

# How should stunning be treated?

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*Stunning is, by definition, a state of fully reversible contractile dysfunction which recovers spontaneously. Therefore, with reperfusion the most important therapeutic intervention has already occurred. Since, in the clinical setting, stunning may coexist with persistently ischemic and infarcting myocardium, the benefit of therapeutic interventions on the stunned myocardium must be weighed against potential deleterious effects on the ischemic myocardium. Temperature, heart rate, and loading conditions must be optimized to minimize stunning. Pretreatment with adenosine, antioxidants, calcium antagonists, and ACE inhibitors attenuates stunning. With full reperfusion warranted, inotropic interventions attenuate stunning effectively without jeopardizing myocardial integrity.*

Pure stunning is by definition a state of fully reversible postischemic contractile dysfunction that persists after blood flow to the previously ischemic myocardium has been restored. Therefore, the most important therapeutic intervention, ie, reperfusion of the previously ischemic myocardium, has already occurred. Since the depressed contractile function will spontaneously recover over time, stunning per se requires no additional treatment at all. Nevertheless, therapeutic interventions may be required when stunning is severe and involves large parts of the ventricle such that ventricular pump function and the maintenance of adequate cardiac output and blood pressure are jeopardized.

Pure stunning in the absence of any irreversible damage may be primarily a laboratory phenomenon and occur clinically only in the scenario of controlled interventions such as percutaneous transluminal coronary angioplasty (PTCA) where, however, persistent impairment of systolic function is rare and diastolic abnormalities are only mild. Clinically more frequent may be a combination of stunned myocardium with persistently ischemic or even infarcted myocardium. In such a setting, the potential benefit of therapeutic interventions on the stunned myocardium must be weighed against potential deleterious effects on the ischemic myocardium.

## **Optimization of temperature, heart rate, and load**

Stunned myocardium is exquisitely sensitive to all factors that determine contractile function; in fact, as compared to normal myocardium, it may even be hypersensitive. An increase in body temperature from 37°C to 38°C has little impact on normal myocardium but depresses contractile function of stunned myocardium by as much as 40% of baseline values. End-diastolic dimensions and thus preload are a major determinant of contractile function in both normal and stunned myocardium; increased preload can actually reverse regional dyskinesia into a state of positive, yet still hypokinetic contraction. Along the same lines, increased heart rate reduces diastolic duration, resulting in reduced end-diastolic dimensions and, finally, further reduced contractile function. Stunned myocardium is much more sensitive to increases in afterload than normal myocardium; a reduction in systolic blood pressure from hypertensive to normal values can also reverse regional dyskinesia into a state of positive, yet, still hypokinetic contraction. In conclusion, to minimize stunning, temperature, heart rate, and loading should be optimized, and hyperthermia, tachycardia, hypovolemia, and hypertension corrected.

## **Vasodilators**

It is obvious that full reperfusion should be confirmed and

persistent ischemia excluded when contractile dysfunction is observed following reperfusion. A remaining flow restriction limits reactive hyperemia and the associated transient recovery of regional contractile function. However, even when blood flow to the previously ischemic myocardium is fully or almost fully restored, contractile dysfunction persists, but may then be alleviated by vasodilator therapy, using adenosine, dipyridamole, papaverine, or nitroglycerin. The improved contractile function in response to increased flow appears not to be related to a Gregg phenomenon, ie, an increase in contractile function secondary to an increase in blood flow above the autoregulatory range. Whether or not ischemia, which is alleviated by vasodilator therapy, persists in discrete areas at a microvascular level, even at normalized overall flow, is not clear at present. In stunned myocardium, coronary vasomotor responses to a number of vasoactive substances may or may not be altered. In any event, such vascular stunning is clearly dissociated from myocardial stunning and occurs probably only with more marked ischemia/reperfusion injury.

### **Adenosine in stunned myocardium**

Preischemic treatment with exogenous adenosine as well as augmentation of endogenous adenosine mitigate the severity of myocardial stunning, while treatment after the onset of reperfusion is ineffective. This beneficial action of adenosine cannot be attributed to increased collateral blood flow during coronary artery occlusion

or reperfusion, or to more favorable hemodynamics. Adenosine exerts a number of actions that could beneficially affect myocardial stunning, such as: (i) reduction of norepinephrine release from sympathetic nerve endings; (ii) inhibition of catecholamine-induced stimulation of adenylate cyclase; (iii) blockade of cardiomyocyte L-type Ca<sup>2+</sup> channels; and (iv) activation of cardiomyocyte ATP-dependent potassium channels. All pathways will ultimately decrease the intracellular calcium concentration, thereby potentially attenuating ischemic calcium overload and subsequently attenuating myocardial stunning.

### **Inotropic interventions**

Even while baseline function of stunned myocardium is depressed it retains the capacity to respond to various inotropic interventions, such as the addition of extracellular calcium, postextrasystolic potentiation, and paired pacing, or the infusion of inotropic drugs such as norepinephrine, epinephrine, isoproterenol, xamoterol, dopamine, dobutamine, and the purported calcium sensitizers AR-L 57 and EMD 60263. Even inotropic stimulation for up to several hours by isoproterenol or xamoterol does not deteriorate metabolism or precipitate irreversible injury. Studies on more prolonged inotropic stimulation of stunned myocardium are lacking. Whereas it appears effective and safe to improve contractile function of stunned myocardium with positive inotropic drugs, at least over shorter periods of time, any inotropic stimulation will further impair the situation of potentially coexistent ischemic areas and precipitate infarction there.

### **Antioxidants**

There is firm evidence for a causal involvement of free radicals in myocardial reperfusion injury. Both pharmacological attenuation of free radical formation as well as their enhanced elimination through low-molecular-weight antioxidants or antioxidant enzymes have been documented to improve the recovery of stunned myocardium. Although free radicals continue to be formed for hours after the onset of reperfusion, only those radicals which are generated immediately after the onset of reperfusion are important in stunning, as effective antioxidant therapy must be started at the time of reperfusion. Even combined and timely antioxidant therapy, however, does not prevent stunning completely.

### **Calcium antagonists**

There is unequivocal evidence from both in vitro and in vivo studies that pretreatment with calcium antagonists before ischemia improves the recovery of contractile function during reperfusion, ie, attenuates myocardial stunning. The consistent attenuation of stunning by pretreatment with calcium antagonists cannot be explained by an improvement in myocardial blood flow during ischemia or reperfusion or by more favorable hemodynamic conditions, eg, a reduction in heart rate or afterload.

In contrast, the potential benefit from calcium antagonists when given during reperfusion remains somewhat controversial. Two studies showed a beneficial effect also when treatment with a calcium antagonist was started during reperfusion. In the study



by Przyklenk et al (1989) a very low dose of nifedipine was infused directly into the previously ischemic myocardium starting at 30 minutes of reperfusion. Regional function returned almost to normal, although systemic hemodynamics and regional myocardial blood flow were not altered. It is not clear why this effect was observed, since nifedipine exhibits a high degree of vascular selectivity and would be expected to exert coronary dilator effects before having any effect on the myocardium. On the other hand, increased cytosolic calcium levels, which nifedipine might attenuate, return to normal within a few minutes of reperfusion.

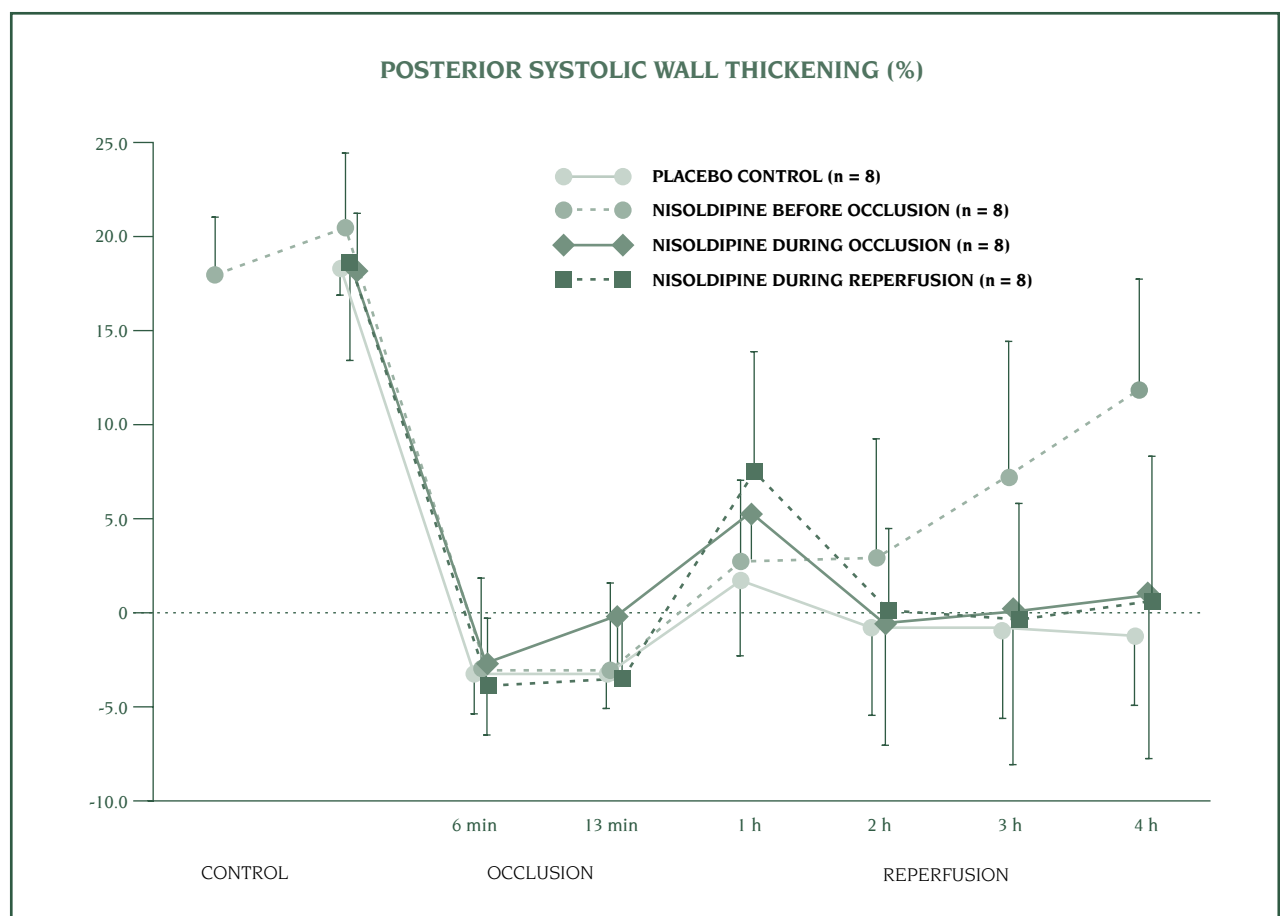
Also, the beneficial effect of nifedipine in this study is unlikely

to be attributed to the protection of membranes from damage induced by free radicals. Free radicals are formed for up to 3 hours after only 15 minutes of ischemia. However, the free radicals that might be responsible for stunning must be the ones generated immediately upon reperfusion, as antioxidant therapy is only effective at the onset of reperfusion. Finally, a 50% reduction in free radical-induced lipid peroxidation of myocardial membranes *in vitro* by nifedipine requires 80 to 1000 times higher concentrations of the drug than those used by Przyklenk et al (1989).

In isolated perfused rat hearts, nisoldipine given within the first 5 minutes of reperfusion improved

postischemic myocardial function. In contrast, a further deterioration in function was observed when nisoldipine was administered later, after established reperfusion. This study suggests that nisoldipine may attenuate the increase in the cytosolic calcium concentration during early reperfusion. During late reperfusion, when the cytosolic calcium is normal again, nisoldipine may induce a decrease in cytosolic calcium, resulting in an aggravation of stunning.

In a study from our laboratory, the effect of nisoldipine on regional myocardial blood flow and function during ischemia and reperfusion was investigated in open-chest dogs. The functional recovery after pretreatment with nisoldipine, after administration



**Figure 1.** Only after pretreatment with the calcium antagonist nisoldipine did posterior systolic wall thickening recover significantly following 4 h of reperfusion.

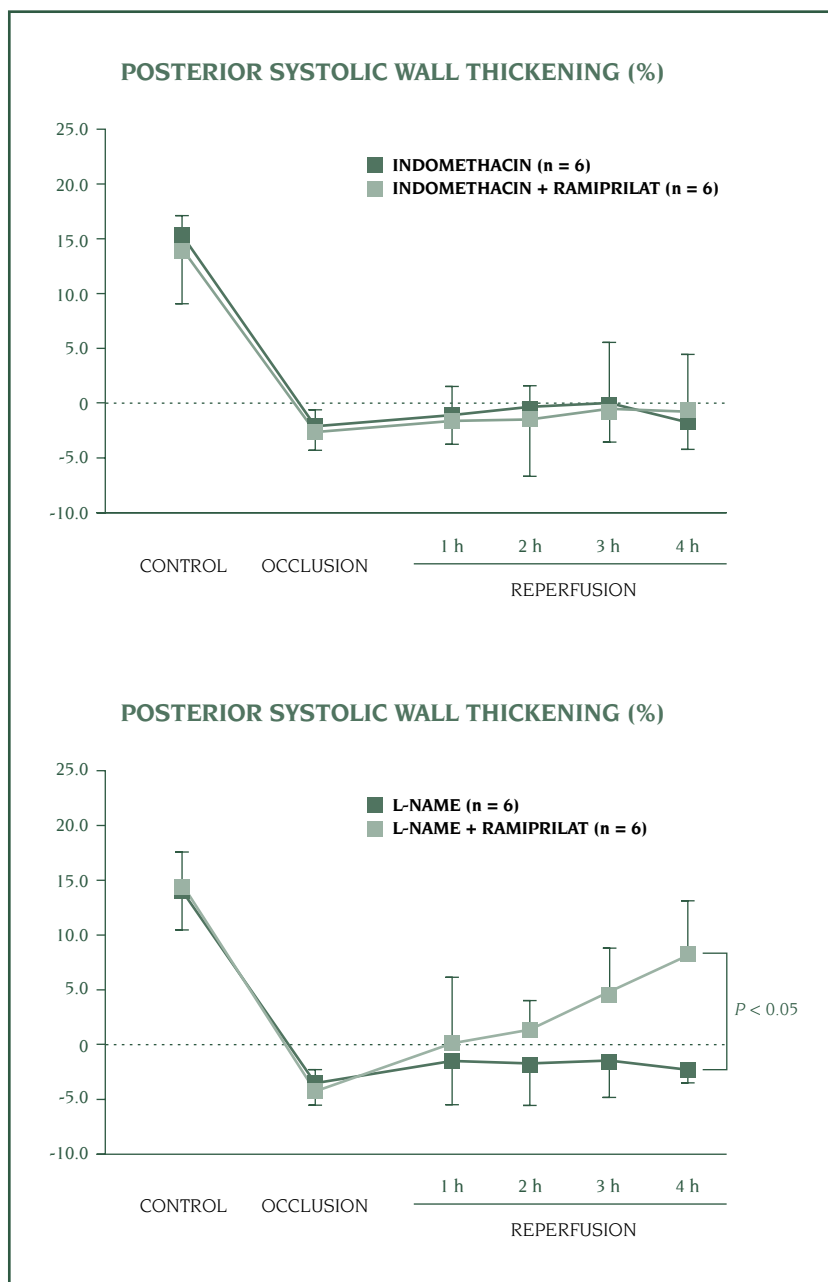
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of nisoldipine during ischemia, and after administration of nisoldipine early during reperfusion was compared with the functional recovery of a placebo group. Mean aortic pressure and heart rate were kept constant. The results clearly demonstrated a better functional outcome after pretreatment with nisoldipine, but no effect of nisoldipine when given late during ischemia or after established reperfusion (Figure 1).

The potential benefit from calcium antagonists when given during reperfusion thus remains somewhat controversial, although it is certainly clear that better recovery of function can be achieved when calcium antagonist treatment is started before ischemia. So far, therefore, the potential clinical use of treatment with calcium antagonists in attenuating myocardial stunning is limited to controlled interventions involving ischemia-reperfusion such as PTCA. On the other hand, patients already under treatment with calcium antagonists will not only experience a reduction in the severity of ischemia but also a better recovery of contractile function after termination of ischemia.

**ACE inhibitors in stunned myocardium**

The attenuation of myocardial stunning by several angiotensin converting-enzyme (ACE) inhibitors has been demonstrated in a number of experimental studies in vitro and in vivo. The mechanism underlying the cardioprotective action of ACE inhibitors, however, is not fully clear. Apparently, the beneficial effect of ACE inhibitors is not secondary to reduced formation of angiotensin, but rather to



**Figure 2.** The acceleration of recovery of contractile function with ramiprilat was prevented by cyclooxygenase inhibition with indomethacin, but not by nitric oxide synthase inhibition with L-NAME.

reduced breakdown of bradykinin; therefore, such a beneficial effect is abolished by bradykinin B<sub>2</sub>-receptor antagonists. Activation of endothelial bradykinin B<sub>2</sub>-receptors, in turn, increases the formation of NO and prostacyclin. Thus, stimulation of the prostaglandin pathway or production of NO could potentially mediate

the beneficial effect of ACE inhibitors on myocardial function during reperfusion. While in isolated hearts the cardioprotective effect of ramiprilat appears to be mediated by NO, this is not the case in the in situ heart where this effect is mediated by a signal cascade of bradykinin and prostaglandins (Figure 2).



### Concluding remarks

Most of the arguments presented above are derived from experimental studies. Therefore, they should be extrapolated to the clinical setting in humans only with great caution. It appears to be prudent and safe to confirm the full restoration of myocardial blood flow and to optimize temperature, heart rate, and ventricular loading whenever contractile dysfunction is observed after reperfusion. When attempting a causal treatment of myocardial stunning, antioxidant or calcium antagonist treatment appear to be most appropriate, although convincing clinical data are still lacking. In any event, such treatment must be started before the ischemic event that leaves the myocardium stunned, or at the latest with the onset of reperfusion. Positive inotropic interventions appear to be effective and safe over a few hours; data over prolonged periods of time are lacking. Before using positive inotropic interventions, however, persistently ischemic myocardium must be excluded as its integrity will definitely be jeopardized.

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