Myocardial Stunning

Editorial

Lead Article

Expert Answers to Three Key Questions

Summaries of Ten Seminal Papers 42

Bibliography of Key Papers

Editorial

The world is not short of medical journals, especially in cardiology where many publications deliver to their readership the most current advances in clinical and laboratory research. The challenge of keeping up to date with the flood of new studies often means that busy physicians do not have the time to reflect in depth on the progress and impact of a single topic of cardiological relevance. Journals abound with a potpourri of exciting but often unrelated investigations, and sometimes it is difficult to trace and fully appreciate the complex matrix of studies that, when combined, represent the current body of knowledge on a specific area of cardiovascular medicine. ***Dialogues in Cardiovascular Medicine*** *seeks to address this problem.*

Our editorial objective is to devote each issue of ***Dialogues*** *to a single topic of clinical relevance, to explore it in concise detail, to place it into clinical perspective and identify pressing questions that dominate the field. We will do this with the help of undisputed experts, authoritative investigators who have made a major contribution to the development of a concept and to the fundamental understanding of the mechanisms and management of cardiovascular disease. Our aim will be to deliver to the practising cardiologist the very best overviews from the best of authors.*

This first issue of ***Dialogues*** *epitomizes our goals. Myocardial stunning is a phenomenon that was first characterized in the laboratory, and for the past 20 years, the cardiological literature has been enriched by many hundreds of papers describing painstaking experimental and clinical studies that, taken together, provide a remarkable insight into the pathophysiology of stunning. Although first recognized in the experimental laboratory, stunning is of great relevance to both the cardiologist and the cardiac surgeon; a thorough understanding of the essentials of stunning will undoubtedly improve patient management. However, busy surgeons and cardiologists rarely have the time to digest an enormous (and sometimes contradictory) literature, hence the birth of* ***Dialogues****.*

In assembling this first issue of ***Dialogues*** *we sought the help of a cardiologist who, without doubt, has made the greatest single contribution to our understanding of stunning. Over the past decade Roberto Bolli has published over fifty keynote papers on the subject, so who better than he to give, in the Lead Article, a concise overview of the relevance of stunning to the cardiologist.*

No field is ever without conflict or controversy, and, however advanced, questions always remain, and thus it is with stunning. Roberto Bolli has therefore been asked to conclude his article with the three most important questions that a cardiologist might ask about stunning.

We have then invited three more experts to provide personal answers. In short, crisp Expert Answers to Three Key Questions, Philip Poole-Wilson shares his views on the clinical manifestations of stunning, Robert Bonow explains how it can be best detected and quantified, and Gerd Heusch addresses the means and importance of therapy. This will be the pattern that will characterize future issues of ***Dialogues****.*

Although our objective is to create concise and digestible overviews that will allow the essence of a major topic to be rapidly assimilated, we have no doubt that these articles will stimulate a deeper interest for many readers - if it does not, then we will have failed our editorial challenge. We will, therefore, also publish a selected Bibliography of One Hundred Key Papers to allow rapid access to the literature. Furthermore, each issue will contain Summaries of Ten Seminal Papers pertaining to the area under consideration.

We hope that this new publication will be a help to cardiologists worldwide, and we are indebted to the Servier Research Group for providing a generous educational grant to support this venture, a further demonstration of their commitment to advancing knowledge in cardiovascular medicine.

Roberto Ferrari and David J. Hearse
Editors in Chief

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 reperfusion[1] (the term "myocardial stunning" was coined in 1982[2]). 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 experimentalists[3] and clinicians[4] 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* I. CLASSIFICATION OF MYOCARDIAL STUNNING AND EVIDENCE FOR THE VARIOUS MECHANISMS PROPOSED IN EXPERIMENTAL ANIMALS**

	Evidence for a pathogenetic role of			
Experimental setting	*Oxygen radicals*	*Sarcoplasmic reticulum dysfunction*	*Calcium overload*	*Reduced calcium sensitivity*
Stunning due to decreased blood flow				
Regional ischemia				
Single, completely reversible ischemic episode	++	?	?	+
Multiple, completely reversible ischemic episodes	+	+	?	–
Single, partly irreversible ischemic episode (subendocardial infarction)	±	?	?	?
Global ischemia				
Isolated heart in vitro	+	?	+	+
Cardioplegic arrest in vivo	+	?	?	?
Stunning due to increased O_2 demands				
Exercise-induced ischemia				
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 pathophysiologic substrates, it is important to discuss briefly the differences among the various settings.

The experimental observations can be classified into the following categories[3] (*Table* I):

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 myocardium[6]; 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 colleagues[1] 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) D*ecreased responsiveness of myofilaments to calcium*. In isolated ferret hearts subjected to 15 min of normothermic global ischemia, Kusuoka et al[11] 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 hearts[16]; 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 myocardium[11] 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 al[32] have recently shown that nisoldipine attenuates myocardial stunning in conscious pigs via a direct cardioprotective action. T*he 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 injury[17] (see below).

c) E*xcitation-contraction uncoupling due to sarcoplasmic reticulum dysfunction.* Krause et al[33] 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]

T*he oxyradical hypothesis*

a) E*ffect 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 •OH, produced a significant and sustained improvement in the function of the stunned myocardium,[3,19] suggesting that the •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 •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) D*irect 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 nitrone (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. T*hese 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 desferrioxamine[36] suppressed the production of free radicals in the stunned myocardium and, at the same time, attenuated postischemic dysfunction[19] (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 •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 •OH is produced in the stunned myocardium upon reperfusion; moreover, •OH scavengers suppressed tyrosine production and attenuated the dysfunction, suggesting a key role of •OH as a mediator of stunning.[22] T*he similarity of the results obtained with two*

completely different techniques (spin trapping[19-21] and aromatic hydroxylation[22]) 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 stunning[15] and the magnitude of free radical generation[23] 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 min[23]; (ii) that antioxidants (desferrioxamine and MPG) markedly attenuate this burst of free radical generation[24]; 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^+-Ca^{2+} 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^+-Ca^{2+} 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 Hearse[26] 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 1990[3] and is illustrated in F*igure* 1 (a detailed description of the postulated

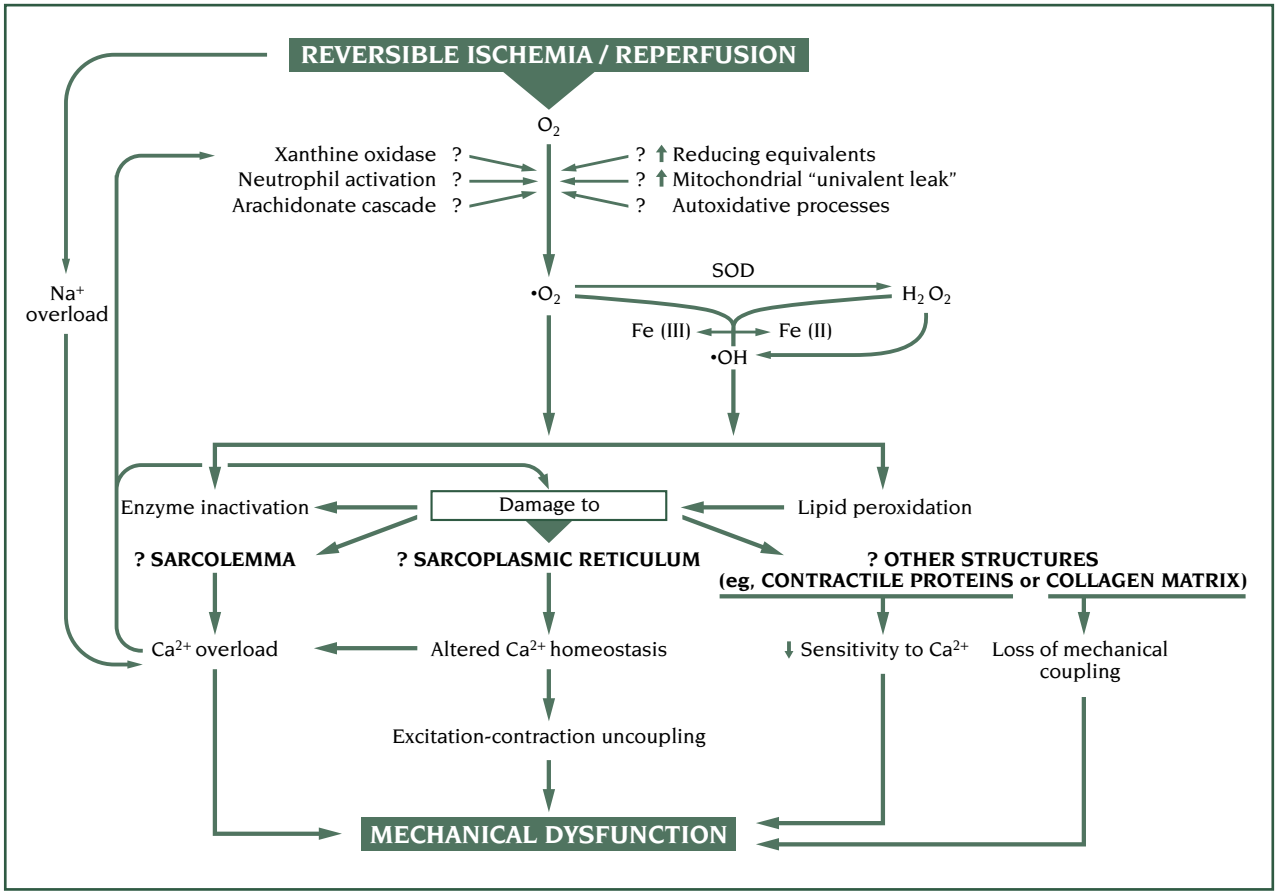

Figure 1. *Illustration of the proposed pathogenesis of postischemic myocardial dysfunction. This proposal integrates and reconciles different mechanisms into a unifying pathogenetic hypothesis. Transient reversible ischemia followed by reperfusion could result in increased production of superoxide radicals (·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 ·O_2- to hydrogen peroxide (H_2O_2); in the presence of catalytic iron, ·O_2- and H_2O_2 interreact in a Haber-Weiss reaction to generate the hydroxyl radical (·OH). H_2O_2 can also generate ·OH in the absence of ·O_2- through a Fenton reaction provided that other substances (such as ascorbate) reduce Fe (III) to Fe (II). ·O_2- and ·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 Na^+-K^+-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 Na^+-K^+-ATPase, and (2) acidosis and Na^+-H^+ exchange. This could further exaggerate calcium overload via increased Na^+-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.*

Hearse[26] 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 study[22] 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.* ^{18}FDG, 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 dysfunction[5] 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 F*igure* 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 (F*igure* 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 (F*igure* 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 (F*igure* 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 (F*igure* 2, *panel* D).

If the underlying, fixed coronary stenosis is sufficiently severe, these acute reductions in flow and the ensuing stunning could be *superimposed* on hibernation (F*igure* 2, *panel* F). Finally, a phase of stunning may *follow* a phase of hibernation (F*igure* 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-

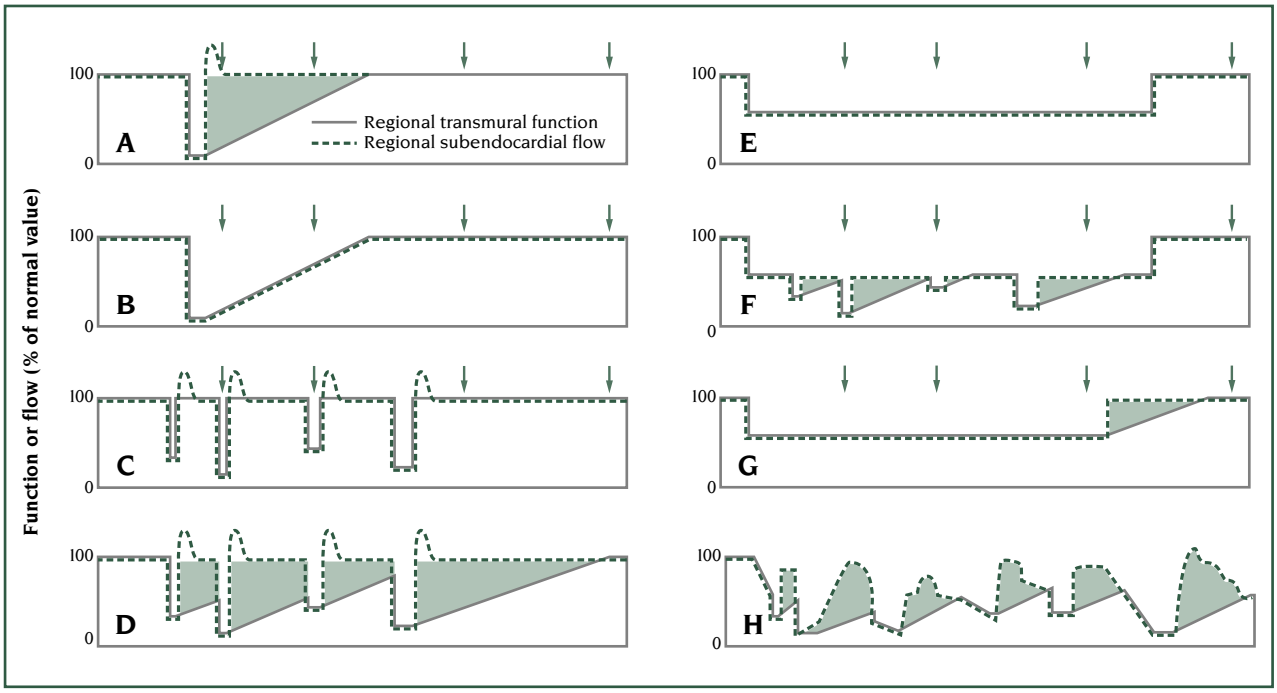

Figure 2. *Schematic illustration of several possible scenarios that could occur in a patient with a fixed critical coronary stenosis sufficient to blunt reactive hyperemia. Stunning is indicated by the cross-hatched areas. (A) Brief episode of ischemia (due to thrombosis and/or vasoconstriction) followed 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 ⩽20 minutes)	→ 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	→ 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 al[37] 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 insult[3] (*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 al[38] 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 al[29] 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 al[39] and de Zwaan et al[40] 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 al[43] 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.

M*yocardial 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 al[44] who reported persisting wall motion abnormalities 30 min after exercise-induced ischemia in 6 of 16 (38%) patients with coronary artery disease. Stoddard et al[45] 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.

M*yocardial 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 al[30] 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 al[47] 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 humans[4] 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 episode[8] 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 (F*igure* 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 F*igure* 2, *panel* D. Support for this concept is provided by both experimental and clinical data. Experimentally, Shen et al[49] 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. A*s 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* F*igure* 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 al[50] 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 al[51] 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 1992[4] 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 (F*igure* 2, *panel* D) rather than to a chronic low-flow state (that is, hibernation) (F*igure* 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 (F*igure* 2, *panel* F).

I*n 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 therapy[31] (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, ^{201}Tl 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 ^{201}Tl 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 ^{201}Tl 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, Zughaib 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 Ca^{2+} 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 nitrone.
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.

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, Wijnss W, Ladha Z, Col J.
Reversal of segmental hypokinesis 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.

Myocardial Stunning

Expert Answers to Three Key Questions

1

Myocardial stunning: does it occur in man?

P.A. Poole-Wilson

2

How can stunning be detected clinically?

R.O. Bonow

3

How should stunning be treated?

G. Heusch

Myocardial stunning: does it occur in man?

P.A. Poole-Wilson, MD, FRCP, FACC, FESC

National Heart and Lung Institute - Dovehouse Street - London SW3 6LY - ENGLAND

The commonest cause of abnormal contraction of heart muscle is obstruction of the blood supply to that muscle as a consequence of the development of atheromatous plaques in the coronary arteries.
Coronary heart disease can manifest itself as many well-described clinical syndromes, such as angina and myocardial infarction. The word stunning has come to refer to the reduced contraction of heart muscle which follows a period of restriction of blood flow and which occurs in the presence of the restoration of a normal blood flow. This entity may form part of the clinical syndromes of angina, unstable angina, and following cardiac surgery. Understanding the mechanisms may lead to more appropriate and even novel treatments for these conditions.

Many researchers have observed the slow recovery of myocardial function after cardiac muscle has been exposed to a variety of negative inotropic conditions. The delayed and protracted recovery of ventricular function following brief periods of ischemia was described[1] succinctly in 1975 and subsequently given the name of "stunning."[2] This name rapidly gained popularity and the entity has been the subject of much recent research.

One definition of 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."[3,4] The entity needs to be distinguished from "hibernating myocardium" where long-term ventricular dysfunction is accompanied by a maintained reduction of coronary flow.[5,6] A formal definition of hibernation is rather complex, indicating the difficulty of reconciling the concept with clinical practice. The usual definition is "a state of persistently impaired myocardial and left ventricular function at rest due to reduced coronary blood flow that can be partially or completely restored to normal if the myocardial oxygen supply/demand relationship is favorably altered, either by improving blood flow and/or reducing demand."[5,6] This definition was written by a clinician and the careful wording reflects the many relevant clinical factors requiring consideration.

There is an unequalled opportunity for semantic chaos if hibernation is considered as stuttering,[7] or repetitive stunning, or if stunning is merely the modern word for reperfusion damage after a brief period of ischemia. Another current concept which further confuses the situation is preconditioning,[8] by which is meant the observation that damage to the myocardium is lessened by previous short-term exposure to a period of ischemia of between 2 and 15 minutes.

Stunning is a concept which arose from experiments performed under control conditions in dogs and later in other animal species. The experimental models which have been studied differ substantially. Some are not perfused at all while others are perfused with physiological solutions and have a high coronary flow. Many of the apparent controversies almost certainly reflect differences in the response to ischemia or a surrogate of ischemia in an individual model rather than providing a ubiquitous truth.

If the definition of stunning, stated above, is accepted, then three issues need to be addressed. The coronary flow must be normal. No damage must be present in the myocardium. The state of ventricular dysfunction must be reversible.

Coronary flow is notoriously difficult to measure in man. All the current

techniques are able to measure "coronary reserve," that is, the ratio of blood flow at rest and after maximum vasodilatation. But the measurement of blood flow at rest is highly inaccurate within a patient over a period of time. Short-term changes can be recorded with some accuracy using Doppler flow catheters. Even if total blood flow can be shown to be near normal this does not exclude major differences in endocardial versus epicardial flow nor does it exclude major effects of shunting or steal in the microvasculature. In animal models flow does fall after short periods of ischemia, returns to normal over many minutes, and the reduction can be partially reversed by calcium antagonists.[9,10] The relationship between blood flow and function is complex, being nonlinear and varying with time and the experimental conditions.[11] The second requirement is an absence of myocardial damage. That is impossible to exclude in man. Light microscopy and electron microscopy in human tissue show numerous abnormalities in cardiac muscle from patients with heart failure. Similar findings have been reported adjacent to ischemic tissue or in hibernating myocardium. Furthermore, a subtle loss of intracellular structural proteins such as the intermediate filaments or microtubules, or of minor damage to the extracellular cytoskeleton, would lead to a reduction in myocardial function. The third criterion of reversibility is perhaps the easiest to establish in man. Many techniques can be used such as simple measurements of ventricular size, ejection fraction, or incoordinate contraction, or more sophisticated techniques such as stress echocardiography, thallium imaging, PET scanning, magnetic resonance, or fast CT scanning. In a formal sense it is doubtful that stunning can ever be shown to exist in man.

The putative causes of stunning are numerous. There is evidence for abnormalities of the sarcoplasmic reticulum calcium ATPase responsible for the uptake of calcium from the cytosol[12] and for calcium overload of the cell.[13] The response of the myofibrils to calcium is diminished and the calcium transient may be normal.[14] Oxygen free radicals certainly are a major contributor to stunning[3,4] and the effect can be suppressed either by preventing free radical accumulation or by the presence of calcium antagonists.[13] An attractive hypothesis is that stunning is a consequence of the early accumulation of free radicals after a period of ischemia. The free radicals, depending on their site of formation and on the local concentration, could alter the function of proteins by sulfhydryl linkage. These proteins will include ion release channels (eg, the calcium release channel in the sarcoplasmic reticulum), uptake pathways (eg, the sarcoplasmic reticulum calcium ATPase), exchange pathways (eg, the sodium-calcium exchanger), intracellular cytoskeletal proteins, and the contractile proteins.

The reader might have a sensation of déjà vu. This is exactly the same story that has been put forward to explain the entity of reperfusion damage.[15-17] Thus, stunning might be just the early events preceding reperfusion damage. That is probably correct.

Application of the concept of stunning to clinical syndromes associated with coronary heart disease is a challenge to the cardiologist (*Table* I). But it is an intellectual exercise which may be of limited or no significance whatsoever to the patient. Ventricular dysfunction is almost a universal finding in all the clinical syndromes associated with heart disease and coronary heart disease in particular. The clinical problem is easily stated. By far the commonest cause of ventricular dysfunction in clinical practice is coronary heart disease. Left ventricular dysfunction can be a consequence of a loss of myocardial cells (the myocytes) or a result of incoordinate contraction.

***Table* I. VENTRICULAR DYSFUNCTION, "STUNNING," AND CLINICAL SYNDROMES**

ACUTE VENTRICULAR DYSFUNCTION	
Immediate contractile failure (<2 min)	• Angioplasty (PTCA)
"Stunning" (approx >2 min <15 min) but before any structural change, with near-normal coronary flow and reversible dysfunction	• Stable or unstable angina • Prinzmetal's angina • Early thrombolysis • Cardiac surgery
CHRONIC VENTRICULAR DYSFUNCTION	
Early "hibernation" (hours but <3 months) or "repetitive stunning"	• Unstable angina • Postinfarction • Silent ischemia
Chronic "hibernation" (>3 months) Dysfunction with reduced coronary blood flow but reversible	• Stable angina • Heart failure due to coronary heart disease? • Aortic stenosis

Regional or global depression of contractility is frequently observed. Once these two causes of reduced myocardial function have been excluded, then diminished function of the heart is attributable either to architectural changes such as ventricular shape, cell orientation, or extracellular fibrosis, or to cellular abnormalities such as reduced systolic contraction or diastolic relaxation.

There are several short-term clinical syndromes in patients with coronary heart disease in which stunning might be anticipated. These include percutaneous transluminal coronary angioplasty (PTCA), coronary artery spasm, and exercise-induced angina. Numerous studies have reported on the changes in ventricular function during and after angioplasty. In general, function returns to normal within approximately 5 minutes following occlusion of the artery for approximately 60 seconds. Repetitive angioplasties do not appear to have a cumulative effect. Abnormalities of diastolic relaxation can be demonstrated more easily during angioplasty than a reduction in systolic function. Some diastolic features such as left ventricular wall stiffness can persist rather longer than the systolic abnormality, perhaps up to 15 or 20 minutes. Such data are difficult to interpret because, undoubtedly, during and after angioplasty there may be patient anxiety and activation of the neurohormonal systems. Nevertheless, there is little evidence to support the concept that there is an important depression of myocardial function which persists after the longest occlusion.

Clinical experience would lead most physicians to conclude that a similar lack of persisting ventricular dysfunction follows either coronary vasospasm (variant angina or Prinzmetal's angina) or exercise-induced chronic angina. However, there are several reports in the literature which do suggest that a more prolonged period of diminished ischemia function can occur, but this is usually in patients who have had repetitive episodes of ischemia. Since patients with these conditions do not deteriorate progressively, persisting myocardial damage or any degree of cell necrosis is unlikely. It is not possible to establish whether coronary flow has fully recovered and whether the function of the microcirculation is normal. Similarly, in chronic stable angina left ventricular dysfunction is not a common problem. The walk-through phenomenon would indicate that persons can improve following an initial episode of angina. Possibly, the severity and duration of ischemia in a typical anginal episode are insufficient to cause any important degree of stunning. Even patients with a repetitive angina do not appear to have this condition. Tiredness and fatigue seem to be the symptoms most commonly afflicting these patients. They do not complain of shortness of breath or have an inability or changed pattern of exercise.

Other cardiac conditions result in ischemia of the myocardium for a longer period of time. This may be for several minutes or intermittently over several hours. Such conditions include unstable angina, ischemic episodes, or coronary occlusion in the presence of established collaterals. Unstable angina is a heterogeneous syndrome with a variable pathology. Much of what is observed may, in effect, be reperfusion damage or the consequence of stuttering obliteration of the coronary arteries. Neurohumoral systems and particularly the sympathetic system may be activated by pain and make measurements of ventricular function difficult to interpret. In general, studies have shown an improvement in function from the time when the unstable angina was diagnosed to a time later when the situation has resolved by whatever means. That is hardly surprising and does not provide detailed information on the time course of supposed stunning. Improvement in function will undoubtedly follow a reperfusion procedure to a vessel where that vessel is giving rise to ischemia in the subserved myocardium.

Coronary occlusion can lead to either death of the distal myocardium or to a limited infarct if there is substantial collateral blood flow. Under these conditions, the initial depression of ventricular function is very often followed by subsequent improvement. That improvement may be greater if successful thrombolysis has been performed. The situation is rather analogous to what was previously referred to as reperfusion damage. This ventricular dysfunction may well be given the term stunning.

The final clinical entity to be considered is heart failure in the presence of chronic underperfusion. This is the entity which is often referred to as hibernating myocardium. Many of these patients do seem to benefit from surgery or reperfusion so that the reduction in function is clearly related to the reduction in coronary flow.

One particular situation where stunning may be evident is following cardiovascular surgery. Here a myriad of factors contrive to bring about depression of the contraction of the myocardium. These factors include drugs, temperature, ischemia, and handling of the myocardium. Every cardiologist will be aware that subsequent to

cardiac surgery, a reduction in muscle function is common and that improvement occurs over the subsequent 36 hours. That entity almost certainly does represent stunning, but whether using that word is an advantage in comparison to ventricular dysfunction is questionable. There may well be small degrees of ventricular damage. There is little evidence to establish whether the coronary flow is normal. Some of the ventricular dysfunction will almost be certainly related to reduced perfusion.

How then should the physician regard the conceptual entity of stunning? Certainly it is an enticing concept and word. A precise definition does allow the physician to determine whether the entity is or is not present in the various syndromes related to coronary heart disease. But because of difficulties in measuring function, flow, and tissue damage, stunning will almost certainly never be positively demonstrated in any condition in man. Probably the greatest benefit emanating from the concept of stunning is that it directs the physician to the idea that the observed ventricular dysfunction can be reversed by a period devoid of ischemic episodes in which blood flow is optimized. That is the principle that guides many treatments of angina pectoris. Physicians should not seek any direct relationship between the clinical problem of ventricular dysfunction, the concept of stunning, and the many clinical syndromes which are observed in patients with coronary heart disease. Stunning has much in common with, may be synonymous with, and is a useful shorthand for, early reperfusion damage of the myocardium.

In the future, the clinician needs to understand the cellular mechanism of ventricular dysfunction and be able to identify which mechanism is relevant in which patient. The causal and mechanistic link between the presence of ventricular dysfunction and the related symptoms needs to be established. The merits of different therapeutic options need to be tested in homogeneous groups of patients in controlled randomized trials. In this way the management of individual patients will be improved.

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. Rahimtoola SH.
A perspective on the three large multicenter randomized clinical trials of coronary bypass surgery for chronic stable angina.
Circulation. 1985;72:V123-V135.

6. Rahimtoola SH, Griffith GC.
The hibernating myocardium.
Am Heart J. 1989;117:211-221.

7. Poole-Wilson PA.
Angina: pathological mechanism, clinical expression and treatment.
Postgrad Med J. 1983;59(suppl 3):11-21.

8. Murry CE, Jennings RB, Reimer KA.
Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium.
Circulation. 1986:74:1124-1136.

9. Fleetwood G, Poole-Wilson PA.
Diastolic coronary resistance in the isolated rabbit heart during and after ischaemia: contribution of extracellular forces.
Cardiovasc Res. 1986;20:883-890.

10. Fleetwood G, Poole-Wilson PA.
Diastolic coronary resistance after ischaemia in the isolated rabbit heart: effect of nifedipine.
J Mol Cell Cardiol. 1986;18:139-147.

11. Ross J.
Myocardial perfusion-contraction matching. Implications for coronary heart disease and hibernation.
Circulation. 1991;83:1076-1083.

12. Poole-Wilson PA, Holmberg SRM, Williams AJ.
A possible molecular mechanism for "stunning" of the myocardium.
Eur Heart J. 1991;12(suppl F):25-29.

13. Opie LH.
Myocardial stunning - are calcium antagonists useful?
Cardiovasc Drugs Ther. 1994;8:533-541.

14. Marban E.
Myocardial stunning and hibernation. The physiology behind the colloquialisms.
Circulation. 1991;83:681-688.

15. Nayler WG, Elz JS.
Reperfusion injury: laboratory artifact or clinical dilemma?
Circulation. 1986;74:215-221.

16. Opie LH.
Reperfusion injury and its pharmacologic modification.
Circulation. 1989;80:1049-1062.

17. Kloner RA.
Does reperfusion injury exist in humans?
J Am Coll Cardiol. 1993;21:537-545.

How can stunning be detected clinically?

R.O. Bonow, MD

Division of Cardiology - Northwestern University Medical School - 250 East Superior Street, Suite 524 - Chicago, Illinois 60611 - USA

Noninvasive imaging is well-suited to the assessment of myocardial viability. In PET, preserved metabolic activity in regions with reduced blood flow is an accurate clinical marker, with ≈ 85% accuracy for predicting the efficacy of revascularization. Nevertheless, early after reperfusion therapy, this method may overestimate the presence and extent of viable myocardium. Regions of severely ischemic or hibernating myocardium may also be identified by Tl 201 imaging, using late redistribution imaging, thallium reinjection imaging, or rest-redistribution protocols. Tc 99m sestamibi has theoretic weaknesses for viability assessment, but recent data suggest that this agent is very satisfactory for clinical viability assessment. Low-dose dobutamine echocardiography is also useful for detection of viable myocardium. Although these methods appear to have similar diagnostic accuracy, large-scale studies comparing PET, Tl 201, and dobutamine echocardiography are required early after reperfusion therapy or revascularization to determine their relative efficacies.

In a large subset of patients recovering from acute myocardial infarction, left ventricular (LV) performance is reduced on the basis of regionally stunned or hibernating myocardium (or a combination of stunned and hibernating myocardium) rather than irreversibly infarcted myocardium. The detection of reversibly dysfunctional myocardium is clinically relevant, as regional and global LV function in such patients may improve substantially after revascularization. Noninvasive imaging methods to assess myocardial metabolic activity, membrane integrity, and inotropic reserve are ideally suited for this assessment.

Positron emission tomography

Positron emission tomography (PET) has emerged as a promising method for demonstrating viable myocardium in patients with coronary artery disease and chronic LV dysfunction. Myocardial viability by PET is identified on the basis of intact metabolic activity in regions of severely underperfused and dysfunctional myocardium. The most extensive experience thus far has been achieved using ^{18}F-fluorodeoxyglucose (FDG) as a marker of regional exogenous glucose utilization in such hypoperfused regions. In particular, a pattern of enhanced FDG uptake in regions with reduced perfusion (termed the FDG/blood flow "mismatch") indicates viable tissue that has preferentially shifted its metabolic substrate toward glucose rather than fatty acids or lactate. The finding of preserved metabolic activity in myocardial regions with reduced blood flow has been demonstrated in several studies to be an accurate clinical marker with which to distinguish viable myocardium from myocardial fibrosis, with positive and negative predictive accuracies in the range of 85% for identifying regions that will manifest improved function after revascularization. Thus, PET appears to yield excellent viability information in patients with chronic coronary artery disease.

However, the use of metabolic imaging with FDG may be limited early after reperfusion therapy for acute myocardial infarction. Although the kinetics of glycolysis after myocardial reperfusion is incompletely understood, the available data suggest that recovery of glucose metabolism is rapid and returns to either aerobic levels or is only slightly increased in stunned myocardium after restoration of blood flow.

PET is more promising in regions with persistent hypoperfusion, as there is a high predictive accuracy that a region with reduced FDG uptake represents irreversibly damaged myocardium. In contrast, the predictive accuracy that a region with FDG/blood flow

mismatch represents viable tissue that will improve in function is only 50%. Thus, metabolic imaging with FDG early after reperfusion therapy identifies necrotic myocardium accurately but may substantially overestimate the presence and extent of viable myocardium. PET imaging with ^{11}C-acetate has also emerged as a means to evaluate myocardial viability as a marker of blood flow and oxidative metabolism. In one study, preservation of myocardial oxidative metabolism was predictive of restoration of mechanical function after revascularization in patients with recent myocardial infarction. However, in another study,[11] C-acetate did not provide additional independent information in terms of myocardial viability beyond that provided by regional blood flow and glucose metabolism.

Thallium 201 imaging

The requirements for cellular viability include intact sarcolemmal function to maintain electrochemical gradients across the cell membrane, as well as preserved metabolic activity to generate high-energy phosphates. These processes also require adequate myocardial blood flow to deliver substrates and wash out the metabolites of the metabolic processes. As the retention of thallium 201 is an active process that is a function of cell viability and cell membrane activity, as well as blood flow, thallium 201 should in theory be taken up and retained by viable myocardial regions that also retain FDG and other metabolic tracers. However, initial thallium uptake appears to overestimate myocardial viability early after reperfusion therapy (up to several hours after reperfusion).
Hence, early thallium uptake after reperfusion cannot differentiate viable from necrotic myocardium. On the other hand, necrotic myocardium cannot retain thallium and, despite its initial uptake, thallium washout is accelerated in necrotic tissue. Consequently, rapid early thallium washout might be used to indicate nonviability. This concept underscores the importance of redistribution imaging several hours after thallium administration, to allow for washout from necrotic myocardium and "wash-in" of viable regions served by a coronary artery with a residual flow-limiting stenosis.

In patients studied several days to weeks after myocardial infarction, testing for myocardial viability follows the same algorithms as in patients with chronic LV dysfunction. As many regions of severely ischemic or hibernating myocardium appear to have irreversible thallium defects on standard exercise-redistribution imaging, standard thallium scintigraphy may not provide satisfactory precision in identifying viable myocardium. These relatively poor results with exercise-redistribution imaging may be overcome using other imaging protocols. These include: (i) late (24-72-hour) redistribution imaging; (ii) thallium reinjection imaging, in which imaging is repeated after a small additional dose of thallium is injected at rest after a period of redistribution following stress imaging;
or (iii) thallium imaging without exercise using a rest-redistribution protocol. In each of these protocols, both defect reversibility and severity of the thallium defect are important markers of viable myocardium.

Technetium Tc 99m sestamibi imaging

Technetium 99m sestamibi, like thallium 201, requires intact sarcolemmal and mitochondrial processes for retention, and this agent has been shown to be an excellent marker of cellular viability. In both experimental and clinical settings in which sestamibi delivery is adequate to dysfunctional myocardium, such as after reperfusion to previously ischemic or damaged myocardium, the uptake and retention of sestamibi tracks with markers of myocardial viability rather than pure markers of perfusion. However, sestamibi does not redistribute as readily as thallium after its initial uptake either during exercise or at rest. Thus, compared to thallium, sestamibi has inherent weaknesses for viability assessment in clinical situations in which blood flow is severely impaired and tracer delivery is reduced. Several studies comparing rest-exercise sestamibi imaging to thallium imaging indicate that sestamibi underestimates viable myocardium in patients with chronic coronary artery disease and left ventricular dysfunction. In addition, a large percentage of sestamibi defects in patients with left ventricular dysfunction demonstrate FDG activity by PET imaging, indicating viability. However, three recent studies indicate that a quantitative analysis of regional sestamibi activity after administration at rest substantially increases the accuracy for identifying viable myocardium compared to thallium imaging and PET imaging.
These recent findings with sestamibi should be considered preliminary in nature until confirmed by larger, more definitive studies.

Dobutamine echocardiography

Previously ischemic, stunned myocardium can be identified following administration of inotropic agents such as dopamine, isoproterenol, and dobutamine, as well as by postextrasystolic

potentiation. Experimental studies in dogs have demonstrated that postischemic dysfunctional myocardium bears considerable contractile reserve that may be recruited after moderate inotropic stimulation without causing detrimental effects.
Recently, low-dose dobutamine infusion to enhance regional systolic wall thickening during echocardiography has been proposed and applied successfully to patients after thrombolytic therapy for acute myocardial infarction and in patients with chronic LV dysfunction.
The results of these studies, thus far in small numbers of patients, suggest that this method provides data at least as accurate as that achieved using scintigraphic methods.

Clinical implications

The identification of viable myocardium has become an area of intense interest for several reasons. Among these is the rather unique potential of nuclear cardiology techniques to distinguish viable regions on the basis of perfusion, cell membrane integrity, and metabolic activity, and the ability of dobutamine echocardiography to assess regional inotropic reserve. Although the available data imply that each of these methods has similar diagnostic accuracy, larger-scale studies comparing PET, thallium 201, Tc 99m sestamibi and dobutamine echocardiography are required in patients studied early after reperfusion therapy for acute myocardial infarction and those undergoing revascularization to determine the relative efficacies of these methods in identifying viable myocardium.

References

1. Braunwald E, Kloner RA.
The stunned myocardium: prolonged, postischemic ventricular dysfunction.
Circulation. 1982;66:1146-1149.

2. Bolli R.
Myocardial "stunning" in man.
Circulation. 1992;86:1671-1691.

3. Dilsizian V, Bonow RO.
Current diagnostic techniques of assessing myocardial viability in hibernating and stunned myocardium.
Circulation. 1993;87:1-20.

4. Schwaiger M, Brunken R, Grover-McKay M, et al.
Regional myocardial metabolism in patients with acute myocardial infarction assessed by positron emission tomography.
J Am Coll Cardiol. 1986;8:800-808.

5. Gropler RJ, Siegel BA, Sampathkumaran K, et al.
Dependence of recovery of contractile function on maintenance of oxidative metabolism after myocardial infarction.
J Am Coll Cardiol. 1992;20:569-577.

6. Simoons ML, Wijns W, Balakumaran K, et al.
The effect of intracoronary thrombolysis with streptokinase on myocardial thallium distribution and left ventricular function assessed by blood-pool scintigraphy.
Eur Heart J. 1982;3:433-440.

7. Moore CA, Cannon J, Watson DD, Kaul S, Beller GA.
Thallium-201 kinetics in stunned myocardium characterized by severe postischemic systolic dysfunction.
Circulation. 1990;81:1622-1632.

8. Sinusas AJ, Watson DD, Cannon JM, Beller GA.
Effect of ischemia and postischemic dysfunction on myocardial uptake of technetium-99m-labeled methoxyisobutyl isonitrile and thallium-201.
J Am Coll Cardiol. 1989;14:1785-1793.

9. Pierard LA, De Lansheere CM, Berthe C, Rigo P, Kulbertus HA.
Identification of viable myocardium by echocardiography during dobutamine infusion in patients with myocardial infarction after thrombolytic therapy: comparison with positron emission tomography.
J Am Coll Cardiol. 1990;15:1021-1031.

10. Smart SC, Sawada S, Ryan T, et al.
Low-dose dobutamine echocardiography detects reversible dysfunction after thrombolytic therapy of acute myocardial infarction.
Circulation. 1993;88:405-415.

How should stunning be treated?

G. Heusch, MD, FESC, FACC

Direktor der Abteilung für Pathophysiologie - Zentrum für Innere Medizin - Universitätsklinikum Essen
Hufelandstrasse 55 - 45122 Essen - GERMANY

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

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

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

Optimization of temperature, heart rate, and load

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

Vasodilators

It is obvious that full reperfusion should be confirmed and

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

Adenosine in stunned myocardium

Preischemic treatment with exogenous adenosine as well as augmentation of endogenous adenosine mitigate the severity of myocardial stunning, while treatment after the onset of reperfusion is ineffective.
This beneficial action of adenosine cannot be attributed to increased collateral blood flow during coronary artery occlusion or reperfusion, or to more favorable hemodynamics. Adenosine exerts a number of actions that could beneficially affect myocardial stunning, such as: (i) reduction of norepinephrine release from sympathetic nerve endings; (ii) inhibition of catecholamine-induced stimulation of adenylate cyclase; (iii) blockade of cardiomyocyte L-type Ca^{2+} channels; and (iv) activation of cardiomyocyte ATP-dependent potassium channels. All pathways will ultimately decrease the intracellular calcium concentration, thereby potentially attenuating ischemic calcium overload and subsequently attenuating myocardial stunning.

Inotropic interventions

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

Antioxidants

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

Calcium antagonists

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

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

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

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

In isolated perfused rat hearts, nisoldipine given within the first 5 minutes of reperfusion improved postischemic myocardial function. In contrast, a further deterioration in function was observed when nisoldipine was administered later, after established reperfusion. This study suggests that nisoldipine may attenuate the increase in the cytosolic calcium concentration during early reperfusion. During late reperfusion, when the cytosolic calcium is normal again, nisoldipine may induce a decrease in cytosolic calcium, resulting in an aggravation of stunning.

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

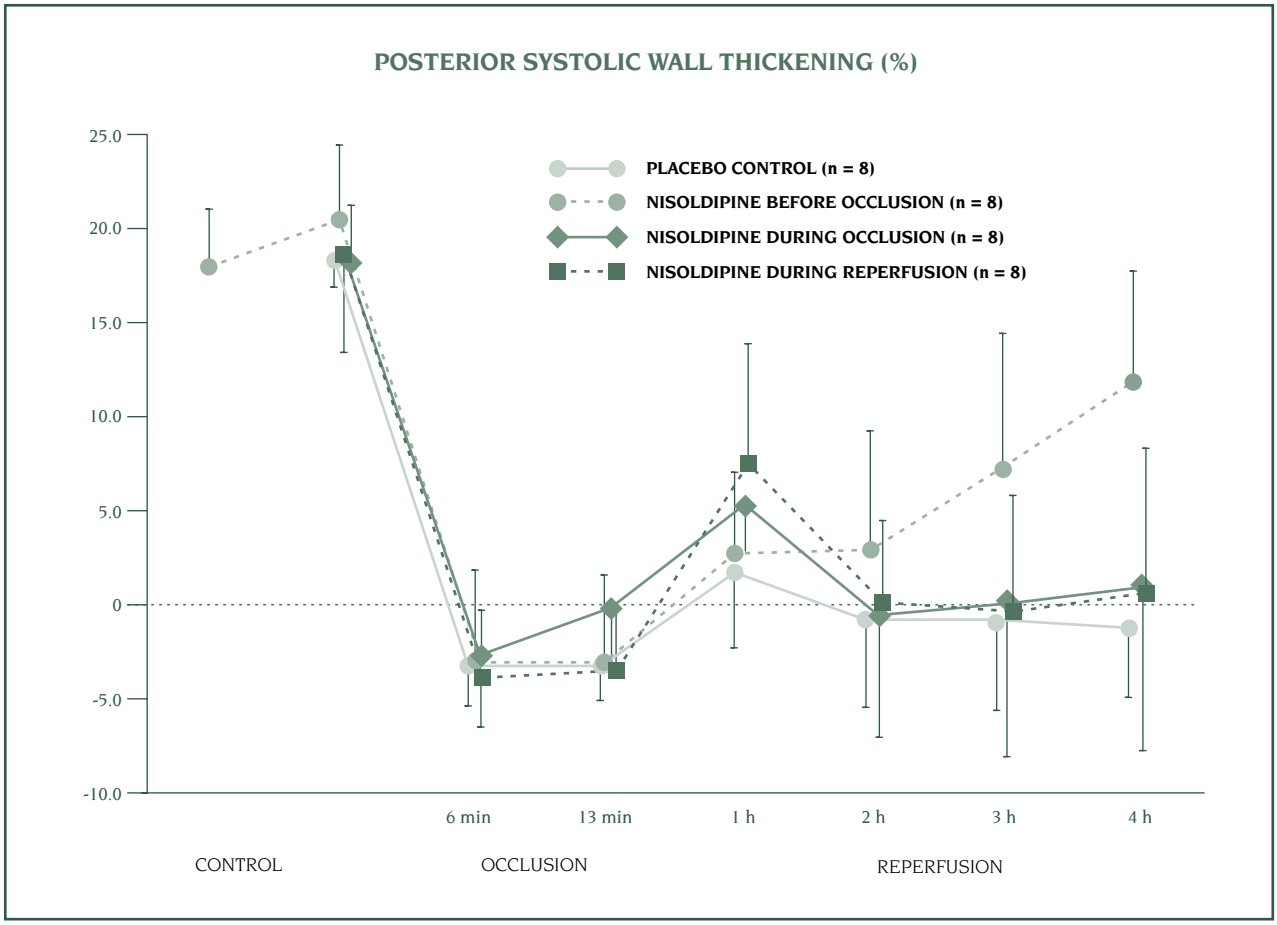

Figure 1. *Only after pretreatment with the calcium antagonist nisoldipine did posterior systolic wall thickening recover significantly following 4 h of reperfusion.*

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

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

ACE inhibitors in stunned myocardium

The attenuation of myocardial stunning by several angiotensin converting-enzyme (ACE) inhibitors has been demonstrated in a number of experimental studies in vitro and in vivo. The mechanism underlying the cardioprotective action of ACE inhibitors, however, is not fully clear. Apparently, the beneficial effect of ACE inhibitors is not secondary to reduced formation of angiotensin, but rather to reduced breakdown of bradykinin; therefore, such a beneficial effect is abolished by bradykinin B_2-receptor antagonists. Activation of endothelial bradykinin B_2-receptors, in turn, increases the formation of NO and prostacyclin. Thus, stimulation of the prostaglandin pathway or production of NO could potentially mediate the beneficial effect of ACE inhibitors on myocardial function during reperfusion. While in isolated hearts the cardioprotective effect of ramiprilat appears to be mediated by NO, this is not the case in the in situ heart where this effect is mediated by a signal cascade of bradykinin and prostaglandins (F*igure* 2).

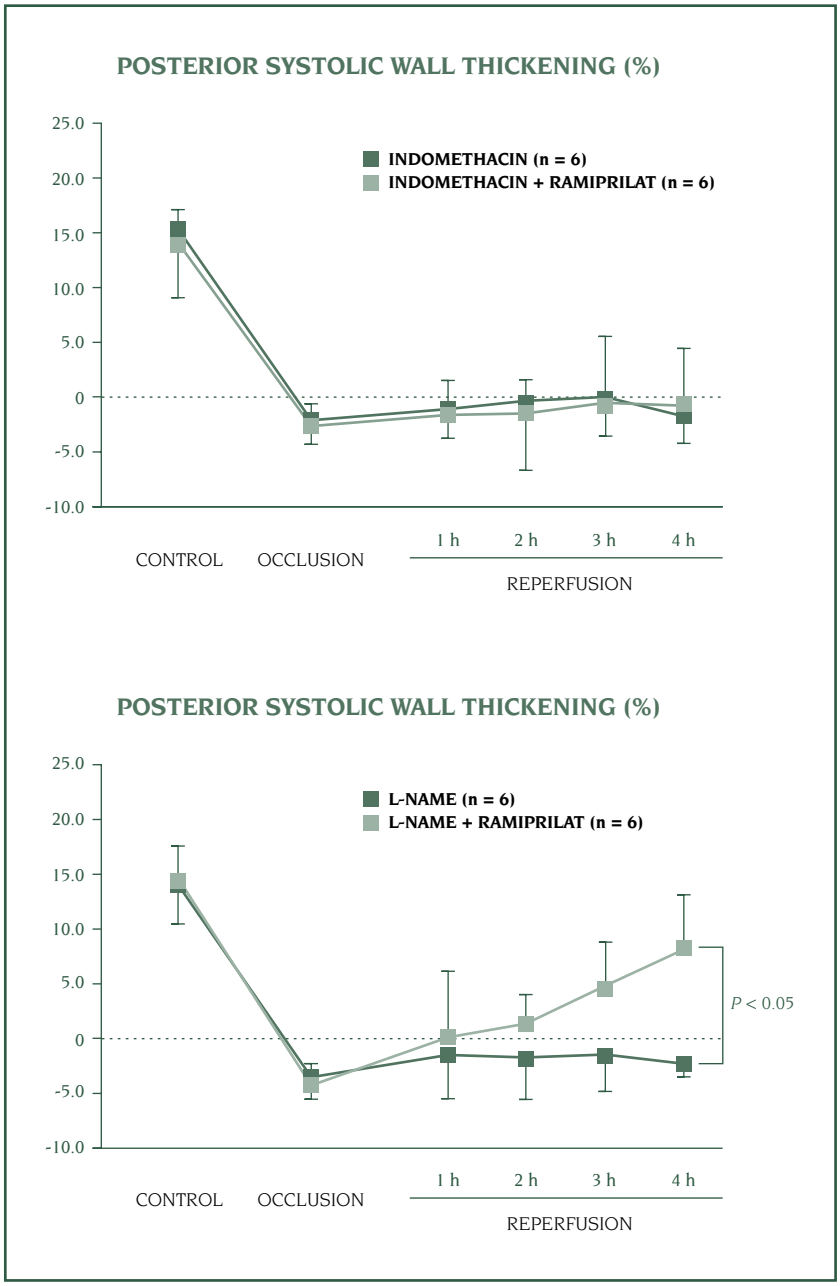

Figure 2. *The acceleration of recovery of contractile function with ramiprilat was prevented by cyclooxygenase inhibition with indomethacin, but not by nitric oxide synthase inhibition with L-NAME.*

Concluding remarks

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

References

1. Bolli R.
Mechanism of myocardial "stunning."
Circulation. 1990;82:723-738.

---

2. Bolli R.
Myocardial "stunning" in man.
Circulation. 1992;86:1671-1691.

---

3. Bolli R, Zhu WX, Myers ML, Hartley CJ, Roberts R.
Beta-adrenergic stimulation reverses postischemic myocardial dysfunction without producing subsequent deterioration.
Am J Cardiol. 1985;56:964-968.

---

4. Du Toit EF, Opie LH.
Modulation of severity of reperfusion stunning in the isolated rat heart by agents altering calcium flux at the onset of reperfusion.
Circ Res. 1992;70:960-967.

---

5. Ehring T, Baumgart D, Krajcar M, Hümmelgen M, Kompa S, Heusch G.
Attenuation of myocardial stunning by the ACE-inhibitor ramiprilat through a signal cascade of bradykinin and prostaglandins, but not nitric oxide.
Circulation. 1994;90:1368-1385.

---

6. Ehring T, Böhm M, Heusch G.
The calcium antagonist nisoldipine improves the functional recovery of reperfused myocardium only when given before ischemia.
J Cardiovasc Pharmacol. 1992;20:63-74.

---

7. Heusch G, Schäfer S, Kröger K.
Recruitment of inotropic reserve in "stunned" myocardium by the cardiotonic agent AR-L 57.
Basic Res Cardiol. 1988;83:602-610.

---

8. Przyklenk K, Ghafari GB, Eitzman DT, Kloner RA.
Nifedipine administered after reperfusion ablates systolic contractile dysfunction of postischemic "stunned" myocardium.
J Am Coll Cardiol. 1989;13:1176-1183.

---

9. Przyklenk K, Kloner RA.
Effect of verapamil on postischemic "stunned" myocardium: importance of the timing of treatment.
J Am Coll Cardiol. 1988;11:614-623.

---

10. Schäfer S, Heusch G.
Recruitment of a time-dependent inotropic reserve by postextrasystolic potentiation in normal and reperfused myocardium.
Basic Res Cardiol. 1990;85:257-269.

Myocardial Stunning

Summaries of Ten Seminal Papers

1

Myocardial "stunning" in man

R. Bolli. *Circ Res*. 1992

2

Low-dose dobutamine echocardiography detects reversible dysfunction after thrombolytic therapy of acute myocardial infarction

S.C. Smart, S. Sawada, T. Ryan, et al.
Circ Res. 1993

3

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

H. Ito, T. Tomooka, N. Sakai, et al. *Circulation*. 1993

4

Marked reduction of free radical generation and contractile dysfunction by antioxidant therapy begun at the time of reperfusion

R. Bolli, M.O. Jeroudi, B.S. Patel, et al. *Circ Res*. 1986

5

Cellular mechanisms of myocardial stunning

H. Kusuoka, E. Marban. *Annu Rev Physiol*. 1992

6

Mechanism of myocardial stunning

R. Bolli. *Circulation*. 1990

7

Demonstration of free radical generation in the "stunned" myocardium in the conscious dog and identification of major differences between conscious and open-chest dogs

X.Y. Li, P.B. McCay, M. Zughaib, M.O. Jeroudi, J.F. Triana, R. Bolli. *J Clin Invest*. 1993

8

Mechanisms of chronic regional postischemic dysfunction in humans

J.L.J. Vanoverschelde, W. Wijns, C. Depré, et al.
Circulation. 1993

9

Current diagnostic techniques of assessing myocardial viability in patients with hibernating and stunned myocardium

V. Dilsizian, R. Bonow. *Circulation*. 1993

10

Occurrence of oxidative stress during reperfusion of the human heart

R. Ferrari, O. Alfieri, S. Curello, et al. *Circulation*. 1990

Myocardial "stunning" in man

R. Bolli

Circ Res. 1992;86:1671-1691.

This landmark paper by Bolli on the clinical relevance of myocardial stunning is the first attempt to build a bridge between laboratory and real clinical conditions. Clinically, stunning is the mechanical dysfunction that persists after reperfusion despite the absence of irreversible damage and restoration of normal or near-normal coronary flow. Implicit in this definition is that stunning is fully reversible provided the myocardium has sufficient time to recover. Thus, the contractile abnormality must be reversible and the dysfunctional myocardium have a normal or near-normal flow, points not always easy to determine in the clinical setting. Major clinical situations in which myocardial stunning may occur:

a) S*tunning after ischemia induced by percutaneous transluminal coronary angioplasty* (PTCA). This clinical condition best resembles the experimental setting for stunning. Brief ischemia associated with simple, uncomplicated PTCA is usually not sufficient to cause long-lasting systolic abnormalities, even after multiple balloon inflations, but it may induce persistent diastolic abnormalities resulting in decreased left ventricular compliance. The exact incidence, severity, and duration of these diastolic abnormalities are unknown, but they are well tolerated provided the contractile reserve is intact. However, myocardial stunning can occur in less favorable situations, eg, in patients with baseline left ventricular dysfunction, unstable angina, severe simple-vessel disease, and complicated PTCA.

b) S*tunning in unstable angina* is often associated with reversible wall motion abnormalities. Although consistent with stunning, these abnormalities could also be caused by hibernation and/or ongoing silent ischemia. Precise diagnosis of stunning requires concomitant measurement of regional function and flow and determination of the time course of the contractile abnormalities. As patients with proximal left anterior descending coronary artery lesions and persistently negative T waves on precordial leads often exhibit improvement in wall motion, this could be considered good evidence for stunning in unstable angina.

c) S*tunning in variant angina*. Single episodes of variant angina promptly treated with vasodilators usually do not cause stunning, probably because they are too short. However, if coronary spasm persists, stunning results, which, if not resolved, can pose a threat to life.

d) S*tunning after acute myocardial infarction* (AMI). In AMI, improvement of systolic and diastolic function or myocardial salvage by reperfusion does not occur immediately after reflow - a good demonstration of stunning. Sequential measurements of regional left ventricular function are thus needed to clearly define the time course of stunning in AMI.

e) S*tunning after exercise-induced angina*. Although some echocardiographic observations suggest that exercise-induced ischemia may result in prolonged contractile abnormalities, this does not appear to be clinically significant. The occurrence and severity of postexercise stunning probably depend on the intensity and duration of exercise and on the severity of the coronary inflow restriction.

f) S*tunning after cardiac surgery*. Transient depression of ventricular contractility due to stunning is very common after cardiopulmonary bypass, and is usually reversible within 24 to 38 hours. In high-risk patients subjected to cardiac surgery, stunning can pose a crucial clinical problem which needs treatment and, if possible, prevention.

g) S*tunning after cardiac transplantation*. There is considerable evidence that cardiac function is reversibly depressed in the first hours or days after transplantation, which may complicate the postoperative management of these rather unstable patients.

In conclusion, Bolli's hypotheses about myocardial stunning in humans have all been proven in clinical practice. Though he also hinted that repetitive stunning might cause a chronic condition similar to "hibernation," the clinical distinction may not be vital, as in both cases reperfusion is required - to improve flow in hibernation and coronary reserve in repetitive stunning. Thus, the real clinical issue is whether the left ventricular abnormality is reversible or not.

Low-dose dobutamine echocardiography detects reversible dysfunction after thrombolytic therapy of acute myocardial infarction

S.C. Smart, S. Sawada, T. Ryan, D. Segar, L. Atherton, K. Berkovitz, P.D.V. Bourdillon, H. Feigenbaum

Circ Res. 1993;88:405-415.

This paper addresses the crucial issue of whether myocardial stunning may occur after thrombolytic treatment of acute myocardial infarction and whether low-dose dobutamine echocardiography may be useful in distinguishing reversible from irreversible injury after thrombolytic therapy.

This issue is pivotal since prognosis correlates with postmyocardial infarction ventricular function, and early, accurate identification of reversible dysfunction may be very helpful for patient management. In this study, the authors hypothesized that: (i) dobutamine-responsive wall motion would specifically identify reversible postischemic dysfunction irrespective of infarct location and early revascularization; (ii) the sensitivity of dobutamine-responsive wall motion for reversible dysfunction would be maximized by infusing doses that did not alter hemodynamics; and (iii) dobutamine echocardiography would incorporate clinical and angioplastic data to more accurately identify reversible dysfunction after thrombolytic treatment of acute myocardial infarction.

Sixty-three patients were studied out of the 121 admitted to the Indiana University Hospital for thrombolytic treatment of acute myocardial infarction. Multistage dobutamine echocardiography was performed (before and after administration of a 4-, 12-, and 40-$\mu g \cdot kg^{-1} \cdot min^{-1}$ dose) within 7 days of thrombolytic therapy. Resting echocardiography was then repeated within 4 weeks of myocardial infarction, and reversible dysfunction or stunning was defined as an improvement in wall motion at these time points. The accuracy of dobutamine-responsive wall motion was compared with that of signs of early reperfusion, evidence of non-Q wave myocardial infarction, and peak creatine kinase (CPK) levels. Dobutamine-responsive wall motion during all stages of dobutamine echocardiography was highly specific for reversible dysfunction (90% to 93%), but sensitive only when hemodynamics were unaltered (86%). This happened at the low dose of 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Non-Q wave myocardial infarction and low peak CPK (<1000 U/mL) were also specific (89% to 93%), although less sensitive (64% and 55%, respectively) than low-dose dobutamine echocardiography. Interestingly, signs of early reperfusion did not identify postischemic dysfunction.

The authors were thus able to show that low-dose dobutamine-responsive wall motion and non-Q wave myocardial infarction independently identify reversible dysfunction, but only dobutamine-responsive wall motion is sensitive for all infarct locations, while non-Q wave myocardial infarction is sensitive only for anterior infarction.

In conclusion, this valuable study shows that dobutamine echocardiography can be safely performed early after thrombolytic treatment of acute myocardial infarction. Dobutamine-responsive wall motion is specific for reversible dysfunction, but sensitive only at a low doses. The decrease in sensitivity at higher doses correlates with an increase in heart rate and systolic blood pressure. Clinical parameters such as ECG, evidence of non-Q wave myocardial infarction, and low peak CPK are specific only for anterior myocardial infarction, while a positive response to dobutamine is sensitive for either anterior, inferior, posterior, or lateral infarction. The low-dose dobutamine test is also accurate in diagnosing stunning in patients who were either revascularized or not revascularized on the basis of angiographic criteria.

Thus, low-dose dobutamine echocardiography and ECG (non-Q wave myocardial infarction) may be useful tools for early and accurate identification of reversible dysfunction and, therefore, of stunning after thrombolytic treatment of acute myocardial infarction.

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

H. Ito, T. Tomooka, N. Sakai, Y. Higashino, K. Fujii, O. Katoh, T. Masuyama, A. Kitabatake, T. Minamino

Circulation. 1993;87:355-362.

Myocardial stunning was first described and its mechanisms characterized in the dog heart. Indeed, stunning has been described as an experimental phenomenon in search of a clinical manifestation. While it has been speculated that stunning occurs in a variety of clinical settings where the myocardium is subjected to transient ischemia (such as with unstable or variant angina, acute myocardial infarction with early thrombolysis, and in cardiac surgery and transplantation) its convincing demonstration in the human heart is a far greater challenge than in the laboratory. The clear demonstration of stunning in man is complicated by a variety of factors including the heterogeneity of tissue injury, the wide variation in the amount and location of involved tissue, and the requirement to study contractile function sequentially over many hours or days.

Intracoronary thrombolysis and coronary angioplasty are widely and successfully used to restore coronary flow in patients with acute myocardial infarction. There is no doubt that coronary reflow can limit the extent of necrosis (infarct size reduction) so long as reperfusion is achieved at an ***early*** stage of the infarction process. Such tissue salvage would be expected to result in a sustained and clinically important improvement in contractile function. However, the extent to which reperfusion salvages function of severely ischemic human myocardium is controversial because the identification and quantification of the risk area in patients in the acute phase of infarction is difficult. Since the risk area varies greatly among patients, analysis of change in infarct size and regional function are meaningful only if examined in relation to the initial risk area. Furthermore, the analysis of salvage of function may be confounded by the occurrence of infarction.
The study by Ito and colleagues is notable in that in addition to addressing the issue of the relation between functional salvage and risk zone size it also convincingly demonstrates the occurrence of a stunning-like phenomenon in patients and defines the time course of recovery from this stunning.

The beneficial effects of coronary reflow on myocardial salvage can be assessed accurately if the size of the ischemic risk area is taken into account. This was achieved by Ito and colleagues using contrast echocardiography in a population of 21 patients with anterior myocardial infarction who were successfully reperfused by thrombolysis or angioplasty within 6 hours of the onset of symptoms. Echocardiography was performed by injection of contrast medium into the right and left coronary arteries before coronary reflow and the risk area was defined as the area of contrast perfusion defect in the apical long axis view. Correction was then made for patient-to-patient variation in ischemic zone size by calculating the ratio of the endocardial length of abnormal contraction (dyskinesis / akinesis) segment to that of contrast defect segment. In an ambitious study, this was determined 1, 2, 3, 7, 14, and 28 days after reflow.

Before reflow, the length of the contrast defect correlated well with the segment length of dyskinesis / akinesis. After successful reperfusion, the values for the recovery of function, corrected for risk zone size, progressively increased until day 14, the values being 1.00 ± 0.02 at day 1, 0.93 ± 0.11 at day 2, 0.84 ± 0.16 at day 3, 0.80 ± 0.13 at day 7, 0.73 ± 0.10 at day 14, and 0.72 ± 0.10 at day 28. This slow but progressive profile for contractile recovery bears a remarkable similarity to that seen in dogs and other laboratory animals and provides powerful evidence for the occurrence of stunning in man. The study convincingly demonstrates that, in addition to salvaging tissue (an average of 28% in segment length of the risk area was salvaged), early reperfusion results in improved contractile function, but that this cannot be fully appreciated until 7-14 days after reflow.

Ito and colleagues were also able to demonstrate that, as would be predicted from laboratory studies, a greater improvement in function occurred in hearts that were reperfused early. Thus, in patients reperfused within 4 hours the mean value for the contractile deficit index was 0.64 ± 0.12 at day 28, whereas in patients that required more than 4 hours for reperfusion the mean value was 0.75 ± 0.09.

Marked reduction of free radical generation and contractile dysfunction by antioxidant therapy begun at the time of reperfusion

R. Bolli, M.O. Jeroudi, B.S. Patel, O.I. Aruoma, B. Halliwell, E.K. Lai, P.B. McCay

Circ Res. 1986;65:607-622.

In this key paper Bolli et al discuss the complex and controversial issue of "reperfusion injury," whether it exists, and which mechanisms are involved. Four essential questions relating to myocardial stunning are addressed: (i) to determine whether the critical free radical-mediated damage (proposed as a major factor in the induction of myocardial stunning) takes place during ischemia, after reperfusion, or both; (ii) to identify the time window over which such damage occurs; (iii) to determine whether antioxidants, which are known to attenuate stunning, achieve this effect via an inhibition of radical-mediated reactions; and (iv) to identify the species of free radicals that might be responsible.

Bolli et al used a familiar model, namely the open-chest anesthetized dog in which the heart was subjected to a 15-min regional ischemia induced by occlusion of the left anterior descending coronary artery, followed by a 4-h reperfusion. In a meticulously designed protocol, four groups of dogs (n = 8-10 animals in each group) were subjected to:

1) intracoronary infusion of 8 mg/kg/h of the potent cell-permeable antioxidant N-(2-mercaptopropionyl)-glycine (MPG) starting 15 min before occlusion and ending 2 h after the initiation of reperfusion;
2) intracoronary infusion of MPG starting 1 min before reperfusion and ending 2 h after the initiation of reperfusion;
3) intracoronary infusion of MPG starting 1 min after reperfusion and ending 2 h and 15 min after the initiation of reperfusion;
4) control dogs with an intravenous infusion of vehicle.

Contractile function (systolic wall thickening) was assessed using epicardial Doppler probes. Recovery of contractile function was similarly slow and poor in groups 3 and 4, with thickening fraction failing to recover to positive values even after 4 h of reperfusion. By contrast, hearts given MPG during ischemia (group 1) or just before reperfusion (group 2), recovered rapidly and well, reaching >40% of baseline by 4 h of reperfusion. These findings strikingly illustrate the potent antistunning properties of MPG (administered before reperfusion) and the fact that the drug appears to exert its protective actions entirely during reperfusion. Comparison of groups 2 and 3 provides compelling evidence that the protection occurs in the very early minutes of reperfusion. This latter observation provides one of the most convincing pieces of evidence for the existence of reversible reperfusion injury.

In additional studies to determine whether protection against reperfusion injury was attributable to inhibition of free-radical reactions, the authors used electron paramagnetic resonance (EPR) spectroscopy to detect and quantify free-radical production in the ischemic and reperfused heart. The spin trap α-phenyl N-*tert*-butyl nitrone (PBN) was administered by intracoronary infusion starting 10 min before and ending 10 min after reperfusion. Sequential blood samples were analyzed by EPR for radical adduct production. In control dogs not treated with antioxidant, free-radical adducts of PBN were detected in the coronary venous blood during reperfusion, with a burst in the first 5 min. In MPG-treated dogs, when the antioxidant was given at or before the onset of reperfusion (groups 1 and 2), radical adduct reduction decreased by 80% to 90%. The authors could then claim that the radicals important in myocardial stunning appeared to be those generated immediately after reperfusion. They went on to argue that the most likely culprit was the hydroxyl radical, other reactive forms of oxygen such as superoxide and hydrogen peroxide being relatively unimportant.

In conclusion, the authors provided convincing evidence for: (i) the role of free radicals in the genesis of myocardial stunning; (ii) the existence of reversible reperfusion injury; (iii) the relatively narrow time window over which much of the damage occurs; and (iv) the potential for the use of antioxidants for the pharmacological control of stunning.

Cellular mechanisms of myocardial stunning

H. Kusuoka, E. Marban

Annu Rev Physiol. 1992;54:243-256.

After stressing that stunning can only be studied in models that allow the myocardium to be vascularly perfused, rendered truly ischemic, and reperfused via the native coronary circulation, explaining the usual choice of the intact canine heart model, Kusuoka and Marban suggest using the isolated perfused heart model. In the perfused ferret heart, the authors showed that 15 min of global ischemia induces classic acute contractile failure, with rapid onset of diastolic arrest, maintained throughout the ischemic period, without any development of diastolic dysfunction. Reperfusion leads to rapid and full recovery of pressure development, with a transient period of ***hyperactivity***, which rapidly declines so that developed pressure is less than 50% of preischemic values. This is followed by slow and progressive recovery of function, which although not reaching 100% within the time course of the experiment would, by extrapolation from findings in the intact animal, eventually be complete. The authors give an example of the hyperactivity that is characteristic of the early phases of recovery in the stunned myocardium, a phenomenon almost invariably observed, but rarely reported by investigators.

Regarding the mechanisms of stunning, the authors' emphasis is on the contribution of calcium and free radicals. They do acknowledge that myocardial ATP depletion during ischemia and slow resynthesis during reperfusion were long thought to be the basis of stunning, but claim this is no longer so, pointing out that enhancing the ATP repletion rate during reperfusion is not always associated with amelioration of stunning.
Likewise, functional recovery can be improved without accompanying enhancement of tissue ATP content.
The authors' claim that "in contrast to the controversy that surrounds the question of whether free radicals figure prominently in the irreversible tissue injury following longer periods of ischemia, agreement regarding the importance of free radicals in stunning is virtually unanimous" is based on measurements evidencing transient free-radical generation just after a reperfusion and on the improvement of functional recovery by free-radical scavengers and related strategies.

Nevertheless, the authors find two major gaps in the argument for free radicals as the mediator of stunning: failure to adequately mimic stunning with free radicals, and absence of a convincing mechanism for their deleterious effects. Understanding of stunning would be greatly enhanced if the locus of the lesion in excitation-contraction coupling could be elucidated.
Two general types of mechanism have been proposed: a decrease in activator calcium or a decrease in the sensitivity of the contractile machinery.

The authors then discuss three ways in which impairment of calcium availability could be involved in the genesis of stunning: (i) through a mechanism influencing excitability and transsarcolemmal ion transport - but this is considered unlikely since there is little evidence both for the abnormalities in membrane currents or gap junctions required to produce persistent dysfunction and for the primary lesion being at the level of ion translocating proteins such as calcium ATPase, sodium-potassium ATPase, or the sodium-calcium exchanger; (ii) through an alteration of cytoplasmic calcium availability due to ischemia- or reperfusion-induced injury to the sarcoplasmic reticulum - however, although changes in calcium uptake rates and calcium ATPase activity have been observed, they are more likely to account for the impaired relaxation that is sometimes seen in stunning rather than the systolic dysfunction that is central to the phenomenon; (iii) through a disturbance of calcium transients.
Some studies suggest that calcium availability might be paradoxically greater in stunned hearts, implying that some lesion causes desensitization of the myofilaments to calcium. This phenomenon may represent an "after-effect" of the transient cytosolic calcium overload, possibly leading to covalent modification of the contractile proteins caused either by calcium-mediated phosphorylation or proteolysis. It is thus not unreasonable to expect transient rises in cytosolic calcium to have long-lasting after-effects. The authors conclude by asking: "How do free radicals fit in?" Their answer is that free radicals may contribute to the calcium overload possibly by inhibiting glycolysis, which they believe plays a role in maintaining ionic homeostasis.

Mechanism of myocardial stunning

R. Bolli

Circulation. 1990;82:723-738.

Although now 6 years old, there can be little doubt that this review has stood the test of time and that it is surely required reading for anyone interested in myocardial stunning and its possible clinical relevance.

The use of the singular for "mechanism" in the title gives advanced warning of the author's belief that there is only one important mechanism underlying stunning. Nevertheless, he treats us to a comprehensive review of the definition and classification of stunning. A clear definition of stunning is necessary because this term is sometimes loosely applied to situations in which the persistence of contractile abnormalities in postischemic tissue is due to other causes such as myocellular death. Bolli states: "myocardial stunning is the mechanical dysfunction that persists after reperfusion *despite the absence* of irreversible damage. The essential point of this definition is that postischemic dysfunction, no matter how severe or prolonged, is a fully reversible abnormality. Diagnosis of stunning should not be made unless reasonable assurance can be provided that the tissue in question is still entirely viable."

Bolli subdivides stunning into six classifications characterized by different pathophysiological features: (i) stunning after one completely reversible ischemic episode, eg, in the dog heart after <20 min of severe ischemia; (ii) stunning after multiple completely reversible episodes of ischemia , eg, with repeated brief (5-10 min) episodes of ischemia; (iii) stunning after one partly irreversible ischemic episode where assessment of contractile impairment is confounded by subendocardial infarction and its consequences; (iv) stunning after global ischemia in isolated hearts; (v) stunning after global ischemia in vivo, eg, during cardiac surgery; and (vi) stunning evoked by exercise-induced angina.

The many mechanisms of stunning proposed in the literature are then reviewed, several of which Bolli dismisses as putative mechanisms, such as insufficient energy production by mitochondria, impaired energy use by myofibrils, impaired sympathetic neural responsiveness, impaired myocardial perfusion, damage to the extracellular collagen matrix, and decreased sensitivity of the myofilaments to calcium. The author then goes on to consider what he believes are the most likely mechanisms of myocardial stunning: (i) calcium overload; (ii) excitation-contraction uncoupling due to sarcoplasmic reticulum dysfunction; and (iii) generation of oxygen-derived free radicals. Bolli concedes that evidence points to a role for calcium overload in the pathogenesis of stunning and that the concept of inadequate delivery of calcium to the contractile proteins, secondary to sarcoplasmic reticulum dysfunction, is also an attractive hypothesis, but finally declares his preference for free radicals as mediators of the phenomenon.

In support of the free radical hypothesis, Bolli reviews his own extensive work and that of others showing that many agents that either inhibit the production of free oxygen radicals (or scavenge them once formed) are able to attenuate stunning. He reinforces the indirect association between free radicals and stunning by reviewing studies in which spin traps and electron paramagnetic resonance have been used to demonstrate that, during the early minutes of reperfusion, a burst of free radicals occurs that can be attenuated by a variety of antioxidants, the latter also being able to reduce the severity of stunning. Bolli then looks at the mechanisms by which free radicals might mediate contractile dysfunction, eg, membrane lipid peroxidation or direct oxyradical injury to sarcolemmal and sarcoplasmic reticulum proteins, which might lead to ion regulation disturbances resulting in myocardial stunning. Such mechanisms could reconcile the oxyradical and calcium overload hypotheses of stunning.

Bolli also looks into the still unresolved issue of the nature and source of the injurious radicals. He reviews the time course of radical production in relation to the genesis of stunning and argues that stunning is, at least in part, a consequence of "reperfusion injury." Finally, he addresses the issue of the clinical implications of stunning and prospects for its control, suggesting that it may be better to prevent the occurrence of stunning rather than attempting to overrride it with inotropic agents.

Demonstration of free radical generation in the "stunned" myocardium in the conscious dog and identification of major differences between conscious and open-chest dogs

X.Y. Li, P.B. McCay, M. Zughaib, M.O. Jeroudi, J. F. Triana, R. Bolli

J Clin Invest. 1993;92:1025-1041.

This paper describes yet another key investigation from the laboratory of Bolli and colleagues who have contributed greatly to our understanding of the genesis, mechanisms, and pharmacological control of myocardial stunning, notably by providing strong evidence that stunning is, at least in part, a manifestation of reperfusion injury and that this injury is caused, again at least in part, by free radical-mediated injury resulting from a transient but severe burst of radical production during the early minutes of reperfusion. In most studies, Bolli and colleagues have used the anesthetized open-chest dog as an experimental model with transient regional ischemia induced by a 15-min occlusion of the left anterior descending coronary artery. In these studies reperfusion has been for periods as short as 3 h or as long as 7 days.

Despite their meticulous nature with well-designed and controlled protocols, the studies and conclusions of Bolli and colleagues have been criticized on the grounds that they are carried out in open-chest anesthetized dogs with all the possible confounding factors of anesthesia, surgical stress, abnormal hemodynamics, and high levels of circulating catecholamines. Recognizing this limitation, the present study significantly advances our understanding of stunning by comparing the phenomenon in conscious versus anesthetized dogs, and by relating the severity of stunning to the magnitude of reperfusion-induced radical production.

Based on their earlier observations that: (i) the severity of stunning after a 15-min period of regional ischemia was greatly amplified in the barbiturate-anesthetized dog; and (ii) the time course for recovery from stunning was quite different in conscious vs anesthetized dog, Li et al, in the present study, used 108 dogs, 76 of which were instrumented at least 7 days before study (they were also trained for at least 3 days until they became acclimatized to the laboratory). Regional contractile function was measured using epicardial Doppler probes, free-radical production was measured by electron paramagnetic (EPR) spectroscopic analysis of plasma samples using α-phenyl *N-tert*-butyl nitrone (PBN) as a spin trap, and a wide variety of potential confounding variables such as collateral flow to the ischemic zone, risk-zone size, hemodynamic function, blood gases, hematocrit, and temperature were measured and controlled for.

In conscious dogs with 15 min of coronary occlusion and 6 h of reperfusion, a prolonged release of free radical adducts was observed, characterized by a burst during the initial minutes of reperfusion (peaking at 3 min) and then abating; however, free radical production could be detected for the first 1-3 h of reperfusion. Analysis of EPR signals suggested the trapping of several carbon-centered radicals, possibly due to oxygen radical-initiated membrane lipid peroxidation. An important new observation was that no radical production could be detected when collateral flow to the ischemic zone exceeded 30% to 40% of the flow to the nonischemic tissue, indicating that a flow reduction of at least 60% might be necessary to trigger radical production during reperfusion after 15 min of ischemia. Of considerable significance was the observation of a direct relationship between the magnitude of radical adduct production and the severity of contractile dysfunction ($r = 0.77$), providing further indirect evidence that radical production plays a causal role in myocardial stunning.

Total radical adduct production during the first 3 h of reperfusion was 5 times greater in anesthetized than in conscious dogs and the extent of stunning was twice as great in the anesthetized hearts. Coupled with the observation that stunning was less severe in conscious dogs and the recovery of function was better, the authors were able to present convincing evidence that the use of open-chest anesthetized preparations exaggerates the magnitude of stunning and as such cannot be automatically extrapolated to conscious dogs or to all humans.

This conclusion, however, does not negate the clinical significance of stunning since it is a frequent complication in anesthetized open-chest humans during cardiac surgery!

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

J.L.J. Vanoverschelde, W. Wijns, C. Depré, B. Essamri, G.R. Heyndrickx, M. Borgers, A. Bol, J.A Melin

Circulation. 1993;87:1513-1523.

In this interesting study, Vanoverschelde and colleagues address the issue of patients with coronary artery disease who have not suffered a myocardial infarction and who present wall-motion abnormalities that are reversible either spontaneously or after recanalization. Such postischemic dysfunction could be due either to stunning or myocardial hibernation, the difference between the two being the presence of either normal or reduced flow.

In view of determining to which of the two invoked mechanisms the chronic regional dysfunction which is often observed in patients with angina and noninfarcted collateral-dependent myocardium could be attributed, the authors have studied 26 anginal patients with chronic occlusion of a major coronary artery without previous myocardial infarction by positron emission tomography (PET) in order to measure absolute regional myocardial blood flow with ^{13}N-ammonia at rest and after intravenous dipyridamole. In addition, the kinetics of ^{18}F-deoxyglucose and ^{11}C-acetate were measured to calculate the rate of exogenous glucose uptake and the regional oxidative metabolism.

The patients were then subjected to coronary revascularization procedures and transmural myocardial biopsies from the collateral-dependent area were obtained during bypass surgery and analyzed by optical and electron microscopy. The patients were separated into two groups according to the resting regional wall motion, one group with and the other without dysfunction of the collateral-dependent segments. In patients with normal wall motion, regional myocardial blood flow, oxidative metabolism, and glucose uptake were found to be similar among collateral-dependent and remote segments. By contrast, in patients with regional dysfunction, collateral-dependent segments exhibited lower myocardial blood flow and higher glucose uptake in comparison with remote segments. However, myocardial blood flow values were similar among collateral-dependent segments of patients with and without segmental dysfunction. After intravenous dipyridamole, the authors showed that collateral-dependent myocardial blood flow increased in three patients with normal wall motion and in eight patients with regional dysfunction. There was a significant inverse correlation between wall motion abnormality and collateral flow reserve. Analysis of the tissue samples obtained at the time of bypass surgery evidenced profound structural changes in dysfunctioning collateral-dependent areas, including cellular swelling swelling, loss of myofibrillar content, and accumulation of glycogen. However, despite these alterations, there was a late improvement in regional wall motion score in the patients studied 3 months after revascularization.

Based on the findings from this study, Vanoverschelde and colleagues conclude that in a subgroup of patients with noninfarcted collateral-dependent myocardium, immature or insufficiently developed collaterals do not provide adequate flow reserve. Despite nearly normal resting flow and oxygen consumption, these collateral-dependent segments exhibit chronically depressed wall motion and demonstrate marked ultrastructural alterations on morphological analysis.

Current diagnostic techniques of assessing myocardial viability in patients with hibernating and stunned myocardium

V. Dilsizian, R. Bonow

Circulation. 1993;87:1-20.

This review by Dilsizian and Bonow on the differentiation of viable from nonviable myocardium in patients with coronary artery disease and left ventricular dysfunction - an issue of increasing clinical relevance - represents a substantial contribution to improving the management of such patients.

The prospective identification of potentially reversible ventricular dysfunction caused by either hibernating or stunned myocardium carries significant clinical implications. Available data suggest that an improvement in ventricular function in such patients will translate into improved prognosis.

From the perspective of determining patient management, the authors stress that knowledge that a large portion of dysfunctional myocardium is viable rather than fibrotic can justify a revascularization procedure even in high-risk patients with left ventricular dysfunction.

Nonetheless, a recommendation for myocardial revascularization in patients with ventricular dysfunction is dependent on a number of considerations of which myocardial viability is just one. These considerations include: (i) the symptomatic status of the patient; (ii) coronary anatomy; (iii) severity of left ventricular dysfunction and operative risk. In some patients, as Dilsizian and Bonow point out, the accurate determination of the presence and extent of underperfused but viable myocardium is indeed a momentous issue that will eventually dictate whether or not revascularization should be performed.

At present, it seems that positron emission tomography (PET) technology is the gold standard for viability. Nevertheless, this technique is very expensive, requires cyclotron technology, and is not readily available. On the other hand, thallium is widely available for clinical use and provides a less expensive alternative to PET assessment of regional metabolic activity.

Recent publications suggest that either stress-redistribution-reinjection or rest-redistribution thallium protocols may provide cost-effective, efficient, and accurate information regarding myocardial viability in the majority of patients with chronic ischemic left ventricular dysfunction. Therefore, only a small number of patients in whom thallium results may be equivocal would require metabolic assessment with PET.

Another possibility for identifying viability is to search for residual contractile reserve. This can be determined mainly by echocardiography after infusion of dobutamine or another positive inotropic agent. This technique has the advantage of better estimating the operative risk and is cost effective. Interestingly, the authors conclude, this technique provides information that compares favorably with the results of thallium scintigraphy.

Occurrence of oxidative stress during reperfusion of the human heart

R. Ferrari, O. Alfieri, S. Curello, C. Ceconi, A. Cargnoni, P. Marzollo, A. Pardini, E. Caradonna, O. Visioli

Circulation. 1990;81:201-211.

This article addresses for the first time the existence of a possible link between oxidative stress and stunning occurring immediately after aortocoronary bypass grafting in humans. The work is of particular relevance as it contributes to bridging the gap between the experimental evidence of oxidative stress as a possible cause of stunning and its clinical counterpart.

Ferrari and colleagues studied 20 patients subjected to aortocoronary bypass grafting. The patients were selected on the basis of having normal left ventricular function (the patients had normal ejection fraction and left ventricular end-diastolic pressure before the operation) and anatomic extent of coronary artery disease (every patient had to have a coronary lesion of the left anterior descending coronary artery greater than 90%, and in addition, could have lesions involving other branches of the coronary tree (circumflex coronary artery and right coronary artery).

The authors measured the occurrence of oxidative stress by measuring the formation and release of oxidized glutathione (GSSG) in the coronary sinus immediately before aortic cross-clamping and 1, 5, and 20 min after removal of the aortic cross-clamp, as well as 10 and 20 min after the end of cardiopulmonary bypass.

The coronary sinus is known to collect blood mainly from the anterior region of the left ventricle, which explains that a sampling of the coronary sinus is particularly suitable for assessment of events occurring in the anterior portion of the myocardium. GSSG was chosen as an index of oxidative stress as its increased formation and release, either active or passive, from the myocyte reflects glutathione peroxidase activity. The increase in GSSG thereby indicates the inability of the cell to produce reducing equivalents for reduced glutathione (GSH) resynthesis, so that it may be considered to be a very sensitive and specific index of myocardial oxidative stress.

In addition to GSSG, GSH, lactate, and creatine phosphokinase release were also monitored at the same time points. Standard hemodynamic measurements were recorded at the end of cardiopulmonary bypass and continuously for 24 hours after termination of cardiopulmonary bypass.

Patients were divided into two groups according to the duration of the cross-clamping (= ischemic) period: less than 30 min (group 1) and longer than 30 min (group 2). Reperfusion of patients of group 1 resulted in a small and transient release of GSSG and GSH into the coronary sinus, and a progressive improvement in hemodynamic parameters reaching a stable state 4 hours after the operation. In the patients of group 2, reperfusion induced a marked and sustained release of GSSG, lactate, and GSH that was still continuing at the end of the cardiopulmonary bypass. Interestingly, the arterial/coronary sinus difference for GSSG was still negative at the end of cardiopulmonary bypass, thereby clearly indicating the occurrence of oxidative stress. In these patients the rate of functional recovery was significantly delayed, suggesting the occurrence of myocardial stunning during the 24 hours following the operation. There was a positive correlation between duration of ischemia, extent of stunning, and degree of oxidative stress, indicating that all these factors are interrelated: the longer the period of ischemia, the higher the oxidative stress and the more severe the myocardial stunning.

In conclusion, although the paper does not unequivocally prove that oxidative stress is the cause of stunning, it does strongly indicate that the two processes are closely linked. It is therefore reasonable to assume, based on this study as well as on other experimental findings, that this correlation is not accidental.

Myocardial Stunning

Bibliography of Key Papers

Afridi I, Kleiman NS, Raizner AE, Zoghbi WA.

Dobutamine echocardiography in myocardial hibernation: optimal dose and accuracy in predicting recovery of ventricular function after coronary angioplasty.

Circulation. 1995;91:663-670.

Alam M, Khaja F, Brymer J, Marzelli M, Goldstein S.

Echocardiographic evaluation of left ventricular function during coronary artery angioplasty.

Am J Cardiol. 1986;57:20-25.

Alderman EL, Fisher LD, Litwin P, et al.

Results of coronary artery surgery in patients with poor left ventricular function (CASS).

Circulation. 1983;68:785-795.

Ambrosio G, Jacobus WE, Bergman CA, Weisman HF, Becker LC.

Preserved high energy phosphate metabolic reserve in globally "stunned" hearts despite reduction of basal ATP content and contractility.

J Mol Cell Cardiol. 1987;19:953-964.

Ambrosio G, Jacobus WE, Mitchel MC, Litt MR, Becker LC.

Effects of ATP precursors on ATP and free ADP content and functional recovery of postischemic hearts.

Am J Physiol. 1989;256:H560-H566.

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.

Ambrosio G, Weisfeldt ML, Jacobus WE, et al.

Evidence for a reversible oxygen radical-mediated component of reperfusion injury: reduction by recombinant human superoxide dismutase administered at the time of reflow.

Circulation. 1987;75:282-291.

Ambrosio G, Zweier JL, Jacobus WE, Weisfeldt ML, Flaherty JT.

Improvement of postischemic myocardial function and metabolism induced by administration of desferrioxamine at the time of reflow: the role of iron in the pathogenesis of reperfusion injury.

Circulation. 1987;76:906-915.

Anderson JL, Marshall HW, Askins JC, et al.

A randomized trial of intravenous and intracoronary streptokinase in patients with acute myocardial infarction.

Circulation. 1984;70:606-618.

Bibliography of Key Papers

Anderson JL, Marshall HW, Bray BE, et al.

A randomized trial of intracoronary streptokinase in the treatment of acute myocardial infarction.
N Engl J Med. 1983;308:1313-1318.

Asinger RW, Peterson DA, Elsperger KJ, Homans D.

Long-term recovery of LV wall thickening after 1 hour of ischemia is not affected when superoxide dismutase and catalase are administered during the first 45 minutes of reperfusion.
J Am Coll Cardiol. 1988;2:163A. Abstract.

Auchampach JA, Maruyama M, Cavero I, Gross GJ.

Pharmacological evidence for a role of ATP-dependent potassium channels in myocardial stunning.
Circulation. 1992;86:311-319.

Baker WB, Klein MS, Reardon MJ, Verani MS, Zoghbi WA.

Reversible cardiac dysfunction (hibernation) from ischemia due to compression of the coronary arteries by a pseudoaneurysm.
N Engl J Med. 1991;325:1858-1861.

Ballantyne CM, Verani MS, Short HD, Hyatt C, Noon GP.

Delayed recovery of severely "stunned" myocardium with the support of a left ventricular assist device after coronary artery bypass graft surgery.
J Am Coll Cardiol. 1987;10:710-712.

Barilla F, Gheorghiade M, Alam M, Khaja F, Goldstein S.

Low-dose dobutamine in patients with acute myocardial infarction identifies viable but not contractile myocardium and predicts the magnitude of improvement in wall motion abnormalities in response to coronary revascularization.
Am Heart J. 1991;122:1522-1531.

Bateman TM, Czer LSC, Gray RJ, et al.

Transient pathologic Q-waves during acute ischemic events: an electrocardiographic correlate of stunned but viable myocardium.
Am Heart J. 1983;6:1421-1426.

Becker LC, Levine JH, DiPaula AF, Guarnieri T, Aversano TR.

Reversal of dysfunction in postischemic stunned myocardium by epinephrine and postextrasystolic potentiation.
J Am Coll Cardiol. 1986;7:580-589.

Bennett WR, Yawn DH, Migliore PJ, et al.

Activation of the complement system by recombinant tissue plasminogen activator.
J Am Coll Cardiol. 1987;10:627-632.

Berger HJ, Reduto LA, Johnston DE, et al.

Global and regional left ventricular response to bicycle exercise in coronary artery disease: assessment by quantitative radionuclide angiocardiography.
Am J Med. 1979;66:13-21.

Bigger JT Jr, Fleiss JL, Kleiger R, et al.

The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction.
Circulation. 1984;69:250-258.

Bolli R.
Mechanism of myocardial "stunning."
Circulation. 1990;82:723-738.

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

Bolli R.
Myocardial "stunning" in man.
Circulation. 1992;86:1671-1691.

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

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.

Bolli R.
Common methodological problems and artifacts associated with studies of myocardial stunning in vivo.
Basic Res Cardiol. 1995;90:257-262.

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.

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.

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.

Bolli R, McCay PB.
Use of spin traps in intact animals undergoing myocardial ischemia/reperfusion: a new approach to assessing the role of oxygen radicals in myocardial "stunning."
Free Radic Res Commun. 1990;9:169-180.

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.

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.

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 nitrone.

J Clin Invest. 1988;82:476-485.

Bolli R, Patel BS, Zhu WX, O'Neill PG, Charlat ML, Roberts R.

The iron chelator desferrioxamine attenuates postischemic ventricular dysfunction.

Am J Physiol. 1987;253:H1372-H1380.

Bolli R, Zhu WX, Hartley CJ, et al.

Attenuation of dysfunction in the postischemic "stunned" myocardium by dimethylthiourea.

Circulation. 1987;76:458-468.

Bolli R, Zhu WX, Myers ML, Hartley CJ, Roberts R. Kloner RA.

Beta-adrenergic stimulation reverses postischemic myocardial dysfunction without producing subsequent functional deterioration.

Am J Cardiol. 1985;56:964-968.

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.

Bolli R, Zughaib M, Li XY, et al.

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.

Bourdillon PDV, Broderick TM, Williams ES, et al.

Early recovery of regional left ventricular function after reperfusion in acute myocardial infarction assessed by serial two-dimensional echocardiography.

Am J Cardiol. 1989;63:641-646.

Braunwald E, Kloner RA.

The stunned myocardium: prolonged, postischemic ventricular dysfunction.

Circulation. 1982;66:1146-1149.

Braunwald E, Rutherford JD.

Reversible ischemic left ventricular dysfunction: evidence for the "hibernating myocardium."

J Am Coll Cardiol. 1986;8:1467-1470.

Breisblatt WM, Stein KL, Wolfe CJ, et al.

Acute myocardial dysfunction and recovery: a common occurrence after coronary bypass surgery.

J Am Coll Cardiol. 1990;15:1261-1269.

Bush LR, Buja LM, Samowitz W, et al.

Recovery of left ventricular segmental function after long-term reperfusion following temporary coronary occlusion in conscious dogs: comparison of 2- and 4-hour occlusions.

Circ Res. 1983;53:248-263.

Casale AS, Bulkley GB, Bulkley BH, Flaherty JT, Gott VL, Gardner TJ.

Oxygen free radical scavengers protect the arrested globally ischemic heart upon reperfusion.

Surg Forum. 1983;34:313-316.

Charlat ML, O'Neill PG, Egan JM, et al.

Evidence for a pathogenetic role of xanthine oxidase in the "stunned" myocardium.

Am J Physiol. 1989;252:H566-H577.

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.

Charney R, Schwinger ME, Chun J, et al.

Dobutamine echocardiography and resting-redistribution thallium-201 scintigraphy predicts recovery of hibernating myocardium after coronary revascularization.

Am Heart J. 1994;128:864-869.

Charuzi Y, Beeder C, Marshall LA, et al.

Improvement in regional and global left ventricular function after intracoronary thrombolysis: assessment with two-dimensional echocardiography.

Am J Cardiol. 1984;53:662-665.

Cigarroa CG, deFilippi CR, Brickner E, Alvarez LG, Wait MA, Grayburn PA.

Dobutamine stress echocardiography identifies hibernating myocardium and predicts recovery of left ventricular function after coronary revascularization.

Circulation. 1993;88:430-436.

Cohen MV, Downey JM.

Myocardial stunning in dogs: preconditioning effect and influence of coronary collateral flow.

Am Heart J. 1990;120:282-291.

Cunningham JN Jr, Adams PX, Knopp EA, et al.

Preservation of ATP, ultrastructure, and ventricular function after aortic cross-clamping and reperfusion: clinical use of blood potassium cardioplegia.

J Thorac Cardiovasc Surg. 1979;78:708-720.

Czer L, Hamer A, Murphy F, et al.

Transient hemodynamic dysfunction after myocardial revascularization: temperature dependence.

J Thorac Cardiovasc Surg. 1983;86:226-234.

Davies SW, Ranjadayalan K, Wickens DG, Dormandy TL, Timmis AD.

Free radicals, reperfusion and thrombolysis.

Eur Heart J. 1989;10(suppl):274.

---

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.

Deanfield JE, Selwyn AP, Chierchia S, et al.

Myocardial ischaemia during daily life in patients with stable angina: its relation to symptoms and heart rate changes.

Lancet. 1983;2:753-758.

Deantonio HJ, Kaul S, Lerman BB.

Reversible myocardial depression in survivors of cardiac arrest.

PACE. 1990;13:982-985.

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.

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.

Doorey AJ, Mehmel HC, Schwartz FX, Kuble W.

Amelioration by nitroglycerin of left ventricular ischemia induced by percutaneous transluminal coronary angioplasty: assessment by hemodynamic variables and left ventriculography.

J Am Coll Cardiol. 1985;6:267-274.

Dunlap E, Millard RW.

Amlodipine, a new long-acting calcium channel blocking agent, improves recovery of "stunned" myocardium.

Pharmacologist. 1989;31:145. Abstract.

Dymond DS, Foster C, Grenier RP, Carpenter J, Schmidt DH.

Peak exercise and immediate postexercise imaging for the detection of left ventricular function abnormalities in coronary artery disease.

Am J Cardiol. 1984;53:1532-1537.

Eddy LJ, Stewart JR, Jones HP, Engerson TD, McCord JM, Downey JM.

Free-radical producing enzyme, xanthine oxidase, is undetectable in human hearts.

Am J Physiol. 1987;253:H709-H711.

Ehring T, Baumgart D, Krajcar M, Hummelgen M, Kompa S, Heusch G.

Attenuation of myocardial stunning by the ACE inhibitor ramiprilat through a signal cascade of bradykinin and prostaglandins but not nitric oxide.

Circulation. 1994;90:1368-1385.

Ehring T, Boehm M, Heusch G.

The calcium antagonist nisoldipine improves the functional recovery of reperfused myocardium only when given before ischemia.

J Cardiovasc Pharmacol. 1992;20:63-74.

Ellis SE, Wynne J, Braunwald E, Henschke CI, Sandor T,

Response of reperfusion-salvaged, stunned myocardium to inotropic-stimulation.

Am Heart J. 1984;107:9-13.

Erbel R, Pop T, Henrichs K, et al.

Percutaneous transluminal coronary angioplasty after thrombolytic therapy: a prospective controlled randomized trial.

J Am Coll Cardiol. 1986;8:485-495.

Farber NE, Vercellotti GM, Jacobs HS, Pieper GM, Gross GJ.

Evidence for a role of iron-catalyzed oxidants in functional and metabolic stunning in the canine heart.

Circ Res. 1988;63:351-360.

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

Occurrence of oxidative stress during reperfusion of the human heart.

Circulation. 1990;81:201-211.

Ferreira R, Llesuy S, Milei J, et al.

Assessment of myocardial oxidative stress in patients after myocardial revascularization.
Am Heart J. 1988;115:307-312.

Forman MB, Puett DW, Cates CU, et al.

Glutathione redox pathway and reperfusion injury. Effect of N-acetylcysteine on infarct size and ventricular function.
Circulation. 1988;78:202-213.

Foster E, O'Kelly B, LaPidus A, et al.

Segmental analysis of resting echocardiography function and stress scintigraphic perfusion: implications for myocardial viability.
Am Heart J. 1995;129:7-14.

Fournier C, Boujon B, Hebert JL, Zamani K, Grimon G, Blondeau M.

Stunned myocardium following coronary spasm.
Am Heart J. 1991;121:593-595.

Fremes SE, Christakis GT, Weisel RD, et al.

A clinical trial of blood and crystalloid cardioplegia.
J Thorac Cardiovasc Surg. 1984;88:725-741.

Fremes SE, Weisel RD, Mickle DAG, et al.

Myocardial metabolism and ventricular function following cold potassium cardioplegia.
J Thorac Cardiovasc Surg. 1985;89:531-546.

Fuster V, Badimon L, Badimon JJ, Chesebro JH.

The pathogenesis of coronary artery disease and the acute coronary syndromes
N Engl J Med. 1992;326:242-250;310-318.

Gardner TJ.

Oxygen radicals in cardiac surgery.
Free Radic Biol Med. 1988;4:45-50.

Garlick PB, Davies MJ, Hearse DJ, Slater TF.

Direct detection of free radicals in the reperfused rat heart using electron spin resonance spectroscopy.
Circ Res. 1987;61:757-760.

Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G.

Silent ischemia as a marker for early unfavorable outcomes in patients with unstable angina.
N Engl J Med. 1986;314:1214-1219.

Gray R, Maddhai J, Berman D, et al.

Scintigraphic and hemodynamic demonstration of transient left ventricular dysfunction immediately after uncomplicated coronary artery bypass grafting.
J Thorac Cardiovasc Surg. 1979;77:504-510.

Grinwald PM.

Calcium uptake during postischemic reperfusion in the isolated rat heart: influence of extracellular sodium.
J Mol Cell Cardiol. 1982;14:359-365.

Gross GJ, Farber NE, Hardman HF, Warltier DC.

Beneficial actions of superoxide dismutase and catalase in stunned myocardium of dogs.
Am J Physiol. 1986;250:H372-H377.

Guarnieri T.

Direct measurement of [Ca^{2+}]i in early and late reperfused myocardium.

Circulation. 1989;80(suppl II):II-241. Abstract.

Hartley CJ, Rabinovitz RS, Lee HS, Chelly JE, Noon GP, Bolli R.

Postoperative measurements of ventricular function in man using an implantable ultrasonic sensor. In: West AL, ed.

Catheter-Based Sensing and Imaging Technology. Proc SPIE; 1989:1068:53-58.

Hauser AM, Gangadharan V, Ramos RG, Gordon S, Timmis GC, Dudlets P.

Sequence of mechanical, electrocardiographic and clinical effects of repeated coronary artery occlusion in human beings: echocardiographic observations during coronary angioplasty.

J Am Coll Cardiol. 1985;5:193-197.

Hearse DJ.

Stunning: a radical review.

Cardiovasc Drugs Ther. 1991;5:853-876.

Hearse DJ, Humphrey SM, Bullock GR.

The oxygen paradox and the calcium paradox: two facets of the same problem?

J Mol Cell Cardiol. 1978;10:641-668.

Heusch G.

Myocardial stunning: a role for calcium antagonists during ischemia?

Cardiovasc Res. 1992;26:14-19.

Heusch G, Schafer S, Kroger K.

Recruitment of inotropic reserve in "stunned" myocardium by the cardiotonic agent AR-L 57.

Basic Res Cardiol. 1988;83:602-610.

Heyndrickx GR, Baig H, Nellens P, Leusen I, Fishbein MC, Vatner SF.

Depression of regional blood flow and wall thickening after brief coronary occlusions.

Am J Physiol. 1978;234:H653-H659.

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.

Hittinger L, Shannon RP, Kohin S, Manders WT, Kelly P, Vatner SF.

Exercise-induced subendocardial dysfunction in dogs with left ventricular hypertrophy.

Circ Res. 1990;66:329-343.

Homans DC, Asinger R, Pavek T, et al.

Effect of superoxide dismutase and catalase on regional dysfunction after exercise-induced ischemia.

Am J Physiol. 1992;263:H392-H398.

Homans DC, Laxson DD, Sublett E, Lindstrom P, Bache RJ.

Cumulative deterioration of myocardial function after repeated episodes of exercise-induced ischemia.

Am J Physiol. 1989;256(Heart Circ Physiol 25):H1462-H1471.

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.

Illes RW, Silverman NA, Krukenkamp IB, del Nido PJ, Levitsky S.

Amelioration of postischemic stunning by deferoxamine-blood cardioplegia.
Circulation. 1989;80(suppl III):III-30-III-35.

Ito BR, Tate H, Kobayashi M, Schaper W.

Reversibly injured, postischemic canine myocardium retains normal contractile reserve.
Circ Resp. 1987;61:834-846.

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.

Jarasch ED, Bruder G, Heid HW.

Significance of xanthine oxidase in capillary endothelial cells.
Acta Physiol Scand. 1986;548(suppl):39-46.

Jennings RB, Reimer KA.

Factors involved in salvaging ischemic myocardium. Effects of reperfusion of arterial blood.
Circulation. 1983;68(suppl I):125-136.

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.

Jeroudi MO, Tang XL, Abd-Elfattah AS, Bolli R.

Effect of adenosine on myocardial stunning. In: Abd-Elfattah AS, Wechsler AS, eds.
Purines and Myocardial Protection.
Boston, Mass: Kluwer Academic Publishers; 1996:297-313.

Jeroudi MO, Tang XL, Abd-Elfattah A, Sun JZ, Bolli R.

Effect of adenosine A_1-receptor activation on myocardial stunning in intact dogs.
Circulation. 1994;90:I-479. Abstract.

Jeroudi MO, Triana FJ, Patel BS, Bolli R.

Effect of superoxide dismutase and catalase, given separately, on myocardial "stunning."
Am J Physiol. 1990;259:H889-H901.

Johnson DL, Homeffer PJ, Dinatale JM Jr, Gott VL, Gardner TJ.

Free radical scavengers improve functional recovery of stunned myocardium in a model of surgical coronary revascularization.
Surgery. 1987;102:334-340.

Kaneko M, Beamish RE, Dhalla NS.

Depression of heart sarcolemmal Ca^{2+}-pump activity by oxygen free radicals.
Am J Physiol. 1989;256:H368-H374.

Kaneko M, Elimban V, Dhalla NS.

Mechanism for depression of heart sarcolemmal Ca^{2+} pump by oxygen free radicals.
Am J Physiol. 1989;257:H804-H811.

Kim MS, Akera T.

O^2 free radicals: cause of ischemia-reperfusion injury to cardiac Na^+-K^+-ATPase.

Am J Physiol. 1987;252:H252-H257.

Kitakaze M, Weisfeldt ML, Marban E.

Acidosis during early reperfusion prevents myocardial stunning in perfused ferret hearts.

J Clin Invest. 1988;82:920-927.

Klein HH, Neuhaus KL.

Delayed improvement of myocardial function after recanalization of a chronic coronary occlusion in a patient with intractable heart failure.

Eur Heart J. 1990;11:280-286.

Klein HH, Pich S, Schuff-Werner P, Niedmann P, Blattmann U, Nebendahl K.

The effects of Trolox, a water-soluble vitamin E analogue, in regionally ischemic, reperfused hearts.

Int J Cardiol. 1991;32:291-302.

Kloner RA, Allen J, Cox TA, Zheng Y, Ruiz CE.

Stunned left ventricular myocardium after exercise treadmill testing in coronary artery disease.

Am J Cardiol. 1991;68:329-334.

Koemer JE, Anderson BA, Dage RC.

Protection against postischemic myocardial dysfunction in anesthetized rabbits with scavengers of oxygen-derived free radicals: superoxide dismutase plus catalase, N-2-mercaptopropionyl glycine and captopril.

J Cardiovasc Pharmacol. 1991;17:185-191.

Kolibask AJ, Goodenow JS, Busk CA, Tetalman MR, Lewis RP.

Improvement of myocardial perfusion and left ventricular function after coronary artery bypass grafting in patients with unstable angina.

Circulation. 1979;59:66-74.

Kramer JH, Arroyo CM, Dickens BF, Weglicki WB.

Spin-trapping evidence that graded myocardial ischemia alters postischemic superoxide production.

Free Radic Biol Med. 1987;3:153-159.

Krause SM, Hess ML.

Characterization of cardiac sarcoplasmic reticulum dysfunction during short-term normothermic global ischemia.

Circ Res. 1985;55:176-184.

Krause SM, Jacobus WE, Becker LC.

Alterations in cardiac sarcoplasmic reticulum calcium transport in the postischemic "stunned" myocardium.

Circ Res. 1989;65:526-530.

Kusuoka H, Koretsune Y, Chacko VP, Weisfeldt ML, Marban E.

Excitation-contraction coupling in postischemic myocardium: does failure of activator Ca^{2+} transients underlie stunning?

Circ Res. 1990;66:1268-1276.

Kusuoka H, Marban E.

Cellular mechanisms of myocardial stunning.

Annu Rev Physiol. 1992;54:243-256.

Kusuoka H, Porterfield JK, Weisman HF, Weisfeldt ML, Marban E.

Pathophysiology and pathogenesis of stunned myocardium. Depressed Ca^{2+} activation of contraction as a consequence of reperfusion-induced cellular calcium overload in ferret hearts.

J Clin Invest. 1987;79:950-961.

La Canna G, Alfieri O, Giubbini R, Gargano M, Ferrari R, Visioli O.

Echocardiography during infusion of dobutamine for identification of reversible dysfunction in patients with chronic coronary artery disease.

J Am Coll Cardiol. 1994;23:617-626.

Mathias P, Kerin NZ, Blevins RD, Cascase P, Rubenfire M.

Coronary vasospasm as a cause of stunned myocardium.

Am Heart J. 1987;113:383-385.

Matsuzaki M, Gallagher KP, Kemper WS, White F, Ross J Jr.

Sustained regional dysfunction produced by prolonged coronary stenosis: gradual recovery after reperfusion.

Circulation. 1983;68:170-182.

Labovitz AJ, Lewen MK, Kern M, Vandormael M, Deligonal U, Kennedy HL.

Evaluation of left ventricular systolic and diastolic dysfunction during transient myocardial ischemia produced by angioplasty.

J Am Coll Cardiol. 1987;10:748-755.

Lamping KA, Gross GJ.

Improved recovery of myocardial segment function following a short coronary occlusion in dogs by nicorandil, a potential new antianginal agent, and nifedipine.

J Cardiovasc Pharmacol. 1985;7:158-166.

Lavallee M, Cox D, Patrick TA, Vatner SF.

Salvage of myocardial function by coronary artery reperfusion 1, 2 and 3 hours after occlusion in conscious dogs.

Circ Res. 1983;53:235-247.

Lazdunski M, Frelin C, Vigue P.

The sodium/hydrogen exchange system in cardiac cells: its biochemical and pharmacological properties and its role in regulating internal concentrations of sodium and internal pH.

J Mol Cell Cardiol. 1985;17:1029-1042.

Lee HC, Smith N, Mohabir R, Clusin WT.

Cytosolic calcium transients from the beating mammalian heart.

Proc Natl Acad Sci USA. 1987;84:7793-7797.

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.

Manche A, Edmondson SJ, Hearse DJ.

Dynamics on early postischemic myocardial function recovery: evidence of reperfusion-induced injury?

Circulation. 1995;92:526-534.

Mangano DT.

Biventricular function after myocardial revascularization in humans: deterioration and recovery patterns during the first 24 hours.

Anesthesiology. 1985;62:571-577.

Marban E, Kitakaze M, Koretsune Y, Yue DT, Chacko VP, Pike MM.

Quantification of [Ca^{2+}]i in perfused hearts: critical evaluation of the ^{5}F-BAPTA and nuclear magnetic resonance method as applied to the study of ischemia and reperfusion.

Circ Res. 1990;66:1255-1267.

Marban E, Kitakaze M, Kusuoka H, Porterfield JK, Yue DT, Chacko VP.

Intracellular free calcium concentration measured with ^{19}F NMR spectroscopy in intact ferret hearts.

Proc Natl Acad Sci USA. 1987;84:6005-6009.

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.

Marchlinski FE, Buxton AE, Waxman HL, et al.

Identifying patients at risk of sudden death after myocardial infarction.

Am J Cardiol. 1983;52:1190-1196.

Mariani MA, Palagi C, Donatelli F, et al.

Identification of hibernating myocardium: a comparison between dobutamine echocardiography and study of perfusion and metabolism in patients with severe left ventricular dysfunction.

Am J Cardiac Imag. 1995;9:1-8.

Marzullo P, Parodi O, Reisenhofer B, et al.

Value of rest thallium-201/technetium-99m sestamibi scans and dobutamine echocardiography for detecting myocardial viability.

Am J Cardiol. 1993;71:166-172.

Mathias P, Kerin NZ, Blevins RD, Cascase P, Rubenfire M.

Coronary vasospasm as a cause of stunned myocardium.

Am Heart J. 1987;113:383-385.

Matsuzaki M, Gallagher KP, Kemper WS, White F, Ross J Jr.

Sustained regional dysfunction produced by prolonged coronary stenosis: gradual recovery after reperfusion.

Circulation. 1983;68:170-182.

McCord JM.

Oxygen-derived free radicals in postischemic tissue injury.

N Engl J Med. 1985;312:159-163.

McMurray J, Chopra M, Stewart J, Blaney S, Smith WE, Dargie HJ.

Does free radical generation occur in unstable angina?
J Mol Cell Cardiol. 1990;22(suppl III):S.120. Abstract.

Menasche P, Grousset C, Gauduel Y, PiZAwnica A.

A comparative study of free radical scavengers in cardioplegic solutions. Improved protection with peroxidase.

J Thorac Cardiovasc Surg. 1986;92:264-271.

Mercier JC, Lando U, Kanmatsuse K, et al.

Divergent effects of inotropic stimulation on the ischemic and severely depressed reperfused myocardium.

Circulation. 1982;66:397-400.

Moore CA, Cannon J, Watson DD, Kaul S, Beller GA.

Thallium-201 kinetics in stunned myocardium characterized by severe postischemic systolic dysfunction.

Circulation. 1990;81:1622-1632.

Murphy JG, Smith TW, Marsh JD.

Mechanisms of reoxygenation-induced calcium overload in cultured chick embryo heart cells.

Am J Physiol. 1988;254:H1133-H1141.

Murry CE, Richard VJ, Jennings RB, Reimer KA.

Free radicals do not cause myocardial stunning after four 5-minute coronary occlusions.

Circulation. 1989;80(suppl II):II-296. Abstract.

Myers CL, Weiss SJ, Kirsh MM, Shepard BM, Shlafer M.

Effects of supplementing hypothermic crystalloid cardioplegic solution with catalase, superoxide dismutase, allopurinol, or deferoxamine on functional recovery of globally ischemic and reperfused isolated hearts.

J Thorac Cardiovasc Surg. 1986;91:281-289.

Myers ML, Bolli R, Lekich RF, Hartley CJ, Michael LH, Roberts R.

N-2-mercaptopropionylglycine improves recovery of myocardial function following reversible regional ischemia.

J Am Coll Cardiol. 1986;8:1161-1168.

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.

Nademanee K, Intarachot V, Singh PN, Josephson MA, Singh BN.

Characteristics and clinical significance of silent myocardial ischemia in unstable angina.

Am J Cardiol. 1986;58:26B-33B.

Nejima J, Knight DR, Fallon JT, et al.

Superoxide dismutase reduces reperfusion arrhythmias but fails to salvage regional myocardial function or myocardium at risk in conscious dogs.

Circulation. 1989;79:143-153.

Nesto RW, Chon LH, Collins JJ Jr, Wynne J, Holman L, Cohn PR.

Inotropic contractile reserve: a useful predictor of increased 5-year survival and improved postoperative left ventricular function in patients with coronary artery disease and reduced ejection fraction.

Am J Cardiol. 1982;50:39-44.

Nicklas JM, Becker LC, Bulkley BH.

Effects of repeated brief coronary occlusion on regional left ventricular function and dimension in dogs.

Am J Cardiol. 1985;56:473-478.

Nicod P, Corbett JR, Firth BG, et al.

Prognostic value of resting and submaximal exercise radionuclide ventriculography after acute myocardial infarction in high-risk patients with single and multivessel disease.

Am J Cardiol. 1983;52:30-36.

Nienaber CA, Brunken RC, Sherman CT, et al.

Metabolic and functional recovery of ischemic human myocardium after coronary angioplasty.

J Am Coll Cardiol. 1991;18:966-978.

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.

O'Neill PG, Charlat ML, Michael LH, Roberts R, Bolli R.

Influence of neutrophil depletion on myocardial function and flow after reversible ischemia.

Am J Physiol. 1989;256:H341-H351.

Opie LH.

Reperfusion injury and its pharmacologic modification.

Circulation. 1989;80:1049-1062.

Panza JA, Dilsizian V, Laurienzo JM, Curiel RV, Kastsiyiannis PT.

Relation between thallium uptake and contractile response to dobutamine: implications regarding myocardial viability in patients with chronic coronary artery disease and left ventricular dysfunction.

Circulation. 1995;91:990-998.

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.

Patel BS, Jeroudi MO, O'Neill PG, Roberts R, Bolli R.

Effect of human recombinant superoxide dismutase on canine myocardial infarction.

Am J Physiol. 1990;258:H369-H380.

Pfisterer M, Zuber M, Wenzel R, Burkhart F.

Prolonged myocardial stunning after thrombolysis: can left ventricular function be assessed definitely at hospital discharge?

Eur Heart J. 1991;12:214-217.

Piérard LA, De Lansheere CM, Berthe C, Rigo P, Kulbertus HA.

Identification of viable myocardium by echocardiography during dobutamine infusion in patients with myocardial infarction after thrombolytic therapy: comparison with positron emission tomography.

J Am Coll Cardiol. 1990;15:1021-1031.

Pigott JD, Kouchoukos NT, Oberman A, Cutter GR.

Late results of surgical and medical therapy for patients with coronary artery disease and depressed left ventricular function.

J Am Coll Cardiol. 1985;5:1036-1045.

Preuss KC, Gross GJ, Brooks HL, Warltier DC.

Time-course of "stunned" myocardium following variable periods of ischemia in conscious and anesthetized dogs.

Am Heart J. 1987;114:696-703.

Previtali M, Poli A, Lanzarini L, Fetiveau R, Mussini A, Ferrario M.

Dobutamine stress echocardiography for assessment of myocardial viability and ischemia in acute myocardial infarction treated with thrombolysis.

Am J Cardiol. 1993;72:124G-130G.

Priest MF, Curry GC, Smith LR, et al.

Changes in left ventricular segmental wall motion following randomization to medicine or surgery in patients with unstable angina.

Circulation. 1978;58(suppl I):162-168.

Przyklenk K, Kloner RA.

Superoxide dismutase plus catalase improve contractile function in the canine model of the "stunned" myocardium.

Circ Res. 1986;58:148-156.

Przyklenk K, Kloner RA.

Effect of verapamil on postischemic "stunned" myocardium: importance of the timing of treatment.

J Am Coll Cardiol. 1988;11:614-623.

Przyklenk K, Kloner RA.

"Reperfusion injury" by oxygen-derived free radicals? Effect of superoxide dismutase plus catalase, given at the time of reperfusion, on myocardial infarct size, contractile function, coronary microvasculature, and regional myocardial blood flow.

Circ Res. 1989;64:86-96.

Puett DW, Forman MB, Cates CU, et al.

Oxypurinol limits myocardial stunning but does not reduce infarct size after reperfusion.

Circulation. 1987;76:678-686.

Qiu Y, Manche A, Hearse DJ.

Contractile and vascular consequences of blood versus crystalloid cardioplegia in the isolated blood-perfused rat heart.

Eur J Cardiothorac Surg. 1993;7:137-145.

Rahimtoola SH.

A perspective on the three large multicenter randomized clinical trials of coronary bypass surgery for chronic stable angina.

Circulation. 1985;75(suppl V):V123-V135.

Rahimtoola SH.

The hibernating myocardium.

Am Heart J. 1989;117:211-221.

Reduto LA, Lawrie GM, Reid JW, et al.

Sequential postoperative assessment of left ventricular performance with gated cardiac blood pool imaging following aortocoronary bypass surgery.

Am Heart J. 1981;101:59-66.

Reduto LA, Smalling RW, Freund GC, Gould KL.

Intracoronary infusion of streptokinase in patients with acute myocardial infarction: effects of reperfusion on left ventricular performance.

Am J Cardiol. 1981;48:403-409.

Reeves JP, Bailey CA, Halle CC.

Redox modification of sodium-calcium exchange activity in cardiac sarcolemmal vesicles.

J Biol Chem. 1986;261:4948-4955.

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

Reversal of segmental hypokinesis 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.

Renlund DG, Gerstenblith G, Lakatta EG, Jacobus WE, Kallman CH, Weisfeldt ML.

Perfusate sodium during ischemia modifies postischemic functional and metabolic recovery in the rabbit heart.

J Mol Cell Cardiol. 1984;16:795-801.

Roberts AJ, Niarchos AP, Subramanian VA, et al.

Systemic hypertension associated with coronary bypass surgery. Predisposing factors, hemodynamic characteristics, humoral profile, and treatment.

J Thorac Cardiovasc Surg. 1977;74:846.

Roberts AJ, Spies M, Meyers SN, et al.

Early and long-term improvement in left ventricular performance following coronary bypass surgery.

Surgery. 1980;88:467-475.

Roberts AJ, Spies M, Sanders JH, et al.

Serial assessment of left ventricular performance following coronary artery bypass grafting.

J Thorac Cardiovasc Surg. 1981;81:69-84.

Roberts MJD, Trimble ER, Wilson CM, et al.

Transient release of lipid peroxides after coronary artery balloon angioplasty.

Lancet. 1990;336:143-145.

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.

Ross J Jr.

Myocardial perfusion-contraction matching: implications for coronary heart disease and hibernation.

Circulation. 1991;83:1076-1083.

Rowe GT, Manson NH, Caplan M, Hess ML.

Hydrogen peroxide and hydroxyl radical mediation of activated leukocyte depression of cardiac sarcoplasmic reticulum: participation of the cyclooxygenase pathway.

Circ Res. 1983;53:584-591.

Salustri A, Elhendy A, Garyfallydis P, et al.

Prediction of improvement of ventricular function after first acute myocardial infarction using low-dose dobutamine stress echocardiography.

Am J Cardiol. 1994;74:853-856.

Schmidt WG, Sheehan FH, von Essen R, Vebis R, Effert S.

Evolution of left ventricular function after intracoronary thrombolysis for acute myocardial infarction.

Am J Cardiol. 1989;63:497-502.

Schneider RM, Weintraub WS, Klein LW, Seelaus PA, Agarwai JB, Helfant RH.

Rate of left ventricular function recovery by radionuclide angiography after exercise in coronary artery disease.

Am J Cardiol. 1986;57:927-932.

Schroder E, Kieso RA, Laughlin D, Schroder M, Meng R, Kerber RE.

Altered response of reperfused myocardium to repeated coronary occlusion in dogs.

J Am Coll Cardiol. 1987;10:898-905.

Schroeder R, Biamino G, von Leitner ER, et al.

Intravenous short-term infusion of streptokinase in acute myocardial infarction.

Circulation. 1983;67:536-548.

Scognamiglio R, Ponchia A, Fasoli G, Miraglia G, Dalla-Volta S.

Exercise-induced left ventricular dysfunction in coronary heart disease: a model for studying the stunned myocardium in man.

Eur Heart J. 1991;12(suppl G):16-19.

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.

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.

Serruys PW, Simoons ML, Suryapranata H, et al.

Preservation of global and regional left ventricular function after early thrombolysis in acute myocardial infarction.

J Am Coll Cardiol. 1986;7:729-742.

Serruys PW, Wijns W, van den Brand M, et al.

Left ventricular performance, regional blood flow, wall motion and lactate metabolism during transluminal angioplasty.

Circulation. 1984;70:24-36.

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.

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.

Shlafer M, Kane PF, Kirsh MM.

Superoxide dismutase plus catalase enhances the efficacy of hypothermic cardioplegia to protect the globally ischemic, reperfused heart.

J Thorac Cardiovasc Surg. 1982;83:830-839.

Shlafer M, Kane PF, Wiggins VY, Kirsh MM.

Possible role for cytotoxic oxygen metabolites in the pathogenesis of cardiac ischemic injury.

Circulation. 1982;66(suppl I):185-192.

Sinusas AJ, Watson DD, Cannon JM, Beller GA.

Effect of ischemia and postischemic dysfunction on myocardial uptake of technetium-99m-labeled methoxyisobutyl isonitrile and thallium-201.

J Am Coll Cardiol. 1989;14:1785-1793.

Bibliography of Key Papers

Smart SC, Sawada S, Ryan T, et al.

Low-dose dobutamine echocardiography detects reversible dysfunction after thrombolytic therapy of acute myocardial infarction.

Circulation. 1993;88:405-415.

Stack RS, Phillips HR III, Grierson DS, et al.

Functional improvement of jeopardized myocardium following intracoronary streptokinase infusion in acute myocardial infarction.

J Clin Invest. 1983;72:84-95.

Stahl LD, Aversano TR, Becker LC.

Selective enhancement of function of stunned myocardium by increased flow.

Circulation. 1986;74:843-851.

Stahl LD, Weiss HR, Becker LC.

Myocardial oxygen consumption, oxygen supply/demand heterogeneity, and microvascular patency in regionally stunned myocardium.

Circulation. 1988;77:865-872.

Steenbergen C, Murphy E, Levy L, London RE.

Elevation in cytosolic free calcium concentration early in myocardial ischemia in perfused rat heart.

Circ Res. 1987;60:700-707.

Stewart JR, Blackwell WH, Crute SL, Loughlin V, Greenfield LJ, Hess ML.

Inhibition of surgically induced ischemia/reperfusion injury by oxygen free radical scavengers.

J Thorac Cardiovasc Surg. 1983;86:262-272.

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.

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.

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.

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.

Taegtmeyer H, Roberts AFC, Raine AEG.

Energy metabolism in reperfused heart muscle: metabolic correlates to return of function.

J Am Coll Cardiol. 1985;6:864-870.

Takatsu F, Suzuki A, Nagaya T.

Variant angina pectoris with prolonged electrical and mechanical stunning.

Am J Cardiol. 1986;58:647-649.

Tani M, Neely JR.

Role of intracellular Na^+ in Ca^{2+} overload and depressed recovery of ventricular function of reperfused ischemic rat hearts. Possible involvement of H^+-Na^+ and Na^+-Ca^{2+} exchange.

Circ Res. 1989;65:1045-1056.

Taylor AL, Golino P, Eckels R, Pastor P, Buja LM, Willerson JT.

Differential enhancement of postischemic segmental systolic thickening by diltiazem.

J Am Coll Cardiol. 1990;15:737-747.

Theroux P, Ross J Jr, Franklin D, Kemper WS, Sasayama S.

Coronary arterial reperfusion. III. Early and late effects on regional myocardial function and dimensions in conscious dogs.

Am J Cardiol. 1976;38:599-606.

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.

Topol EJ, Weiss JL, Brinker JA, et al.

Regional wall motion improvement after coronary thrombolysis with recombinant tissue plasminogen activator: importance of coronary angioplasty.

J Am Coll Cardiol. 1985;6:426-433.

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.

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.

Visser CA, David GK, Kan G, et al.

Two-dimensional echocardiography during percutaneous transluminal coronary angioplasty.

Am Heart J. 1986;111:1035-1046.

Warltier DC, Gross GJ, Brooks HL, Preuss KC.

Improvement of postischemic, contractile function by the calcium channel blocking agent nitrendipine in conscious dog.

J Cardiovasc Pharmacol. 1988;12(suppl 4):S120-S124.

Watada H, Ito H, Oh H, et al.

Dobutamine stress echocardiography predicts reversible dysfunction and quantitates the extent of irreversibly damaged myocardium after reperfusion of anterior myocardial infarction.

J Am Coll Cardiol. 1994;24:624-630.

Weiner JM, Apstein CS, Arthur JH, Pirzada FA, Hood WB Jr.

Persistence of myocardial injury following brief periods of coronary occlusion.

Cardiovasc Res. 1976;10:678-686.

Weisel RD, Mickle DAG, Finkle CD, et al.

Myocardial free-radical injury after cardioplegia.

Circulation. 1989;80(suppl III):III-14-III-18.

Wicomb WN, Cooper DKC, Novitzky D, Barnard CN.

Cardiac transplantation following storage of the donor heart by a portable hypothermic perfusion system.

Ann Thorac Surg. 1984;37:243-248.

Wijns W, Serruys PW, Stager CJ, et al.

Effect of coronary occlusion during percutaneous transluminal angioplasty in humans on left ventricular chamber stiffness and regional diastolic pressure-radius relations.

J Am Coll Cardiol. 1986;7:455-461.

Williamson BD, Lim MJ, Buda AJ.

Transient left ventricular filling abnormalities (diastolic stunning) after acute myocardial infarction.

Am J Cardiol. 1990;12:897-903.

Wohlgelernter D, Cleman M, Highman HA, et al.

Regional myocardial dysfunction during coronary angioplasty: evaluation by two-dimensional echocardiography and 12-lead electrocardiography.

J Am Coll Cardiol. 1986;7:1245-1254.

Ytrehus K, Gunnes S, Myklebust R, Mjos OD.

Protection by superoxide dismutase and catalase in the isolated rat heart reperfused after prolonged cardioplegia: a combined study of metabolic, functional and morphometric ultrastructural variables.

Cardiovasc Res. 1987;21:492-499.

Zoghbi WA, Marian A, Cheirif JB, Roberts R, Quinones MA.

Time-course of recovery of regional function following thrombolysis in acute myocardial infarction (TIMI): preliminary observations for the TIMI trial phase II.

J Am Coll Cardiol. 1990;15:233A. Abstract.

Zughaib ME, Abd-Elfattah AS, Jeroudi MO, Sun JZ, Sekili S, Tang XL, Bolli R.

Augmentation of endogenous adenosine attenuates myocardial "stunning" independently of coronary flow or hemodynamic effects.

Circulation. 1993;88:2359-2369.

Zughaib ME, Sun JZ, Bolli R.

Effect of angiotensin-converting enzyme inhibitors on myocardial ischemia/reperfusion injury: a overview. In: Grobecker H, Heusch G, Strauer BE, eds.

Angiotensin and the Heart.
New York, NY: Springer-Verlag; 1993:155-167.
