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Low Dose Dobutamine Echocardiography Predicts Improvement in Functional Capacity After Exercise Training in Patients With Ischemic Cardiomyopathy: Prognostic Implication

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Objectives. **This study sought to investigate whether the identification of hibernating myocardium by low dose dobutamine stress echocardiography (LDSE) may predict an improvement in functional capacity after moderate exercise training in patients with ischemic cardiomyopathy. Another objective was to assess whether exercise training may affect the outcome.**

Background. **There is evidence that exercise training improves left ventricular (LV) function as well as functional capacity in patients with a previous myocardial infarction and LV dysfunction. We hypothesized that the magnitude of these improvements might be related to the extent of hibernating myocardium.**

Methods. **We studied 71 consecutive patients 56 ± 9 years old (mean ± SD) with chronic heart failure secondary to ischemic cardiomyopathy (LV ejection fraction [LVEF] <40%). All patients were in sinus rhythm and were clinically stable during the previous 3 months. Patients were randomized into two matched groups. Group T (n = 36) underwent exercise training at 60% of peak oxygen uptake ($\dot{V}O_2$) three times a week for 10 weeks. Group C (n = 35) did not exercise. At study entry and end, all patients underwent an exercise test with gas exchange analysis and LDSE (5 to 20 μg/kg body weight per min).**

Results. **At baseline, a positive contractile response (CS+) to LDSE was observed in 317 of 576 segments in group T and 291 of 560 segments in group C. After 10 weeks, peak $\dot{V}O_2$ and peak work rate increased only in trained patients (peak $\dot{V}O_2$: from 16.2 ± 3 to 20.8 ± 4 ml/kg per min; work capacity: from 108 ± 20 to 131 ± 25 W, p < 0.001 vs. group C for both). The presence of CS+ at baseline was associated with a sensitivity of 70% and a specificity of 77% for predicting an increase in the functional capacity after exercise training. Positive and negative predictive values of LDSE were 84% and 59%, respectively. Independent predictors of cardiac events were a pre-to-posttraining difference in LVEF at peak dobutamine infusion and the presence of a viable response at baseline (p = 0.004 and 0.008, respectively). The log-rank test demonstrated that trained patients had a significantly lower probability of cardiac events during follow-up than sedentary control patients (p < 0.001).**

Conclusions. **The presence of hibernating myocardium as assessed by LDSE predicts the magnitude of improvement in functional capacity after moderate exercise training in patients with chronic heart failure. A significant increase in functional capacity after exercise training is associated with a lower incidence of cardiac events during follow-up.**

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Patients with ischemic heart disease and left ventricular (LV) dysfunction have a reduced exercise tolerance because of a reduced ability of the circulatory supply of oxygen in meeting the cellular metabolic requirements under conditions of physical stress. There is evidence that exercise training can reduce the functional impairment by inducing both central and peripheral adaptations (1,2). Although peripheral modifications represent the major contributors to the improvement in exercise tolerance after exercise training, it is still a matter of debate whether exercise conditioning can increase myocardial contractility and whether this increase can contribute to the improvement in the exercise tolerance of these patients.

In the past, increases in both myocardial perfusion and contractility have been described after an adequate training stimulus in patients with chronic coronary artery disease and different levels of LV dysfunction (3–6). The extent of improvement in LV function in response to physical activity seemed more marked among patients with provokable myocardial ischemia or effort angina, or both, than in patients without them. An explanation could be that only viable/ischemic myocardium retains the capability to improve function after restoration of adequate perfusion to chronically underperfused dysfunctional myocardium.

The relation between perfusion and function is evidenced by the objective improvement in rest LV ejection fraction (LVEF) obtained in 25% to 40% of patients with ischemic cardiomyopathy who undergo coronary artery bypass surgery

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Abbreviations and Acronyms

ECG = electrocardiographic
LDSE = low dose dobutamine stress echocardiography
LV = left ventricular
LVEDV = left ventricular end-diastolic volume
LVEDVI = left ventricular end-diastolic volume index
LVEF = left ventricular ejection fraction
LVESV = left ventricular end-systolic volume
LVESVI = left ventricular end-systolic volume index
Peak $\dot{V}O_2$ = oxygen uptake at peak exercise
SWTI = systolic wall thickening score index

or percutaneous transluminal coronary angioplasty (7,8). Thus, the search for an accurate and noninvasive method for detecting viable myocardium has become an important component of the diagnostic assessment of patients with depressed LV function. Among them, low dose dobutamine stress echocardiography (LDSE) has the unique capability to evaluate the contractile response of dysfunctional myocardium. Only viable myocardium is capable of enhancing contractile function in response to inotropic stimulation and its assessment has been demonstrated to have predictive value as well as prognostic significance (9,10).

On the basis of these premises, we hypothesized that moderate exercise training could improve LV contractility in patients with chronic heart failure due to ischemic cardiomyopathy. These effects can contribute to an increase in functional capacity and also have prognostic implications.

Methods

Patients. Over a 2-year period, 71 consecutive patients 56 ± 9 years old (range 35 to 68 y) with chronic heart failure were studied. All patients were in sinus rhythm and clinically stable for the 3 months preceding the study. Chronic heart failure was diagnosed when definite radiographic evidence of pulmonary congestion was associated with typical signs and symptoms of heart failure for >3 months. All patients had had one or more myocardial infarctions during the past 2 years. LVEF was 33 ± 6% (mean ± SD). Twelve patients had undergone coronary artery bypass graft surgery. Patients with a recent myocardial infarction (<3 months), unstable angina, high grade arrhythmias, uncontrolled hypertension, uncompensated congestive heart failure, hemodynamically significant valvular heart disease, renal insufficiency (serum creatinine >2.2 mg/dl) and orthopedic limitations were excluded. All patients had coronary angiography within 6 months of the beginning of the study. Forty-three percent of patients had >70% lumen narrowing of all three major epicardial coronary arteries; 38% of patients had two-vessel disease; and 19% had one stenotic vessel. Medications were similar in the two groups and were not altered throughout the study.

Protocol. The protocol was approved by the ethics Committee of Lancisi Hospital, Ancona, Italy. All patients provided written informed consent and were randomized to an exercise group (group T) or a control group (group C) (Table 1). At baseline and at the end of the study all patients underwent an LDSE study and an incremental exercise test with gas exchange analysis.

Dobutamine stress echocardiography. Echocardiographic studies were performed with the patient supine in the left lateral position. Under continuous electrocardiographic (ECG) monitoring, dobutamine was infused into a peripheral vein at an incremental regimen of 5 μg/kg body weight per min every 3 minutes until a maximum of 20 μg/kg per min. Systolic blood pressure was taken at baseline and at the end of each stage. End points of the study included a new wall motion abnormality, significant ST segment changes (i.e., ST segment depression or elevation ≥1 mm or more in two contiguous leads), significant symptoms or arrhythmias or completion of the protocol. A 12-lead ECG recording was taken every minute with pediatric sized precordial electrodes to maximize the chest area available for echocardiography. Two-dimensional echocardiographic images were continuously recorded from the parasternal long-axis, short axis and apical four- and two-chamber views using a wide-angle mechanical scanner (Challenge-ESAOTE).

Measurements. End-diastole was defined as the frame coinciding with the peak of the R wave of the QRS complex on the ECG. *End-systole* was defined as the frame at the end of the T wave. LV end-diastolic volume and end-systolic volume were obtained from the apical four- and two-chamber views using a modified Simpson's rule, from which LVEF was automatically calculated as the difference between end-diastolic volume (EDV) and end-systolic volume (ESV) normalized to EDV.

Table 1. Clinical Characteristics of 71 Study Patients

	Exercise Group (n = 36)	Control Group (n = 35)
Male/female	31/5	30/5
Age (yr)	55 ± 9	57 ± 9
MI	36	35
Ant	19	18
Inf	6	7
Lat	2	2
Ant+Inf	9	8
Peak $\dot{V}O_2$ (ml/kg per min)	16.2 ± 4	16 ± 4
LVEF (%)	33 ± 6	31 ± 7
NYHA functional class		
II	27	25
III	9	10
Medications		
Nitrates	26	28
Diuretic drugs	16	15
ACE inhibitors	32	31
Aspirin	16	16
Warfarin	20	19

Data presented are mean value ± SD or number of patients. ACE = angiotensin-converting enzyme; Ant = anterior; Inf = inferior; Lat = lateral; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; $\dot{V}O_2$ = oxygen uptake.

We used a biplane algorithm to calculate LV volumes (11). A 16-segment model was used for analysis, as recommended by the American Society of Echocardiography (11). Each segment was visually graded using a semiquantitative scoring system, where 1 = normal; 2 = hypokinetic; 3 = akinetic; and 4 = dyskinetic. A regional *systolic wall thickening score index* (SWTI) was defined as the sum of each segment score divided by the number of interpreted segments. *Abnormal regional wall motion* was defined as a value falling outside the established 95% confidence intervals for each segment for a normal population database from our laboratory. Normal values from our laboratory were calculated from a group of 150 healthy subjects (75 men, 75 women; mean age 54 ± 17 years, range 19 to 80) consecutively studied by three independent, experienced physicians. All subjects underwent three echocardiographic studies on different days over 2 weeks. A mean value for LV volumes (LV end-diastolic volume index [LVEDVI] 53.9 ± 8.7 ml/m^2; LV end-systolic volume index [LVESVI] 22.5 ± 5 ml/m^2) and derived LVEF (58.1 ± 6.9%) was obtained from five consecutive cycles for each study. To test the intraobserver variability, each study was reexamined by the same observer on a separate day (EDV 0.91 ± 15 ml; ESV 1.5 ± 11 ml; LVEF 0.9 ± 6.6%). A second observer reviewed each study to test for interobserver variability (EDV 0.05 ± 12 ml; ESV −1.1 ± 10.8 ml; LVEF 1.9 ± 8.4%).

The regional systolic wall thickening score index (SWTI) was calculated at rest and at each stage of dobutamine infusion. A 20% reduction in SWTI represents the 95% confidence interval, discriminating a significant difference between normal and abnormal contractile response to low dose dobutamine by two-dimensional echocardiography in our laboratory.

Data analysis. All studies were analyzed with an off-line system equipped with digital processing (Panasonic AG 7700). Representative cycles of rest and peak dobutamine dose images in comparable views were digitized and positioned side by side on a quad screen format. The echocardiographic images were evaluated in a blinded manner by two independent, experienced observers who adopted the same assessment criteria. Disagreement between the two observers occurred in 6% of the studies. Differences in interpretation were resolved by a third independent cardiologist. A response was considered *normal* when segments with normal wall thickening at rest had a persistent hyperdynamic response to dobutamine. A *viable response* was considered an improvement in SWTI by at least one grade in two adjacent segments with rest asynergy at any stage of dobutamine infusion (i.e., from score 3 at rest to 2 or 1 during infusion). An *ischemic response* was considered the development of hypokinesia, akinesia or dyskinesia from normal segments at rest or initial improvement in wall thickening from an abnormal segment at rest followed by worsening thickening at higher doses of dobutamine infusion. On follow-up studies, improvement in the contractile response to dobutamine, compared with baseline studies, was considered a reduction in SWTI by ≥1 at peak infusion or a ≥20% reduction in SWTI in at least two adjacent segments, or both.

Cardiopulmonary exercise test. All patients performed a familiarization incremental exercise test on a cycle ergometer 1 or 2 weeks before the randomization. On study entry, a symptom-limited exercise test with gas exchange analysis was repeated in all patients. Patients pedaled in upright position at 60 rpm with the aid of a visual display on an electronically braked cycle ergometer (Ergometrics 800, Sensormedics). The work rate was progressively increased by 1 W every 4 s in a ramp pattern. Every minute, a 12-lead ECG was recorded, and blood pressure was measured. During each test, gas exchange analysis was performed breath by breath (Sensormedics 2900 Z). *Peak oxygen uptake* ($\dot{V}O_2$) was defined as the average $\dot{V}O_2$ during the last 15 s of exercise. *Ventilatory threshold* was measured by the V-slope method (12). A *positive exercise test* was defined by ST segment depression ≥2 mm in at least two adjacent ECG leads during exercise persisting >3 min into recovery or ST segment elevation or angina pectoris, or both, during exercise.

Exercise training. The exercise group underwent a program of exercise training of moderate intensity (60% of peak $\dot{V}O_2$) three times a week for 10 weeks. Control patients performed no exercise. Each session consisted of a warm-up phase of stretching exercise and calisthenics (10 to 15 min), followed by 40 min of cycling on an electronically braked cycle ergometer. Heart rate and blood pressure were measured at baseline, at midcycling time and at recovery. A cardiologist was present during each session. Care was taken to avoid exercise intensities above or below the initial target. Patients in both groups were asked not to exercise at home. Both trained and control patients were visited monthly by a cardiologist in the hospital.

Follow-up. Patients were followed up for 23 ± 6 months (range 11 to 26) from the day after the completion of the protocol. The follow-up period ended at the time of study closure or with a cardiac event. *Events* were defined as cardiac death, myocardial infarction, unstable angina and development of congestive heart failure requiring hospital admission and potentiation of medical therapy. Patients in both groups were instructed not to exercise at home on a regular basis. Patients were visited by a cardiologist at our hospital every 6 months. During the follow-up period, patients or their families filled in a standard questionnaire at home to be shown at any visit to provide information about home activities, symptoms and medications.

Statistical analysis. A two-tailed Student *t* test was used for intragroup (paired) and intergroup (unpaired) comparisons. The effects of exercise training on metabolic and hemodynamic variables were analyzed by two-way analysis of variance. The effects of exercise training on the contractile response to dobutamine and functional capacity were analyzed on the basis of patients rather than myocardial segments to increase the power of statistical analysis.

Patients were classified as those with and without a viable/ischemic response. A score was created, where 0 = no change; +1 = improvement; and −1 = deterioration. Changes in this score as a function of exercise training versus control were analyzed using a nonparametric test (Mann-Whitney rank

Table 2. Metabolic and Hemodynamic Variables on Study Entry and at 10 Weeks

	Exercise Group		Control Group		
	Study Entry	10 wk	Study Entry	10 wk	p Value*
Peak oxygen uptake (ml/kg per min)	16.2 ± 3	20.8 ± 4	16 ± 3	16.3 ± 3	0.001
Ventilatory threshold (ml/kg per min)	10.9 ± 2	14.3 ± 2	10.5 ± 2	10.6 ± 2	0.001
Ventilation (liter/min)	46 ± 9	61 ± 12	49 ± 11	48 ± 12	0.001
Respiratory exchange ratio	1.15 ± 0.05	1.16 ± 0.07	1.16 ± 0.05	1.16 ± 0.05	0.26
Work rate (W)	108 ± 20	131 ± 25	101 ± 22	103 ± 22	0.001
Rest heart rate (beats/min)	86 ± 11	76 ± 8	82 ± 9	85 ± 10	0.001
Peak heart rate (beats/min)	137 ± 17	139 ± 10	135 ± 10	138 ± 15	0.88
Peak systolic blood pressure (mm Hg)	168 ± 24	175 ± 23	160 ± 20	155 ± 21	0.007
Rate-pressure product (beats/min × mm Hg)	22,797 ± 4,607	24,474 ± 6,671	21,980 ± 4,370	21,867 ± 4,452	0.005

*Changes after 10 weeks, exercise versus control group by unpaired *t* test.

test). The Fisher exact test was used to determine whether the response of the SWTI during dobutamine infusion on study entry predicted the improvement in functional capacity after exercise training.

Univariate analysis to assess correlations between pre- and posttraining changes in peak $\dot{V}O_2$ and all clinical, echocardiographic and metabolic variables was performed. Variables with significant correlations ($p < 0.05$) were then entered into a stepwise linear regression model to determine the best predictors of posttraining improvement in functional capacity. The effect of covariates on the outcome was assessed by stepwise logistic regression analysis. Cardiac mortality was compared between groups by means of log-rank tests. Cardiac event-free curves for the trained and untrained patients were computed using the Kaplan-Meier method. Results expressed as mean value ± SD. Statistical significance was assumed for $p \leq 0.05$.

Results

Patients. All patients completed the exercise training protocol. As shown in Table 2, trained patients had significant improvements in peak $\dot{V}O_2$ (28%), ventilatory threshold (31%), ventilation at peak exercise (33%) and work rate (21%). Compared with control subjects, all these changes were statistically significant. No differences in respiratory exchange ratio and heart rate at peak exercise were observed in the two groups.

Eleven patients in the exercise group and 10 in the control group had a positive ECG stress test at baseline. After 10 weeks, 8 of the 11 patients who underwent exercise training and none of the control patients had a negative ECG stress test ($p < 0.001$).

Dobutamine stress echocardiography. All patients attained the peak dose of dobutamine (20 μg/kg per min). No major complications occurred during dobutamine stress testing. One patient had a nonsustained ventricular tachycardia (19 beats); two patients had atrial tachycardia; and seven patients had isolated premature ventricular contractions. Hypotension occurred in two patients after the completion of the test. There were no significant differences in end-diastolic diameter, heart rate or systolic blood pressure between patients with and without viable myocardium. The number of coronary arteries with significant stenoses was not different in patients with and without contractile response.

Effects of exercise training on LV function. Of the 71 patients who underwent LDSE at baseline, 36 had viable myocardium (19 in group T, 17 in group C), 30 (42%) had a positive inotropic response to dobutamine, and 6 (8%) had an ischemic response only. Rest SWTI and LVEF were similar in patients who underwent exercise training and patients who did not (Table 3). After 10 weeks, both SWTI and LVEF at peak dobutamine levels improved significantly in trained patients only (25% and 27%, respectively, $p < 0.001$ trained vs. control for both variables). The improvement in LVEF at peak dobutamine was due to a reduction in LVESVI (−23%; $p < 0.001$). There were neither significant differences in LVEDVI nor changes in systolic blood pressure at any relative work rate, indicating that changes in SWTI and LVEF at peak dobutamine were unrelated to changes in loading conditions.

Table 3. Rest and Peak Hemodynamic Variables on Dobutamine Stress Echocardiography at Baseline and at 10 Weeks

	Exercise Group		Control Group	
	Baseline	10 wk	Baseline	10 wk
Rest				
HR (beats/min)	88 ± 10	79 ± 9	90 ± 8	93 ± 10
LVEDVI (ml/m^2)	101 ± 6	99 ± 7	104 ± 8	106 ± 10
LVESVI (ml/m^2)	68 ± 8	67 ± 9	70 ± 10	72 ± 11
LVEF (%)	34 ± 6	33 ± 7	33 ± 5	32 ± 8
SWTI	2.2 ± 0.2	2.1 ± 0.2	2.3 ± 0.3	2.2 ± 0.3
Peak				
HR (beats/min)	137 ± 7	135 ± 9	133 ± 10	137 ± 9
LVEDVI (ml/m^2)	92 ± 5	90 ± 5	95 ± 9	97 ± 10
LVESVI (ml/m^2)	58 ± 8	42 ± 9*	60 ± 11	63 ± 10
LVEF (%)	37 ± 7	53 ± 10	38 ± 8	39 ± 9
SWTI	1.89 ± 0.2	1.52 ± 0.2*	1.91 ± 0.3	1.90 ± 0.3

*$p < 0.001$, exercise group versus control group. HR = heart rate; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; SWTI = systolic wall thickening score index.

Table 4. Clinical and Rest Echocardiographic Variables in Patients With Viable Myocardium at Baseline and Improvement in Functional Capacity After Exercise Training and in Patients Without Viable Myocardium at Baseline and No Improvement in Functional Capacity After Exercise Training

	CS+ Peak $\dot{V}O_2$+ (n = 16)			CS− Peak $\dot{V}O_2$− (n = 10)		
	Study Entry	10 wk	Δ	Study Entry	10 wk	Δ
HR (beats/min)	82 ± 11	71 ± 9	11 ± 10*	80.7 ± 14	78 ± 14	2.3 ± 14
Peak $\dot{V}O_2$ (ml/kg per min)	16.6 ± 2	20.6 ± 3	−3 ± 3*	13.5 ± 0.8	14.2 ± 0.9	−0.7 ± 0.9
LVEF (%)	34.3 ± 6.5	33.6 ± 8	0.68 ± 4	31.6 ± 7	30.7 ± 7	0.89 ± 2.6
LVEDVI (ml/m^2)	99 ± 5	96.4 ± 5	2.6 ± 3	102 ± 6	99.4 ± 7.3	2.78 ± 5.4
LVESVI (ml/m^2)	65.6 ± 9	64.1 ± 10	1.48 ± 3	70.9 ± 7.7	70 ± 8	0.9 ± 2.6
SWTI	2 ± 0.07	2 ± 0.09	0.01 ± 0.08*	2.5 ± 0.1	2.35 ± 0.2	0.15 ± 0.2

*$p < 0.001$ for changes (Δ) between the two subgroups. CS+ Peak $\dot{V}O_2$+ = viable myocardium at baseline and improved functional capacity after exercise training; CS− Peak $\dot{V}O_2$− = no viable myocardium at baseline and no improvement in functional capacity after exercise training; other abbreviations as in Tables 1 and 3.

More specifically, 45 of 206 hypokinetic segments at baseline improved the SWTI after exercise training, along with 38 of 94 akinetic and 2 of 17 dyskinetic segments. Only 6% of myocardial segments (17 of 291) in the control group improved contractility on follow-up studies (chi-square 46.3; $p < 0.001$, group T vs. group C).

Prediction of improvement in functional capacity by LDSE. Of the 19 patients in the exercise group with a positive contractile response to dobutamine at baseline, 16 had a significant improvement in peak $\dot{V}O_2$ after exercise training (from 16.6 ± 2 to 20.6 ± 3 ml/kg per min, $p < 0.001$). Of the 17 patients with no evidence of viable myocardium on the initial LDSE, 7 had an increased peak $\dot{V}O_2$ after exercise training (from 15.9 ± 2 to 19.5 ± 2 ml/kg per min, $p < 0.001$). Ten patients with no viable myocardium at baseline had no significant increase in peak $\dot{V}O_2$ after exercise training (baseline 13.5 ± 0.8 ml/kg per min; study end 14.2 ± 0.9 ml/kg per min, $p = 0.10$). Positive and negative predictive values of LDSE were 84% and 59%, respectively. Of interest, the subgroup of patients with viable myocardium and improved functional capacity after exercise training had a higher peak $\dot{V}O_2$ and a lower SWTI at baseline than the subgroup of patients with no viable myocardium on the initial LDSE and no increase in functional capacity after exercise training (Table 4). As shown in Figure 1, patients with viable myocardium and improved functional capacity had a significantly greater improvement in posttraining rest peak LVEF and SWTI in response to dobutamine infusion than patients with no viable myocardium and no improvement in functional capacity. Moreover, there were no significant differences in heart rate, systolic blood pressure or LV end-diastolic dimension between patients with and without contractile improvement, suggesting that the presence of contractile response to dobutamine was independent of heart rate, afterload or preload.

Outcome. Completed follow-up data were obtained in all patients over a period of 23 ± 6 months. Cardiac events occurred in 8 group T patients (22%) and 18 group C patients (51%) ($p < 0.001$, group T vs. group C). As shown in Figure 2, the number of patients at risk in each group was 34 and 30 at 12 months, and 28 and 17 at 24 months, respectively. Cardiac events in the eight patients of the group T were cardiac death in one patient, unstable angina in two, acute myocardial infarction in two and hospital admission for worsening heart failure in three. In the control group, cardiac death occurred in four patients, unstable angina in five, acute myocardial infarction in three and worsening heart failure in six. Patients with a cardiac event had a significantly higher SWTI at baseline than patients with no cardiac events (2.04 ± 0.2 vs. 1.83 ± 0.2, $p = 0.02$). No significant differences in age, gender, heart rate at rest and peak exercise, peak $\dot{V}O_2$, peak systolic blood pressure,

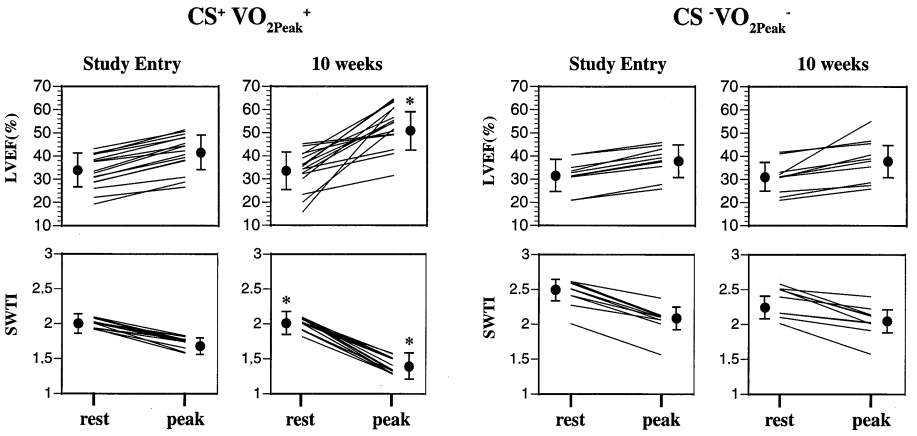

Figure 1. LVEF and SWTI at rest and peak dobutamine infusion in each individual patient with viable myocardium who improved functional capacity after exercise training (CS+ VO_{2Peak}+) and each patient without viable myocardium who had no change in functional capacity after 10 weeks (CS+ VO_{2Peak}−). **Solid circles** = mean values. *$p < 0.001$, CS+ VO_{2Peak} + versus CS+ VO_{2Peak}−.

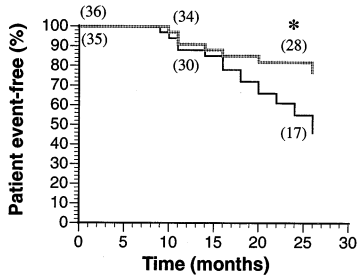

Figure 2. Event-free rates in patients who underwent exercise training **(thick line)** and control patients **(thin line)**. Numbers of patients at risk in each group on study entry at 12 and 24 months are shown in **parentheses**. Trained patients have a significantly lower probability of cardiac events than sedentary control patients during follow-up; *$p < 0.001$ by log-rank test.

resting LVEF and LV volumes were observed between patients with and without cardiac events. There was no significant difference between the prevalence of risk factors or medication between patients of the two groups with and without cardiac events.

Univariate and multivariate analysis. Stepwise linear regression analysis showed that group (trained or untrained) (chi-square 28.618, $p < 0.001$), pre- to posttraining changes in work capacity (chi-square 8.115, $p < 0.004$) and SWTI at baseline (chi-square 8.282, $p = 0.004$) were the best independent predictors of improvement in functional capacity after exercise conditioning. Stepwise logistic regression analysis with event as the outcome showed that the pre- to posttraining change in LVEF at peak dobutamine and the presence of a viable response at baseline were the best significant discriminant variables ($p = 0.004$ and 0.008, respectively) (Table 5). The survival model (log-rank test) showed significantly lower event-free survival in patients who underwent the exercise training program ($p < 0.001$).

Discussion

The results of the present longitudinal study indicate that, in patients with chronic heart failure, exercise training of moderate intensity increases both functional capacity and the contractile response of hibernating myocardium to low dose dobutamine. The identification of hibernating myocardium at baseline by LDSE was associated with a sensitivity of 70% and a specificity of 77% for predicting an increase in functional capacity after exercise training. Positive and negative predictive values were 84% and 59%, respectively. A significant increase in functional capacity, observed only in the trained group, was associated with a lower incidence of cardiac events during follow-up ($p < 0.001$).

Table 5. Multivariate Analysis of Events as Dependent Variable

Event	Beta-Coefficient	p Value
ΔLVEF (%)	74.8	0.004
CS+ at baseline	−1.7	0.008

CS+ = presence of viable myocardium; ΔLVEF = change in left ventricular ejection fraction before and after training.

Exercise training and myocardial contractility. Our findings confirm the results of a recent preliminary report (13) showing that a moderate exercise training regimen can improve LV contractility in patients with chronic heart failure and ischemic heart disease. In the past, similar results were obtained using exercise training protocols of higher intensities and longer duration (14,15). With both moderate and intense exercise training regimens, LV contractility did not change at baseline. However, the results of the present study indicate that myocardial contractility may improve in response to moderate beta-adrenergic stimulation. From our data, this improvement seems unrelated to changes in loading conditions. In fact, both peak exercise systolic blood pressure and LVEDVI were unchanged after training.

The improvement in LV contractility in response to a moderate physical regimen was more marked among patients with provokable myocardial ischemia or effort angina, or both, than in patients with no inducible ischemia or who were asymptomatic. A possible explanation may be that only ischemic or viable myocardium retains the capability to improve function after physical training. Moreover, a remarkable result from the present study was that 73% of positive exercise tests at baseline became negative after exercise training ($p < 0.001$ vs. control subjects). As previously demonstrated in animals (16,17) and humans with (1,6) and without (18) coronary artery disease, exercise training can improve LV function through improvements in myocardial perfusion sustained by both structural and functional coronary artery adaptations (19–21). The effect of moderate exercise training should be more evident at the level of small coronary vessels because the severity of epicardial stenoses was unchanged after training (22). Therefore, one mechanism for improvement in LV contractility could be a reduction in myocardial ischemia. This hypothesis was confirmed by the absence of spontaneous improvement in contractility as well as ischemic threshold in untrained patients on the follow-up study. It is likely that exercise training determines an improvement in myocardial oxygenation rather than a lower myocardial oxygen requirement (1). In fact, we found a posttraining increase in peak exercise heart rate, which indicates a higher myocardial oxygen demand.

Clinical and prognostic implications. Patients with hibernating myocardium at baseline had a higher peak $\dot{V}O_2$ as well as a lower SWTI after training (Table 4). We also found that the improvement in contractility was more marked among less dysfunctional myocardial segments at baseline. In fact, a quantitative correlation between the extent of viable myocardium assessed by positron emission tomography and the magnitude of improvement in heart failure symptoms and functional capacity has recently been demonstrated after coronary artery bypass surgery in patients with ischemic cardiomyopathy (23). Although the effects of exercise training on LV function cannot be compared with those obtained with standard procedures of myocardial revascularization, these preliminary observations suggest that even a short-term regimen of

moderate physical activity may induce a favorable effect on myocardial contractility. Because we did not use high doses of dobutamine we could not assess the contractile reserve of dysfunctional myocardium. Nonetheless, the enhanced contractility after moderate inotropic stimulation can be extrapolated to situations of daily life when mild to moderate physical activities are performed. The implication is that quality of life can be improved by improvement in LV contractility.

Furthermore, patients who completed the exercise training regimen had a significantly lower occurrence of untoward cardiac events during follow-up than did the untrained patients. Stepwise logistic regression analysis with event as the outcome selected the pre- to posttraining change in LVEF at peak dobutamine infusion and the presence of hibernating myocardium at baseline as the best discriminant variables. Most patients with no viable response at baseline had no improvement in either LV contractility or functional capacity after training, and they also had an adverse outcome.

Thus, the presence of hibernating myocardium at baseline represents the "conditio sine qua non" to obtain an improvement in LV function as well as functional capacity after exercise training. Both factors can cooperate to improve the clinical outcome. It is unclear why patients who underwent exercise training for only 10 weeks had a lower incidence of cardiac events than control patients over the following 2 years. In fact, central adaptations after exercise training are generally lost after a few weeks of inactivity, even in well trained healthy humans (24). It is likely that a higher exercise tolerance after training, in conjunction with an improved LV contractility, can allow a more active lifestyle, which in turn can maintain a higher functional capacity for a longer period than expected.

Study limitations. As with any imaging technique, LDSE has advantages and disadvantages. The advantages are reproducibility, good specificity and compliance. The disadvantages are subjective interpretation of data, relatively low sensitivity and lack of an accurate quantitative method for assessing wall motion abnormalities and wall thickening.

The use of dobutamine at doses $\leq$20 μg/kg per min could lead to underestimation of the contractile response. However, Panza et al. (25) showed that the great majority of myocardial segments respond to doses $\leq$20 μg/kg per min. Moreover, in the setting of severe coronary artery stenosis, dobutamine may provoke ischemic rather than contractile response. Another cause of underestimation of myocardial viability may be the absence of a contractile response despite normal perfusion. This behavior has been described when subendocardial necrosis occurs and LV thickening is significantly reduced or absent. In this case, the contribution of the middle and outer layers of the LV wall to thickening is modest or negligible.

Conclusions. Patients with chronic heart failure secondary to ischemic heart disease can improve their functional capacity with exercise training of moderate intensity, whereas patients who do not exercise have no significant change in their functional capacity. A significant posttraining increase in LV contractility was also observed, supporting the implication that even short-term moderate exercise training can improve quality of life by improving LV function during mild to moderate physical activities. The identification of dysfunctional but viable myocardium by LDSE is predictive of posttraining improvement in functional capacity. Importantly, patients with improved functional capacity after exercise training had a better outcome than patients who did not exercise. These findings suggest that LDSE can be usefully employed for identifying patients with chronic heart failure who will benefit most from exercise training. In contrast, the absence of a viable response at baseline can predict patients who will not benefit from exercising and who will not have a favorable clinical outcome. The clinical and prognostic significance of these data need to be confirmed in larger studies.

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