Cardiovascular Drugs and Therapy 1994;8:371–380

Left Ventricular Dysfunction due to Stunning and Hibernation in Patients

R. Ferrari,[1] G. La Canna,[1] R. Giubbini,[2] E. Milan,[2] C. Ceconi,[3] F. de Giuli,[3] P. Berra,[1] O. Alfieri,[4] and O. Visioli[1]

[1]Cattedra di Cardiologia, Universita degli Studi di Brescia, Brescia, Italy; [2]Divisione di Medicina Nucleare, Spedali Civili, Brescia, Italy; [3]Fondazione Clinica del Lavoro di Pavia. Centro di Fisiopatologia Cardiovascolare "Salvatore Maugeri" Gussago, Brescia, Italy; [4]II Divisione di Cardiochirurgia, Spedali Civili, Brescia, Italy

Summary. **Left ventricular dysfunction is in most cases the consequence of myocardial ischemia. It may occur transiently during an attack of angina and usually it is reversible. It may persist over hours or even days in patients after an episode of ischemia followed by reperfusion, leading to the so-called condition of stunning. In patients with persistent limitation of coronary flow, left ventricular dysfunction may be present over months and years, or indefinitely in subjects with fibrosis, scar formation, and remodeling after myocardial infarction. However, chronic left ventricular dysfunction does not mean permanent or irreversible cell damage. Hypoperfused myocytes can remain viable but akinetic. This type of dysfunction has been called *hibernating myocardium*. The dysfunction due to hibernation can be partially or completely restored to normal by reperfusion. It is, therefore, important to clinically recognize a hibernating myocardium. In the present article we evaluate stunning and hibernation with respect to clinical decision making and, when possible, we refer to our ongoing clinical experience.**

Cardiovasc Drugs Ther 1994;8:371–380

Key Words. **left ventricular dysfunction, stunning, hibernation**

The commonest cause of ventricular dysfunction is coronary artery disease [1]. Dysfunction may be of short duration in patients with stable angina, last hours or even days in patients with unstable angina or after an episode of ischemia followed by reperfusion, or be prolonged over months or years in patients with persistent limitation of coronary flow or indefinitely in patients with fibrosis, scar formation, and remodeling after myocardial infarction. Severe ventricular dysfunction leads to the syndrome of heart failure, which is a progressive condition in which further damage to the heart may occur from increased afterload, fluid retention, or remodeling.

The recognition that ventricular dysfunction does not mean permanent or irreversible cell damage is of clinical relevance. It introduces a new diagnostic and therapeutic challenge for the clinician when facing patients with left ventricular dysfunction in which revascularization has already occurred or is considered beneficial. Thus, reversible dysfunction occurring in particular clinical circumstances and in selected experimental models has been given the names of *stunning* and *hibernation*. This is useful shorthand, as it helps to understand the concept, but it might also give rise to confusion. Table 1 reports the most important differences between stunning and hibernation.

The purpose of the present article is to review the available information regarding the occurrence of reversible left ventricular dysfunction in humans and to report, when available, our clinical experience and diagnostic approach. It is impossible to discuss this topic without referring to the concepts of stunning and hibernation. Therefore, as a working hypothesis, we will first try to provide a definition of these terms, which is essential to avoid confusion, and then discuss the different clinical conditions in which ventricular dysfunction may occur. This article will not address the pathogenesis, pathophysiology, and therapy of these conditions, which have recently been reviewed elsewhere [2–4].

Ventricular Dysfunction due to Myocardial Stunning

Stunning defines a transient left ventricular dysfunction that persists after reperfusion despite the absence of irreversible damage and despite restoration of normal or near normal coronary flow [2,5]. It is

Address for correspondence: Prof. Roberto Ferrari, Cattedra di Cardiologia, Universita' degli Studi di Brescia, c/o Spedali Civili, P.le Spedali Civili, 1, 25123 Brescia, Italy.

Received 22 June 1993, accepted in revised form 11 November 1993.

Table 1. Differences between stunning and hibernation

	Stunning	Hibernation
Concept	Experimental model	Clinical observation
Left ventricular function	Depressed	Depressed
Coronary flow	Normal	Reduced
Reversibility	Spontaneous	Upon reperfusion
Occurrence	On reperfusion after ischemia	On chronic ischemia or after repetitive ischemia
Clinical condition	After cardiac surgery, thrombolysis, AMI, exercise-induced ischemia, unstable angina, coronary spasm	After angina, AMI, severe valvular disease, and idiopathic cardiomyopathy

implicit in this definition that (a) stunning is a transient, fully reversible abnormality provided that sufficient time is allowed for recovery; (b) stunning is a mild, sublethal injury that must be kept distinct from the irreversible damage occuring in myocardial infarction; (c) stunned myocardium has a normal or near normal coronary flow (Table 1). Thus, the hallmark of this condition is the presence of a flow-function "mismatch," with normal flow but abnormal function. This is quite in contrast to the other forms of reversible myocardial dysfunction, such as ischemia and hibernation, in which depressed flow and function are matched.

A clear definition is certainly desirable and important, but its application to the clinical condition is often problematic. Diagnosis of stunning in patients would require demonstration of two major points: (a) the contractile abnormality is reversible with time; (b) the dysfunctional myocardium has normal or near normal coronary flow [6]. This implies that it is possible to measure with accuracy regional myocardial function and blood flow in humans. The resolution of the available techniques utilized for these purposes (contrast ventriculography, radionuclide angiography, two-dimensional echocardiography, positron emission tomography), however, is not comparable to that obtainable with sonomicrometry and radioactive microspheres in experimental animals.

To fulfill the second point, before making a definitive diagnosis of stunning the physician should allow sufficient time for the myocardium to recover. This, in turn, suggests that in general myocardial stunning is a well-tolerated condition and that its diagnosis is important retrospectively for the better appreciation of the effects of reperfusion, but does not imply a decisionmaking process for clinical management of the patient, basically because the myocardium is already reperfused. It could be argued that in some high-risk situations stunning can become dangerous. Therefore, stunning should be recognized and treated with positive inotropic interventions and/or agents increasing preload or decreasing afterload [7]. Dramatic cases illustrating this point have been recently reported [9–16]. In clinical practice stunning is dangerous when the degree and extent of the left ventricular dysfunction is associated with a low output syndrome. Under these circumstances, however, therapy with inotropic and afterload-reducing agents is a common approach, independent of the diagnosis of stunning.

It has been suggested that recognition of stunning may be important in high risk conditions (such as thrombolysis after acute myocardial infarction and reperfusion after cardiac surgery or transplantation) because the physician could try to prevent it from occurring [6]. Experimentally, stunning can be prevented by calcium antagonists administered before ischemia [17,18] or by antioxidants given just before reflow [2]. At present, no controlled clinical data on the efficacy of those therapies are available. It is also essential to identify the "high risk conditions" that need to be treated in order to avoid unnecessary therapy in a vast population for the benefit of a few patients.

Left Ventricular Dysfunction due to Repetitive Stunning

It has been shown that patients with coronary artery disease experience recurrent episodes of ischemia, often silent, in the same territory [19,20]. The myocardium is not able to recover completely between the frequent episodes and its function remains persistently depressed [6]. Often recurrent ischemia is a consequence of recurrent coronary artery spasm [20,21]. Thus, some of the chronic alterations in regional function that have been ascribed to hibernation could, in fact, be caused by stunning, resulting from repetitive episodes of ischemia [6]. Recently Bol et al. [22], using quantitative emission tomography, have observed that myocardial perfusion in collateral-dependent dysfunctioning regions without overt infarction is similar to that measured in hearts without dysfunction. This observation supports the view that at least a proportion of hibernating regions may be dysfunctioning because of repeat stunning.

We believe that for clinical decisionmaking it is useful to obtain a series of information, besides the dis-

tinction whether the dysfunctioning myocardium is stunned or hibernating. First, it is important to establish whether the dysfunctioning myocardium is viable or not, and whether it is normally perfused or hypoperfused. Second, it is useful to test the contractile reserve of the akinetic myocardium. Third, and perhaps more importantly, it is essential to establish by coronary angiography whether the perfusion defect is susceptible to interventional or pharmacological correction. All this information will allow the correct management of the left ventricular dysfunction, independent of whether it is the result of stunning or hibernation.

However, at least as a working hypothesis, for the present discussion and for future research, we believe that, in general, it is important to distinguish between left ventricular dysfunction due to stunning or to hibernation. In both cases the dysfunction is reversible. This is certainly encouraging and clinically relevant. Thus, the major difference is that blood flow is normal or near normal in stunned myocardium, whereas it is reduced in hibernating myocardium (Table 1).

There are numerous clinical conditions in which the myocardium is subjected to transient ischemia followed by reperfusion. These include spontaneous reperfusion after coronary artery spasm, unstable angina, exercise-induced ischemia, acute myocardial infarction with early reperfusion, angioplasty, open heart surgery with cardioplegic arrest, and cardiac transplantation. In all these conditions the occurrence of postischemic left ventricular dysfunction or stunning has been demonstrated or, at least, suggested. An excellent critical review of the problem is available [6].

Left Ventricular Dysfunction After Angioplasty and Resolution of Coronary Artery Spasm

In our experience, left ventricular dysfunction after percutaneous transluminal coronary angioplasty (PTCA) or after resolution of coronary artery spasm (Prinzmetal's angina) is a rare phenomenon. This probably is in relation to the extremely short period of regional ischemia occurring under these conditions. The available evidence agrees that reperfusion in the setting of PTCA or of Prinzmetal's angina is well tolerated and usually does not cause postischemic systolic dysfunction [23–28]. Angioplasty may induce diastolic abnormalities resulting in a transient decrease of left ventricular compliance [29,30]. This abnormality, however, is well tolerated.

Left Ventricular Dysfunction After Exercise-Induced Angina

Studies with two-dimensional echocardiography after treadmill testing suggest the occurrence of left ventricular dysfunction persisting after the resolution of chest pain and of the electrocardiographic abnormalities [31,32]. The degree of the wall motion abnormalities seems to be correlated to the intensity and duration of exercise, the severity and extension of coronary artery disease, and sympathetic stimulation [33]. These observations have been extended only to 30 minutes after exercise. It follows that the abnormalities could be the consequence of subendocardial ischemia rather than to a classical stunning and, in any case, seem to be well tolerated [34].

These results have not been confirmed by studies using radionuclide angiography, which have failed to demonstrate left ventricular dysfunction beyond the first 5 minutes after exercise [35–37]. We have attempted to approach this topic by determining the changes in ventricular volumes at rest and after exercise by using 99 mTc-sestamibi SPECT in a group of 129 consecutive patients studied by stress-rest with sestamibi imaging to exclude coronary artery disease [38].

Regional uptake of the radiotracer refers to regional blood flow at the time of injection which, in our study, was performed at baseline and at peak exercise. The acquisition, however, was obtained 2 hours after sestamibi administration, following exercise. In this way we had the opportunity to evaluate the persistence of postischemic ventricular dilatation, which, in turn, is an indirect index of stunning. In our patients with coronary artery disease (110 out of the initial 129), we could not detect significant enlargement of external left ventricular volume in comparison with a group of normal subjects, suggesting that stunning is not a common phenomenon when analyzed 2 hours after exercise testing. When present, however, it has important prognostic implication as a reflection of severe and extensive coronary artery disease.

Left Ventricular Dysfunction After Acute Myocardial Infarction and Unstable Angina

The studies assessing recovery of left ventricular function in acute myocardial infarction after thrombolysis and/or PTCA uniformly suggest a delayed improvement after reperfusion [39–43]. The precise time course of recovery of myocardial function is not established, although most of the improvement is likely to take place within the first 7–10 days after infarction [40,44]. Interestingly, the severity of the residual stenosis appears to be an important determinant of the rate of recovery after thrombolytic therapy, suggesting that the dysfunction could also be due to persistent subendocardial ischemia or hibernation [45,46].

From our experience in 105 cases of intracoronary thrombolysis [47,48], it is clear that the degree of regional postischemic left ventricular dysfunction is also

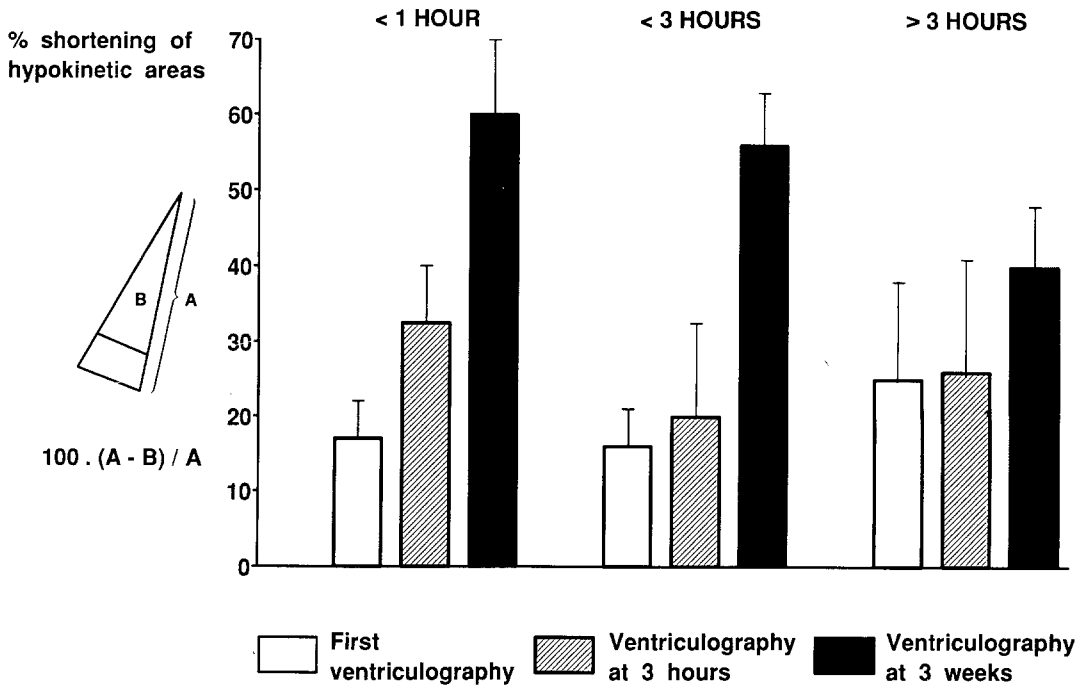

Fig. 1. Recovery of percentage shortening of hypokinetic areas immediately after or at 3 weeks after successful thrombolysis. Relation to the duration of ischemia. Left ventricular ejection fraction was determined by left ventricular angiography [47]. Results are expressed as mean ± SEM.

related to the duration of the ischemic period, as early recovery of percentage segmental area change after reperfusion (3 hours) was higher in those patients receiving the thrombolytic agent within 1 hour from the onset of typical chest pain (Figure 1).

Postischemic left ventricular dysfunction is also likely to occur in patients with acute myocardial infarction who have not been treated with thrombolysis or PTCA, as coronary reperfusion may occur spontaneously. Similarly, stunning is likely in patients with unstable angina, as this syndrome is caused by transient episodes of severe ischemia and reperfusion, not associated with irreversible damage [49]. Both these conditions have been associated with reversible wall motion abnormalities, which could reflect reversible postischemic left ventricular dysfunction [50,51]. However, the same abnormalities could also be caused by hibernation, ongoing silent ischemia, or both. Unfortunately, appropriate controlled studies monitoring the time course of the ventricular dysfunction and coronary flow are still lacking.

During acute myocardial infarction it is not uncommon to observe ventricular dysfunction, which, in turn, causes a mitral incompetence. Transient administration of a positive inotropic agent causes a clear and sustained improvement of ventricular function with resolution of the valvular dysfunction and improvement of global ejection fraction. A typical example recorded by Doppler echocardiography is reported in Figure 2. It is worthwhile to recall here that administration of dobutamine at a dose of 10 μg/kg did not cause further ischemia, suggesting that the dysfunctioning myocardium retained an important contractile reserve and, most likely, was well perfused.

Left Ventricular Dysfunction After Open Heart Surgery

There is a general consensus that a transient depression of myocardial function is common after cardiopulmonary bypass [52–55]. Probably the surgeons were aware of this possibility long before the description of stunning, because they often successfully used calcium or positive inotropic agents to stimulate those hearts having difficulty in recovering after reperfusion despite the absence of evidence of myocardial necrosis. Most likely, the stunning is consequent on a period of global and total ischemia. This type of ventricular dysfunction is reversible within 24–48 hours in most cases. We have demonstrated that, as in the case of thrombolysis, the dysfunction is related to the duration of the previous ischemic period and to the degree of oxidative stress occurring on reperfusion [56,57] (Figure 2).

It has been suggested that postsurgical stunning in subgroups of high risk patients with poor preoperative ventricular function, prolonged aortic cross-clamping time, or with unstable angina before surgery could have adverse effects on morbidity and mortality

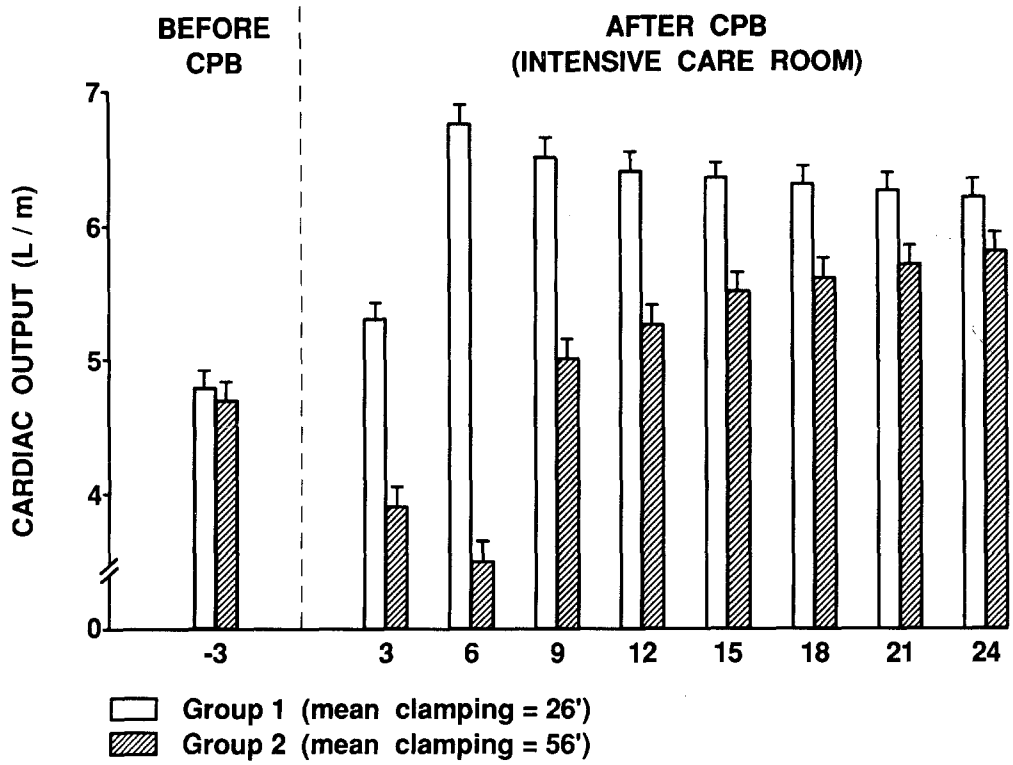

Fig. 2. Recovery of cardiac output after surgery for coronary artery bypass in relation to the duration of global ischemia (clamping). CPB = coronary pulmonary bypass. Results are expressed as mean ± SEM.

[6]. Clear, controlled data, however, are not available. If we define stunning as a reversible condition, it is difficult to accept this concept. Probably the high operative risk of such patients is related to the higher incidence of irreversible damage during the operation. Interestingly, it has also been suggested, particularly after surgery when the patient is hospitalized and resting in bed, that stunning could represent a normal reparative process, beneficial for the patient [58]. A slow recovery in function will, in fact, reduce energetic demand of the myocardium and allow complete recovery of metabolism and restoration of high energy stores.

Finally, stunning could also develop in the course of cardiac transplantation as the heart is subjected to prolonged ischemia followed by reperfusion. There is considerable and largely anecdotal evidence that cardiac function is reversibly depressed in the first hours or days after transplantation, but controlled studies have not been performed.

Ventricular Dysfunction due to Hibernation

Hibernation presents as chronic left ventricular regional dysfunction. The condition arises from prolonged myocardial hypoperfusion in which myocytes remain viable but contraction is depressed [1,59]. The dysfunction can be partially or completely restored to normal if the myocardial oxygen supply is favorably altered by improving blood flow with reperfusion and/or by reducing demand [1]. On imaging the heart, the dysfunction presents as areas of left ventricular wall that may be hypokinetic, akinetic, or dyskinetic.

It is implicit in this definition that hibernation: (a) is a chronic, reversible abnormality, provided that coronary flow is restored (in the case of ischemic heart disease) or oxygen demand is reduced (in the case of chronic left ventricular overload); (b) represents a viable myocardium, showing residual contractile and coronary flow reserve, which must be distinguished from the irreversibly damaged tissue present after myocardial infarction [60,61]; and (c) has a moderately reduced coronary flow. Thus the hallmark of this condition is a "matching" reduction in both flow and function [62].

The diagnosis of hibernation is clinically relevant because it may have diagnostic and therapeutic implications, particularly in patients with coronary artery disease. In such patients, differentiation of viable from nonviable myocardium is important, as regional and global left ventricular function due to hibernation will improve after revascularization, and this is associated with improved survival [60,62,63].

It follows that the true clinical gold standard for

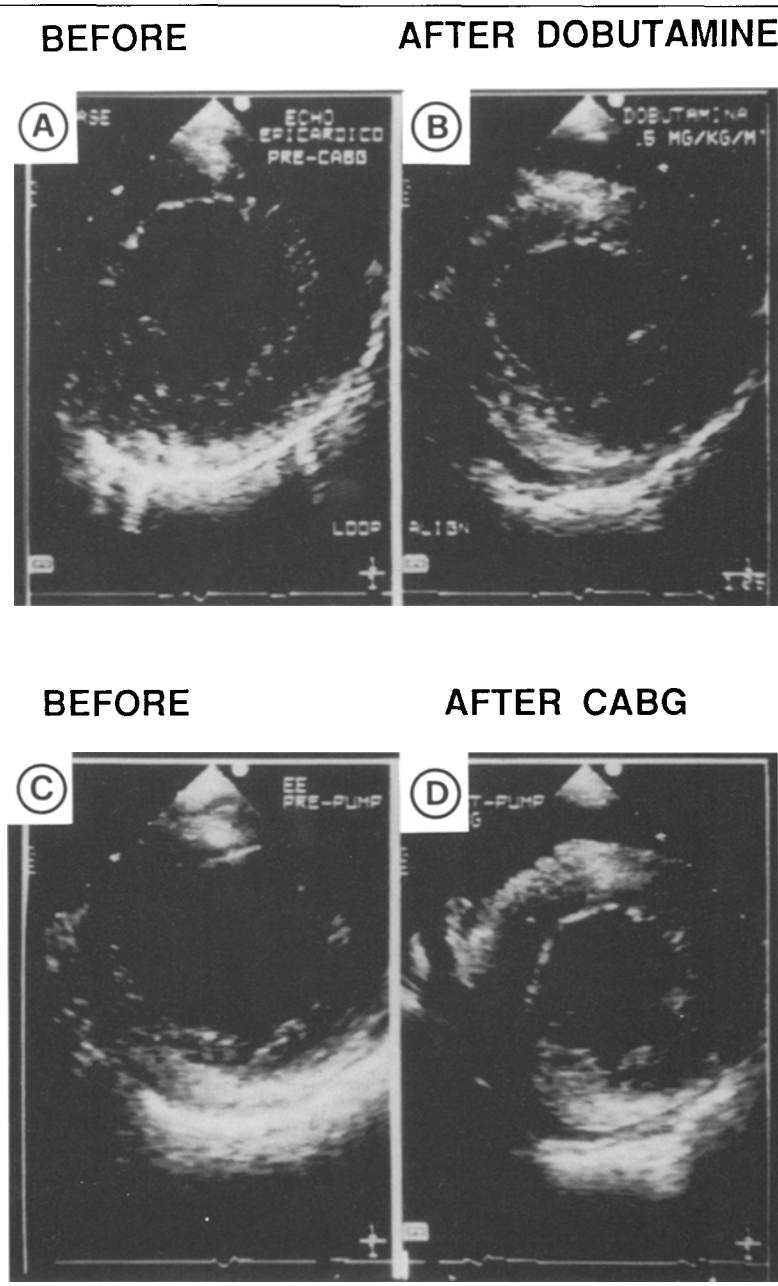

Fig. 3. *Intraoperative epicardial echocardiography end-systolic frames of a left ventricular short axis view before (A) and after (B) dobutamine infusion with clear improvement of the anterior and septal baseline akinesia. In C and D is shown a study of the same patient before (C) and immediately after (D) coronary artery bypass. The immediate improvement of the same segments is evident.*

hibernation is the improvement in systolic function of dysfunctional myocardial segments after revascularization. Such a retrospective standard, however, is insufficient. An accurate prospective diagnosis of patients with potentially reversible left ventricular dysfunction is essential for identification of ideal candidates for revascularization procedures. Variables for identifying viable but dysfunctional myocardium at present under consideration are preserved metabolic activity as detected with positron emission tomography (using ^{18}F-fluorodeoxyglucose or ^{11}C-acetate); thallium redistribution using exercise-redistribution or rest-redistribution protocols; uptake of thallium using a reinjection protocol in patients with irreversible defects on exercise-redistribution studies; and enhanced regional wall motion using low dose dobutamine echocardiography [4,64].

Chronic Left Ventricular Dysfunction due to Ischemic Heart Disease

Many groups approached the problem of establishing the reversibility of resting left ventricular dysfunction in the 1970s. At that time we performed dynamic ventriculography before and after K-strophanthin administration [65,66]. Digitalis was found to have different actions on asynergic areas: improvement in some, worsening in others, and little or no action on normokinetic areas [66]. We concluded that improvement of asynergic segments could be related to the presence of a viable myocardium, while paradoxical systolic motion would suggest the presence of frank fibrosis or acute ischemia.

Rahimtoola was the first to clearly show that abnormal left ventricular function at rest may be due to chronic, painless, persistent severe myocardial ischemia and that the dysfunction may be reversible upon reperfusion [67,68]. Two years later he used the term *hibernating myocardium* [69]. Thereafter several studies have shown that recovery of left ventricular function after revascularization occurs in a large subset of patients, confirming that many asynergic regions represent viable, hibernating myocardium [70–75].

In our ongoing experience, it is possible to detect the combination of a viable myocardium (determined by thallium rest-redistribution) with a preserved contractile reserve (determined by low-dose dobutamine echocardiography) in approximately 85% of patients with coronary artery disease and chronic left ventricular dysfunction [75–77]. These patients showed an immediate early recovery after reperfusion (detected by intraoperative echocardiography), which was confirmed at discharge from hospital and in the consequent follow-up at 6 months. A typical example of recovery of left ventricular function before and after dobutamine infusion and after coronary artery bypass surgery detected by intraoperative echocardiography is shown in Figure 3. The early recovery of contractile function immediately after revascularization is surprising as one would expect that stunning should occur after reperfusion of the hibernating myocardium [78–80]. Similar data have been previously obtained by Topol et al. [81]. In our case the early recovery on reperfusion can be explained considering the severe inclusion criteria utilized and the fact that all patients had a positive test for contractile reserve, which, in turn, seems to be a good predictor of early recovery on reperfusion [77].

Chronic Left Ventricular Dysfunction due to Other Etiologies

It has been suggested that reversible chronic left ventricular dysfunction might occur in patients with dilated congestive cardiomyopathy of unknown etiology and without coronary artery disease [1,82,83]. We found that patients with idiopathic cardiomyopathy with no history of myocardial ischemia might have a positive rest-redistribution thallium test, suggesting a viable, but underperfused myocardium. Further studies, however, are needed to clarify this topic.

Equally, patients with severe valvular disease, such as aortic stenosis and/or regurgitation, might have chronic left ventricular dysfunction, which is reversible after administration of afterload-reducing agents and surgical correction of the valvular defect. As this pathology in its advanced stage is associated with relative myocardial ischemia despite normal coronary anatomy, it is conceivable that the chronic dysfunction due to left ventricular overload is worsened by the relative hypoperfusion. Resolution of overload might ameliorate left ventricular performance directly or by optimizing the ratio between oxygen demand and supply. Therefore, chronic hypoperfusion could be the potential mechanism of the left ventricular dysfunction in these subjects.

Acknowledgments

This work was supported by the National Research Council (CNR) target project "Prevention and Control of Disease Factors," no. 9100156 pf 41. We thank Miss Silvia Brognoli and Miss Roberta Bonetti for their secretarial assistance in preparing the manuscript.

References

1. Rahimtoola S. The hibernating myocardium. *Am Heart J* 1989;117:211–221.
2. Bolli R. Mechanism of myocardial "stunning." *Circulation* 1990;82:723–738.
3. Kusuoka H, Marban E. Cellular mechanisms of myocardial stunning. *Annu Rev Physiol* 1992;54:243–256.

4. Dilsizian V, Bonow R. Current diagnostic techniques of assessing myocardial viability in patients with hibernating and stunned myocardium. *Circulation* 1993;87:1–20.
5. Braunwald E, Kloner RA. The stunned myocardium: Prolonged, postischemic ventricular dysfunction. *Circulation* 1982;66:1146–1149.
6. Bolli R. Myocardial stunning in man. *Circulation* 1993;86: 1671–1691.
7. Pierard LA, De Landsheere CM, Berthe C, Rigo P, Kulbertus HE. Identification of viable myocardium by echocardiography during dobutamine infusion in patients with myocardial infarction after thrombolytic therapy: Comparison with positron emission tomography. *J Am Coll Cardiol* 1990;15: 1021–1031.
8. Takatsu F, Suzuki A, Nagaya T. Variant angina pectoris with prolonged electrical and mechanical stunning. *Am J Cardiol* 1986;58:647–649.
9. Mathias P, Kerin NZ, Blevins RD, Cascase P, Rubenfire M. Coronary vasospasm as a cause of stunned myocardium. *Am Heart J* 1987;113:383–385.
10. Lette J, Gagnon A, Waters D. Acute pulmonary edema caused by prolonged myocardial stunning after dipyridamole-thallium imaging. *Am J Med* 1989;87:461–463.
11. Yuki K, Kodama Y, Onda J, Emoto K, Morimoto T, Uozumi T. Coronary vasospasm following subarachnoid hemorrhage as a cause of stunned myocardium. *J Neurosurg* 1991;75: 308–311.
12. Takahashi A, Ono Y, Shishido F, Uemura K, Kadowaki K, Kumagai T. PET evaluations of ischemic heart disease showing transient ST-T elevation: Report of two cases. *J Cardiol* 1990;20:241–248.
13. Chikamori D, Hamashige N, Odawara H, et al. A case of severe cardiac failure due to myocardial stunning. *J Cardiol* 1989;22(Suppl):79–82.
14. Yakushijin Y, Yamada A, Higuchi S, Ogata Y, Ashihara T, Fukuyama T. A case of stunned myocardium determined by nuclear cardiac imaging. *Jpn J Nucl Med* 1990;27: 1433–1438.
15. Shahian DM, St Ledger S, Kimmell W, Bogosian M, Abraham W, Johnson ME. Successful recovery of postischemic stunned myocardium using centrifugal left ventricular assist. *J Cardiothorac Vasc Anesth* 1990;4:84–88.
16. Kobayashi T, Imagawa H, Satoh H, Yoshino T, Fudemoto Y, Matsuwaka R. Biventricular assist support using centrifugal pump in cardiogenic shock following coronary bypass grafting: A case report of long survival. *J Jpn Assoc Thorac Surg* 1991;39:924–929.
17. Heusch G. Myocardial stunning: A role for calcium antagonists during ischemia? *Cardiovasc Res* 1992;26:14–19.
18. Ferrari R, Visioli O. Calcium channel blockers and ischaemia heart disease: Theoretical expectation and clinical experience. *Eur Heart J* 1991;12:18–24.
19. Homans DC, Laxson DD, Sublett E, Lindstrom P, Bache RJ. Cumulative deterioration of myocardial function after repeated episodes of exercise-induced ischemia. *Am J Physiol* 1989;256:H1462–H1471.
20. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. *N Engl J Med* 1992;326:242–250; 310–318.
21. Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent ischemia as a marker for early unfavorable outcomes in patients with unstable angina. *N Engl J Med* 1986;314:1214–1219.
22. Bol A, Melin JA, Vanoverschelde JL, et al. Direct comparison of [^{13}N] ammonia and [^{15}O] water estimates of perfusion with quantification of regional myocardial blood flow by microspheres. *Circulation* 1993;87:512–525.
23. Serruys PW, Wijns W, van den Brand M, et al. Left ventricular performance, regional blood flow, wall motion and lactate metabolism during transluminal angioplasty. *Circulation* 1984;70:24–36.
24. Visser CA, David GK, Kan G, et al. Two-dimensional echocardiography during percutaneous transluminal coronary angioplasty. *Am Heart J* 1986;111:1035–1046.
25. Labovitz AJ, Lewen MK, Kern M, Vandormael M, Deligonal U, Kennedy HL. Evaluation of left ventricular systolic and diastolic dysfunction during transient myocardial ischemia produced by angioplasty. *J Am Coll Cardiol* 1987;10: 748–755.
26. Alam M, Khaja B, Brymer J, Marzelli M, Goldstein S. Echocardiographic evaluation of left ventricular function during coronary artery angioplasty. *Am J Cardiol* 1986;57:20–25.
27. Hauser AM, Gangadharan V, Ramos RG, Gordon S, Timmis GC, Dudlets P. Sequence of mechanical, electrocardiographic and clinical effects of repeated coronary artery occlusion in human beings: Echocardiographic observations during coronary angioplasty. *J Am Coll Cardiol* 1985;5: 193–197.
28. Fournier C, Boujon B, Hebert JL, Zamani K, Grimon G, Blondeau M. Stunned myocardium following coronary spasm. *Am Heart J* 1991;121:593–595.
29. Wijns W, Serruys PW, Slager CJ, et al. Effect of coronary occlusion during percutaneous transluminal angioplasty in humans on left ventricular chamber stiffness and regional diastolic pressure-radius relations. *J Am Coll Cardiol* 1986; 7:455–461.
30. Zoghbi WA, Bolli R. The increasing complexity of assessing diastolic function from ventricular filling dynamics. *J Am Coll Cardiol* 1991;17:237–238.
31. Scognamiglio R, Ponchia A, Fasoli G, Miraglia G, Dalla-Volta S. Exercise-induced left ventricular dysfunction in coronary heart disease: A model for studying the stunned myocardium in man. *Eur Heart J* 1991;12(Suppl G):16–19.
32. Kloner RA, Allen J, Cox TA, Zhen Y, Ruiz CE. Stunned left ventricular myocardium after exercise treadmill testing in coronary artery disease. *Am J Cardiol* 1991;68:329–334.
33. Homans DC, Laxson DD, Sublett E, Pavek T, Crampton M. Effect of exercise intensity and duration on regional function during and after exercise-induced ischemia. *Circulation* 1991;83:2029–2037.
34. Robertson WS, Feigenbaum H, Armstrong WF, Dillon JC, O'Donnell J, McHenry PW. Exercise echocardiography: A clinical practical addition in the evaluation of coronary artery disease. *J Am Coll Cardiol* 1983;6:1085–1089.
35. Berger HJ, Reduto LA, Johnstone DE, et al. Global and regional left ventricular response to bicycle exercise in coronary artery disease: Assessment by quantitative radionuclide angiocardiography. *Am J Med* 1979;66:13–21.
36. Dymond DS, Foster C, Grenier RP, Carpenter J, Schmidt DH. Peak exercise and immediate postexercise imaging for the detection of left ventricular function abnormalities in coronary artery disease. *Am J Cardiol* 1984;53:1532–1537.
37. Schneider RM, Weintraub WS, Klein LW, Seelaus PA, Agarwai JB, Helfant RH. Rate of left ventricular function recovery by radionuclide angiography after exercise in coronary artery disease. *Am J Cardiol* 1986;57:927–932.
38. Milan E, Rossini PL, Metra M, Giubbini R. Changes in post exercise 99mTc-Sesta-MIBI left ventricular volumes

(abstr). First International Congress of Nuclear Cardiology, Cannes, France 1992, p. 1202.
39. Anderson JL, Marshall HW, Bray BE, et al. A randomized trial of intracoronary streptokinase in the treatment of acute myocardial infarction. *N Engl J Med* 1983;308:1313–1318.
40. Bourdillon PDV, Broderick TM, Williams ES, et al. Early recovery of regional left ventricular function after reperfusion in acute myocardial infarction assessed by serial two-dimensional echocardiography. *Am J Cardiol* 1989;63: 641–646.
41. Schmidt WG, Sheehan FH, von Essen R, Vebis R, Effert S. Evolution of left ventricular function after intracoronary thrombolysis for acute myocardial infarction. *Am J Cardiol* 1989;63:497–502.
42. Anderson JL, Marshall HW, Askins JC, et al. A randomized trial of intravenous and intracoronary streptokinase in patients with acute myocardial infarction. *Circulation* 1984;70: 606–618.
43. Schroeder R, Biamino G, von Leitner E-R, et al. Intravenous short-term infusion of streptokinase in acute myocardial infarction. *Circulation* 1983;67:536–548.
44. Zaret BL, Wackers FJT, Terrin ML, et al. Assessment of global and regional left ventricular performance at rest and during exercise after thrombolytic therapy for acute myocardial infarction: Results of the thrombolysis in myocardial infarction (TIMI) II study. *Am J Cardiol* 1992;69:1–9.
45. Patel B, Kloner RA, Przyklenk K, Braunwald E. Postischemic myocardial "stunning": A clinically relevant phenomenon. *Ann Intern Med* 1988;108:626–628.
46. Sheehan FH, Mathey DG, Schofer J, Dodge HT, Bolson EL. Factors that determine recovery of left ventricular function after thrombolysis in patients with acute myocardial infarction. *Circulation* 1985;71:1121–1128.
47. Valente M, Klugman S, Niccoli L, et al. Importance of early recanalization of the occluded coronary artery in acute myocardial infarction for preservation of left ventricular function. *J Moll Cell Cardiol* 1988;20:145–154.
48. Ferrari R, La Canna G, Giubbini R, Alfieri O, Visioli O. Stunned and hibernating myocardium possibility of intervention. *J Cardiovasc Pharmacol* 1992;20:5–13.
49. Braunwald E. Unstable angina: A classification. *Circulation* 1989;80:410–414.
50. de Zwaan C, Cheriex EC, Braat SHJG, Stappers JLM, Wellens HJJ. Improvement of systolic and diastolic left ventricular wall motion by serial echocardiograms in selected patients treated for unstable angina. *Am Heart J* 1991; 121:789–797.
51. Renkin J, Wijns W, Ladha Z, Col J. Reversal of segmental hypokinesis by coronary angioplasty in patients with unstable angina, persistent T wave inversion, and left anterior descending coronary artery stenosis: Additional evidence for myocardial stunning in humans. *Circulation* 1990;82: 913–921.
52. Fremes SE, Christakis GT, Weisel RD, et al. A clinical trial of blood and crystalloid cardioplegia. *J Thorac Cardiovasc Surg* 1984;88:725–741.
53. Czer L, Hamer A, Murphy F, et al. Transient hemodynamic dysfunction after myocardial revascularization: Temperature dependence. *J Thorac Cardiovasc Surg* 1983;86:226–234.
54. Fremes SE, Weisel RD, Mickle DAG, et al. Myocardial metabolism and ventricular function following cold potassium cardioplegia. *J Thorac Cardiovasc Surg* 1985;89:531–546.
55. Ferrari R, Curello S, Ceconi C, de Giuli F, Scotti C, Alfieri O. II fenomeno dello stordimento del miocardio in cardiochirurgia. In: Fazzini PF, Parodi O, eds. *Il Punto su: Il Miocardio Ischemico,* OIC Medical Press, Firenze 1991: 203–212.
56. Ferrari R, Alfieri O, Curello S, et al. Occurrence of oxidative stress during reperfusion of the human heart. *Circulation* 1990;81:201–211.
57. Ferrari R, Curello S, Boffa GM, et al. Oxygen free radical mediated heart injury in animal models and during by-pass surgery in humans. In: Diplock AT, Machlin LJ, Packer L, Pryor WA, eds. *Vitamin E, Biochemistry and Health Implications. Ann NY Acad Sci* 1990;2:237–253.
58. Ferrari R, Visioli O. Stunning: Damaging or protective to the myocardium? *Cardiovasc Drugs Ther* 1991;5:939–946.
59. Rahimtoola SH. Coronary bypass surgery for chronic angina—1981: A perspective. *Circulation* 1982;65:225–241.
60. Braunwald E, Rutherford JD. Reversible ischemic left ventricular dysfunction: Evidence for the "hibernating myocardium." *J Am Coll Cardiol* 1986;8:1467–1470.
61. Ross J Jr. Myocardial perfusion-contraction matching: Implications for coronary heart disease and hibernation. *Circulation* 1991;83:1076–1082.
62. Alderman EL, Fisher LD, Litwin P, et al. Results of coronary artery surgery in patients with poor left ventricular function (CASS). *Circulation* 1983;68:785–795.
63. Pigott JD, Kouchoukos NT, Oberman A, Cutter GR. Late results of surgical medical therapy for patients with coronary artery disease and depressed left ventricular function. *J Am Coll Cardiol* 1985;5:1036–1045.
64. Tillisch J, Brunken R, Marshall R, et al. Reversibility of cardial wall-motion abnormalities predicted by positron tomography. *N Engl J Med* 1986;314:884–888.
65. Cucchini F, Di Donato M, Fappani A, Ferrari R, Visioli O. L'azione differenziale della strofantina sulle aree asinergiche e su quelle normocinetiche del ventricolo sinistro nell'insufficienza coronarica. *Boll Soc Ital Card* 1977;7:968–973.
66. Cucchini F, Di Donato M, Ferrari R, Visioli O. Dynamic ventriculography with K-strophanthin. *Eur J Cardiol* 1978; 81:75–85.
67. Rahimtoola SH. Postoperative exercise response in the evaluation of the physiologic status after coronary bypass surgery. *Circulation* 1982;65:II106–II114.
68. Rahimtoola SH. Coronary bypass surgery for chronic angina—1981: A perspective. *Circulation* 1982;65:225–241.
69. Braunwald E, Hollingsworth C, Passamani E, eds. NHLBI Workshop on Surgery in the Treatment of Coronary Artery Disease, September 6 and 7, 1984, Bethesda, Maryland. *Circulation* 1985;72:V1–V2.
70. Rees G, Bristow JD, Kremkau EL, et al. Influence of aortocoronary bypass surgery on left ventricular performance. *N Engl J Med* 1971;284:1116–1125.
71. Chatterjee K, Swan HJC, Parmley WW, Sustaita H, Marcus HS, Matloff J. Influence of direct myocardial revascularization on left ventricular asynergy and function in patients with coronary heart disease. *Circulation* 1973;47: 276–286.
72. Rozanski A, Berman DS, Gray R, et al. Use of thallium-201 redistribution scintigraphy in the preoperative differentiation of reversible and nonreversible myocardial asynergy. *Circulation* 1981;64:936–944.
73. Brundage BH, Massie BM, Botvinick EH. Improved regional ventricular function after successful surgical revascularization. *J Am Coll Cardiol* 1984;3:902–908.
74. Dilsizian V, Bonow RO, Cannon III RO, et al. The effect of

coronary artery bypass grafting on left ventricular systolic function at rest: Evidence for preoperative subclinical myocardial ischemia. *Am J Cardiol* 1988;61:1248–1254.
75. Giubbini R, Milan E, Rossini L, et al. Combined evaluation of perfusion and function for the identification of viable myocardium. *J Nucl Biol Med* 1992;36:126–129.
76. Ferrari R, La Canna G, Giubbini R, Alfieri O, Visioli O. Hibernating myocardium in patients with coronary artery disease: Identification and clinical importance. *Cardiovasc Drugs Ther* 1992;6:287–293.
77. La Canna G, Alfieri O, Giubbini R, Gargano M, Ferrari R, Visioli O. Echocardiography during infusion of dobutamine for identification of hibernating myocardium in patients with coronary artery disease and chronic left ventricular dysfunction. *J Am Coll Cardiol* 1994, in press.
78. Carlson EB, Cowley MJ, Wolfgang TC, Vetrovec GW. Acute changes in global and regional rest left ventricular function after successful coronary angioplasty: Comparative results in stable and unstable angina. *J Am Coll Cardiol* 1989;13:1262–1269.
79. Mizuno K, Arakawa K, Shibuya T, et al. Improved regional and global diastolic performance in patients with coronary artery disease after percutaneous transluminal coronary angioplasty. *Am Heart J* 1988;115:302–306.
80. Van den Berg EK Jr, Popma JJ, Dehmer GJ, et al. Reversible segmental left ventricular dysfunction after coronary angioplasty. *Circulation* 1990;81:1210–1216.
81. Topol EJ, Weiss JL, Guzman PA, et al. Immediate improvement of dysfunctional myocardial segments after coronary revascularization: Detection by intraoperative transesophageal echocardiograph. *J Am Coll Cardiol* 1984;4:1123–1134.
82. Demakis JG, Proskey A, Rahimtoola SH, et al. The natural course of alcoholic cardiomyopathy. *Ann Intern Med* 1974; 80:293–304.
83. Demakis JG, Rahimtoola SH. Peripartum cardiomyopathy. *Circulation* 1971;44:964–978.