Effects of Moderate Exercise Training on Thallium Uptake and Contractile Response to Low-Dose Dobutamine of Dysfunctional Myocardium in Patients With Ischemic Cardiomyopathy

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Background—There is evidence that exercise training can induce myocardial and coronary adaptations in both animals and humans. However, the significance of these potentially important changes remains to be determined in patients with ischemic heart disease and left ventricular (LV) systolic dysfunction.

Methods and Results—To investigate whether exercise training can improve thallium uptake and the contractile response to low-dose dobutamine of dysfunctional myocardium, 46 patients (42 men, 4 women; mean age, 57±9 years) with chronic coronary artery disease and impaired LV systolic function (ejection fraction <40%) were randomly assigned to two groups. The exercise group (n=26) underwent exercise training at 60% of peak oxygen uptake for 8 weeks. The control group (n=20) was not exercised. At baseline and after 8 weeks all patients underwent an exercise test with gas exchange analysis and stress echocardiography using low-dose dobutamine (5 to 10 μg/kg per minute) followed by thallium myocardial scintigraphy. Coronary angiography was performed in 23 patients at baseline and after 8 weeks. After 8 weeks, peak oxygen uptake increased significantly only in trained patients (24%). Significant improvements in the contractile response to dobutamine and thallium activity were observed in trained patients (28% and 31%, respectively; trained versus control: $P<.001$ for both). In a subgroup of trained patients, both improvements were correlated with an increase in the coronary collateral score ($P<.005$ and $P<.001$, respectively).

Conclusions—Moderate exercise training improves both thallium activity and the contractile response of dysfunctional myocardium to low doses of dobutamine in patients with ischemic cardiomyopathy. The implication of this study is that even a short-term exercise training may improve quality of life by improvement of LV systolic function during mild-to-moderate physical activity in patients with ischemic cardiomyopathy. **(*Circulation*. 1998;97:553-561.)**

Key Words: exercise ■ thallium ■ contractility ■ myocardium ■ ischemia ■ cardiomyopathy

Formal exercise training in patients with coronary artery disease and a prior myocardial infarction has established benefits, including improvement of left ventricular systolic function.[1–3] The mechanisms contributing to this adaptation are not well defined. However, one hypothesis suggests that β-adrenergic stimulation enhances contractile response.[4] An alternative explanation is that coronary vascular changes improve function in chronically hypoperfused myocardium.[5] In fact, collateral growth in the presence of a critical coronary stenosis has been demonstrated after exercise training in animals[6,7] and humans.[8] While these adaptations may enhance metabolic activity and contractile reserve of hibernating myocardium, the clinical and prognostic significance of the potentially favorable effects of exercise must be confirmed.

The ability of positron emission tomography to identify viable myocardium in patients with wall motion abnormalities at rest has been compared with that of dobutamine stress echocardiography or thallium scintigraphy.[9] Nuclear cardiology techniques have the unique potential to distinguish viable tissue on the basis of perfusion, cell-membrane integrity, and metabolic activity, while dobutamine echocardiography provides information on inotropic reserve of dysfunctional segments. The former are more sensitive, while the latter is more specific in identifying myocardial viability; the concordance between the two methods ranges from 68% to 79%.[10,11]

Low-dose dobutamine stress echocardiography has been compared with positron emission tomography in detecting viable postischemic myocardium, giving excellent results.[11] Low doses of dobutamine can determine inotropic stimulation with minimal increase in heart rate and reduced onset of myocardial ischemia as well as ventricular arrhythmias. By comparing pretraining and posttraining responses to low-dose dobutamine infusion, we should be able to obtain differential information about the effects of moderate exercise training on

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indexes of left ventricular systolic performance as well as postischemic myocardial viability.

In the past, Wyatt et al[12] and Spina et al[4] reported increased inotropic response to high doses of catecholamines after endurance exercise training. However, it is not clear whether the enhanced contractility after training can be observed in patients with ischemic heart disease by using small doses of dobutamine and whether the identification of dysfunctional but viable myocardium can predict the improvement in contractility after moderate exercise training.

The purpose of the present study was to determine whether a 2-month exercise training program of moderate intensity (60% of peak oxygen uptake) can improve thallium activity and the contractile response to low-dose dobutamine of dysfunctional myocardium in patients with coronary artery disease and depressed left ventricular function. We hypothesized that both adaptations are related to a training-induced improvement of coronary collaterals and that a combination of these adaptations may improve left ventricular contractility in response to β-adrenergic stimulation.

Methods

Fifty patients with coronary artery disease and depressed left ventricular (LV) systolic function were initially enrolled. Patients were in sinus rhythm and clinically stable in the last 3 months. All patients gave informed written consent. The Ethical Committee at the Lancisi hospital approved the protocol. All patients had had a myocardial infarction 6 or more months before enrollment. Patients were excluded if they had unstable angina, severe (New York Heart Association functional class IV) or uncompensated congestive heart failure, high-grade arrhythmias, significant renal insufficiency (serum creatinine $\geq$2.2 mg/dL), known contrast allergies, and any orthopedic or neurological illness that limited their ability to exercise. Pregnant patients were also excluded. Patients were randomly assigned to one of two matched groups: an exercise group (n=26) and a control group (n=24). At baseline and after 8 weeks, all patients underwent an exercise test with gas exchange analysis, thallium scintigraphy with a low-dose dobutamine stress-redistribution-reinjection protocol, and a two-dimensional echocardiogram during the same dobutamine infusion. Four control patients were excluded because of inadequate echocardiographic images. All patients underwent coronary angiography shortly before enrollment. All patients were asked to have a second coronary angiography after 8 weeks. However, refusal to undergo the second coronary arteriogram after 8 weeks was not an exclusion criterion (Table 1).

Exercise Training

The exercise group underwent a supervised program of physical training at 60% of the peak oxygen uptake three times a week for 8 weeks. Each exercise session lasted about 1 hour and consisted of an initial warming up with calisthenics and stretching exercises (15 minutes), followed by stationary cycling on an electromagnetically-braked cycle ergometer (Ergometrics 800S) for 40 minutes. Care was taken to avoid training intensities above or below the initial target. Periodic adjustments of exercise intensity were made according to individual progression. All patients were monitored by means of telemetry. Control patients were recommended to avoid regular exercise at home and any form of physical activity with caloric expenditure >80% of peak oxygen uptake measured during the baseline cardiopulmonary exercise test. A list of acceptable and unacceptable home physical activities, based on calculated metabolic equivalents, was provided to each patient in both groups. Every 2 weeks, clinical condition of each patient was evaluated by a cardiologist in the hospital.

Cardiopulmonary Exercise Test

At baseline and after 8 weeks, all patients performed a symptom-limited incremental exercise test with gas exchange analysis. Patients pedaled in an upright position on an electronically braked cycle ergometer (Sensormedics 800 S). Every minute, a 12-lead ECG was recorded and blood pressure was measured. Gas exchange measurements were obtained breath-by-breath using a metabolic chart (Sensormedics 2900 Z). Ventilatory threshold was calculated by the V-slope method.[13] Peak oxygen uptake was the average oxygen uptake over the last 15 seconds of exercise. The oxygen pulse (oxygen uptake/heart rate) was calculated at the same absolute as well as relative submaximal exercise intensities (20, 40, and 60 W and 25%, 50%, and 75% of peak work rate, respectively), and at peak exercise. This measurement is useful because it equals the product of stroke volume and arterial-venous (A-V) O_2 difference.

TABLE 1. Clinical Characteristics

	Exercise Group	Control Group
No.	26	20
Male/female	24/2	18/2
Age, y	57±8*	56±9*
Myocardial infarction, No.	26	20
Anterior	14	11
Inferior	6	5
Lateral	1	1
Ant+Inf	5	3
Peak Vo_2, mL/kg per minute	17.0±3*	18.1±4*
Ejection fraction, %	35±6*	34±8*
Diseased coronary vessels, No.	2.5±1.2*	2.4±0.9*
Left anterior descending coronary	16	12
Right coronary	7	9
Circumflex coronary	7	5
Collateral score	0.75±0.7*	0.91±0.7*
Medications, No.		
Nitrates	24	18
Diuretics	10	9
ACE Inhibitors	22	18
Aspirin	16	14
Warfarin	10	6

*Values are mean±SD.

Dobutamine Stress Echocardiography

Under continuous ECG monitoring, dobutamine was infused into a peripheral vein in an incremental regimen of 5 μg/kg per minute every 5 minutes to a maximum of 10 μg/kg per minute. Systolic blood pressure was taken at baseline and every 5 minutes. End points of the study included a significant new wall motion abnormality, significant ST-segment changes, that is, ST-segment depression or elevation of $\geq$1 mm in two contiguous leads, significant symptoms or arrhythmias, or completion of the protocol. Two-dimensional echocardiography from standard views was continuously recorded using a wide-angle mechanical scanner (Challenge-ESAOTE).

Regional Left Ventricular Function

Regional wall thickening was assessed following the recommendations of the American Society of Echocardiography.[14] A 15-segment model was used for analysis in order to facilitate the comparison with myocardial segments analyzed with thallium scintigraphy. We considered both wall motion and wall thickening for analysis.[15] However, since endocardial excursion in itself is not a good index of contraction given the translocation and rotation of the heart during the cardiac cycle, particular attention was paid to systolic wall thickening rather than endocardial excursion. Regional systolic wall thickening was visually graded using a

semiquantitative scoring system wherein 1=normal or hyperkinetic, 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 limits for each segment for a normal population database from our laboratory. Change from score 4 at rest to score 3 with dobutamine was considered as unchanged wall thickening, while change from score 3 at rest to score 2 or 1 during infusion and/or from 2 at rest to 1 was considered improved wall thickening. A positive contractile response to dobutamine was defined as an improvement in systolic wall thickening in at least 2 adjacent segments and a ≥20% reduction in wall thickening score index.

After 8 weeks, improvement in the contractile response to dobutamine, as compared with the initial study, was defined as a reduction in systolic wall thickening grade by 1 or more at peak infusion in at least two adjacent segments and/or a ≥20% reduction in wall thickening score.

Data Analysis

Each study was recorded on a super-VHS videotape (Panasonic AG 7700) both conventionally and in slow motion cineloop format by using the internal memory mode of the scanner to aid wall motion analysis. Images were then entered into a personal computer (Macintosh Quadra 660 AV) to obtain simultaneous side-by-side displaying of rest and stress images for any individual study as well as any set of images taken at similar infusion times during initial and follow-up studies. Left ventricular end-diastolic (onset of the ECG QRS) and end-systolic (the videotape frame just prior to the mitral valve opening) images were identified on the videotape recording in which all or nearly all of the endocardium and epicardium could be visualized on a single stop-frame image. The endocardium of the end-diastolic image and the endocardium of the end-systolic image were visually identified and manually digitized. The left ventricular apex was defined as the point on the endocardial contour furthest from the midpoint of the mitral valve plane and the left ventricular long axis as a line connecting the mitral plane midpoint and the apex.

Left Ventricular Systolic Function

Measurements of left ventricular end-diastolic volume (EDV) and left ventricular end-systolic volume (ESV) were obtained from the apical view using a modified single-plane Simpson's rule from which left ventricular ejection fraction was automatically calculated as (EDV−ESV)/EDV · 100. Left ventricular end-systolic wall stress (σes) was calculated, as described by Grossman et al[16] as $\sigma es(g/cm^2) = P \cdot r/2\,hours \cdot (1+h/2r)$, where P is systolic blood pressure, r is end-systolic radius (end-systolic diameter/2) and h is posterior wall thickness at end systole. To calculate end-systolic wall stress, measurements were obtained from the parasternal short axis view. The end-diastolic diameter was considered the distance between the left ventricular endocardial border of interventricular septum and the posterior endocardium at the onset of the QRS complex of the simultaneously recorded ECG. The end-systolic diameter was the distance between the endocardial border of interventricular septum and the posterior wall endocardium measured at the end of T wave on ECG recording. To control for the confounding effect of afterload, the rest-to-peak dobutamine changes in end-systolic volume index were compared at similar levels of σes changes both before and after training. Analysis of the systolic blood pressure–end-systolic volume index[17] and the σes–end-systolic volume index relationships were performed at rest and peak dobutamine infusion both on study entry and follow-up to assess 1) the response of left ventricular contractile performance to small doses of dobutamine and 2) the effect of exercise training on this response.

Two independent experienced observers evaluated the echocardiographic images in a blinded manner from videotape playback. The observers were also blinded with regard to the patient's identity and allocation into the training or control group. The two observers disagreed in 7% of the studies; a third independent experienced cardiologist resolved differences in interpretation.

Thallium Scintigraphy

At the end of dobutamine infusion, 3 mCi of thallium was injected into an antecubital vein. Planar ^{201}Tl imaging was performed in the fasting state (Apex Elscint). Images were acquired using a parallel-hole collimator. Image acquisition started within 5 minutes in the anterior 45° left anterior oblique and 70° left anterior oblique. Redistribution studies were performed 3 hours after stress imaging. After 24 hours, 1 mCi of thallium was reinjected in patients with scintigraphic evidence of a fixed defect after the redistribution studies. After reinjection, a third set of images was reacquired within 15 minutes.

Data Analysis

The left ventricle on each view was divided into 5 segments (15 segments in total). Planar images were interpreted qualitatively by visual analysis with the aid of computer quantification.[18,19]

Qualitative Analysis

Each segment was visually graded on a five-point scale: 0 (normal uptake), 1 (mild reduction), 2 (evident reduction), 3 (severe reduction), and 4 (absent uptake). We defined the thallium activity score index as the sum of thallium score of each myocardial segment divided by the number of segments analyzed. After automatic normalization to the maximal activity of stress images, each set of three planar views were simultaneously displayed. "White on black" display using a linear gray scale was used. The video display was automatically arranged by computer program in order to obtain both uniformity of imaging presentation on different studies and reproducibility of analysis.

Segments with a score ≥2 on stress images were considered abnormal. Segments with an initial perfusion abnormality were considered completely reversible when the score was <2 on delayed scans and partially reversible when score improved by one grade on delayed images. Defects with no change in thallium score between initial and delayed images were considered irreversible. Myocardial segments with irreversible defects were considered to have enhanced thallium activity after reinjection as compared to redistribution study if regional score decreased by one or more.

Quantitative Analysis

After background correction, the relative distribution of ^{201}Tl in the myocardium was quantitatively assessed using circumferential count profiles analysis.[18,19] In each patient, the myocardial region with the maximum counts on thallium scintigraphy was used as the normal reference region for that patient. Circumferential profiles were normalized to the segment with the highest tracer activity and compared with those of a normal database from our laboratory. The thallium activity in all other myocardial segments was expressed as a percentage of thallium activity measured in the reference region for each stress, redistribution, and reinjection image. Severity of perfusion abnormalities was assessed by computing the average percent reduction of the relative myocardial thallium uptake below the lower limit of normal (mean−2 SD). Thallium activity <85% of the maximum was considered a perfusion defect, also considering previous measurements of reproducibility obtained in our laboratory. A perfusion defect was reversible when relative thallium activity increased by ≥10% in the redistribution image. Defects were completely reversible if thallium activity was ≥85% relative to the reference region and partially reversible if relative thallium counts remained <85% of the maximum activity. Defects were considered irreversible if thallium activity was unchanged or increased <10% on redistribution studies. Similar methods were followed for analysis of images after reinjection. Enhanced thallium activity after reinjection was defined an increase in relative thallium counts >10% compared with the redistribution studies, while thallium activity was considered unchanged if it was unaltered or increased by <10%.

Myocardial segments with reduced thallium uptake on the stress images were considered viable when thallium activity increased by at least one grade in the redistribution or reinjection images. If a reduced thallium activity on the stress images did not change during redistribution or reinjection, the segment was considered nonviable.

Thallium images obtained after 8 weeks were read using the same methods as the baseline study and compared side by side to the corresponding pretraining images. Improvement in thallium uptake, as

TABLE 2. Changes in Metabolic and Hemodynamic Variables

	Exercise Group			Control Group			
	Study Entry	8 Weeks	Δ	Study Entry	8 Weeks	Δ	*P*
Peak oxygen uptake, mL/kg per minute	17.0±3	21.0±4	−4.2±2.6	18.1±4	17.1±2.5	1±3.1	.001
Ventilatory threshold, mL/kg per minute	10.6±2.3	13.8±1.7	−3.1±2.4	10.8±2.4	10.5±2	0.38±0.75	.001
Ventilation, L/min	47±7	63±13	−16±10	52±14	51±13	1±3.1	.001
Respiratory exchange ratio	1.13±0.06	1.15±0.07	−0.02±0.08	1.13±0.05	1.13±0.05	0.005±0.02	.26
Work rate, W	101±23	128±29	−27±16	108±31	102±28	6.5±6.6	.001
Resting heart rate, bpm	84±9	76±8	8±6	77±8	79±10	−2±5	.001
Peak heart rate, bpm	132±12	139±10	−7.5±7.8	139±10	138±12	0.64±5	.008
Peak systolic blood pressure, mm Hg	158±19	176±28	−17.5±20	166±34	159±24	6.8±19	.007

P refers to comparison of changes in any variables between exercise and control groups.

compared with the initial study, was defined as an increase in thallium activity by one or more grades in any of the three acquisition imaging series.

The serial thallium images were visually analyzed by two independent observers using consensus readings. A third observer was asked to resolve the difference when agreement was not achieved. A consensus decision was obtained in all cases.

Coronary Angiography

Coronary angiography was performed by Judkins' technique.[20] Multiple projections including cranial and caudal-angulated views were obtained (Optimus M200, Philips, The Netherlands). Coronary cineangiographic films were analyzed by a computer-assisted edge detection coronary quantitative system (Digital Cardiac Imaging, Philips). Images of interest were digitized and then processed. A stenosis was considered hemodynamically significant if a ≥50% reduction in luminal diameter was detected. After 8 weeks, changes in coronary stenoses were scored as follows: 0=unchanged (<10% change); +1=progression (>10% change); −1=regression (negative difference of >10%). The extent of perfusion by collateral vessels was scored as follows[21]: 0=absent (no collaterals); 1=some (incomplete delayed filling of the infarct-related artery); 2=well-formed (delayed filling of the infarct-related artery); and 3=abundant (the infarct-related artery is completely filled as the injected artery). Two experienced interventional cardiologists independently interpreted the studies in a blinded manner. Disagreement between the two readers was resolved by consensus.

Statistical Analysis

The effects of exercise training on the contractile response to dobutamine, thallium uptake, and coronary collaterals were analyzed on the basis of patients. Therefore, we created a score as follows: 0=no change; +1=improvement; and −1=deterioration. Then, the change in this score as a function of exercise training versus control was analyzed using a nonparametric test (Mann-Whitney rank test). Fisher's exact test was used to determine whether the response of the systolic wall thickening score index during dobutamine infusion at baseline predicted improvement in contractility after exercise training. McNemar's test was performed to compare sensitivities, specificities and predictive values between thallium scintigraphy and dobutamine stress echocardiography. Correlation coefficients were used to assess relationships between variables. Statistical significance was assumed for a value of $P<.05$. Values are expressed as mean±SD.

Results

All patients completed the protocol. The compliance was excellent in both groups. All patients in the training group performed the 24 scheduled sessions. Two patients of group T had hypotension during recovery from cycling, which promptly resolved with supine positioning. Three patients of group T had sporadic ventricular premature contractions during the initial sessions (first 2 weeks). No patient had angina during the training sessions. In the control group, 2 patients reported short episodes of palpitations (twice and three times in 2 months, respectively), not requiring changes in medications. One control patient had unstable angina on week 4 and was hospitalized. No other adverse events were reported.

After 8 weeks, peak oxygen uptake, ventilatory threshold and peak work rate were all increased in trained patients (24%, 30%, and 27%, respectively) (Table 2). Ventilation at peak exercise also increased after exercise training, while respiratory exchange ratio was unchanged. No changes were observed in the controls. The oxygen pulse was significantly higher at the same absolute exercise intensity after training by an average of 16% ($P<.01$). At the same relative exercise intensity, O_2 pulse was also increased (average 23%; $P<.001$). The heart rate response to the same relative intensity was unchanged. No changes in O_2 pulse were observed in the control group.

Dobutamine Stress Echocardiography

On study entry, the exercise group showed a positive response to dobutamine in 141 of the 257 segments with resting wall motion abnormalities (55%) (Table 3). This response occurred more frequently among initially hypokinetic (105 of 145) segments than it did among akinetic (32 of 68) or dyskinetic (4 of 44) segments. The control group had similar proportion of segments with contractile response (111 of 192).

After 8 weeks, in trained patients, of 252 segments with resting wall motion abnormalities, 178 (71%) demonstrated improved contractility compared with 55% (141 of 257) with positive inotropic response on initial evaluation. Of the abnormal segments with contractile response, 125 were hypokinetic, 48 akinetic, and 5 dyskinetic. On both initial and final dobutamine stress echocardiographic studies, all the changes in systolic wall thickening were observed during the first 5 minutes of infusion. At peak infusion, we did not have any further response. Of interest, only the trained patients had a 28% improvement in the systolic wall thickening score index at peak infusion, indicating an increased inotropic response to low-dose dobutamine after exercise training. The improvement in systolic wall thickening score index was related to an increased number of dysfunctional myocardial segments with an enhanced inotropic response to dobutamine. As shown in Table 3, the improvement in the contractile response was more evident among initially akinetic and hypokinetic than dyskinetic segments (+29%, 11%, and 4%, respectively). The inotropic response to dobutamine

TABLE 3. Echocardiographic and Scintigraphic Responses to Dobutamine on Study Entry and After 8 Weeks in the Exercise and Control Groups

	Exercise Group						Control Group					
	Study Entry			8 Weeks			Study Entry			8 Weeks		
		Peak			Peak			Peak			Peak	
	Rest	CS+	CS−	Rest	CS+	CS−	Rest	CS+	CS−	Rest	CS+	CS−
Stress echo												
Hypokinesis	145	105	40	147	125	22	128	89	39	130	92	38
Akinesis	68	32	36	63	48	15	52	20	32	51	18	33
Dyskinesis	44	4	40	42	5	37	12	2	10	14	5	9
Total (%)	257 (66)	141 (55)	116 (45)	252 (65)	178 (71)	74 (29)	192 (64)	111 (58)	81 (42)	195 (65)	115 (59)	80 (41)
	V		nV	V		nV	V		nV	V		nV
Thallium scintigraphy												
Normal uptake	48		...	45		...	38		...	36		
Complete reversibility	22		...	77		...	30		...	33		...
Partial reversibility	106		...	76		...	62		...	65		...
Late reversibility	17		...	26		...	10		...	10		...
Total (%)	193 (75)		64 (25)	224 (89)		28 (11)	140 (73)		52 (27)	144 (74)		50 (26)

CS+ indicates contractile improvement; CS−, no contractile improvement; V, viable myocardium; and nV, nonviable myocardium.

was unchanged in the unexercised control patients. Since the doses of dobutamine used in both initial and follow-up studies were identical, the observed improvement in the inotropic response to dobutamine in the training group seems likely due to exercise training itself.

Left Ventricular Systolic Function

After 8 weeks, 22 of 26 trained patients and only 1 of 20 control patients showed improvement in ejection fraction and end-systolic volume index at peak dobutamine (trained versus control: $P<.001$ for both). The ejection fraction at rest was not significantly different in both groups after 8 weeks (Table 4). As shown in Fig 1, left ventricular end-systolic volume index at peak dobutamine was significantly lower after training than before, while the systolic blood pressure at peak dobutamine increased after training. This results in a shift of the end-systolic pressure-volume relationship upward and to the left. In untrained patients no significant changes in the pressure-volume relationship occurred (trained versus control: $P<.001$).

Left ventricular end-systolic wall stress decreased on study entry and after 8 weeks in trained patients (study entry: rest 89±6 g/cm^2; peak dobutamine, 71±5 g/cm^2; after training: rest, 87±6 g/cm^2; peak dobutamine, 70±5 g/cm^2). However, from the relation between pretraining and posttraining changes in rest-to-peak dobutamine end-systolic volume index and comparable changes in rest-to-peak end-systolic wall stress, we found a greater decrease in end-systolic volume index only in trained patients (pre: −10±6 mL/m^2; post: −23±9 mL/m^2; $P<.001$). Since no concurrent changes in end-diastolic volume index at comparable levels of end-systolic wall stress were observed, the effects of exercise training on left ventricular contractility were likely unrelated to changes in either preload or afterload.

Thallium Scintigraphy

At baseline, in the training group, of the 257 myocardial segments with resting wall thickening abnormalities, 193 (75%)

TABLE 4. Left Ventricular Response to Dobutamine on Study Entry and After 8 Weeks in the Exercise and Control Groups

	Study Entry			8 Weeks		
	Rest	5 min	10 min	Rest	5 min	10 min
Exercise group						
End-systolic volume index, mL/m^2	73±8	64±6	63±5	69±8	53±7	46±11*
End-diastolic volume index, mL/m^2	112±9	105±7	101±7	109±10	94±9	92±9
Ejection fraction, %	35±6	39±5	38±6	37±7	44±9	50±8*
Systolic wall thickening score	2.4±0.9	1.87±0.7	1.8±0.7	2.2±0.8	1.5±0.7	1.3±0.6*
Control group						
End-systolic volume index, mL/m^2	72±8	68±12	63±10	75±9	70±10	64±9
End-diastolic volume index, mL/m^2	110±10	106±11	104±9	112±11	105±10	101±8
Ejection fraction, %	34±8	35±10	39±10	32±8	36±8	37±9
Systolic wall thickening score	2.3±0.8	1.8±0.8	1.8±0.9	2.1±1	1.8±1	1.7±1.2

*$P<.001$ vs changes in the control group after 8 weeks.

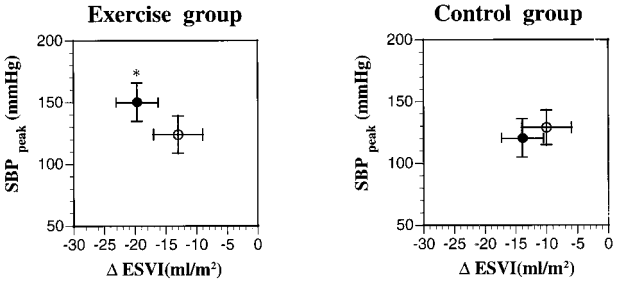

Figure 1. Effect of exercise training on systolic blood pressure–end-systolic volume index (SBP-ESVI) relationship. In the exercise group, an increase in SBP was accompanied by a reduction in ESVI from rest to peak dobutamine. The pressure-volume relationship was shifted upward and to the left ($P<.001$). No significant changes in the pressure-volume relationship were observed in the control group. ○, Baseline; ●, 8 weeks.

had normal or only mild to moderate reduction in thallium uptake, and 64 (25%) had severely reduced or absent thallium activity. A total of 48 of the 257 segments with resting wall motion abnormalities had normal thallium uptake on the stress images. Of the remaining 145 segments, 22 were completely reversible on the redistribution images and 106 were partially reversible; 17 had increased thallium uptake after reinjection. Of these 145 segments with reversible thallium defects, 77 segments received a score of 2, 60 a score of 3, and 8 a score of 4 on the stress images. Control subjects showed similar thallium activity scores (Table 3).

After 8 weeks, thallium activity improved in 21 out of 26 trained patients and only 1 control subject (trained versus control: $P<.001$). Of 252 segments with wall thickening abnormalities at rest, 224 (89%) were considered viable. Thallium activity score index improved by 31% after exercise training (from 2.6±0.3 to 1.8±0.2; $P<.001$) but did not change in the control group (2.5±0.5 versus 2.6±0.8; $P=.68$; trained versus control: $P<.001$).

Relation Between Stress Echocardiography and Thallium Scintigraphy

The number of segments considered viable on thallium imaging and showing improved contractile response to dobutamine increased significantly only in trained patients (from 131 to 170) (Table 5). By contrast, the number of segments considered nonviable on thallium imaging and showing no contractile response to dobutamine was reduced in the exercise group (from 61 to 34) but not in the control subjects. In the exercise group, the concordance between the two tests was 75% on initial studies and 81% on follow-up; in the control group, concordance was 76% and 78%, respectively.

Coronary Morphology and Collaterals

A total of 23 patients (12 trained and 11 control) repeated coronary angiography at the end of protocol. On baseline studies, the greater the collateral score, the greater was the reduction in systolic wall thickening score ($r=-.86$; $P<.001$) and thallium activity score ($r=-.74$; $P<.005$) in response to dobutamine infusion.

After 8 weeks, mean collateral score increased significantly only in the training group (baseline: 0.75±0.75; after training: 2.5±0.80) without concomitant changes in the severity of stenotic lesions. No changes were observed in the control group (baseline: 0.91±0.78; after 8 weeks: 0.82±0.79; training versus control: $P<.001$). Of 11 control patients, 9 had no change, 1 had a reduced score (from 2 to 1), and 1 a greater score (from 0 to 1) after 8 weeks (Fig 2). None of them had changes in wall thickening and thallium activity scores (trained versus control: $P<.001$). However, of 12 trained patients, all but 1 improved the collateral score, which correlated with improvements in wall thickening ($r=-.76$; $P<.005$) and thallium activity scores ($r=-.88$;$P<.001$) in response to dobutamine. An example of pretraining and posttraining thallium uptake, contractile response of dysfunctional myocardium and coronary collaterals for one representative patient is shown in Fig 3.

TABLE 5. Relation Between Stress Echocardiography and Thallium Scintigraphy on Study Entry and After 8 Weeks in the Exercise and Control Groups

	Thallium Imaging						
	Study Entry				8 Weeks		
	V	nV			V	nV	
Exercise group, n							
CS+	131	10	141	CS+	170	8	178
CS−	55	61	116	CS−	40	34	74
Total	186	71	257		210	42	252
Control group, n							
CS+	106	5	111	CS+	108	7	115
CS−	41	40	81	CS−	36	44	80
Total	147	45	192		144	50	195

CS+ indicates contractile improvement; CS−, no contractile improvement; V, viable myocardium; nV, nonviable myocardium. For explanations, see text.

Discussion

The results of the present study indicate that short-term exercise training of moderate intensity improves thallium uptake and the contractile response to low-dose dobutamine of dysfunctional myocardium and significantly increases exercise

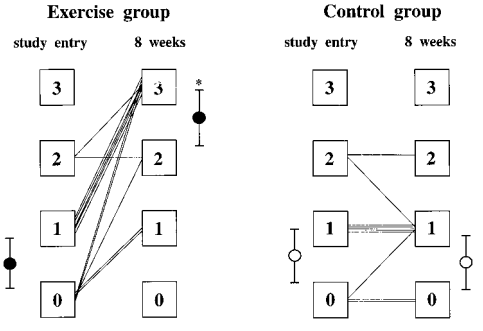

Figure 2. Collateral score on study entry and after 8 weeks in the exercise and control patients. Of 12 trained patients, all but 1 improved the collateral score after exercise training. Mean collateral score increased significantly (from 0.75±0.75 to 2.5±0.8). In contrast, of 11 control patients, 9 had no changes, 1 had a reduced score (from 2 to 1), and 1 a greater score (from 0 to 1) after 8 weeks. Mean collateral score was unchanged (trained vs control: $P<.001$). ●, Mean value±SD of collateral score in the exercise group at baseline and after 8 weeks. ○, Mean value±SD for collateral score in the control group at baseline and after 8 weeks. For details, see text.

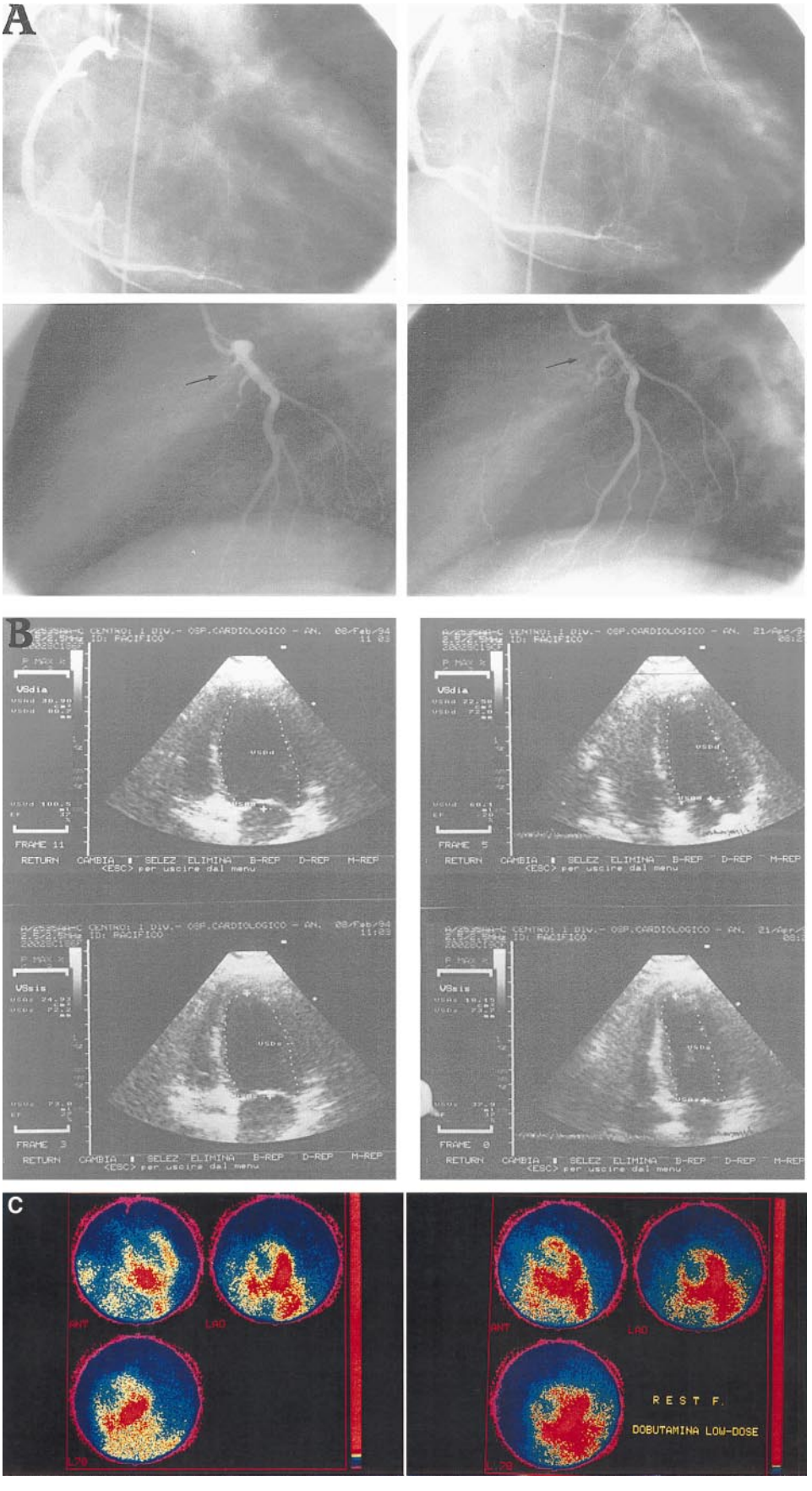

Figure 3. A 49-year-old man with a prior (7 month) anterior myocardial infarction and depressed left ventricular systolic function (resting ejection fraction, 28%). A (left), Baseline coronary angiogram in right anterior oblique (top) and left lateral (bottom) projections. The right coronary artery (RCA) is normal. In both images there is no opacification of the left anterior descending artery (LAD) due to total occlusion of its first tract. Collaterals were scarcely developed from RCA to LAD. A (right), After exercise training, evident collaterals developed from RCA to LAD, partly through the septal branches (top panel). On left lateral projection (bottom panel), the occlusion of the first tract of LAD was unchanged from the baseline study. B, Dobutamine stress echocardiography at baseline (left side: end diastole, top panel; end systole, bottom panel) and after training in apical four-chamber view. Images were taken at peak dobutamine infusion. At baseline, akinesis of apical anterior and inferior interventricular septum and apical, mid, and apical lateral segments was observed. After training, a reduction in end-systolic volume (−26%) (right side: bottom panel) as well as an improvement in the contractile response to dobutamine in all the above cited myocardial segments was observed. C, ^{201}Tl scintigrams from redistribution studies in the three standard projections at baseline (left panel) and after exercise training (right panel). On study entry, a marked reduction of thallium uptake was observed in the anterolateral, septal, and anterior segments. After training (bottom), an evident improvement in thallium uptake was observed in the basal and mid anterolateral segments.

tolerance in patients with ischemic cardiomyopathy. A posttraining increase in the collateral score, evident only in a subgroup of trained patients, was correlated with improvements in both thallium uptake and systolic wall thickening scores, indicating a linkage between training-induced effects on collateral circulation and both perfusion and contractility of dysfunctional myocardial segments. The improvement in the collateral score after 8 weeks of moderate exercise training was not accompanied by changes in the severity of coronary artery stenoses, suggesting that mechanisms other than regression of preexisting coronary artery obstructions can be involved in explaining this improvement.

Exercise Training and Left Ventricular Systolic Performance

The results of the present study are in agreement with those of previous reports in animals[12,22] and humans with no coronary artery disease[4] demonstrating an improvement in myocardial contractile response to β-adrenergic stimulation after exercise training. In this study, however, the enhanced myocardial contractility was observed after a shorter and milder exercise training program using a lower β-adrenergic stimulation. The improvement in left ventricular systolic function in response to low-dose dobutamine can be considered similar to responses to submaximal exercise. Therefore, the implication is that even a short-term, moderate-intensity exercise training may improve myocardial contractile function, which is a useful adaptation during daily physical activity in patients with severe coronary artery disease and depressed left ventricular function. On the other hand, the results of the present study cannot be extrapolated to exercise intensities approaching maximal effort because this adaptation may be lost.

Under basal conditions, ejection fraction and left ventricular volumes were unchanged after training (Table 4). This result was not surprising, since even exercise training regimens of higher intensities failed to improve basal contractility in patients with ischemic heart disease.[2,3,17] However, we found a greater reduction in end-systolic volume index in response to dobutamine at similar changes in end-systolic wall stress and a shifting of systolic blood pressure-end-systolic volume index relationship upward and to the left after exercise conditioning. These changes, in conjunction with no significant modification of end-diastolic volume index to the same doses of dobutamine, support the view that the improved myocardial contractility after exercise training is unrelated to either afterload or preload.

Those patients with higher inotropic response to dobutamine and greater thallium uptake at baseline seemed to benefit most from exercise training. In fact, in accordance with the results of a recent study,[23] we observed that the improvement in contractility after training was more marked among initially hypokinetic or akinetic than dyskinetic myocardial segments. The clinical and prognostic implication of the relationship between the presence of dysfunctional but viable myocardium at baseline and the magnitude of the improvement in LV contractility after moderate exercise training is not known at present. A preliminary report showed that patients with improved contractile response to low-dose dobutamine after moderate exercise training have a better outcome compared with sedentary patients with ischemic cardiomyopathy.[24]

The majority of myocardial segments with enhanced contractile response after physical conditioning had also an improvement in thallium uptake. Since the severity of coronary artery stenoses was unchanged after training, the improved myocardial perfusion should reflect structural and/or functional adaptations at the level of small coronary vessels. Improvements in myocardial contractility and perfusion may contribute to a higher stroke volume at submaximal and peak exercise, as previously demonstrated in patients with ischemic heart disease after intense exercise training.[25] As a matter of fact, we found a significant posttraining increase in O_2 pulse—a good approximation of stroke volume—at the same absolute as well as relative exercise intensities. This increase was essentially due to a higher oxygen uptake, being the heart rate response unchanged after training. Since the A-V O_2 difference has been demonstrated to remain stable at submaximal exercise intensities after training,[26] the observed increase in O_2 pulse can be interpreted as reflecting an increase in stroke volume at submaximal work rate exercise.

Exercise Training and Coronary Collaterals

The present results support the original observation by Eckstein[27] that chronic exercise promotes coronary collateral development. An interest observation from the present study is that physical training must not necessarily be intensive and longer than 2 months to improve coronary collaterals, and factors such as the type of exercise, medications or the extension of preexisting collaterals may play a role.

The development of collaterals was more marked in patients with a higher score at baseline, indicating that the initial level of coronary collateral expression is predictive of the final development. Although a direct relation between collateral development and severity of coronary stenoses has been recently described,[28] we obtained an improvement in collaterals without progression of coronary stenoses. Changes in coronary artery stenoses have been observed after longer and heavier exercise training programs.[29] It is possible that exercise training, by inducing intermittent myocardial ischemia, may provide the stimulus for vascular endothelial growth resulting in new vessel formation. Functional adaptations of coronary arteries may be also involved.[5] A greater capacity of coronary vessels to vasodilate in response to vasoactive substances may result in an increase in blood flow capacity and capillary exchange capacity in the territories of infarct-related arteries of trained patients.[30,31]

Limitations

We used low-dose dobutamine stress echocardiography in conjunction with thallium imaging to obtain simultaneous information on contractility and metabolic activity of myocardial segments. However, the use of low doses of dobutamine could lead to underestimation of viability by both techniques. Panza et al[10] showed that the entity of this phenomenon is very small. In their study, the vast majority of segments responded at doses $\leq$10 μg/kg per minute, and only 2.3% (4 segments out of 173) had contractile improvement at higher doses. Moreover, all methods generally underestimate viability.

We used peak systolic pressure rather than end-systolic pressure for calculation of end-systolic wall stress. Though the σ_{es} values reported here may be not precise in absolute terms,

we used the same approach for the calculation of σ_{es} at baseline and after exercise training. Thus the degree of error should be minimal.

Some degree of error can be derived from the use of planar technique, which poorly differentiates between a hypoperfused bed and a normally perfused underlying or overlying myocardium. However, planar imaging has been previously validated for measurement of residual thallium uptake on rest, stress and redistribution scintigrams, giving uniform consensus. Moreover, the planar data reported in this study are similar to those from other laboratories using positron emission tomography.[32]

Not all patients underwent second coronary angiography. However, when we compared the clinical characteristics of patients who repeated coronary angiography with those who did not, we found no significant differences.

In conclusion, moderate exercise training improves both thallium activity and the contractile response of dysfunctional myocardium to low doses of dobutamine in patients with chronic coronary artery disease and left ventricular systolic dysfunction without affecting the basal level of contractility. The results in a subgroup of patients indicate that the training-induced improvements in thallium uptake and contractility are correlated with increased coronary collaterals. The implication of these results is that even a short-term exercise training regimen may improve quality of life by improvement in left ventricular function during mild-to-moderate physical activity in patients with ischemic cardiomyopathy. More follow-up studies with larger populations are needed to confirm these preliminary results and evaluate whether these adaptations may favorably affect the outcome.

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