependent NO formation and NOS-independent nitrite reduction [Jennings R.B. et al., 2001; Krause S., Hess M.L., 2001]. Recently, it has been shown that the pathways of oxygen radical and NO generation interact and can modulate each other. Under conditions of oxidant stress, NOS can switch from NO to oxygen radical generation. Under ischemic conditions, xanthine oxidase can reduce nitrite to generate NO. NO and peroxynitrite can inhibit pathways of oxygen radical generation, and, in turn, oxidants can inhibit NO synthesis from

NOS [Krause S., Hess M.L., 2001]. Ischemic preconditioning markedly decreases NO and oxidant generation, and this appears to be an important mechanism contributing to preconditioning-induced myocardial protection [Zweier J.L., Talukder M.A., 2006].

The early phase of preconditioning (PC) lasts 2 to 3 hours and protects against myocardial infarction, but not against stunning. In contrast, the late phase of PC lasts for 3 to 4 days and protects against both myocardial stunning and infarction, making this phenomenon more clinically relevant. Late PC is a genetic reprogramming of the heart that involves the activation of several stress-responsive genes, which ultimately results in the development of a cardioprotective phenotype. Sublethal ischemic insults release chemical signals (nitric oxide [NO], adenosine, and reactive oxygen species) that trigger a series of signaling events (e.g., activation of protein kinase C, Src protein tyrosine kinases, Janus kinases 1/2, and nuclear factor-kappaB) and culminate in increased synthesis of inducible NO synthase, cyclooxygenase-2, hemoxygenase-1, aldose reductase, superoxide dismutase, and probably other cardioprotective proteins. In addition to ischemia, heat stress, exercise, and cytokines can also induce a similar series of events [Jennings R.B. et al., 2002]. Perhaps most importantly, many pharmacologic agents (e.g., NO-donors, adenosine receptor agonists, endotoxin derivatives, or opioid receptor agonists) can mimic the effects of ischemia in inducing the late phase of PC, suggesting that this phenomenon might be explored therapeutically.

These data represent an obvious pathway for therapeutic intervention.

Drugs, which partially inhibit the fatty acid oxidation overactivity, may be effective in the treatment of reperfusion injury in stunning. Inhibition of fatty acid oxidation with long-chain of 3-ketoacyl-coenzyme A thiolase (3-KAT), an enzyme of mitochondrial fatty acid beta oxidation, increases glucose and pyruvate oxidation and decreases lactate production resulting an improved contractile function during ischemia

and preservation of myocardium against metabolic injury [Brottier L., et al, 1990; Fragasso G., et al., 2003; Lee L. et al., 2004].

Patients referred for cardiac rehabilitation may benefit from combining trimetazidine with exercise training because both treatments produce synergic benefits on the cardiovascular system [Belardinelli R. et al, 2006]. There is evidence that trimetazidine improves left ventricular (LV) function in patients with ischemic and diabetic cardiomyopathy by shifting the cellular energy substrate reference from fatty acids to glucose oxidation, and that this effect is associated with a better outcome [Brottier L. et al., 1990; Fragasso G. et al., 2003; Fragasso G. et al., 2006 ; Rosano G.M. et al., 2003]. Recently, results have demonstrated that trimetazidine improves radial artery endothelium-dependent relaxation related to its antioxidant properties. Similarly, exercise training has been demonstrated to improve diastolic filling and systolic

function in patients with ischemic cardiomyopathy, in relation to enhanced perfusion and contractility of dysfunctional myocardium. Patients with viable myocardium, in theory, should have the greatest benefits because trimetazidine improves contractility of dysfunctional hibernating/stunned myocardium, whereas exercise has documented efficacy in improving endothelial vasomotor response of coronary arteries, stimulating coronary collateral circulation and small vessel growth, improving LV function, and increasing functional capacity [Belardinelli R., Purcano A., 2001]. At present, there are no published reports about the efficacy of the combination of trimetazidine with exercise training. In this article, we discuss the rationale for using trimetazidine in cardiac rehabilitation, the identification of patients referred for cardiac rehabilitation who might mostly benefit from the addition of trimetazidine to standard therapy, and the documented benefits.

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