Hibernating Myocardium

Lead Article

Expert Answers to Three Key Questions

Summaries of Ten Seminal Papers - *P.B. Garlick*   93

Bibliography of One Hundred Key Papers   105

Myocardial hibernation:
clinical manifestations and importance

Shahbudin H. Rahimtoola, MB, FRCP, MACP

Distinguished Professor - George C. Griffith Professor of Cardiology - Chairman, Griffith Center - Professor of Medicine
University of Southern California - Los Angeles, California - USA

Hibernating myocardium (HM) is a result of reduced myocardial blood flow that causes impaired left ventricular (LV) function at rest and can be reversed by revascularization. Although HM is not ischemia "in the strict sense," it may be viewed as an example of an "exquisitely regulated tissue successfully adapting its activity to prevailing circumstances." The clinical diagnosis of HM is based on documenting an area of LV dysfunction at rest with viable myocardium. HM has been demonstrated to occur in chronic and unstable angina, acute myocardial infarction, heart failure and/or severe LV dysfunction, and anomalous origin of the left coronary artery from the pulmonary artery. HM is characterized as clinically acute, subacute, or chronic on the basis of the rate of recovery of resting LV dysfunction after revascularization and the study of the morphologic changes in the dysfunctioning myocardium. However, such a classification into three precisely separated states may be somewhat arbitrary and HM may be best described as a spectrum. The outcome of patients with coronary artery disease is determined not only by the extent and severity of the disease, but also by the amount of HM and LV myocardium that is or can be irreversibly damaged. Successful revascularization of the HM is able to reduce LV dysfunction and the amount of myocardium at risk.

Reprint requests: Shahbudin R. Rahimtoola, MD - Distinguished Professor - University of Southern California - 2025 Zonal Avenue - Los Angeles, CA 90033 - USA

The term *hibernating myocardium* was coined to describe a state of persistently impaired myocardial and left ventricular (LV) function at rest due to reduced coronary blood flow that can be partially or completely restored to normal if the myocardial oxygen supply/demand relationship is favorably altered, either by improving blood flow and/or reducing demand *(Figure 1).*[1,2] It likely results from a relatively uncommon response to reduced myocardial blood flow at rest whereby the heart downgrades its myocardial function to the extent that blood flow and function are once again in equilibrium, and as a result, neither myocardial necrosis nor ischemic symptoms are present. Obviously, if the myocardial oxygen supply/demand balance is subsequently altered unfavorably either temporarily or permanently, then symptoms and signs of ischemia and/or of necrosis again occur. Repeated episodes of ischemia may lead to necrosis[3] and therefore are undesirable; thus, the hibernating response of the heart, namely, a reduction of function to cope with a reduced myocardial blood flow, could be considered an act of self-preservation (little blood, little work) and the heart could be considered to be a *"smart heart"* as appeared in an editorial in the *American Heart Journal.*[4]

Some earlier work and many subsequent studies have confirmed that most, if not all, of the initial postulates were correct. For example, short-term/acute hibernation results from both an adaptation[5-8] and a downregulation[9] in response to reduced myocardial blood flow (MBF), and hibernating myocardium (HM) in the clinical setting is associated with a reduced MBF.[10] My attention was first drawn to this problem by data presented at the American Heart Association annual scientific sessions in 1973 and published in 1974.[11] It was shown that in some patients, although one graft had occluded after coronary bypass surgery (CBS), resting preoperative LV systolic dysfunction had still improved and at times

Myocardial hibernation: clinical manifestations and importance - *Rahimtoola*

PREOPERATIVE
Single-vessel disease—occluded LAD

Control
LVEDV=128 mL
EF=0.37

Post-NTG
LVEDV=101 mL
EF=0.51

8 MONTHS POSTOPERATIVE
Patient coronary bypass graft to LAD

LVEDV=104 mL
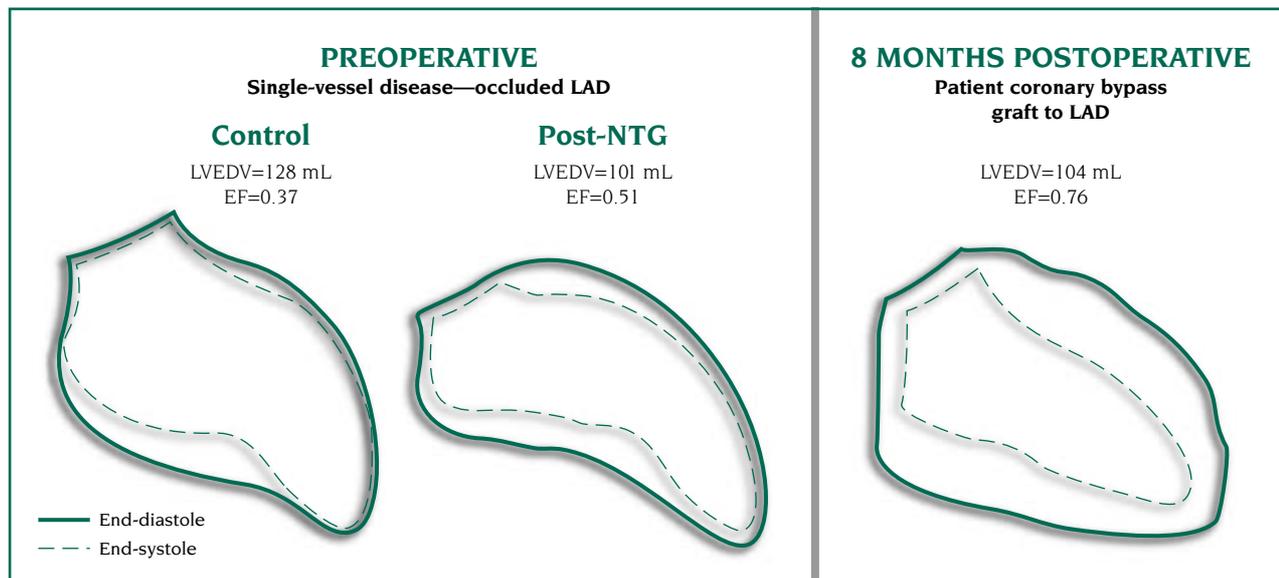EF=0.76

—— End-diastole
– — · End-systole

Figure 1. End-diastolic and end-systolic silhouettes of the LV from the right anterior oblique ventriculogram. In the preoperative studies (left), the ejection fraction (EF) in the control state was 0.37 and there was a large akinetic area involving the anteroapical wall. After nitroglycerin (NTG), there was an improvement of wall motion in the akinetic zone, and EF improved to 0.51. The patient had no history of MI. Coronary ateriography showed single-vessel disease with a totally occluded left anterior descending coronary artery (LAD). The distal LAD was filled by collaterals from the circumflex coronary artery and the posterior descending coronary artery. At 8 months postoperatively (right) on routine study, the graft was fully patent and there was good filling of the LAD. The patient now shows normal LV wall motion function and a normal EF of 0.76. LVEDV = left ventricular end-diastolic volume. Reprinted from reference 29, with permission.

even global LV systolic dysfunction had normalized. This occurred because other grafts in the same patient were patent and provided adequate collaterals to myocardial segments supplied by the occluded graft.

BACKGROUND

In the 1970s, many workers[12-27] focused their attention on proving the reversibility of resting LV dysfunction with CBS and on its detection preoperatively. In the 1980 Consensus Development Conference on Coronary Artery Bypass Surgery,[28] I failed to convince people about the presence of abnormal LV function at rest that was due to chronic, painless, persistent, severe myocardial "ischemia" at rest, and which was reversible.[29,30] The reasons this concept was not accepted likely were: (i) chronic, persistent, low-flow ischemia was not thought possible; (ii) painless ischemia was not generally accepted, particularly in the USA; and (iii) there were no experimental studies documenting its occurrence. At that time it was generally believed that persistent abnormal LV function at rest was due to irreversible myocardial necrosis, and that prolonged "ischemia" with or without pain was not possible. Even though painless ischemia had been described in the 1970s, only in the 1980s did it become

widely recognized that painless ischemia was quite common in patients with a variety of anginal syndromes.[31,32]

It is of interest that in 1979 "fixed" perfusion defects by thallium 201 imaging on stress and redistribution were shown to improve and even normalize with CBS.[33] This was confirmed in 1983 in a larger number of patients.[34] These "fixed" defects were considered to be the result of irreversible myocardial damage until Dilsizian and coworkers[35] documented in 1990 that on reinjection of thallium 201 after the redistribution images had been obtained, many segments with "fixed" defects had uptake of the tracer and were therefore viable. It is possible that a very large number of patients were denied revascularization because of these "fixed" defects, emphasizing the need for caution in applying knowledge about tests to all patients when the knowledge is incomplete. Also in 1979, Gewirtz and coworkers[36] documented that thallium 201 could be taken up on redistribution after a rest study, but the clinical significance of this observation was initially not fully appreciated.

From 1983 to 1985, I was unable to convince my colleagues at the national level that it was worth dedicating research funds to the study of the problem

of chronic painless ischemia and the associated LV dysfunction. I realized that a short, less complex term was needed to describe this phenomenon (abnormal LV function at rest due to chronic painless, resting, persisting myocardial "ischemia," and which was reversible) before it would gain more widespread recognition and acceptance. Therefore, I used the term "hibernating myocardium" in 1984[2] at a National Heart, Lung, and Blood Institute (NHLBI) Workshop on the Treatment of Coronary Artery Disease.[37]

It was better accepted than at the 1980 Conference, probably because painless ischemia was being more widely recognized and attention was focused on the other more important statements about CBS. Bashour's editorial[38] in August 1986 drew attention to HM and the concept of "electrical stunning" (transient Q waves from profound myocardial ischemia). Braunwald and Rutherford's subsequent editorial[39] in December 1986 endorsed the concept of HM, believed it was an appropriate use of the term, and confirmed its occurrence in patients.

ADVANTAGES OF THE TERM HIBERNATING MYOCARDIUM

Acceptance of the concept and the term HM has been beneficial, as the subsequent decade has seen: (i) much basic and clinical research in this area; (ii) a reassessment of the definition of ischemia[40]; (iii) development and assessment of tests for diagnosis of HM; and (iv) better treatment of patients. Much work still needs to be done in this field.

DEFINITION

HM can be *described* by the clinical situation, that is, it is impaired LV function at rest that is reversible by revascularization. Thus, Ross[41] has *described* HM as a perfusion-contraction matching, which it is. However, in the normal heart and probably also in one with myocardial infarction (MI) and a high degree of interstitial fibrosis and of myocytes with myolysis or loss of sarcomeres, there is also a match

between perfusion and contraction.[42,43] Ross also suggested that sustained perfusion-contraction matching seen in acute experimental studies and some clinical settings be termed "short-term hibernation" and that chronic perfusion-contraction matching seen in clinical syndromes be called "chronic hibernation."[41] Some of the differences between short-term and chronic hibernation are shown in *Table I*.

Hearse[40] has *defined* HM as "exquisitely regulated tissue successfully adapting its activity to prevailing circumstances."

TERMINOLOGY	
Experimental	
Short term	Chronic
Clinical	
Acute	Subacute
Subacute	Chronic
MYOCARDIUM	
Hibernating	
Normal	Near-normal
Some structural changes	Some structural changes
	Marked structural changes*
Adjacent	
Infarcted	Infarcted
Fibrotic	Fibrotic
Normal	Normal
PRIOR TO HIBERNATION	
Acute ischemic episode(s)	Acute ischemic episode(s)
Gradual reduction of blood flow	Gradual reduction of blood flow
Stunning?	Stunning?
RECOVERY FROM HIBERNATION	
Rapid/slow stunning may occur	Rapid/slow/very slow stunning?
LV function: normal or less abnormal	LV function: normal or less abnormal

*"Dedifferentiation" or "diffuse atrophy/wasting from prolonged inactivity and unloading of muscle" and varying degrees of degeneration/fibrosis from infarction.

***Table I.** Some characteristics of various manifestations of hibernating myocardium.*

HIBERNATION AND ISCHEMIA

The question of whether HM is ischemia or not is to some extent a semantic one depending on the definition of ischemia. Amazingly, even in 1994 there was no clear accepted definition of ischemia.[40] If ischemia is defined as just a reduction of MBF, then HM is a form of ischemia. On the other hand, if one defines ischemia as a reduced MBF that is associated with evidence of an effect of reduced MBF (apart from reduced LV contraction), then HM is likely not ischemic myocardium. The definition of ischemia as an imbalance between supply and demand may be too simplistic; at a minimum, "demand" should be changed to "need."[44]

One definition of ischemia could be: a reduction of MBF associated with perturbations of cardiac function(s) and/or structure.[44] The definition could be modified or expanded to take care of special situations, such as "absolute" vs "relative" reduction of flow, anemia, specific biochemical abnormalities, removal of metabolites, release of cytokines, alteration of cardiac genes and gene products, etc. One could also subcategorize myocardial ischemia into physiological ischemia and/or biochemical ischemia as suggested by Hearse.[40]

Clinically, significant myocardial ischemia has been assumed to be present when there was some abnormality that could be demonstrated with the ischemic episode. Therefore, I had postulated that HM may not represent ischemia "in the strict sense."[4] Indeed, HM may be a unique pathophysiological state that we may not be able to characterize or define

perfectly at the present time[44]; more research and data are needed. Hearse's suggestion that it may be more appropriately viewed as an example of an "exquisitely regulated tissue successfully adapting its activity to prevailing circumstances" may be most apt.[40]

MYOCARDIAL BLOOD FLOW IN HIBERNATING MYOCARDIUM

There are at least seven studies that have documented reduced MBF in patients with HM,[10] six of which measured MBF by positron emission tomography (PET) with use of [^{13}N]ammonia.

1. *Vanoverschelde et al*[45] reported on 17 patients who had no MI, had a totally occluded artery that supplied an area of myocardium that was collateral-dependent for flow, and had resting wall motion abnormality. MBF in dysfunctional LV segments was significantly lower than in normally functioning LV segments in the same 17 patients (77.1 ± 24.6 vs 95.5 ± 26.7 mL/min per 100 g; $P<0.001$; *Table II*).[1,4] The importance of comparing MBF in HM with that in normal areas in the same heart can be appreciated from this study.[46] MBF in normally functioning LV segments in these 17 patients was greater than that in another group of nine patients with coronary artery disease (CAD) and formal LV function (95.5 ± 26 vs 82.7 ± 18.0 mL/min per 100 g; $P<0.05$).[45,46] One reason for the increased MBF in the 17 patients with LV dysfunction was that these 17 patients had a 5.6% higher rate-pressure product and 21.7% larger LV volume than the nine patients with normal LV function,[46] and thus their MVO_2 needs would be greater.

	No. of patients	Myocardial blood flow (mL/min per 100 g)		
		Areas with normal LV function*	Areas with HM*	*P* value
Vanoverschelde et al[45]	17	95.5±26.7	77.1±24.6	<0.001
Czernin et al[47]	22	83±20	57±20	<0.05
Marzullo et al[42]	14	100±24	42±12	†
Shivalkar et al[43]	18	93.4±12.6	63.8±12.8	<0.005 ‡
Sun et al[50]	5	80.8±26	59.2±25	0.004

*In the same patients in each study. Mean±SD; † In each patient MBF was >2 SD below the mean in normals; ‡ Flameng, personal communication.

Note: Sambuceti et al[48] described six patients with LV dysfunction, all had MBF >2 SD below normal values (see text).

Table II. *Myocardial blood flow at rest by PET using [^{13}N]ammonia in hibernating myocardium (HM). Reprinted from reference 10, with permission.*

2. *Czernin et al*[47] reported on 22 patients with recent MI. They showed that MBF in mismatch regions was lower than in normal regions in the same patients (57±20 vs 83±20 mL/min per 100 g; *P*<0.05). Of the 20 patients who had coronary arteriography, 10, 7, and 3 had one-, two-, and three-vessel disease, respectively.

3. *Marzullo et al*[42] studied 14 patients with previous MI, infarct-related single-vessel CAD, and regional LV dysfunction. LV segments with impaired LV systolic pump function and metabolically viable myocardium had MBF that was >2 SD below the mean of normally contracting segments (42±12 vs 100±24 mL/min per 100 g).

4. *Sambuceti et al*[48] studied 19 patients without MI, with totally occluded single-vessel CAD supplying myocardium that was dependent on collaterals for flow; 6 had wall motion abnormalities in the collateral-dependent myocardium. "All 6 with a wall motion abnormality showed flow values >2 SD below normal values."[48]

5. *Shivalkar et al*[43] have shown that 18 of 50 patients undergoing CBS had reduced regional myocardial function (regional ejection fraction), reduced MBF, and normal metabolism (HM). The HM subgroup was the only subgroup that had improved regional ejection fraction after revascularization; MBF also increased after revascularization. Before revascularization, this subgroup had MBF that was 67±10% of control region. The mean 33% reduction in transmural MBF would be expected to result in reduction of subendocardial MBF of ≈55% to 60%.[5,49] In these 18 patients, MBF in the HM was lower than in the control regions (63.8±12.8 vs 93.4± 12.6 mL/min per 100 g; *P*<0.005; Flameng, personal communication).

6. *Sun et al*[50] reported on MBF in five patients with mismatch. MBF in the mismatch region was 59±25 vs 81±26 mL/min/100 g in normal remote regions in the same patients, *P*=0.004.

7. *Arani et al*[51] studied seven patients, using the inert gas technique for measurement of MBF. They showed, in collateral-dependent segments of a totally occluded left anterior descending coronary artery with wall motion abnormalities, that MBF was reduced (>2 SD below the mean) compared with normal subjects with the same rate-pressure product (38±8 vs 70±13 mL/min per 100 g)[51,52] and with total MBF (normal plus abnormal flow regions) in the same patients (38±8 vs 51±8 mL/min per 100 g; *P*=0.02).[51]

For a detailed discussion of MBF in HM in patients, please see reference 10.

DIAGNOSIS

The diagnosis of HM in patients should be considered in the presence of LV dysfunction at rest, the causes of which are listed in *Table III.* The clinical diagnosis of HM is based on: (i) documenting LV dysfunction at rest; and (ii) documenting that this area of LV dysfunction at rest has viable myocardium *(Table IV)*. It is relatively easy to document LV dysfunction at rest by either two-dimensional echocardiography, or radionuclide or contrast ventriculography. Demonstrating that the area of LV dysfunction at rest has viable myocardium at rest is easy in some patients and in others may be quite difficult.

NORMAL
DYSFUNCTIONAL AT REST
Irreversibly damaged (infarcted)
Stunned
Hibernating
ISCHEMIC DUE TO
Increased myocardial needs* and/or
Reduced myocardial supply*
*For O$_2$, substrates, etc.

Table III. *Some functional characteristics of LV myocardium.*

Copyright © S. H. Rahimtoola.

DOCUMENTING LV DYSFUNCTION AT REST BY
Two-dimensional echocardiography
Radionuclide ventriculography
Contrast ventriculography
DOCUMENTING AREA OF LV DYSFUNCTION HAS VIABLE MYOCARDIUM BY
Assessing regional function
• LV wall thickness
• Change in LV wall motion:
- Nitroglycerin
- Postextrasystolic potentiation
- Exercise
- Catecholamine infusion, eg, dobutamine
Assessing perfusion, membrane integrity, and metabolism
• Thallium 201/Tc-99m sestamibi scintigraphy
• Positron emission tomography

Table IV. *Diagnosis of hibernating myocardium.*

Copyright © S. H. Rahimtoola.

CLINICAL SYNDROMES

HM has been demonstrated to occur in a variety of clinical syndromes *(Table V).*

Chronic and unstable angina

Angina is usually the result of myocardial ischemia, which results in LV dysfunction; LV wall motion may be hypokinetic, akinetic, or even dyskinetic.

A large number of clinical studies have documented that LV dysfunction at rest can improve with revascularization.* These studies show that HM is common in these clinical syndromes. After CBS, the best predictor of an improvement in resting LV ejection fraction is the number of viable, asynergic myocardial segments per patient, that is, the number of segments that were hibernating; there was no correlation with angina.[63,65]

ANGINA
Chronic stable
Unstable
ACUTE MYOCARDIAL INFARCTION
HEART FAILURE AND/OR SEVERE LV DYSFUNCTION
ALCAPA*

Table V. *Clinical syndromes in which hibernating myocardium occurs. *Anomalous origin of left coronary artery from pulmonary artery.*

Copyright © S. H. Rahimtoola.

The group from the University of Virginia,[33,34] using quantitative thallium 201 imaging on exercise and redistribution, demonstrated that 64% (18 of 28) of patients with persistent thallium defects of 25% to 50% showed improvement or normalization after revascularization, whereas this improvement was seen in only 21% (3 of 14) of patients with persistent thallium defects of >50%. Bonow, Dilsizian, and coworkers[35,68] documented that approximately 50% of LV wall segments that show a persistent thallium 201 defect on redistribution or delayed studies after exercise have HM that improves or returns to normal after revascularization.

It appears that reinjection of thallium identifies viable myocardium in 31% to 49% of myocardial regions considered irreversible using conventional 3- to 4-hour redistribution images.[35,69-71] La Canna et al[60] have studied 33 patients with dobutamine echocardiography. Of 314 myocardial segments that were akinetic preoperatively, 160 (51%) were normal and 19 (6%)

* References 1, 2, 4, 11, 17, 26, 29, 30, 33-35, 39, 50, 53, 54, 56-67, 72.

were hypokinetic 3 months after CBS. More recently, the group from the Mayo Clinic showed that 33% of patients undergoing CBS had HM,[73] and Shivalkar and coworkers[43] very carefully and precisely documented that HM was present in 18 of 50 (36%) patients undergoing CBS.

The frequency of HM in stable and unstable angina has been documented: Carlson et al[55] showed that it was present in 75% (18 of 24) of patients with unstable angina and in only 28% (5 of 18) of patients with stable angina. We have shown that long-term (10-year) survival after CBS was significantly better in patients with unstable angina and preoperative LV dysfunction than in those with stable angina and preoperative LV dysfunction[4]; up to 6 years after surgery, survival in patients with unstable angina was similar to that in patients with unstable or stable angina who had normal preoperative LV function.[4] This finding is compatible with the hypothesis that it is more usual for the preoperative abnormal LV to improve or return to normal in patients with unstable angina than in those with stable angina.

Acute myocardial infarction

HM is known to occur in a region of LV wall at a distance from the area of MI *(Figure 2).*[4] This finding

FIRST MYOCARDIAL INFARCTION: INFERIOR

19 days post-AMI

Hibernating

Stunned (± hibernating)

— End-diastole
--- End-systole
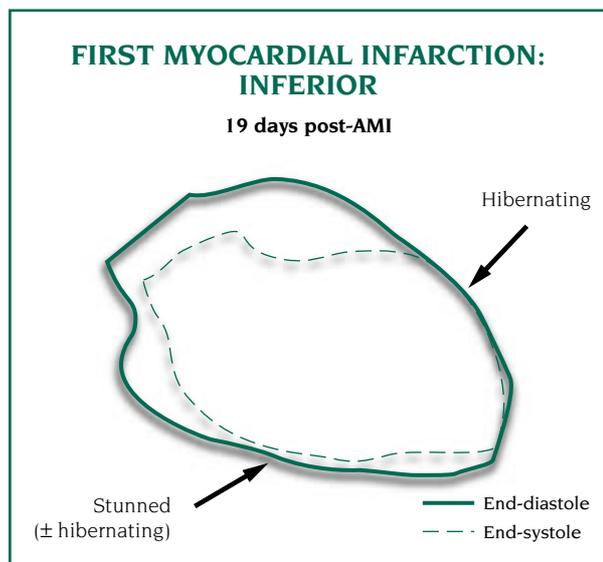
Figure 2. *Preoperative ventriculogram of a patient with severe four-vessel CAD and ejection fraction of 0.45. After CBS, LV function was normal (ejection fraction of 0.63). This shows a good example of the difference between the hibernating and stunned myocardium. The anterior wall is hibernating and the inferior wall is stunned. However, since it is possible that blood flow may not have been fully restored to the posterior descending artery, the inferior wall could have been hibernating as well. AMI = acute myocardial infarction. Reprinted from reference 4, with permission.*

Figure 3. *Ventriculography in a patient with acute MI. A 48-year-old woman who sustained an acute MI in the anterior wall was treated with tissue plasminogen activator 2 hours after onset of chest pain. Twe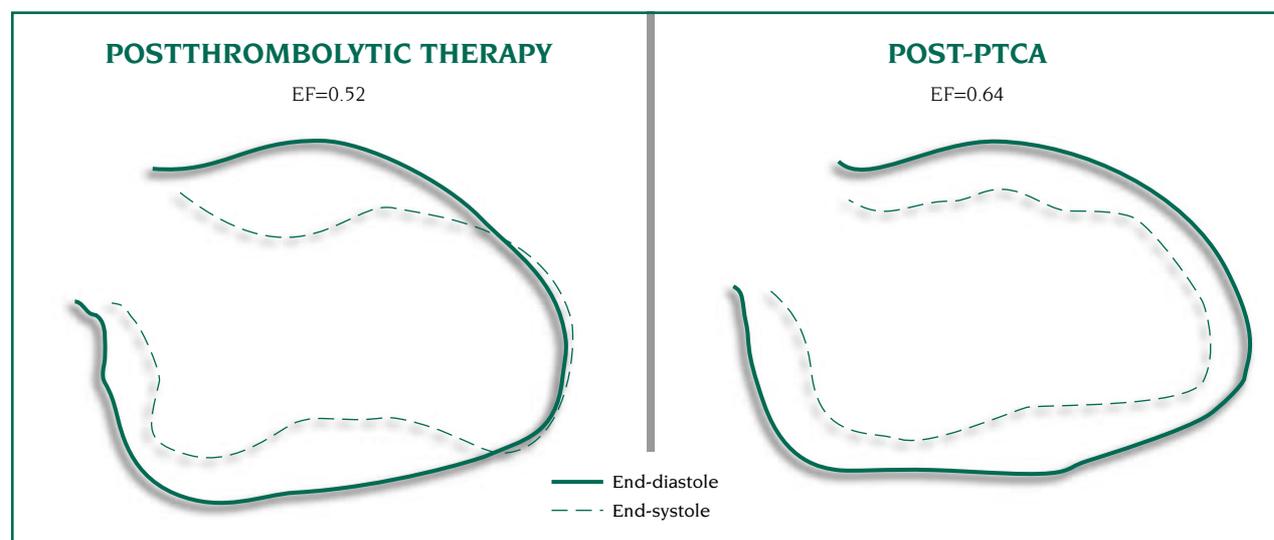nty-four hours later, the patient had recurrent angina and underwent emergency cardiac catheterization and coronary angioplasty. A tracing of right antero-oblique left ventriculogram is shown. Left panel, anterior akinesis/dyskinesis after thrombolytic therapy. The patient underwent percutaneous transluminal coronary angioplasty (PTCA) of a high-grade stenosis of left anterior descending and circumflex coronary arteries. Right panel, repeat ventriculography 1 week later demonstrated dramatic recovery of abnormal wall motion and improvement in global systolic function. EF = ejection fraction. From Kulick and Rahimtoola. Assessment of the survivors of acute MI: the case for coronary angiography. Reprinted from reference 10, with permission.*

suggests that LV dysfunction away from the area of a first infarct is presumptive evidence of HM in that area until proven otherwise. HM is also known to occur in the LV wall in the area of MI *(Figure 3).*[74]

Adams and coworkers[75] have studied 41 patients at an average of 8 days after a first acute MI; all patients had received thrombolytic therapy. Using PET, they demonstrated mismatch (HM) in 78% of the patients; 31% of patients had a large area of mismatch. This study documents the frequency of HM in the setting of acute MI after thrombolytic therapy.

Using PET, Tamaki et al[76] demonstrated increased [^{18}F]fluorodeoxyglucose (FDG) uptake, indicating HM, in 48 of 84 (57%) patients after MI. At follow-up, a cardiac event (cardiac death, nonfatal MI, unstable angina, and late revascularization) occurred in 3% of patients with no increase in FDG and in 33% of patients who had increased FDG uptake. It is noteworthy that 16 of 17 patients who had a subsequent event had an increase in FDG; multivariate analysis showed that an increase in FDG uptake was the most significant predictor of a subsequent cardiac event (P=0.0006), followed by the number of diseased vessels (P=0.008). This study demonstrates that HM occurs in many patients after MI and is associated with a high incidence of subsequent cardiac events.

Montalescot et al[77] performed a randomized trial of percutaneous transluminal coronary angioplasty (PTCA) versus no PTCA of the infarct-related artery 6 weeks after acute MI in patients who had single-vessel disease with no clinical or exercise-induced evidence of myocardial ischemia. Patients who were randomized to PTCA had increased coronary blood flow, an improvement in the thallium 201 pathologic:normal ratio after exercise, and improved LV wall motion. LV ejection fraction did not change significantly (0.51±0.03 to 0.52±0.04) in the group randomized to no PTCA, whereas it increased from 0.48±0.03 to 0.51±0.04 (P<0.04) in the PTCA group. This study demonstrates the occurrence of HM in the infarcted area or in an area that was presumed to be infarcted as well as the improvement in LV function after revascularization of HM.

Brunken and coworkers[78] studied 20 patients with chronic Q waves on the ECG. Of 31 dysfunctional LV segments, 6 (20%) had perfusion-metabolism mismatch (HM) on PET studies. This study suggests that some patients with an old MI and chronic Q waves on the ECG may have HM.

Heart failure and/or severe LV dysfunction

Akins et al[53] studied two patients with heart failure but without angina; they were shown to have severe CAD and stress-induced ischemia. CBS improved the

abnormal resting LV function and clinical heart failure. Shanes et al[79] reported on a patient with heart failure and presumed dilated LV. The patient had severe CAD with stress-induced ischemia and the LV dysfunction returned to normal after CBS.

Data from patients referred for cardiac transplantation to UCLA have been presented, which are most interesting and important. Luu et al[80] reported on a gradual improvement in LV function over a 1-year postoperative period in one patient in whom revascularization instead of transplantation was carried out *(Table VI)*. Among the 207 patients evaluated for heart transplantation from 1984 to 1990, 22 (11%) had CBS instead of transplantation and their 40-month actuarial survival was 72%; almost all of the deaths were perioperative.[81] More recently, Duong et al[82] reported on 112 patients with a diagnosis of idiopathic dilated cardiomyopathy who were referred for cardiac transplantation from April 1987 to July 1994. The LV ejection fraction was ≤0.35 and on PET studies 38 (34%) had perfusion-metabolism mismatch (HM). With CBS, hospital mortality was 10% and the 5-year survival was 71.4%. These studies document that patients with *chronic resistant heart failure* due to CAD or to presumed idiopathic dilated cardiomyopathy may have HM that needs to be diagnosed and appropriately treated early.

Lee et al[83] studied 50 patients with perfusion-metabolism mismatch (HM) who were revascularized; they had a 4% mortality and a 4% incidence of angina/MI, whereas 21 patients who were not revascularized had a mortality of 14%, and angina/MI occurred in 62%. Using PET, Eitzman et al[84] studied 82 patients with an LV ejection fraction of 0.34±0.13. HM, indicated by a mismatch on PET, was present in 54% (44 of 82) of patients. On follow-up, death or MI had occurred in 5% (2 of 38) of patients who had no hibernation, in 4% (1 of 26) of patients who had HM and were revascularized, and in 50% (9 of 18) of patients who had HM but were

not revascularized. DiCarli et al[85] from UCLA have presented results in patients with severe LV dysfunction (ejection fraction 0.25±0.07) who had angina or were referred for cardiac transplantation. HM, demonstrated by PET, was present in 46% (43 of 93) of patients. Patients with HM who were revascularized had a much lower incidence of cardiac death than those who were not revascularized (4% vs 33%; 2-year actuarial survival, 88% vs 50%; *P*=0.03).

These studies demonstrate the presence of HM in many patients with severe LV dysfunction with or without heart failure; the incidence of death or MI was high in patients who were not revascularized. As was mentioned earlier, Ragosta et al[63] have shown, using multivariate analysis, that the postrevascularization improvement in LV ejection fraction was predicted by the number of viable, asynergic myocardial segments per patient, that is, the number of myocardial segments that were hibernating; angina was not correlated.

Role of hibernating myocardium in heart failure

LV dysfunction is an important consequence of CAD and results from acute myocardial ischemia, HM, or MI. Stunning may be superimposed on any of these syndromes. It may eventually lead to heart failure *(Figure 4)*. Occasionally, however, CAD produces a mechanical defect (eg, mitral regurgitation, ventricular septal defect) that may result in clinical heart failure without significant LV systolic dysfunction. Myocardial stunning, which is a "short-term" phenomenon, may supervene on myocardial ischemia, hibernation, or MI, and exacerbates LV dysfunction. LV dysfunction from any cause results in, or contributes to, myocardial ischemia by increasing myocardial oxygen need and reducing coronary blood flow.[86] Structural changes commonly occur in LV dysfunction, which, if it persists, may lead to heart failure. HM can be

Time	Left ventricular end-diastolic dimension (mm)	Doppler mitral regurgitation	Radionuclide ejection fraction (%)	
			Rest	Exercise
Initial	66	Severe	16	15
4 weeks postoperatively	68	Moderate	26	24
6 weeks postoperatively	52	Mild	33	34
1 year postoperatively*	50	—	52	—

*Stevenson, personal communication, 1992.

Table VI. *Left ventricular function before and after coronary artery bypass grafting. Reprinted from reference 80, with permission.*
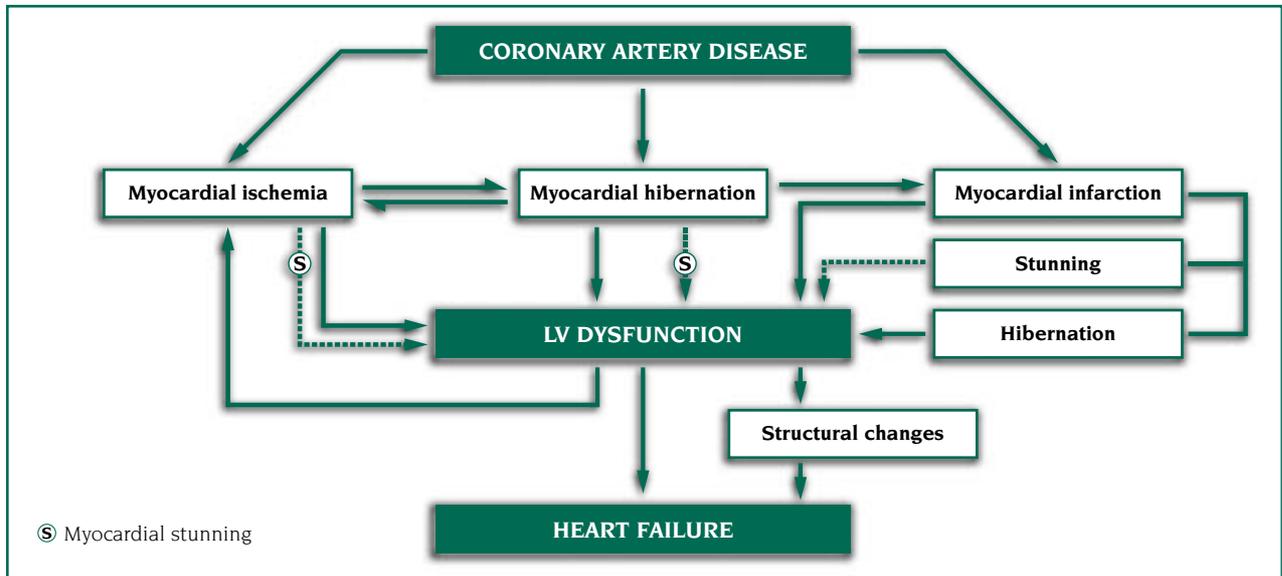
Figure 4. *Sequelae of CAD. CAD may result in myocardial ischemia, hibernation, or MI, all of which are associated with LV dysfunction. Hibernation may also be associated with subsequent acute ischemia or MI. Stunning may be superimposed on ischemia or HM upon reperfusion. Both hibernating and stunned myocardium can be present in patients who have MI. By definition, stunning usually improves spontaneously over a period of time. LV dysfunction, with or without associated structural changes, may produce clinical heart failure. Except for infarcted myocardial tissue, all other states are potentially reversible with appropriate and timely treatment. S = myocardial stunning. Reprinted from reference 87, with permission.*

partially or completely restored to normal with therapy; LV systolic dysfunction may normalize or be improved. The extent and time to improvement of LV function is dependent on the adequacy of revascularization and the extent and severity of myocardial changes that had been present prior to revascularization. Thus, LV dysfunction or heart failure caused or exacerbated by HM can be improved with appropriate therapy. On the other hand, if the HM is not appropriately treated in a timely manner, it may be associated with progressive cellular damage, recurrent myocardial ischemia, MI, heart failure, and death.[87]

Anomalous origin of left coronary artery from pulmonary artery (ALCAPA)

This syndrome[88-94] is a congenital anomaly. The clinical picture is varied; LV dysfunction is common but LV function may be normal in myocardial ischemia and MI may occur. HM may be present because of chronic reduction of MBF; detailed pathological and ultrastructural changes have been documented.[93] After reimplantation of the coronary artery into the aorta, LV function improves and even normalizes.[74,88-92] The improvement in LV

function may be rapid or slow over 12 or more months, and is dependent on the severity of structural changes of HM. The extent of irreversibly damaged myocardium will determine the extent of postoperative LV dysfunction. LV dilatation occurs as a result of LV dysfunction and MI. Associated mitral regurgitation is due to the LV dilatation and MI. Surgery consists of excising a button of the pulmonary artery surrounding the ostium of the left coronary artery and anastomosing the button of the pulmonary artery with the left coronary artery into the aorta; the mitral regurgitation may or may not need surgical attention. Early diagnosis and surgery is important.

TREATMENT OF HIBERNATING MYOCARDIUM

The most definitive evidence of improvement of HM has been with revascularization either by percutaneous catheter techniques or CBS.***** The aim is to obtain complete myocardial revascularization, or alternatively, as complete a revascularization as is possible. The decision to perform revascularization and by which technique is made after a consideration of several

- Suitability of coronary artery(ies) for revascularization

- Severity of LV dysfunction

- Symptoms (±)

- Risks of revascularization

- Extent of hibernating myocardium

- Estimate of LV functional recovery after revascularization

Table VII. *Some factors to be considered when discussing revascularization for HM.*

Copyright © S. H. Rahimtoola.

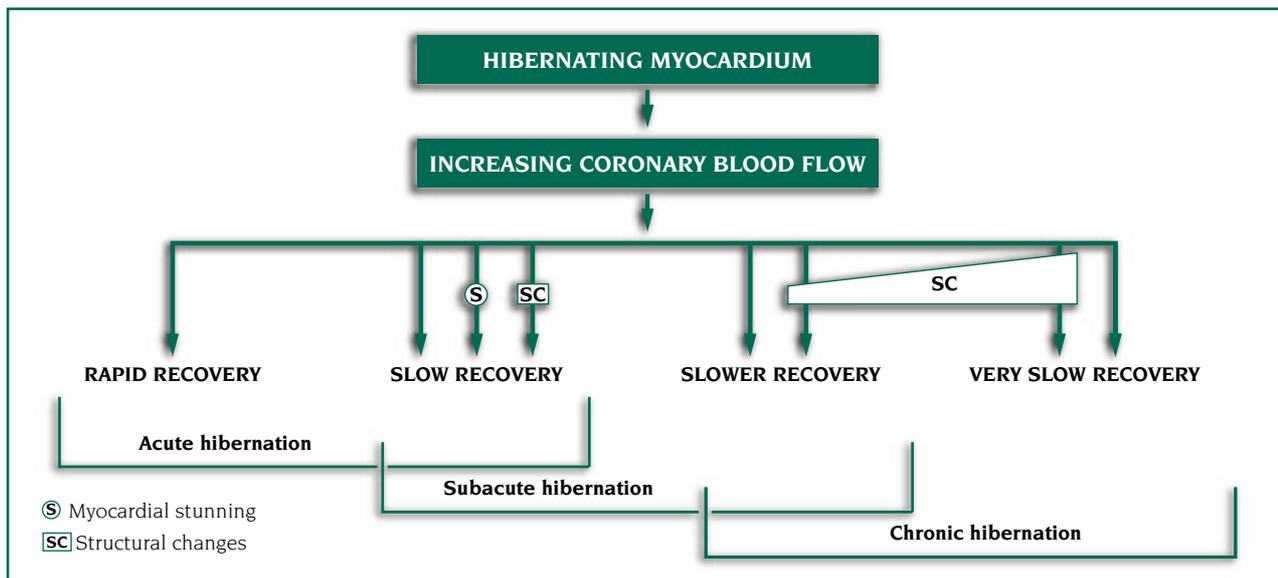***References 1, 2, 4, 11, 17, 26, 29, 30, 33-35, 50, 54, 56-67.**

Figure 5. *Rates of recovery (rapid to very slow) of LV function after increasing coronary blood flow in HM. The role of stunned myocardium (S) and of structural changes (SC) in the myocardium is shown (see text). The possible range of acute, subacute, and chronic HM based on rate of recovery of LV function is illustrated. Adapted from reference 108, reprinted with permission.*

factors *(Table VII)*: (i) the suitability of the coronary arteries for revascularization; (ii) the extent of HM; (iii) the risks of revascularization; and (iv) estimation of functional recovery after revascularization. Symptoms are of secondary consideration. The greater the severity of angina, the greater the need for revascularization. Heart failure symptoms also may signify a very significant need for revascularization. Since all the factors to be considered in recommending revascularization cannot be accurately quantitated at the

present time, there is a need for *clinical judgment* in the decision to recommend revascularization.

RECOVERY OF MYOCARDIAL HIBERNATION

The rate of recovery of resting LV dysfunction after revascularization and the study of the morphologic changes in the dysfunctional myocardium may allow us to characterize clinical HM as acute, subacute, or chronic *(Figure 5)*.[87,95]
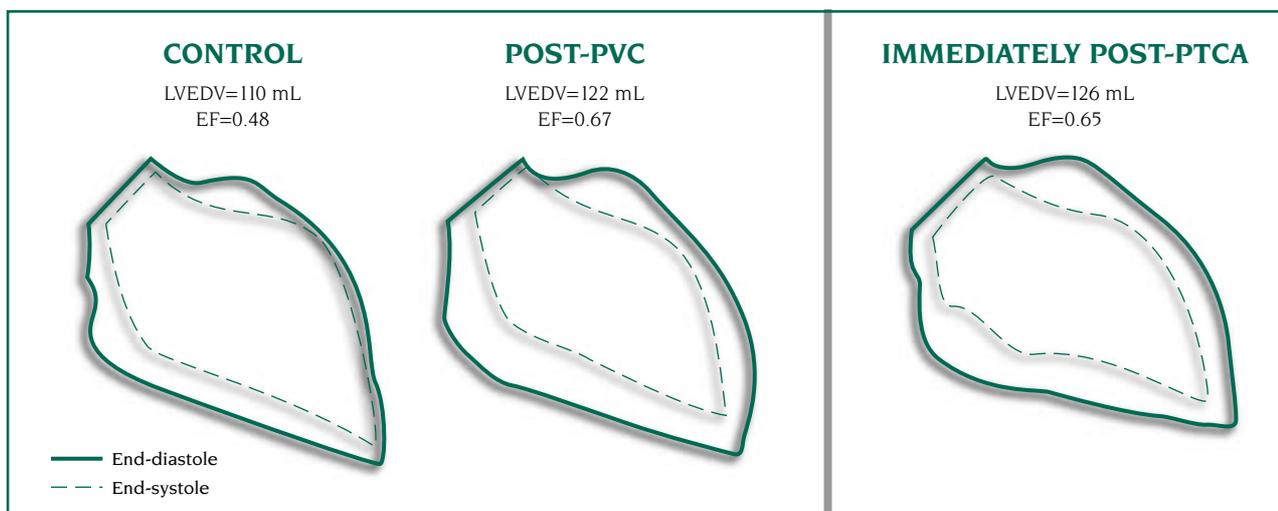
Figure 6. *An example of HM. The patient had severe (95% to 99%) stenosis of the proximal left anterior descending coronary artery. At rest, the anterior LV wall was severely hypokinetic or akinetic and the LVEF was 0.48. In the postpremature ventricular contraction (PVC) beat, the wall motion and EF were normal. Immediately after successful percutaneous transluminal coronary angioplasty (PTCA), LV wall motion and EF were normal. LVEDV = Left ventricular end-diastolic volume. Reprinted from reference 109, with permission.*

Acute

When HM recovers "immediately" or very rapidly after revascularization[57,60,66] *(Figure 6)*, it is presumptive evidence that the myocardium is normal or almost normal. This is confirmed by electron microscopic studies of transmural myocardial biopsy samples in patients undergoing CBS[96] and by histologic examination at autopsy.[97] Acute experimental studies of hibernation (short-term HM) also confirm this.[6-9]

Chronic

After revascularization, it may take HM up to 1 year to recover *(Table VI)*. Electron microscopic studies of transmural myocardial biopsy samples taken at CBS have demonstrated marked abnormalities. The most striking features are loss of myofibrillar content and excessive accumulation of glycogen[45,98,99]; these can be expected to take time to recover after revascularization. Animal models of a longer duration of reduced coronary blood flow are being developed.[15,100-103]

Subacute

Data presented by Matsuzaki et al[104] from an experimental study showed that after 5 hours of reduced perfusion and reduced contraction and little or no MI (hibernation) reperfusion was followed by a gradual recovery of LV function over a 7-day period. This most likely represents stunning following reperfusion of HM. In a patient with HM reported by Baker et al,[105] recovery of LV function occurred over 10 to 60 weeks. Some patients revascularized with CBS[61] and by PTCA[106] showed a similar slow recovery of LV function. Hibernation may have been subacute since it was likely to have been present for a long time prior to reperfusion. In addition, since LV function recovered over months after revascularization in these patients, there may have been changes in the myocardium, or early changes similar to those that may occur in chronic hibernation, which take time to return to normal. The delayed recovery in function might also represent stunning following hibernation.[107] It is likely

that both could occur, that is, in some patients reperfusion of HM is followed by stunning and in others myocardial abnormalities associated with subacute hibernation take time to recover after reperfusion.

The differences between acute and chronic hibernation are summarized in *Table I.*

It must be *emphasized* that the characterization of HM into three precisely separated states (acute, subacute, and chronic) is partly arbitrary, HM may be a spectrum. For example, "chronic" hibernation may have all myocardium that is normal or a sufficient amount of normal myocardium to improve or normalize LV function immediately or early after revascularization. The characterization of HM into three states may have to be revised as more data become available. However, at the present time, this classification serves the purpose of emphasizing the fact that there are different rates of recovery of LV function after revascularization, and that several mechanisms may be responsible for the observed different rates of recovery of LV function.

IMPORTANCE FOR CLINICIANS

It is important to point out that the outcome of patients with CAD is determined not only by the extent and severity of CAD but also by the amount of LV myocardium that is or can be irreversibly damaged. The myocardium that may be irreversibly damaged (the amount of myocardium that is at risk) is the myocardium that is hibernating and/or which is at risk from acute ischemic episodes *(Table III)*. In patients with LV dysfunction at rest, the combination(s) of irreversibly damaged myocardium and HM at risk that may be present in a patient are shown in *Table VIII.*

One of the goals in clinical practice is to reduce the amount of irreversibly damaged myocardium, and therefore, to salvage HM and protect the ischemic myocardium. HM results in LV dysfunction at rest. Therefore, in clinical practice, when one sees a patient with LV dysfunction at rest, one should ask the question whether there is HM (viable myocardium) in the area of LV dysfunction. The need to assess the presence and extent of HM in patients with mild-to-moderate LV dysfunction at rest with respect to the extent of CAD in patients with various clinical syndromes and in those with objective evidence of stress-induced ischemia is shown in *Tables IX* and *X*, respectively. In patients with severe LV dysfunction at rest, one usually needs to assess the presence and extent of CAD and of HM in almost all patients. Successful revascularization of

Myocardium	LV dysfunction at rest				
Irreversibly damaged	+	+	+	–	–
Viable and at risk					
- Hibernating	–	+	–	+	–
- Ischemic on "stress"	–	–	+	–	–

Table VIII. *Possible combinations of myocardial state and its function at rest.*

Copyright © S. H. Rahimtoola.

Clinical syndrome	Extent of coronary artery disease			
	LMCAD	3-VD	LAD + 1-VD	1-VD
Unstable angina	–	–	±	±
Stable angina:				
- severe	–	–	±	±
- mild	±	±	+	+
No angina	+	+	+	+
Heart failure	+	+	+	+

LMCAD = left main coronary artery disease; **VD** = vessel disease; **LAD** = left anterior descending (artery). **+** = yes; **±** = varies; **–** = no.

Table IX. *Need to assess presence and extent of hibernating myocardium in patients with mild-to-moderate LV dysfunction at rest.*

Copyright © S. H. Rahimtoola.

the HM is able to reduce LV dysfunction and the amount of myocardium at risk. This may prolong life and reduce and/or correct clinical heart failure and the symptomatic state of the patient.

In the following section of this issue, three authors will focus on aspects that were discussed only briefly here: Gerd Heusch will detail the **mechanisms of myocardial hibernation,** while Robert Bonow shows **how to diagnose myocardial hibernation.**
For his part, Giovanni La Canna expounds the contributions of the **surgical and pharmacological approaches to the treatment of the hibernating myocardium.**

Objective evidence of ischemia	Extent of coronary artery disease			
	LMCAD	3-VD	LAD + 1-VD	1-VD
Moderate to severe	–	–	±	±
Mild	±	±	±	+
None	±	±	+	+

LMCAD = left main coronary artery disease; **VD** = vessel disease; **LAD** = left anterior descending (artery). **+** = yes; **±** = varies; **–** = no.

Table X. *Need to assess presence and extent of hibernating myocardium in patients with mild-to-moderate LV dysfunction at rest.*

Copyright © S. H. Rahimtoola.

REFERENCES

1. Rahimtoola SH.
Unstable angina: current status.
Mod Concepts Cardiovasc Dis. 1985;54:19-23.

2. Rahimtoola SH.
A perspective on the three large multicenter randomized clinical trials of coronary bypass surgery for chronic stable angina.
Circulation. 1985;72(suppl V):V-123-V-135.

3. Geft IL, Fishbein MC, Ninomiya K, et al.
Intermittent brief periods of ischemia have a cumulative effect and may cause myocardial necrosis.
Circulation. 1982;66:1150-1153.

4. Rahimtoola SH.
The hibernating myocardium.
Am Heart J. 1989;117:211-221.

5. Pantely GA, Malone SA, Rhen WS, et al.
Regeneration of myocardial phosphocreatine in pigs despite continued moderate ischemia.
Circ Res. 1990;67:1481-1493.

6. Arai AE, Pantely GA, Anselone CG, Bristow J, Bristow JD.
Active downregulation of myocardial energy requirements during prolonged moderate ischemia in swine.
Circ Res. 1991;69:1458-1469.

7. Schulz R, Guth BD, Pieper K, Martin C, Heusch G.
Recruitment of an inotropic reserve in moderately ischemic myocardium at the expense of metabolic recovery: a model of short-term hibernation.
Circ Res. 1992;70:1282-1295.

8. Schulz R, Rose J, Margin C, Brodde OE, Heusch G.
Development of short-term myocardial hibernation: its limitation by the severity of ischemia and inotropic stimulation.
Circulation. 1993;88:684-695.

9. Arai AE, Grauer SE, Anselone CG, Pantely GA, Bristow JD.
Metabolic adaptation to a gradual reduction in myocardial blood flow.
Circulation. 1995;92:244-252.

10. Rahimtoola SH.
Hibernating myocardium has reduced blood flow at rest that increases with low-dose dobutamine.
Circulation. 1996;94:3055-3061. Editorial.

11. Bonchek LI, Rahimtoola SH, Chaitman BR, Rösch J, Anderson RP, Starr A.
Vein graft occlusion: immediate and late consequences and therapeutic implications.
Circulation. 1974;50(suppl II):II-84-II-97.

12. Anderson RP.

Effects of coronary bypass graft occlusion on left ventricular performance.

Circulation. 1972;46:507-513.

13. Banka VS, Bodenheimer MM, Shah R, Helfant RH.

Intervention ventriculography: comparative value of nitroglycerin, post-extrasystolic potentiation and nitroglycerin plus post-extrasystolic potentiation.

Circulation. 1976;53:632-637.

14. Bodenheimer MM, Banka VS, Fooshee C, Hermann GA, Helfant RH.

Relationship between regional myocardial perfusion and the presence, severity and reversibility of asynergy in patients with coronary heart disease.

Circulation. 1978;58:789-795.

15. Bolukoglu H, Liedtke AJ, Nellis SH, Eggleston A, Subramanian R, Renstrom B.

An animal model of chronic coronary stenosis resulting in hibernating myocardium.

Am J Physiol. 1992;263(1, pt 2):H20-H29.

16. Bourrassa M, Lesperance J, Campeau J, Campeau L, Saltiel J.

Fate of left ventricular contraction following aortocoronary venous grafts: early and late postoperative modifications.

Circulation. 1972;46:724-730.

17. 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.

18. Chesebro JH, Ritman EL, Frye RL, et al.

Regional myocardial wall thickening response to nitroglycerin. A predictor of myocardial response to aortocoronary bypass surgery.

Circulation. 1978;57:952-957.

19. Dyke SH, Cohn PF, Gorlin R, Sonnenblick EJ.

Detection of residual myocardial function in coronary artery disease using post-extrasystolic potentiation.

Circulation. 1974;50:694-699.

20. Helfant RH, Pine R, Meister SG, Feldman MS, Trout RG, Banka VS.

Nitroglycerin to unmask reversible asynergy. Correlation with postcoronary bypass ventriculography.

Circulation. 1974;50:108-113.

21. Horn HR, Teicholz LE, Cohn PF, Herman MV, Gorlin R.

Augmentation of left ventricular contraction pattern in coronary artery disease by inotropic catecholamine: the epinephrine ventriculogram.

Circulation. 1974;49:1063-1071.

22. Klausner SC, Ratshin RA, Tybert JV, Lappin HA, Chatterjee K, Parmley WW.

The similarity of changes in segmental contraction patterns induced by postextrasystolic potentiation and nitroglycerin.

Circulation. 1976;54:615-623.

23. Massie B, Botvinick EH, Brundage BH, Greenberg B, Shames D, Gelberg H.

Relationship of regional myocardial perfusion to segmental wall motion. Physiological basis for understanding the presence and the reversibility of asynergy.

Circulation. 1978;58:1154-1163.

24. McAnulty JH, Hattenhauer MT, Rösch J, Kloster FE, Rahimtoola SH.

Improvement in left ventricular wall motion following nitroglycerin.

Circulation. 1975;51:140-145.

25. Popio KA, Gorlin R, Bechtel D, Levine JA.

Postextrasystolic potentiation as a predictor of potential myocardial viability: preoperative analyses compared with studies after coronary bypass surgery.

Am J Cardiol. 1977;39:944-953.

26. Rees G, Bristow JD, Kremkau EL, Green GS, Herr RH, Griswold HE, Starr A.

Influence of aortocoronary bypass surgery on left ventricular performance.

N Engl J Med. 1971;284:1116-1120.

27. Stadius M, McAnulty JH, Culter J, Rösch J, Rahimtoola SH.

Specificity, sensitivity and accuracy of the nitroglycerin ventriculogram as a predictor of surgically reversible wall motion abnormalities.

Am J Cardiol. 1980;45:399. Abstract.

28. *Consensus Development Conference on Coronary Artery Bypass Surgery, Medical and Scientific Aspects. NIH, December 3-5, 1990. Frye RL, Frommer PL, eds.*

Circulation. 1982;65(suppl II):II-1-II-129.

29. Rahimtoola SH.
Coronary bypass surgery for chronic angina - 1981: a perspective.
Circulation. 1982;65:225-241.

30. Rahimtoola SH.

Postoperative exercise response in the evaluation of the physiologic status after coronary bypass surgery.

Circulation. 1982;65(suppl II):II-106-II-114.

31. Deanfield J, Maseri A, Selwyn AP, et al.

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

Lancet. 1983;2:753-758.

32. Maseri A.

The changing face of angina pectoris: practical implications.

Lancet. 1983;1:746-749.

33. Berger BC, Watson DD, Burwell LR, et al.

Redistribution of thallium at rest in patients with stable and unstable angina and the effect of coronary artery bypass surgery.

Circulation. 1979;60:1114-1125.

34. Gibson RS, Watson DD, Taylor GJ, et al.

Prospective assessment of regional myocardial perfusion before and after coronary revascularization surgery by quantitative thallium 201 scintigraphy.

J Am Coll Cardiol. 1983;1:804-815.

35. Dilsizian V, Rocco TP, Freedman NMT, Leon MB, Bonow RO.

Enhanced detection of ischemic but viable myocardium by the reinjection of thallium after stress redistribution imaging.

N Engl J Med. 1990;323:141-146.

36. Gerwirtz H, Beller GA, Strauss HW, et al.

Transient defects of resting thallium scans in patients with coronary artery disease.

Circulation. 1979;59:707-713.

37. *NHLBI Workshop on Surgery in the Treatment of Coronary Artery Disease, September 6 and 7, 1984, Bethesda, Maryland. Braunwald E, Hollingsworth C, Passamani E, eds.*

Circulation. 1985;72(suppl V):V-1-V-168.

38. Bashour TT.

Of myocardial life, hibernation and death.

Am Heart J. 1986;112:427-428.

39. Braunwald E, Rutherford JD.

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

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

40. Hearse DJ.

Myocardial ischemia: can we agree on a definition for the 21st century?

Cardiovasc Res. 1994;28:1737-1744.

41. Ross J Jr.

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

Circulation. 1991;83:1076-1082.

42. Marzullo P, Parodi O, Sambuceti G, et al.

Residual coronary reserve identifies segmental viability in patients with wall motion abnormalities.

J Am Coll Cardiol. 1995;26:342-350.

43. Shivalkar B, Maes A, Borgers M, et al.

Only hibernating myocardium shows early recovery after coronary revascularization.

Circulation. 1996;94:308-315.

44. Rahimtoola SH.

Commentary on "The definition of ischemia."

Cardiovasc Res. 1994;28:1745.

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

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

Circulation. 1993;87:1513-1523.

46. Rahimtoola SH.

Chronic myocardial hibernation.

Circulation. 1994;89:1097-1098. Letter to the Editor.

47. Czernin J, Porenta G, Brunken R, et al.

Regional blood flow, oxidative metabolism, and glucose utilization in patients with recent myocardial infarction.

Circulation. 1993;88:884-895.

48. Sambuceti G, Parodi O, Giorgetti A, et al.

Microvascular dysfunction in collateral-dependent myocardium.

J Am Coll Cardiol. 1995;26:615-623.

49. Gallagher KP, Matsuzaki M, Koziol JA, Kemper WS, Ross J Jr.

Regional myocardial perfusion and wall thickening during ischemia in conscious dogs.

Am J Physiol. 1984;247(5, pt 2):H727-H738.

50. Sun KT, Czernin J, Krirokapich J, et al.

Effects of dobutamine stimulation on myocardial blood flow, glucose metabolism and wall motion in normal and dysfunctional myocardium.

Circulation. 1996;74:3146-3154.

51. Arani DT, Greene DG, Bunnell IL, Smith GL, Klocke FJ.

Reductions in coronary flow under resting conditions in collateral-dependent myocardium of patients with complete occlusion of the left anterior descending coronary artery.

J Am Coll Cardiol. 1984;3:668-674.

52. Klocke FJ, Bunnell IL, Greene DG, Wittenberg SM, Visco JP.

Average coronary blood flow per unit weight of left ventricle in patients with and without coronary artery disease.

Circulation. 1974;50:547-559.

53. Akins CW, Pohost GM, DeSanctis RW, Block PC.

Selection of angina-free patients with severe left ventricular dysfunction for myocardial revascularization.

Am J Cardiol. 1980;46:695-700.

54. Brundage BH, Massie BM, Botvinick EH.

Improved regional ventricular function after successful surgical revascularization.

J Am Coll Cardiol. 1984;3:902-908.

55. Carlson EB, Cowley MJ, Wolfgang TC, Vetrovec GW.

Acute changes in global and regional rest ventricular function after successful coronary angioplasty: comparative results in stable and unstable angina.

J Am Coll Cardiol. 1989;13:1262-1269.

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

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

Circulation. 1993;88:430-436.

57. Cohen M, Chainey R, Hershman R, Fuster V, Gorlin R.

Reversal of chronic ischemic myocardial dysfunction after transluminal coronary angioplasty.

J Am Coll Cardiol. 1988;12:1193-1198.

58. Elefteriades JS, Tolis G Jr, Levi E, Mills LK, Zaret BL.

Coronary artery bypass grafting in severe left ventricular dysfunction: excellent survival with improved ejection fraction and function state.

J Am Coll Cardiol. 1993;22:1411-1417.

59. 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.

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

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

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

61. Marwick THE, MacIntyre WJ, Lafont A, Nemec JJ, Salcedo EE.

Metabolic responses of hibernating and infarcted myocardium to revascularization: a follow-up study of regional perfusion, function, and metabolism.

Circulation. 1992;85:1347-1353.

62. 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.

63. Ragosta M, Beller GA, Watson DD, Kaul S, Gimple LW.

Quantitative planar rest-redistribution thallium 201 imaging in detection of myocardial viability and prediction of improvement in left ventricular function after coronary bypass surgery in patients with severely depressed left ventricular function.

Circulation. 1993;87:1630-1641.

64. Takeishi Y, Tono-Oka I, Kuboba I, et al.

Functional recovery of hibernating myocardium after coronary bypass surgery: does it coincide with improvement in perfusion?

Am Heart J. 1991;122:665-670.

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

Reversibility of cardiac wall motion abnormalities predicted by positron tomography.

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

66. Topol EJ, Weiss JL, Guzman PA, et al.

Immediate improvement of dysfunctional myocardial segments or after coronary revascularization: detection by intraoperative transesophageal echocardiography.

J Am Coll Cardiol. 1984;4:1123-1134.

67. Van den Berg EK Jr, Popma JJ, Dehmer GJ, et al.

Reversible segmental left ventricular dysfunction after coronary angioplasty.

Circulation. 1990;81:1210-1216.

68. Bonow RO, Dilsizian V, Cuocolo A, Bacharach SL.

Identification of viable myocardium in patients with coronary artery disease and left ventricular dysfunction: comparison of thallium scintigraphy with reinjection and PET imaging with ^{18}F-fluorodeoxyglucose.

Circulation. 1991;83:26-37.

69. Ohtani H, Tamaki N, Yonekura Y, et al.

Value of thallium 201 reinjection after delayed SPECT imaging for predicting reversible ischemia after coronary artery bypass grafting.

Am J Cardiol. 1990;66:394-399.

70. Rocco TP, Dilsizian V, McKusick KA, Fischman AJ, Boucher CA, Strauss HW.

Comparison of thallium redistribution with rest "reinjection" imaging for the detection of a viable myocardium.

Am J Cardiol. 1990;66:158-163.

71. Tamaki N, Ohtani H, Yonekura Y, et al.

Significance of fill-in after thallium 201 reinjection following delayed imaging: comparison with regional wall motion and angiographic findings.

J Nucl Med. 1990;31:1617-1623.

72. Gropler RJ, Geltman EM, Sampathkumaran K, et al.

Functional recovery after coronary revascularization for chronic coronary artery disease is dependent on maintenance of oxidative metabolism.

J Am Coll Cardiol. 1992;20:569-577.

---

73. Christian TF, Miller TD, Hodge DO, Gibbon RJ.

What is the prevalence of hibernating myocardium?

J Am Coll Cardiol. 1996;27(2, suppl A):162A. Abstract.

---

74. Kulick D, Rahimtoola SH.

Assessment of the survivors of acute myocardial infarction: the case for coronary angiography. In: Gersh B, Rahimtoola SH, eds.

Acute Myocardial Infarction. Amsterdam, the Netherlands: Elsevier Science Publ; 1991:448-468.

---

75. Adams JN, Norton M, Trent R, Mikecz P, Walton S, Evans N.

Hibernating myocardium after acute myocardial infarction treated with thrombolysis.

Eur Heart J. 1995;16:36. Abstract.

---

76. Tamaki N, Kawamoto M, Takahashi N, et al.

Prognostic value of an increase in fluorine-18 deoxyglucose uptake in patients with myocardial infarction: comparison with stress thallium imaging.

J Am Coll Cardiol. 1992;22:1621-1627.

---

77. Montalescot G, Faraggi M, Drobinski G, et al.

Myocardial viability in patients with Q wave myocardial infarction and no residual ischemia.

Circulation. 1992;86:47-55.

---

78. Brunken R, Tillisch J, Schwaiger M, et al.

Regional perfusion, glucose metabolism, and wall motion in patients with chronic electrocardiographic Q wave infarction. Evidence for persistence of viable tissue in some infarct regions by positron emission tomography.

Circulation. 1986;73:951-963.

---

79. Shanes JG, Kondos GT, Levitsky S, Pavel D, Subramania R, Brundage BH.

Coronary artery obstruction: a potentially reversible cause of dilated cardiomyopathy.

Am Heart J. 1985;110:173-178.

---

80. Luu M, Stevenson LW, Brunken RC, Drinkwater DC, Schelbert TR, Tillisch JH.

Delayed recovery of revascularized myocardium after referral for cardiac transplantation.

Am Heart J. 1990;119:668-670.

---

81. Louie HW, Laks H, Milgalter E, et al.

Ischemic cardiomyopathy: criteria for coronary revascularization and cardiac transplantation.

Circulation. 1991;84(suppl III):III-290-III-295.

---

82. Duong TH, Hendi P, Fonarow G, et al.

Role of positron emission tomographic assessment of myocardial viability in the management of patients who are referred for cardiac transplantation.

Circulation. 1995;92:I-123. Abstract.

---

83. Lee KS, Marwick THE, Cook SA, et al.

Prognosis of patients with left ventricular dysfunction, with and without viable myocardium after myocardial infarction. Relative efficacy of medical therapy and vascularization.

Circulation. 1994;90:2687-2694.

---

84. Eitzman D, Al-Aonar Z, Kanter HL, et al.

Clinical outcome of patients with advanced coronary artery disease after viability studies with positron emission tomography.

J Am Coll Cardiol. 1992;20:559-565.

---

85. DiCarli M, Davidson M, Little R, et al.

Value of metabolic imaging with positron emission tomography for evaluating prognosis in patients with coronary artery disease and left ventricular dysfunction.

Am J Cardiol. 1994;73:527-533.

---

86. Knight C, Fox KM.

The vicious circle of ischemic left ventricular dysfunction.

Am J Cardiol. 1995;76:4B-7B.

---

87. Rahimtoola SH.

From coronary artery disease to heart failure: role of the hibernating myocardium.

Am J Cardiol. 1995;75:16E-22E.

---

88. Levitsky S, van der Horst RL, Hastreiter AR, Fisher EA.

Anomalous left coronary artery in the infant. Recovery of ventricular function following early direct aortic implantation.

J Thorac Cardiovasc Surg. 1980;79:598-602.

---

89. Rein AJJT, Colan SD, Parness IA, Sanders SP.

Regional and global left ventricular function in infants with anomalous origin of the left coronary artery from the pulmonary trunk: preoperative and postoperative assessment.

Circulation. 1987;75:115-123.

---

90. Hurwitz RA, Caldwell RL, Girod DA, Brown J, King H.

Clinical and hemodynamic course of infants and children with anomalous left coronary artery.

Am Heart J. 1989;118:1176-1181.

---

91. Carvalho JS, Redington AN, Oldershaw PJ, Shinebourne EA, Lincoln CR, Gibson DG.

Analysis of left ventricular wall movement before and after reimplantation of anomalous left coronary artery in infancy.

Br Heart J. 1991;65:218-222.

92. Jin Z, Berger F, Uhlemann F, et al.

Improvement in left ventricular dysfunction after aortic reimplantation in 11 consecutive pediatric patients with anomalous origin of the left coronary artery from the pulmonary artery. Early results of a serial echocardiographic follow-up.

Eur Heart J. 1994;15:1044-1049.

93. Shivalkar B, Borgers M, Daenen W, Gewillig M, Flameng W.

ALCAPA syndrome: an example of chronic myocardial hypoperfusion?

J Am Coll Cardiol. 1994;23:772-778.

94. Lambert V, Touchot A, Losay J, et al.

Mid-term results after surgical repair of the anomalous origin of the coronary artery.

Circulation. 1996;94(suppl II):II-38-II-43.

95. Rahimtoola SH.

The hibernating myocardium in ischemic and congestive heart failure.

Eur Heart J. 1993;14(suppl A):A22-A26.

96. Flameng W, Vanhaecke J, Van Belle H, Borgers M, DeBeer L, Minten J.

Relation between coronary artery stenosis and myocardial purine metabolism, histology and regional function in humans.

J Am Coll Cardiol. 1987;9:1235-1242.

97. Cabin HS, Clubb S, Vita N, Zaret BL.

Regional dysfunction by equilibrium radionuclide angiocardiography: a clinical-pathologic study evaluating the relation of degree of dysfunction to the presence and extent of myocardial infarction.

J Am Coll Cardiol. 1987;10:743-747.

98. Borgers M, Thone F, Wonters L, Ausina J, Shivalkar B, Flameng W.

Structural correlates of regional myocardial dysfunction in patients with critical coronary artery stenosis: chronic hibernation?

Cardiovasc Pathol. 1993;2:237-245.

99. Flameng W, Suy R, Schwarz F, et al.

Ultrastructural correlates of left ventricular contraction abnormalities in patients with chronic ischemic heart disease: determinations of reversible segmental asynergy postrevascularization surgery.

Am Heart J. 1981;102:846-857.

100. Canty JM Jr, Klocke FJ.

Reductions in regional myocardial function at rest in conscious dogs with chronically reduced regional coronary artery pressure.

Circ Res. 1987;61(suppl II):II-107-II-116.

101. Fedele FA, Gerwitz H, Capone RJ, Sharaf B, Most AS.

Metabolic response to prolonged reduction of myocardial blood flow distal to a severe coronary artery stenosis.

Circulation. 1988;78:729-735.

102. Mills I, Fallon JT, Wrenn D, et al.

Adaptive responses of coronary circulation and myocardium to chronic reduction in perfusion pressure and flow.

Am J Physiol. 1994;266(2, pt 2):H447-H457.

103. Chen C, Chen L, Fallon JT, et al.

Functional and structural alterations with 24-hour myocardial hibernation and recovery after reperfusion: a pig model of myocardial hibernation.

Circulation. 1996;94:507-516.

104. Matsuzaki M, Gallagher KP, White F, Ross J Jr.

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

Circulation. 1983;68:170-182.

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

Reversible cardiac dysfunction (hibernation) from ischemia due to compression of the coronary arteries by a pseudoaneurysm.

N Engl J Med. 1991;325:1858-1861.

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

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

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

107. Kloner RA, Przyklenk K.

Hibernation and stunning of the myocardium.

N Engl J Med. 1991;325:1877-1879.

108. Rahimtoola SH.

Hibernating myocardium: a brief article.

Basic Res Cardiol. 1995;90:38-40.

109. Rahimtoola SH.

Clinical overview of management of chronic ischemic heart disease.

Circulation. 1991;84(suppl I):I-81-I-84.

Hibernating Myocardium

Expert Answers to Three Key Questions

———————— (1) ————————

What are the underlying mechanisms of myocardial hibernation?

G. Heusch

———————— (2) ————————

How is it possible to diagnose myocardial hibernation?

R.O. Bonow

———————— (3) ————————

Treating myocardial hibernation: surgery, pharmacology, or both?

G. La Canna

What are the underlying mechanisms of myocardial hibernation?

Gerd Heusch, MD, PhD, FESC, FACC

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

Much less is known about the pathogenesis of myocardial hibernation than about that of stunning and ischemic preconditioning. Mechanistic data are only available from animal models of short-term hibernation. Such studies have taken perfusion-contraction matching, recovery of metabolic markers, persistent inotropic reserve, and lack of infarction as criteria of hibernation. On these premises, a downregulation of ß-adrenoceptor density and an involvement of adenosine and activation of K_{ATP} channels have been excluded. The role of acidosis and triggering events is still unclear. Hibernating myocardium has, however, a reduced calcium responsiveness.

The concept of myocardial hibernation did not originate in the laboratory, instead it was entirely founded on clinical grounds when, in the mid eighties, Rahimtoola reviewed the results of coronary bypass surgery trials and identified a subset of patients with coronary artery disease and chronic left ventricular dysfunction that improved upon revascularization. The observed reduction of contractile function was viewed as an adaptive response to the reduction in blood flow, and this regulatory event was thought to avoid an ongoing energetic deficit and thereby maintain myocardial integrity and viability.

Experimental models looking at myocardial hibernation on a timescale of months to years, as occurring clinically, are not available. However, the concept of myocardial hibernation has gained support from well-controlled animal studies on a timescale of several hours. Such models of short-term myocardial hibernation have revealed several essential features:

- perfusion-contraction matching;
- metabolic and energetic recovery;
- persistent inotropic reserve;
- lack of necrosis.

In most animal models of short-term hibernation the observation period was not long enough to follow the recovery of contractile function upon reperfusion.

The situation of myocardial hibernation is thus quite different from that of stunning and ischemic preconditioning, which are both primarily laboratory phenomena and have subsequently found clinical counterparts. Mechanistic information, which is usually derived from establishing experimental models and plentiful for stunning and ischemic preconditioning, is therefore scarce for myocardial hibernation and entirely limited to models of short-term hibernation.

ENERGY METABOLISM AND SHORT-TERM MYOCARDIAL HIBERNATION

In anesthetized pigs with controlled coronary hypoperfusion, creatine phosphate is quickly reduced following the onset of ischemia/hypoperfusion. However, with ongoing ischemia at an unchanged level of coronary hypoperfusion and of regional contractile dysfunction, creatine phosphate recovers to control values over 60 to 90 minutes. ATP is somewhat reduced, but remains stable at that reduced level. Model calculations indicated a return of the free energy change of ATP hydrolysis to control values, and we have recently confirmed these calculations by direct measurements of ATP, creatine phosphate, creatine, and inorganic phosphate. These data support the concept of an active and adaptive downreg-
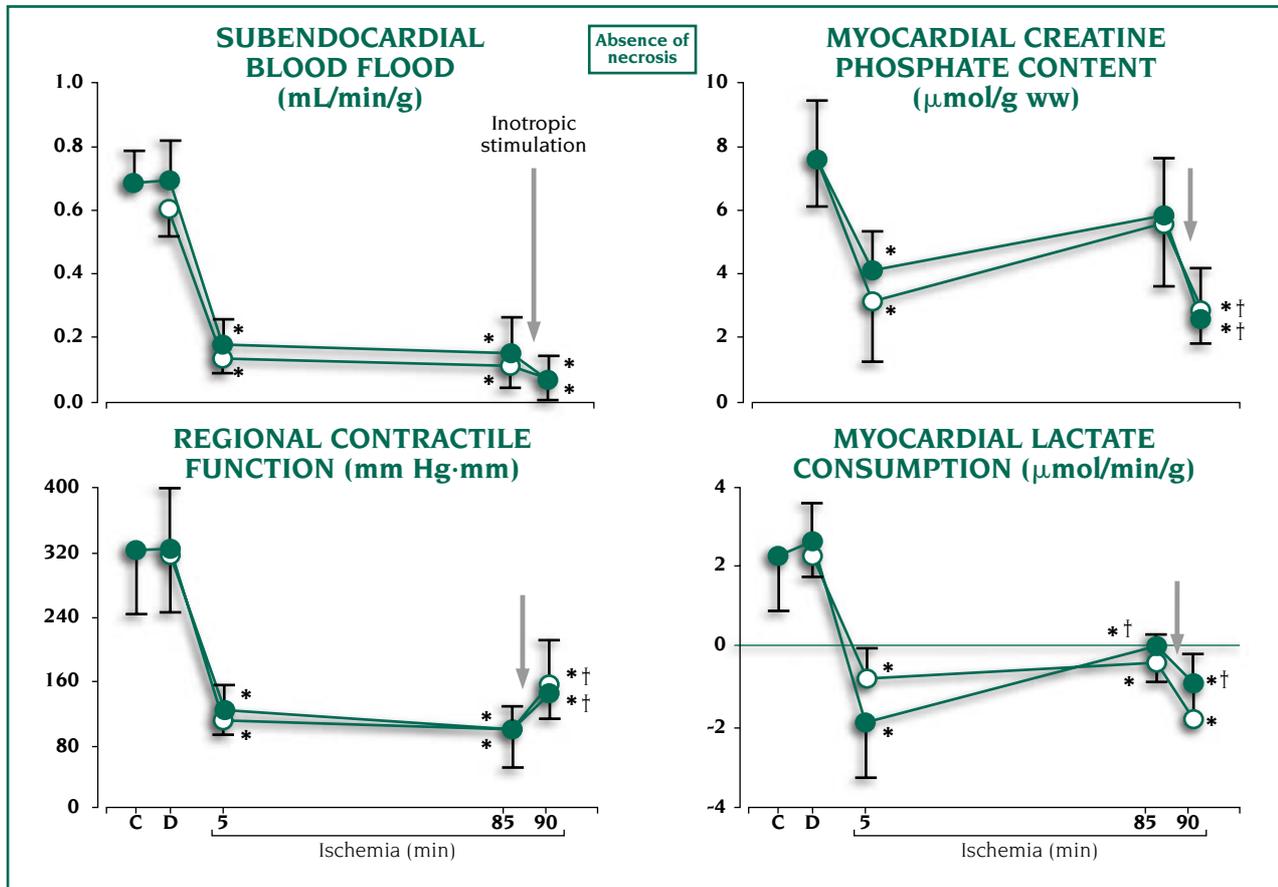
Figure 1. *The reduction in subendocardial blood flow of the anterior myocardium at 5 min of ischemia is associated with decreased regional contractile function in placebo pigs and pigs receiving adenosine deaminase. Within the first 5 min of ischemia, creatine phosphate concentration decreases and lactate consumption is reversed to net lactate production in both groups of pigs. With the extension of ischemia to 85 min at a constant subendocardial blood flow, there is a tendency towards a further decrease in regional contractile function in both groups of pigs. In contrast, lactate production is attenuated and the creatine phosphate concentration recovers to a value no longer significantly different from the corresponding control value. Infusion of dobutamine after 90 min of ischemia increases regional contractile function at an unchanged subendocardial blood flow to a comparable extent in both groups of pigs. This increase in contractile function, however, is associated once more with increased lactate production and a decreased creatine phosphate concentration. ○ Placebo; ● Adenosine-deaminase (D, 5 IU/mL blood/min IC); C, control; D, deaminase; *$P<0.05$ vs control; †$P<0.05$ vs preceding value*

ulation of contractile function aimed at avoiding an ongoing energetic deficit and maintaining integrity and viability during short-term myocardial hibernation.

ADENOSINE AND SHORT-TERM MYOCARDIAL HIBERNATION

Adenosine is a key trigger and mediator of ischemic preconditioning. Endogenous adenosine is released during ischemia and might act through a number of secondary mechanisms, such as inhibition of norepinephrine release from sympathetic nerve terminals, inhibition of adenylate cyclase, or inhibition of L-type calcium channels, to attenuate the decrease in high-energy phosphates and the increase in intracellular calcium, thereby preserving myocardial viability. However, a role of endogenous adenosine in the development of short-term hibernation has been excluded using the above criteria. In an anesthetized pig preparation with 90 minutes' controlled coronary hypoperfusion, increased catabolism of endogenous adenosine by intracoronary infusion of adenosine deaminase did not alter perfusion-contraction matching and recovery of metabolic parameters (creatine phosphate, lactate), did not impair inotropic reserve, and did not induce necrosis *(Figure 1)*.

K$_{ATP}$ CHANNEL ACTIVATION AND SHORT-TERM MYOCARDIAL HIBERNATION

Activation of K$_{ATP}$ channels is a key event in ischemic preconditioning; conversely, blockade of K$_{ATP}$ channels prevents ischemic preconditioning. Activation of K$_{ATP}$ channels reduces action potential duration and
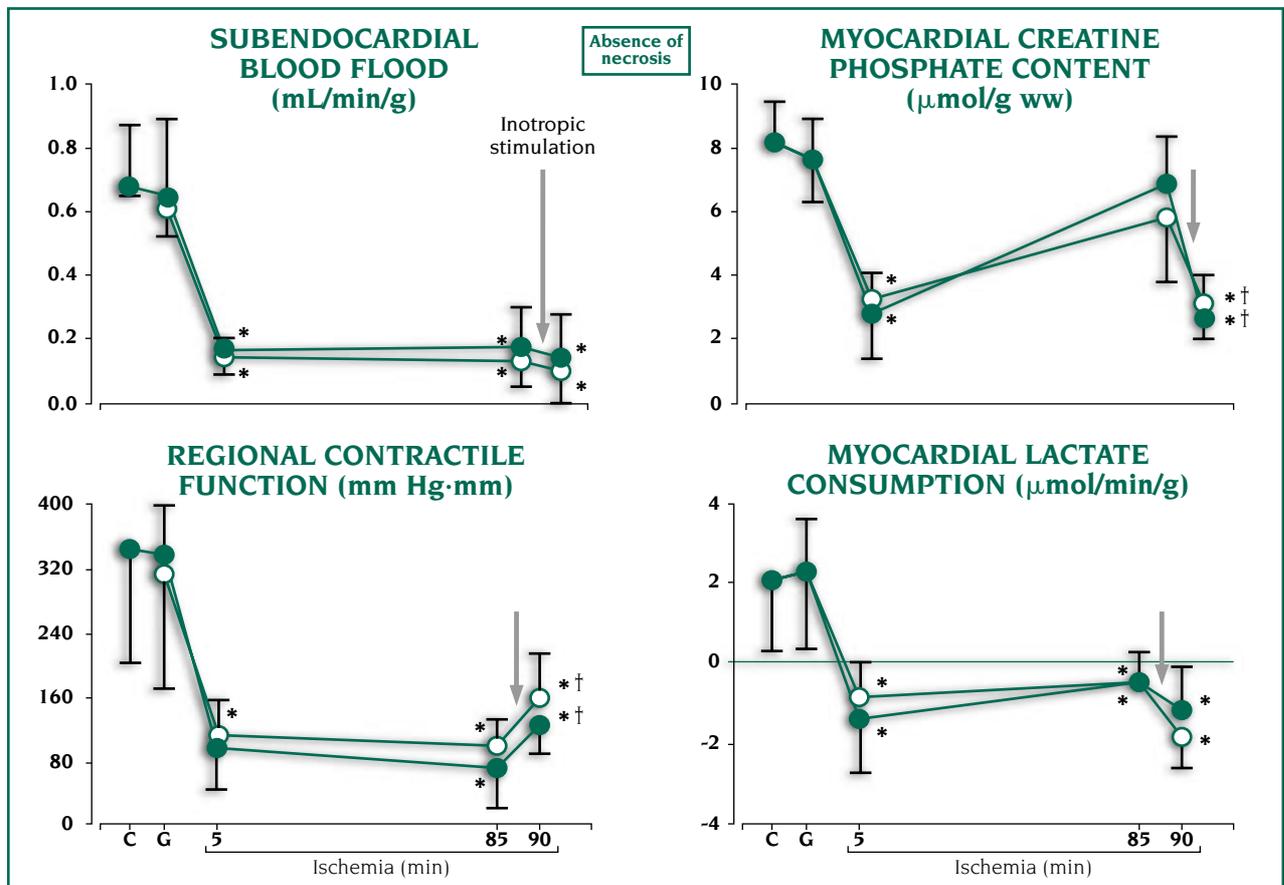
Figure 2. *Findings with glibenclamide closely resemble those with adenosine deaminase described in* Figure 1, *indicating that the activation of K_{ATP} channels plays no role in short-term myocardial hibernation, in contrast to ischemic preconditioning.* ● *Glibenclamide (G, 0.5 mg/kg IV + 50 µg/min IV); other symbols same as in* Figure 1.

calcium influx into cardiac myocytes. The attenuation of calcium overload during ischemia may act to preserve myocardial integrity and viability. In an anesthetized pig preparation with 90 minutes' controlled coronary hypoperfusion, K_{ATP} channels were indeed activated, as indicated by reduced action potential duration. However, blockade of K_{ATP} channels with glibenclamide abolished the reduction in action potential duration, but failed to alter perfusion- contraction matching and the recovery of metabolic parameters (creatine phosphate, lactate), did not impair inotropic reserve, and did not induce necrosis *(Figure 2).*
Thus, activation of K_{ATP} channels is not the underlying mechanism of short-term hibernation.

β-ADRENOCEPTORS AND SHORT-TERM MYOCARDIAL HIBERNATION

β-Adrenoceptor density and affinity are not altered in a porcine model of short-term hibernation.
The maintained inotropic response to dobutamine also excludes an uncoupling of β-adrenoceptor activation from the subsequent signal cascade. However, detailed analyses of adrenergic signal cascade in hibernation are not available.

ACIDOSIS AND TRIGGERING EVENTS IN SHORT-TERM MYOCARDIAL HIBERNATION

A metabolic adaptation to severe sustained (4 hours) low-flow ischemia was evident in isolated

buffer-perfused rabbit hearts when there was a preceding short episode (10 min) of no-flow ischemia. In these hearts, the early decline in contractile function was more pronounced and significantly faster than in control hearts that did not have the brief episode of no-flow ischemia. The rapid decline in contractile function during the brief episode of no-flow ischemia was accompanied by a greater decrease in interstitial and intracellular pH, and the contractile quiescence was attributed to a faster development of myocardial acidosis. The faster achievement of contractile quiescence, in turn, was thought to facilitate the balance between energy supply and demand. Indeed, hearts with a preceding episode of low-flow ischemia had

better recovery of contractile function and less creatine kinase release upon reperfusion.

Protection from infarction was also found in anesthetized pigs when a sustained (80 minutes) low-flow ischemia was preceded by a short (10 minutes) episode of no-flow ischemia. The reduction in infarct size, as compared to hearts undergoing 90 minutes' low-flow ischemia without a preceding episode of no-flow ischemia, was not related to acidosis and could be prevented by the K_{ATP} channel blocker glibenclamide, indicating that the protection afforded by the initial stimulus/ trigger of very severe ischemia was related to ischemic preconditioning without an intervening reperfusion.

Thus, the role of an initial trigger as well as the importance of acidosis in the development of short-term hibernation remain to be better defined. An initial trigger of severe ischemia, however, may represent a link between hibernation and ischemic preconditioning.

EXCITATION-CONTRACTION COUPLING AND SHORT-TERM MYOCARDIAL HIBERNATION

It is not surprising that, in the search for possible mechanisms of hibernation, attention has been directed to calcium. In isolated buffer-perfused ferret hearts, moderately decreased coronary perfusion resulted in decreased calcium transients and contractile force without any change in high-energy phosphates. In anesthetized pigs with controlled coronary hypoperfusion for 90 minutes, regional contractile responses to intracoronary calcium were substantially reduced, indicating impaired calcium responsiveness. This reduced calcium responsiveness was largely attributable to a decrease in maximal developed force and not to a decrease in calcium sensitivity, as the relations between fractional increase in contractile function and in intracoronary calcium dose were not different in normally perfused hearts and short-term myocardial hibernation *(Figure 3)*. Thus, short-term myocardial

hibernation has reduced calcium responsiveness and possibly also calcium transients.

REPETITIVE STUNNING AND LONG-TERM MYOCARDIAL HIBERNATION

In experimental studies using chronic coronary stenosis in conscious pigs, regional contractile dysfunction was observed in the absence of reduced regional blood flow, but in the presence of reduced flow reserve. With reference to anecdotal episodes of stress-induced ischemia, it was proposed that hibernation was not an adaptation to persistent ischemia but rather the manifestation of repetitive stunning. However, this particular study failed to monitor flow and function continuously, and there is no study available in which the phenotype of hibernation was induced as a consequence of controlled protocols of multiple episodes of ischemia/reperfusion. Several clinical studies also found disproportionately greater reductions in regional function than in regional blood flow. However, the positron emission tomography (PET) measurements in such studies lacked sufficient transmural resolution to exclude substantial subendocardial ischemia. Other studies have even found a sizable reduction in regional blood flow with PET in areas of hibernating myocardium. Thus, the interrelation between hibernation and stunning remains to be better defined. It is conceivable, however, that with some residual blood flow a component of reperfusion, involving stunning, is superimposed on hibernation.

CONCLUSION AND PERSPECTIVES

The triggers and mediators of myocardial hibernation are still poorly understood. I propose a
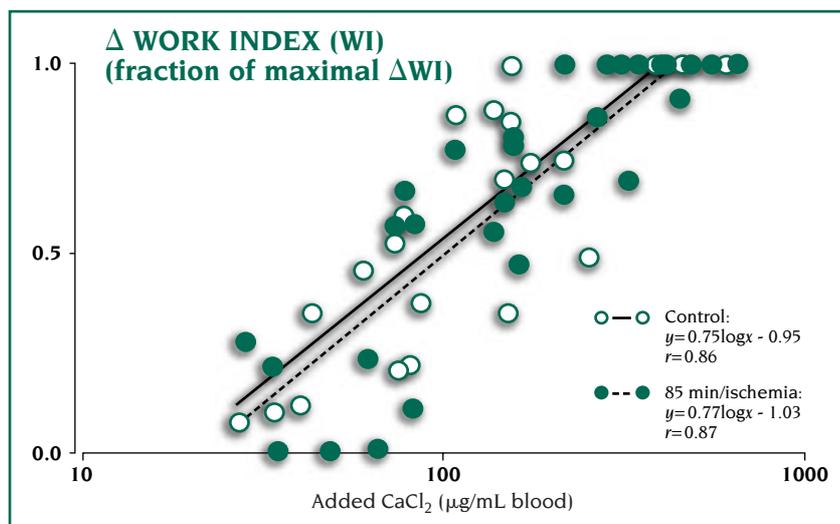
Figure 3. *Relationship between the added intracoronary calcium chloride (on a logarithmic scale) and the increase in regional myocardial work (as a fraction of the maximal increase). The relationships obtained under control conditions and at 85 min of ischemia are superimposable. At 85 min of ischemia, perfusion-contraction matching and viability were maintained, and creatine phosphate had recovered to control values, indicating short-term hibernation.*

conceptual three-stage model of hibernation:

- Very rapidly after a reduction in coronary blood flow, a biochemical mechanism is switched on which reduces contractile function and restores the energy balance between energy supply/blood flow and energy demand/contractile function. Adenosine and activation of K_{ATP} channels are not important here, but acidosis and reduced calcium responsiveness deserve to be studied in more detail.

- With prolongation of ischemia, the expression of a number of genes and subsequently proteins is increased. Alterations in the amount and activity of calcium-handling proteins may decrease contractile function and thus replace or add to the initial biochemical mechanism in reducing contractile function. No data are available here.

- Increased expression of genes and proteins involved in apoptosis may induce controlled cardiac myocyte death and thus improve blood supply to the surviving cardiac myocytes. No data are available here.

The semantic distinction between hibernation, stunning, and ischemic preconditioning may be clearer than the reality. Triggering events may link hibernation and ischemic preconditioning, and with some residual blood flow a component of reperfusion/stunning may be superimposed on hibernation.

Further reading

1. Rahimtoola SH.
A perspective on the three large multicenter randomized clinical trials of coronary bypass surgery for chronic stable angina.
Circulation. 1985;72(suppl V):V-12 -V-135.

2. Arai AE, Pantely GA, Anselone CG, Bristow J, Bristow JD.
Active downregulation of myocardial energy requirements during prolonged moderate ischemia in swine.
C*irc Res.* 1991;69:1458-1469.

3. Ferrari R, Cargnoni A, Bernocchi P, et al.
Metabolic adaptation during a sequence of no-flow and low-flow ischaemia: a possible trigger for hibernation.
Circulation. 1996;94:2587-2596.

4. Heusch G, Ferrari R, Hearse DJ, Ruigrok TJC, Schulz R.
"Myocardial hibernation": questions and controversies.
Cardiovasc Res. In press.

5. Heusch G, Rose J, Skyschally A, Post H, Schulz R.
Calcium responsiveness in regional myocardial short-term hibernation and stunning in the in situ porcine heart: inotropic responses to postextrasystolic potentiation and intracoronary calcium.
Circulation. 1996;93:1556-1566.

6. Heusch G, Schulz R.
Hibernating myocardium: a review.
J Mol Cell Cardiol. 1996;28:2359-2372.

7. Kitakaze M, Marban E.
Cellular mechanism of the modulation of contractile function by coronary perfusion pressure in ferret hearts.
J Physiol. 1989;414:455-472.

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

9. Schulz R, Guth BD, Pieper K, Martin C, Heusch G.
Recruitment of an inotropic reserve in moderately ischemic myocardium at the expense of metabolic recovery: a model of short-term hibernation.
Circ Res. 1992;70:1282-1295.

10. Schulz R, Post H, Sakka S, Wallbridge DR, Heusch G.
Intraischemic preconditioning. Increased tolerance to sustained low-flow ischemia by a brief episode of no-flow ischemia without intermittent reperfusion.
Circ Res. 1995;76:942-950.

11. Schulz R, Rose J, Martin C, Brodde OE, Heusch G.
Development of short-term myocardial hibernation: its limitation by the severity of ischemia and inotropic stimulation.
Circulation. 1993;88:684-695.

12. Schulz R, Rose J, Post H, Heusch G.
Regional short-term hibernation in swine does not involve endogenous adenosine or K_{ATP} channels.
Am J Physiol. 1995;268(6, pt 2):H2294-H2301.

13. Shen YT, Vatner SF.
Mechanism of impaired myocardial function during progressive coronary stenosis in conscious pigs. Hibernation versus stunning.
Circ Res. 1995;76:479-488.

14. van Binsbergen XA, van Emous JG, Ferrari R, van Echteld CJA, Ruigrok TJC.
Metabolic and functional consequences of successive no-flow and sustained low-flow ischaemia: a ^{31}P MRS study in rat hearts.
J Mol Cell Cardiol. 1996;28;2373-2381.

How is it possible to diagnose myocardial hibernation?

Robert O. Bonow, MD

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

Diagnostic testing to evaluate the potential for recovery of viable but dysfunctional myocardium has become an important component of the assessment of patients with chronic coronary artery disease (CAD) and left ventricular (LV) dysfunction, as bypass surgery or angioplasty are associated with an increased risk of mortality and morbidity in these patients. Single photon emission computed tomography (SPECT) as well as positron emission tomography (PET), can be used to investigate perfusion, cell membrane integrity, and metabolic activity, whereas dobutamine echocardiography can assess myocardial contractile reserve.
Assessment of myocardial viability with thallium 201 imaging may provide critically important data for risk stratification and revascularization decision-making in patients with CAD and LV dysfunction, although this decision should also be based on clinical presentation, coronary anatomy, LV function, and evidence of inducible ischemia.

In recent years, it has become well recognized that impaired left ventricular (LV) function in patients with chronic coronary artery disease (CAD) is often not an irreversible process representing previous myocardial infarction, as myocardial revascularization procedures may result in substantial improvement in regional and global LV function in many patients. The identification of viable myocardium has important prognostic and therapeutic implications. As a result, diagnostic testing to evaluate the potential for recovery of viable but dysfunctional myocardium has become an important component of the clinical assessment of patients with chronic CAD and LV dysfunction.

The mechanism for improved systolic function after revascularization is the subject of considerable ongoing debate, as persistent but reversible LV dysfunction may arise either from repeated episodes of myocardial ischemia leading to repetitive stunning, or from chronic myocardial hypoperfusion leading to myocardial hibernation, or a combination of these processes. It is clear, however, that many patients have evidence of reduced regional myocardial blood flow under resting conditions with associated contractile dysfunction, and that restoration of blood flow under resting conditions is associated with significant improvement in regional wall motion and ejection fraction.

These characteristics fulfill the definition of myocardial hibernation.

It has been estimated that between 25% and 40% of patients with chronic CAD and global LV dysfunction have the potential for significant improvement in LV ejection fraction after revascularization. The differentiation of viable from nonviable myocardium is an important diagnostic issue in patients being considered for revascularization, as bypass surgery or angioplasty are associated with an increased risk of morbidity and mortality in patients with LV dysfunction. However, these are also the patients with the most to gain from revascularization.

There are several clinically available methods that can be employed as accurate physiologic markers of viability. Indexes of regional coronary blood flow, regional wall motion, and regional systolic wall thickening are accurate markers of viability if they are normal or near-normal. However, these indexes have major limitations in identifying viable myocardium when they are reduced or absent, as regional perfusion and systolic function will be severely reduced or absent, by definition, in hibernating myocardium, despite maintenance of tissue viability.

Techniques to assess cellular metabolic processes, cell membrane

integrity, and myocardial contractile reserve have intrinsic advantages over indexes of resting function and blood flow. Nuclear cardiology techniques, involving single photon emission computed tomography (SPECT) as well as positron emission tomography (PET), can be used to investigate perfusion, cell membrane integrity, and metabolic activity, and dobutamine echocardiography can assess myocardial contractile reserve. Thus, SPECT, PET, or echocardiography can provide critically important viability information in patients with LV dysfunction.

POSITRON EMISSION TOMOGRAPHY

PET has become an established method for demonstrating viable myocardium in patients with compromised LV function, by demonstrating intact metabolic activity in regions of severely underperfused and dysfunctional myocardium. For this purpose, [^{18}F]fluorodeoxyglucose (FDG) is used as a marker of regional exogenous glucose utilization and compared regional perfusion data. Regions with enhanced FDG uptake relative to perfusion (termed the FDG:blood flow "mismatch") represent ischemic or hibernating myocardium that has preferentially shifted its metabolic substrate toward glucose rather than fatty acids or lactate. Several studies, involving a total of 146 patients, have shown that preserved metabolic activity in myocardial regions with reduced blood flow is an accurate clinical marker of viable myocardium, with an average positive predictive value of 82% and negative predictive value of 83% in identifying regions that will manifest improved function after revascularization. Moreover, the extent and magnitude of FDG:blood flow mismatch can be used to predict the magnitude of recovery in global LV function after revascularization.

PATIENT OUTCOME

The increase in LV ejection fraction after revascularization in patients with FDG:blood flow mismatch also appears to translate into an improvement in prognosis, as myocardial revascularization in patients with LV dysfunction and FDG:blood flow mismatch enhances survival significantly compared to the survival of similar patients treated medically. The improvement in LV function after revascularization, as predicted by FDG:blood flow mismatch, is also associated with a significant improvement in symptoms of congestive heart failure. It should be pointed out that the few studies addressing prognosis share several common limitations. These were retrospective, nonrandomized studies involving relatively small numbers of patients. The factors selecting some patients for revascularization and others for medical therapy are unspecified, and it is unclear if other predictors of outcome, such as severity of angina or inducible myocardial ischemia, were used to guide the selection toward revascularization. Although more definitive data are required before full conclusions can be drawn, these data nonetheless suggest that patients with impaired LV function and FDG:blood flow mismatch are a subgroup of patients who may have substantial improvement in outcome if identified and treated by myocardial revascularization. These patients appear to have the potential for improved LV function, improved symptoms, and improved survival.

THALLIUM 201 IMAGING

The uptake and retention of thallium 201 is an active process that is a function of cell viability and cell membrane activity, as well as blood flow. Hence, thallium 201 should in theory be taken up and retained by myocardial regions that also retain FDG and other metabolic tracers. Thallium redistribution, even in asynergic regions, predicts improvement of regional contraction after revascularization. The two imaging protocols that have been shown to have the greatest value for viability assessment are stress-redistribution-reinjection imaging and rest-distribution imaging.

THALLIUM REINJECTION TECHNIQUES

The reinjection of thallium at rest immediately after the standard 4-hour redistribution image overcomes many of the limitations of standard stress-redistribution imaging and may be used to assess viability in myocardium with apparently irreversible thallium defects on standard early or late redistribution images. Up to 49% of "irreversible" defects on 4-hour redistribution studies demonstrate improved or normal uptake after thallium reinjection.

That the uptake of thallium after reinjection represents viable myocardium is substantiated in revascularization studies. Among 95 patients reported in 9 studies of stress-redistribution-reinjection SPECT imaging, the cumulative positive and negative predictive accuracies were 69% and 89%, respectively, for predictive improved regional function 3 to 6 months after revascularization. This experience indicates that thallium reinjection imaging yields a higher negative predictive value, owing to its higher sensitivity, and a lower positive predictive value, owing to its lower specificity, compared to metabolic PET imaging.

REST-REDISTRIBUTION THALLIUM IMAGING

The demonstration of exercise-induced ischemia in a patient with LV dysfunction has important prognostic implications in that under most conditions it identifies that patient as a candidate for revascularization therapy. Thus, exercise-redistribution-reinjection thallium protocols are attractive, as they provide important information regarding both myocardial ischemia and myocardial viability. However, in many patients, the sole clinical issue to be addressed is the viability of one or more regions of dysfunctional LV myocardium, and not whether there is also inducible ischemia. In such patients, rest-redistribution thallium imaging is a practical approach that can yield accurate viability data. It is essential to obtain not only initial images (indicating regional perfusion) but also subsequent redistribution images. Although early investigations more than a decade ago yielded mixed results regarding the predictive accuracy of rest-redistribution imaging, recent studies indicate that a quantitative analysis of regional thallium activity in rest-redistribution studies predicts recovery of regional LV function and compares favorably to the results of thallium exercise-reinjection imaging. Four recent studies of rest-redistribution SPECT imaging, involving 83 patients, have shown positive and negative predictive accuracies of 69% and 92%, respectively, for improvement in regional LV function after revascularization. The similarity of stress-distribution-reinjection imaging and rest-redistribution imaging in predicting functional recovery is not surprising, given the excellent concordance in regional thallium activity between these two thallium methods when studied in the same patients.

PATIENT OUTCOME

Similar to outcome studies with PET, recovery of LV function after revascularization in patients with evidence of myocardial viability by thallium 201 imaging also appears to translate into an improvement in prognosis, although the prognostic implications of viability assessment using thallium imaging are less well advanced at present. Thallium imaging may also identify those patients with LV dysfunction who should not undergo myocardial revascularization. Patients with impaired LV function who have no evidence of viability in dysfunctional regions, or who have only a small number of viable regions, appear to have a significantly greater mortality after revascularization surgery than do patients who undergo revascularization with evidence of extensive viable myocardium in the dysfunctional segments.

Thus, assessment of myocardial viability with thallium 201 imaging may provide critically important data for risk stratification and revascularization decision-making in patients with CAD and LV dysfunction.

TECHNETIUM 99m SESTAMIBI IMAGING

Unlike thallium 201, Tc 99m sestamibi does not redistribute appreciably after an injection during exercise or at rest. Thus, sestamibi may have inherent disadvantages relative to thallium for viability assessment, especially in situations in which resting blood flow is reduced. This concept is supported by studies demonstrating that rest-exercise sestamibi imaging underestimates viable myocardium in patients with chronic CAD and LV dysfunction compared to exercise-redistribution-reinjection thallium imaging. Further evidence for the underestimation of myocardial

viability was demonstrated when Tc 99m sestamibi was compared with thallium reinjection or positron emission tomography.

QUANTITATION OF REGIONAL SESTAMIBI ACTIVITY

Recent studies have reported more promising results with quantitation of regional Tc 99m sestamibi activity to increase the accuracy of detecting viable myocardium. Sestamibi activity correlates with preserved metabolic activity, histologic markers of cellular viability, and improvement in ventricular function after revascularization. There is a high concordance between quantitative resting thallium and Tc 99m sestamibi activities in viable segments of patients with regional LV dysfunction. Of greater importance, however, has been the finding in two studies that analysis of Tc 99m sestamibi activity has high positive and negative predictive values for the recovery of ventricular function following coronary revascularization, which are similar to those obtained with thallium imaging. It has also been proposed that the administration of nitroglycerin prior to the acquisition of resting Tc 99m sestamibi images may enhance viability detection, as the resting perfusion defect size is reduced with nitroglycerin administration in the majority of patients who manifest functional recovery after revascularization.

SPECT METABOLIC MARKERS

The role of SPECT imaging using metabolic tracers has been less extensively studied compared to the large number of patients studied with FDG PET or with thallium 201 or Tc 99m sestamibi. Technetium-

based or iodinated fatty acids have been studied in preliminary trials and appear promising. In addition, the ability to image PET tracers such as FDG, using high energy collimators, is a new and unique application of current SPECT technology that may allow more routine use of PET tracers for viability assessment. The accuracy of SPECT imaging of PET tracers for this purpose in patients before and after revascularization is now undergoing extensive evaluation, with promising initial results.

DOBUTAMINE ECHOCARDIOGRAPHY

Dobutamine echocardiography to assess inotropic reserve in viable myocardium has also shown considerable promise in assessing myocardial viability, in keeping with the presence of residual inotropic reserve in stunned and/or hibernating myocardium that may be elicited through catecholamine stimulation. The available data indicate that more patients and more myocardial segments appear viable based on thallium imaging than with dobutamine echocardiography, suggesting that myocardial perfusion imaging with SPECT is more sensitive in detecting viable myocardium. Regional discordance has also been noted, with greater evidence of viability in the anterior and septal regions with thallium scintigraphy compared to dobutamine echocardiography. Similarly, a greater number of dysfunctional myocardial segments have been identified as viable by PET than by echocardiography, indicating that there are regions of viable myocardium that are metabolically active but lack inotropic reserve. The regions with discordant findings between the two techniques tend to be those in which blood flow is reduced at rest

and are presumably hibernating. In contrast, there is an excellent agreement between PET and dobutamine echocardiography in identifying dysfunctional myocardial regions that have preserved blood flow at rest and are presumably stunned.

Despite the potential for reduced predictive power of dobutamine echocardiography in chronic CAD, the positive and negative predictive values of this technique are excellent for identifying dysfunctional myocardium that will improve in function after revascularization. In the last 4 years, 15 studies of 402 patients with chronic CAD and LV dysfunction undergoing dobutamine echocardiography before revascularization have demonstrated that the predictive accuracy of this method regarding recovery of LV function after revascularization is equivalent to that achieved using PET or thallium SPECT protocols. The cumulative positive predictive accuracy of dobutamine echocardiography is 83%, with a negative predictive accuracy of 81%.

CLINICAL IMPLICATIONS

Nuclear cardiology techniques have the unique potential to distinguish viable from fibrotic myocardium on the basis of perfusion, cell membrane integrity, and metabolic activity, thereby providing greater precision than can be achieved by assessment of regional anatomy or function. In addition, dobutamine echocardiography is also superbly suited to assess myocardial contractile reserve. The unresolved issues are the relative efficacy of these methods when applied to larger numbers of patients than reported to date, as well as the precise identification of patients most likely to benefit from this

assessment. Although roughly 85% of dysfunctional myocardial regions identified as viable by these various imaging techniques may improve after revascularization, it is unlikely that this will actually lead to clinical benefit in 85% of patients. Whether or not a clinically relevant change in ventricular performance occurs, and whether this translates into improved lifestyle and prognosis, will depend upon a number of factors, many of which are only poorly defined at present. The amount of dysfunctional but viable myocardium certainly is one such factor. However, the identification of viable myocardium is not in itself an indication for revascularization. As in any other patient with CAD, this decision should be based on clinical presentation, coronary anatomy, LV function, and evidence of inducible ischemia. The knowledge that a large region of LV myocardium is viable rather than irreversibly damaged will aid in this decision-making process.

Further reading

1. Dilsizian V, Rocco TP, Freedman NMT, Leon MB, Bonow RO.

Enhanced detection of ischemic but viable myocardium by the reinjection of thallium after stress-redistribution imaging.

N Engl J Med. 1990;323:141-146.

2. Ragosta M, Beller GA, Watson DD, Kaul S, Gimple LW.

Quantitative planar rest-redistribution ^{201}Tl imaging in detection of myocardial viability and prediction of improvement in left ventricular function after coronary bypass surgery in patients with severely depressed left ventricular function.

Circulation. 1993;87:1630-1641.

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

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

Circulation. 1993;88:430-436.

4. Udelson JE, Coleman PS, Matherall JA, et al.

Predicting recovery of severe regional ventricular dysfunction: comparison of resting scintigraphy with thallium 201 and technetium 99m sestamibi.

Circulation. 1994;89:2552-2561.

5. Maddahi J, Schelbert H, Brunken R, Di Carli M.

Role of thallium 201 and PET imaging in evaluation of myocardial viability and management of patients with coronary artery disease and left ventricular dysfunction.

J Nucl Med. 1994;35:707-715.

6. Smart SC.

The clinical utility of echocardiography in the assessment of myocardial viability.

J Nucl Med. 1994;35(suppl):49S-58S.

7. Bisi G, Sciagra R, Santoro GM, Fazzani PF.

Rest technetium 99m sestamibi in combination with short-term administration of nitrates: feasibility and reliability for prediction of postrevascularization outcome of asynergic territories.

J Am Coll Cardiol. 1994;24:1282-1289.

8. Vanoverschelde JJ, D'Hondt AM, Marwick T, et al.

Head-to-head comparison of exercise-redistribution-reinjection thallium single-photon emission computed tomography and low-dose dobutamine echocardiography for prediction of reversibility of chronic left ventricular ischemic dysfunction.

J Am Coll Cardiol. 1996;28:432-442.

9. Bax JJ, Cornel JH, Visser FC, et al.

Prediction of recovery of regional ventricular dysfunction following revascularization: comparison of fluorine-18-fluorodeoxyglucose/ thallium-201 SPECT, thallium-201 stress-reinjection SPECT and dobutamine echo-cardiography.

J Am Coll Cardiol. 1996;28:558-564.

10. Perrone-Filardi P, Pace L, Prastaro M, et al.

Assessment of myocardial viability in patients with chronic coronary artery disease: rest-4-hour-24-hour ^{201}Tl tomography versus dobutamine echocardiography.

Circulation. 1996;94:2712-2719.

11. Bonow RO.

Identification of viable myocardium.

Circulation. 1996;94:2674-2680.

12. Beller GA.

Comparison of thallium 201 scintigraphy and low-dose dobutamine echocardiography for the noninvasive assessment of myocardial viability.

Circulation. 1996;94:2681-2684.

13. Hendel RC, Chaudhry FA, Bonow RO.

Myocardial viability.

Curr Probl Cardiol. 1996;21:145-224.

Treating myocardial hibernation: surgery, pharmacology, or both?

Giovanni La Canna, MD

Cattedra di Cardiologia - Spedali Civili - P. le Spedali Civili, 1 - 25123 Brescia - ITALY

In patients with coronary artery disease (CAD) and left ventricular dysfunction, the presence of myocardial viability is a marker of clinical instability and unfavorable prognosis, unless the myocardium is reperfused. Identification of viable myocardium is therefore essential to the final outcome, particularly in cases of cardiac failure. Development of heart failure in CAD is a complex process involving recurrent ischemia, stunning, hibernation, and fibrosis. Surgical revascularization is, at present, the best therapeutic solution for myocardial hibernation. Pharmacological treatment is useful adjunct to optimize surgical results and reduce symptoms of heart failure, although no specific pharmacotherapy can be recommended at present. Contractile recovery linked to surgical revascularization is determined by completeness of revascularization, myocardial protection, postsurgical stunning, and transmural extension of the subendocardial damage.

The hibernating myocardium is a unique clinical condition in which myocytes downregulate contraction and avoid the occurrence of necrosis, maintaining viability.[1]

How long this condition can persist is, at present, unknown. The histopathological changes documented from biopsies performed on patients with a prolonged contractile dysfunction clearly suggest time-dependency. Intracellular glycogen increases and extracellular matrix proteins (such as desmins, tubulin, and vinculin) accumulate. Thin filament complexes are reduced, and the remaining myofibrils and the sarcoplasmic reticulum are disorganized. Several small "doughnut-like" mitochondria are often observed. Up to a certain degree of severity, these degenerative alterations appear to be reversible and can play an important role in determining the likelihood of contractile recovery upon reperfusion.[2] It follows that the hibernating myocardium is a therapeutic target of coronary artery disease (CAD) aimed at preventing structural remodeling and avoiding development of further fibrosis. Clinical studies suggest that the presence of myocardial viability in CAD patients with ventricular dysfunction is a marker of unfavorable prognosis and clinical

instability unless the myocardium is reperfused.[3,4] It follows that revascularization is the primary therapeutic goal of the hibernating myocardium, and contractile recovery after revascularization is the clinical standard that defines this condition.[1]

HIBERNATING MYOCARDIUM AND HEART FAILURE: THE ROLE OF SURGICAL REVASCULARIZATION

In CAD patients, it is quite common for an initial ventricular dysfunction to lead to a cardiomyopathy, which is a primary indication of heart transplantation, accounting for 40% to 50% of transplantations performed. Development of cardiac failure in CAD is a complex process involving several different pathophysiological mechanisms such as recurrent ischemia, stunning, hibernation, and fibrosis. All these conditions may result in progressive remodeling with consequent further ventricular dilatation, increased parietal stress and filling pressure, reduction in global systolic function, mitral incompetence, alteration of pulmonary circulation leading to right ventricular dysfunction, and systemic venous congestion. In a small number of CAD patients, hibernating myocardium can be the cause initiating the whole

process. It follows that revascularization by coronary artery bypass with the consequent restoration of contractile function can indeed be of clinical benefit.[5]

Identification of viable myocardium with all the available techniques is of paramount importance to the final outcome. In this context, estimation of the contractile reserve of the akinetic myocardium may be crucial to establish the need for surgery (which is proportionally related to the extension of the hibernating myocardium) and to estimate the operative risk (which is related to an early recovery of function after surgery).

Di Carli et al[6] have shown that the extension of viability to >18% of the ventricle is correlated with a functional and clinical benefit, even if it is associated with a high perioperative mortality (10%). It is also worthwhile underlining that a reversible mitral incompetence due to the hibernation of the anterior or inferior region of the ventricle is an important criterion for predicting a favorable clinical outcome, in addition to the extension of the viable area. Even under these circumstances, the demonstration of contractile reserve is excellent for the stratification of patients.

The benefits of revascularization are usually linked to the recovery of the functional kinetics of the hibernating segments. However, in addition to other factors, such as completeness of revascularization, myocardial protection, and postsurgical stunning, contractile recovery is also determined by the transmural extension of the subendocardial damage. Values of subendocardial extension of 20% cause absence of contraction with potential underestimation of the benefits of surgery.

PHARMACOLOGICAL TREATMENT OF THE HIBERNATING MYOCARDIUM

It is possible to enhance the contractile status of hibernating myocardium by low-dose inotropic challenge, which is often followed by a reduction in contraction due to a deterioration of the coronary reserve.[7,8] Such a biphasic response to increasing doses of inotropic stimuli suggests that the hibernating myocardium is a condition at risk for recurrent ischemia, which may potentially benefit from anti-ischemic treatment aimed at reducing afterload and improving oxygen delivery. Theoretically, the prevention of ischemic episodes and the improvement in coronary microcirculation could also cause a functional recovery of the akinetic areas. Athough it appears certain that standard pharmacological therapy could delay the evolution from left ventricular dysfunction to heart failure, it does not cause a clear improvement in prognosis, in contrast to surgery.[9,10] However, pharmacological treatment is particularly appropriate when a condition of repetitive stunning, which is itself due to recurrent episodes of ischemia, mimicks hibernation. Treatment of ischemia should interrupt this vicious circle.

Aside from these general considerations, and without a reliable understanding of the mechanism of hibernation, no specific pharmacotherapy can be recommended at present.

Other than for diagnostic purposes, inotropic stimulation has not been studied in patients with hibernation or in models of long-term hibernation. However, any prolonged inotropic stimulation will probably be detrimental, regardless of whether the hibernating myocardium is associated with persistently reduced blood flow and cannot meet the enhanced energy demand resulting from inotropic stimulation, or whether only the coronary reserve is reduced and ischemia is induced by inotropic stimulation.

Since the hibernating myocardium is characterized by a reduced resting flow, any increase in blood flow would be expected to attenuate the contractile dysfunction. Indeed, in Rahimtoola's landmark paper,[1] a positive response of contractile function to nitroglycerin was part of the original definition of myocardial hibernation. If, however, the hibernating myocardium has a normal resting flow, an increase in flow might not necessarily improve contractile function. Under such circumstances, substances that can attenuate exercise-induced ischemia might alleviate cumulative stunning. Unfortunately, none of these hypotheses has yet been studied experimentally or clinically. There is a clear need for more studies with better models.

CONCLUSION

Surgical revascularization is at present the most suitable therapeutic solution for patients with myocardial hibernation. Pharmacological treatment is a useful adjunct to optimize surgical results and reduce the symptoms of heart failure.

REFERENCES

1. Rahimtoola SH.
The hibernating myocardium.
Am Heart J. 1989;117:211-221.

---

2. Shivalkar B, Maes A, Borgers M, et al.
Only hibernating myocardium invariably shows early recovery after coronary revascularization.
Circulation. 1996;94:308-315.

---

3. Eitzman D, Al-Aquar Z, Kanter H, et al.
Clinical outcome of patients with advanced coronary artery disease after viability studies with positron emission tomography.
J Am Coll Cardiol. 1992;20:559-565.

---

4. Williams MJ, Odabashian J, Laurer MS, Thomas JD, Marwick TH.
Prognostic value of dobutamine echocardiography in patients with left ventricular dysfunction.
J Am Coll Cardiol. 1996;27:132-139.

---

5. Backer DW, Jones R, Hodges J, Massie BM, Konstam MA, Rose EA.
Management of heart failure. III. The role of revascularization in the treatment of patients with moderate or severe left ventricular dysfunction.
JAMA. 1994;272:1528-1534.

---

6. Di Carli M, Asgarzadie F, Schelbert HR, et al.
Quantitative relation between myocardial viability and improvement in heart failure symptoms after revascularization in patients with ischemic cardiomyopathy.
Circulation. 1995;92:3436-3444.

---

7. La Canna G, Alfieri O, Giubbini R, et al.
Echocardiography during infusion of dobutamine for identification of reversible dysfunction in patients with chronic coronary artery disease.
J Am Coll Cardiol. 1994;23:617-626.

---

8. Afridi I, Kleiman NS, Raizner AE, Zoghbi WA.
Dobutamine echocardiography in myocardial hibernation: optimal dose and accuracy in predicting recovery of ventricular function after coronary angioplasty.
Circulation. 1995;91:663-670.

---

9. The SOLVD Investigators.
Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fraction.
N Engl J Med. 1992;327:685-691.

---

10. Australia/New Zealand Heart Failure Research Collaborative Group.
Randomized, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischemic heart disease.
Lancet. 1997;349:875-880.

Hibernating Myocardium

Summaries of Ten Seminal Papers

①

Reversibility of cardiac wall motion abnormalities
predicted by positron tomography

J. Tillisch and others. *N Engl J Med.* 1986

②

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

I. Afridi and others.
Circulation. 1995

③

Metabolic adaptation to a gradual reduction
in myocardial blood flow

A.E. Arai and others. *Circulation.* 1995

④

Enhanced detection of ischemic but viable
myocardium by the reinjection of thallium
after stress redistribution imaging

V. Dilsizian and others. *N Engl J Med.* 1990

⑤

Adaptive responses of coronary circulation
and myocardium to chronic reduction
in perfusion pressure and flow

I. Mills and others. *Am J Physiol.* 1994

⑥

Ischemic cardiomyopathy: criteria for coronary
revascularization and cardiac transplantation

H.W. Louie and others. *Circulation.* 1991

⑦

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

G. La Canna and others.
J Am Coll Cardiol. 1994

⑧

The hibernating myocardium

S.H. Rahimtoola.
Am Heart J. 1989

⑨

Recruitment of an inotropic reserve in moderately
ischemic myocardium at the expense of metabolic
recovery: a model of short-term hibernation

R. Schulz and others. *Circ Res.* 1992

⑩

Metabolic adaptation during a sequence
of no-flow and low-flow ischemia:
a possible trigger for hibernation

R. Ferrari and others. *Circulation.* 1996

Summaries prepared by **Dr Pamela B. Garlick**
Division of Radiological Sciences, Guy's Hospital, London SE1 9RT - UK

Reversibility of cardiac wall motion abnormalities predicted by positron tomography

J. Tillisch, R. Brunken, R. Marshall, M. Schwaiger, M. Madelkorn, P. Phelps, H. Schelbert

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

This key, early clinical study from the UCLA Medical Center was one of the first to investigate whether the technique of positron emission tomography (PET) can be used to predict the metabolic viability of the myocardium. This prospective study was designed to test whether a pair of PET scans, one using a regional blood flow tracer such as ammonia ($^{13}NH_3$) and the other using a glucose analogue ([^{18}F]fluorodeoxyglucose, ^{18}FDG) could be used to predict viable, as opposed to infarcted, tissue. The patterns of myocardial uptake of these two radiotracers, in regions with abnormal wall motion at rest, were analyzed and used to predict the reversibility of wall motion abnormalities upon surgical revascularization.

Seventeen patients with wall motion abnormalities who had been referred for bypass grafting were included in the study. All the patients had preoperative PET scans with $^{13}NH_3$ and ^{18}FDG, and all of them also had both preoperative and postoperative wall motion studies performed (by either contrast or radionuclide angiography). It was found that the PET scans obtained from each patient fitted into one of three patterns: firstly, normal or increased uptake of ^{18}FDG was observed with normal uptake of $^{13}NH_3$; secondly, normal or increased uptake of ^{18}FDG was observed with decreased uptake of $^{13}NH_3$; and thirdly, decreased uptake of both $^{13}NH_3$ and ^{18}FDG was observed. It was hypothesized that the first two patterns predicted that the wall motion abnormalities could be reversed by revascularization, while the last pattern, in which decreased uptake of both PET tracers was seen, predicted infarcted tissue and thus irreversibility. In the regions that were predicted to be reversible, the wall motion score improved from a preoperative value of 2.0 to a postoperative value of 0.6 ($P<0.05$). However, in the regions that were predicted to be irreversible, wall motion score did not change significantly (2.4 and 2.6, preoperatively and postoperatively, respectively). In the 11 patients in whom regional wall motion did improve, a concomitant increase in the ejection fraction, from 30% to 45% ($P<0.05$), was noted. There were 73 regions in total that showed abnormal wall motion preoperatively, and the predictive accuracy of $^{13}NH_3$ and

^{18}FDG scans was found to be 85% for reversible regions (normal or increased uptake of ^{18}FDG with decreased uptake of $^{13}NH_3$) and 92% for irreversible regions (decreased uptake of both tracers). Predictive accuracy in the septum was found to be less successful than in other regions of the myocardium. It is suggested that this may be due, not to inadequate restoration of blood flow to the region, but rather to electromechanical factors that either impair septal contractility or cause a change in its motion compared to the rest of the myocardium. Interestingly, the presence of Q waves preoperatively in regions of abnormal wall motion was not found to correlate with irreversibility after revascularization; thus, the notion that Q waves are evidence of transmural infarction needs to be reassessed.

The authors offer a brief discussion of the biochemistry underlying increased ^{18}FDG uptake in hypokinetic regions. They point out that mild ischemia produces an increase in glucose metabolism relative to fatty acid metabolism, while severe ischemia leads to cell injury, and ultimately death, due to the lack of washout of the inhibitory end products of glycolysis. They suggest that, if the flow reduction were mild or "subcritical," cellular viability could be maintained, albeit in a situation of decreased contractility. They observe that "it is possible that in patients with these features, this metabolic state may become chronic and clinically stable—that is, without angina or progress to infarction." Although the authors may not have been aware of it at the time, this would seem to be a very accurate definition of myocardial hibernation.

1986

Argentina wins the World Cup, helped by "the hand of God;" Clint Eastwood, Hollywood star, becomes mayor of Carmel, California; and Cary Grant, the nonchalant matinee idol, dies aged 82 years

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

I. Afridi, N.S. Kleiman, A.E. Raizer, W.A. Zoghbi

Circulation. 1995;91:663-670

The aims of this prospective clinical study were: (i) to investigate whether hearts that are hibernating can be identified by dobutamine echocardiography; and (ii) to determine whether a dose-response curve for dobutamine can improve the accuracy of the test. The patients in the study all had stable coronary artery disease with regional left ventricular (LV) dysfunction and were about to undergo percutaneous transluminal coronary angioplasty (PTCA). The two main inclusion criteria were >70% occlusion of at least one epicardial coronary artery and evidence of resting regional LV dysfunction. The authors used a 6-point scoring system for grading wall motion in each of the 16 LV segments, and computed a wall motion score index (WMSI) for the whole left ventricle (total score divided by the number of segments involved) plus one for the left anterior descending (LAD) bed and one for the rest of the left ventricle. The dobutamine infusion was given in incremental doses of 3 minutes each, starting at 2.5 µg/kg/min and increasing to 5.0, 7.5, 10.0, 20.0, 30.0, and 40.0 µg/kg/min. A total of 20 patients were investigated, with a mean age of 60 years. None had suffered a recent infarction or had unstable angina. PTCA was successful in 18 of the 20 patients with the mean coronary stenosis decreasing from 88% to 22%. A significant improvement was seen in the WMSI of the revascularized territories, with a decrease from 2.9 to 2.1. The global WMSI, however, although it decreased after PTCA, never reached statistical significance. No changes were observed in the WMSI in the nonrevascularized territories. Of a total of 318 that could be adequately visualized, 148 had abnormal resting wall motion, and of these, 114 were revascularized. A significant improvement in motion (defined as >2 grades) was seen in 25% early after, and 38% late after PTCA. Only one of the 34 segments that was not revascularized showed any improvement in wall motion.

Four types of responses were observed, with increasing dobutamine concentrations, in the 114 abnormal segments that were revascularized: (i) a biphasic response in 28% of the segments; (ii) a sustained improvement in 18%; (iii) a worsening in 15%; and (iv) no change in 39%. The authors found that the biphasic response was best for prediction of LV recovery, in that 72% of the 32 segments that exhibited a biphasic response showed recovery at late follow-up. The responses of sustained improvement, worsening, and no change showed recoveries of 15%, 35%, and 13%, respectively. Combining the segments that showed either the biphasic or the worsening response to dobutamine, the sensitivity of the test was 74% and its specificity was 73%, with a positive predictive value of 59% and a negative predictive value of 86%. When analyzed by individual patients, 8 out of 9 patients with a biphasic response showed recovery of function in at least 2 contiguous segments after PTCA.

The authors conclude that the prediction of LV functional recovery depends on the dose of dobutamine. They suggest that a biphasic response may be observed because low doses result in recruitment of contractile reserve while high doses cause ischemia. They point out that although a biphasic response has never been previously observed in the hibernating myocardium, a similar response has been seen in stunned myocardium (infarcted plus thrombolysis). The 18% of hibernating segments that showed worsening of wall motion tended to be those supplied by very stenosed arteries. Why did the sustained improvement response have such a low predictive value? The authors could not answer this question but suggest that, since segments in this group never demonstrate ischemia even at maximal doses, their LV dysfunction was probably not caused by chronic ischemia.

— 1995 —

Forrest Gump wins six Oscars including
Best Actor (Tom Hanks);
a man is sentenced in California to 25 years
in prison for stealing a slice of pizza;
and Odette Hallowes,
the Second World War heroine,
dies aged 83 years

Metabolic adaptation to a gradual reduction in myocardial blood flow

A.E. Arai, S.E. Grauer, C.G. Anselone, G.A. Pantely, J.D. Bristow

Can the heart downregulate itself in response to a gradual reduction of blood flow or are the transient metabolic abnormalities, associated with a sudden decrease in flow, necessary for such adaptation?

To address this question, the authors of this experimental study carefully and extensively instrumented 10 open-chest pigs. A hydraulic occluder and an electromagnetic flow probe were positioned around the left anterior descending (LAD) coronary artery and a pair of ultrasonic crystals were implanted to measure wall thickness within the LAD perfusion bed. Catheters were positioned in relevant vessels to monitor regional myocardial oxygen consumption (MVO_2), lactate consumption, and coronary perfusion pressure, and for the injection of radiolabelled microspheres. Transmural left ventricular (LV) biopsies were taken when required with a drill biopsy gun; after dividing each sample into subendocardial, midmyocardial, and subepicardial thirds, using a blue dye to delineate the epicardial surface, the tissue was analyzed for ATP and phosphocreatine (PCr). After control measurements had been made, the LAD flow was gradually decreased, at a rate of 1% per minute for 35 minutes. The flow was then held constant for a further 25 minutes at this new level (65% of control).

In terms of metabolism, lactate production was found to be very variable from animal to animal. During the control period, all animals showed lactate consumption; this decreased during the experimental protocol and, although on average the group did not develop significant lactate production, 7 out of the 10 animals produced lactate at some time during the experiment. A gradual decrease in LV wall thickening in the LAD zone was observed, with a time course that paralleled the decrease in LAD blood flow. Wall thickening was 45% during the control period and this decreased to 18% by 60 minutes of ischemia. When wall thickening was analyzed in individual animals, it was found that it had significantly decreased before any net production of lactate had occurred; lactate production, therefore, is not necessary for hypokinesis to occur. Subendocardial and midmyocardial ATP levels had decreased by 30 minutes, but were fairly stable between 30 and 60 minutes. PCr in all regions had decreased by 30 minutes, but had increased to ≈87% of control by 60 minutes. The subendocardial and transmural PCr:ATP ratios were 1.6 and 1.7, respectively, during the control period; neither changed significantly during the protocol.

The authors concluded that contractile changes paralleled flow changes such that the downregulation of function essentially kept pace with the gradual reduction in blood flow. The fact that no change was observed in the PCr:ATP ratio and that no significant lactate production was observed meant that tightly regulated control mechanisms were in operation. In the second part of their discussion, the authors deftly introduce the "time-flow deficit" integral (calculated as the cumulative integral of time multiplied by the percentage transmural LAD flow reduction for each animal). This enables them to discuss, at great length, how their currently obtained data relate to data from three previous studies, where they had used sudden- (rather than gradual-) onset ischemia of varying degrees (22,% 30%, and 43%) to induce hibernation. One was left wondering why they had chosen a fourth degree of flow reduction (35%) for their present study, instead of using one of the previous three! Utilizing animals with similar "time-flow-deficit" integrals from their different studies, they found that the PCr:ATP ratio could be low, normal, or high, depending on when the ratio was measured and whether the ischemia was gradual or sudden. They made the important point that knowledge of this would be vital in magnetic resonance spectroscopy (MRS) examinations, where the ratio of PCr:ATP is often measured in preference to absolute levels of the metabolites.

1995

Barings Bank collapses
and Nick Leeson starts running;
a bomb in Oklahoma City wrecks
a federal building and claims 160 lives;
and Christopher Reeve (Superman)
is paralyzed in a riding accident

Enhanced detection of ischemic but viable myocardium by the reinjection of thallium after stress redistribution imaging

V. Dilsizian, T.P. Rocco, N.M.T. Freedman, M.B. Leon, R.O. Bonow

N Engl J Med. 1990;323:141-146

Dilsizian and colleagues begin this clinical paper by stressing the importance of identifying patients with reversible left ventricular dysfunction, ie, hibernating myocardium, who, as a subgroup, would benefit from revascularization. To this end, they report the results of a study in which they have investigated whether the predictive value of thallium 201 redistribution images can be improved by giving a second thallium 201 injection after the exercise period.

Thallium redistribution scans (taken 3 to 4 hours after the original injection, at rest), when compared with scans showing perfusion defects during exercise (stress images), often reveal regions of the myocardium that have become "filled in"; such areas are taken to indicate the existence of ischemic but viable tissue. Some regions, however, that are in fact viable, still appear as defects in the redistribution scans, and thus are mistakenly classified as infarcted myocardium. The authors postulate that a defective area may not be "filled in" on the resdistribution scan, not because of a lack of perfusion at rest, but because of an insufficiently high level of thallium in the blood; they therefore propose that a second injection of thallium 201 be given immediately after the first redistribution scan.

The authors studied a large number of patients (100 in total) with coronary artery disease, with a >50% decrease in the luminal diameter of one epicardial coronary artery, as determined by coronary angiography. Each patient was given three thallium 201, single photon emission computed tomography (SPECT) scans: the first was during treadmill exercise; the second was a rest-redistribution scan 3 to 4 hours later; and the third was 15 minutes after a second injection of thallium 201. Each short axis image was divided into 4 regions (anterior, lateral, inferior, and septal) each of which was then subdivided into 16 sectors for quantitative analysis. Thus, a total of 400 regions (6400 sectors) were analyzed.

It was found that 92 out of the 100 patients had thallium defects during exercise and that among these 92 patients, 260 regions were graded as abnormal. Of these 260 regions, 88 (34%) were normal on the redistribution images,

87 were partially reversed, and 85 remained fixed (totally irreversible). Of the 87 partially reversed regions, 49 showed further thallium uptake upon reinjection, 45 of which increased to normal levels. Of the 85 fixed defects, 42 showed further thallium uptake upon reinjection, 23 of which increased to normal levels.

The authors concluded that, in their study, scans taken after thallium reinjection had successfully identified viable myocardium in 101 of the 172 segments that had previously shown persistent defects in the redistribution images. They discuss their results in comparison with several other studies in which differences were observed between rest-redistribution thallium images (in which defects were observed in approximately 50% of the scans), and simple rest images without prior exercise (in which defects were observed in only about 30% of scans). The reason for these differences becomes apparent from the images obtained after a second injection of thallium. Also, the authors report that their results agree with those obtained using positron emission tomography (PET) scans, where viability is reported in 47% of segments with supposedly fixed defects and 64% of segments with partial defects seen on redistribution scans. The numbers from the present reinjection study are very similar, at 49% and 56%, respectively.

In the small subgroup of patients undergoing percutaneous transluminal coronary angioplasty (n=20), the authors correctly predicted viability in 13 of the 15 regions that showed "filling in" of defects in the thallium reinjection scans; all of the 15 regions had shown persistent defects in the redistribution scans. The authors conclude that scanning patients at rest, after reinjection of thallium 201, is a good alternative to the use of PET techniques, especially in view of the latter's high costs, in the delineation of ischemic but viable myocardium.

_____ 1990 _____

Daniel Day-Lewis wins an Oscar (Best Actor) for My Left Foot; Concorde celebrates its 21st birthday (March 2); and Greta Garbo, the Swedish-born actress, dies aged 84 years

Adaptive responses of coronary circulation and myocardium to chronic reduction in perfusion pressure and flow

I. Mills, J.T. Fallon, D. Wrenn, H. Sasken, W. Gray, J. Bier, D. Levine, S. Berman, M. Gilson, H. Gewirtz

In this study pigs were used to investigate the response of the myocardium and the coronary circulation to chronic ischemia (of 4 to 32 weeks duration). The authors hypothesize that a chronic reduction in perfusion pressure and coronary flow will induce a state of "hibernation" characterized by a reduction in myocardial oxygen consumption (MVO_2) and the persistence of dilator reserve in the distal coronary vasculature. The authors also sought to investigate the changes occurring in the thickness of the vessel wall and protein synthesis therein. They cite evidence for the response of larger microvessels (>100 μm) in the peripheral circulation to changes in blood pressure, in that chronic hypertension causes hypertrophy of walls whereas atrophy develops distal to a constriction. They rightly state that what happens to the coronary circulation during chronic stenosis is not known.

During open-chest surgery of 21 pigs, the proximal third of the left anterior coronary artery (LAD) was dissected free and an extraluminal occluder (inner bore of 1.5 mm) placed around it. The animals were then allowed to recover for 4 to 32 weeks; sadly, the authors never explain why the recovery period was so variable, nor do they analyze their data in subgroups with similar recovery times. At the end of the stenosis treatment period, coronary angiography was performed to check the patency of the stenosis and assess the development of collaterals. The animals (n=17 at this time, since 4 had died) were then divided into groups for analysis of the coronary vessels. Two regions of the myocardium were defined—the "stenosis zone," which referred to the myocardium or microvessels distal to the stenosis, and the "normal zone" which referred to the control region, ie, the circumflex coronary territory. Coronary flow reserve was assessed in Group I (n=6), using adenosine infusion, with and without phenylephrine; protein synthesis was measured in Group II (n=7), using ³⁵S-labelled methionine; morphometric analysis was performed in Group III (n=4).

The authors report that the lumen of the LAD was decreased by ≈80% in all animals and that 83% showed an absence of collaterals. In Group I, regional myocardial blood flow (MBF) in the "stenosis zone" was decreased in both epicardial and endocardial layers, compared to the "normal zone." The flow increased in both layers in both zones upon infusion of adenosine and phenylephrine; when infusion was discontinued, flow in the "stenosis zone" returned to the same level as that in the "normal zone." In response to a subsequent infusion of adenosine alone, blood flow in the "stenosis zone" did not change. Regional MVO_2 was decreased compared to "historical controls" without stenosis. In Group II, all vessels in the "stenosis zone" had decreased protein synthesis compared to vessels in the "normal zone." One-dimensional polyacrylamide gel electrophoresis (PAGE) demonstrated quantitative differences in protein composition between the two regions in only a single band (≈60 kDa). In 6 of the 7 animals, vessels in the "stenosed zone" had less of this protein than vessels in the "normal zone"; the authors postulate that it may be tropoelastin. In Group III, it was found that, in the "stenosis zone," the smaller microvessels (<75 μm) had thicker walls and the larger microvessels (>75 μm) thinner walls than their "normal zone" counterparts. It was also found that the distribution of fibrous tissue in the "stenosis zone" was not typical of healed infarction.

The authors conclude that they have demonstrated myocardial hibernation (decreased flow and decreased regional myocardial oxygen consumption) in a pig model. They have shown that the "stenosis zone" retains dilator reserve in both epicardial and endocardial layers and they hypothesize that the changes in protein synthesis and vessel wall thickness that they have observed in the "stenosis zone" may underly the ability of these vessels to maintain this dilator reserve.

--- 1994 ---

350 000 people celebrate the 25th anniversary
of the original Woodstock Concert;
Lisa Presley confirms rumors of her marriage to
Michael Jackson; and Ayrton Senna,
the Brazilian Formula One driver, dies aged 34 years

Ischemic cardiomyopathy: criteria for coronary revascularization and cardiac transplantation

H.W. Louie, H. Laks, E. Milgalter, D.C. Drinkwater Jr, M.A. Hamilton, R.C.Brunken, L.W. Stevenson

Circulation. 1991;84(suppl III):III-290-III-295

Another clinical study from the UCLA School of Medicine is described here, from the same department as the paper by Tillisch et al (see page 94); this time, however, the study is a retrospective one in which the authors attempt to evaluate the optimal criteria for the prediction of successful coronary revascularization. The reasoning behind their study is that "it is crucial to identify those patients with ischemic cardiomyopathy who may benefit from coronary revascularization despite eligibility for transplantation." The paper is rather frustrating because, like most retrospective studies, not all of the patients have undergone identical treatment or had identical scans, so, although from a cursory reading of the beginning of the abstract it would appear that the study involves 207 patients, the true number is considerably smaller. Between 1984 and 1990, a total of 22 patients had revascularization procedures performed at UCLA Medical Center (19 by surgery and 3 by percutaneous transluminal coronary angioplasty, [PTCA]), and of these, 12 also had preoperative positron emission tomography (PET) scans.

The authors analyze the functional data from the patients in two groups, depending on the success or otherwise of the revascularization procedure. The mean preoperative ejection fraction of the successful cases (n=16) was 26%, and this increased to 36% ($P<0.05$) after surgery. The mean left ventricular end-diastolic dimension (LVEDD) showed a nonsignificant decrease from 68 to 64 mm. The preoperative New York Heart Association (NYHA) functional class of IV improved to I ($P<0.05$) after successful revascularization, and the patients were subsequently free of anginal symptoms. In the nonsuccessful cases (n=6), the mean preoperative ejection fraction was 15% (not significantly different from the successful cases) and the mean preoperative LVEDD was 81 mm ($P<0.05$ compared to successful cases). Only 12 of the 22 patients had PET scans. Ten of these patients showed preserved or enhanced uptake of the glucose analogue, [^{18}F]fluorodeoxyglucose (^{18}FDG), in regions that showed decreased perfusion (on the ^{13}NH$_3$ scan). All 10 patients were successfully revascularized and their 3-year survival was not different from that seen in

similar patients undergoing transplantation. In contrast, the patients who underwent surgery had a much better 3-year survival than similar patients who received tailored medical therapy. The two remaining patients had PET scans that showed decreased uptake of ^{18}FDG together with decreased perfusion (^{13}NH$_3$); revascularization was unsuccessful in these patients. The authors acknowledge, however, that since n=2, the statistical significance of this finding has yet to be confirmed with a study using a larger number of patients.

The authors set out to find the optimal criteria to select for patients in whom coronary revascularization will improve LV function and survival. In their 10 successful patients, the mean preoperative ejection fraction was 23%, the mean preoperative LVEDD was 68 mm, and the PET scans all showed preserved or enhanced ^{18}FDG uptake in regions that showed decreased perfusion (^{13}NH$_3$ scan). In the two unsuccessful patients, the preoperative ejection fractions were 12% and 15%, the preoperative LVEDDs were 76 and 78 mm, and the PET scans showed decreased ^{18}FDG uptake in regions that showed decreased perfusion (^{13}NH$_3$). The authors therefore suggest that an initial ejection fraction of >20%, an initial LVEDD <70 mm, and a PET scan showing preserved or enhanced ^{18}FDG uptake in regions that showed decreased perfusion (^{13}NH$_3$) were all a good indicators. They conclude that all three indicators (ejection fraction, LVEDD, and PET scans) can be associated for a better prediction and suggest strongly that "coronary revascularization appears to be a reasonable procedure in select patients with end-stage ischemic cardiomyopathy for whom it should be considered before heart transplantation."

1991

Lazio, the Rome football club,
pays £6 million for Paul (Gazza) Gascoigne;
Rajiv Gandhi is assassinated; and the Nobel Peace
Prize is awarded to Aung San Suu Kyi,
still under house arrest in Myanmar (formerly Burma)

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

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

The aim of this prospective study from Italy was to test whether the contractile response to low-dose dobutamine was useful in the detection of myocardial viability in patients with coronary artery disease and left ventricular (LV) dysfunction. The authors chose to evaluate this technique since it had been found to compare favorably with positron emission tomography (PET) in the assessment of viability in patients who had undergone thrombolysis post-infarction.

Of the 99 patients screened for the study, only 33 met all seven of the (fairly strict) inclusion criteria. These included: narrowing (>75%) of coronary arteries subtending the akinetic areas; the suitability of the arteries for surgical revascularization; absence of rest angina; no acute infarction or unstable angina within 6 months of the study; and an LV ejection fraction <50%. The mean age of the patients was 56 years, the mean ejection fraction was 33%, and all of them had been selected for bypass surgery on the basis of the viable segments that had been detected in the thallium 201 rest-redistribution studies. The initial contractile response of each patient to low-dose dobutamine (5 µg/kg/min for 5 minutes, followed by 10 µg/kg/min for another 5 minutes) was measured by two-dimensional transthoracic echocardiography within 15 days of their bypass surgery. In the echo-analysis, the left ventricle was divided into 16 segments and a "conventional" scoring system of 1 to 4 was used to quantify regional wall motion. The quotes around conventional are not in the original paper, but have been inserted to highlight the discrepancies (and potential confusion) between wall motion scoring systems used by different clinicians (see summary of Afridi et al's paper on page 95). During bypass surgery itself, epicardial echocardiographic measurements were made, and in the postoperative period (2 weeks and 3 months later) transthoracic measurements were again performed. A total of 528 segments were analyzed in the 33 patients. Initially, 314 were akinetic, 20 hypokinetic, and 194 were normal; each patient had at least 2 akinetic segments. The results of all four of the echocardiographic examinations are given in two simple, but beautifully clear figures. These figures demonstrate

that clarity is often much easier to achieve in carefully designed diagrams than in text or multiple-entry tables; this view will, unfortunately, probably be confirmed in the following sentences! After dobutamine infusion, 198 of the 314 akinetic segments improved, 183 of them becoming normokinetic and 15 becoming hypokinetic; 116 still remained akinetic. The mean wall motion score had improved from 2.2 to 1.5 ($P<0.001$). Of significance in connection with the paper by Afridi et al, 5 patients showed improvement in 10 segments after the lower dose but a deterioration after the higher dose.

After coronary artery bypass surgery, 205 of the 314 akinetic segments had improved and of those 205 segments, 182 had become normokinetic. The mean wall motion score improved from 2.2 to 1.5 after surgery and was still the same 2 weeks later, prior to discharge. The authors are aware that their selection procedure may have been biased towards patients with reversible dysfunction and that this may account for the large number of segments that became normal after surgery. Overall, the authors found that the sensitivity of the dobutamine infusion test was 86.8% and the specificity was 81.6%. The accuracy of predicting reversibility of wall motion after surgery was 85%.

The authors suggest in the discussion that, since coronary artery surgery carries a high risk for patients with low ejection fraction and extensive LV dysfunction, the ideal diagnostic technique should identify not only viable myocardium, but also the chance of early functional recovery. They claim that dobutamine, by measuring contractile reserve, can predict early functional recovery, and is thus superior to PET or thallium 201 imaging, both of which are techniques that only look at viability.

1994

Martti Ahtisaari is elected President of Finland;
Nancy Kerrigan, US ice-skater, is attacked with
a crowbar at an ice rink in Detroit;
and Lady Victoria Wemyss, last surviving godchild
of Queen Victoria, dies aged 104 years

The hibernating myocardium

S.H. Rahimtoola

Rahimtoola, who is generally regarded as the "father" of hibernation, begins this editorial by giving a definition of the hibernating myocardium; it is, he says, "a state of persistently impaired left ventricular (LV) function at rest due to reduced coronary blood flow that can be partially or completely restored to normal if the myocardial oxygen supply/demand relationship is favorably altered either by improving blood flow and/or reducing demand." He suggests that hibernation occurs when the heart downgrades its function so that blood flow and function are once again in equilibrium. He stresses that the hibernating myocardium must be distinguished from both stunned myocardium and transient left ventricular dysfunction due to stress-induced ischemia, although, hibernation can, in fact, coexist with both conditions.

The editorial makes "easy reading" since it is divided into eight sections each of which deals with a specific question and, usually, provides some answers. The first section shows how myocardium with abnormal LV function at rest can recover. This is based on: (i) autopsy reports indicating that myocardial tissue designated as akinetic/hypokinetic in situ is actually morphologically normal; and (ii) positron emission tomography (PET) data from Tillisch et al (see page 94) and other data from nitrate and thallium studies indicating that the initially observed functional defects can be reversed by coronary revascularization. The second and third sections ask questions related to the mechanism by which hibernation occurs and to the reason(s) underlying the lack of hibernation in many severely ischemic hearts. These interesting questions, however, remain unanswered. The fourth section deals with the detection of the hibernating myocardium. Improved regional LV function upon either reduction of myocardial oxygen consumption (MVO_2) (by nitrates) or inotropic stimulation is indicative of hibernation. PET demonstration of the persistence of metabolism (^{18}FDG scan) in regions of decreased perfusion ($^{13}NH_3$ scan) is another method. It is suggested that defects in thallium 201 scans observed during reversible ischemia may also be useful.

The fifth section lists the clinical syndromes in which myocardial hibernation is most likely to occur—

Rahimtoola suggests the likelihood is greatest in patients experiencing silent ischemia: unstable angina, post myocardial infarction, chronic stable angina, and LV dysfunction of unknown origin.

The sixth section asks whether the hibernating myocardium is different from the stunned myocardium. The answer is a resounding yes. Stunned myocardium is defined as a condition in which, after ischemia, although coronary blood flow has been fully restored to the myocardium, functional, biochemical, and structural abnormalities still persist for prolonged periods. However, Rahimtoola cautions, it is possible to detect the coexistence of both stunned and hibernating myocardium in a single patient. In the penultimate section, the author says that a combination of drugs or surgical revascularization are the two optimal methods of treatment for the patient with hibernating myocardium. The final section is concerned with how long the myocardium can hibernate and how soon after reperfusion the hibernating myocardium will exhibit normal function. The answers are not really known; in one animal model, poor function during a 5-hour circumflex coronary occlusion took a week to reverse although, in a clinical study, an immediate improvement was seen after surgery. The author summarizes by saying that, although much is now known about the hibernating myocardium in terms of what it is, which clinical subgroups are affected, and which methods are presently best for its detection, "its full clinical presence and impact are not adequately defined."

1989

Ayatollah Khomeini issues a "fatwa" against Salman Rushdie for his "Satanic Verses"; Geoffrey Palmer becomes Prime Minister of New Zealand; and Lord Olivier, the British actor, dies aged 82 years

Recruitment of an inotropic reserve in moderately ischemic myocardium at the expense of metabolic recovery: a model of short-term hibernation

R. Schulz, B.D. Guth, K. Pieper, C. Martin, G. Heusch

Circ Res. 1992;70:1282-1295.

In this experimental study, Schulz et al use open-chest minipigs to create a model of short-term myocardial hibernation in order to characterize its functional and metabolic status and to investigate the effects of inotropic stimulation.

A total of 35 animals were used fasted for 10 hours prior to the experiments; the authors unfortunately make no comment about the increase in myocardial glycogen that will be caused by this fasting and the effects that this may have on the ability of the heart to withstand subsequent periods of ischemia. The left anterior descending (LAD) coronary artery was cannulated and perfused at constant flow. The vein parallel to it was also cannulated for lactate and O_2 measurements. Two pairs of ultrasonic crystals were implanted to measure wall thickness, one pair within the perfusion bed of the LAD and the other in a remote "control" region. Left atrial pacing wires were also implanted. Radiolabelled microspheres were used in the determination of regional myocardial blood flow. Transmural biopsies were taken when required, using a modified dental drill; the samples were analyzed for ATP, phosphocreatine, and glycogen.

After control measurements had been made, LAD blood flow was adjusted (over 3 minutes) until regional function had decreased to 50% of control. Animals in different groups were then subjected to 5, 25, 40, or 85 minutes of ischemia followed by a dobutamine challenge (5-minute infusion of 2.5 μg/min). A further group was reperfused for 2 hours, after 85 minutes of ischemia followed by dobutamine, prior to histological analysis.

The authors present their results for the different groups under control conditions in a rather daunting 126-entry table; this could maybe have been presented more succinctly as a single data set, together with the statement that "no differences were observed among the groups under control conditions." During ischemia, it was found that phosphocreatine first decreased, from 9 to 6 μmol/g after 5 minutes of ischemia, and to 3 μmol/g after 25 minutes, and then gradually recovered until, after 85 minutes of ischemia, the levels were approximately 70% of controls (6 μmol/g). Lactate, which was consumed by the heart under control conditions, was produced by the ischemic heart; the amount produced, however, decreased after 25 minutes of ischemia. ATP and glycogen levels did not change during ischemia. During the challenges with dobutamine, all groups showed increases in the regional myocardial work indices with no changes in regional blood flow measurements. The levels of phosphocreatine and glycogen decreased while those of lactate increased, indicating increased anaerobic metabolism; ATP remained constant. There was no evidence of necrosis in the group subjected to 85 minutes of ischemia, dobutamine, and reperfusion; the authors caution that this may be a species-linked finding since dog myocardium subjected to this treatment would have shown damage.

In the discussion, the authors suggest that the recovery of the phosphocreatine content during ischemia may be a characteristic feature of myocardium that has compensated for reduced flow and may be diagnostic of tissue that will not undergo infarction. They highlight the fact that the continued lactate production during ischemia is not at the expense of glycogen stores, but probably comes from exogenous glucose. This is in contrast to the response of the myocardium to dobutamine, where an increase in anaerobic metabolism is observed with a concomitant decrease in glycogen. The authors conclude that the inotropic reserve is maintained for at least 90 minutes of moderate ischemia and that inotropic challenge worsens the metabolic markers of ischemia.

1992

The Swiss vote against the banning
of animals in medical research;
the Nobel Prize for Literature is awarded
to Derek Walcott, from Trinidad;
and Satyajit Ray, the Indian film director,
dies aged 70 years

Metabolic adaptation during a sequence of no-flow and low-flow ischemia: a possible trigger for hibernation

R. Ferrari, A. Cargnoni, P. Bernocchi, E. Pasini, S. Carello, C. Ceconi, T.J.C. Ruigrok

In this experimental study, Ferrari and colleagues develop a protocol that mimics the clinical situation that precedes the development of myocardial hibernation; isolated, perfused hearts are subjected to an initial period of total global ischemia prior to an extended period of low-flow perfusion and a subsequent period of reperfusion. The metabolic adaptive processes that occur during this protocol and their significance for the maintenance of viability are determined. Ferrari and coworkers measure a large number of metabolic and functional parameters. Phosphocreatine (PCr), ATP, reduced glutathione (GSH), oxidized glutathione (GSSG), the NAD:NADH ratio, and calcium content were measured in extracts of myocardial tissue, while lactate, glutathione, and creatine kinase were measured in the coronary effluent. Interstitial pH and myocardial function (using a left ventricular balloon) were both measured in the perfused heart. Mitochondrial function was assessed in isolated mitochondria.

A total of 138 isolated, buffer-perfused rabbit hearts were used in the study; all were instrumented with an intraventricular balloon (with the end-diastolic pressure set to <1 mm Hg) and all were paced. Four 350-min protocols were followed, each of which started with a 50-min equilibration period: the main "hibernation group" was subjected to 10 min of total, global ischemia, followed by 230 min of low-flow ischemia (10% of control flow) and 60 min of reperfusion; the second group had normal flow throughout; the third group had 240 min of total ischemia, followed by reperfusion; and the final group had 240 min of low-flow ischemia (10% of control), followed by reperfusion.

The 10-min period of total ischemia resulted in the expected changes; a quiescent heart with decreased interstitial pH (from 7.2 to 6.2), decreased PCr (55 to 5 µmol/g dry wt) and decreased ATP (from 25 to 15 µmol/g dry wt). The subsequent period of low-flow perfusion resulted in increases in PCr (from 5 to 20 µmol/g dry wt) and interstitial pH (from 6.2 to 6.8), but no significant changes in ATP or contractility. Restoration of full flow, after 230 min of low-flow perfusion resulted in the recovery of developed pressure (to 92% of control) and of interstitial pH, but surprisingly, was not accompanied by any significant improvement in either of the high-energy phosphates. The importance of the initial period of total ischemia was highlighted by the results of the hearts in the group subjected solely to 240 min of low-flow ischemia. Hearts in this group suffered progressive damage during the low-flow period (developed pressure fell to 7% of control, interstitial pH fell to 6.2, diastolic pressure increased to 34 mm Hg, and both PCr and ATP decreased (to 10 and 8 µmol/g dry wt, respectively). Upon restoration of full flow, the hearts only recovered 47% of their original developed pressure, although they did show a significant increase in their PCr content (from 10 to 19 µmol/g dry wt). The importance of even low levels of coronary flow in maintaining viability is confirmed by the complete absence of any functional recovery upon reperfusion in the group subjected to 240 min of total ischemia.

In their discussion, the authors stress that their model was specifically designed to mimic events that often occur in the history of patients who have hibernating myocardium. The 10-min period of total ischemia before the 230 min of low-flow perfusion resulted in a resetting of metabolism and a downregulation of function that did not occur in the absence of the period of total ischemia. This period of total ischemia may have preconditioned the hearts, even in the absence of intermittent reperfusion; furthermore, due to the high coronary flow rates and the lack of both fatty acids and cells in the perfusate, the results should not be extrapolated to the in situ heart without further experimentation.

1996

Manchester United wins both the League and the FA Cup; the Centennial Olympics in Atlanta are marred by a bomb blast; and American golfer Tom Lehman wins the 125th British Open

Hibernating Myocardium

Bibliography of One Hundred Key Papers

Adams JN, Norton M, Trent R, Mikecz P, Walton S, Evans N.
Hibernating myocardium after acute myocardial infarction treated with thrombolysis.
Eur Heart J. 1995;16:36. Abstract.

Afridi I, Kleiman NS, Raizer AE, Zoghbi WA.
Dobutamine echocardiography in myocardial hibernation. Optimal dose and accuracy in predicting recovery of ventricular function after coronary angioplasty.
Circulation. 1995;91:663-670.

Akins CW, Pohost GM, DeSanctis RW, Block PC.
Selection of angina-free patients with severe left ventricular dysfunction for myocardial revascularization.
Am J Cardiol. 1980;46:695-700.

Alderman EL, Fisher LD, Litwiw P, et al.
Results of coronary artery surgery in patients with poor left ventricular function (CASS).
Circulation. 1983;68:785-795.

Arai AE, Grauer SE, Anselone CG, Pantely GA, Bristow JD.
Metabolic adaptation to a gradual reduction in myocardial blood flow.
Circulation. 1995;92:244-252.

Arai AE, Pantely GA, Anselone CG, Bristow J, Bristow JD.
Active downregulation of myocardial energy requirements during prolonged moderate ischemia in swine.
Circ Res. 1991;69:1458-1469.

Arani DT, Greene DG, Bunnell IL, Smith GL, Klocke FJ.
Reductions in coronary flow under resting conditions in collateral-dependent myocardium of patients with complete occlusion of the left anterior descending coronary artery.
J Am Coll Cardiol. 1984;3:668-674.

Arnese M, Cornel JH, Salustri A, et al.
Prediction of improvement of regional left ventricular function after surgical revascularization.
Circulation. 1995;91:2748-2752.

Ausma J, Schaart G, Thoné F, et al.
Chronic ischemic viable myocardium in man: aspects of dedifferentiation.
Cardiovasc Pathol. 1995;4:29-37.

Baer FM, Voth E, Schneider CA, Theissen P, Schicha H, Sechtem U.
Comparison of low-dose dobutamine-gradient-echo magnetic resonance imaging and positron emission tomography with [18F]-fluorodeoxyglucose in patients with chronic coronary artery disease.
Circulation. 1995;91:1006-1015.

Baker WB, Klein MS, Reardon MJ, Verani MS, Zoghbi WA.
Reversible cardiac dysfunction (hibernation) from ischemia due to compression of the coronary arteries by a pseudoaneurysm.
N Engl J Med. 1991;325:1858-1861.

Banka VS, Bodenheimer MM, Shah R, Helfant RH.
Intervention ventriculography: comparative value of nitroglycerin, post-extrasystolic potentiation and nitroglycerin plus post-extrasystolic potentiation.
Circulation. 1976;53:632-637.

Bibliography of One Hundred Key Papers

Barilla F, Gheorghiade M, Alam M, Khaja F, Goldstein S.	*Low-dose dobutamine in patients with acute myocardial infarction identifies viable but not contractile myocardium and predicts the magnitude of improvement in wall motion abnormalities in response to coronary revascularization.* ***Am Heart J.*** 1991;122:1522-1531.
Beleslin BD, Ostojic M, Stepanovic J, et al.	*Stress echocardiography in the detection of myocardial ischemia. Head-to-head comparison of exercise, dobutamine, and dipyridamole tests.* ***Circulation.*** 1994;90:1168-1176.
Berger BC, Watson DD, Burwell LR, et al.	*Redistribution of thallium at rest in patients with stable and unstable angina and the effect of coronary artery bypass surgery.* ***Circulation.*** 1979;60:1114-1125.
Berman M, Fischman AJ, Southern J, et al.	*Myocardial adaptation during and after sustained, demand-induced ischemia: observations in closed-chest domestic swine.* ***Circulation.*** 1996;94:755-762.
Bodenheimer MM, Banka VS, Fooshee C, Hermann GA, Helfant RH.	*Relationship between regional myocardial perfusion and the presence, severity and reversibility of asynergy in patients with coronary heart disease.* ***Circulation.*** 1978;58:789-795.
Bonow RO.	*Identification of viable myocardium.* ***Circulation.*** 1996;94:2674-2680. Editorial.
Bonow RO, Dilsizian V, Cuocolo A, Bacharach SL.	*Identification of viable myocardium in patients with chronic coronary artery disease and left ventricular dysfunction: comparison of thallium scintigraphy with reinjection and PET imaging with ^{18}F-fluorodeoxyglucose.* ***Circulation.*** 1991;83:26-37.
Borgers M, Thone F, Wonters L, Ausina J, Shivalkar B, Flameng W.	*Structural correlates of regional myocardial dysfunction in patients with critical coronary artery stenosis: chronic hibernation?* ***Cardiovasc Pathol.*** 1993;2:237-245.
Braunwald E, Rutherford JD.	*Reversible ischemic left ventricular dysfunction: evidence for the "hibernating myocardium."* ***J Am Coll Cardiol.*** 1986;8:1467-1470.
Bristow JD, Arai AE, Anselone CG, Pantely GA.	*Response to myocardial ischemia as a regulated process.* ***Circulation.*** 1991;84:2580-2587.
Brown KA, Okada RD, Boucher CA, Phillips HR, Strauss HW, Pohost GM.	*Serial thallium 201 imaging at rest in patients with unstable and stable angina pectoris: relationship of myocardial perfusion at rest to presenting clinical syndrome.* ***Am Heart J.*** 1983;106:70-77.
Brunken R, Tillisch J, Schwaiger M, et al.	*Regional perfusion, glucose metabolism, and wall motion in patients with chronic electrocardiographic Q wave infarction. Evidence for persistence of viable tissue in some infarct regions by positron emission tomography.* ***Circulation.*** 1986;73:951-963.
Cabin HS, Clubb S, Vita N, Zaret BL.	*Regional dysfunction by equilibrium radionuclide angiocardiography: a clinical-pathologic study evaluating the relation of degree of dysfunction to the presence and extent of myocardial infarction.* ***J Am Coll Cardiol.*** 1987;10:743-747.

Carlson EB, Cowley MJ, Wolfgang TC, Vetrovec GW.

Acute changes in global and regional rest ventricular function after successful coronary angioplasty: comparative results in stable and unstable angina.

J Am Coll Cardiol. 1989;13:1262-1269.

Carvalho JS, Redington AN, Oldershaw PJ, Shinebourne EA, Lincoln CR, Gibson DG.

Analysis of left ventricular wall movement before and after reimplantation of anomalous left coronary artery in infancy.

Br Heart J. 1991;65:218-222.

Chan RKM, Lee KJ, Calafiore P, Berlangieri SU, McKay WJ, Tonkin AM.

Comparison of dobutamine echocardiography and positron emission tomography in patients with chronic ischemic left ventricular dysfunction.

J Am Coll Cardiol. 1996;27:1601-1607.

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.

Chen C, Chen L, Fallon JT, et al.

Functional and structural alterations with 24-hour myocardial hibernation and recovery after reperfusion: a pig model of myocardial hibernation.

Circulation. 1996;94:507-516.

Chen C, Li L, Chen LL, Prada JV, et al.

Incremental doses of dobutamine induce a biphasic response in dysfunctional left ventricular regions subtending coronary stenoses.

Circulation. 1995;92:756-766.

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

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

Circulation. 1993;88:430-436.

Cohen M, Chainey R, Hershman R, Fuster V, Gorlin R.

Reversal of chronic ischemic myocardial dysfunction after transluminal coronary angioplasty.

J Am Coll Cardiol. 1988;12:1193-1198.

Cohn PF, Gorlin R, Harmann MV, et al.

Relation between contractile reserve and prognosis in patients with coronary artery disease and a depressed ejection fraction.

Circulation. 1975;51:414-420.

Czernin J, Porenta G, Brunken R, et al.

Regional blood flow, oxidative metabolism, and glucose utilization in patients with recent myocardial infarction.

Circulation. 1993;88:884-895.

DeKock M, Dion R, Wijns W, Melin JA.

Head-to-head comparison of exercise-redistribution-reinjection thallium single-photon emission computed tomography and low-dose dobutamine echocardiography for prediction of reversibility of chronic left ventricular ischemic dysfunction.

J Am Coll Cardiol. 1996;28:432-442.

Depré C, Vanoverschelde JLJ, Melin J, et al.

Structural and metabolic correlates of the reversibility of chronic left ventricular ischemic dysfunction in humans.

Am J Physiol. 1995;268(3, pt 2):H1265-H1275.

DiCarli M, Davidson M, Little R, et al.

Value of metabolic imaging with positron emission tomography for evaluating prognosis in patients with coronary artery disease and left ventricular dysfunction.

Am J Cardiol. 1994;73:527-533.

Bibliography of One Hundred Key Papers

Dilsizian V.

Myocardial viability: contractile reserve or cell membrane integrity.
J Am Coll Cardiol. 1996;28:443-446.

Dilsizian V, Rocco TP, Freedman NMT, Leon MB, Bonow RO.

Enhanced detection of ischemic but viable myocardium by the reinjection of thallium after stress redistribution imaging.
N Engl J Med. 1990;323:141-146.

Downing SE, Chen V.

Myocardial hibernation in the ischemic neonatal heart.
Circ Res. 1990;66:763-772.

Downing SE, Chen V.

Acute hibernation and reperfusion of the ischemic heart.
Circulation. 1992;82:699-707.

Eitzman D, Al-Aonar Z, Kanter HL, et al.

Clinical outcome of patients with advanced coronary artery disease after viability studies with positron emission tomography.
J Am Coll Cardiol. 1992;20:559-565.

Elefteriades JS, Tolis G Jr, Levi E, Mills LK, Zaret BL.

Coronary artery bypass grafting in severe left ventricular dysfunction: excellent survival with improved ejection fraction and function state.
J Am Coll Cardiol. 1993;22:1411-1417.

Fedele FA, Gerwitz H, Capone RJ, Sharaf B, Most AS.

Metabolic response to prolonged reduction of myocardial blood flow distal to a severe coronary artery stenosis.
Circulation. 1988;78:729-735.

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.

Ferrari R, La Canna G, Giubbini R, et al.

Left ventricular dysfunction due to stunning and hibernation in patients.
Cardiovasc Drugs Ther. 1994;8:371-380.

Flameng W, Suy R, Schwarz F, et al.

Ultrastructural correlates of left ventricular contraction abnormalities in patients with chronic ischemic heart disease: determinations of reversible segmental asynergy postrevascularization surgery.
Am Heart J. 1981;102:846-857.

Flameng W, Vanhaecke J, Van Belle H, Borgers M, DeBeer L, Minten J.

Relation between coronary artery stenosis and myocardial purine metabolism, histology and regional function in humans.
J Am Coll Cardiol. 1987;9:1235-1242.

Gallagher KP, Matsuzaki M, Koziol JA, Kemper WS, Ross J Jr.

Regional myocardial perfusion and wall thickening during ischemia in conscious dogs.
Am J Physiol. 1984;247(5, pt 2):H727-H738.

Geft IL, Fishbein MC, Ninomiya K, et al.

Intermittent brief periods of ischemia have a cumulative effect and may cause myocardial necrosis.
Circulation. 1982;66:1150-1153.

Gewirtz H.

Myocardial hibernation: unresolved physiological and clinical issues.
Basic Res Cardiol. 1995;90:32-34.

Gewirtz H, Fischman AJ, Abraham S, Gilson M, Strauss HV, Alpert NM.

Positron emission tomographic measurements of absolute regional myocardial blood flow permits identification of nonviable myocardium in patients with chronic myocardial infarction.
J Am Coll Cardiol. 1994;23:851-859.

Gropler RJ, Geltman EM, Sampathkumaran K, et al.

Functional recovery after coronary revascularization for chronic coronary artery disease is dependent on maintenance of oxidative metabolism.

J Am Coll Cardiol. 1992;20:569-577.

Hearse DJ.

Myocardial ischemia: can we agree on a definition for the 21st century?

Cardiovasc Res. 1994; 28:1737-1744.

Hearse DJ.

Myocardial hibernation: a form of endogenous protection.

Eur Heart J. 1997;18(suppl A):A2-A7.

Helfant RH, Pine R, Meister SG, Feldman MS, Trout RG, Banka VS.

Nitroglycerin to unmask reversible asynergy. Correlation with postcoronary bypass ventriculography.

Circulation. 1974;50:108-113.

Hong RA, Bhandari AK, McKay CR, Au PK, Rahimtoola SH.

Life-threatening ventricular tachycardia and fibrillation induced by painless myocardial ischemia during exercise testing.

JAMA. 1987;257:1937-1940.

Hurwitz RA, Caldwell RL, Girod DA, Brown J, King H.

Clinical and hemodynamic course of infants and children with anomalous left coronary artery.

Am Heart J. 1989;118:1176-1181.

Jin Z, Berger F, Uhlemann F, et al.

Improvement in left ventricular dysfunction after aortic reimplantation in 11 consecutive pediatric patients with anomalous origin of the left coronary artery from the pulmonary artery. Early results of a serial echocardiographic follow-up.

Eur Heart J. 1994;15:1044-1049.

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

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

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

Lambert V, Touchot A, Losay J, et al.

Mid-term results after surgical repair of the anomalous origin of the coronary artery.

Circulation. 1996;94(suppl II):II-38-II-43.

Lee KS, Marwick TH, Cook SA, et al.

Prognosis of patients with left ventricular dysfunction, with and without viable myocardium after myocardial infarction. Relative efficacy of medical therapy and vascularization.

Circulation. 1994;90:2687-2694.

Levitsky S, van der Horst RL, Hastreiter AR, Fisher EA.

Anomalous left coronary artery in the infant. Recovery of ventricular function following early direct aortic implantation.

J Thorac Cardiovasc Surg. 1980;79:598-602.

Louie HW, Laks H, Milgalter E, et al.

Ischemic cardiomyopathy: criteria for coronary revascularization and cardiac transplantation.

Circulation. 1991;84(suppl III):III-290-III-295.

Luu M, Stevenson LW, Brunken RC, Drinkwater DC, Schelbert TR, Tillisch JH.

Delayed recovery of revascularized myocardium after referral for cardiac transplantation.

Am Heart J. 1990;119:668-670.

Maes A, Flameng W, Nuyts J, et al.

Histological alternations in chronically hypoperfused myocardium.

Circulation. 1994;90:735-745.

Marban E.

Myocardial stunning and hibernation. The physiology behind the colloquialisms.

Circulation. 1991;83:681-688.

Bibliography of One Hundred Key Papers

Margonato A, Mailhac A, Bonetti F, et al.

Exercise-induced ischemic arrhythmias in patients with previous myocardial infarction. Role of perfusion and tissue viability.
J Am Coll Cardiol. 1996;27:593-598.

Marwick TH, MacIntyre WJ, Lafont A, Nemec JJ, Salcedo EE.

Metabolic responses of hibernating and infarcted myocardium to revascularization: a follow-up study of regional perfusion, function, and metabolism.
Circulation. 1992;85:1347-1353.

Marzullo P, Parodi O, Sambuceti G, et al.

Residual coronary reserve identifies segmental viability in patients with wall motion abnormalities.
J Am Coll Cardiol. 1995;26:342-350.

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

Sustained regional dysfunction produced by prolonged coronary stenosis: gradual recovery after reperfusion.
Circulation. 1983;68:170-182.

McAnulty JH, Hattenbauer MT, Rösch J, Kloster FE, Rahimtoola SH.

Improvement in left ventricular wall motion following nitroglycerin.
Circulation. 1975;51:140-145.

Mills I, Fallon JT, Wrenn D, et al.

Adaptive responses of coronary circulation and myocardium to chronic reduction in perfusion pressure and flow.
Am J Physiol. 1994;266(2, pt 2):H447-H457.

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.

Montalescot G, Faraggi M, Drobinski G, et al.

Myocardial viability in patients with Q wave myocardial infarction and no residual ischemia.
Circulation. 1992;86:47-55.

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

Metabolic and functional recovery of ischemic human myocardium after coronary angioplasty.
J Am Coll Cardiol. 1991;18:966-978.

Pantely GA, Malone SA, Rhen WS, et al.

Regeneration of myocardial phosphocreatine in pigs despite continued moderate ischemia.
Circ Res. 1990;67:1481-1493.

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

Relation between thallium uptake and contractile response to dobutamine.
Circulation. 1995;91:990-998.

Perrone-Filardi P, Pace L, Prastaro M, et al.

Dobutamine echocardiography predicts improvement of hypoperfused dysfunctional myocardium; after revascularization in patients with coronary artery disease.
Circulation. 1995;91:2556-2565.

Piérard LA, DeLandsheere 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.

Pouleur H, van Eyll C, Gurne O, Rousseau MF.

Effects of prolonged nisoldipine administration on the "hibernating" myocardium.
J Cardiovasc Pharmacol. 1992;20(suppl 5):S73-S78.

Ragosta M, Beller GA, Watson DD, Kaul S, Gimple LW.

Quantitative planar rest-redistribution thallium 201 imaging in detection of myocardial viability and prediction of improvement in left ventricular function after coronary bypass surgery in patients with severely depressed left ventricular function.
Circulation. 1993;87:1630-1641.

Rahimtoola SH.

Coronary bypass surgery for chronic angina - 1981: a perspective.
Circulation. 1982;65:225-241.

Rahimtoola SH.

Postoperative exercise response in the evaluation of the physiologic status after coronary bypass surgery.
Circulation. 1982;65(suppl II):II-106-II-114.

Rahimtoola SH.

Coronary bypass surgery for unstable angina.
Circulation. 1984;69:842-848.

Rahimtoola SH.

A perspective on the three large multicenter randomized clinical trials of coronary bypass surgery for chronic stable angina.
Circulation. 1985;72(suppl V):V-123-V-135.

Rahimtoola SH.

The hibernating myocardium.
Am Heart J. 1989;117:211-221.

Rahimtoola SH.

From coronary artery disease to heart failure: role of the hibernating myocardium.
Am J Cardiol. 1995;75:16E-22E.

Rahimtoola SH.

Hibernating myocardium has reduced blood flow at rest that increases with low-dose dobutamine.
Circulation. 1996;94:3055-3061. Editorial.

Rein AJJT, Colan SD, Parness IA, Sanders SP.

Regional and global left ventricular function in infants with anomalous origin of the left coronary artery from the pulmonary trunk: preoperative and postoperative assessment.
Circulation. 1987;75:115-123.

Rocco TP, Dilsizian V, McKusick KA, Fischman AJ, Boucher CA, Strauss HW.

Comparison of thallium redistribution with rest "reinjection" imaging for the detection of a viable myocardium.
Am J Cardiol. 1990;66:158-163.

Ross J Jr.

Myocardial perfusion-contraction matching: implications for coronary heart disease and hibernation.
Circulation. 1991;83:1076-1082.

Sambuceti G, Parodi O, Giorgetti A, et al.

Microvascular dysfunction in collateral-dependent myocardium.
J Am Coll Cardiol. 1995;26:615-623.

Sambuceti G, Parodi O, Marcassa C, et al.

Alteration in regulation of myocardial blood flow in one-vessel coronary artery disease determined by positron emission tomography.
Am J Cardiol. 1993;72:538-543.

Schulz R, Guth BD, Pieper K, Martin C, Heusch G.

Recruitment of an inotropic reserve in moderately ischemic myocardium at the expense of metabolic recovery: a model of short-term hibernation.
Circ Res. 1992;70:1282-1295.

Schulz R, Rose J, Margin C, Brodde OE, Heusch G.

Development of short-term myocardial hibernation: its limitation by the severity of ischemia and inotropic stimulation.
Circulation. 1993;88:684-695.

Bibliography of One Hundred Key Papers

Schwarz ER, Schaper J, von Dahl J, et al.

Myocyte degeneration and cell death in hibernating human myocardium.

J Am Coll Cardiol. 1996;27:1577-1585.

Shivalkar B, Borgers M, Daenen W, Gewillig M, Flameng W.

ALCAPA syndrome: an example of chronic myocardial hypoperfusion?
J Am Coll Cardiol. 1994;23:772-778.

Shivalkar B, Maes A, Borgers M, et al.

Only hibernating myocardium shows early recovery after coronary revascularization.

Circulation. 1996;94:308-315.

Shopicki HA, Abraham SA, Weissman NJ, et al.

Factor influencing regional myocardial contractile response to inotropic stimulation: analysis in humans with stable ischemic heart disease.

Circulation. 1996;94:643-650.

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

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

Circulation. 1993;88:405-411.

Sun KT, Czernin J, Krirokapich J, et al.

Effects of dobutamine stimulation on myocardial blood flow, glucose metabolism and wall motion in normal and dysfunctional myocardium.

Circulation. 1996;74:3146-3154.

Tamaki N, Kawamoto M, Takahashi N, et al.

Prognostic value of an increase in fluorine-18 deoxyglucose uptake in patients with myocardial infarction: comparison with stress thallium imaging.

J Am Coll Cardiol. 1993;22:1621-1627.

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

Reversibility of cardiac wall motion abnormalities predicted by positron tomography.

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

Topol EJ, Weiss JL, Guzman PA, et al.

Immediate improvement of dysfunctional myocardial segments or after coronary revascularization: detection by intraoperative transesophageal echocardiography.

J Am Coll Cardiol. 1984;4:1123-1134.

Udelson JE, Coleman PS, Metherall J, et al.

Predicting recovery of severe regional ventricular dysfunction. Comparison of resting scintigraphy with ^{201}Tl and ^{99m}Tc-Sestamibi.
Circulation. 1994;89:2552-2561.

Van den Berg EK Jr, Popma JJ, Dehmer GJ, et al.

Reversible segmental left ventricular dysfunction after coronary angioplasty.
Circulation. 1990;81:1210-1216.

Vatner SF.

Correlation between acute reductions in myocardial blood flow and function in conscious dogs.
Circ Res. 1980;47:201-207.

---

von Dahl J, Altehoefer C, Sheehan FH, et al.

Recovery of regional left ventricular dysfunction after coronary revascularization: impact of myocardial viability assessed by nuclear imaging and vessel patency at follow-up angiography.
J Am Coll Cardiol. 1996;28:948-958.

Willerson JT, Hutton I, Watson JT, Platt MR, Templeton GH.

Influence of dobutamine on regional myocardial blood flow and ventricular performance during acute and chronic myocardial ischemia in dogs.
Circulation. 1976;53:828-833.