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Prolonged Myocardial Hibernation Exacerbates Cardiomyocyte Degeneration and Impairs Recovery of Function After Revascularization

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Objectives. **We sought to define the effects of time on contractile function, morphology and functional recovery after coronary revascularization in patients with dysfunctional but viable (hibernating) myocardium.**

Background. **Functional recovery after coronary artery bypass graft surgery in patients with chronic myocardial hibernation is incomplete or delayed. The proposed cause is a progressive temporal degeneration of cardiomyocytes.**

Methods. **In 32 patients with multivessel coronary disease, regional wall motion analysis was performed in hypoperfused but metabolically active areas before and 6 months after bypass surgery. During bypass surgery, transmural biopsy samples were obtained from the center of the hypokinetic zone for light and electron microscopic analyses. The proposed duration of myocardial hibernation was retrospectively assessed.**

Results. **Patients with a subacute hibernating condition (<50 days) demonstrated a higher preoperative ejection fraction (EF, 50 ± 8%), and a better preserved wall motion (WM) in the supraapical wall (−1.4 ± 0.4) than did patients with intermediate-term (>50 days, EF 37 ± 9%, $p < 0.05$; WM −2.4 ± 1.5, $p = 0.08$) or chronic (>6 months, EF 40 ± 14%, WM −2.7 ± 0.9, $p < 0.005$) ischemia. Structural degeneration correlated with the duration of ischemia ($r = 0.56$, $p < 0.05$). Postoperative recovery of function was enhanced in patients with a short history of hibernation compared with patients with an intermediate-term or chronic condition (EF 60 ± 10% vs. 40 ± 10%, $p < 0.001$, and vs. 47 ± 14%, $p < 0.05$).**

Conclusions. **Hibernating myocardium exhibits time-dependent deterioration due to progressive structural degeneration with enhanced fibrosis. Early revascularization should be attempted to salvage the jeopardized tissue and improve postoperative outcome.**

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The term "hibernating myocardium," introduced by Rahimtoola, describes a condition of reduced contractile function due to chronically reduced blood flow with the ability to recover after restoration of an adequate blood supply (1,2). This restoration of flow can be achieved by reducing demand (3) or increasing oxygen delivery by percutaneous transluminal coronary angioplasty (4–6) or coronary artery bypass graft surgery (1,7–10).

The identification of viable but dysfunctional myocardium by different noninvasive techniques, such as thallium-201 with single photon emission computed tomography (SPECT) (11), fluorine-18-fluorodeoxyglucose (F-18 FDG) with positron emission tomography (PET) (10) or dobutamine echocardiography (12), may predict recovery of dysfunctional myocardium. Coronary revascularization results in myocardial salvage even in patients with severely reduced contractile function. In particular, in the presence of viable but dysfunctional myocardium, conservative treatment has been shown to be less effective (13). Furthermore, these patients with severe coronary artery disease are at risk for future cardiac events and, if revascularization is not performed, have a worse prognosis (14).

In contrast to initial reports of prompt recovery (15), most recent studies have demonstrated a delayed or incomplete functional recovery of hibernating myocardium (16,17). This delay might be caused by the severity of the structural degeneration with loss of contractile material and different degrees of fibrosis due to chronic ischemia (18–23).

Although hibernating myocardium may represent a reduction in function to preserve structure and is believed to maintain this steady state for long periods, experimental findings indicate a relatively unstable condition of the myocar-

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Abbreviations and Acronyms

ANOVA	=	analysis of variance
CCS	=	Canadian Cardiovascular Society
EF	=	ejection fraction
F-18 FDG	=	fluorine-18 fluorodeoxyglucose
LAD	=	left anterior descending coronary artery
NYHA	=	New York Heart Association
PET	=	positron emission tomography (tomographic)
SPECT	=	single photon emission computed tomography (tomographic)
Tc-99m	=	technetium-99m

dium with a high vulnerability to increases in demand or reductions in oxygen supply (24). Therefore, ongoing chronic ischemia, as well as recurrent acute ischemic episodes, may have deleterious consequences on the adaptive balance between reduced energy supply and demand, with additional worsening of function becoming insufficient to further preserve structural integrity. To elucidate this hypothesis, we assessed the effects of the duration of suspected hibernating myocardium on myocardial function, morphology and recovery after coronary revascularization.

Methods

Patient selection. Thirty-eight patients were recruited for the study. Diagnostic coronary angiography was performed for the clinical symptoms of angina or heart failure. All patients fulfilled clinical criteria for surgical revascularization. Before bypass surgery, nuclear imaging was performed for assessment of viability in the dysfunctional territory of the left anterior descending coronary artery (LAD). Patients were included if they had 1) a high degree of stenosis (>80%) or total occlusion of the LAD; 2) severe hypokinesia or akinesia within the LAD territory; 3) a mismatch between regional perfusion and metabolic activity in dysfunctional portions of the anterior left ventricular wall, as assessed with nuclear imaging studies; 4) the clinical indication for surgical revascularization with a coronary anatomy suitable for bypass surgery; and 5) provided informed consent. The study protocol was approved by the local institutional ethical committee.

Preoperative diagnostics. Clinical status with regard to dyspnea at rest or during exercise according to the New York Heart Association (NYHA) classification and symptoms of angina pectoris according to the Canadian Cardiovascular Society (CCS) classification were determined before surgery.

Cardiac catheterization. Coronary and left ventricular angiography was performed using routine methods with the Judkins technique, with left ventricular angiography preceding coronary angiography. Left ventricular volume and ejection fraction (EF) were calculated according to the area-length method (25). Regional wall motion was analyzed using a modified centerline method provided by a computer program (AWOS 4.01; Siemens, Erlangen, Germany) in the distribution territory of the LAD and expressed in units of SD of the normal mean value (26).

Assessment of regional perfusion. SPECT with technetium-99m (Tc-99m) sestamibi was performed according to our standard protocols (27,28). In brief, patients were studied at rest after the bolus injection of 10 mCi of Tc-99m sestamibi (Cardiolite, DuPont) with the use of a Gammasonics ROTA double-head camera (Siemens). Transaxial slices (6.25-mm thickness) were reconstructed using a Butterworth filter third order and a cutoff frequency of 0.5 with a MaxDelta computer system (Siemens).

Assessment of metabolic activity. F-18 FDG with PET was used to measure metabolic activity as described previously (27,28). After oral glucose loading with 50 g of dextrose, 6 to 8 mCi of F-18 FDG (Department of Radiochemistry, Nuclear Research Center, Juelich, Germany) was injected intravenously as a slow bolus. Static ungated imaging was initiated 30 to 45 min after tracer injection. For semiquantitative analysis, the transaxial PET image files were converted to the structure of the SPECT files (29). Regional Tc-99m sestamibi and F-18 FDG uptake was expressed in percent of uptake in the region with maximum sestamibi uptake (reference region) in each patient. Reduced Tc-99m sestamibi uptake (<70%) with preserved FDG activity (>70%) represented a perfusion/metabolism mismatch, indicating hypoperfused and dysfunctional but viable (hibernating) myocardium.

Bypass surgery, intraoperative tissue sampling and morphologic analysis. Complete revascularization was attempted in all patients, including internal mammary arterial grafts to the LAD. Transmural myocardial biopsy samples using TruCut biopsy needles (Travenol Laboratories) were obtained from the center of the dysfunctional areas of the territory supplied by the LAD in all patients. To properly identify this region at follow-up, a metal clip was sutured intraoperatively. In 12 patients, additional biopsy samples were obtained from the border between dysfunction and normal myocardium, which was identified by its visible hypocontractility, which appeared less than in the central dysfunctional region, and from a control (normokinetic) region of the left ventricular anterior wall. Specimens were fixed for 2 to 4 h in 0.1 mol/liter sodium cacodylate plus 7.5% sucrose with 3% glutaraldehyde (pH 7.4, 400 mOsm) within 10 s. Thereafter, specimens were postfixed in 1% osmium tetroxide and embedded in Epon as described previously (17). Semithin sections were stained with toluidine blue and examined with a Leitz Aristoplan light microscope. Ultrathin sections were stained with uranyl acetate and lead citrate and were studied with a Philips CM 10 electron microscope by one investigator (S.K.) without knowledge of the clinical variables.

Morphometry. The volume density of fibrosis was estimated with the light microscope using an ocular grid according to the "point counting" method (30). The grid consisted of 121 cross-points per unit area, and each unit area was 0.25 mm^2 (magnification 200×). The volume density of fibrosis was expressed as a percentage of the number of cross-points

overlying the connective tissue per total cross-points overlying the biopsy tissue.

Postoperative studies. At 6 ± 1.5 months after operation, clinical status was redetermined according to the NYHA, and CCS classifications. Coronary angiography; cineventriculography, including assessment of EF; and regional wall motion analysis were repeated. The two films from each patient (preoperative and postoperative catheterization) were analyzed independently in random order without knowledge of clinical data. Wall motion data from 10 adjacent chords in the midanterior and supraapical (LAD) territory were summarized, and the mean values of each 10 chords were used for analysis.

Assessment of time intervals. Four time intervals were evaluated from a detailed preoperative history obtained from the patients, their families or the referring physician by two independent observers who had no knowledge of the angiographic and nuclear data and from the records: 1) days from precipitous onset of new symptoms, worsening of symptoms or onset of overt heart failure to aortocoronary bypass surgery; this was defined as new onset of dyspnea at rest, severe clinical impairment including frequent attacks of dyspnea precipitated by distinctly less exertion, increasing signs of severe left ventricular dysfunction or heart failure leading to repeated consultations or to hospital admittance. 2) Days from diagnosis of wall motion abnormalities to surgery. The decision for bypass surgery was made shortly after cardiac catheterization (3 ± 3 days). Nuclear imaging studies were performed within 2 ± 2 weeks after cardiac catheterization in all patients. The duration of the existence of hibernating myocardium as assessed on the basis of the clinical condition did not affect the time interval between diagnosis and bypass surgery. 3) Postoperative days in the intensive care unit. 4) Days with postoperative catecholamine support (except for low dose dopamine to improve renal perfusion). The procedure in intensive care unit met the criteria for routine patient management and was not influenced by the ongoing study design. Patients were observed in the intensive care unit until a stable clinical condition with regard to global hemodynamic variables without catecholamine support, stable kidney function and consciousness was reached.

Analysis. Baseline variables, recovery of wall motion and morphologic assessment of myocardial biopsy samples and morphometric evaluation of the amount of fibrosis were first analyzed for the entire study group. For additional subgroup analysis, patients were classified into three groups according to the time interval between the precipitous onset of new symptoms, worsening of symptoms or onset of overt heart failure and surgical revascularization (referred to as "duration of ischemia"). *Group 1* included patients with a duration of ischemia of <50 days and was considered to represent those with a subacute ischemic condition. *Group 2* included patients with intermediate ischemia >50 days but <6 months. *Group 3* included patients with chronic (>6 months) ischemia. These time intervals were empiric and chosen on a post hoc basis. Preoperative and postoperative values within the groups were compared with the use of paired *t* tests. For variables that were measured twice and compared among the three subgroups, a two-factor analysis of variance with repeated measures was used. For the subgroup analysis, differences in fibrosis, wall motion abnormalities, EF and CCS and NYHA classification were tested using analysis of variance (ANOVA) for discrete variables and linear regression for continuous variables. A p value <0.05 was considered significant. When significant differences were found using ANOVA, multiple comparisons were performed with the Student-Newman-Keuls test. Correlation analyses were performed among the time intervals, angiographic appearance of the LAD, preoperative and postoperative hemodynamic variables and fibrosis. Pearson correlation coefficients are reported.

Results

Analysis of the study cohort. Thirty-eight patients were recruited for the study. Before surgical revascularization, 4 of 38 patients died of sudden cardiac death, cardiac shock after myocardial infarction, progressive heart failure or unknown reasons (n = 1 each). Postoperatively, 1 patient died on day 5 of progressive cardiac and renal failure. One patient had an extensive apoplectic insult 2 days after operation. These patients were excluded from further analysis. The remaining 32 patients (mean [±SD] age 63.5 ± 6.6 years, 4 women, 28 men) had coronary artery disease affecting either two (n = 5) or three (n = 27) major coronary arteries. At recruitment, all patients were in CCS class III or IV (mean 3.2 ± 0.4) and NYHA class II to IV (mean 2.1 ± 1.3). Twenty-seven patients had a history of Q wave or non–Q wave myocardial infarction in the anterior or anterolateral wall (n = 13) or the inferior, posterior or posterolateral wall (n = 6) or had a previous anterior and posterior myocardial infarction (n = 8). The history of coronary artery disease ranged from 15 days to 17 years. Coronary angiography revealed total occlusion of the LAD in 15 (47%) patients.

Global EF at baseline was 41 ± 12%, and the midanterior and supraapical areas of the left ventricle were hypokinetic or akinetic (−1.8 ± 1.2 and −2.2 ± 1.2, respectively). Nuclear imaging demonstrated slightly reduced Tc-99m sestamibi uptake on SPECT in the midanterior and supraapical wall (55 ± 14% and 65 ± 12%, respectively) with preserved or increased F-18 FDG uptake on PET (92 ± 33% and 92 ± 34%, respectively), indicating a mismatch between perfusion and metabolism.

As expected (17), microscopic analysis of biopsies obtained from the center of wall motion abnormalities demonstrated three distinct alterations: 1) changes in size and shape of myocytes, 2) alterations in the extracellular matrix and 3) heterogeneous cardiomyocyte degeneration. Ultrastructural changes indicative of degeneration were loss of myofilaments; aggregation of glycogen and mitochondria in areas of myofilament loss; proliferation of sarcoplasmic reticulum; abnormal size, shape and configuration of mitochondria; aggregation of abnormal Z-band–like material and cytoskeletal filaments;

accumulation of vacuoles, lipofuscin and myelin figures; and cellular debris in the interstitial space. Degenerative changes were defined as focal or diffuse and were qualitatively graded as mild or severe, as described previously (17). In cells with mild degeneration, the changes were focal or confined to the perinuclear region, myofilaments were still prominent and extracellular fibrosis was found only occasionally. Severe degeneration was characterized by a significant loss of contractile material and glycogen accumulation, accompanied by significant fibrosis. The quantitative assessment of the amount of fibrosis was used as an index of cellular integrity. Comparison of biopsy samples from different regions of the left ventricle revealed an increase in degenerative alterations with fibrosis from the control areas (16 ± 14% fibrosis, which is considered to be within the normal range [31]) to the margin zones (22 ± 26% fibrosis) and the center zones (29 ± 18% fibrosis, $p < 0.05$ vs. control samples).

After bypass surgery, the average stay in the intensive care unit was 4.5 ± 4.3 days, and catecholamine treatment was necessary for 3.3 ± 4.4 days. Follow-up examination was performed 6 ± 1 months after operation and revealed improvement in symptoms and cardiac function. CCS and NYHA classifications improved to 0.4 ± 0.5 and 0.5 ± 0.9 ($p < 0.001$ vs. before operation), respectively, whereas EF improved to 48 ± 14% ($p < 0.05$ vs. before operation). In contrast, regional wall motion in the midanterior and supraapical wall improved only slightly (from −1.8 ± 1.2 to −1.4 ± 1 and from −2.2 ± 1.2 to −1.5 ± 1.0, respectively).

Analysis according to the duration of ischemia. *Time intervals.* Of the 32 patients for whom data were obtained, 9, 14 and 9 had an ischemic duration of ≤50 days, >50 days and >6 months, respectively (Table 1). Preoperative and postoperative data were analyzed separately for the three groups. The time interval from diagnosis to bypass surgery was shorter for group 1 patients than for group 2 and 3 patients ($p < 0.05$). A history of anterior or anterior plus posterior myocardial infarction was found in 6 (66%) patients in group 1, 8 (57%) patients in group 2 and 7 (78%) patients in group 3.

Preoperative perfusion and metabolism imaging. Regional perfusion in the midanterior and supraapical wall was higher in group 1 patients (63 ± 9% and 70 ± 6%, respectively) than in groups 2 (53 ± 13% and 62 ± 11%, $p < 0.05$ for both comparisons) and 3 (46 ± 15%, $p < 0.005$, and 65 ± 17%, p = NS). No differences were found between groups 2 and 3. Regional F-18 FDG uptake was comparable among the three groups (Fig. 1).

Morphologic tissue analysis. In groups 2 and 3, cardiomyocyte degeneration and fibrosis were significantly more severe than in group 1 (Fig. 2 a and b; subendocardial fibrosis: group 2 39.1 ± 22.7%, group 3 41.9 ± 22.1%, group 1 21.4 ± 9.8%, $p < 0.05$ group 1 vs. groups 2 and 3). Fibrosis tended to be more common in group 3 than in group 2 but did not reach significance.

Postoperative follow-up. Postoperative stay in the intensive care unit and duration of catecholamine therapy are presented in Table 1. No significant differences were found among the groups.

Global left ventricular function. Patients in group 1 demonstrated a higher baseline EF (50 ± 8%) than those in group 2 (37 ± 9, $p < 0.05$) or group 3 (40 ± 14%, $p < 0.05$). EF was not significantly different between groups 2 and 3. Postoperatively, EF improved to 60 ± 10% in group 1 ($p < 0.05$ vs. baseline and vs. groups 2 and 3), to 41 ± 11% in groups 2 (p = NS) and to 46 ± 15% in group 3 (p = NS) (Fig. 3 and 4).

Regional wall motion. After revascularization, regional wall motion in the supraapical anterior region improved in all group 1 patients (from −1.4 ± 0.4 at baseline to −0.4 ± 0.6, $p < 0.005$). In group 2 patients, baseline wall motion was lower in the midanterior wall than that in group 1 patients ($p < 0.05$) but only slightly lower in the supraapical wall (p = 0.08), and in both regions values changed only slightly (from −2.0 ± 1.1 at baseline to −1.7 ± 0.7 and from −2.4 ± 1.5 to −2.2 ± 0.5, respectively, p = NS vs. baseline) after operation. In group 3 patients, baseline wall motion in the supraapical region was significantly lower than that in group 1 patients (−2.7 ± 0.9 vs. −1.4 ± 0.4, $p < 0.005$). Postoperatively, no significant improvement in regional wall motion was obtained.

Clinical symptoms according to NYHA and CCS classification. CCS and NYHA classifications in group 1 patients were 3.1 ± 0.3 and 1.4 ± 1.2 preoperatively and improved to 0.1 ± 0.3 and 0.1 ± 0.3 postoperatively ($p < 0.001$, respectively). Similar results were obtained in the other two groups.

Correlation between variables. Regression analysis revealed that total LAD occlusion was associated with poor preoperative and postoperative wall motion, EF, preoperative NYHA classification and a longer postoperative stay in an intensive care unit compared with LAD stenosis (r values between 0.40 and 0.88, $p < 0.01$ or < 0.05). In contrast, a high correlation was found between the duration of ischemia and the amount of fibrosis (Fig. 5), indicating an increased amount of fibrosis (and cellular degeneration) with increasing duration of ischemia.

Discussion

To our knowledge, this is the first study to examine the relation between duration of ischemic symptoms, amount of cardiomyocyte degeneration and fibrosis, and magnitude of functional recovery after restoration of blood flow in hibernating myocardium. We found that the degree of myocyte degeneration and fibrosis is much more advanced in patients with a history of >50 days (group 2) than in patients with a shorter history (group 1). Although we cannot completely rule out the effect of prior myocardial infarction, nuclear imaging demonstrated viable myocardium even in patients with a history of infarction (in all three groups). However, surgical revascularization resulted in only a slight improvement in regional function postoperatively in this group, even though the clinical status also improved significantly in these patients. With regard to objective hemodynamic parameters, however, the lowest

Table 1. Patient Characteristics and Time Intervals for Patients With Clinically Suspected Hibernating Myocardium ≤50 Days (group 1), >50 Days but ≤6 Months (group 2) and >6 Months (group 3)

		Interval (days)*			
Patient No./Gender	Age (yr)	Impairment in Symptoms to Bypass Surgery (days)	Diagnosis to Bypass Surgery (days)	Intensive Care Unit (days)	Catecholamines After Bypass Surgery (days)
Group 1 (n = 9)					
1/F	69	36	32	3	3
2/M	70	17	12	3	3
3/M	60	30	14	3	3
4/M	68	50	14	4	3
5/M	54	50	50	3	3
6/M	64	40	25	5	2
7/M	52	15	11	3	0
8/M	63	50	44	3	2
9/F	56	45	31	3	2
Mean	62	37	26	3	2
SD	6.30	12.97	13.63	0.67	0.94
Group 2 (n = 14)					
10/M	70	180	48	3	2
11/M	64	97	29	3	2
12/M	65	89	113	3	3
13/M	51	120	89	3	0
14/F	66	150	77	4	3
15/M	68	150	88	5	4
16/M	70	120	69	3	2
17/M	72	105	76	3	3
18/M	61	150	57	4	3
19/M	48	60	43	3	2
20/M	63	90	58	3	2
21/M	71	120	45	2	1
22/M	61	60	45	3	2
23/M	66	60	6	13	10
Mean	64	111	60	4	3
SD	6.83	36.38	26.50	2.60	2.21
Group 3 (n = 9)					
24/M	70	630	16	3	3
25/F	67	300	17	4	3
26/M	54	210	85	5	4
27/M	68	210	78	4	3
28/M	67	270	29	4	4
29/M	55	330	92	3	3
30/M	63	210	28	6	5
31/M	72	390	49	4	3
32/M	65	210	77	26	26
Mean	65	307	52	7	6
SD	5.91	129.44	29.11	6.93	7.10

*The shorter time interval between diagnosis and operation in group 1 patients than in group 2 and 3 patients might be caused by the more acute status of symptoms in these patients, leading to early operation.

rate of recovery is correlated to the longest duration of ischemia.

These findings may be explained as follows: a condition of severe hypoperfusion due to coronary artery stenosis or occlusion causes alterations in metabolic and contractile function to preserve cellular integrity. With increasing duration of low blood flow, however, myocardial adaptation in response to the ongoing ischemic condition might be exhausted or inadequate, leading to progressive myocyte degeneration, onset of focal necrosis and fibrosis (17,32,33). Consequently, contractile function deteriorates. On reperfusion (i.e., aortocoronary bypass surgery), functional recovery is incomplete and delayed despite preserved overall viability (17). Rebuilding of lost contractile material is a time-dependent process (18) and thus may be not successfully completed, if at all, by follow-up after 6 months. Ongoing ischemia also may affect functional recovery.

All patients in our study showed reduced regional perfusion in the LAD territory. Perfusion in group 1 patients was higher than that in groups 2 and 3; when the entire population was considered, there was a significant correlation between total

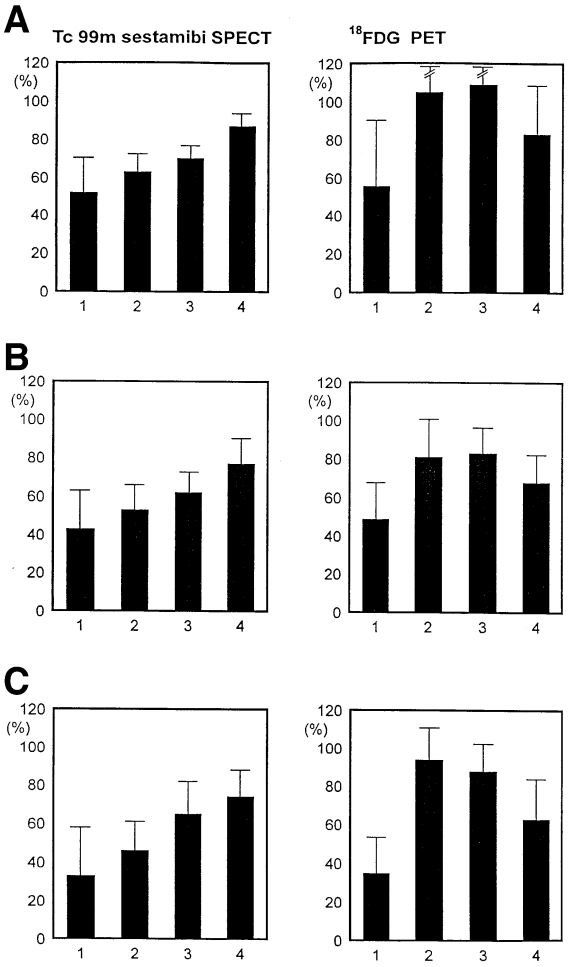

Figure 1. Preoperative nuclear imaging for the three groups of patients with different durations of clinically suspected hibernating myocardium. Perfusion was measured with Tc-99m sestamibi uptake in SPECT, and metabolic activity was measured with F-18 FDG uptake on PET. **Regions 1 to 4** represent the left ventricular anterior wall from base **(region 1)** to apex **(region 4).** Data are given in percentage of the region with maximal perfusion. In all groups, regional perfusion in the midanterior and supraapical wall was reduced (<75%), whereas glucose metabolism was increased (>80%).

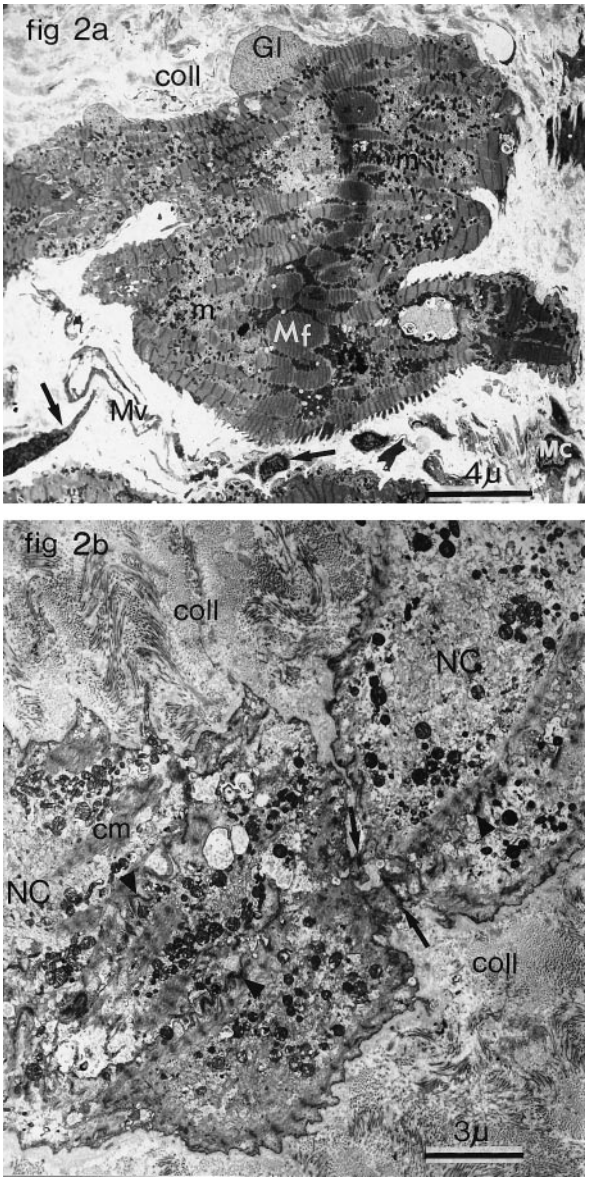

Figure 2. Electron microscopic findings in hibernating myocardium. **a,** Electron photomicrograph showing a myocyte with mild degenerative changes from a patient in group 1. The myofibrils (Mf) are overcontracted but still prominent. Note the small foci of myofilament loss in a peripheral part of the myocyte filled with glycogen (Gl). Mitochondria (m) appear small and dark. There is only a slight increase in collagen fibrils (coll) in the interstitial connective tissue containing microvessels (Mv), fibroblasts (**arrows**) and macrophages (Mc). **Bar** = 4 μm. **b,** Electron micrograph showing severely degenerated myocytes from a patient in group 3. Myocytes are surrounded by thick collagen bundles (coll) and exhibit lack of contractile material (cm) replaced by nonspecific cytoplasm (NC) and displaced to the periphery of the cells. **Arrows** point to the remnants of the intercalated disc between two seperated myocytes. Numerous small side-to-side intercalated discs are indicated by **arrowheads. Bar** = 3 μm.

LAD occlusion and myocardial function. These findings support the concept that the duration and severity of hypoperfusion play a role in dysfunctional myocardium and emphasize the importance of residual coronary blood flow in the preservation of myocardial structure. Importantly, however, patients with chronic low blood flow also may undergo repeated ischemic episodes (i.e., due to alterations in daily energy demand or changes of oxygen supply), which may further jeopardize the myocardial tissue.

Interestingly, there was no difference in baseline wall motion, morphologic structure or functional follow-up on revascularization between patients with ischemic symptoms of >50 days (group 2) and >6 months (group 3). However, regression analysis (Fig. 5) implies that deterioration is progressive. These findings indicate that additional structural and functional deterioration may occur if the time interval is prolonged (i.e., after years). Another explanation could be that the establishment of a chronic steady state with reduced function but maintained viability takes time for demand to adapt to the reduced oxygen supply. Once this hibernating

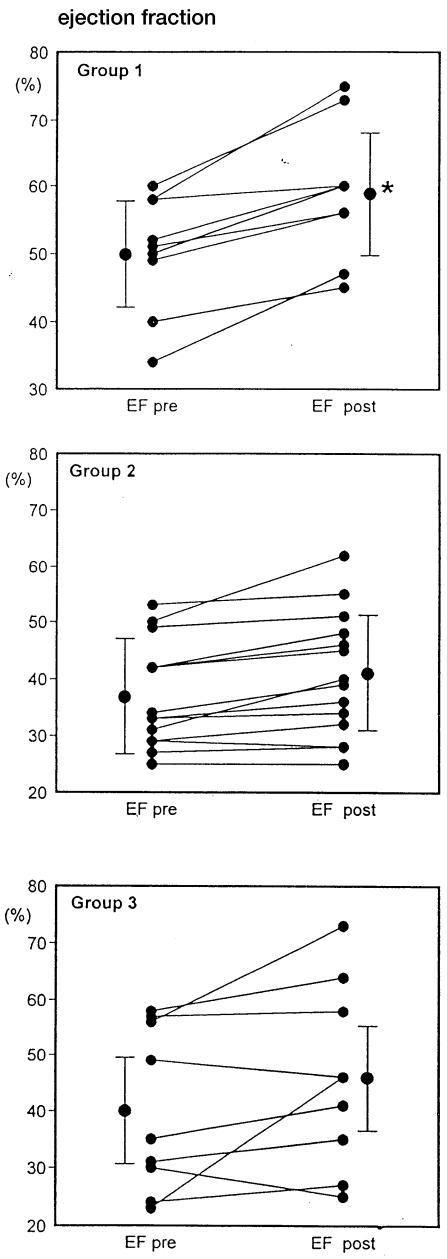

Figure 3. EF before and after operation for the three groups of patients with a short (≤50 days, group 1 **[top]**), intermediate (>50 days but ≤6 months, group 2 **[middle]**) and chronic (>6 months, group 3 **[bottom]**) duration of ischemic (hibernating) myocardium. Except for two patients in group 3, all showed improvement in EF at 6 months after operation. *$p < 0.05$ versus preoperative EF.

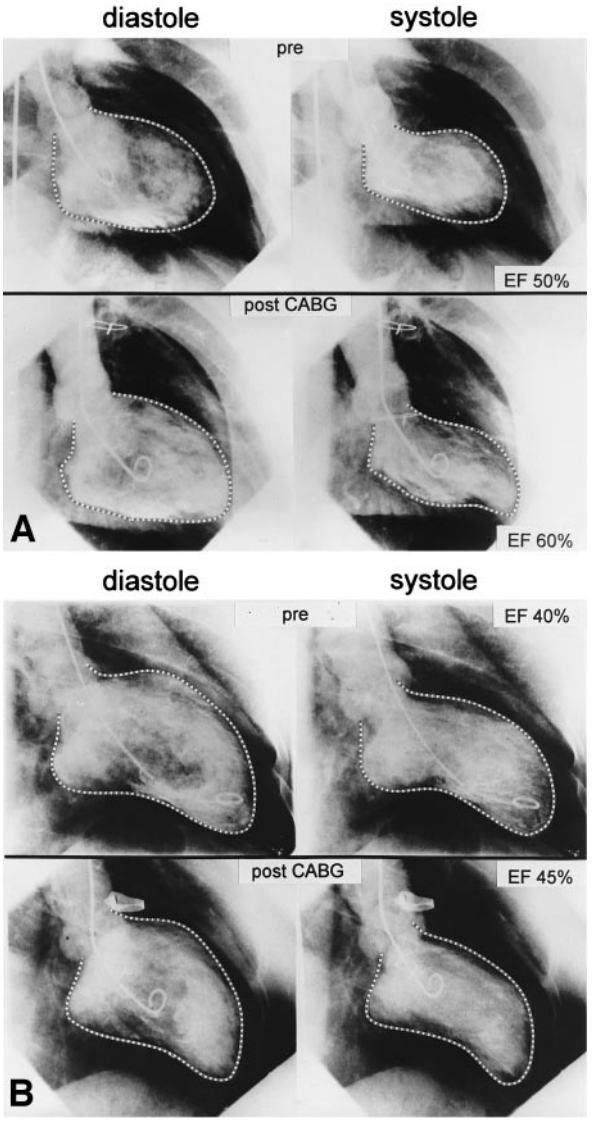

Figure 4. Ventriculograms from two patients before and 6 months after aortocoronary bypass surgery (CABG). **A,** A 68-year old man had a 30-day history (group 1). **B,** A 69-year old woman had a long-standing history of heart failure before bypass surgery was performed (group 3).

condition is reached, the cells may possess a higher stress tolerance, so unchanged chronic ischemia as well as repeated acute ischemic episodes are less effective, at least to a certain extent. This hypothesis is supported by findings in the Bland-White-Garland syndrome, in which functional recovery has been observed after years, even in the presence of severe fibrosis (34,35). However, if ischemia is overwhelming, progressive cellular alterations, apoptosis and cell death are predetermined.

In the pig model, progressive reductions in blood flow result in reduced myocardial injury (i.e., attenuated coronary venous lactate and P_{CO_2} production and smaller infarcts) compared with abrupt coronary occlusion. Ito (36) proposed a time-dependent component for metabolic adjustments, because the rate of reduction in flow had an influence on myocardial damage. With regard to the present results, it is possible that adaptive mechanisms in chronically hypoperfused (hibernating) myocardium take time to stabilize. This probably is influenced by the magnitude of residual blood flow, either via flow through a stenotic lesion or via collateral flow in the case of total coronary occlusion. However, to stop structural deterioration, avoid further attenuation of contractile function and obtain better postoperative outcome, these patients should be revascularized on an urgent basis.

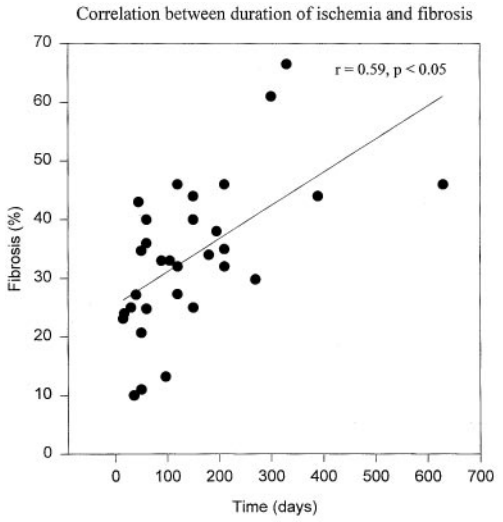

Figure 5. Regression analysis for subendocardial fibrosis and duration of the clinical condition suspicious for hibernating myocardium expressed in days from precipitous onset of new symptoms or worsening of preexisting symptoms or new onset of heart failure to aortocoronary bypass grafting. There is a positive correlation between the amount of replacement fibrosis and duration of the clinical condition of hibernation.

Study limitations. A major limitation of this study is that assessment of the exact time point of the onset of the hibernating condition is difficult. Clinical symptoms might not reflect regional dysfunction; thus, the more severe condition involving global myocardial dysfunction has been recognized clinically. Furthermore, due to changes in coronary vascular tone, perfusion pressure, endogenous catecholamine output and exogenous oxygen supply, changes in the hibernating condition might exist frequently and influence the condition. Such alterations might not be recognized clinically (37). Second, using an average of 10 chords according to the modified centerline method from a single region (midanterior or supraapical) may result in underestimation of the differences in wall motion within this area. However, this approach seems to be reasonable on a clinical basis and facilitates the topographic correlation of regions obtained with cineventriculography to corresponding regions obtained with nuclear imaging. Electron microscopic analysis of transmural specimen ultimately does not represent the entire left ventricular wall; however, we attempted to obtain biopsy samples from the regions of interest that were clearly absence of scar tissue but had visible dysfunction.

Conclusions. With increasing ischemic duration, the adaptive mechanisms in hibernating myocardium become insufficient to further preserve structural integrity and contractile function deteriorates. Patients with a longer duration of ischemia have reduced wall motion and EF with more severe symptoms, a higher degree of cardiomyocyte degeneration and fibrosis and a worse postoperative recovery of contractile function compared with patients with a shorter duration of ischemia. Timely revascularization is required to prevent progressive cellular degeneration and improve functional outcome.

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