Clinical Progress

Myocardial ‘Stunning’ in Man

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The progress of medicine is often driven by the development of new ideas in the experimental laboratory and their subsequent application to clinical practice. Sometimes the clinical usefulness of these ideas may not be evident when they are first formulated but becomes apparent after a period of time. The concept of postischemic myocardial dysfunction, or “myocardial stunning,”1 is a classic example of these patterns. Initially described by Vatner’s group in 1975 (Heyndrickx et al.), for several years this phenomenon received little or no attention among cardiologists because at that time coronary reperfusion was thought to be a rare occurrence. Postischemic dysfunction was regarded primarily as a laboratory curiosity. During the 1980s, however, the widespread use of thrombolytic therapy and other forms of interventional recanalization for the treatment of acute ischemic syndromes, coupled with the recognition that many patients with coronary artery disease experience spontaneous reperfusion after coronary spasm or thrombosis, led to a remarkable growth of interest in the phenomenon of myocardial stunning.

Indeed, as shown in Figure 1, in the past decade there has been an impressive increase in the number of publications dealing with stunning at the experimental animal level, followed after a 3–5-year lag by a similar increase at the clinical level. The phenomenon of stunning is now commonly invoked by cardiologists to explain a variety of clinical observations. Decisions to revascularize hypokinetic myocardial regions are based on the presumption that the contractile dysfunction is caused by stunning. New therapies designed to prevent stunning are being investigated in preclinical studies, and soon will be tested in clinical trials. In short, the concept that the myocardium can remain reversibly depressed for extended periods of time after ischemia is changing our understanding of the pathophysiology of coronary artery disease and our approach to the management of this disorder.

The purpose of this essay is to review critically—and in detail—the available information regarding the occurrence of myocardial stunning in humans and to discuss the pathophysiological and therapeutic implications of this concept in the clinical arena. The problems inherent in the recognition and differential diagnosis of stunning will be emphasized, and the major gaps of knowledge and areas for future research will be identified. This article will not address the pathogenesis, pathophysiology, and therapy of stunning in experimental animals, all of which have recently been reviewed elsewhere.3,4

Definition of Myocardial Stunning and 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. A clear definition of these terms is essential to avoid confusion. 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 Implicit in this definition is that postischemic dysfunction is a fully reversible abnormality, provided of course that sufficient time is allowed for the myocardium to recover. Thus, the diagnosis of stunning in patients requires demonstration of two major points: 1) that the contractile abnormality is reversible and 2) that the dysfunctional myocardium has normal or near-normal flow (Table 1). While the first point has frequently been documented, only in rare instances has the second point been demonstrated in clinical studies (see below).

The definition of hibernating myocardium is more difficult because, unlike the concept of stunning, which was initially developed and characterized in experimental models and subsequently extended to humans, the concept of hibernation is derived from clinical observations5–9 and has not been investigated extensively in animal studies (there are still no experimental models of chronic hibernation). Consequently, the pathophysiology and pathogenesis of hibernating myocardium are unknown. This term has been used to describe different things. A reasonable definition of hibernating myocardium could be that of a persistent (at least several hours) contractile dysfunction that is associated with reduced coronary flow but preserved myocardial viability. 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.8,9 Once coronary flow is restored, the dysfunction is completely reversed.5–9 The diagnosis of hibernation has been made in patients in whom regional contractile abnormalities 1) are detected during angina-free intervals, 2) are associated with reduced perfusion, and 3) are corrected by coronary revascularization (Table 1).5–9
Thus, stunning and hibernation have in common the fact that in both cases the left ventricular (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.

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. First, although stunning often involves regional contractile abnormalities, none of the methods available to measure regional myocardial function in humans (contrast ventriculography, radionuclide angiography, two-dimensional echocardiography) offers accuracy and resolution comparable to those of sonomicrometry in experimental animals. For example, reproducible detection of a relatively minor (e.g., 25%) change in regional wall motion in patients would be problematic. Second, many factors that have a major influence on the mechanical function of the stunned myocardium (i.e., 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. For example, catecholamine levels are generally higher at the onset of an acute myocardial infarction (AMI) than before hospital discharge; on the other hand, at the time of discharge many patients receive preload-reducing, afterload-reducing, and negative or positive inotropic agents that were not being administered at the onset of the AMI. Third, it is difficult to measure regional myocardial blood flow during acute myocardial ischemia in humans; even when this is done, the accuracy of the measurements is not comparable to that obtainable with radioactive microspheres in experimental animals. Because the severity of ischemia is the primary determinant of the severity of postischemic dysfunction,10 the inability to quantify ischemic flow makes it arduous to distinguish situations in which stunning is likely to be significant from situations in which it is likely to be mild or even absent.

Perhaps the major problem encountered in clinical studies, however, is to discern whether a reversible defect of contractility is caused by stunning, silent ischemia, or hibernation. This problem is illustrated in Figure 2. When a patient experiences an episode of angina (at rest or on exertion), one cannot usually establish whether, after the resolution of the clinical symptoms, blood flow to the ischemic region is completely restored. If reperfusion occurs in the presence of a tight coronary stenosis, or if the thrombus or spasm responsible for the acute ischemic event resolves gradually rather than rapidly, then there could be persistent subendocardial ischemia that, depending on its severity, could be painless or not even detectable on the electrocardiogram but nevertheless could be sufficient to prevent full recovery of contractile function (Figure 2, panel B). Thus, silent ischemia occurring after an episode of painful ischemia could mimic stunning. Silent ischemia could also mimic stunning when it develops de novo. In this case, measurements taken during the episode of painless ischemia would reveal a contractile abnormality that disappears later on, when ischemia resolves; if silent ischemia is not recognized, the dysfunction could be erroneously ascribed to delayed recovery from a previous attack of angina (Figure 2, panel C). Finally, an incorrect diagnosis of stunning could be made in the presence of hibernating myocardium. Because hibernation will resolve after blood flow is restored (either spontaneously or therapeutically), patients who develop hibernating myocardium may exhibit an impairment of LV wall motion followed by an improvement, which, again, could be interpreted as delayed recovery from an acute ischemic episode (Figure 2, panel E). On the other hand, it is conceivable that stunning might sometimes coexist with hibernation and/or silent ischemia. Bouts of silent ischemia may cause a loss of function during the reduction of flow followed by slow recovery (i.e., stunning) after perfusion is restored (Figure 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 (Figure 2, panel F). Finally, a phase of stunning may follow a phase of hibernation (Figure 2, panel G), in accordance with recent observations11-13 suggesting that revascularization of hibernating myocardium results in slow improvement of function despite rapid normalization of flow. Taken together, all of these considerations emphasize the need for rigorous criteria in diagnosing stunned myocardium.

![Figure 1. Bar graph showing the number of full-length original manuscripts published on the topic of myocardial stunning since 1982, when this term was coined by Braunwald and Kloner. The papers were identified through a MEDLINE literature search using the following key words: stunned myocardium, myocardial stunning, and postischemic myocardial dysfunction. Reviews and abstracts are not included in this figure.](image-url)

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<th>Table 1. Differential Diagnosis of Reversible Contractile Dysfunction Observed During an Angina-Free Interval*</th>
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*This table is concerned only with reversible contractile dysfunction that is observed at a time when the patient is not experiencing angina. 18FDG, 18F-deoxyglucose.
would pattern function could situation stunning. If flow episode myocardium because flow, is ischemic episodes of and/or a caused by stunning (i.e., by thrombosis and/or vasoconstriction). Note that function is initially downregulated to a low level 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 caused by a combination of ischemic dysfunction (during the brief decreases in flow), stunning (during the slow return of function to the downregulated level after each brief flow reduction), and hibernation. Panel 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. Panel 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 and 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 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.

The critical difference between stunning, silent ischemia, and hibernation is that myocardial perfusion is normal or near normal in the first condition but reduced in the other two (Table 1). 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 quantify the level of perfusion in the LV regions that were thought to be stunned.

In summary, there are numerous problems in detecting postischemic contractile dysfunction in patients. The chief difficulty stems from the confounding effects of
silent ischemia and hibernation, two conditions that could either mimic stunning or coexist with it. Future studies should measure myocardial perfusion and function at the same time in order to differentiate stunned myocardium from silently ischemic or hibernating myocardium. It is essential to keep in mind that the reversibility of a contractile abnormality, in itself, does not necessarily indicate stunning.

Evidence for the Occurrence of Myocardial Stunning in Man

The major clinical situations in which myocardial stunning could occur are summarized in Table 2, along with their correspondent experimental settings. The common denominator to all of these situations is the fact that the heart is exposed to an episode of transient ischemia followed by reperfusion.

Myocardial Stunning After Ischemia Induced by Percutaneous Transluminal Coronary Angioplasty

In experimental animals, stunned myocardium is classically observed after a brief coronary occlusion followed by reperfusion. 3 Percutaneous transluminal coronary angioplasty (PTCA) resembles this setting in that a coronary artery is completely occluded during balloon inflation and abruptly reperfused upon deflation, thus creating a situation of transient ischemia that could, in theory, cause myocardial stunning (Table 2). Compared with other clinical situations, PTCA offers several advantages for investigating postischemic dysfunction: 1) it is possible to obtain baseline (preischemic) measurements of function, 2) the artery is uniformly occluded in all patients, 3) the duration of occlusion is precisely known and is reasonably similar in different patients, 4) the persistence of a flow-limiting stenosis after reperfusion is unlikely,14 5) the presence of collaterals can be assessed by angiography, 6) other potentially confounding variables (loading conditions, hemodynamics, etc.) can be kept reasonably stable, and 7) sophisticated measurements of LV function can be obtained by use of high-fidelity pressure transducers in conjunction with LV angiography.14

Despite these considerations, however, one should not expect significant postischemic dysfunction after PTCA because the duration of the coronary occlusion is too short (usually <2 minutes). Experimental studies indicate that when the ischemic period lasts only 1–2 minutes, the recovery of systolic function is very quick, and any persistent deficit, if present, is so small that it is unlikely to be detected with clinically applicable methods. For example, no appreciable decrease in segment shortening is observed after a single 100-second coronary occlusion in conscious dogs15; after a single 3-minute occlusion in open-chest dogs, systolic shortening is decreased by <10%.16 Although multiple consecutive 3-minute occlusions have additive effects,16 the cumulative decrease of systolic shortening reported after five 3-minute occlusions is still relatively small (≤ -30%).16 and would certainly be smaller with occlusions lasting <2 minutes.

In view of these facts, it is not surprising that no persistent impairment of myocardial systolic performance has been found after PTCA-induced ischemia. For example, Serruys et al14 observed that, after four to six balloon inflations (average duration of each inflation, 51 seconds; average total occlusion time, 252 seconds), the regional wall motion abnormalities disappeared within 5 minutes after completion of the PTCA procedure, concomitant with the normalization of myocardial lactate metabolism; the indexes of ventricular relaxation (peak negative dP/dt and early time constants of relaxation) also returned to normal within 5 minutes.14 The authors concluded that four to six coronary occlusions of 40–60 seconds do not cause any persistent abnormality in myocardial mechanics.14 Many subsequent studies using either contrast ventriculography17 or two-dimensional echocardiography18–22 have confirmed that regional LV wall motion recovers promptly (in <2 minutes) and completely after balloon deflation and that multiple consecutive coronary occlusions (up to five to nine inflations of 60–70 seconds19) have no cumulative effect.

It is clear from these results14,17–22 that uncomplicated PTCA does not cause systolic myocardial stunning. A further analysis23 of the patients previously described by Serruys et al,14 however, revealed that despite the rapid normalization of systolic function and isovolumic relaxation, the recovery of diastolic function after PTCA was not complete. In this report, Wijns et al23 assessed global LV chamber stiffness from the LV pressure-volume relation and regional LV chamber stiffness from the LV pressure–segment radius length relation using high-fidelity transducers and contrast ventriculography. They found that 12 minutes after the end of the PTCA procedure, regional stiffness in the ischemic/reperfused segments was still significantly increased compared with preangioplasty measurements; although global LV chamber stiffness was not significantly increased after PTCA, it remained above preangioplasty values in five of nine patients.23 Thus, diastolic abnormalities, namely, reduced chamber distensibility, persisted after PTCA at a time when regional systolic function and the indexes of LV relaxation had fully recovered, suggesting that diastolic function may be more sensitive to myocardial stunning than systolic function. Although interesting, these observations23 were limited to nine patients and to the first 12 minutes after PTCA. Larger numbers of patients and longer follow-ups will be necessary to fully assess the clinical importance of the increased chamber stiffness reported by these authors.23 Unlike the observations of Wijns et al,23 persistence of global diastolic
dysfunction after PTCA was not observed by Labovitza, 22 who found that the LV filling dynamics (assessed by Doppler echocardiography) returned to baseline immediately (within 15 seconds) after release of a single balloon inflation. It must be noted, however, that Doppler indexes of LV filling offer only an indirect measure of LV diastolic compliance 24 and that Labovitz et al 22 evaluated the recovery of global (rather than regional) diastolic function after one balloon inflation (as opposed to three to 10 inflations in the Wijns study 25). It is entirely possible that regional ventricular compliance was persistently decreased after the end of the procedure in the patients studied by Labovitz et al. 22

One point that needs to be underscored is that the studies reviewed above 14,17 –22 were conducted in patients with normal baseline LV function and with an uncomplicated PTCA of a single lesion. The immediate recovery of regional wall motion and the lack of cumulative effect of repeated inflations observed in these studies may not necessarily apply to patients with underlying depression of LV function, with unstable angina, or with severe multiple-vessel disease. Moreover, the recovery from PTCA-induced ischemia is likely to be delayed by complications (such as arterial dissection or abrupt occlusion) that prolong the duration of coronary occlusion. There is little, if any, quantitative information regarding the impact of PTCA in these situations.

In summary, the brief ischemia associated with simple, uncomplicated PTCA is not sufficient to cause prolonged systolic abnormalities, even after multiple balloon inflations; however, it may induce persistent diastolic abnormalities manifested as a decrease in LV compliance. The exact incidence, severity, and duration of such diastolic derangements remain unknown, but in any case, they are obviously well tolerated in patients with intact contractile reserve. What remains to be elucidated is whether the sequelae of PTCA-induced ischemia can be more pronounced in less favorable situations, specifically, in patients with baseline LV dysfunction, unstable angina, severe multiple-vessel disease, and complicated PTCA.

Myocardial Stunning in Unstable Angina

It seems logical to expect myocardial stunning in patients with unstable angina because this syndrome is caused by transient episodes of ischemia that are often severe but, by definition, do not produce irreversible damage. 25 The presence of stunning would seem more likely in this condition than in situations such as PTCA (where ischemia is shorter) or exercise (where ischemia is milder). Rest angina (a major form of unstable angina) is usually caused by a reduction of coronary flow that resolves spontaneously in a matter of minutes. 26 As such, it resembles the "classic" animal model of stunned myocardium produced by a completely reversible (<20-minute) ischemic insult, 2 and indeed it could be considered the clinical counterpart of this experimental setting (Table 2).

In practice, however, conclusive demonstration of stunning in unstable angina is hindered by some major difficulties. The first problem is the heterogeneous nature of this syndrome, which spans from severe angina at rest to exercise-induced chest pain.25 Even within the setting of angina at rest, the coronary obstructions responsible for the symptoms can range from a complete luminal occlusion to variable degrees of incomplete occlusion, 26 and in some patients angina may be caused primarily by an increase in oxygen demands rather than by a decrease in supply. 25 Thus, the syndrome of unstable angina encompasses a broad spectrum of conditions that differ importantly with respect to the severity of the ischemic insult. Inasmuch as the severity of ischemia is the major determinant of the severity of stunning, 10 one would expect a broad spectrum of postischemic contractile abnormalities in unstable angina. The mildest abnormalities probably develop in patients with exertional chest pain, in whom little or no postischemic dysfunction may be detectable. At the other end of the spectrum are patients with rest angina and transient ST segment elevation associated with transient complete coronary occlusion, in whom marked depression of contractility may persist after the pain. Patients with chest pain at rest and incomplete coronary occlusion probably fall into an intermediate category. Thus, postischemic dysfunction in unstable angina is likely to be quite variable, just as the manifestations of ischemia can be quite variable. To complicate matters further, different investigators use different definitions of unstable angina 25

The second problem is the presence of an unstable atherosclerotic plaque between successive episodes of angina, which may lead to fluctuations of coronary cross-sectional area as a result of continuous changes in thrombus size and/or vasomotor tone. 26 This situation may cause moderate, painless reductions in subendocardial perfusion (i.e., silent ischemia), which could either persist after an episode of angina (Figure 2, panel B) or develop de novo between one anginal attack and the next (Figure 2, panel C). In either case, asymptomatic subendocardial ischemia could mimic stunning, as noted earlier (Figure 2, compare panels A, B, and C). The demonstration of reversible perfusion deficits 27–29 and electrocardiographic evidence of ischemia 30,31 during pain-free periods in patients with unstable angina lends support to this supposition and greatly complicates the interpretation of reversible wall motion abnormalities.

These difficulties are compounded by the fact that the literature contains a surprising paucity of data regarding the occurrence of postischemic dysfunction in unstable angina. In contrast to the settings of PTCA-induced ischemia, exercise-induced ischemia, AMI, and cardiac surgery, there is no published report in which the recovery of regional function was serially monitored in this syndrome. The only data available are the results of studies 29-32 –36 that measured ventricular function at two time points: shortly after hospital admission (during the acute phase of unstable angina) and several days or weeks later (after the syndrome had resolved). These studies 29,32–36 have consistently documented an improvement of wall motion from the first to the second time point, both with medical therapy 29,36 and with mechanical revascularization (either PTCA 34–36 or coronary artery bypass grafting [CABG] 29,32). Because all of the measurements were obtained when the patients were pain-free, 29,32–36 the reversible abnormalities noted on admission could have represented myocardial stunning secondary to earlier acute ischemia.

A review of these studies 29,32–36 is in order to understand the major gaps of knowledge that still remain.
Initial observations made in the 1970s documented improvement of regional myocardial function after CABG in many patients with unstable angina. Nixon et al subsequently provided evidence that the mechanical dysfunction associated with unstable angina can be reversible even in the absence of CABG (or PTCA). Using two-dimensional echocardiography, these authors studied patients treated with medical therapy only and found that in five of 11 subjects, the regional wall motion abnormalities noted at the time of admission had disappeared by the time of discharge (7–10 days later). Analogous observations were recently reported by de Zwaan et al in 18 patients who were managed with medical therapy.

With the advent of PTCA, several investigators demonstrated partial or complete resolution of wall motion abnormalities after this procedure. For example, de Feyter et al assessed regional LV function by contrast ventriculography in 68 patients with angina at rest who underwent successful PTCA. They found that regional wall motion was abnormal before PTCA (at an average of 43 hours after the last episode of chest pain) but was significantly improved on repeat angiographic examination 3 months later. In the subset of patients with PTCA of the left anterior descending coronary artery (LAD), this improvement in regional function was associated with a significant increase in global LV ejection fraction (LVEF), presumably because of the large territory subserved by the LAD. Other studies similarly suggest that patients with LAD disease constitute a particularly suitable subset for demonstrating the reversibility of the wall motion abnormalities associated with unstable angina. Renkin et al observed a striking improvement in anterior LV wall motion, as well as in global LVEF, in 32 patients with angina at rest and critical LAD lesions who were studied by contrast angiography before and 6 months after successful PTCA of the LAD. All of these patients had persistently negative T waves in the precordial leads before PTCA; by contrast, no improvement in regional wall motion was noted in a comparable group of patients with positive T waves before PTCA. Consonant findings were obtained by de Zwaan et al in 35 patients with unstable angina, inverted T waves in the precordial leads, and proximal LAD disease. Regional wall motion was abnormal on the initial echocardiographic study (performed at an average of 24 hours after the last episode of chest pain) but improved on the repeat study 2 months later, regardless of whether mechanical revascularization or medical therapy was used. Interestingly, in an earlier report, these investigators had noted that the presence of contractile abnormalities in a similar group of patients depended on the interval elapsed between the last episode of chest pain and the LV angiography: in 137 patients with wall motion abnormalities, this interval averaged 4.1 days, whereas in 43 patients without wall motion abnormalities, it was significantly longer (6.4 days), suggesting delayed recovery from the previous anginal attack as the mechanism for the impaired contractility. Both Renkin et al and de Zwaan et al noted that resolution of the mechanical dysfunction was associated with normalization of the T waves. They concluded that persistently negative T waves in the precordial leads identify a subset of patients with unstable angina in whom wall motion abnormalities are often reversible.

To gain insights into the time course of the contractile abnormalities, in a recent study we used two-dimensional echocardiography to serially assess the recovery of LV function after an episode of chest pain at rest in six patients with unstable angina. Regional wall motion abnormalities were noted at the end of the anginal episode in all cases. The improvement of these abnormalities was found to be slow, such that in five of the six patients, regional LV dysfunction persisted for hours after the pain had ceased.

In view of all of these studies, there can be no doubt that unstable angina is associated with wall motion abnormalities that persist during the pain-free intervals (particularly in patients with persistently negative T waves) and that eventually resolve, either with medical therapy or after mechanical revascularization. The critical question is what causes these abnormalities. Are they the consequence of previous bouts of acute ischemia that leave behind prolonged postischemic dysfunction, i.e., stunning (Figure 2, panels A and D)? Are they the manifestation of a persistent, moderate reduction of coronary flow that is associated with an adaptive decrease of myocardial contraction, i.e., hibernation (Figure 2, 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, i.e., silent ischemia (Figure 2, panel C)?

All three explanations are possible. Stunning could develop after a brief ischemic episode (painful or painless) and persist for hours or days. Hibernation (of variable duration) could also develop in the setting of a critical or subtotal coronary stenosis, such as that present in unstable angina. Finally, silent ischemia has been reported in many patients with unstable angina. The observation of increased glucose uptake in the absence of perfusion abnormalities in patients with unstable angina suggests the presence of prolonged metabolic derangements after a transient ischemic episode and would be consistent with stunning. On the other hand, the presence of reversible perfusion defects during pain-free intervals in patients with unstable angina is well documented and is compatible with either hibernation or silent ischemia. It should be noted that bouts of silent ischemia could cause not only ischemic dysfunction during the phase of flow reduction (Figure 2, panel C) but also postischemic dysfunction (i.e., stunning) during the phase of flow restoration (Figure 2, panel D). For example, the observation that among patients with unstable angina, the LVEF is lower in those with silent ischemia than in those without it is compatible with a persistent depression of contractility after asymptomatic bouts of ischemia, i.e., with stunning.

As emphasized earlier, the most conclusive way to discern stunning from hibernation and ongoing silent ischemia is to measure regional perfusion simultaneously with regional function. Another helpful approach would be to monitor the changes in contractile function at serial times: a relatively steady depression would be consistent with hibernation, “dips” followed by slow recoveries would favor stunning, and dips followed by
quick normalizations would suggest silent bouts of ischemia (Figure 2, panels E, D, and C, respectively).

In summary, unstable angina is associated with reversible wall motion abnormalities, at times striking. Although these abnormalities are consistent with stunning, they could also be caused by hibernation, ongoing silent ischemia, or some combination thereof. To resolve this issue, it is essential that future studies measure regional function and flow at the same time (or in close temporal proximity). It is also important that the time course of the contractile abnormalities be characterized with sequential observations. Patients with proximal LAD lesions and persistently negative T waves on precordial leads often exhibit an improvement in wall motion, and thus could be an appropriate subset to investigate stunning in unstable angina. In this connection, further research will be needed to determine whether sustained T wave inversion is an electrical marker of stunned myocardium or an indicator of persistent subendocardial hyperperfusion resulting in hibernation or both.

**Myocardial Stunning in Variant Angina**

Variant (Prinzmetal’s) angina is another situation in which myocardial stunning would be expected to occur, because this syndrome is caused by vasospasm of an epicardial coronary artery resulting in transmural myocardial ischemia, a situation that is similar to the brief transmural ischemia used to produce stunning in experimental animals (Table 2).3 However, investigation of postischemic dysfunction in Prinzmetal’s angina is fraught with many of the problems discussed above for unstable angina and is further hindered by the comparatively lower prevalence of this condition.

The available evidence for the occurrence of stunning in variant angina consists of three case reports. Takatsu et al40 noted akinesis of the anterior LV wall in a patient studied with contrast ventriculography shortly after recurrent attacks of vasospastic angina associated with minimal elevation of cardiac enzymes. Following the last anginal attack, the wall motion abnormalities gradually resolved, but complete normalization required approximately 2 weeks. Mathias et al41 described a patient with recurrent coronary vasospasm who demonstrated prolonged postischemic LV dysfunction by radionuclide angiography at a time when resting thallium scintigraphy showed normal perfusion. There was no evidence of myocardial infarction. The contractile abnormality (a large akinetic area involving the anteroseptal and apical walls) resolved almost completely over the ensuing 10 days. The importance of this observation41 lies in the fact that unlike most studies dealing with stunning, it demonstrates that regional perfusion was fully restored at a time when regional wall motion was still depressed, thereby excluding silent ischemia or hibernation as possible explanations for the persistent contractile dysfunction. Fournier et al42 reported a similar case of Prinzmetal’s angina in which marked anterograde hypokinesis (noted during pain-free intervals) persisted for days and then gradually disappeared. This regional wall motion abnormality was severe enough to produce clinical signs of LV failure.42 It is of interest that in all three of these cases,40-42 the reversible contractile dysfunction was associated with T wave inversion, in analogy with the observations made in unstable angina35,36 (see above). This raises again the possibility that persistently negative T waves may be an electrocardiographic correlate of stunned myocardium.

In apparent contrast with these anecdotal observations,40-42 Distante et al34,44 failed to detect persistent abnormalities in a large series of patients with Prinzmetal’s angina in whom regional wall motion was continuously monitored during and after an ischemic episode by M-mode echocardiography (29 episodes, 12 patients)43 or two-dimensional echocardiography (55 episodes, 20 patients).44 All patients had ST segment elevation, suggesting transmural ischemia. After the ischemic episode, approximately half of the patients actually exhibited a transient overshoot of wall motion above preischemic levels,44 which is reminiscent of observations made in dogs after a 100-second coronary occlusion43 and in humans after the brief occlusion associated with PTCA.19,20

Given that variant angina is usually associated with transmural ischemia, how can one reconcile the rapid recovery of contractility noted in this syndrome43,44 with the possibility that postischemic dysfunction may occur in unstable angina,39,42-46 as discussed above? There are several possible explanations. First, the severity of postischemic dysfunction is affected to a major extent by the duration of the antecedent ischemia.3 The duration of the attacks of Prinzmetal’s angina in the Distante studies34,44 was not reported but was likely short, given 1) the usually prompt response of coronary spasm to nitroglycerin and other vasodilators and 2) the postischemic overshoot in contractility noted by the authors.43,44 A phenomenon that in experimental animals is observed only with short (<5-minute) coronary occlusions. In contrast, many episodes of unstable angina at rest last 10–20 minutes or even longer. Second, Distante et al studied the changes in wall motion after one single attack of Prinzmetal’s angina, whereas the studies of unstable angina discussed above39,42-46 included patients with multiple recurrent episodes of angina, in whom a cumulative effect may have taken place. This would also explain the difference between the results of Distante et al and the three case reports discussed above,40-42 all of which described patients with multiple recurrent attacks of variant angina.

In summary, the available evidence suggests that a single episode of variant angina promptly treated with vasodilators does not usually cause postischemic systolic dysfunction (although the presence of diastolic dysfunction has not been explored), probably because it is too short. In this sense, the setting of Prinzmetal’s angina is not very dissimilar from that of PTCA-induced ischemia. However, the effect of variant angina likely depends on the frequency, severity, and duration of the ischemic attacks; the possibility that recurrent and/or prolonged episodes of variant angina may cause myocardial stunning is plausible and remains to be systematically investigated.

**Myocardial Stunning After AMI With Early Reperfusion**

In patients with AMI, coronary reperfusion may occur either spontaneously or as a result of interventional recanalization (thrombolytic therapy and/or PTCA). When reperfusion begins early after the onset of ischemia, variable amounts of subepicardial tissue
otherwise destined to die are salvaged, so that a potentially transmural infarction is converted into a subendocardial infarction. This situation resembles experimental models of coronary occlusion lasting 2 hours or less, in which the subepicardial region salvaged by reperfusion exhibits a slow recovery of contractility (Table 2).45,46

Indeed, studies assessing the recovery of regional LV function after thrombolysis and/or PTCA uniformly indicate that the improvement does not occur immediately after reperfusion but instead is delayed for several days, a time course similar to that observed in experimental animals.45,46 Reduto et al47 noted that in patients reperfused with intracoronary streptokinase, the LVEF did not change between before and immediately after reperfusion but increased significantly at hospital discharge. Anderson et al48 reported the effects of intracoronary streptokinase on regional wall motion (assessed by two-dimensional echocardiography) in patients successfully reperfused within 5 hours of the onset of symptoms of AMI. Although there was an improvement in wall motion at 1 day after recanalization compared with before recanalization, regional function continued to improve between 1 and 10 days after reperfusion, at which time it apparently stabilized. In a cohort of patients recanalized with intracoronary streptokinase within 6 hours of the onset of symptoms, Stack et al49 noted that percent radial shortening in the infarct-related region (assessed by LV contrast angiography) did not change between before and 24 hours after lysis (8±4% versus 8±3%, respectively). At 16 days after reperfusion, however, mean radial shortening had increased to 18±5%. Because of resolution of compensatory hyperkinesis in the nonischemic regions, this improvement in regional wall motion was not accompanied by any change in global LVEF, suggesting that regional indexes are more sensitive than global indexes in assessing the benefits of reperfusion therapy. Indeed, there is now a general consensus that global LVEF is not an optimal parameter to evaluate the extent of salvage and the severity of regional stunning after thrombolysis.

The observation of no immediate change in regional LV function after reperfusion of patients with AMI and of a subsequent improvement over the ensuing days has been a consistent one.50-56 The precise time course of the recovery of myocardial function, however, remains unclear. A study by Schmidt et al57 in 264 patients suggests that the improvement of systolic performance in the reperfused region (measured by contrast ventriculography using the centerline method) is modest in the first 3 days (0.2 SD) and that a considerably greater recovery (1.0 SD) occurs thereafter (i.e., in the interval between 3 days and 6 months) (no measurements were taken between 3 days and 6 months). In contrast, Bourdillon et al58 reported that in 23 patients most of the improvement in regional function (assessed by two-dimensional echocardiography) occurred within the first 3 days (often within 24 hours) and that by 7 days there was only a modest additional improvement. Occasional patients, however, exhibited significant improvement of regional wall motion after 7 days.58 Using radionuclide angiography, Zaret et al59 observed no improvement in regional or global LVEF at rest between hospital discharge (at an average of 9 days after AMI) and the 6-week follow-up in a large cohort of patients enrolled in the TIMI II study; such lack of improvement was noted both in patients assigned to a “conservative” strategy and in those assigned to an “invasive” strategy. In a recent echocardiographic study in 28 patients, Zoghbi et al60 found that the recovery of regional LV function occurred predominantly in the first 10 days; in seven of the 28 patients, however, a further improvement was noted at 6 weeks, suggesting that in some cases myocardial stunning may indeed persist beyond 10 days. This concept is corroborated by the observations of Pfisterer et al,61 who found that LVEF (measured by contrast ventriculography) increased between 9 days and 3–6 months in 17 patients with depressed LVEF at 9 days (no change was noted in patients with normal LVEF at 9 days). The differences between these investigations57-61 probably depend on many factors, including number of patients, time to reperfusion, and method of wall motion analysis.

A recent report by Williamson et al62 indicates that, in patients with AMI who undergo interventional recanalization, LV diastolic filling (assessed by Doppler echocardiography) is abnormal at 24 hours after the onset of the infarction (i.e., soon after reperfusion) and improves by 7 days, suggesting the existence of diastolic stunning in this clinical setting.

An alternative explanation for the delayed recovery of contractility after thrombolytic therapy is that it may be due to the presence of a high-grade, flow-limiting residual stenosis, which could cause persistent subendocardial ischemia or hibernation.63 This hypothesis is supported by the observation that the severity of the residual stenosis appears to be an important determinant of the recovery of function after thrombolytic therapy and that, even in the absence of reclosure, there is no functional improvement when the minimal diameter of the infarct-related vessel is <0.4 mm.64 In the days after administration of thrombolytic therapy, gradual lysis of the thrombus and/or remodeling of the plaque could lessen the severity of the stenosis and bring about a gradual increase in subendocardial flow, thereby resulting in slow recovery of function (Figure 2, panel B). To evaluate this possibility, future studies should measure both stenosis severity (or regional perfusion) and regional wall motion, so that the changes in these two variables can be correlated. Finally, the hypothesis has been raised that some of the improvement in wall motion may reflect increased stiffness of the scar, but this seems unlikely to be an important factor because, in the absence of reperfusion, wall motion generally does not improve.

In summary, studies of patients with AMI have consistently demonstrated that the improvement in systolic and diastolic function of the myocardium salvaged by reperfusion does not occur immediately after reflow. Although most of the improvement takes place within the first 7–10 days after infarction, it is not clear when it can be considered complete. Longitudinal studies using sequential measurements of regional LV function are needed to precisely define the time course of this recovery and to determine whether it extends beyond the first 7–10 days. An important, unresolved issue is how much of this improvement is due to resolution of stunning and how much to gradual lysis of thrombus or decrease in stenosis severity.
Myocardial Stunning After Exercise-Induced Ischemia

Although persistent myocardial dysfunction after exercise-induced ischemia has been well documented in experimental animals,\textsuperscript{65–71} demonstration of this phenomenon in humans remains elusive. The large experience accumulated with radionuclide angiography has consistently indicated that the regional wall motion abnormalities observed during either supine or upright exercise resolve promptly (within 5 minutes) after cessation of exercise,\textsuperscript{72–74} even in patients with three-vessel disease and pronounced LV asynergy during stress.\textsuperscript{74} In contrast, initial observations obtained by two-dimensional echocardiography\textsuperscript{75–77} seem to be compatible with the occurrence of stunning. Robertson et al\textsuperscript{75} performed serial two-dimensional echocardiograms before and up to 30 minutes after treadmill testing. In all six patients with one-vessel coronary artery disease, the wall motion abnormalities induced by exercise resolved within 30 minutes; however, the wall motion abnormalities persisted for at least 30 minutes after exercise in the majority of patients (six of 10) with two- or three-vessel disease.\textsuperscript{75} More recently, Scognamiglio et al\textsuperscript{76} noted that the increased asynergy associated with upright bicycle exercise was still present at 30 minutes after exercise in 22 (84%) of 26 patients. Similarly, Kloner et al\textsuperscript{77} found a persistent deterioration of regional wall motion at 30 minutes after treadmill exercise compared with rest in 19 of 21 patients, at a time when the chest pain and the electrocardiographic abnormalities had resolved. Most of these patients (14 of 19) had three-vessel disease. Interestingly, the percentage of patients exhibiting wall motion abnormalities was greater at 30 minutes (90%) than immediately after exercise (73%), a finding that the authors attributed to increased sympathetic stimulation at the end of exercise. It should be noted that this study\textsuperscript{77} was performed in a selected cohort in whom the diagnosis was known before treadmill testing and the extent of coronary narrowing was severe; hence, the results may be not applicable to the general population of patients undergoing stress testing.

Definitive proof of postexercise stunning in humans will require considerable additional work. First, the reversibility of the wall motion abnormalities observed 30 minutes after exercise\textsuperscript{75–77} has not been demonstrated, because all of the studies discussed above\textsuperscript{75–77} were terminated at this time point. In experimental animals, the stunning induced by a single exercise trial exhibits variable duration depending on several factors\textsuperscript{71,78}; generally, but not always,\textsuperscript{68} it disappears within 2 hours.\textsuperscript{66,67,71} Echocardiographic examinations need to be extended beyond the initial 30-minute postexercise period to document the resolution and the time course of exercise-induced dysfunction.

Second, although the persistence of wall motion abnormalities after exercise\textsuperscript{75–77} is compatible with stunned myocardium, it could also be caused by persistent, mild subendocardial ischemia that is electrocardiographically and clinically silent. A transmural maldistribution of flow, resulting in subendocardial ischemia, is known to be present immediately (1 minute) after cessation of stress\textsuperscript{67,71}; what is unknown is exactly how long this abnormality persists. In a study of dogs with a coronary stenosis, the subendocardial hypoperfusion resolved within 5 minutes after exercise.\textsuperscript{69} In patients undergoing bicycle ergometer testing, however, a regional defect in \textsuperscript{82}Rb uptake was noted to persist as late as 14–20 minutes after cessation of exercise,\textsuperscript{79,80} after angiography and electrocardiographic signs of ischemia had resolved. Conceivably, the duration of subendocardial ischemia varies with the severity of the coronary stenosis, the degree of collateral flow, the intensity and duration of exercise, and the magnitude and duration of the hemodynamic alterations induced by exercise. Since regional myocardial function is closely and almost linearly related to subendocardial perfusion, even a mild (e.g., 20–30%) decrement in subendocardial flow would be expected to produce a parallel (=20–30%) decrement in transmural myocardial contraction.\textsuperscript{9} It is, therefore, important that regional perfusion be assessed in future studies of postexercise myocardial dysfunction.

Finally, as mentioned above, the echocardiographic observations\textsuperscript{75–77} are at variance with the results of numerous studies using radionuclide angiography,\textsuperscript{72–74} which have failed to demonstrate delayed recovery of wall motion beyond the first 5 minutes after exercise. The reason for this discrepancy is unknown, but could relate to the different sensitivities of the two techniques. It is important to bear in mind that the postischemic dysfunction observed after a single exercise trial in experimental animals is a relatively subtle abnormality. For example, in conscious dogs with a coronary stenosis resulting in severe exercise-induced ischemia (sufficient to reduce systolic shortening or thickening by \approx 60\%,\textsuperscript{67,69} 70\%,\textsuperscript{71} or even 80\%),\textsuperscript{68} measurements of contractile function return to \approx 75\% of control values at 15 and 30 minutes after exercise and improve steadily thereafter.\textsuperscript{67,68,71} In some cases, the decrease in function measured at 30 minutes fails to attain statistical significance.\textsuperscript{66} Even when the experimental stenosis is more severe (resulting in a 50\% reduction of resting flow) and the exercise extremely strenuous, systolic shortening recovers to \approx 80\% of control values by 10 minutes after exercise.\textsuperscript{65} Clearly, the detection of such a mild depression of regional function is highly dependent on the sensitivity of the technique used. (Stunning can be more severe after repetitive exercise trials,\textsuperscript{68} but this is not the case in patients undergoing clinical exercise testing.) Unlike radionuclide ventriculography, which reveals only the movement of the endocardial surface, two-dimensional echocardiography allows assessment of LV wall thickening and thus might be more suitable for analyzing relatively subtle changes. A comparison of the two techniques would seem important to further characterize postexercise stunning and to establish whether two-dimensional echocardiography is the method of choice for studying this phenomenon.

If the occurrence of postexercise stunning in patients is confirmed, this concept could have significant implications for several reasons. Stresses such as exercise are a very common (if not the most common) cause of myocardial ischemia. Although a single episode of exercise-induced ischemia produces relatively minor postischemic contractile abnormalities (as noted above), repetitive episodes in close temporal proximity (1 hour apart) have been demonstrated experimentally to have a cumulative effect, causing a progressively greater impairment of systolic function that can become quite severe and persistent.\textsuperscript{68} Thus, resumption of exercise...
shortly after anginal pain might lead to progressive dysfunction. Whether cumulative postexercise stunning should be taken into consideration when prescribing exercise and/or rehabilitation programs to cardiac patients remains unclear. Furthermore, the persistence of wall motion abnormalities in the late recovery period could serve as a marker of exercise-induced ischemia and thus could enhance the diagnostic usefulness of stress echocardiography. Finally, it is interesting to note that in animals with pressure-overload LV hypertrophy, exercise can induce prolonged mechanical dysfunction even in the absence of epicardial coronary artery stenosis.70 If these results are applicable to humans, post-exercise stunning could be particularly pronounced in patients with LV hypertrophy.

Because the mechanical derangements observed in postischemic myocardium are associated with distinctive biochemical perturbations,13 there has also been interest in the aftereffects of exercise on myocardial metabolism in humans. Camici et al80 used positron emission tomography (PET) to assess myocardial blood flow and glucose uptake in eight patients undergoing a treadmill test. In seven of the eight patients, the uptake of 18F-2-fluoro-2-deoxyglucose in the previously ischemic regions increased for at least 1 hour after exercise above the levels observed in the nonischemic regions, suggesting enhanced glycogen resynthesis and/or glycolytic flux in the postischemic myocardium. Although these results do not necessarily indicate stunning, they do suggest that a brief episode of exercise-induced ischemia can provoke prolonged metabolic abnormalities. Further studies are needed to characterize the time course of this increased glucose uptake in larger groups of patients and to clarify its relation to the recovery of regional wall motion.

In summary, a limited number of echocardiographic observations suggest that exercise-induced ischemia may result in prolonged contractile abnormalities. Although these observations are consistent with myocardial stunning, they do not represent conclusive proof because the reversibility of such abnormalities remains to be demonstrated, because the persistence of subendocardial ischemia needs to be ruled out, and because the apparent discrepancy between echocardiographic and scintigraphic studies has not been resolved. The occurrence and severity of postexercise stunning probably depend on the intensity and duration of exercise71 and on the severity of the coronary inflow restriction.78 In general, however, it seems clear that this is a mild abnormality, which is probably the reason why it has been so difficult to document.

Myocardial Stunning After Cardiac Surgery

Despite improvements in operative techniques and methods for myocardial protection, postoperative LV dysfunction remains a common problem in patients undergoing cardiac surgery. Because in these patients the heart is rendered globally ischemic during aortic cross-clamping and then reperfused, and because in most cases no myocardial necrosis is demonstrable, the most likely explanation for this postoperative dysfunction is that it represents a form of global myocardial stunning, in analogy with observations made in experimental models of cardiopulmonary bypass (Table 2).3,81

Concerns regarding the adequacy of myocardial preservation during cardiac surgery have prompted extensive investigation of the rate and extent of the postoperative recovery of contractility.82-94 Despite some differences, the general consensus that emerges from this large body of literature82-94 is that a transient depression of myocardial function is common in the postoperative period. For example, Gray et al82 reported a decrease in cardiac index, LV stroke work index, and LVEF at 1–5 hours after CABG, with full recovery occurring by 48 hours. Similar results were obtained by Roberts et al84,85 in 40 patients undergoing CABG. The average LVEF fell from 50% before surgery to 38% 2 hours after surgery and returned to preoperative levels by 24 hours; this decrease in LVEF occurred in 90% of the patients (36 of 40) and was accompanied by a decrease in cardiac index and LV stroke work index.84,85 Reduto et al86 found a significant decline in LVEF 2–5 hours after CABG in 26 of 57 patients, with full recovery by 1 week (no measurements were taken between 5 hours and 1 week). Using function curves generated by altering preload, Mangano90 noted biventricular dysfunction in all 22 patients evaluated in the early postoperative period; patients with preoperative LVEF >55% and no dyssynergy recovered almost completely within 4 hours after CABG, whereas patients with LVEF <45% or dyssynergy exhibited more severe dysfunction that persisted at 24 hours (no measurements were performed after 24 hours). More recently, Breisblatt et al94 demonstrated a significant postoperative depression of both right ventricular and LV ejection fraction and of cardiac index and LV stroke work index, with a nadir at ≈4 hours after CABG and complete recovery within 24–48 hours; the average decrease in LVEF was marked (from 58% before surgery to 37% at trough) and was seen in 96% of the patients (23 of 24).94 We92,93 analyzed the recovery of myocardial function after CABG in 31 patients in whom a pulsed Doppler ultrasonic probe was sutured to the epicardial surface and left in situ for 2–3 days postoperatively. This technique permits continuous, highly accurate measurements of systolic wall thickening.93,95 In most patients LV wall thickening fell after surgery, reaching a nadir at 2–6 hours, and subsequently improved, usually returning to baseline levels by 24–48 hours.92,93 This postoperative depression of function occurred despite the frequent use of inotropic and afterload-reducing therapy and despite the maintenance of adequate LV filling pressures. Occasionally, the dysfunction was marked and required the use of mechanical devices to support the circulation.92 Although a postoperative reduction in LV function has been consistently observed, its severity has varied considerably not only from study to study, but also within the same study.82-94 These differences may be related to the patient population examined (low-risk versus high-risk), the therapy given in the postoperative period, and the techniques and timing of the assessment of cardiac performance. In addition, the development of LV dysfunction may depend on the method of cardioplegia used (crystalloid versus blood, intermittent versus continuous, antegrade versus retrograde, temperature of the solution, etc.)98,99 and on the degree of body core cooling.83
An extreme example of reversible postoperative depression of contractility was reported by Ballantyne et al. These authors described a patient with a preoperative LVEF of 50% who underwent repeat CABG requiring a total aortic cross-clamping time of 1 hour and 42 minutes. During the postoperative period, the patient developed severe LV dysfunction (requiring placement of a LV assist device and intra-aortic balloon pump), which persisted for several days but eventually resolved. Serial radionuclide ventriculograms demonstrated a LVEF of only 6% 12 hours after surgery, with no change at 60 hours after surgery. By 7 days, however, the LVEF had improved to 28%, and at 8 days it was 38%. This case is a dramatic demonstration that postoperative myocardial stunning can be life-threatening and that hemodynamic support with mechanical devices and pharmacological therapy may allow recovery in patients whose prognosis initially appears to be hopeless. Had the LV dysfunction been deemed irreversible, this patient probably would have succumbed.

Before ascribing postoperative cardiac dysfunction to stunning, however, one must also consider the possibility that it may be caused by other factors, such as changes in temperature or loading conditions. Commonly used indexes of LV function, such as LVEF, cardiac index, and LV stroke work index, are temperature dependent, preload dependent, and afterload dependent. Therefore, it would be expected to decrease when hypothermia, reduced LV filling, and/or increased systemic vascular resistance develop in the postoperative period. Indeed, Czer et al. found that cardiac index and LV stroke work index were lowest when core temperature was lowest (i.e., immediately after surgery) and that the subsequent increases in these variables during the rewarming period were directly related to the rise in core temperature; nonetheless, the LV dysfunction persisted even after hypothermia resolved (which is in keeping with common clinical experience). During rewarming, an inverse relation between cardiac index and systemic vascular resistance was also observed. Similarly, Frenes et al. noted that the fall in cardiac index and LV stroke work index immediately after surgery was associated with a fall in temperature, a decrease in LV filling pressure, and an increase in systemic vascular resistance. However, LV function improved significantly between 6 and 24 hours after CABG in the absence of significant changes in temperature, preload, or afterload. Thus, hypothermia and unfavorable loading conditions could not have accounted for all of the LV dysfunction noted in these studies. Similarly, the decreases in ejection fraction and cardiac index observed by others were not explainable solely by changes in temperature, LV filling pressure, or systemic resistance. In conclusion, it is important to recognize that changes in temperature, preload, and afterload can contribute to postoperative LV dysfunction and that these variables must be taken into consideration when one evaluates cardiac performance after open-heart surgery, especially during the rewarming period. Nevertheless, these factors do not account for all of the postoperative LV dysfunction.

Compared with other clinical situations, the setting of open-heart surgery offers several advantages for investigations of myocardial stunning: 1) baseline (preischemic) measurements of function are possible; 2) the onset of ischemia can be anticipated; 3) the exact duration of ischemia is known and is relatively uniform; 4) the degree of flow reduction is similar in all patients; 5) the persistence of ischemia after reperfusion is unlikely, particularly after CABG; 6) the effect of the collateral circulation is minimized; 7) because the entire left ventricle is rendered ischemic, myocardial performance can be assessed with measurements of global LV function (which are more accurate and standardized than those of regional function); 8) metabolic measurements are possible in coronary venous blood or myocardial tissue; 9) protective therapies can be given before ischemia; and 10) the degree of stunning is such that evaluation of therapeutic interventions is facilitated. The major disadvantage is that factors such as myocardial temperature, loading conditions, adrenergic activity, and inotropic and vasodilator therapy vary at different times, exerting confounding effects on the serial assessment of LV function, particularly if load-dependent parameters are used. As mentioned above. Nevertheless, among all of the clinical situations in which stunning may occur, cardiac surgery is the most propitious to the investigation of this phenomenon and the only one where the pathogenesis of stunning has been explored thus far. It seems likely that future studies performed in this setting will contribute importantly to our understanding of postischemic dysfunction in humans.

Aside from these considerations, it is important to stress that postoperative cardiac dysfunction represents a serious clinical problem because the degree of myocardial preservation provided by current methods of cardioplegia is unsatisfactory, as evidenced by the hemodynamic instability after cardiopulmonary bypass and the need for postoperative circulatory support with drugs or mechanical devices. This problem is more evident in patients with compromised myocardial reserve and in those requiring prolonged aortic cross-clamping or urgent CABG. The studies reviewed above were conducted in low-risk patients (i.e., patients with good preoperative LV function and elective CABG). When one considers that the deterioration seen in some of these studies (for example, the 21% fall in LVEF noted by Breisblatt et al.) can also occur in patients with a baseline impairment of LV function or other high-risk conditions, it is not difficult to envision how the effects of stunning on the postoperative outcome can be quite serious. Therefore, there is a need to develop interventions that can enhance the protection afforded by hypothermic cardioplegia. At the same time, evaluation of such interventions is facilitated by the conditions associated with cardiac surgery, as elaborated above. Thus, among all the clinical settings of stunning, open-heart surgery is perhaps the one where therapies designed to mitigate postischemic dysfunction can be tested most easily and can find the most widespread application.

In summary, transient depression of ventricular contractility is common after cardiopulmonary bypass. This mechanical dysfunction, which is usually reversible within 24-48 hours, is most likely caused by myocardial stunning. Because in the immediate postoperative period many patients receive inotropic and/or afterload-reducing therapy and because plasma catecholamines increase markedly after CABG, it is probable that
stunning is partly masked by these therapeutic manipulations and neurohumoral adaptations; thus, the severity of this phenomenon might be actually greater than what can be inferred from the published studies. Although in low-risk patients this posts ischemic dysfunction can be managed without significant consequences, in subgroups at high risk (specifically, patients with poor preoperative LV function, prolonged aortic cross-clamping time, repeat coronary bypass procedure, unstable angina, left main coronary artery disease, or concurrent valve replacement), postoperative myocardial stunning may have more serious effects on morbidity and mortality. Cardiac surgery is the 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, probably because it impairs the function of the entire left and right ventricle. If therapies against stunning become available in patients, cardiac surgery will probably be the first setting where they will be tested and used.

**Myocardial Stunning After Cardiac Transplantation**

Since in the course of cardiac transplantation the heart is subjected to a period of global ischemia followed by reperfusion, a phase of myocardial stunning would be expected to develop. Indeed, despite the use of cardioplegia and hypothermia during harvest and storage of human hearts, transient hemodynamic instability is commonly observed in the immediate postoperative period (long before rejection becomes a factor), so that vigorous pharmacological support of the circulation is usually required. Because the transplanted heart has normal baseline function and because the hemodynamic instability is temporary, it seems likely that this mechanical failure is due, at least in part, to myocardial stunning.

Published information regarding the mechanical abnormalities that occur immediately after cardiac transplantation is surprisingly scarce. Barnard’s group (Wicomb et al) described two patients who received heterotopic heart transplantation. Initially, the donor heart function was poor and the organ was clearly unable to support the circulation, requiring the use of intense inotropic support. After 20 hours, however, the donor heart recovered dramatically and after 36 hours took over the circulation almost entirely. In a recent study, Verani et al (unpublished observations) described serial measurements of LVEF by radionuclide angiography in 22 patients undergoing orthotopic heart transplantation. The authors noted an initial depression followed by a gradual recovery over the next 4 days, with the average LVEF increasing from 44% at 8 hours after transplantation to 52% at 4 days. Experimental studies assessing the resolution of mechanical abnormalities after cardiac transplantation are also scarce because of technical difficulties. Nevertheless, there are reports that systolic and diastolic function are abnormal immediately after experimental transplantation and then gradually improve.

In summary, there is considerable (although largely anecdotal) evidence that cardiac function is reversibly depressed in the first hours or days after transplantation, suggesting stunning. As in the setting of CABG, it is likely that the severity of such dysfunction would be more obvious if patients did not receive the intense inotropic therapy that is usually administered in these circumstances.

The presence of stunning after transplantation is clinically important because it complicates the postoperative management of these unstable patients. In addition, stunning may contribute (along with other factors) to limit the maximal time interval during which the organs can be stored before being successfully transplanted. Given that the severity of stunning associated with regional ischemia increases in proportion to the duration of coronary occlusion, it is plausible that a positive relation also exists between the severity of stunning observed after transplantation and the duration of the preceding ischemic period. Simple hypothermic storage of normal hearts has generally been found to be satisfactory for periods of up to 4 hours, but there is clear functional deterioration after 3 hours and severe dysfunction after 6–8 hours. This limits long-term (>6-hour) preservation and long-distance procurement of the organ and therefore aggravates the problem of the shortage of donor hearts. Part of this dysfunction is undoubtedly caused by irreversible damage (cell death). Nonetheless, if stunning is responsible for a portion of this posts ischemic contractile failure, then its prevention could prolong the duration of the ischemic period during which donor hearts can be safely stored. It is interesting to note that, in experimental studies, antioxidant therapy has extended successful preservation of donor hearts beyond 4–6 hours (e.g., Reference 102).

**Biochemical evidence for the occurrence of myocardial stunning in humans.** In addition to the studies reviewed above, biochemical observations consistent with the presence of stunning in humans should also be mentioned. Flameng et al analyzed high-energy phosphate metabolism and histological appearance in LV biopsy specimens obtained before CABG. In 27 patients with a severe coronary artery stenosis (five with unstable angina and 22 with stable angina), the dependent territory exhibited reduced wall motion (as assessed by the preoperative LV angiogram) and partial depletion of ATP despite absence of necrosis (as assessed by histology) and despite seemingly normal mitochondrial oxidative phosphorylation, i.e., normal energy production (as assessed by the ADP/ATP ratio, the energy charge, and the creatine phosphate/ATP ratio). These changes are analogous to those observed in experimental models of stunned myocardium. A major issue that needs to be elucidated, however, is whether the same biochemical changes can also be caused by hibernation.

**Mechanism of Myocardial Stunning in Man**

Information regarding the pathogenesis of posts ischemic dysfunction in humans is quite scarce. Almost all of the data are derived from the setting of cardiac surgery, perhaps because mitigation of postoperative LV dysfunction has been a major clinical concern for many years and because surgery provides easy access to myocardial and coronary venous blood specimens for biochemical assays (in addition to the other advantages discussed earlier).

Experimental studies suggest two major mechanisms for myocardial stunning (which are not mutually exclusive): 1) generation of oxygen-derived free radicals with consequent oxidative stress ("oxyradical hypothe-
sics") have 2) impaired calcium homeostasis resulting in transient calcium overload, excitation–contraction uncoupling, and/or decreased myofilibrillar sensitivity to calcium ("calcium hypothesis"). While little information is as yet available regarding calcium homeostasis, some evidence supporting the oxradical hypothesis has recently been obtained. In particular, a number of observations are consistent with the concept that oxradicals contribute to the pathogenesis of postoperative LV dysfunction after CABG. Ferreira et al. reported that hydroperoxide-initiated chemiluminescence was significantly increased in myocardial biopsies obtained 10 minutes after reperfusion compared with biopsies obtained before ischemia, suggesting a decrease in tissue antioxidant defenses, possibly as a result of oxidative stress. Weisel et al. noted that conjugated dienes (which are products of oxradical-initiated lipid peroxidation) were released into the coronary sinus blood at 3 and 60 minutes after reperfusion; in addition, the myocardial concentration of α-tocopherol decreased after reperfusion, suggesting consumption of the major membrane antioxidant. More recently, Ferrari et al. reported that reperfusion 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 the release of GSSG is a sensitive index of cellular oxidative stress, these results suggest a link between oxradical-mediated injury at reperfusion and subsequent contractile dysfunction. The magnitude of GSSG release was found to be directly related to the duration of the antecedent ischemia, suggesting that the intensity of the ischemic insult is a major determinant of the myocardial oxidative damage, in accordance with experimental observations. Thus, three different indexes of oxidative stress (stimulated chemiluminescence, production of conjugated dienes, release of GSSG) have been found to be abnormal after reperfusion of human hearts subjected to ischemia during cardiopulmonary arrest, suggesting that reactive oxygen species are being generated. (It should be noted that there are at least two mechanisms that can result in free radical production during open-heart surgery. First, cardiopulmonary bypass per se results in complement-mediated activation of leukocytes that become sequestered in the myocardium and in other tissues. Second, the myocardium itself, which was rendered ischemic during aortic cross-clamping, could become a source of radical species upon reperfusion.)

Despite the lack of control data (which would have been extremely difficult to obtain), these findings provide a rationale for testing antioxidant therapy in patients undergoing CABG. In particular, two major questions need to be addressed in future studies: 1) Do antioxidants reduce postoperative LV dysfunction after CABG? 2) If so, does this effect correlate with reduced oxidative stress? The results obtained with antioxidant therapy in experimental models of postoperative LV dysfunction have been encouraging. In addition, recent developments may make it possible to measure oxygen radicals at the time of surgery with the use of techniques that are sensitive and noninjurious. Of all the clinical settings of stunning, cardiac surgery is probably the one where the oxradical hypothesis can be meaningfully tested in the near future.

Few studies of oxidative stress are available outside of cardiac surgery. Bennett et al. have demonstrated activation of the complement system by thrombolytic therapy with recombinant tissue-type plasminogen activator in AMI, and recent reports indicate a decrease in plasma reduced thiol groups in unstable angina. Others have documented myocardial release of thiobarbituric acid (TBA)–reactive substances (among which is malondialdehyde) after balloon deflation in PTCA and after thrombolysis in AMI. Because malondialdeyde is a product of lipid peroxidation, these data are compatible with oxidative stress, but their interpretation is complicated by the lack of specificity of the TBA assay.

In summary, investigation of the oxradical hypothesis in humans is still in its infancy. The few studies performed thus far have used only indirect approaches and have not provided control data. Despite these limitations, however, there is evidence that in some clinical settings, particularly cardiac surgery, myocardial stunning is associated with oxidative stress. These observations agree with experimental results and are consistent with the hypothesis that oxygen radicals play a pathogenetic role in postischemic dysfunction in humans, a concept that has significant therapeutic implications (see below). Conclusive evaluation of the oxradical hypothesis in patients undergoing CABG is both timely and feasible and represents an important area for future research.

**Diagnosis of Myocardial Stunning in Man**

One cannot overemphasize the importance of developing widely applicable methods to prospectively identify stunned myocardium in patients. The prevalence of this syndrome and its clinical impact will remain uncertain until its diagnosis becomes practical and reliable. Furthermore, appropriate management of patients with stunned myocardium (see below) requires that this diagnosis be made while the phenomenon is still occurring (not retrospectively) and that it be available to most clinicians.

Table 3 summarizes the techniques that are potentially useful in identifying myocardial stunning. One

### Table 3. Potentially Useful Techniques for the Prospective Diagnosis of Myocardial Stunning

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<td>Techniques that can measure both function and perfusion simultaneously</td>
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<td>• 99mTc-sestamibi imaging</td>
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group of such techniques is based on the fact that the stunned myocardium is characterized by a perfusion-contraction "mismatch," i.e., by decreased contractile function in the face of normal perfusion (see above). Within this group of techniques, PET can be considered the "gold standard" because it is the best-validated method for measuring absolute regional myocardial flow in the clinical setting. By demonstrating normal perfusion in a dysfunctional region, PET can positively establish the diagnosis of stunned myocardium and can differentiate this syndrome from hibernating or ischemic myocardium, both of which will exhibit reduced flow. However, PET is expensive and not available to the vast majority of clinicians. A more practical approach could be the use of \textsuperscript{201}TI scintigraphy. Because thallium extraction and washout kinetics in stunned myocardium are normal,\textsuperscript{118} a segment that is dysfunctional because of stunning should manifest normal uptake after injection of thallium at rest. In contrast, a segment that is dysfunctional because of hibernation, silent ischemia, or infarction should manifest decreased uptake; in hibernating or silently ischemic myocardium, a redistribution of thallium would then be expected to occur at 4 hours, since the tissue is still viable. Thallium imaging, however, necessitates the use of other techniques to measure regional wall motion at the same time. This problem can be obviated by the use of \textsuperscript{99m}Tc-sestamibi imaging, which enables assessment of both myocardial perfusion and myocardial contraction with a single injection. The retention of \textsuperscript{99m}Tc-sestamibi in stunned myocardium is comparable to that of \textsuperscript{201}TI,\textsuperscript{119} and this agent has been found to be an accurate marker of viability\textsuperscript{119,126}; however, since it does not redistribute, it may not distinguish between hibernating myocardium and scarred myocardium. Additional investigation of these techniques is in order, because most of the studies performed thus far with \textsuperscript{201}TI and \textsuperscript{99m}Tc-sestamibi after thrombolysis have dealt with hypoperfused segments, which are probably hibernating rather than stunned. One problem to keep in mind, however, is that both of these methods provide estimates of relative differences in tracer distribution rather than absolute flow.

Another group of techniques is based on the fact that the stunned myocardium retains considerable inotropic reserve and is exquisitely responsive to virtually any inotropic stimulus.\textsuperscript{3} Within this group of techniques, low-dose dobutamine infusion during two-dimensional 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 early after thrombolysis in AMI, can be quite useful in predicting the eventual degree of functional recovery (and hence, of myocardial salvage).\textsuperscript{121,122} For example, Pierard et al.\textsuperscript{121} found that an increase in regional systolic wall thickening during administration of dobutamine (10 \(\mu\)g · kg\(^{-1}\) · min\(^{-1}\)) at 7 days after AMI was associated with improved resting wall motion at 9 months (five patients), whereas a failure to respond to dobutamine was associated with no subsequent improvement in wall motion (six patients). In this small study,\textsuperscript{121} the interpretation of dobutamine echocardiography was concordant with that of PET in 79% of the myocardial segments. Similar results have been reported by others.\textsuperscript{122}

There is little doubt that low-dose dobutamine echocardiography can differentiate stunned from infarcted myocardium; what remains unclear is whether it can differentiate stunned from hibernating myocardium. Information regarding the inotropic responsiveness of hibernating myocardium is quite scarce. In the study discussed above, Pierard et al.\textsuperscript{121} found that 7 days after AMI segments with decreased wall motion, decreased perfusion, and high glucose uptake (a pattern indicative of hibernation) manifested improved systolic thickening during a brief (5-minute) dobutamine infusion. Similarly, a recent study\textsuperscript{123} has shown that a brief (5-minute) infusion of dobutamine can augment myocardial work in an experimental model of short-term (90-minute) hibernation; however, this contractile response occurred at the expense of a worsening of the metabolic markers of ischemia (i.e., increase in lactate production and decrease in glycogen and creatine phosphate stores). Whether hibernating myocardium can respond to prolonged inotropic stimulation is unknown, but one would expect that any increase in contractility should be short-lived and then be followed by a deterioration as the precarious balance between energy supply and demand is upset by the inotropic challenge.

A potential limitation of dobutamine echocardiography is that, in the presence of a severe coronary stenosis, the stunned myocardium may not be able to increase its contractile function because of the restricted arterial inflow. Perhaps the major limitation, however, is that an inotropic response to dobutamine can result from increased contractility in normal myocardial cells adjacent to injured cells; for example, the response of a region containing a mixture of infarcted tissue and viable (but not stunned) tissue can be similar to the response of a stunned region.

Other potential methods of recruiting contractile reserve in stunned myocardium include postextrasystolic potentiation,\textsuperscript{124-126} infusion of other catecholamines such as epinephrine,\textsuperscript{127} administration of nitroglycerin,\textsuperscript{125,128,129} and exercise.\textsuperscript{130} However, none of these techniques has been widely used. Electrocardiographic methods (i.e., detection of persistently inverted T waves\textsuperscript{35,36}) await clinical testing, particularly with regard to the issue of specificity. In summary, both scintigraphic and echocardiographic techniques (in particular, \textsuperscript{99m}Tc-sestamibi imaging and low-dose dobutamine echocardiography) appear promising for the prospective diagnosis of stunned myocardium, but larger validation studies are needed in various settings (other than after AMI) and the issues of specificity and sensitivity remain to be addressed. This is an important area for future research.

A fundamental problem is that "pure" stunning (Figure 2, panels A and D) or "pure" hibernation (Figure 2, panels E and G) may be relatively uncommon. The clinical situation is likely to be more complex than could be predicted on the basis of a single paradigm. For example, in some patients a steady depression of function caused by hibernation could be punctuated by "dips" caused by acute, silent reductions of flow followed by stunning (Figure 2, panel F). Moreover, in many patients with a severe coronary stenosis, the same myocardial region probably contains an admixture of subendocardial scar and subepicardial viable myocardium in which stunning and hibernation can both occur,
either in close temporal proximity (Figure 2, panel G) or even simultaneously (Figure 2, panel F). Given the resolution limits of current techniques used for measuring regional perfusion, the correct diagnostic classification of these patients will be a formidable challenge. Another major problem is that the very nature of hibernation remains unclear. It seems unlikely that resting flow can be steadily reduced for sustained periods of time, because a critical stenosis should result in loss of local coronary autoregulation and therefore in wide fluctuations of flow (Figure 2, panel H) (this concept is elaborated in the legend to panel H). Do these fluctuations cause stunning, hibernation, or both?

Management of Myocardial Stunning in Man: Treatment Versus Prevention

In patients with otherwise normal LV function, myocardial stunning is likely to be well tolerated and probably requires no therapy at all. It is in the high-risk situations mentioned earlier that stunning can become dangerous and should be treated.

There are two basic approaches to the management of stunned myocardium: One is to correct this abnormality after it has developed, and the other is to prevent it before it develops. The former approach is surprisingly effective. Experimental studies have clearly shown that posts ischemic dysfunction can be completely reversed with dopamine, epinephrine, isoproterenol, calcium, postextrasystolic potentiation, or other inotropic stimuli. Basically, any positive inotropic intervention tested thus far has produced a dramatic response in animal models of stunned myocardium. This response is sustained so long as the inotropic stimulus is maintained (although long-term stimulation has not been investigated). Clinical studies have similarly suggested that stunned myocardium after thrombolysis can be recruited with dobutamine (see above). In addition, the contractile function of the stunned myocardium can be markedly improved by increasing preload or by decreasing afterload. It is difficult to think of other forms of LV dysfunction in which the effects of pharmacological therapy are equally dramatic.

In clinical practice, inotropic and afterload-reducing therapy are the standard approach to the management of LV dysfunction in situations in which stunning is likely to occur (e.g., after cardiac surgery or transplantation, after thrombolysis in AMI). It is probable that the routine use of such therapy has masked the severity of stunning. The extraordinary pharmacological responsiveness of the stunned myocardium may have led us to underestimate the impact of this abnormality and may have hindered its recognition.

Should we, then, be satisfied with the current practice of infusing catecholamines, optimizing LV filling pressures, and correcting elevated systemic vascular resistance? Although these maneuvers are quite useful, a strong argument can be made for a better approach. If possible, why not prevent stunning from occurring in the first place instead of trying to overcome it forcibly after it has developed? There are several obvious advantages to averting the development of stunning. Positive inotropic agents increase myocardial oxygen consumption, which may be undesirable in patients with severe, flow-limiting coronary stenoses in the reperfused vascular bed or in other beds. Many of these agents also have the potential to cause arrhythmias. Furthermore, intravenous therapy with inotropic and vasodilator drugs often requires invasive hemodynamic monitoring and thus may prolong the length of the stay in intensive care units. In addition, prevention of stunning might shorten the duration of hemodynamic instability after CABG, cardiac transplantation, or thrombolysis in AMI; in the former two settings, it might also facilitate rapid weaning from cardiopulmonary bypass. Finally, the safety of inotropic therapy remains an unresolved issue. Although brief infusion of catecholamines appears to be harmless, it is unknown whether long-term (e.g., ≥24-hour) inotropic stimulation of stunned myocardium has deleterious effects.

According to experimental studies, stunning can be prevented in at least two ways: 1) by administering calcium antagonists before ischemia (but not just before reperfusion) or 2) by giving antioxidants just before reflow. There are, as yet, no controlled clinical data on the efficacy of these therapies, but both approaches are clinically applicable and there is mounting interest in their evaluation not only in the medical community but also in the pharmaceutical industry. Some antioxidants (allopurinol, desferrioxamine, mercaptopropionyl glycine, probucol) are already used in various clinical situations, while others (polyethylene glycol–conjugated superoxide dismutase [PEG-SOD], vitamin E analogues) are being developed for clinical application. Initial clinical trials are being (or will soon be) conducted to examine the effect of calcium antagonists (such as nisoldipine) or antioxidants (such as desferrioxamine and PEG-SOD) on postoperative LV dysfunction after CABG. Recently, the effects of SOD or iloprost (a prostacyclin analogue) on infarct size have been explored in patients receiving reperfusion therapy for AMI, but these studies were not designed to evaluate stunning.

In summary, the therapy of stunning has the potential to be quite successful, which is one of the reasons why this phenomenon is important. The conventional treatment of stunned myocardium is the same as that conventionally used for other forms of LV dysfunction, i.e., administration of inotropic and vasodilator drugs. Although such treatment is probably very effective, new approaches are being explored in an attempt to prevent stunning from developing in the first place. If the experimental results are applicable to humans, pharmacological prophylaxis of stunning may become a clinical reality.

Importance of Myocardial Stunning in Man

At the conclusion of this analysis, it is appropriate to discuss the practical relevance of posts ischemic dysfunction. The observations reviewed in this essay strongly suggest that myocardial stunning occurs in several clinical situations. However, because this abnormality is by definition reversible, it could be argued that it is unimportant: if myocardial stunning will resolve spontaneously, why should the clinician be concerned about it? And why are so much time and effort devoted to the study of a phenomenon that could be viewed as a normal reparative process, that has no ultrastructural basis, and that, in the final analysis, amounts to a temporary dysfunction that is relatively short-lived (hours or days) and completely reversible?
Apart from the many pathophysiological implications of stunning, \(^3\text{,}^4\) which are beyond the scope of this review, and apart from the fact that this phenomenon represents not only the process of recovery from ischemic injury but also the result of a separate, preventable component of reperfusion injury, \(^3\text{,}^4\text{,}^13\text{,}^6\) several aspects must be considered that have practical importance for the clinician.

First, myocardial stunning may be a cause of morbidity and mortality. Dramatic cases illustrating this point have been reviewed above, \(^40\text{–}42\text{,}^91\) and many other similar cases have been published. \(^137\text{–}150\) In those patients with unstable angina or AMI in whom the size of the ischemic region is large (e.g., patients with proximal LAD lesions), the development of postischemic stunning may cause hemodynamic instability requiring intensive monitoring, pharmacological and/or mechanical circulatory support, and urgent revascularization under suboptimal conditions. Furthermore, as mentioned above, stunning may adversely affect the outcome of CABG in patients who are at high risk because of conditions such as impaired baseline contractile reserve, large aortic clamping time, repeat CABG, unstable angina, left main coronary disease, or concomitant valve replacement; indeed, stunning is probably the most frequent cause of myocardial dysfunction and low cardiac output syndrome after CABG. It is important to keep in mind that virtually all of the studies reviewed in this article were conducted in patients with good baseline LV function and that, in any clinical setting, the consequences of stunning will be more serious when this abnormality is superimposed on an already depressed contractile function.

Second, the concept of stunning implies that the mechanical abnormalities associated with the aforementioned clinical situations could be reversed and possibly even prevented. As discussed earlier, experimental studies have repeatedly demonstrated that stunning can be corrected with inotropic therapy. \(^3\) In addition, there is considerable evidence that this form of contractile failure is preventable by calcium antagonists \(^134\text{,}^\) or by antioxidant therapy. \(^3\text{,}^104\) A decade of experimental research indicates that the stunned myocardium is exquisitely responsive to therapeutic manipulations that are both safe and clinically applicable (see above).

Third, 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 AMI cannot be immediately appreciated because the recovery of function in viable tissue may require several days or possibly even longer. However, the magnitude of the myocardial salvage effected by reperfusion can be estimated from the improvement in wall motion at the time of hospital discharge (7–10 days after the AMI), although it is still unclear whether further improvement will accrue after this time. Because stunned myocardium possesses considerable inotropic reserve, \(^7\) a more immediate assessment of the amount of salvage achieved may be possible by the measurement of regional inotropic reserve with catecholamine infusion or postextrasystolic potentiation, as discussed above. Such information may be important in deciding whether to perform PTCA on the infarct-related vessel and may have significant prognostic value.

Fourth, the notion that contractility cannot be used as a measure of viability in postischemic myocardium poses major dilemmas to the clinician. Let us consider the case of the patient with AMI who is successfully treated with thrombolytic therapy but continues to exhibit a large akinetic LV region: How can one determine, soon after recanalization, 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 maneuvers would not be useful)? Even more compelling is the problem of the patient who remains in cardiogenic shock after cardiac surgery or after thrombolytic therapy for AMI: How long should aggressive therapy be pursued in this situation? Is the pump failure caused by necrosis (in which case an aggressive treatment would be futile) or by stunning (in which case such a treatment could be life-saving)? Obviously, the usefulness of maintaining pharmacological and/or mechanical circulatory support for extended periods of time will depend on whether the ventricular dysfunction is reversible. There is clearly a need for techniques that can distinguish stunned from infarcted myocardium and that can be used to justify the termination of, or the exclusion of patients from, aggressive therapeutic approaches.

Fifth, the recognition of myocardial stunning requires a reassessment of the criteria traditionally used to decide whether coronary revascularization is indicated in patients with stable or unstable angina. Because the presence of hypokinesia/dyskinesia does not necessarily signify loss of viability, the decision as to whether to proceed with PTCA or CABG cannot be predicated solely on the resting LV wall motion. Indeed, the demonstration that a dysfunctional LV region is still viable may justify CABG or PTCA in patients who otherwise would be managed medically. In this case, differentiation between stunning and hibernation may not be crucial, because both conditions will benefit from revascularization; what is crucial is to distinguish stunned or hibernating myocardium from infarcted myocardium. Further studies are needed to establish the relative usefulness of various techniques (particularly \(^20\)TI scintigraphy and dobutamine echocardiography) that could help make this differential diagnosis, as discussed above.

Can Myocardial Stunning Cause Chronic Ventricular Dysfunction?

Perhaps the most intriguing clinical implication of the concept of stunning is the possibility that this contractile abnormality may become persistent or even chronic. Stunning is commonly regarded as a short-term phenomenon because our knowledge of its pathophysiology is derived exclusively from short-term animal experiments. The possibility that recurrent episodes of stunning may lead to long-term mechanical dysfunction has not been explored experimentally or clinically, but nevertheless is plausible. Short-term animal studies have shown that repeated brief episodes of ischemia have a cumulative effect on contractility, such that myocardial function remains depressed much longer than with a single ischemic episode. \(^69\text{,}151\text{,}152\) This has been demonstrated both after low-flow ischemia (e.g., 5-minute coronary occlusions \(^151\text{,}152\)) and after high-flow ischemia (i.e., exercise-induced ischemia \(^69\)). 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 a higher frequency than previously suspected, up to 10–20 times per day. Under these circumstances, the myocardium may not be able to recover fully between episodes and thus may remain reversibly depressed for extended periods of time (Figure 2, panel D).

It is important to note that many of the alterations in regional function that have been ascribed to hibernation could in fact be caused by stunning resulting from repetitive episodes of ischemia (painless or painful) alternating with reperfusion, as illustrated in Figure 2 (panel D). Support for this concept is provided by the observations of Tillish et al, who studied with PET 17 patients with regional wall motion abnormalities at rest who did not have unstable angina, AMI, or variant angina. In this relatively stable 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 stunning rather than by hibernation. The concept that recurrent bouts of ischemia can result in prolonged postischemic dysfunction is also consistent with the findings of Nienaber et al, who noted that, in four patients with unstable angina, the recovery of wall motion after PTCA was delayed for several days despite immediate restoration of flow (documented by PET).

The existence of a chronic but reversible depression of contractility in patients with coronary artery disease is supported by numerous observations. First, as shown in studies by Flameng and colleagues, analysis of LV biopsies obtained from hypokinetic myocardial segments at the time of CABG surgery often reveals myocellular degenerative changes (mainly loss of contractile filaments) but not myocardial fibrosis or ultrastructural evidence of irreversible injury, suggesting that the abnormal wall motion observed in these segments is long-lasting (because of the loss of myofibrils) but not necessarily caused by cell death. Many other studies have also documented reduced contractile function in segments containing little or no fibrosis. Second, dysfunctional LV regions can manifest a substantial improvement of contractility in response to nitroglycerin, postextrasystolic potentiation, catecholamine infusion, and exercise, indicating the presence of a significant contractile reserve. Third, pathological examination of hearts of patients with “ischemic cardiomyopathy” sometimes fails to reveal myocardial scarring sufficiently extensive to account for the clinical syndrome of congestive failure or for the segmental wall motion abnormalities. Finally, many abnormally contracting LV regions exhibit improved wall motion after CABG or PTCA, even in patients with stable angina. What remains unclear is whether the reversible dysfunction observed in all of these studies was caused by repetitive episodes of stunning occurring in clusters (Figure 2, panel D), by a chronic low-flow state (that is, hibernation) (Figure 2, panel E), or (as seems more likely) by a combination of these two conditions (Figure 2, panel F). In view of its far-reaching implications for our understanding and management of coronary disease, elucidation of this problem represents one of the most fascinating and important areas for future research.

Summary

Myocardial stunning has been observed in all species examined thus far, and there is no reason to suspect that humans are an exception. Unfortunately, the investigation of this phenomenon in patients has been plagued by several problems, including the limited accuracy of the methods available to measure regional LV function, the inability to quantify regional myocardial blood flow during acute ischemia, and the uncontrolled influence of variables (such as preload, afterload, adrenergic tone, and inotropic therapy) that have a major impact on postischemic dysfunction. The most vexing problem has been the inability to discern whether a reversible decrease in contractility is caused by stunning, ongoing silent ischemia, or hibernation. This differential diagnosis requires simultaneous measurements of regional myocardial function and flow, which thus far has not generally been possible. Despite these obstacles, however, numerous observations suggest that stunning does occur in various settings in which the myocardium is exposed to transient ischemia, including unstable angina, AMI with early reperfusion, open-heart surgery, cardiac transplantation, and possibly exercise-induced angina. Stunning might also occur in selected cases after PTCA or variant angina, although it is not usually observed in such situations. Recognition of this entity is important, among other reasons, because it is likely to cause significant morbidity and because it is potentially correctable (e.g., with inotropic therapy) or even preventable (e.g., with antioxidants or calcium antagonists). In addition, the appreciation of the phenomenon of stunning should allow the clinician to assess the efficacy of reperfusion therapy with greater accuracy and should stimulate the search for better criteria for selecting patients who will benefit from mechanical revascularization. Perhaps the most intriguing implication is the possibility that in patients who experience frequent episodes of ischemia in the same territory, the myocardium may not be able to recover fully between episodes and thus may remain reversibly depressed for prolonged periods of time or even chronically.

We are only at the beginning of an effort to elucidate the clinical significance of myocardial stunning. Our understanding of this phenomenon in humans is still inadequate and will not significantly improve until regional myocardial perfusion and function are assessed at the same time. The diagnosis of stunning has thus far been made retrospectively on the basis of an otherwise inexplicable improvement of LV function; methods need to be developed for establishing this diagnosis prospectively with techniques that are reliable, practical, and widely available. The possibility should be addressed that stunning may in some cases be superimposed on or coexist with hibernation in the same myocardial region. Other important areas for future research include the investigation of whether stunning can become chronic, the elucidation of the role of oxidative stress in its pathogenesis, and the evaluation
of the efficacy of therapies designed to prevent this contractile abnormality.

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