

Myocardial “stunning” 20 years later: a summary of current concepts regarding its pathophysiology, pathogenesis, and clinical significance

R. Bolli, MD

University of Louisville - 550 South Jackson Street - Louisville, Kentucky 40292 - USA

Among the pathogenetic mechanisms proposed for myocardial stunning, three have emerged as more likely: generation of oxygen radicals, calcium overload, and decreased responsiveness of contractile filaments to calcium. These are not mutually exclusive and may represent different steps of the same pathophysiological cascade. Thus, generation of oxyradicals may cause calcium overload, both processes resulting in damage and dysfunction of myofilaments. Unravelling the molecular mechanisms whereby a brief episode of ischemia can cause such a prolonged period of contractile dysfunction will be a major challenge. Stunning appears to develop in various settings in which transient ischemia occurs, eg, unstable angina, acute myocardial infarction with early reperfusion, exercise-induced ischemia, cardiac surgery, and cardiac transplantation. A potentially important consideration is that frequent episodes of ischemia, particularly in the ambulatory setting, may have a cumulative effect and cause protracted or chronic postischemic LV dysfunction, mistakenly diagnosed as hibernation when in fact it is a result of repetitive stunning. Recognition of myocardial stunning may impact upon patient management, as imaging techniques now allow prospective diagnosis. While no current diagnostic technique is ideal, thallium-201 scintigraphy or dobutamine echocardiography are available and should be applied in the appropriate clinical setting.

It was 20 years ago that postischemic myocardial dysfunction was first described by Vatner's group in conscious dogs undergoing brief coronary occlusions followed by reperfusion¹ (the term “myocardial stunning” was coined in 1982²). At the time of its discovery, this phenomenon received relatively little attention because coronary reperfusion was thought to be a rare occurrence. Myocardial stunning was regarded mostly as a laboratory curiosity. Beginning in the 1980s and continuing to an even greater extent in the 1990s, however, postischemic dysfunction has become the focus of increasing interest both among experimentalists³ and clinicians⁴ for two major reasons. First, coronary reperfusion by means of thrombolytic therapy, percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass graft (CABG) surgery has become a standard approach to the management of acute ischemic syndromes in patients with coronary artery disease. Second, several studies have demonstrated that many patients experience spontaneous reperfusion as a result of lysis of coronary thrombi or release of coronary spasm. Accordingly, it has become increasingly evident that postischemic myocardial stunning is a part of the natural history of coronary artery disease and may contribute significantly to the morbidity associated with this disorder. These are indeed the reasons for the growing popularity of stunning among cardiologists, who now often invoke this phenomenon as an explanation for clinical observations or as a basis for decision-making.

As a result of the increasing interest at both the experimental and the clinical level, our knowledge regarding myocardial stunning has increased dramatically over the past decade. Rarely has so much progress been made in such a short time. It is indeed astonishing to compare what we know about stunning now with what we knew only 10 years ago. It seems

likely that much more progress will be made in the next few years, as the investigation of this phenomenon moves more and more into the molecular mechanisms of the contractile defect, on the one hand, and into the clinical arena, on the other. Interest in stunning will also be propelled by the mounting interest in other related areas, such as the phenomenon of ischemic preconditioning and the changes in gene expression induced by brief ischemia, which are associated with stunning and are inextricably related to its pathophysiologic mechanisms.

The purpose of this article is to summarize our current knowledge regarding myocardial stunning in a format that is targeted at both investigators and clinicians. Emphasis will be placed on general concepts rather than on a detailed review of data. The first part of the article will deal with the experimental aspects of stunning, whereas the second part will deal with its clinical implications.

Definition of myocardial stunning

One cannot overemphasize the importance of a clear definition of myocardial stunning, for this term is

sometimes inappropriately applied to situations in which the persistence of contractile abnormalities in postischemic tissue is due to other causes (such as myocellular death, persistent ischemia, nonischemic injury, etc). *Postischemic dysfunction, or myocardial stunning, is the mechanical dysfunction that persists after reperfusion despite the absence of irreversible damage and despite restoration of normal or near-normal coronary flow.*³ The two essential points of this definition are: (i) that postischemic dysfunction, no matter how severe or prolonged, is a fully reversible abnormality; and (ii) that the dysfunction is not caused by a primary deficit of perfusion.³ Two corollaries follow from the above definition. First, in experimental settings the diagnosis of myocardial stunning should not be made unless reasonable assurance can be provided that the tissue in question is still entirely viable and that flow is normal or near-normal.³ Second, the diagnosis of stunning in patients requires demonstration of two major points: (i) that the contractile abnormality is reversible; and (ii) that the dysfunctional myocardium has normal or near-normal flow.⁴ While the first point has been frequently documented, only in rare instances has the second point been demonstrated in clinical studies (see below).

Table 1. CLASSIFICATION OF MYOCARDIAL STUNNING AND EVIDENCE FOR THE VARIOUS MECHANISMS PROPOSED IN EXPERIMENTAL ANIMALS

Experimental setting	EVIDENCE FOR A PATHOGENETIC ROLE OF			
	Oxygen radicals	Sarcoplasmic reticulum dysfunction	Calcium overload	Reduced calcium sensitivity
STUNNING DUE TO DECREASED BLOOD FLOW				
<i>Regional ischemia</i>				
Single, completely reversible ischemic episode	++	?	?	+
Multiple, completely reversible ischemic episodes	+	+	?	-
Single, partly irreversible ischemic episode (subendocardial infarction)	±	?	?	?
<i>Global ischemia</i>				
Isolated heart in vitro	+	?	+	+
Cardioplegic arrest in vivo	+	?	?	?
STUNNING DUE TO INCREASED O₂ DEMANDS				
<i>Exercise-induced ischemia</i>				
In the presence of coronary stenosis	-	?	?	?
In the absence of coronary stenosis (hypertrophy)	?	?	?	?

Legend: (+) Published studies support this mechanism; (++) Published studies from multiple laboratories consistently support this mechanism; evidence is also available in conscious animal preparations; (-) Published studies do not support this mechanism; (±) Published studies are conflicting; (?) No data are available. Adapted with permission of the American Heart Association from *Circulation*. 1990;82:723-738.



In accordance with this definition, myocardial stunning is a relatively mild, sublethal injury that must be kept quite distinct from myocardial infarction. It is unknown whether these two conditions share a common mechanism, and therefore data obtained in models of infarction should not be extrapolated to models of stunning.

MYOCARDIAL STUNNING IN THE EXPERIMENTAL LABORATORY

Experimental settings of myocardial stunning

Myocardial stunning, as defined above, is not a single entity but rather a “syndrome” that has been observed in a wide variety of experimental settings with major pathophysiological differences. The common denominator to these heterogeneous settings is that in all of them the myocardium is exposed to a transient ischemic episode that is not long enough to cause irreversible injury. Since the heterogeneity of the experimental models of stunning is likely to be associated with heterogeneous pathogenetic and pathophysiological substrates, it is important to discuss briefly the differences among the various settings.

The experimental observations can be classified into the following categories³ (Table 1):

Myocardial stunning after a single, completely reversible ischemic episode. In the dog, a coronary occlusion lasting < 20 min does not result in any myocardial necrosis, but upon reperfusion, the recovery of contractile performance in the previously ischemic myocardium is delayed for several hours.^{1-3,5-7} This is the “classic” model of myocardial stunning, the one in which the phenomenon was originally described,¹ and the one most commonly used in experimental investigations.³ The exact duration of postischemic contractile abnormalities in this model has varied in different experimental preparations. We have shown that in conscious dogs, the average transmural systolic wall thickening (an integrated measure of function across the ventricular wall) remains depressed up to 24 h after a single 15-min coronary occlusion.⁵ The rate of recovery, however, is faster in the subepicardium than in the subendocardium, suggesting that stunning is a nonuniform phenomenon that is most severe in the subendocardium.⁷ Both systolic and diastolic function are depressed in stunned myocardium⁶; thus, myocardial stunning must be viewed as a global derangement of the mechanical properties of the heart.

Myocardial stunning after multiple, completely reversible ischemic episodes. Repeated brief (2-10 min) coronary occlusions depress systolic function and result in prolonged contractile impairment despite absence of irreversible damage.^{3,8-10} This model of myocardial stunning differs from the single 10- or 15-min occlusion model in several respects: the mechanical dysfunction develops more gradually, is associated with a considerably greater total ischemic burden (20-60 min vs 10-15 min), its severity is not related to collateral perfusion during ischemia, and, as explained below, a preconditioning effect develops during the first three ischemic episodes.⁸ Whether recurrent ischemic episodes have a preconditioning effect or a cumulative effect on contractile function in this model is not entirely clear. We have recently shown that the first 5-min occlusion preconditions the myocardium against the next two occlusions, so that the overall severity of stunning is the same after one or three occlusions; however, after the third occlusion this preconditioning effect is lost, and additional occlusions cause a cumulative depression of contractility.⁸

Myocardial stunning after a single, partly irreversible ischemic episode (subendocardial infarction). In the dog, when reperfusion is instituted after a period of coronary occlusion > 20 min but < 3 h, the subendocardial portion of the region at risk is generally found to be infarcted, whereas variable quantities of subepicardial tissue remain viable. This subepicardial tissue salvaged by reperfusion may require days or weeks to recover its contractile function.³ Thus, early reperfusion during acute myocardial infarction results in an admixture of infarcted subendocardium and stunned subepicardium (ie, irreversible and reversible dysfunction, respectively).

Myocardial stunning after global ischemia in isolated hearts. Cellular viability in these preparations depends on many factors, including species, temperature, duration of ischemia, and perfusate composition. Although in these models the reversibility of the contractile abnormalities cannot be verified, under selected conditions isolated hearts reperfused after transient ischemia exhibit complete normalization of phosphocreatine content and intracellular pH.^{3,11,12} suggesting that viability is generally preserved. Accordingly, despite the numerous obvious differences from ischemia in vivo, myocardial stunning can be mimicked in isolated heart preparations. Obviously, the relevance to stunning becomes questionable in cases where these preparations are associated with significant cell death.³

Myocardial stunning after global ischemia during cardioplegic arrest in vivo. Despite the use of hypothermic

cardioplegia, global ischemia in intact animals is usually followed by prolonged contractile abnormalities.³ The reversibility of these derangements has not been documented, but under carefully controlled conditions they are likely to be due mostly to stunning.

Myocardial stunning after exercise-induced ischemia.

Exercise-induced increases in myocardial oxygen demands in the face of limited supply (flow-limiting stenosis) may provoke myocardial ischemia and dysfunction in animals. These contractile abnormalities persist after cessation of exercise, even if the stenosis is released.¹³ Importantly, Vatner and colleagues¹ have recently shown that, in dogs with LV hypertrophy, exercise can induce both ischemic myocardial dysfunction and postischemic myocardial stunning in the absence of any coronary stenosis - an observation that could have major clinical implications, as discussed below. In summary, myocardial stunning can also occur after high-flow ischemia in which the primary problem is an increase in oxygen demands rather than a decrease in supply.

Because of the many significant pathophysiological differences among these situations, one cannot assume that observations made in one setting necessarily apply to the others. An important, unresolved issue is whether or not all forms of stunning share a common pathogenesis.

Factors that determine the severity of myocardial stunning

As a general concept, the stunned myocardium is a "hypersensitive" myocardium.¹⁴ That is, every factor that affects contractile performance in the normal, healthy myocardium can be expected to have a greater impact on the stunned, convalescent myocardium. The factors that determine the severity of stunning have been recently reviewed,¹⁴ and include, among others, the severity and duration of flow deprivation, the myocardial temperature, the size of the ischemic region, and the loading conditions of the heart. The severity and duration of flow deprivation and the myocardial temperature are probably the most important. In conscious dogs undergoing a 15-min coronary occlusion there is a close coupling between the degree of myocardial dysfunction after reperfusion and the collateral blood flow during the preceding period of ischemia, whereby even small differences in ischemic perfusion are associated with large differences in postischemic recovery.⁵ Furthermore, as discussed above, the severity of stunning is greater in the inner layers of the left ventricular wall, which are the most severely ischemic, than in the outer layers.⁷ Another important factor is the duration of flow deprivation: the longer

the ischemic period, the greater the ensuing mechanical abnormalities.³ Temperature is an enormously important but frequently overlooked determinant of stunning^{14,15}: even small changes in myocardial temperature are associated with major changes in the severity of the contractile abnormalities.¹⁵

The fact that the severity of postischemic dysfunction is determined to a large extent by the severity and duration of the antecedent ischemia has two important implications.³ First, whatever the precise mechanism responsible for stunning may be, such a mechanism must be initiated and modulated by perturbations associated with ischemia. Although stunning appears to be, in part, a form of "reperfusion injury" (see below), it is ischemia that "primes" the myocardium for the development of such injury. Second, any intervention that attenuates the severity of ischemia would be expected to attenuate stunning after reflow. This is the reason why interventions that alleviate the injury incurred during ischemia (eg, adenosine, calcium antagonists, K_{ATP} channel openers) are so effective in mitigating myocardial stunning, despite the fact that they have no direct effect on the reperfusion injury component of stunning (see below). *An important concept is that reducing the severity of ischemia is probably the most effective way to reduce the severity of postischemic dysfunction.³*

Mechanism of myocardial stunning

Thus, in very general terms, postischemic dysfunction is modulated by abnormalities occurring during ischemia. But what is the specific sequence of events whereby transient ischemia leads to prolonged depression of contractility?

A number of hypotheses were proposed in the 1980s, most of which have been subsequently abandoned (Table II) (these hypotheses are reviewed in ref 3). At present, the two viable hypotheses regarding the pathogenesis of myocardial stunning are the "calcium" hypothesis and the "oxyradical" hypothesis (Table II). As pointed out previously,³ these theories are not mutually exclusive, and probably represent different facets of the same pathophysiological process.

The calcium hypothesis. In a very broad sense, the calcium hypothesis postulates that stunning is the result of a disturbance of cellular calcium homeostasis. This hypothesis encompasses three distinct postulated mechanisms: decreased responsiveness of myofilaments to calcium, calcium overload, and excitation-contraction uncoupling due to sarcoplasmic reticulum dysfunction (Table II).



Table II. MECHANISMS PROPOSED FOR MYOCARDIAL STUNNING

MOST PLAUSIBLE

1. Oxyradical hypothesis
(generation of oxygen-derived free radicals)
2. Calcium hypothesis
 - a) Excitation-contraction uncoupling due to sarcoplasmic reticulum dysfunction
 - b) Calcium overload
 - c) Decreased responsiveness of myofilaments to calcium

NOT PLAUSIBLE

1. Insufficient energy production by mitochondria
2. Impaired energy use by myofibrils
3. Impairment of sympathetic neural responsiveness
4. Impairment of myocardial perfusion
5. Damage of the extracellular collagen matrix

a) Decreased responsiveness of myofilaments to calcium.

In isolated ferret hearts subjected to 15 min of normothermic global ischemia, Kusuoka et al¹¹ observed that the stunned myocardium exhibited decreased responsiveness to calcium, as manifested by a decrease in the maximal calcium-activated force and a decrease in the myocardial sensitivity to extracellular calcium. The authors speculated that the reduced sensitivity to extracellular calcium, in turn, could be due to either a decrease in the intracellular free Ca^{2+} concentration ($[Ca]_i$) transient or a decrease in the sensitivity of myofilaments to calcium.¹¹ Subsequent studies refuted the former theory by demonstrating that the calcium transient is (paradoxically) *increased* in the stunned myocardium after global ischemia in isolated hearts. It was therefore proposed that the fundamental problem in postischemic dysfunction is a reduced responsiveness of the contractile apparatus to calcium (ie, reduced maximal calcium-activated force and/or reduced sensitivity) rather than an insufficient availability of free cytosolic calcium during systole.¹⁶ Further studies will be necessary to elucidate these issues and determine whether stunning is due to decreased myofilament sensitivity, decreased maximal calcium-activated force, or both. One problem with this hypothesis derived from in vitro studies is that it does not explain two observations made in vivo: (i) the stunned myocardium exhibits a normal or near-normal contractile reserve when challenged with inotropic stimuli; and (ii) the apparent sensitivity of the

stunned myocardium to intracoronary calcium is not decreased (reviewed in ref 3).

b) Calcium overload. A transient calcium overload after reperfusion has been postulated to contribute to myocardial stunning.¹⁶ Recent studies have shown that $[Ca]_i$ increases between 10 and 20 min of global ischemia in isolated hearts¹⁶; in these models, $[Ca]_i$ appears to remain transiently elevated during very early reflow, but returns to normal values within few minutes after reperfusion. It should be noted, however, that the measurements performed thus far have failed to show a postreperfusion rise of $[Ca]_i$ to levels *higher* than those attained during ischemia.

At first sight, the calcium overload theory may appear paradoxical in view of the fact that exogenous calcium ameliorates function in the stunned myocardium¹¹ However, this discrepancy is only apparent, since the increase in $[Ca]_i$ is postulated to be a *brief* phenomenon occurring immediately after reflow, following which there would be a normalization of $[Ca]_i$ transients.

How does $[Ca]_i$ rise during ischemia? One possibility is through decreased calcium uptake by the sarcoplasmic reticulum. Na^+Ca^{2+} exchange could also play a role with a rise in intracellular Na^+ during ischemia due both to metabolic inhibition of the $Na^+K^+ATPase$, and to acidosis and consequent Na^+H^+ exchange. The mechanism(s) by which a transient calcium overload could induce prolonged contractile dysfunction is (are) also unclear, although it is known that increased cytosolic calcium can activate protein kinases, phospholipases, and other degradative enzymes.^{12,16}

Calcium channel blockers, including verapamil, diltiazem, nifedipine, nitrendipine, and amlodipine, have been shown to improve recovery of function in regionally stunned myocardium in intact animals.³ However, it is unclear whether these beneficial effects reflected a *direct* protective action of the drugs or were mediated by favorable modifications of afterload, preload, heart rate, and regional myocardial blood flow, all of which could modulate the contractile performance of the stunned myocardium.¹⁴ Heusch has demonstrated that nisoldipine attenuates myocardial stunning only when given before ischemia, not when given at reperfusion, and that this effect is independent of hemodynamic effects.¹⁷ Park et al³² have recently shown that nisoldipine attenuates myocardial stunning in conscious pigs via a direct cardioprotective action. *The ability of calcium antagonists to alleviate stunning, however, does not imply the existence of a calcium overload after reperfusion:* calcium antagonists probably work by decreasing the influx of calcium during ischemia, resulting in decreased ATP consumption,

attenuation of ischemic injury, and, as a secondary effect, attenuation of reperfusion injury¹⁷ (see below).

c) Excitation-contraction uncoupling due to sarcoplasmic reticulum dysfunction. Krause et al³³ demonstrated that sarcoplasmic reticulum isolated from stunned myocardium had a decreased ability to transport calcium, and postulated that a decrease in the amount of calcium stored in the sarcoplasmic reticulum as a result of a reduction in the calcium pump activity could diminish contractile protein activation via attenuated calcium release during systole. This hypothesis now seems implausible, because it implies that the amplitude of the $[Ca]_i$ transient is decreased, whereas in vitro data have shown that this is not the case,^{3,16} as mentioned above. Indeed, there is now ample evidence that calcium availability is not the limiting factor in stunning.¹⁶

The oxyradical hypothesis

a) Effect of antioxidants on myocardial stunning after a brief coronary occlusion. In the early 1980s, a number of investigators, including ourselves, postulated that myocardial stunning is caused in part by the generation of reactive oxygen metabolites [eg, superoxide anion ($\bullet O_2^-$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($\bullet OH$)]. To test this hypothesis, we employed an open-chest dog preparation in which the left anterior descending coronary artery is occluded for 15 min and then reperfused; as indicated above, the mechanical derangements observed after reperfusion in this model can be entirely ascribed to stunning.

In the first experiment,¹⁸ we found that administration of superoxide dismutase (SOD) (which catalyzes the dismutation of $\bullet O_2^-$ to O_2 and H_2O_2) and catalase (which reduces H_2O_2 to O_2 and H_2O) significantly enhanced recovery of function after reperfusion. This was the first study to suggest a role of oxyradicals in myocardial stunning. Similar findings with SOD and catalase were subsequently reported by other investigators using similar models.³ We subsequently observed that both dimethylthiourea and mercapto-propionyl glycine (MPG), two scavengers of $\bullet OH$, produced a significant and sustained improvement in the function of the stunned myocardium,^{3,19} suggesting that the $\bullet OH$ radical is an important mediator of postischemic dysfunction. In addition, the iron chelator, desferrioxamine, was found to attenuate postischemic dysfunction,³ presumably through prevention of the iron-catalyzed formation of $\bullet OH$ (through the Haber-Weiss or Fenton mechanisms). Numerous other studies have demonstrated the ability of a wide variety of antioxidants, targeted at different steps of the univalent

pathway of reduction of O_2 , to attenuate myocardial stunning after a 15-min coronary occlusion in different animal species, including rabbits and pigs (reviewed in ref 20).

b) Direct evidence for the oxyradical hypothesis. Despite this impressive body of evidence supporting the oxyradical hypothesis, all of these studies are limited by the fact that the evidence for a causative role of oxygen metabolites in postischemic dysfunction was indirect and, therefore, inconclusive. Therefore, in order to definitively validate the oxyradical hypothesis of stunning, it was necessary to directly demonstrate and quantitate free radical generation in the stunned myocardium in the presence and absence of antioxidant interventions.

We used the spin trap, alpha-phenyl N-tert-butyl nitron (PBN), and electron paramagnetic resonance (EPR) spectroscopy to detect and measure production of free radicals in our open-chest dog model of postischemic dysfunction (15-min coronary occlusion). In the initial study,²¹ we demonstrated a burst of free radical production immediately after reperfusion. We also found a linear, positive relation between the magnitude of free radical production and the magnitude of ischemic flow reduction, indicating that the intensity of free radical generation after reflow is proportional to the severity of the antecedent ischemia: hence, the greater the degree of hypoperfusion, the greater the subsequent production of free radicals and, by inference, the severity of reperfusion injury. *These findings imply that interventions that alleviate the severity of ischemia will indirectly attenuate free radical reactions after reflow (see below).* We subsequently found that SOD plus catalase,³⁴ MPG,³⁵ and desferrioxamine³⁶ suppressed the production of free radicals in the stunned myocardium and, at the same time, attenuated postischemic dysfunction¹⁹ (reviewed in ref 20), suggesting a cause-and-effect relationship between the production of free radicals in the stunned myocardium and the depression of contractility.

More recently, we have used a different technique (aromatic hydroxylation of phenylalanine) to specifically investigate the role of $\bullet OH$ in myocardial stunning.²² We have observed generation of hydroxylated derivatives of phenylalanine (ortho-, meta-, and para-tyrosine) during the first few minutes of reperfusion after a 15-min occlusion, indicating that $\bullet OH$ is produced in the stunned myocardium upon reperfusion; moreover, $\bullet OH$ scavengers suppressed tyrosine production and attenuated the dysfunction, suggesting a key role of $\bullet OH$ as a mediator of stunning.²² *The similarity of the results obtained with two*



completely different techniques (spin trapping¹⁹⁻²¹ and aromatic hydroxylation²²) further corroborates the concept that reactive oxygen species play a significant role in the pathogenesis of postischemic ventricular dysfunction.

c) Is the oxyradical hypothesis applicable to conscious animals?

Although the studies discussed above [reviewed in ref 20] consistently support the oxyradical hypothesis, their significance is limited by the fact that they were all performed in open-chest animals. Thus, artifacts due to the combined effects of anesthesia, hypothermia, surgical trauma, volume and ionic imbalances, unphysiologic conditions and attendant neurohumoral perturbations, as well as other potentially confounding variables, cannot be excluded. Indeed, we have demonstrated that both the severity of myocardial stunning¹⁵ and the magnitude of free radical generation²³ after a 15-min coronary occlusion are greatly exaggerated in open-chest as compared with conscious dogs, even when differences in collateral flow are taken into account and fundamental physiological variables in the open-chest preparation are carefully kept within normal limits. The striking differences between the two models indicate the presence of artifacts in the open-chest dog model and raise the possibility that results obtained in this model may not be applicable to more physiological conditions. It was therefore important that the oxyradical hypothesis be tested in conscious animal preparations. In a series of studies in conscious dogs subjected to a 15-min coronary occlusion, we demonstrated (using EPR spectroscopy): (i) that free radicals are generated following reperfusion, with a burst peaking at 2-3 min after reflow and abating within 20 min²³; (ii) that antioxidants (desferrioxamine and MPG) markedly attenuate this burst of free radical generation²⁴; and (iii) that these same antioxidants also attenuate myocardial stunning,^{15,24} indicating that free radicals are necessary for myocardial stunning to occur. Taken together, these results^{15,23,24} indicate that the oxyradical hypothesis of myocardial stunning is applicable to the conscious animal preparation, ie, to the most physiological animal preparation available.

In summary, numerous investigations from several independent laboratories and in a variety of models^{15,18,19,21-24} (reviewed in ref 20) uniformly suggest that oxygen metabolites play a significant role in the genesis of myocardial stunning after a 15-min period of ischemia, both in open-chest and in conscious animals. At the time of writing, there are at least 22 full-length published articles examining the effect of antioxidants on myocardial stunning after a brief (15-min) coronary occlusion; all of these studies (except those that used superoxide dismutase alone

or catalase alone), have uniformly shown a protective effect of antioxidants against stunning (reviewed in ref 20). This is indeed a rare example of concordance among different investigators, particularly in the area of free radical-mediated injury. This concordance is in striking contrast to the bewildering controversy that surrounds the role of oxyradicals in myocardial infarction.²⁵ *In the setting of a 15-min ischemic episode, the oxyradical hypothesis of myocardial stunning is now widely accepted and, from a practical standpoint, it can be regarded as a proven hypothesis.*

d) Mechanism of oxyradical-mediated contractile dysfunction.

Both in vitro and in vivo studies have demonstrated that oxygen metabolites depress myocardial function (reviewed in ref 3). The exact mechanism whereby oxygen metabolites depress contractile function remains speculative and represents one of the major unresolved issues pertaining to the pathogenesis of myocardial stunning. In an elegant review,²⁶ Hearse provides a thoughtful discussion of this problem and proposes a set of intriguing hypotheses reconciling the oxyradical hypothesis with the calcium hypothesis. Free radicals are reactive species that can attack nonspecifically virtually all cellular components. Theoretically, every abnormality described thus far in the stunned myocardium (see above) could be caused by oxyradicals. At least two key cellular components, proteins and lipids, could be the targets of free radical-initiated reactions, leading to protein denaturation and enzyme inactivation, as well as peroxidation of the polyunsaturated fatty acids contained in cellular membranes.²⁶ The latter effect would impair selective membrane permeability and interfere with the function of various cellular organelles.²⁶

The sarcolemma may be a critical target of free radical-mediated damage, since oxyradicals interfere with its calcium transport and calcium-stimulated ATPase activity.^{3,26} Oxygen radicals have also been shown to interfere with the Na⁺-Ca²⁺ exchange and to inhibit the Na⁺-K⁺-ATPase activity.²⁶ Impairment of the Na⁺-K⁺-ATPase activity results in Na⁺ overload, with consequent activation of the Na⁺-Ca²⁺ exchange activity.²⁶ These observations imply that excessive production of oxyradicals could result in increased transsarcolemmal calcium influx and cellular calcium overload. It is also plausible that oxyradicals cause decreased responsiveness of myofilaments to calcium by producing selective damage of contractile proteins, for example, by oxidation of critical thiol groups.³ Finally, oxyradicals have been shown to impair sarcoplasmic reticulum function.²⁶ It is important to point out that the foregoing postulated mechanisms involve alterations in calcium homeostasis, and thus

would reconcile the oxyradical hypothesis and the calcium overload hypothesis of stunning into one pathogenetic mechanism.

e) Sources of oxygen radicals in the stunned myocardium.

The exact sources of oxygen radical production in the stunned myocardium remain unclear. In the canine model of myocardial stunning, xanthine oxidase appears to be a source of free radicals,³ whereas it is now definitely established that neutrophils are unimportant.²⁷ The role of xanthine oxidase in humans is uncertain because data regarding the myocardial content of this enzyme in the human heart are conflicting. There are several other processes that could generate free radicals during reperfusion, including activation of the arachidonate cascade, autoxidation of catecholamines and other compounds, and perhaps more importantly, damage of the mitochondrial electron transport chain.

f) Role of oxygen radicals in other forms of myocardial stunning (Table I). The investigations reviewed thus far employed a single brief (15-min) coronary occlusion. In recent studies in open-chest dogs subjected to ten 5-min coronary occlusions separated by 10-min reflow periods, we have provided direct evidence that oxyradicals contribute to the genesis of myocardial stunning after multiple brief ischemic episodes.⁸ Further, the surgical literature abounds with evidence for a pathogenetic role of oxygen radicals in postischemic dysfunction after global ischemia in *in vivo* models of cardioplegic arrest.³ Finally, antioxidants consistently alleviate mechanical dysfunction after global ischemia in isolated hearts,³ but, as discussed above, the relevance of these *in vitro* preparations to myocardial stunning is often uncertain.

Whether oxygen radicals play a role in myocardial stunning after a prolonged (>20 min) coronary occlusion (resulting in some degree of cell death) is still unclear. Three studies failed to detect improvement in functional recovery with SOD and catalase after coronary occlusions lasting 1 h, 90 min, and 2 h in open-chest or conscious dogs.²⁰ We also observed that SOD fails to enhance recovery of contractility after a 2-h coronary occlusion in anesthetized dogs.²⁰ These results suggest that short-term administration of antioxidant enzymes is not effective in mitigating myocardial stunning associated with subendocardial infarction, perhaps because the pathogenesis of postischemic dysfunction is different when this abnormality is caused by a prolonged period of ischemia. However, other studies have shown that the *cell-permeant* antioxidants, oxypurinol, N-acetylcysteine and Trolox, attenuate myocardial stunning independently of infarct size limitation in closed-chest dogs subjected

to 90 min of coronary occlusion and 24 h of reflow, and in open-chest pigs subjected to 45 min of coronary occlusion and 72 h of reperfusion (reviewed in ref 20).

Exercise-induced stunning is not alleviated by SOD and catalase.

In summary, there is strong evidence that oxyradicals contribute to postischemic dysfunction after global ischemia (*in vitro* as well as *in vivo*) and after multiple episodes of regional ischemia. There is presently no evidence that they contribute to exercise-induced postischemic dysfunction. The role of oxygen radicals in myocardial stunning after a prolonged, partly irreversible ischemic insult remains uncertain and represents a major unresolved problem. Elucidation of this issue will be difficult because the dysfunction is due in part to the presence of infarction and in part to the presence of stunning - a situation that complicates the evaluation of therapy.

Integration of different hypotheses

*Myocardial stunning is probably a multifactorial process that involves complex sequences of cellular perturbations and the interaction of multiple pathogenetic mechanisms.*³

Much remains to be learned regarding this phenomenon, as none of the theories discussed herein explains the entire cascade of events that culminates in postischemic contractile abnormalities. For example, the origin(s) of reactive oxygen species as well as the mechanism whereby they induce mechanical dysfunction remain uncertain.³ Integration of the various hypotheses is complicated by the fact that, for the most part, each hypothesis has been developed in a different experimental preparation (Table I).

*Nevertheless, it is important to emphasize that these hypotheses are not mutually exclusive and in fact may represent different parts of the same pathophysiological sequence.*³

A number of molecular mechanisms involving both oxidative stress and abnormal calcium homeostasis have been proposed by Hearse²⁶ and represent plausible hypotheses that should be investigated in future years to elucidate the molecular basis of stunning. There is indeed considerable evidence to suggest a link between generation of oxygen radicals and perturbed calcium homeostasis. For example, the damage associated with the "calcium paradox" resembles that associated with the "oxygen paradox" and probably has a similar pathogenetic mechanism. Furthermore, as discussed above, oxyradicals generated upon reperfusion can cause dysfunction of the sarcoplasmic reticulum and alter calcium flux across the sarcolemma.²⁶ These actions would result in



excitation-contraction uncoupling and cellular calcium overload.^{3,26} Oxygen radicals could also damage the contractile proteins and impair their responsiveness to calcium.³ On the other hand, calcium overload may exaggerate oxyradical production by promoting the conversion of xanthine dehydrogenase to xanthine

oxidase, which appears to be mediated by a calcium-dependent protease, thereby leading to a vicious circle.

A unifying hypothesis for the pathogenesis of myocardial stunning was proposed in 1990³ and is illustrated in Figure 1 (a detailed description of the postulated

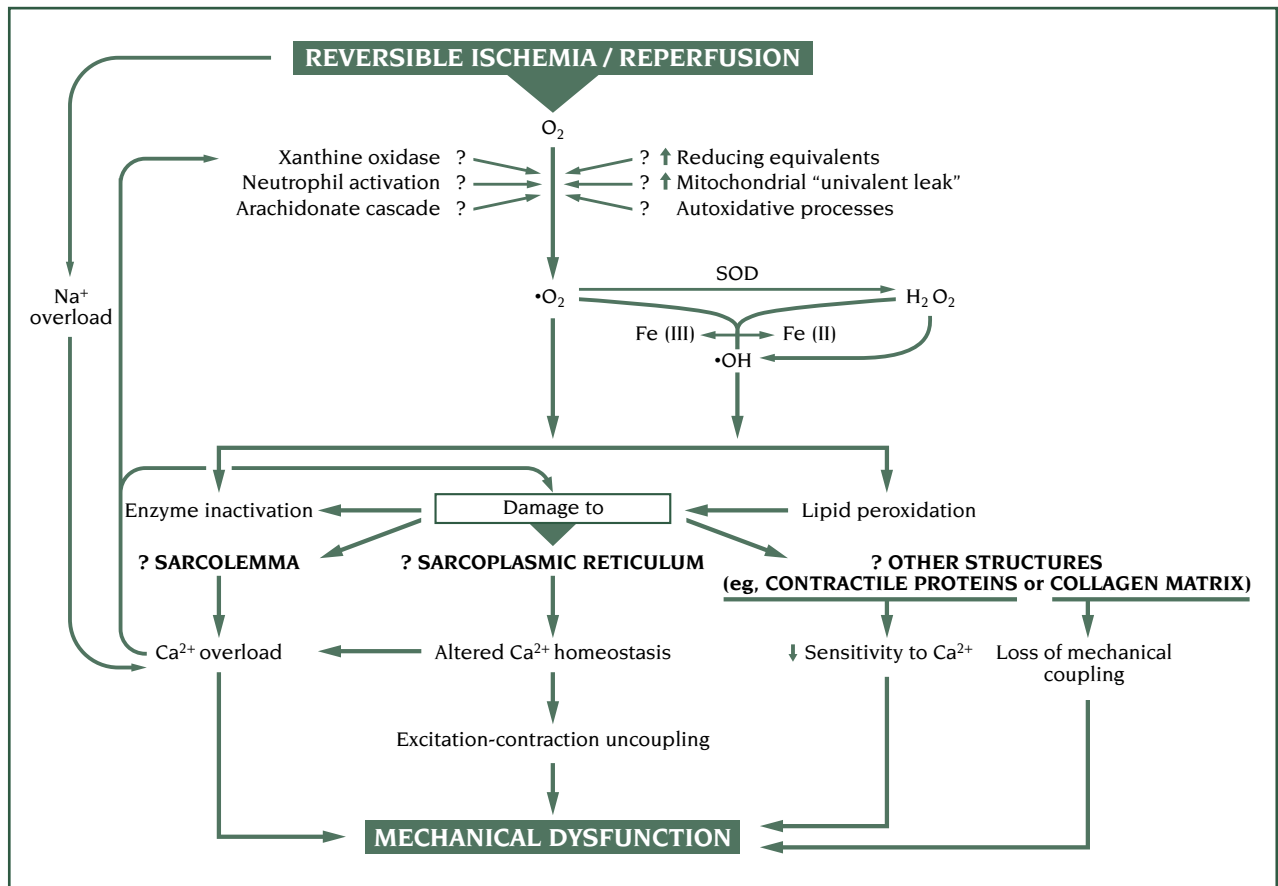


Figure 1. Illustration of the proposed pathogenesis of postischemic myocardial dysfunction. This proposal integrates and reconciles different mechanisms into a unifying pathogenetic hypothesis. Transient reversible ischemia followed by reperfusion could result in increased production of superoxide radicals ($\cdot\text{O}_2^-$) through several mechanisms, including: (1) increased activity of xanthine oxidase; (2) activation of neutrophils; (3) activation of the arachidonate cascade; (4) accumulation of reducing equivalents during oxygen deprivation; (5) derangements of the mitochondrial electron transport system resulting in increased univalent reduction of oxygen; and (6) autoxidation of catecholamines and other substances. Superoxide dismutase (SOD) dismutates $\cdot\text{O}_2^-$ to hydrogen peroxide (H_2O_2); in the presence of catalytic iron, $\cdot\text{O}_2^-$ and H_2O_2 interreact in a Haber-Weiss reaction to generate the hydroxyl radical ($\cdot\text{OH}$). H_2O_2 can also generate $\cdot\text{OH}$ in the absence of $\cdot\text{O}_2^-$ through a Fenton reaction provided that other substances (such as ascorbate) reduce Fe (III) to Fe (II). $\cdot\text{O}_2^-$ and $\cdot\text{OH}$ attack proteins and polyunsaturated fatty acids, causing enzyme inactivation and lipid peroxidation, respectively. In the setting of reversible ischemia, the intensity of this damage is not sufficient to cause cell death, but is sufficient to produce dysfunction of key cellular organelles. Postulated targets of free radical damage include: (1) The sarcolemma, with consequent loss of selective permeability, impairment of calcium-stimulated ATPase activity and calcium transport out of the cell, and impairment of the $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity. The net result of these perturbations would be increased transsarcolemmal calcium influx and cellular calcium overload. (2) The sarcoplasmic reticulum, with consequent impairment of calcium-stimulated ATPase activity and calcium transport. This would result in impaired calcium homeostasis: specifically, decreased calcium sequestration (which would contribute to increase free cytosolic calcium) and decreased calcium release during systole (which would cause excitation-contraction uncoupling). (3) Possibly, other structures, such as the extracellular collagen matrix (with consequent loss of mechanical coupling) or the contractile proteins (with consequent decreased responsiveness to calcium). At the same time, reversible ischemia/reperfusion could cause cellular Na^+ overload due to: (1) inhibition of sarcolemmal $\text{Na}^+\text{-K}^+\text{-ATPase}$, and (2) acidosis and $\text{Na}^+\text{-H}^+$ exchange. This could further exaggerate calcium overload via increased $\text{Na}^+\text{-Ca}^{2+}$ exchange. An increase in free cytosolic calcium would activate protein kinases, phospholipases, and other degradative enzymes, and further exacerbate the injury to the aforementioned key subcellular structures (sarcolemma, sarcoplasmic reticulum, and contractile proteins). Thus, calcium overload could serve to amplify the damage initiated by oxygen radicals. In addition, calcium overload could in itself impair contractile performance and contribute to mechanical dysfunction. It is also possible that the increase in free cytosolic calcium could increase oxyradical production by promoting the conversion of xanthine dehydrogenase to xanthine oxidase. The ultimate consequence of this complex series of perturbations is a reversible depression of contractility. Reproduced with permission of the American Heart Association from *Circulation*. 1990;82:723-738.

mechanisms is provided in the figure legend). This paradigm is largely speculative, but nevertheless encompasses the evidence available at this time and discussed in this review. According to this conceptual scheme (Figure 1), oxyradical generation, calcium overload, and decreased myofilament responsiveness can be viewed as different facets of the same pathogenetic mechanism, thereby reconciling the three major current hypotheses of myocardial stunning.³

Is myocardial stunning a form of reperfusion injury?

We have observed that infusion of the antioxidant MPG attenuated postischemic dysfunction to a similar extent whether the infusion was started before ischemia or 1 min before reperfusion; however, infusion started 1 min *after* reflow was ineffective, suggesting that the critical radical-mediated injury occurs in the first few moments of reperfusion.¹⁹ We have subsequently obtained similar results with desferrioxamine (reviewed in ref 20). Furthermore, the spin trap, PBN, enhances contractile recovery in open-chest animals even when the infusion is commenced 20 s before reflow; the magnitude of the protective effect is similar to that observed when the infusion is started before ischemia.²¹ That a substantial portion of the cellular damage responsible for stunning occurs immediately after reflow is further corroborated by direct measurements of free radicals in the stunned myocardium, which have shown a burst in the initial moments after reperfusion.^{8,19-24} Furthermore, if free radical production is inhibited *during* this initial burst, postischemic dysfunction is mitigated; however, if free radical production is inhibited *after* the first 5 min of reperfusion (ie, *after* the initial burst), no functional improvement is observed.¹⁹ *These findings suggest that the*

free radicals important in causing myocardial stunning are those produced immediately after reflow. The demonstration that there is an initial recovery of function immediately after reperfusion, followed by a subsequent decline, also supports the occurrence of additional injury in the initial phase of reflow.

In summary, as proposed in 1989,¹⁹ myocardial stunning appears to be, in part, a form of oxyradical-mediated “reperfusion injury.” *This concept may have significant therapeutic implications, because it suggests that antioxidant therapies begun after the onset of ischemia could still be effective in preventing postischemic dysfunction; however, a delay in the implementation of such therapies until after reperfusion would result in loss of efficacy.*

Hearse²⁶ has appropriately pointed out that myocardial stunning is not likely to be *entirely* caused by reperfusion injury. Indeed, as stated above, myocardial stunning is *in part* a form of reperfusion injury. The reason for the qualifier “in part” is that none of the antioxidant interventions used thus far *completely* prevented myocardial stunning. More importantly, a recent study²² found that despite administration of “broad-spectrum” antioxidant therapy (a combination of superoxide dismutase, catalase, desferrioxamine, MPG, and phenylalanine), myocardial stunning was attenuated but not *completely* prevented. Therefore, in accordance with Hearse’s proposal,²⁶ there appears to be a component of stunning that is not responsive to antioxidant therapy (no matter how vigorous) and thus is likely to be caused by derangements that occur during ischemia rather than after reperfusion. On the basis of these facts, it is reasonable to propose that the injury responsible for myocardial stunning consists of two components: (i) a component that develops during ischemia (ischemic injury); and (ii) another component that develops after reperfusion

Table III. DIFFERENTIAL DIAGNOSIS OF REVERSIBLE CONTRACTILE DYSFUNCTION OBSERVED DURING AN ANGINA-FREE INTERVAL*

	STUNNING	SILENT ISCHEMIA	HIBERNATION
Contractile function	Decreased	Decreased	Decreased
Reversibility	Complete	Complete	Complete
Coronary flow	Normal	Decreased	Decreased
¹⁸ FDG uptake	Normal or Increased	Increased	Increased

*This table is concerned only with reversible contractile dysfunction that is observed at a time when the patient is not experiencing angina. ¹⁸FDG, F-18 deoxyglucose. Reproduced with permission of the American Heart Association from *Circulation*. 1992;86:1671-1691.



(reperfusion injury). Judging from the effects of antioxidants in models of myocardial stunning, the reperfusion injury component appears to be larger than the ischemic injury component.³

As reviewed above, the studies that have directly measured free radicals in experimental models of myocardial stunning have found that the magnitude of the free radical generation after reperfusion was proportional to the magnitude of the flow deficit during the antecedent coronary occlusion^{19,21,23} (and, by inference, to the severity of the antecedent ischemic injury) (reviewed in ref 20). *These facts support the important concept (proposed in ref 28) that the severity of the reperfusion injury component of myocardial stunning is proportional to the severity of the ischemic injury component. Accordingly, any intervention that attenuates the severity of the ischemic injury will also, indirectly, attenuate the severity of the subsequent reperfusion injury.*²⁸ For example, adenosine,²⁸ calcium antagonists,¹⁷ and K_{ATP} channel openers, all attenuate myocardial stunning by decreasing the ischemic injury component and, indirectly, the reperfusion injury component as well.

MYOCARDIAL STUNNING IN THE CLINICAL ARENA

Myocardial stunning vs hibernation

It would be impossible to discuss the problem of clinical stunning without mentioning the concept of hibernating myocardium, from which stunned myocardium must be distinguished.

Myocardial stunning has been defined above. Hibernating myocardium could be defined as a persistent (at least several hours) contractile dysfunction that is associated with reduced coronary flow but preserved myocardial viability.⁴ This phenomenon is postulated to be a teleologically adaptive response of the heart to low flow, whereby oxygen demands are downregulated to the point where the reduced oxygen supply can be tolerated for extended periods of time without cell death and without clinical or metabolic evidence of ischemia. Once coronary flow is restored, the dysfunction is completely reversed. Thus, stunning and hibernation have in common the fact that in both cases the LV dysfunction is reversible. *The major difference is that blood flow is normal or near-normal in stunned myocardium whereas it is reduced in hibernating myocardium*⁴ (Table III).

Problems inherent in studies of myocardial stunning in man

Despite the multiplicity of situations in which myocardial stunning would be expected to occur, investigation of

this phenomenon in the clinical setting has been hampered by several fundamental problems.⁴ First, the accuracy and resolution of the methods available to measure regional myocardial function in humans are limited. Second, many factors that have a major influence on the mechanical function of the stunned myocardium (ie, preload, afterload, heart rate, regional myocardial blood flow, catecholamine levels, and positive inotropic therapy) are likely to change with time in the same patient, and cannot be controlled. Third, regional myocardial blood flow during acute myocardial ischemia (which is the primary determinant of postischemic dysfunction⁵ is difficult to measure in humans.

Perhaps the major problem encountered in clinical studies, however, is to discern whether a reversible defect of contractility is caused by stunning, silent ischemia, or hibernation. This problem is illustrated in Figure 2. When a patient experiences an episode of angina (at rest or on exertion), one cannot usually establish whether, after the resolution of the clinical symptoms, blood flow to the ischemic region is *completely* restored. If reperfusion occurs in the presence of a tight coronary stenosis, or if the thrombus or spasm responsible for the acute ischemic event resolves gradually rather than rapidly, then there could be persistent subendocardial ischemia which, depending on its severity, could be painless or not even detectable on the electrocardiogram but nevertheless could be sufficient to prevent full recovery of contractile function (Figure 2, panel B). Thus, silent ischemia occurring after an episode of painful ischemia could mimic stunning. Silent ischemia could also mimic stunning when it develops *de novo*. In this case, measurements taken *during* the episode of painless ischemia would reveal a contractile abnormality that disappears later on, when ischemia resolves; if silent ischemia is not recognized, the dysfunction could be erroneously ascribed to delayed recovery from a previous attack of angina (Figure 2, panel C). Finally, an incorrect diagnosis of stunning could be made in the presence of hibernating myocardium. Since hibernation will resolve after blood flow is restored (either spontaneously or therapeutically), patients who develop hibernating myocardium may exhibit an impairment of LV wall motion followed by an improvement, which, again, could be interpreted as delayed recovery from an acute ischemic episode (Figure 2, panel E). On the other hand, it is conceivable that stunning might sometimes *coexist* with hibernation and/or silent ischemia. Bouts of silent ischemia may cause a loss of function during the reduction of flow followed by slow recovery (ie, stunning) after perfusion is restored (Figure 2, panel D).

Myocardial “stunning” 20 years later - Bolli

If the underlying, fixed coronary stenosis is sufficiently severe, these acute reductions in flow and the ensuing stunning could be *superimposed* on hibernation (Figure 2, panel F). Finally, a phase of stunning may *follow* a phase of hibernation (Figure 2, panel G), in accordance with recent observations suggesting that revascularization of hibernating myocardium results in slow improvement

of function despite rapid normalization of flow.⁴ Taken together, all of these considerations emphasize the need for rigorous criteria in diagnosing stunned myocardium.

The critical difference between stunning, silent ischemia, and hibernation is that myocardial perfusion is normal or near-

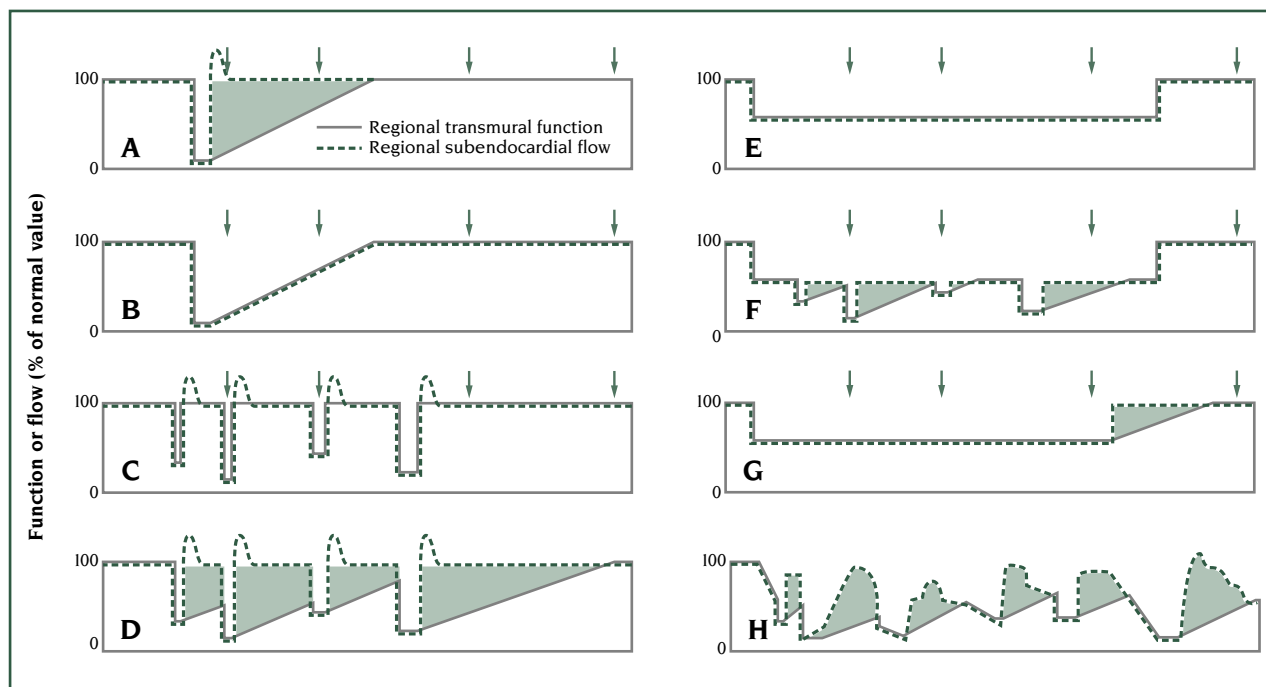


Figure 2. Schematic illustration of several possible scenarios that could occur in a patient with a fixed critical coronary stenosis sufficient to blunt reactive hyperemia. Stunning is indicated by the cross-hatched areas. (A) Brief episode of ischemia (due to thrombosis and/or vasoconstriction) followed by rapid restoration of flow and by stunning (ie, by a perfusion-contraction “mismatch”). (B) Brief episode of ischemia (due to thrombosis and/or vasoconstriction) followed by gradual restoration of subendocardial flow (due to slow lysis of thrombus and/or slow release of vasoconstriction). Note that the recovery of function is identical to that in panel A, but there is no stunning (ie, flow and function are “matched”). If the phase of gradual restoration of flow is painless, and if flow is not measured, this situation could be mistaken for stunning. (C) Recurrent brief episodes of silent ischemia (due to recurrent thrombosis and/or vasoconstriction). In this case there is no stunning, since flow and function are matched. However, if function is measured at the time points marked by the arrows, the pattern would be the same as that in panel A and this situation could also be mistaken for stunning. (D) This is the same situation illustrated in panel C (brief recurrent ischemic episodes caused by thrombosis and/or vasoconstriction) except that each ischemic episode is followed by stunning (ie, by a flow-function mismatch). Note that since the myocardium cannot recover fully between one ischemic episode and the next, recurrent ischemia results in “chronic” stunning. If flow is not measured, this situation could be erroneously interpreted as hibernation. (E) Hibernation in a patient with severe fixed coronary stenosis. According to current views, hibernating myocardium is characterized by a steady, low coronary flow, as depicted in this panel. Function is downregulated to match flow, and recovers immediately after restoration of flow. Note that if function is measured at the time points marked by the arrows and flow is not measured, this situation could be mistaken for stunning. (F) Superimposition of panels D and E, ie, coexistence of hibernation with silent ischemia and stunning. This could be the case of a patient with severe fixed stenosis and superimposed bouts of ischemia due to thrombosis and/or vasoconstriction. Note that function is initially downregulated to a low level in order to match the chronically low flow, but then exhibits further decreases, followed by slow recoveries, because of superimposed brief ischemic episodes followed by stunning. The total deficit of function is therefore due to a combination of ischemic dysfunction (during the brief decreases in flow), stunning (during the slow return of function to the downregulated level following each brief flow reduction), and hibernation. (G) Hibernation followed by stunning. This panel is the same as panel E except that the recovery of function after revascularization is delayed. Note that the four situations depicted in panels B, C, E, and G could be mistaken for stunning if regional flow is not measured simultaneously with function. (H) This is more likely to be the “real” situation in a patient with a severe coronary stenosis. It is unlikely that coronary flow in this setting will be steady as in panels E or G. It is more likely that coronary flow will fluctuate continuously because the severe epicardial stenosis causes loss of coronary autoregulation, so that flow will vary as a result of changes in aortic pressure, in extravascular components of coronary resistance (heart rate, LV filling pressure, etc), and in vascular components of coronary resistance (vasomotor tone, size of thrombus, size of plaque); all of these factors result in a highly unstable level of flow. Thus, although the myocardium may downregulate its function to a low level in order to achieve a metabolic balance between demand and supply, in many cases this balance may be continuously upset by recurrent reductions of flow followed by stunning. In this situation, the deficit of function results from a complex combination of hibernation, ischemic dysfunction, and stunning. The continuous line indicates regional myocardial function; the dashed line indicates regional subendocardial flow; the arrows indicate the time points at which regional function is measured. Reproduced with permission of the American Heart Association from *Circulation*. 1992;86:1671-1691.



normal in the first condition but reduced in the other two (Table III). Accordingly, the differential diagnosis of a reversible impairment of contractility requires simultaneous measurements of myocardial function and flow. The major reason for the uncertainty that still surrounds the occurrence and significance of myocardial stunning in humans is that the vast majority of clinical studies have failed to quantitate the level of perfusion in the LV regions that were thought to be stunned.

Clinical evidence for the occurrence of myocardial stunning

Table IV summarizes the major clinical situations in which myocardial stunning could occur, along with their correspondent experimental settings. Although these clinical situations are rather diverse, the common denominator to all of them is the fact that the myocardium is exposed to transient ischemia followed by reperfusion - which is the substrate for the development of myocardial stunning. Table IV demonstrates that each of the experimental settings of myocardial stunning has a well-defined clinical equivalent; thus, the use of diverse experimental models is useful in developing a broad understanding of the multiple clinical facets of this syndrome.

It is important to stress that in the clinical literature the term “stunning” is sometimes used inappropriately to denote reversible myocardial dysfunction caused by factors other than ischemia (eg, persistent atrial dysfunction following electrical cardioversion of atrial fibrillation). It is an intuitive and rather obvious concept that different causes of dysfunction have different mechanisms. If confusion is to be avoided, this trend towards the bastardization of the term “stunning” must be stemmed.

Myocardial stunning after ischemia induced by percutaneous transluminal coronary angioplasty (PTCA). During PTCA, transient myocardial ischemia is induced by balloon inflation followed by reperfusion upon balloon deflation. Although in theory PTCA could be a cause of myocardial stunning, numerous clinical studies have demonstrated that LV systolic function recovers fully immediately after the procedure, although diastolic function may remain impaired for a few minutes after the last balloon deflation (reviewed in ref 4). In conclusion, it appears that the episodes of ischemia associated with PTCA are too short to cause protracted impairment of LV systolic function, although they may provoke some persisting diastolic abnormalities. This is not surprising, since experimental studies

Table IV. CLINICAL SETTINGS POTENTIALLY ASSOCIATED WITH MYOCARDIAL STUNNING AND THEIR EXPERIMENTAL EQUIVALENTS

EXPERIMENTAL SETTING	CLINICAL SETTING
Regional ischemia	
• Completely reversible ischemic episode (coronary occlusion \leq 20 minutes)	<ul style="list-style-type: none"> —————→ PTCA —————→ Unstable angina —————→ Variant angina
• Partly irreversible ischemic episode (subendocardial infarction) (coronary occlusion >20 minutes, <2 hours)	—————→ Acute myocardial infarction with early reperfusion
• Exercise-induced ischemia in presence of coronary stenosis	—————→ Exercise-induced ischemia in presence of coronary stenosis
Global ischemia	
• Cardioplegic arrest	<ul style="list-style-type: none"> —————→ Cardiac surgery —————→ Cardiac transplantation —————→ Cardiac arrest?
• Exercise-induced ischemia in hypertrophic hearts	—————→ Exercise-induced ischemia in hypertrophic hearts

Adapted with permission of the American Heart Association from *Circulation*. 1992;86:1671-1691.

have demonstrated that coronary occlusions lasting ≤ 2 min do not cause appreciable myocardial stunning.⁴ However, in one recent study by Sheiban et al³⁷ in which the duration of balloon inflation was unusually long (5.5 ± 1.1 min), both systolic and diastolic function were found to remain depressed for at least 24 h and to normalize by 3 days, clearly documenting the occurrence of stunning.

Myocardial stunning in unstable angina. Since by definition unstable angina is characterized by transient myocardial ischemia without necrosis, this syndrome would be expected to be associated with myocardial stunning. Rest angina (a major form of unstable angina) is caused by a decrease in coronary flow that resolves spontaneously in a matter of minutes and, as such, resembles the "classic" animal model of stunned myocardium produced by a completely reversible (<20 min) ischemic insult³ (Table IV). Indeed, a number of studies are consistent with the notion that myocardial stunning is common in patients with unstable angina. The work by Nixon et al³⁸ is usually quoted because it was the first such study. These authors found that in 5 of 11 patients admitted for unstable angina the regional wall motion abnormalities noted at the time of admission disappeared after 7-10 days of medical therapy (see ref 4). This and other studies (reviewed in ref 4) measured wall motion only at two time points, which made it impossible to determine whether the time course of recovery of function in unstable angina is consistent with the progressive improvement characteristic of stunned myocardium in experimental animals.³ Recently, Jeroudi et al²⁹ assessed the time course of wall motion abnormalities after an episode of chest pain at rest in six patients with unstable angina. They found that the wall motion abnormalities exhibited a gradual improvement; they resolved within 2 hours in some patients but persisted for as long as 24 hours after the chest pain in other subjects, despite the fact that no patient had evidence of acute infarction or recurrent ischemia.²⁹ This delayed, gradual recovery of LV function lasting several hours after the resolution of the chest pain is consistent with the progressive recovery of function noted after a brief coronary occlusion in experimental animals.³

The repeated observations of an improvement in function after revascularization with CABG or PTCA in patients with unstable angina further support the existence of myocardial stunning in this syndrome.⁴ Potentially important to the practicing cardiologist are the findings by Renkin et al³⁹ and de Zwaan et al⁴⁰ that inverted T waves in the precordial leads identify a subset of patients with unstable angina who are likely to show an improvement (often striking) of

anterior LV wall motion after PTCA.⁴ Whether or not T-wave inversion identifies stunning, the notion that it presages reversibility of contractile abnormalities should be a strong argument in favor of revascularization.

In summary, it is clear that unstable angina is associated with wall-motion abnormalities that persist during pain-free intervals and eventually resolve, either with medical therapy or with coronary revascularization. The critical, unresolved question is, what causes these abnormalities? Are they the consequence of previous bouts of acute ischemia that leave behind prolonged postischemic dysfunction, ie, stunning (Figure 1, panels A and D)? Are they the manifestation of a persistent, moderate decrease in coronary flow that is associated with an adaptive decrease in myocardial contraction, ie, hibernation (Figure 1, panels E and G)? Or are they simply the result of transient episodes of ischemia that were present at the time when LV function was assessed but remained asymptomatic, ie, silent ischemia (Figure 1, panel C)? As indicated above, a conclusive diagnosis of stunned myocardium, as opposed to hibernating myocardium or silent ischemia, in patients with unstable angina will require simultaneous measurements of regional myocardial perfusion and function.

Myocardial stunning in variant angina. Although variant angina resembles the setting of a brief transmural ischemic insult used to produce stunning in experimental animals (Table IV), evidence for the occurrence of myocardial stunning in patients with variant angina is only anecdotal (reviewed in ref 4). In patients studied after a single episode of variant angina, Distante et al^{41,42} were unable to demonstrate persistent LV wall motion abnormalities.

In summary, it appears that a single episode of variant angina promptly treated with nitrates does not usually cause postischemic systolic dysfunction, probably because it is too short. However, it is plausible that frequent, severe, and/or protracted episodes of variant angina (such as those described in the above-referenced case reports) might lead to myocardial stunning.

Myocardial stunning after acute myocardial infarction with early reperfusion. Over the past 15 years, numerous studies (reviewed in ref 4) assessing the recovery of LV function of patients with acute myocardial infarction treated with thrombolytic therapy or PTCA have uniformly shown that systolic function does not improve immediately after reperfusion; instead, the improvement is usually delayed for several days - a time course that is remarkably similar to that observed in experimental animals after a partly irreversible ischemic episode (subendocardial infarction), in which the



subepicardial region salvaged by reperfusion exhibits a slow recovery of contractility (Table IV).³ Not surprisingly, the delay in the recovery of systolic function has been found to be associated with a delay in the recovery of diastolic function as well. Although there is no doubt that the recovery of myocardial function after reperfusion in patients with acute myocardial infarction is delayed, the precise time course of such recovery is not entirely clear, as the majority of the improvement has been reported to occur within the first 3 days after reperfusion or after the first 3 days of reperfusion. One of the best studies addressing this issue was by Ito et al⁴³ who studied patients fully reperfused (TIMI grade 3; no reocclusion) within 6 h from the onset of an anterior myocardial infarction. In this study, there was a progressive improvement in regional myocardial function from day 1 to day 14, but no significant change between day 14 and day 28. On average, wall motion abnormalities decreased by 28% between day 1 and day 14, suggesting that almost one third of the dysfunction observed immediately after thrombolysis was caused by myocardial stunning, although in individual cases this percentage was larger.

In conclusion, it is clear that in patients with acute myocardial infarction the improvement in systolic and diastolic function of the myocardium salvaged by the reperfusion is delayed, strongly suggesting myocardial stunning. It is clear that most of the improvement takes place within the first 7-10 days after infarction; however, it is not clear when it can be considered complete, as further improvement has been reported beyond 9-10 days.⁴ Further longitudinal studies are needed to precisely define the time course of the recovery.

Myocardial stunning after exercise-induced ischemia.

Although persistent dysfunction after exercise-induced ischemia has been well documented in experimental animals,¹³ demonstration of this phenomenon in humans has been difficult because of the limited sensitivity of the techniques available, particularly radionuclide angiography. With the advent of exercise echocardiography, however, several studies have documented the persistence of regional and global LV dysfunction after exercise-induced ischemia (reviewed in ref 4). The first such study was by Robertson et al⁴⁴ who reported persisting wall motion abnormalities 30 min after exercise-induced ischemia in 6 of 16 (38%) patients with coronary artery disease. Stoddard et al⁴⁵ subsequently demonstrated the persistence of both systolic and diastolic abnormalities 2 h after exercise-induced ischemia. The most convincing demonstration of the occurrence of myocardial stunning after exercise-induced ischemia is provided by a recent report by

Ambrosio et al.⁴⁶ These authors demonstrated two important points for the first time: (i) myocardial function remained depressed after exercise despite normalization of perfusion (measured by ^{99m}Tc-sestamibi); and (ii) contractile function returned to baseline levels between 1 and 2 h after exercise (ie, the wall motion abnormalities were reversible). The fact that most previous studies using radionuclide angiography have failed to demonstrate stunning after exercise-induced ischemia is most likely due to the fact that this abnormality is subtle and can be easily missed by techniques, such as radionuclide angiography, that cannot measure LV wall thickening and thus have limited sensitivity.⁴

In summary, echocardiographic observations indicate that myocardial stunning does occur after exercise-induced ischemia. The occurrence and severity of post-exercise stunning probably depend on the intensity and duration of exercise, although in general this seems to be a mild abnormality.

Myocardial stunning after cardiac surgery. Since in the course of cardiac surgery the heart is exposed to global ischemia during aortic cross-clamping and subsequent reperfusion, myocardial stunning would be expected to occur in this setting. Indeed, a large number of studies have demonstrated that patients undergoing CABG commonly exhibit a transient LV dysfunction peaking in the first few hours after surgery and resolving by 24-48 h (reviewed in ref 4), in analogy with observations made in experimental models of cardioplegic arrest (Table IV).³ Highly accurate measurements of LV systolic wall thickening were obtained by Bolli et al³⁰ in 31 patients undergoing CABG. Using pulsed Doppler ultrasonic probes sutured to the epicardial surface, which have accuracy and sensitivity superior to any other clinically available method, this study showed that LV wall thickening decreased after surgery in almost every patient, reaching a nadir at 2 to 6 h, and then improved progressively, approaching baseline levels by 24 to 48 h after surgery.

In summary, a transient depression of LV function is common after cardiac surgery. Cardiac surgery is the clinical setting in which the evidence for the occurrence of myocardial stunning is most cogent and the one in which this phenomenon is recognized most clearly as a clinical problem. This is due to the fact that, unlike the other settings reviewed above, in which myocardial stunning affects only a *region* of the heart, in cardiac surgery myocardial stunning involves the *entire* left and right ventricles and, consequently, has the potential to produce major hemodynamic derangements. It is important to stress that in the immediate postoperative

period many (if not all) patients receive inotropic and/or afterload-reducing therapy and have markedly elevated plasma catecholamines, both of which probably tend to mask myocardial stunning; consequently, the severity of this phenomenon is probably greater than can be inferred from the published studies.

Cardiac transplantation. Since in the course of cardiac transplantation the heart is subjected to global ischemia followed by reperfusion, myocardial stunning would be expected to develop. Although published information regarding the mechanical abnormalities that occur immediately after transplantation is surprisingly scarce and largely anecdotal, it is a common observation that transient hemodynamic instability develops in the immediate postoperative period (long before rejection becomes a factor), and that vigorous pharmacological support of the circulation is usually required.⁴ This reversible depression of cardiac function is most likely caused by stunning.

Myocardial stunning after cardiac arrest. Since cardiac arrest leads to transient global myocardial ischemia followed by reperfusion after successful resuscitation, it is plausible that myocardial stunning may develop in this situation. A recent study by Deantonio et al⁴⁷ has documented a profound depression of LV function (LV ejection fraction <30%) after resuscitation followed by a complete recovery 2 weeks later. None of the patients had evidence of myocardial infarction, judging from cardiac enzyme levels. Although it is likely that myocardial stunning contributed to this reversible dysfunction, it is also likely that other factors (electric shock, metabolic acidosis, etc) contributed as well. It seems probable, therefore, that myocardial stunning is but one of the factors causing reversible LV dysfunction after cardiac arrest.

Mechanism of myocardial stunning in man

Not surprisingly, information regarding the pathogenesis of myocardial stunning in humans is quite scarce. For example, there is still no published study assessing the effect of antioxidants on myocardial stunning in any clinical setting. Nevertheless, a number of reports are consistent with the concept that oxyradicals contribute to the pathogenesis of postoperative LV dysfunction after CABG (reviewed in ref 4). The most important among these studies was by Ferrari et al,⁴⁸ who found that reperfusion after aortic declamping was associated with release of oxidized glutathione (GSSG) in the coronary sinus and that the magnitude of this release was inversely related to the values of cardiac index measured in the ensuing hours. Because release of GSSG is a

sensitive index of oxidative stress, these findings suggest a link between oxyradical-mediated injury at reperfusion and subsequent contractile dysfunction. A number of studies have been published suggesting the occurrence of oxidative stress after reperfusion in settings other than cardiac surgery, including acute myocardial infarction, unstable angina, and PTCA. Most of these studies, however, employed a nonspecific assay (thiobarbituric acid assay) and are therefore difficult to interpret. A study in patients undergoing prolonged (5.5 ± 1.1 min) balloon inflation during PTCA has demonstrated that pretreatment with the calcium channel antagonist nisoldipine completely prevented stunning (which in nitrate-treated patients lasted >24 h). These data, however, should not be construed as evidence that calcium overload after reperfusion contributes to stunning in man, because it is more likely that the protective effects of nisoldipine were due to its energy-sparing action during ischemia,¹⁷ as discussed above.

In summary, there is evidence that in patients undergoing cardiac surgery, myocardial stunning is associated with oxidative stress, in accordance with experimental data.³ The fact that, to date, no antioxidant intervention has been developed for the purpose of preventing myocardial stunning after cardiac surgery probably reflects the enormous practical difficulties associated with studies of myocardial stunning in humans⁴ and the availability of several other therapies which are effective in alleviating myocardial stunning (eg, adenosine) rather than a lack of evidence for the efficacy of antioxidant therapy.

Why is myocardial stunning clinically important?

Since myocardial stunning is by definition reversible, it could be argued that it is unimportant: if myocardial stunning resolves spontaneously, why should the clinician be concerned about it? This is an important question that requires a thoughtful answer.

Before delving into clinical relevance, it must be pointed out that myocardial stunning has considerable importance from a purely scientific standpoint. The impressive advances made in the pathophysiology and pathogenesis of myocardial stunning have contributed importantly to furthering our understanding of myocardial ischemia and reperfusion in general, and of ischemic preconditioning and ischemia-induced gene regulation (both of which are associated with stunning) in particular. Stunning is also the clearest example of reperfusion injury and is the one setting in which there is a wide consensus among



scientists regarding the role of oxygen radicals as mediators of tissue injury.³ It seems likely that the investigation of stunning will eventually enable us to identify specific molecular defects responsible for this form of cardiac dysfunction, which would be one of the first successful attempts to unravel the molecular basis of a cardiac disorder.

Apart from these scientific considerations, however, there are several practical reasons why myocardial stunning is important to the clinician.⁴

Myocardial stunning can be a cause of morbidity and mortality. Dramatic cases illustrating this point have been previously reviewed.⁴ The impact of myocardial stunning on prognosis is most obvious in two settings: CABG and AMI. In the majority of cases, myocardial stunning after CABG is well tolerated and does not require any specific treatment. In a minority of patients, however, postoperative stunning can profoundly depress LV function and cause hemodynamic instability that requires intensive and prolonged treatment with inotropes, vasoactive agents, and/or mechanical circulatory assisted devices. This occurrence is particularly common in patients who are at high risk because of conditions such as depressed baseline LV function, long aortic clamping time, repeat CABG, unstable angina, left main coronary artery disease, or concomitant valve replacement. In these situations, the development of stunned myocardium can have a major impact on the prognosis. Most surgeons agree that in this minority of patients, postoperative cardiac dysfunction continues to represent a serious problem in spite of the recent improvements in operative techniques and methods for myocardial protection. It is important to stress that in many patients the hemodynamic consequences of myocardial stunning are prevented by the routine administration of inotropic and/or vasodilator therapy; in these cases, myocardial stunning does not impact upon prognosis but probably prolongs the intensive care unit stay, thereby causing significant additional costs.

Similar considerations apply to patients with AMI. In most of these patients, myocardial stunning is well tolerated and does not require any specific treatment. In a minority of cases, specifically, in patients with a preexisting impairment of cardiac function (ie, patients with prior infarction) or in patients in whom the size of the ischemic region is large (ie, patients with proximal LAD lesions), the development of myocardial stunning after reperfusion can cause hemodynamic instability, requiring intensive monitoring, pharmacologic and/or mechanical support, urgent revascularization under suboptimal conditions,

and prolonged coronary care unit stay, with its attendant financial implications.

The concept of stunning implies that the contractile dysfunction associated with the aforementioned clinical situations could be prevented, at least in part.

As discussed earlier, experimental studies have demonstrated that stunning can be prevented by antioxidants,^{15,18-24} calcium antagonists,¹⁷ ACE inhibitors, adenosine and adenosine modulators,²⁸ and K_{ATP} channel blockers. If these interventions are as effective in clinical settings as they are in experimental settings, it should be possible to prevent, at least in part, the adverse impact of stunning on morbidity and mortality.

The appreciation of the phenomenon of stunning should enable the clinician to assess the effects of reperfusion therapy with greater accuracy.

For example, the benefits of thrombolysis in acute myocardial infarction cannot be appreciated immediately because the recovery of function in viable tissue may require several days or possibly even longer, as discussed above. However, the magnitude of the salvage effected by reperfusion can be estimated from the improvement in wall motion at the time of hospital discharge (7-10 days after the acute myocardial infarction). Because stunned myocardium possesses considerable inotropic reserve,⁴ the amount of salvage achieved may be estimated early after thrombolysis by measuring the regional inotropic reserve with dobutamine echocardiography. Such information may be important in deciding whether to perform PTCA on the infarct-related vessel and may have significant diagnostic value.

Recognition of myocardial stunning mandates a careful assessment to distinguish stunned from necrotic myocardium in order to appropriately implement (or deny) aggressive therapeutic approaches.

For example, when a patient with acute myocardial infarction who is successfully treated with thrombolytic therapy continues to exhibit a large akinetic LV region, the cardiologist must be able to determine whether this region is mostly viable but stunned (in which case it could benefit from PTCA or CABG) or mostly necrotic (in which case these interventions would not be useful). Even more compelling is the problem of the patient who remains in cardiogenic shock after CABG or after thrombolytic therapy for acute myocardial infarction: how long should aggressive therapy be pursued in this situation? Is the pump failure caused by necrosis (in which case aggressive treatment would not be indicated) or by stunning (in which case such a treatment would be life-saving)? By using one

of the diagnostic techniques for recognizing stunned myocardium, the cardiologist needs to make a judgment as to whether the LV dysfunction is reversible, because this is the factor that determines whether or not it would be useful to maintain pharmacological and/or mechanical circulatory support for extended periods of time.

Finally, the concept of myocardial stunning may impact on the decision as to whether to proceed with CABG or PTCA, since in some patients this decision is based predominantly on the presence and extent of viable myocardium. As discussed above, stunned myocardium is likely to be a major cause of viable but dysfunctional myocardial segments. Since impaired LV ejection fraction is a strong predictor of mortality, and since enhancement of LV function after revascularization is associated with improved survival, the prospective differentiation of viable from nonviable myocardium in patients with coronary artery disease and impaired LV function is of significant clinical importance in the modern era of myocardial revascularization. For example, the demonstration that a large, hypokinetic/akinetic ventricular region is still viable (as determined by any of the techniques for recognizing myocardial stunning) would be an important factor in recommending coronary revascularization.

Can myocardial stunning cause chronic ventricular dysfunction?

As proposed in a previous review,⁴ the most intriguing and potentially important clinical implication of the concept of stunning is the possibility that this contractile abnormality may become persistent or even chronic. Animal studies have shown that repeated brief episodes of ischemia occurring in close temporal proximity have a cumulative effect on contractility, such that myocardial function remains depressed much longer than with a single ischemic episode⁸ both after ischemia caused by increased oxygen demand and after ischemia caused by reduced blood supply. On the other hand, clinical studies have demonstrated that many patients with coronary artery disease experience recurrent episodes of ischemia in the same territory as a consequence of recurrent coronary spasm and/or thrombosis. Ambulatory electrocardiographic studies suggest that such episodes, often silent, occur with higher frequency than previously suspected, up to 10-20 times per day. Under these circumstances, the myocardium may not be able to recover fully between episodes and thus may remain reversibly depressed for extended periods of time (Figure 2, panel D).⁴

It is important to note that many of the alterations in regional function that have been ascribed to hibernation could in fact be caused by stunning resulting from repetitive episodes of ischemia (painless or painful) alternating with reperfusion, as illustrated in Figure 2, panel D. Support for this concept is provided by both experimental and clinical data. Experimentally, Shen et al⁴⁹ have demonstrated in conscious pigs that during the development of a progressive coronary artery stenosis, LV function remained persistently depressed despite normal perfusion and despite lack of necrosis; they further demonstrated that such dysfunction was associated with recurrent brief episodes of ischemia caused by increased oxygen demands, each of which was followed by a period of stunning. *As emphasized previously, from a physiological standpoint it is very difficult to envision a condition in which coronary blood flow would remain chronically low at a steady level (unless major adaptive changes in coronary vessels occur in response to acute repetitive ischemia), because in the presence of a critical stenosis, local coronary autoregulation is lost and blood flow is likely to fluctuate widely.*⁴ This point is elaborated in the legend to panel H of Figure 2.

Clinically, many lines of evidence indicate the existence of a chronic but reversible depression of contractility in patients with coronary artery disease (reviewed in ref 4). The unanswered question is whether this depression is due to repetitive stunning or to hibernation. In this regard, Tillisch et al⁵⁰ studied, with PET, patients with regional wall motion abnormalities at rest. In this population, blood flow was normal in 37% of dysfunctional segments, and 88% of these segments exhibited improved contraction after CABG, suggesting that the wall motion abnormalities were caused by repetitive stunning rather than by hibernation. Recently, Vanoverschelde et al⁵¹ studied, with PET, patients with chronic occlusion of a major coronary artery but without previous infarction. A subset of patients exhibited regional dysfunction that improved significantly after revascularization, whereas another subset exhibited no regional dysfunction. In the subset with regional dysfunction, regional myocardial blood flow was similar to that of patients without segmental dysfunction; that is, flow was not reduced compared to patients without dysfunction. The authors interpreted these findings as evidence that the dysfunction was caused by repetitive stunning rather than by a primary deficit of flow (ie, hibernation). It must be pointed out, however, that blood flow in the dysfunctional segments was approximately 20% less than that measured in the normal remote segments in the same patients; thus, a decrease in perfusion



(particularly in the subendocardium, which cannot be resolved by PET) could have been present, and hibernation cannot be excluded. On the other hand, the hypothesis of repetitive stunning is bolstered by the demonstration that exercise-induced ischemia (one of the most common, if not the most common, causes of ischemia) results in stunning in humans.

In view of these considerations, it was proposed in 1992⁴ that in many patients in whom reversible LV dysfunction is assumed to be secondary to hibernation, the dysfunction is actually secondary to repetitive episodes of stunning (Figure 2, panel D) rather than to a chronic low-flow state (that is, hibernation) (Figure 2, panel E). The scenario depicted in panel D is far more likely than that depicted in panel E. Furthermore, even if chronic hibernation does occur, it seems likely that it will be superimposed on repetitive stunning, as shown in (Figure 2, panel F).

In conclusion, repetitive stunning could be a heretofore unrecognized cause of chronic LV dysfunction and, possibly, dilated cardiomyopathy.⁴

Should myocardial stunning be reversed or prevented?

Postischemic dysfunction can be temporarily reversed with inotropic therapy³¹ (reviewed in ref 3), and indeed this form of therapy is the standard approach to the treatment of LV dysfunction in clinical situations where stunning is likely to be present. Given that inotropic agents are so effective, shouldn't one be content with this form of treatment?

Inotropic agents may unfortunately not be the optimal approach to the problem. There are several reasons why it is preferable to prevent stunning from occurring in the first place rather than have to treat it with inotropic agents after it has developed.⁴ First, inotropic agents increase myocardial oxygen consumption, which is undesirable in patients with coronary artery disease. Second, most inotropic agents have the potential to cause arrhythmias. Third, inotropic therapy often requires invasive hemodynamic monitoring. Fourth, although brief inotropic therapy appears to be innocuous,³¹ it is unknown whether prolonged inotropic stimulation of stunned myocardium has deleterious effects. Finally, prevention of myocardial stunning might facilitate rapid weaning from bypass after cardiac surgery or transplantation and may shorten the duration of hemodynamic instability after thrombolysis. In view of all of these considerations, prevention of stunning is definitely preferable to treatment of stunning.

Diagnosis of myocardial stunning

Because this topic is discussed in detail in the accompanying article by Dr Bonow, it will not be addressed in detail here. The techniques available for diagnosing myocardial stunning have been reviewed previously.⁴ Briefly, these techniques can be divided into two groups: those based on the demonstration of a perfusion-contraction “mismatch” (ie, decreased contraction in the face of normal perfusion) and those based on the demonstration of preserved inotropic reserve. The former group includes PET, ²⁰¹Tl scintigraphy at rest, and ^{99m}Tc-sestamibi imaging, whereas the latter group includes low-dose dobutamine echocardiography. PET is the “gold standard” diagnostic tool for stunned myocardium because it can measure absolute regional myocardial blood flow and thus distinguish myocardial stunning from hibernation. However, PET is expensive and not available to most clinicians. Alternative techniques are ²⁰¹Tl scintigraphy at rest and ^{99m}Tc-sestamibi imaging. These techniques can demonstrate normal perfusion in the presence of decreased function - the hallmark of myocardial stunning. Low-dose dobutamine echocardiography has recently emerged as a promising method that is practical, non-time consuming, and can be applied at the bedside. Mounting evidence suggests that this technique, when used before PTCA or early after thrombolysis in acute myocardial infarction, can be quite useful in predicting the eventual degree of functional recovery.⁴ The relative values of rest ²⁰¹Tl or ^{99m}Tc-sestamibi scintigraphy and dobutamine echocardiography for detecting myocardial viability have dobutamine echocardiography can distinguish stunned from hibernating myocardium. Further studies examining the dose-response relationship of presumably stunned versus presumably hibernating myocardium to dobutamine challenges will be necessary to clarify this issue.

Concluding remarks

Myocardial stunning has major conceptual and clinical importance. The progress made regarding this phenomenon has been considerable, both at the experimental and at the clinical level. The clinical significance of myocardial stunning is beginning to be appreciated by clinicians. Although the mechanism of stunned myocardium in humans is not yet known, experimental models of stunning are useful in guiding future clinical investigations. Perhaps, such investigations will ultimately lead to the development of medications which can prevent or attenuate the occurrence of stunned myocardium and/or hasten its recovery.

It is hoped that the concepts discussed in this article will provide a conceptual framework for further investigation of the pathophysiology of reversible

ischemia/reperfusion injury, as well as a rationale for developing better diagnostic modalities and new therapeutic strategies designed to prevent postischemic ventricular dysfunction in humans. A better understanding of myocardial stunning should further our knowledge of the effects of ischemia on the heart and of the pathophysiology of coronary artery disease in general.

At the end of this review, I would like to pose three major questions that will be addressed by separate articles: **(i) Does myocardial stunning occur in man? (ii) How can myocardial stunning be diagnosed? and (iii) What are the treatments for myocardial stunning?** These questions will be addressed by Dr Poole-Wilson, Dr Bonow, and Dr Heusch, respectively.

The excellent secretarial assistance of Sandy Dunaway is gratefully acknowledged. The work reported here was supported in part by NIH Grants HL-43151 and HL-55757.

References

- 1. Heyndrickx GR, Millard RW, McRitchie RJ, Maroko PR, Vatner SF.**
Regional myocardial functional and electrophysiological alterations after brief coronary artery occlusion in conscious dogs.
J Clin Invest. 1975;56:978-985.
- 2. Braunwald E, Kloner RA.**
The stunned myocardium: prolonged, postischemic ventricular dysfunction.
Circulation. 1982;66:1146-1149.
- 3. Bolli R.**
Mechanism of myocardial "stunning."
Circulation. 1990;82:723-738.
- 4. Bolli R.**
Myocardial "stunning" in man.
Circulation. 1992;86:1671-1691.
- 5. Bolli R, Zhu WX, Thornby JI, O'Neill PG, Roberts R.**
Time-course and determinants of recovery of function after reversible ischemia in conscious dogs.
Am J Physiol. 1988;254:H102-H114.
- 6. Charlat ML, O'Neill PG, Hartley CJ, Roberts R, Bolli R.**
Prolonged abnormalities of left ventricular diastolic wall thinning in the "stunned" myocardium in conscious dogs: time-course and relation to systolic function.
J Am Coll Cardiol. 1989;13:185-194.
- 7. Bolli R, Patel BS, Hartley CJ, Thornby JI, Jeroudi MO, Roberts R.**
Nonuniform transmural recovery of contractile function in the "stunned" myocardium.
Am J Physiol. 1989;257:H375-H385.
- 8. Bolli R, Zughuib M, Li XY, Tang XL, Sun JZ, Triana JF, McCay P.**
Recurrent ischemia in the canine heart causes recurrent bursts of free radical production that have a cumulative effect on contractile function: a pathophysiological basis for chronic myocardial "stunning."
J Clin Invest. 1995;96:1066-1084.
- 9. Sun JZ, Tang XL, Knowlton AA, Park SW, Qiu Y, Bolli R.**
Late preconditioning against myocardial stunning: an endogenous protective mechanism that confers resistance to postischemic dysfunction 24 hours after brief ischemia in conscious pigs.
J Clin Invest. 1995;95:388-403.
- 10. Sun JZ, Tang XL, Park SW, Qiu Y, Turrens J, Bolli R.**
Evidence for an essential role of reactive oxygen species in the genesis of late preconditioning against myocardial stunning in conscious pigs.
J Clin Invest. 1996;97:562-576.
- 11. Kusuoka H, Porterfield JK, Weisman HF, Weisfeldt ML, Marban E.**
Pathophysiology and pathogenesis of stunned myocardium. Depressed Ca²⁺ activation of contraction as a consequence of reperfusion-induced cellular calcium overload in ferret hearts.
J Clin Invest. 1987;79:950-961.
- 12. Marban E, Koretsune Y, Corretti M, Chacko VP, Kusuoka H.**
Calcium and its role in myocardial cell injury during ischemia and reperfusion.
Circulation. 1989;80(suppl IV):IV-17-IV-22.
- 13. Homans DC, Sublett E, Dai XZ, Bache RJ.**
Persistence of regional left ventricular dysfunction after exercise-induced myocardial ischemia.
J Clin Invest. 1986;77:66-73.
- 14. Bolli R.**
Common methodological problems and artifacts associated with studies of myocardial stunning in vivo.
Basic Res Cardiol. 1995;90:257-262.

**15. Triana JF, Li XY, Jamaluddin U, Thornby JI, Bolli R.**

Postischemic myocardial "stunning." Identification of major differences between the open-chest and the conscious dog and evaluation of the oxygen radical hypothesis in the conscious dog.
Circ Res. 1991;69:731-747.

16. Kusuoka H, Marban E.

Cellular mechanisms of myocardial stunning.
Annu Rev Physiol. 1992;54:243-256.

17. Heusch G.

Myocardial stunning: a role for calcium antagonists during ischaemia?
Cardiovasc Res. 1992;26:14-19.

18. Myers ML, Bolli R, Lekich RF, Hartley CJ, Roberts R.

Enhancement of recovery of myocardial function by oxygen free-radical scavengers after reversible regional ischemia.
Circulation. 1985;72:915-921.

19. Bolli R, Jeroudi MO, Patel BS, et al.

Marked reduction of free radical generation and contractile dysfunction by antioxidant therapy begun at the time of reperfusion: evidence that myocardial "stunning" is a manifestation of reperfusion injury.
Circ Res. 1989;65:607-622.

20. Bolli R.

Role of oxygen radicals in myocardial stunning.
In: Kloner RA, Przyklenk K, eds. *Stunned Myocardium: Properties, Mechanisms, and Clinical Manifestations.*
New York, NY: Marcel Dekker; 1993:155-195.

21. Bolli R, Patel BS, Jeroudi MO, Lai EK, McCay PB.

Demonstration of free radical generation in "stunned" myocardium of intact dogs with the use of the spin trap A-phenyl N-tert-butyl nitron.
J Clin Invest. 1988;82:476-485.

22. Sun JZ, Kaur H, Halliwell B, Li XY, Bolli R.

Use of aromatic hydroxylation of phenylalanine to measure production of hydroxyl radicals after myocardial ischemia in vivo: direct evidence for a pathogenetic role of the hydroxyl radical in myocardial stunning.
Circ Res. 1993;73:534-549.

23. Li XY, McCay PB, Zughaib M, Jeroudi MO, Triana JF, Bolli R.

Demonstration of free radical generation in the "stunned" myocardium in the conscious dog and identification of major differences between conscious and open-chest dogs.
J Clin Invest. 1993;92:1025-1041.

24. Sekili S, McCay PB, Li XY, et al.

Direct evidence that the hydroxyl radical plays a pathogenetic role in myocardial "stunning" in the conscious dog and that stunning can be markedly attenuated without subsequent adverse effects.
Circ Res. 1993;73:705-723.

25. Bolli R.

Superoxide dismutase 10 years later: a drug in search of a use.
J Am Coll Cardiol. 1991;18:231-233.

26. Hearse DJ.

Stunning: a radical re-view.
Cardiovasc Drugs Ther. 1991;5:853-876.

27. Bolli R.

Role of neutrophils in myocardial stunning after brief ischaemia: the end of a six-year-old controversy (1987-1993).
Cardiovasc Res. 1993;27:728-730.

28. Sekili S, Jeroudi MO, Tang XL, Zughaib M, Sun JZ, Bolli R.

Effect of adenosine on myocardial "stunning" in the dog.
Circ Res. 1995;76:82-94.

29. Jeroudi MO, Cheirif J, Habib G, Bolli R.

Prolonged wall motion abnormalities after chest pain at rest in patients with unstable angina: a possible manifestation of myocardial stunning.
Am Heart J. 1994;127:1241-1250.

30. Bolli R, Hartley CJ, Chelly JE, et al.

An accurate nontraumatic ultrasonic method to monitor myocardial wall thickening in patients undergoing cardiac surgery.
J Am Coll Cardiol. 1990;15:1055-1065.

31. Bolli R, Zhu WX, Myers ML, Hartley CJ, Roberts R.

Beta-adrenergic stimulation reverses postischemic myocardial dysfunction without producing subsequent functional deterioration.
Am J Cardiol. 1985;56:964-968.

32. Park SW, Tang XL, Qiu Y, Sun JZ, Bolli R.

Nisoldipine attenuates myocardial stunning induced by multiple coronary occlusions in conscious pigs and this effect is independent of changes in hemodynamics or coronary blood flow.
J Mol Cell Cardiol. In press.

33. Krause SM, Jacobus WE, Becker LC.

Alterations in cardiac sarcoplasmic reticulum calcium transport in the postischemic "stunned" myocardium.
Circ Res. 1989;65:526-530.

Myocardial "stunning" 20 years later - Bolli

34. Bolli R, Jeroudi MO, Patel BS, et al.

Direct evidence that oxygen-derived free radicals contribute to postischemic myocardial dysfunction in the intact dog.

Proc Natl Acad Sci USA. 1989;86:4695-4699.

35. Bolli R, Jeroudi MO, Patel BS, et al.

Marked reduction of free radical generation and contractile dysfunction by antioxidant therapy begun at the time of reperfusion: evidence that myocardial "stunning" is a manifestation of reperfusion injury.

Circ Res. 1989;65:607-622.

36. Bolli R, Patel BS, Jeroudi MO, et al.

Iron-mediated radical reactions upon reperfusion contribute to myocardial "stunning."

Am J Physiol. 1990;259:H1901-H1911.

37. Sheiban I, Tonni S, Benussi P, Marini A, Trevi GP.

Left ventricular dysfunction following transient ischemia induced by transluminal coronary angioplasty. Beneficial effects of calcium antagonists against post-ischemic myocardial stunning.

Eur Heart J. 1993;14(suppl A):14-21.

38. Nixon JV, Brown CN, Smitherman TC.

Identification of transient and persistent segmental wall motion abnormalities in patients with unstable angina by two-dimensional echocardiography.

Circulation. 1982;65:1497-1503.

39. Renkin J, Wijns W, Ladha Z, Col J.

Reversal of segmental hypokinesia by coronary angioplasty in patients with unstable angina, persistent T-wave inversion, and left anterior descending artery stenosis: additional evidence for myocardial stunning in humans.

Circulation. 1990;82:913-921.

40. de Zwaan C, Cheriex EC, Braat SHJG, Stappers JLM, Wellens HJJ.

Improvement of systolic and diastolic left ventricular wall motion by serial echocardiograms in selected patients treated for unstable angina.

Am Heart J. 1991;121:789-797.

41. Distante A, Rovai D, Picano E, et al.

Transient changes in left ventricular mechanics during attacks of Prinzmetal's angina: an M-mode echocardiographic study.

Am Heart J. 1984;107:465-473.

42. Distante A, Rovai D, Picano E, et al.

Transient changes in left ventricular mechanics during attacks of Prinzmetal angina: a two-dimensional echocardiography study.

Am Heart J. 1984;108:440-446.

43. Ito H, Tomooka T, Sakai N, et al.

Time-course of functional improvement in stunned myocardium in risk area in patients with reperfused anterior infarction.

Circulation. 1993;87:355-362.

44. Robertson WS, Feigenbaum H, Armstrong WF, Dillon JC, O'Donnell, McHenry PW.

Exercise echocardiography: a clinical practical addition in the evaluation of coronary artery disease.

J Am Coll Cardiol. 1983;6:1085-1089.

45. Stoddard MF, Johnstone J, Dillon S, Kupersmith J.

The effect of exercise-induced myocardial ischemia on postischemic left ventricular diastolic filling.

Clin Cardiol. 1992;15:265-273.

46. Ambrosio G, Losi MA, Perrone Filardi P, et al.

Persistence of contractile impairment in the absence of flow abnormalities after exercise: evidence for myocardial stunning in patients with stable angina.

Circulation. 1993;88(suppl I):I-646. Abstract.

47. Deantonio HJ, Kaul S, Lerman BB.

Reversible myocardial depression in survivors of cardiac arrest.

PACE. 1990;13:982-985.

48. Ferrari R, Alfieri O, Curello S, et al.

Occurrence of oxidative stress during reperfusion of the human heart.

Circulation. 1990;81:201-211.

49. Shen YT, Vatner SF.

Mechanism of impaired myocardial function during progressive coronary stenosis in conscious pigs: hibernation versus stunning?

Circ Res. 1995;73:479-488.

50. Tillisch J, Brunken R, Marshall R, et al.

Reversibility of cardiac wall-motion abnormalities predicted by positron tomography.

N Engl J Med. 1986;314:884-888.

51. Vanoverschelde JLJ, Wijns W, Depré C, et al.

Mechanisms of chronic regional postischemic dysfunction in humans: new insights from the study of noninfarcted collateral-dependent myocardium.

Circulation. 1993;87:1513-1523.
