Consequences of Brief Ischemia: Stunning, Preconditioning, and Their Clinical Implications
Part 1
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Abstract—In experimental studies in the dog, total proximal coronary artery occlusions of up to 15 minutes result in reversible injury, meaning that the myocytes survive this insult. The 15 minutes of ischemia, however, induce numerous changes in the myocardium, including certain monuments to the brief episode of ischemia that may persist for days. One of these monuments is stunned myocardium, which represents “prolonged postischemic contractile dysfunction of myocardium salvaged by reperfusion.” The mechanism of stunning involves generation of oxygen radicals as well as alteration in calcium homeostasis and possibly alteration in contractile protein structure. Stunning has been observed in several clinical scenarios, including after percutaneous transluminal coronary angioplasty, unstable angina, stress-induced ischemia, after thrombolysis, and after cardiopulmonary bypass. Oxygen radical scavengers and calcium channel blockers have been shown to enhance function of stunned myocardium in experimental studies, and in a few clinical studies, calcium channel blockers have been shown to ameliorate stunning. Although brief periods of ischemia can contribute to prolonged left ventricular dysfunction and even heart failure, they paradoxically play a cardioprotective role. Episodes of ischemia as short as 5 minutes, followed by reperfusion, protect the heart from a subsequent longer coronary artery occlusion by markedly reducing the amount of necrosis that results from the test episode of ischemia. This phenomenon, called ischemic preconditioning, has been observed in virtually every species in which it has been studied and is a powerful cardioprotective effect. The mechanism of ischemic preconditioning involves both triggers and mediators and involves complex second messenger pathways that appear to involve such components as adenosine, adenosine receptors, the epsilon isoform of protein kinase C, the ATP-dependent potassium channels, as well as others, including a paradoxical protective role of oxygen radicals. Both an early and a late phase of preconditioning have been described, and the mechanisms underlying their induction are under investigation. That preconditioning may occur in humans is suggested by the observations that repetitive balloon inflations in the coronary artery are associated with progressively less chest pain, ST-segment elevation, lactate production, the protective effects of preinfarction angina, the anginal “warm-up phenomenon,” and studies performed on human cardiac biopsies that show metabolic properties suggesting preconditioning. Development of pharmacological agents that stimulate second messenger pathways thought to be involved in preconditioning, but without causing ischemia, could result in novel approaches to treating ischemia. Hence, on one hand, brief episodes of ischemia can have a negative effect on the heart: stunning; and on the other hand, they have a protective effect: preconditioning. The future challenge is how to minimize the stunning phenomenon and maximize the preconditioning phenomenon in clinical practice. (Circulation. 2001;104:2981-2989.)

Key Words: ischemia ■ myocardial stunning ■ reperfusion ■ myocardial infarction

Brief episodes of transient myocardial ischemia are tolerated by myocytes. Although no cell death results from the ischemia, the myocytes are damaged. In canine heart, total proximal coronary occlusions of up to 15 minutes result in reversible injury, and beyond that, irreversible injury. The 15-minute period of ischemia, however, induces numerous changes in the noncontracting myocytes, including a marked decrease in high-energy phosphates and the adenine nucleotide pool, depletion of glycogen, accumulation of lactate and H+, and mild intracellular edema observed on ultrastructure; but once blood flow is reestablished, the myocytes eventually recover. The clinical counterparts to brief periods of transient ischemia include angina, unstable angina, coronary vasospasm, and transient ischemia induced by inflation of an angioplasty balloon in the coronary arteries. Patients with coronary artery disease may experience episodes of transient ischemia on a daily basis without developing myocardial necrosis.
Over the past 25 years, we have become aware, both in the experimental laboratory and in the clinical realm, that brief episodes of ischemia influence the myocardium in both positive and negative ways and that this influence may last for days. Brief episodes of ischemia induce both stunned myocardium and ischemic preconditioning, 2 phenomena that have been the subject of intense research over the past 20 years. The purpose of this review is to describe the similarities and differences between these 2 phenomena, to describe the basic biology and potential mechanisms involved, to discuss the clinical evidence that suggests that these phenomena occur in patients, and finally to assess the clinical significance of stunning and preconditioning.

**Physiological and Biochemical Changes Found in Reversibly Injured Myocardium**

**Effect of Ischemia**

Sudden occlusion of a major branch of a coronary artery in a large-animal heart, such as the dog heart, is followed by physiological and metabolic changes that appear within seconds of the cessation of coronary flow. For example, energy metabolism shifts from aerobic or mitochondrial metabolism to anaerobic glycolysis after only 8 seconds of reduced arterial flow.

This shift occurs as soon as the O$_2$ trapped in the tissue as oxyhemoglobin and oxymyoglobin is consumed. Simultaneous with the shift in metabolism, effective contractions diminish and then cease, and the myocardium stretches rather than shortens with each systole. The membrane potential decreases and ECG changes appear. Because the demand of the myocytes for energy far exceeds the supply from anaerobic glycolysis and from reserves of high-energy phosphate (HEP), tissue ATP decreases and ADP begins to accumulate. Creatine phosphate, a major reserve source of HEP, decreases very quickly. It is 90% exhausted after 30 seconds of ischemia, whereas ATP declines more slowly. Late in the reversible phase of ischemia, however, 75% to 80% of the ATP present at the onset of ischemia has disappeared.

An anaerobic glycolysis provides 80% of the new HEP produced in zones of severe or total ischemia. Because little glucose is trapped in the extracellular fluid, anaerobic glycolysis utilizes glucose-1-P from glycogenolysis as its substrate. In this process, 3 μmol HEP is generated per each μmol glucose-1-P converted to 2 μmol lactate. The lactate and its associated H$^+$ accumulate. After only 10 minutes of ischemia, the intracellular pH decreases to 5.8 to 6.0, and the load of intracellular osmotically active particles, lactate, inorganic phosphate, creatine, etc., increases markedly.

This osmotic load, however, causes only a modest increase in intracellular H$_2$O, because relatively little H$_2$O is available in the extracellular space of severely ischemic tissue to support the swelling process. This edema is visible on transmission electron microscopy, however, as an increase in the sarcoplasmic space.

Tissue glycogen decreases and products of anaerobic glycolysis, such as glucose-1-P, glucose-6-phosphate, α-glycerophosphate, and lactate, increase. The adenine nucleotide pool is degraded as the ADP formed from the action of ATPases accumulates, because ADP is being formed quickly, whereas rephosphorylation of ADP to ATP via anaerobic glycolysis is slowed by acidosis and lactate. The HEP of ADP is captured for use via the action of adenylate kinase. In the process, AMP is formed and accumulates intracellularly, where it is degraded to adenosine. The adenosine diffuses to the extracellular fluid and is lost from the adenine nucleotide pool. In the extracellular fluid, adenosine is further degraded to inosine and hypoxanthine. Both metabolites accumulate. The result of these reactions is a reduction in the size of the adenine nucleotide pool (ΣAd), ie, Σ(ADP + ATP + AMP). Late in the reversible phase of ischemia, it falls to 30% to 40% of the initial level.

A variety of substances, such as bradykinin, opioids, norepinephrine, and angiotensin, are released into the extracellular fluid during the first few minutes of ischemia. These join adenosine as agents that can and do bind to receptors on myocytes and thereby stimulate intracellular signaling systems. These reactions occur quickly. For example, phosphorylase is activated only a few seconds after the onset of ischemia by the norepinephrine that is released from intramyocardial sympathetic nerve endings as a response to ischemia.

There is evidence in vitro in the isolated perfused heart that intracellular ionized Ca$^{2+}$ rises slightly late in the reversible phase. This has been difficult to confirm in vivo but seems likely to occur, because the rise in intracellular H$^+$ of ischemia causes intracellular Na to rise via Na$^+/H^+$ exchange. The increase in intracellular Na should serve to drive Ca$^{2+}$ intracellularly via Na$^+/Ca^{2+}$ exchange. Conversely, no increase in total tissue Ca$^{2+}$ or in the specific activity of Ca accumulated in the tissue from the plasma reperfusing the myocardium can be seen after 15 minutes of ischemia and 0.5, 3, or 20 minutes of reperfusion.

**Effect of Reperfusion**

Sudden restoration of arterial flow to ischemic living myocardium results in restoration of aerobic metabolism and salvage of the ischemic myocytes (Figure 1). The tissue develops reactive hyperemia of marked degree (400% to 600% increase in flow), which peaks during the first 5 minutes of reperfusion and then declines. Arterial flow returns to control levels by the time 15 to 20 minutes of reperfusion has passed. A large excess of O$_2$-derived free radicals appears during the first minute of reperfusion and peaks some 4 to 7 minutes after the onset of reperfusion.

Associated with this change is generalized mitochondrial and cell swelling on electron microscopy.

The ECG changes of ischemia disappear after 60 to 120 seconds of arterial reperfusion, and at about the same time, the adenine nucleotide pool is converted to 90% ATP via the rephosphorylation of the ADP and AMP that accumulated while the tissue was ischemic. Lactate decreases to control levels as it is washed to the systemic circulation or is oxidized to CO$_2$ and H$_2$O. The pH of the tissue returns to control levels in 0.5 to 2 minutes.

Tissue creatine phosphate increases markedly, ie, from 30 to 40 μmol/g dry weight in the dog heart to 65 to 70 μmol/g dry weight: the creatine phosphate overshoot.
The delay in resynthesis occurs because de novo synthesis of proteins required to resynthesize it when this depletion is fully repleted, eg, after 15 minutes of ischemia in the dog heart. This delay is known as the overshoot because the intracellular glucose level increases by 4 to 6 times, presumably because of the action of Glut-4 receptors that have moved from the sarcolemma to the sarcoplasm. 21

Monuments to the Episode of Ischemia in the Reversibly Injured Tissue

The ECG changes of ischemia persist for <1 minute of reperfusion, whereas the reactive hyperemia disappears in 10 to 20 minutes. 16 The ultrastructural changes of reversible ischemia disappear after 5 minutes of reperfusion except for rare disrupted mitochondria. The swollen mitochondria observed during the first minutes of reperfusion return to control volume, and the myofibrils become contracted rather than stretched. 4, 22 However, the excess H 2 O and K + found early in reperfusion persist. 4, 23 They still are detected after 3 hours of reflow and probably persist for a longer period of time. The creatine phosphate overshoot is still present after 3 hours of reperfusion, but the increased intracellular glucose is no longer detectable at this time. 20 The time of disappearance of the overshoot is unknown.

The depressed adenine nucleotide pool is a prominent persistent monument to the injury, because many hours are required to resynthesize it when this depletion is fully developed, eg, after 15 minutes of ischemia in the dog heart. The delay in resynthesis occurs because de novo synthesis of adenine nucleotides is slow in myocardium. 24, 25 Conversely, periods of ischemia of only 2 to 3 minutes in duration result in a much smaller loss of the ΣAd pool and are followed by restitution of the pool in minutes or hours rather than days. It is of interest that the depressed pool does not seem to have a significant impact on function, because catecholamine administration results in the expected hemodynamic and contractile responses, all of which require the pool of HEP to turn over quickly.

Another monument to the episode of ischemia is an increase in the content of a variety of proteins within the myocyte, including superoxide dismutase (SOD), 26 heat-shock proteins, 27 and inducible nitric oxide synthase (iNOS). 28 These new proteins are synthesized during reperfusion and are readily detectable after 24 hours of reperfusion; thus, they represent a response of the myocyte to ischemic injury. The signaling process that leads to the activation of the genes involved in their synthesis, however, remains unknown.

Finally, this reperfused, reversibly injured myocardium is “preconditioned” by the episode of ischemia and reperfusion in that it will tolerate a prolonged test episode of ischemia much better than virgin myocardium. Also, reperfused, reversibly injured tissue is “stunned,” ie, it exhibits temporary contractile failure even though it is alive and aerobic.

In summary, these monuments to the effects of the episode of ischemia are striking evidence that the reversibly injured myocardium was damaged by the episode of ischemia and, in some cases, by the reperfusion process itself, even though reperfusion is the only way to prevent the death of the myocytes destined to die in the ischemic zone.

Stunned Myocardium

Definition and Biology of Stunning

Braunwald and Kloner described stunned myocardium as “prolonged, postischemic dysfunction of viable tissue salvaged by reperfusion.” 29 The basic scenario requires a discrete episode of transient ischemia. In the clinical realm, this episode of transient ischemia may be due to a total coronary occlusion, as would occur in the setting of severe coronary spasm, rupture of an atherosclerotic plaque with an attached thrombus, or ischemia induced by an increase in oxygen demand (such as exercise) in the setting of reduced flow reserve because of a significant partial coronary artery stenosis. During the episode of discrete ischemia, regional left ventricular wall motion abnormalities develop in the region of ischemia, because myocytes cease contracting within seconds of the onset of acute ischemia. If the heart is globally ischemic, as might occur during cardiopulmonary bypass, then the entire heart is subject to the global contractile dysfunction. After relief of ischemia, by relaxation of spasm, rapid lysis of a thrombus, cessation of exercise, or restoration of blood flow after cardiopulmonary bypass, the postischemic but viable myocardium requires hours to days before function is fully restored (Figure 2). 30, 31 It is this slow return of cardiac function after resolution of ischemia that has been called stunning. 29 The length of time for function to return is dependent on a number of parameters, including the duration of the original ischemic insult, the severity of ischemia during
Coronary artery occlusion
Endocardial surface in end-diastole
Short occlusion
Extensive Infarct
Endocardial surface in end-systole
Coronary occlusion
Regional wall motion abnormality
Reperfusion
STUNNED HEART
Regional wall motion abnormality after restoration of flow in viable myocardium
PRECONDITIONED HEART (small infarct)
Slow recovery over ~48 hrs. (Stunning)

Figure 2. Schematic of stunning and preconditioning. Short coronary artery occlusions result in stunning, in which there is prolonged regional wall motion abnormality, despite presence of reperfusion and viable myocardial cells. Brief episodes of ischemia/reperfusion also precondition heart. When heart is then exposed to a longer duration of ischemia and reperfusion, myocardial preconditioning occurs. When heart is then reperfusion, regional function remained depressed at 2 hours of reperfusion. Fractional systolic shortening of the left ventricle were measured in dogs that were subjected to coronary artery occlusions of 5 and 15 minutes followed by reperfusion. With a 5-minute coronary artery occlusion and reperfusion, regional function remained depressed at 2 hours of reperfusion but had recovered by 6 hours. When the duration of ischemia was extended to 15 minutes, the left ventricle remained depressed for ~6 hours after restoration of flow. Both ECG abnormalities and coronary blood flow had returned to normal or near normal when postischemic left ventricular dysfunction was fully developed. Hence, an important aspect of stunned myocardium is that there is a flow-function mismatch. At a time when coronary blood flow has been restored to normal or near normal and ischemia is resolved, the myocardium still does not contract.

In one study, the return of regional contractile function in anesthetized dogs was determined after 1, 5, and 15 minutes or after 3 hours of proximal coronary artery occlusion plus 3 hours of reperfusion. Fractional systolic shortening of the ischemic/reperfused zone was measured by sonomicrometry. The degree of recovery of systolic function was dependent on the duration of the occlusion. Thus, with a coronary artery occlusion of only 1 minute, abnormalities in systolic function rapidly recovered and were normal by 30 minutes. With a 5-minute occlusion, systolic function had recovered to only two thirds of normal by 30 minutes and remained depressed at 60 minutes. With 15 minutes to 3 hours of occlusion followed by reperfusion, there was persistent paradoxical systolic bulging at 3 hours. Charlat et al used a conscious canine model and observed that after a 15-minute coronary artery occlusion, 48 hours of reperfusion was needed for full recovery of systolic function.

An important aspect of the biology of stunned myocardium is that stunned myocardium is able to contract when exposed to inotropic stimuli. Hence, dopamine, dobutamine, isoproterenol, postextrasystolic potentiation, and even exogenous calcium can restore contraction of the stunned myocardium. Initially, investigators were concerned that stimulating the stunned myocardium to contract might worsen the long-term recovery of the heart. It was shown, however, that once the inotropic stimulus was removed, recovery of stunned myocardium returned to normal at the same rate as myocardium that had not received inotropic stimulation. Furthermore, enhancing the degree of stunning with a negative inotropic agent (such as a β-blocker) did not speed up the rate of recovery once the negative inotrope was withdrawn. If stunning per se were truly a protective mechanism, nature’s own “splint for an injured heart,” then flogging the stunned tissue with catecholamines could worsen the ultimate recovery and mimicking stunning should hasten recovery, but this was not the case. Stunning itself may not be a protective mechanism; however, as we will discuss later, brief periods of ischemia, by preconditioning the heart, can be very protective.

Mechanisms of Stunning
Most of our knowledge of the mechanism of stunning has come from studies of large-animal hearts subjected to episodes of ischemia designed to reversibly injure, ie, to damage but not to kill, the affected myocytes. Usually, periods of ischemia of ~15 minutes have been used in both conscious closed-chest and unconscious open-chest experiments. The results are similar, but the changes are more marked in anesthetized animals.

It seems certain that stunning also occurs in myocardium salvaged by arterial reperfusion after periods of 1 to 3 hours, ie, periods that result in substantial amounts of necrosis in damaged tissue. The living, reversibly injured myocytes in such areas are believed to be stunned, but the study of contractile function in this tissue is complicated by the presence of the dead myocytes. Because neither necrotic nor persistently ischemic myocytes can contract and because the proportion of dead myocytes varies with collateral flow, study of such tissue yields little information about the mechanisms of stunning. Hence, the main facts about the mechanism of stunning in vivo have come from studies using reversibly injured tissue free of myocyte necrosis.

Oxidative Hypothesis
The results of a series of brilliant experiments of Roberto Bolli and coworkers have shown clearly that 50% to 70% of the stunning effect is due to a burst of O2-derived free radicals liberated during the first few minutes of reperfusion with...
arterial blood. These free radicals are short-lived and include superoxide anion and hydroxyl radical formed from superoxide via heavy metal–catalyzed reactions. This means that much of the stunning effect is a complication of reperfusion and therefore is a form of reperfusion injury.

The evidence that free radicals cause stunning is very strong and began with the demonstration that much of the stunning effect could be prevented by pretreatment of the animals with intravenous infusion of 2 enzymes that scavenge O$_2^-$-derived free radicals, SOD and catalase. Use of permeant scavengers especially suited to scavenge hydroxyl radicals, eg, N-2-mercaptopyrrolion glycine (MPG), gave the maximal benefit but still did not totally prevent stunning. The direct demonstration of the existence of O$_2^-$-derived free radicals came from studies using electron spin resonance techniques to trap products of the reaction between free radicals and with the spin trap a-phenyl N-tert-butyl nitron. These showed that most of the free radicals were released in the first 5 minutes of reperfusion and that one could prevent much of the stunning effect if the scavenger was infused immediately before reperfusion. Thus, the evidence is very strong both that O$_2^-$-generated free radicals cause much of the stunning effect and that stunning is a form of reperfusion injury.

There is good evidence that hydroxyl radical (·OH) is the key mediator of stunning. The ·OH is formed from superoxide by Fe-catalyzed reactions (the Haber-Weiss and Fenton reactions) and reacts with phenylalanine to form hydroxylated derivatives. Because these derivatives are present in stunned tissue and can be detected in the coronary effluent if phenylalanine is infused intravenously before reflow, these data clearly establish that the ·OH radical is released during reperfusion. The fact that defereroxamine, which chelates Fe and thereby prevents the Fe-catalyzed reaction that generates ·OH, prevents much of the stunning effect is further evidence that ·OH is the mediator of stunning.

Also, any NO released during reperfusion can react with superoxide to form peroxynitrite, another strong free radical that can cause stunning. Peroxynitrite also is scavenged by MPG.

Because one cannot totally prevent the stunning effect by scavenger administration, it is possible that damage developing while the tissue is ischemic contributes to stunning. The nature of the ischemic damage, if any, that contributes to the stunning effect, however, has never been identified. In addition, the deleterious effect of free radicals may occur even in the presence of therapy, especially if the burden of radicals produced exceeds the local capacity of endogenous protective mechanisms plus the infused scavenger to trap the radicals.

O$_2^-$-derived free radicals react quickly with proteins, phospholipids, and thiols. These reactions are presumed to be indiscriminant, ie, the free radical reacts with whatever susceptible compound is in its path. Unfortunately, it is not known which reaction or reactions cause the stunning problem.

One feature of the biology that is important in terms of analyzing the tissue for targets of the free radicals is the fact that administration of a catecholamine, such as dobutamine, will restore contractile function to control levels. This means that the contractile systems of the myocyte, including those allowing Ca$^{2+}$ entry and sarcoplasmic reticulum function, the myofibrils, and the mitochondria, are sufficient to allow full contraction. Improvement brought about by catecholamines disappears, however, as the catecholamine is cleared from the circulation.

Although oxygen radicals appear to be involved in the mechanism of stunning and it is known that oxygen free radical scavengers enhance the return of function of stunned myocardium in animal models of brief ischemia, they have not shown consistent benefit in human studies of myocardial infarction. Flaherty and colleagues examined the effect of recombinant human SOD on patients undergoing reperfusion therapy for acute myocardial infarction. SOD did not improve patient outcome, nor did it improve regional or global function compared with placebo. It appeared to have had some antiarrhythmic effect early during reperfusion. There are several possible reasons why SOD did not work in this trial. First, an infarction may be too severe an insult to expect a benefit from scavenging oxygen radicals: because an infarcted heart is a mixture of dead myocytes and salvaged myocytes, it is not a model of pure stunned tissue. Second, SOD does not cross the cell membrane; to show a benefit, a more powerful oxygen radical scavenger may be needed that can cross the cell membrane. Third, SOD may not have been on board early enough. There has been little other information in the literature regarding the effect of oxygen radical scavengers in human trials specific for stunned myocardium. In other trials in which oxygen radical scavengers, such as vitamin E, were administered long-term to patients with coronary artery disease or risk factors for coronary artery disease (such as the HOPE trial), the results have been equally disappointing. On the basis that the stunning effect may cause potentially correctable acute congestive failure in individual patients, the effect of scavengers on stunning itself needs a detailed clinical trial.

**Mechanism of Contractile Failure in Stunning**

The exact change or changes that lead to the failure of contraction in stunning are unknown. Among the possibilities are any alterations in the availability of Ca$^{2+}$ and the sensitivity of the contractile apparatus to Ca$^{2+}$. These are difficult problems to study in vivo. Most data about potential molecular defects in the contractile apparatus have been obtained in the isolated perfused heart or in studies of isolated myocytes. At present, alterations in Ca$^{2+}$ homeostasis seem to be a likely cause. Another theory holds that proteolysis of troponin I is a crucial aspect of the molecular defect of the contractile apparatus that is responsible for stunning. Note that the oxyradical theory and alteration in calcium homeostasis theory are not mutually exclusive. For example, oxygen free radicals could damage membranes, allowing easier calcium overload during reperfusion that could then alter troponin, contributing to reduced myofilament sensitivity to calcium. Alternatively, oxygen radicals might contribute directly to disruption of troponin.
Preconditioning and Stunning

Myocardium that has been preconditioned by a single episode or multiple episodes of ischemia and reperfusion is virtually always stunned. The beneficial effect of preconditioning, however, disappears totally in the dog heart after 180 minutes of reperfusion with arterial blood, even though the stunning exhibited by this tissue is unchanged. Thus, stunning and preconditioning usually coexist but are not necessarily causally related. In vivo, it has not been possible to demonstrate a beneficial effect of classic or early preconditioning on stunning.

Delayed Preconditioning and Stunning

Yellon and coworkers have shown that the protection against cell death exhibited by hearts preconditioned with ischemia returns after 24 hours of reperfusion. This is called “delayed or late preconditioning.” Bolli and coworkers showed that this form of preconditioning protects against stunning (Tang et al) as well as against cell death (Takaro et al). Moreover, Takaro et al established that the protection is mediated by NOS. Increased quantities of NOS are induced (iNOS) in response to the initial episode or episodes of ischemia, with the result that increased quantities of NO are produced during ischemic stress. This NO appears to mediate the protective effect against both stunning and cell death. Furthermore, oxygen-derived free radicals are involved in the genesis of delayed preconditioning in that all of the beneficial effects of iNOS can be prevented by free radical scavengers, such as MPG.

Clinical Evidence for Stunned Myocardium

There are several clinical situations in which stunned myocardium may occur (Table). The clinical situation that would most closely mimic that of the original experimental descriptions of stunned myocardium is controlled coronary artery occlusion in the setting of percutaneous transluminal coronary angioplasty. Initial studies that investigated the effects of angioplasty on coronary function induced coronary occlusions that were 60 seconds in duration, too short to induce prolonged systolic wall motion abnormalities. Some groups of investigators, however, observed relatively prolonged abnormalities in diastolic function of the left ventricle for at least 12 minutes after deflation of the angioplasty balloon. Patients exhibited a pressure-volume relationship in which ventricular pressure remained higher for any given ventricular volume long after systolic function had recovered.

Recently, Sheiban and associates determined the effects of a longer balloon inflation on cardiac function. They inflated the angioplasty balloon for 5 minutes in patients and observed depressed function of left ventricular segments as late as 24 hours, with eventual resolution by 36 hours. These observations parallel in many respects the findings of early studies in which the coronary arteries of dogs were occluded for brief periods of time and then reperfused, and they provide some of the most compelling evidence for the existence of stunned myocardium in humans.

Evidence for stunned myocardium also was observed in patients with unstable angina and now in patients with stress-induced ischemia. Homans et al subjected dogs to coronary artery stenosis plus treadmill exercise testing. Regional left ventricular wall motion abnormalities developed with ischemia and then persisted for at least 60 to 120 minutes after cessation of exercise. Parallel studies have now been reported in patients. An initial echocardiographic study by Robertson et al showed that 4 of 8 patients with double-vessel coronary artery disease and 2 of 2 patients with triple-vessel disease demonstrated a persistent wall motion abnormality 30 minutes after cessation of exercise. To study this phenomenon further, regional wall motion was assessed by 2D echocardiography in coronary patients at rest, immediately after exercise, and at 15 and 30 minutes after exercise. In these patients, most of whom had severe multivessel coronary artery disease, new wall motion abnormalities were observed in 73% of patients during exercise; 95% exhibited persistent wall motion abnormalities at 15 minutes after exercise; and 90% had persistent wall motion abnormalities at 30 minutes after exercise. Because the wall motion abnormalities persisted after cessation of exercise, after resolution of angina and ECG abnormalities, they were not due to ongoing ischemia. Ambrosio et al confirmed and extended these findings by noting that persistent postexercise wall motion abnormalities occurred at a time when myocardial perfusion had recovered fully. The fact that these investigators showed a mismatch between function (depressed) and coronary perfusion (restored) further supports the concept that relatively brief episodes of demand-induced ischemia can result in stunned myocardium in humans. Recently, other forms of stress testing have been shown to cause stunning in
patients, including pharmacological stress testing with dobutamine and dipyridamole.\textsuperscript{74,75}

Stunned myocardium most certainly occurs after reperfusion for acute myocardial infarction, but this picture is complicated by a heart that contains both irreversibly injured cells (necrosis) and cells that have been reversibly injured by ischemia/reperfusion, the salvaged myocardium. The analysis by Reimer and Jennings\textsuperscript{76} showed that after an abrupt coronary artery occlusion, there is a progressive wave front of cell death in the left ventricle that moves across the wall of the heart from the subendocardial to subepicardial layer (see Figure 1). Myocardium salvaged by reperfusion is located primarily in the subepicardium and midmyocardium and displays properties of stunned myocardium.\textsuperscript{77,78} Recovery of this tissue can be observed over the course of a week. This tissue, however, lies over a shell of necrotic myocardium that never will recover function. There may be a degree of tethering that occurs between the shell of infarcted tissue and viable myocardium that overlies it (Figure 1), which can complicate interpretation of what is happening to regional wall motion after reperfusion of an infarct. To further complicate matters, changes in geometry occur as the infarct heals, with the potential for scar shrinkage (in which the size of the scar will be smaller than the size of the original infarct) or infarct expansion and aneurysm formation (in which the size of the scar will be larger than the size of the original infarct). The noninfarcted wall of the ventricle may develop eccentric hypertrophy. Despite these confounding variables, a number of studies that have examined regional wall motion of the left ventricle in patients receiving reperfusion with intracoronary, intravenous thrombolytic agents or angioplasty have shown delayed return of function that required anywhere from 3 days to 6 months.\textsuperscript{38,39,63,64,79} It is likely that the component of delayed recovery due to stunning occurs over a period of weeks rather than months.

Two studies assessed return of regional wall motion after reperfusion in relationship to the risk zone or infarct size.\textsuperscript{80,81} Ito et al\textsuperscript{80} measured ischemic risk zone in patients by performing myocardial contrast echocardiography before reperfusion and simultaneously measuring serial endocardial length of the zone of abnormal contraction assessed by echocardiography. They measured a ratio of endocardial length of abnormal contraction to that of the contrast defect. On day 1, the ratio was 1. On day 2, it was 0.93; on day 3, it was 0.81; on day 7, it was 0.80; on day 14, it was 0.73; and on day 28, it was 0.72. Recovery of function stabilized by day 28. Hence, within the risk zone, defined by an echo contrast agent, the zone of left ventricular dysfunction diminished over time, suggesting recovery of viable but stunned tissue.

Christian et al\textsuperscript{81} studied a measure of myocardial infarct size by performing \textsuperscript{\textsuperscript{99}Tc}-sestamibi perfusion tomographic imaging at hospital discharge. Left ventricular ejection fraction also was measured at hospital discharge and then at 6 weeks. Infarct size was used to predict ejection fraction. Patients received reperfusion with either thrombolytics or angioplasty. Forty-eight of 84 acute infarction patients showed a match between infarct size and predicted ejection fraction at 6 weeks. Twenty-one patients (25%) showed a discharge ejection fraction that was lower than what would have been predicted from infarct size assessment. Furthermore, in these patients, ejection fraction increased from 41% at discharge to 47% at 6 weeks, suggesting recovery of stunned myocardium in this group. Numerous other articles demonstrate slow recovery of ventricular function after reperfusion therapy for acute myocardial infarction; these are discussed in depth in other review articles.\textsuperscript{38,39,63,64,79}

Post–cardiopulmonary bypass is one clinical area in which stunned myocardium can pose a significant problem.\textsuperscript{63,82} Early studies by Gray et al\textsuperscript{83} revealed that patients undergoing uncomplicated coronary artery bypass graft surgery with crystalloid cardioplegia exhibited reduced left ventricular ejection fraction and left ventricular stroke volume index during the first postoperative day. Recovery of ejection fraction had occurred by 48 hours; however, left ventricular stroke work index was still depressed at this time. Starling curves also were depressed during the first 2 days after surgery. Breisblatt et al\textsuperscript{84} described prolonged recovery of left ventricular function after coronary artery bypass surgery in which intermittent blood cardioplegia was given to preserve the myocardium. Although this type of cardioplegia is supposed to provide excellent protection of the heart during cardiopulmonary bypass, 96% of patients demonstrated post-operative decreases in left and right ventricular ejection fraction, as determined by radionuclide angiography. Left ventricular ejection fraction was depressed maximally at 262 minutes after surgery and required 24 to 48 hours to recover. Using a pulsed-Doppler ultrasonic probe to measure systolic wall thickening, Bolli et al\textsuperscript{85} showed a decrease in left ventricular wall thickening in patients after cardiac surgery requiring 24 to 48 hours for recovery. Several other reports in the literature describe prolonged return of function after cardiopulmonary bypass.\textsuperscript{82} This phenomenon occurs independently of preload, afterload, and the type of cardioplegia that was administered. Postoperative stunning is a common clinical occurrence, and patients often require inotropes for the first hours to days after surgery until the stunning resolves.

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