State-of-the-art - Cardiac general

Cardiac stunning in the clinic: the full picture

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1. Introduction

After brief episodes of ischemia and reperfusion, prolonged mechanical dysfunction persists, although no historical signs of irreversible injury to cardiomyocytes exist. This phenomenon was later called 'myocardial stunning' [1]. As a laboratory curiosity, ischemia/reperfusion (I/R) injury received little attention that steadily increased, however, in the following 20 years in the laboratories. For almost 25 years after the first description of myocardial stunning, its clinical relevance was widely acknowledged [2]. Hence, almost 200 publications from the clinic have appeared per year in the last 10 years (Fig. 1). It is mentioned that from the laboratories nearly twice the number of articles were published within the same period. Thus, more and more underlying mechanisms of stunning were described permitting the development of appropriate therapeutic options.

It is now clear that stunning involves different facets. In addition to (1) posts ischemic ventricular dysfunction myocardial (=myocardial stunning), there is evidence of (2) vascular/microvascular/endothelial injury (=vascular stunning; [3]), (3) posts ischemic metabolic dysfunction (=metabolic stunning; [4]), (4) long-lasting impairment of neurotransmission (neuronal/neuronal stunning [5]), and (5) electrophysiological alterations (=electrical stunning; [2]). These different facets will be discussed together with (6) posts ischemic inflammation that might develop after reinitiation of blood flow [6]. The term 'cardiac stunning' is used here to refer to all the different facets that have been observed in a wide variety of experimental settings that are paralleled by clinical settings [7] (Fig. 2).

This review assigns knowledge from the literature to different facets of cardiac stunning, draws attention to their clinical impact and tries to present therapeutic options. It is recalled that cardiac stunning is spontaneously reversible. Thus, any therapy is used to bridge the time needed for recovery. Finally, an outlook is thought to display areas of further development.

2. Clinical implications

The first clinical implications of cardiac stunning were acknowledged already in 1975, when Heyndrickx argued that the electrophysiologic recovery in synchrony with mechanical recovery in stunned myocardium would have implications for potential arrhythmogenicity, excitation-
contraction coupling, and clinical assessment of myocardial viability after thrombolysis [2]. Today, myocardial stunning is an acknowledged and ubiquitous clinical finding and occurs whenever ischemia and reperfusion are present: (a) in cardiology after percutaneous transluminal coronary angioplasty, unstable angina, stress-induced ischemia, thrombolysis [2, 8], (b) in cardiac surgery after coronary bypass operation or cardiac transplantation [2, 8], and (c) following resuscitation [9] (Table 1). More precisely, unstable angina, acute myocardial infarction, post-cardiac surgery, and chronic ischemic cardiomyopathy are clinical scenarios that might require therapy despite successful reperfusion in order to bridge until recovery.

On the basis of current understanding of the pathogenesis of reperfusion injury, numerous therapies have shown to avoid infarction and to improve ventricular function in animal models. Clinical trial experience on patients with acute myocardial infarction has, however, so far been somewhat disappointing for the use of these therapies [10]. On the other hand, therapeutic interventions during myocardial reperfusion have also been shown to convincingly reduce myocardial infarct size – in the case of longer lasting ischemias – and attenuate cardiac dysfunction in the clinic [11, 12]. Hence, it is agreed that cardiac stunning deserves therapy to attenuate its clinical consequences [13].

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<td><strong>Stunning in the clinic.</strong> Today, it is evident that myocardial stunning is an ubiquitous clinical finding and occurs whenever ischemia and reperfusion are present, e.g. in cardiology or in cardiac surgery after coronary bypass operation or cardiac transplantation but also following resuscitation</td>
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### 2.1. Myocardial/functional stunning

Acute I/R produces different facets of derangement, an obvious one being postischemic myocardial dysfunction. In consequence, the patients transiently require inotropic support and/or mechanical assist devices postoperatively, when none was required preoperatively [14].

#### 2.1.1. Free radical scavengers

Although there is clinical evidence that free radicals mediate the pathogenesis of myocardial dysfunction, cardioprotection by antioxidant therapy was inconclusive. Thus, so far using radical scavengers presents no general therapeutical avenue, except for reduction of reperfusion induced arrhythmias [15].

One additional facet, namely atrial stunning, is only recently acknowledged in the context with cardioversion from atrial fibrillation. Hemodynamic stress due to atrial fibrillation can generate highly toxic hydroxyl radicals that could oxidize various cell components and induce myocardial stunning [16].

#### 2.1.2. Positive inotropes

As stunned cardiomyocytes are sensitive towards stimulation, they can improve their mechanical status with positive inotropes [11]. The majority of clinically used positive inotropes act by increasing cytosolic Ca\(^{2+}\) levels. However, these inotropes are expected to worsen stunning, because Ca\(^{2+}\) homeostasis in cardiac dysfunction after I/R
is significantly impaired [7]. To avoid an increased Ca\textsuperscript{2+} load, excessive inotropic therapy should be avoided, while stunned myocardium responds positively to low-dose dobutamine infusion [17].

2.1.3. Ca\textsuperscript{2+} antagonists

Expectedly, Ca\textsuperscript{2+} antagonists attenuate the postischemic dysfunction in the clinic [18]. In contrast, the Ca\textsuperscript{2+} antagonist diltiazem, used in clinical studies after thrombolysis, had no effect on death, non-fatal myocardial infarction, or recurrent ischemia but did reduce non-fatal cardiac events, including myocardial revascularization [19]. Yet, usage of Ca\textsuperscript{2+} antagonists is regarded as an alternative therapy to prevention of Ca\textsuperscript{2+} overload [20].

2.1.4. Ca\textsuperscript{2+} sensitizers

Alternatively, Ca\textsuperscript{2+} sensitizing agents to improve recovery of ventricular function of stunned myocardium should be not only effective but also rational [21]. In fact, myofilament Ca\textsuperscript{2+} sensitizers attenuate myocardial stunning in an experimental scenario. Moreover, the newer Ca\textsuperscript{2+} sensitizers levosimendan seems promising also in patients with various acute heart failure syndromes, including postischemic dysfunction [22].

2.2. Endothelial/vascular/microvascular stunning

Not only cardiomyocytes but also endothelial cells can be stunned. The injury seems to develop independently from cardiomyocyte injury during postischemic reperfusion [23]. After more severe insults, smooth muscle cells are also likely to become stunned [24].

In cardiac surgery, the endothelium should be protected in order to reduce cardiovascular events, e.g. by making use of drugs that improve endothelial dysfunction. However, the role that hypoxic endothelial cell activation plays in myocardial dysfunction after I/R is not entirely understood. An increased understanding should allow therapies to be designed to further attenuate endothelial dysfunction [24].

2.2.1. Flow reserve

The endothelium plays a key role in the injury suffered after I/R [24], thus impairing coronary vasodilator reserve in the clinic for a prolonged time. Hence, when flow reserve is used to assess the functional significance of coronary stenoses, vascular stunned must be considered and could be the cause of variable exercise tolerance in patients with angina pectoris [3].

2.2.2. No-reflow phenomenon

An important consequence of postischemic reperfusion is the impairment to flow at the microvascular level secondary to vasoconstriction and neutrophil plugging, ultimately leading to the paradoxic no-reflow phenomenon [24]. This, however, usually occurs after more prolonged episodes of ischemia [2]. Different approaches to improving function in focal regions of microvascular impairment have been tried, among them a catheter-based method for infusion of aqueous oxygen into blood [25].

2.3. Metabolic/biochemical stunning

Myocardial stunning, as it almost regularly occurs in cardiac surgery, precipitates changes in the aerobic metabolism of glucose, fatty acids, and lactate. As a result, stunned myocardium uses oxygen and substrates only inefficiently, leading to poor functional recovery. Consequently, administration of amino acids prior to ischemia may be used as anaplerotic metabolic substrates during and after ischemia to form high-energy phosphates, allowing for better external contractile work after ischemia [26].

It is remembered that beside alterations in the aerobic metabolism, at least two other components contribute to the relatively high O\textsubscript{2} consumption in stunned myocardium, one being linked to the disturbed O\textsubscript{2} utilization of the contractile apparatus [27], the other to the repair of reversible damage [14].

2.4. Neural/neuronal stunning

Whenever there is appreciable sympathetic drive to the heart, disruption of cardiovascular sympathetic neural responsiveness is another possible facet of postischemic myocardial dysfunction. This form of stunning may occur in several situations, including acute myocardial infarction with early reperfusion, silent myocardial ischemia, and reperfusion after cardiac surgery. The reduced inotropic and coronary vasoconstrictor responses to sympathetic stimulation may be of importance for the functional consequences of reversible myocardial ischemia, in particular, as neural stunning can be long-lasting [28].

Like with other facets of postischemic injury, pharmacologic agents are desirable to either prevent injury or reduce its consequences. Exogenous antioxidant agents could actually be effective in preventing not only myocardial stunning, but also neural stunning in the above situations [29].

2.5. Electrical stunning

Disturbances of cardiac rhythm, including lethal ventricular arrhythmias, are a consequence of reperfusion following clinical instances of myocardial ischemia [2] (Fig. 3). Such arrhythmias might arise from re-establishing flow in Prinzmetal’s angina, cardiopulmonary bypass surgery with ischemic cardiac arrest, and angioplasty/thrombolytic procedures. In addition, atrial fibrillation as another electrical
disturbance, is a frequent corollary of coronary artery bypass surgery [30].

2.5.1. Free radical scavengers
In some clinical studies, free radical scavengers reduced infarct size and diminished oxidative stress and reperfusion arrhythmias [15]. In contrast, other clinical studies with several different agents, such as vitamin E and β-carotene, have been disappointing [31].

2.5.2. Positive inotropes
The disturbed Ca\(^{2+}\) homeostasis was already mentioned in the context with functional stunning. While low dose stimulation using catecholamines improves postischemic ventricular function [17], excessive stimulation can become deleterious to the myocardium by inducing intracellular Ca\(^{2+}\) overload and, hence, reperfusion arrhythmias [2].

2.5.3. ATP-dependent K channels
One potential option to prevent postischemic arrhythmias is selective activation of mitochondrial K\(_{\text{ATP}}\) channels, i.e. the triggering of preconditioning [32]. This intervention produces not only cardioprotective but also anti-arrhythmic effects when administered prior to coronary occlusion. Thus, the cardiomyocyte mitochondrial K\(_{\text{ATP}}\) channel may be a pharmaceutically modulable target of both cardioprotection and anti-arrhythmic activity [33].

2.6. Inflammation
After acute myocardial infarction, neutrophils migrate into the infarct zone during early reperfusion and later, they migrate into healthy myocardial tissue. This process is facilitated by cell-adhesion molecules. The neutrophils, being central cells in acute inflammation, cause vascular plugging and release reactive oxygen species (ROS) and degradative enzymes [34]. Re-initiation of blood flow achieved with percutaneous coronary intervention can lead to an acute local inflammatory response [6] with further myocardial and endothelial damage [10, 34].

Likewise, cardiac surgery is followed by the development of an inflammatory reaction [35] which appears to be extremely complex with regard to its molecular, cellular and tissue mechanisms [36].

As early as 15 years ago, stunning due to an acute inflammatory response to I/R was thought to be largely reversible with appropriate pharmacological interventions [37]. In this regard, administration of certain Ca\(^{2+}\) antagonist drugs exhibited an additional effect on the systemic inflammatory response after cardiopulmonary bypass in humans, by inhibiting the release of the pro-inflammatory cytokine IL-6, which is strong evidence for an anti-inflammatory potency [20]. However, the clinical results have not been convincing, so far.

2.7. Outlook

2.7.1. Animal experiments vs. clinical trials
Oxygen free radical scavengers, complement inhibition, leukocyte depletion, and the use of antibodies against various adhesion molecules have been shown to reduce infarct size in many I/R experimental models. Many of these agents failed to show a benefit in the clinical setting. More recently, positive findings from experiments have only partially been confirmed in humans [12, 36]. Similarly, Ca\(^{2+}\) antagonists have been shown to enhance function of stunned myocardium in experimental studies, and in a few clinical studies have also ameliorated postischemic dysfunction [8].

Other studies examining the potential of stimulating such endogenous cardioprotectants as adenosine, glucose, fatty acids, insulin, and potassium in the I/R setting have also been disappointing. Despite the marked beneficial effects of adenosine treatment in experimental preparations, the results of clinical studies were meager [38], and a prospective study on 20,000 patients reported no cardioprotective benefit from therapy with glucose, insulin, and potassium [39].

2.7.2. Preconditioning
If cardioprotection is one major objective, preconditioning must be mentioned as an additional player. Ischemic preconditioning could be used for cardioprotection as a means to limit infarct size, enhance postischemic recovery of cardiac function, and reduce vascular dysfunction and reperfusion arrhythmias. On the one hand, preconditioning via brief ischemic episodes can exert negative stunning; on the other hand they can exert a protective preconditioning effect. The future challenge is to minimize the former while maximizing the latter in clinical practice [8]. For example: it seems not illogical to exercise a patient with stable angina one day before surgery in order to evoke cardioprotection via delayed preconditioning [40].

Clinically, pharmacologic preconditioning could likewise be effective, because selective openers of K\(_{\text{ATP}}\) channels, adenosine receptor agonists and Na\(^+\)/H\(^+\) exchange (NHE) inhibitors also affect the final effectors of signaling pathways. Such pharmacologic preconditioning requires further exploration in transluminal coronary angioplasty, cardiac surgery and organ transplantation [41], i.e. in a setting, in which the time of intervention can accurately be scheduled.

It is well recognized that intracellular acidosis, the activation of both Na\(^+\)/H\(^+\) - and Na\(^+\)/Ca\(^{2+}\) exchange play an important role in Ca\(^{2+}\) influx in I/R [42]. Indeed, the preconditioning effects of NHE inhibitors, e.g. cariporide and eniporide, have been successfully assessed in a host of I/R models to recovery of ventricular function [42, 43]. Again, the results in the clinical setting are under debate, with some negative [44] and some positive [42]. Thus, the search for novel compounds continues.

2.7.3. Gene expression
It has been clear for nearly 10 years that brief ischemia resulting in stunning is associated with changes in gene expression [7]. One prominent example of such adaptations on the molecular level was found in cardiac surgery, but usage of cardioplegia in that study might have a different impact than ischemia alone. During cardioplegic arrest gene expression was increased, and during reperfusion, expression of some genes was increased or decreased for others.
indicating activation of multiple signaling pathways convergent on cellular growth and repair programs. As an example; the increased expression of genes regulating hemoglobin synthesis suggests a novel cardioprotective pathway evoked during ischemia reperfusion injury. In that particular setting, reversible myocardial I/R was associated with an immediate genomic response, predicting a net cardioprotective phenotype [45].

2.7.4. Complement inhibitor
Further insight into molecular and genomic adaptation to ischemia and reperfusion will help improve the ability to combat reperfusion injury [2, 46] and serve to devise new therapeutic modalities for patients. For example; a compound was designed to inhibit complement-mediated tissue damage associated with reperfusion injury and inflammation. In the I/R setting of cardiopulmonary bypass surgery, the complement inhibitor (plexizumab) appeared to reduce cardiac enzyme release and possibly mortality. Such a new class of therapeutics could improve outcomes for patients undergoing coronary artery bypass surgery (for review see: [47]).

2.7.5. Mechanical interventions
Such interventions could prevent another therapeutic modality to exert cardioprotection. Indeed, pulsatil pulmonary perfusion during cardiopulmonary bypass surgery, the complement inhibitor (H746) appeared to reduce cardiac enzyme release and possibly mortality. Such an intervention strategy of reperfusion therapeutics to postcondition, the mirror image of preconditioning could gain more importance in the clinic (for review see: [50]).

2.7.6. Integrated strategy
This strategy – e.g. combination of pharmaceutical and mechanical cardioprotection – might help to overcome the hitherto unsatisfactory results with using only one single therapeutic approach, as it draws attention to the many factors that contribute to reperfusion injury. Hence, postconditioning could be used independently or in conjunction with a variety of cardioprotective pharmaceuticals in such an integrated strategy of reperfusion therapeutics to reduce the various facets of posts ischemic injury [49]. If only one factor in the complex system of reperfusion injury is targeted, the remaining untargeted mechanisms can still induce injury. Thus, an integrated strategy of reducing reperfusion injury seems mandatory [49]. The potential benefits to patients receiving reperfusion therapy would be enormous [46].

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eComment: Re: Cardiac stunning in the clinic: the full picture

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The field of interest in cardiology and cardiovascular surgery has been focused on cardiac stunning for >30 years. Obviously, there are different facets of cardiac derangement. The term cardiac stunning includes not only myocardial, characterized by myocardial dysfunction, but also endothelial, metabolic, neuronal and electrical stunning [1].

Results of experimental studies on animal models permit differentiation between myocardial and vascular stunning. Results show that, while myocardial function has already recovered, endothelial cells are more severely impaired [2].

There are many published papers focusing on the topic of atrial electrical remodeling, which is defined as the shortening and dispersion of electric refractory period in patients with paroxysmal or persistent tachyarrhythmias [3]. Hence, a concept defined as a cardiac electrical stunning including electrical remodeling and reverse electrical remodeling should be a common characteristic and mechanism of cardiac arrhythmias. Certainly studies should be continued and should focus on understanding the mechanism of stunning and innovation in non-invasive cardiovascular imaging is rapidly advancing our ability to image in great detail the structure and function of the heart and vascular system [4]. New technologies in integrated molecular, functional and anatomical visualization (positron emission tomography/computed tomography [PET/CT]) offer a great potential for translating advances in molecularly targeted imaging into humans.

The main advantage of this review is the detailed analysis of different facets of cardiac stunning in clinical and, what is more important, the different therapeutic interventions which the various types of the cardiac injury might require. This aspect is rather important in patients after cardiovascular surgery with cardiac arrest.

At the Bakulev Center for Cardiovascular Surgery detailed studies using echocardiography with tissue Doppler imaging and evaluation of central hemodynamic in early postoperative period were carried out [5]. According to our data, application of temporary biventricular stimulation is favorable for patients with reduced ejection fraction and different facets of myocardial tissue derangement after cardiac surgery. Application of experimental results will provide a new opportunity for the management of patients with different facets of myocardial injury. It will help to understand the mechanism and integration of therapeutic options according to modern state of the problem of cardiac stunning.

References


