NCC/IBL aanvraagbon A082381321 24072006

Materiaal : Abx PPN: 840279833
Titel : Circulation : the journal of the American Heart Association
:
Auteur :
Deel/Supplem. :
Corporatie : American Heart Associationatabase:
Jaar/Editie : 1950 Extern nummer :
Uitgave : New York [etc.] Grune & Stratton [etc.]
Serie/Sectie :
Pag-ISSN/ISBN : 0009-7322

Plaatscode : 840279833 ; MG T 0248 ; rm ; 1952 V5 - 2003 V108

Jaar : 1995-00-00 Datum indienen : 21-07-2006 14:53
Volume : 91 Datum plaatsing : 21-07-2006 14:53
Aflevering : 11 Datum rappel : 18-08-2006
Leenvorm : KOPIE Particulier : N
Leveringswijze : EP Geplaatst bij : 0036/0001
Cooperatiecode : R Indiener : 0036/9999
Aanvrager : 0036/1008 U UKB
Eindgebruiker : UM12097 Aanvraagident. :
Auteur : Belardinelli, R. Aanvragerident. : MW C.W.C. DE ZWART
Artikel : Exercise training improves left ventricular diastolic filling in patie
Bladzijden : 2775-84
Bron :
Opmerking :

Indiener : 0036/9999 Stuur rekening : N
Aanvrager : 0036/1008 Eindgebruiker : UM12097
Aanvragerident.: MW C.W.C. DE ZWA Aanvraagident. :
Client :

Afleveradres Post Mw. C.W.C. de Zwart
Universiteit Maastricht

Epidemiologie, Postbus 616 (DEB1)
6200 MD MAASTRICHT

NL

Fax
Email conny.dezwart@epid.unimaas.nl
Ftp
Ariel
Telefoon

Factuuradres Clearing House

[1] origineel gestuurd [4] nog niet aanwezig [7] uitgeleend
[2] kopie gestuurd [5] niet aanwezig [8] wordt niet uitgeleend
[3] overige [6] niet beschikbaar [9] bibliografisch onjuist
[0] bij de binder

Aantal eenheden :
Aanvraagnummer : A082381321

Exercise Training Improves Left Ventricular Diastolic Filling in Patients With Dilated Cardiomyopathy

Clinical and Prognostic Implications

Romualdo Belardinelli, MD; Demetrios Georgiou, MD; Giovanni Cianci, MD; Nancy Berman, PhD; Leonard Ginzton, MD; Augusto Purcaro, MD

Background Patients with dilated cardiomyopathy (DCM) often have left ventricular (LV) diastolic dysfunction that can precede the development of systolic dysfunction. Recent reports showed that exercise training (ET) improves the exercise capacity of these patients. Although this improvement is primarily due to peripheral adaptations, the contribution of LV diastolic filling has not been well defined. The purpose of this study was to determine whether ET can induce changes in LV diastolic filling that can account for an increase in exercise capacity and whether these changes can influence prognosis.

Methods and Results We prospectively studied 55 consecutive patients (mean age, 55±7 years) with DCM. Patients were randomized into a training group (36 patients) or a control untrained group (19 patients) and matched for clinical and functional characteristics. All patients underwent a pulsed Doppler echocardiographic study, a radionuclide angiographic study, and a cardiopulmonary exercise test before and after a 2-month ET program. On the basis of the Doppler LV diastolic filling pattern at the beginning of the study, patients were prospectively divided into three subgroups: A (restrictive pattern), B ("normal" pattern), and C (abnormal relaxation pattern). In the trained group, peak V_{O_2} (+12%; $P<.0001$), peak workload (+8.5%; $P<.005$), and lactic acidosis threshold (+12%; $P<.0001$) were significantly increased after training without changes in LV ejection fraction. However, only subgroup C demonstrated significant improvement in peak V_{O_2} (+15%; $P<.005$). No changes were observed in the untrained group. In the trained subgroups a significant increase in rapid filling fraction (RFF), peak filling rate (PFR), peak early filling velocity (E), and E/A ratio was noted. A significant decrease in atrial filling fraction (AFF), peak atrial filling velocity (A), deceleration time of early filling velocity (EDT), and isovolumic relaxation time (IVRT) was observed only in subgroup C. No changes were found in untrained subgroups. A good correlation was found between Doppler and radionuclide LV diastolic filling parameters before and after training ($P<.0001$). Multiple stepwise regression analysis demonstrated that pretraining E/A ratio ($P<.0001$) and peak heart rate ($P<.0002$) were positive predictors of pretraining peak V_{O_2}. Posttraining increase in exercise tolerance ($P<.0001$) and increase in E/A ratio ($P<.0001$) were the strongest predictors of an increase in peak V_{O_2}. The independent predictors of cardiac events were a greater RFF and a shorter IVRT and EDT. Stepwise logistic regression showed that Doppler LV diastolic filling patterns are independent predictors of overall cardiac events ($P=.02$), and restrictive pattern has a worse prognosis compared with B ($P=.04$) and C ($P=.007$). However, ET did not reach statistical significance ($P=.54$) as a predictor of cardiac events.

Conclusions These data demonstrate that ET induces significant improvement in exercise capacity only in patients with DCM and a pattern of abnormal LV relaxation. The improvement in peak V_{O_2} is significantly correlated with an increase in peak early filling rate and peak filling rate as well as a decrease in atrial filling rate. Doppler echocardiography may be a valuable tool in the prognostic assessment of patients with DCM who will benefit from exercise training. (***Circulation.* 1995;91:2775-2784.**)

Key Words • exercise • echocardiography • prognosis • cardiomyopathy

Over the last decade, several studies have reported that exercise training improves the functional capacity of patients with dilated cardiomyopathy (DCM).[1-4] In these patients, several observations suggest that abnormalities of left ventricular (LV) diastolic function occur and often precede the development of systolic dysfunction.[5,6] Although improved LV systolic performance has been observed after training in patients with DCM that can partially account for the increase in peak oxygen consumption,[7,8] the contribution of LV diastolic function to the exercise-induced improvement in exercise capacity is not clear. Moreover, the magnitude and the prognostic significance of training-induced changes in LV diastolic abnormalities have not been defined.

Recently, measurement of transmitral blood flow velocity by pulsed Doppler echocardiography has been used to distinguish different patterns of LV diastolic dysfunction[9-11] and to provide information about prognosis in patients with DCM.[12,13] Although diastole is a complex sequence of interrelated events influenced by changes in loading conditions, myocardial contractility, and heart rate,[14-20] three main Doppler patterns of diastolic dysfunction have been described: restrictive, abnormal relaxation, and "normal."

Received October 5, 1994; revision received December 5, 1994; accepted December 18, 1994.

From Divisione di Cardiologia I, Ospedale Cardiologico "G.M. Lancisi," Ancona, Italy (R.B., G.C., A.P.); the Division of Cardiology, Saint John's Cardiovascular Research Center, Harbor-UCLA Medical Center, Torrance, Calif (D.G., L.G.); and the Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, Calif (N.B.).

Presented at the 43rd Scientific Sessions of the American College of Cardiology, Atlanta, Ga, 1994.

Correspondence to Demetrios Georgiou, MD, South Valley Cardiovascular Group, 700 W 6th St, Suite K, Gilroy, CA 95020.

TABLE 1. Clinical Characteristics

	All Patients		A		B		C	
	T	NT	T	NT	T	NT	T	NT
Patients (M/F)	36 (31/5)	19 (16/3)	17 (15/2)	8 (6/2)	7 (6/1)	4 (4/0)	12 (10/2)	7 (6/1)
Age, y	54.6±7	54.4±8	54±8	55±8	54.3±8	51±7	55.6±5	58.5±7
Diagnosis, No.								
DCM	11	7	7	4	1	1	3	2
ICM	25	12	10	4	6	3	9	5
NYHA class, No.								
II	25	13	12	6	5	3	8	4
III	11	6	5	2	1	1	5	3
Mitral insufficiency	24	11	16	7	3	2	5	2
LV ejection fraction, %	26.5±7	27.5±4	28±4	27.5±6	25.0±8	27.1±6	28.9±6	27.8±2
$\dot{V}O_2$max, mL·kg^{-1}·min^{-1}	15.5±1.3	15.7±1.5	15.4±1.2	14.8±1.6	15.9±1.2	16.2±1.4	16.0±1.0	16.4±1.2
Medications, No.								
ACE inhibitors	33	19	17	7	5	4	11	8
Digitalis	12	6	6	3	3	1	3	2
Diuretics	30	16	13	7	7	3	10	6
Aspirin	14	4	9	1	2	1	3	2
Warfarin	19	12	8	5	6	2	5	5

A indicates Doppler restrictive pattern; B, Doppler "normal" pattern; C, Doppler abnormal relaxation pattern; T, training group; NT, control (nontraining) group; DCM, idiopathic dilated cardiomyopathy; ICM, ischemic dilated cardiomyopathy; NYHA, New York Heart Association; LV, left ventricular; and $\dot{V}O_2$max, peak oxygen consumption.

These patterns reflect different clinical and hemodynamic profiles. Although a restrictive pattern has been found to be associated with a more severe disease and a worse prognosis, the clinical and prognostic significance of the other patterns is not clear. Moreover, the effects of exercise training on Doppler diastolic filling patterns has not been assessed.

The purpose of the study was first, to determine whether exercise training can induce changes in Doppler LV diastolic filling patterns; second, to examine the relationship between training-induced changes in diastolic filling profiles and aerobic capacity; and third, to determine whether these changes are associated with a different prognosis.

Methods

Patients

We studied 55 consecutive patients (55±7 years) with a history of chronic heart failure (CHF) for at least 6 months who were clinically stable for at least 3 months before enrollment in the study. DCM was diagnosed by M-mode echocardiographic demonstration of an increased LV end-diastolic diameter (LVEDD) of >5.8 cm, a fractional shortening of less than 25%, and an increased E point–septal separation of ≥0.8 cm (see Reference 26). Two-dimensional echocardiography showed a dilated nonhypertrophic LV (posterior wall and interventricular septum end-diastolic thickness of ≤1.2 cm) with diffuse wall motion abnormalities in all patients. Patients' clinical characteristics are summarized in Table 1. The etiology of CHF was idiopathic DCM in 18 patients and ischemic cardiomyopathy (ICM) in 37. Patients with alcoholic DCM, hypertensive CM, or other known etiologies were excluded. Unstable angina patients were excluded. Only two patients in the ICM group had stable angina. All patients with ICM had documented previous myocardial infarction. Thirty of the ICM patients underwent coronary angiography. LV ejection fraction (LVEF) was 27±7%. Mitral insufficiency was present in 35 patients and was mild in all 35. All patients had a reduced peak oxygen uptake (15.6±1.3 mL·kg^{-1}·min^{-1}). Thirty-eight patients had New York Heart Association (NYHA) functional class II symptoms and 17 had functional class III symptoms. All patients were in sinus rhythm. Patients were excluded if they had myocardial infarction or unstable angina within the last 6 months. Other exclusion criteria were CHF with NYHA class IV symptoms, significant chronic obstructive pulmonary disease, hemodynamically significant valvular heart disease, uncontrolled hypertension, hypotension, severe anemia, arthritis, or any other orthopedic, peripheral vascular, or neurological disease that would limit their ability to exercise. Patients did not have pulmonary rales, and their exercise test was limited only by dyspnea or fatigue. Medications were not altered throughout the duration of the study.

The protocol was approved by the Research Committee of Lancisi Heart Hospital. All patients gave written informed consent.

Pulsed Doppler echocardiography, radionuclide angiography (RNA), and a cardiopulmonary exercise test were performed before and after the completion of the exercise training program.

Echocardiography

M-mode, two-dimensional, and pulsed Doppler echocardiographic examinations were performed with an ultrasound system combining a two-dimensional mechanical sector scanner (2.5 MHz) with a pulsed Doppler flow analyzer. Each patient was examined in the supine, left lateral position, acccording to the standards of the American Society of Echocardiography.[27] M-mode measurements included LVEDD, LV end-systolic diameter (LVESD), and fractional shortening. Measurements of left ventricular end-diastolic volume and left ventricular end-systolic volume were obtained from the apical view using a modified single-plane Simpson's rule from which LVEF was calculated. Images were recorded on videotape and interpreted by two experienced cardiologists blinded to each other's interpretation. All studies were read twice (once by each observer), and the values were averaged for analysis. The average values of the two measurements were used to categorize the patients into subgroups. Disagreement between the two readers occurred in 8% of the cases. The two cardiologists then reviewed the discordant studies and made a consensus decision.

Pulsed Doppler Mitral Flow Velocity Analysis

Care was taken to position the cursor line through a plane traversing the left ventricle from the apex to the mitral valve annulus in order to achieve the smallest possible angle between the LV inflow and the orientation of the ultrasound beam. The sample volume was set in the mitral orifice on the atrial side

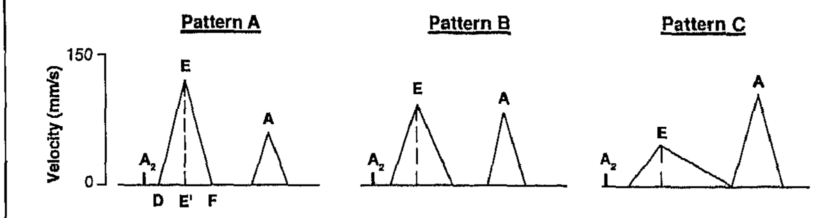

FIG 1. Patterns of left ventricular diastolic dysfunction on pulsed Doppler echocardiography. Pattern A, restrictive pattern; pattern B, "normal pattern"; pattern C, abnormal relaxation pattern; A_2, closure of the aortic valve; A_2D, isovolumic relaxation time; E, peak early filling velocity; A, peak atrial filling velocity; and E'F, deceleration time of peak early filling velocity.

between the mitral leaflet tips during diastole. In each patient, LV diastolic flow velocity waveforms from 5 cardiac cycles were obtained and averaged. The following measurements were obtained: peak velocity of early diastolic filling wave (E); peak velocity of late filling (A); deceleration time of E velocity (EDT); E to A ratio (E/A); and isovolumic relaxation time (IVRT), the interval between the end of aortic velocity profile (aortic closure) and the onset of mitral flow. Rapid filling fraction (RFF) was obtained by dividing rapid filling velocity area by the total diastolic filling velocity area, whereas the atrial filling fraction was obtained by dividing atrial filling velocity area by the total diastolic filling velocity area. The IVRT was measured from the apical five-chamber view, with the sample volume placed between the mitral valve and the LV outflow. The diastolic filling period was defined as the interval from the onset to the end of transmitral flow.

The patients were prospectively assigned to three subgroups before beginning the exercise training program, subgroups A, B, and C (Fig 1), based on the Doppler measurements of LV diastolic filling. Subgroup A consisted of patients with a restrictive Doppler pattern characterized by a short or normal IVRT ($\leq$50 ms), an increased early filling velocity (>105 cm/s) with a shorter deceleration time (<150 ms), and a decreased atrial filling velocity (<50 cm/s). Subgroup B was characterized by a normal Doppler pattern, with normal intervals and velocity profiles. Subgroup C comprised patients with abnormal relaxation characterized by a prolonged IVRT (>80 ms) and EDT (>190 ms), a reduced early filling velocity (<65 cm/s), and an abnormally increased atrial filling velocity (>90 cm/s). Color-flow imaging was performed to assess the severity of mitral regurgitation by grading for area, extent, and duration of regurgitant jet.[28]

Radionuclide Angiography

After the baseline Doppler echocardiographic study, patients underwent in vivo blood pool labeling using stannous pyrophosphate followed by 740 MBq ^{99m}Tc (15 to 20 mCi) 30 minutes later. Thirteen patients refused to undergo RNA studies, so radionuclide data are presented for 42 patients (Table 4). The system, previously validated in other centers,[29,30] has been also validated in our laboratory using a conventional gamma camera (Elscint) (unpublished data). When the optimal position of the nonimaging nuclear probe was identified, the skin was marked. Background radioactivity was then automatically estimated as 74% of end-diastolic counts. After each study, data were smoothed and then processed into a commercially available statistical software package. The time-activity curve was obtained by transforming data into frequency domains. From this curve and its first derivative, we determined the time of end diastole (maximal counts), the time of end systole (minimal counts), the normalized peak filling rate (maximal slope of the first derivative of the early filling portion), the peak early filling rate, and the peak atrial filling rate. Time to peak early filling rate and time to peak atrial filling rate were also calculated. At heart rates of more than 100 beats per minute, single peak filling rate was considered, and the time to single peak filling rate was also measured. Time from end systole to peak early filling rate and time from end systole to peak atrial filling rate were calculated and expressed in milliseconds.

Cardiopulmonary Exercise Test

All patients underwent a familiarization maximal exercise test on a cycle ergometer 4 to 15 days before the beginning of training. After 2 minutes of rest and 3 minutes of unloaded pedaling, the work rate was increased 5 W every 20 seconds (ramp) until volitional fatigue. Heart rate and blood pressure were monitored continuously. All patients repeated an exercise test with the same protocol on an electronically braked, computerized cycle ergometer with gas exchange analysis. The expired volume calibration was carried out by a 3-L syringe. Expired gases were analyzed breath-by-breath using a SensorMedics 2900 Z unit. The O_2 and CO_2 analyzers were calibrated automatically. During the tests, patients pedaled at a constant rate of 60 rpm. Peak oxygen uptake (peak V_{O_2}) was determined in the last 20 to 30 seconds of exercise. The lactic acidosis threshold was calculated by the V-slope method.[31] Body mass index was calculated in all patients before and after the end of the study as weight (kg)/height^2 (cm). In all patients, a cardiopulmonary exercise test was repeated with the same modalities 3 to 7 days after the last training session for trained patients and after a similar time for the untrained patients.

Exercise Training

Patients were randomly assigned to a training group or to an untrained control group. Randomization was performed with the table of casual numbers.[32] After a learning phase of 1 week, patients underwent a supervised program of exercise training (60% of peak V_{O_2}) three times per week for 8 weeks (in 24 sessions). Each session lasted about 1 hour, beginning with a warm-up phase of stretching exercise (15 to 20 minutes) followed by 40 minutes of work on a cycle ergometer. All patients were monitored by means of telemetry. A cardiologist was present during the whole session. The intensity of work was calculated on the basis of the value of heart rate corresponding to 60% of peak V_{O_2} achieved. Periodic adjustments of training intensity were made according to the individual patient's progression of exercise capacity. Care was taken to avoid intensities above the initial target.

Follow-up

The follow-up period began the day after the second Doppler echocardiographic study and ended at the time of study closure or with a cardiac event (death, heart failure, angina). The presence of rales and/or S_3 gallop constituted evidence of heart failure. Patients regularly visited our institution every 3 months. During the follow-up period, patients or their families filled in a standard questionnaire at home. Heart failure was graded as definite, possible, or unlikely, using clinical information.[33] Angina pectoris was scored using the Canadian Cardiovascular Society criteria.[34] Patients were followed for 12±6 months.

TABLE 2. Cardiovascular and Metabolic Variables in All Subroups Before and After Exercise Training

	T						NT					
	A (n=17)		B (n=7)		C (n=12)		A (n=8)		B (n=4)		C (n=7)	
Variable	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
$\dot{V}O_2$max, mL · kg^{-1} · min^{-1}	15.0±1.4	15.3±1.9	15.9±1.3	16.8±1.2	16.6±1.0	19.1±1.3*†‡	14.8±1.6	14.4±1.3	16.2±1.4	15.1±1.8*§	16.4±1.2	15.3±1.9§
LAT, mL · kg^{-1} · min^{-1}	10.4±1.2	11.6±2.2	10.4±1.0	11.1±1.3	11.1±3.0	12.3±2.0	10.5±1.1	9.9±1.2	10.2±1.0	10.7±1.4	11.0±1.1	11.0±1.1
pWL, W	103±8	108±15	101±5	114±9*†	109±11	125±12*†‡	99±8	98±6	114±18	103±10	112±12	106±17§
HR, rest, beats per minute	93±6	90±6*	91±5	88±6*	89±5†	84±6*†	95±10	92±9	93±12	91±6	86±11	83±5
HR, peak, beats per minute	134±12	133±9	138±11	146±9*	135±8	137±8†	134±16	130±11	140±13	143±5	138±12	133±13
SBP, rest, mm Hg	112±17	110±19	121±21	125±17	127±18	123±19	115±21	112±16	122±22	120±18	127±16	123±19
SBP, peak, mm Hg	156±28	152±21	168±31	172±34	161±22	165±26	149±20	151±21	162±19	158±16	158±27	161±19
DBP, rest, mm Hg	84±5	81±6	89±6	82±8	90±3	85±5	81±4	85±6	88±5	90±6	84±4	86±6
LVEF, rest, %	28.0±4	27.7±6	23.5±7	25.0±6	28±7	28±5	25.4±4	26.8±3	27.7±3	27±5	30±5	28±6

LAT indicates lactic acidosis threshold; pWL, peak workload; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; and LVEF, left ventricular ejection fraction. See Table 1 for other abbreviations.

Statistical Analysis

Data were entered into a commercially available statistical program (SAS Institute Inc) for analysis. A two-tailed paired t test was used for intragroup comparisons; an unpaired t test or ANOVA was used for intergroup comparisons. For comparisons among patterns before and after training, two-way ANOVA was used. The χ^2 test was performed to compare groups on categorical variables. Correlation of peak exercise oxygen uptake with metabolic and pulsed Doppler variables before training and after training using change was performed. Variables with significant correlations were then entered into a stepwise linear regression model to determine the best predictors of peak exercise oxygen uptake. Stepwise logistic regression of occurrence of events on pretraining and change in Doppler variables was performed. A stepwise survival model with all pretraining variables as covariates was also done using a single curve for all subjects. Cardiac mortality was compared among subgroups using log rank tests. Cardiac event–free (cardiac death, worsening heart failure, or worsening angina) curves for the trained and untrained groups and for different subgroups were computed using the Kaplan-Meier method. Data were expressed as mean±SD. Statistical significance was assumed for P values <.05.

Results

Clinical and Doppler Echocardiographic Characteristics

Clinical features are summarized in Table 1. Patients were well matched regarding age, diagnosis, NYHA functional class, presence and severity of mitral insufficiency, resting LVEF, peak oxygen uptake, and medications. Mitral insufficiency, when present, was mild in all patients. Idiopathic DCM was diagnosed in 31% of the trained group and in 37% of the untrained group. Ischemic cardiomyopathy was more frequent than DCM in both groups (trained, 69%; untrained, 63%).

Through pulsed Doppler echocardiography, a restrictive pattern of LV diastolic filling was found in 17 patients of the trained group and 8 patients of the untrained group (subgroup A). A "normal" pattern of Doppler LV diastolic filling (subgroup B) was observed in 7 patients of the trained group and 4 patients of the untrained group. A pattern of abnormal LV relaxation (subgroup C) was identified in 12 patients of the trained group and 7 patients of the untrained group. Subgroup A had DCM more frequently (11 of 25, 44%) than subgroup B (2 of 11, 18%) and subgroup C (5 of 19, 26%) (P<.005).

Effects of Exercise Training on Different Subgroups

Cardiovascular Parameters

Peak VO_2 was significantly increased after exercise training only in the trained patients with abnormal relaxation (pattern C) (+15%; P<.005) (Table 2). No changes were observed in the trained patients with pattern A, and only a modest increase occurred in the trained patients with pattern B (+6%; P=NS). This is not unexpected, since group B is too small to obtain statistically significant data for the peak VO_2. In all untrained groups, peak VO_2 was slightly reduced in the 2 months between the exercise tests. However, statistical significance was reached only in those with pattern B (−7%; P<.005). The lactic acidosis threshold was only slightly greater in trained patients after training, whereas it did not change in untrained subgroups. Peak exercise workload increased significantly only in the trained patients with "normal" filling (pattern B) and those with abnormal relaxation (pattern C) (+13% and +15%, respectively; P<.005 for both). Conversely, all untrained subgroups had a trend toward a reduced peak workload that did not achieve significance. Resting heart rate was slightly reduced in all trained subgroups, whereas no changes were observed in untrained subgroups. However, peak heart rate increased significantly only in the trained group with "normal" filling pattern (subgroup B). Both resting and peak exercise systolic blood pressures, diastolic blood pressure, and resting LVEF were unchanged in all trained and untrained subgroups.

Diastolic Filling Parameters

Doppler LV diastolic filling variables before and after exercise training and for the untrained patients over the same time period are summarized in Table 3. No significant changes in overall Doppler parameters were observed in the three untrained subgroups. Among the trained

TABLE 3. Doppler Left Ventricular Diastolic Filling Parameters in All Subgroups Before and After Exercise Training

	T						NT					
	A (n=17)		B (n=7)		C (n=12)		A (n=8)		B (n=4)		C (n=7)	
Variable	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
E, cm/s	107±13	104±17	85.2±14†	77±6†	62.5±17†‡	79±9*†	111±12	103±15	76±17†	76±17†	60.5±6†‡	64±11†‡§
A, cm/s	49.0±11	50.1±9	70.0±15†	60.0±7†	94.0±17†‡	66.5±16*†	51.2±6	55.3±8	58.0±14†	73.2±16†	94.2±6†‡	94.0±15†‡§
E/A	2.0±0.4	2.1±0.5	1.3±0.2†	1.2±0.3†	0.7±0.2†‡	1.2±0.4*†	2.2±0.3	1.9±0.5	1.2±0.5†	1.1±0.5†	0.6±0.2†‡	0.7±0.2†§
EDT, ms	140±20	130±28	160±20†	158±50	239±30†‡	190±32*†	136±23	141±27	176±44†	174±31†	242±28†‡	232±41†‡§
IVRT, ms	43±10	38±12*	63±8†	58±12†	87±6†‡	63±11*†	42.5±10	42.5±10	64±11†	64±11†	92±8†‡	87±12†‡§
DFP, ms	334±60	364±68*	384±44	442±68*†	367±136	536±106*†‡	321±55	329±65	345±48	360±56§	401±73	458±82§
RFF, %	69.6±8	67.0±7*	64.0±7	65.5±4	45.0±6†‡	61.0±7*†	67.0±14	67.6±12	66.0±18	65.0±115	48.0±8†‡	48.0±8†‡§
AFF, %	24.0±8	26.0±6	26.5±7	26.8±3	43.0±7†‡	30.0±6*†	27.0±13	24.0±11	29.0±15	28.4±8	53.5±5†‡	45.0±9†‡§

E indicates peak early filling velocity; A, peak atrial filling velocity; EDT, deceleration time of E; IVRT, isovolumic relaxation time; DFP, diastolic filling period; RFF, rapid filling fraction; and AFF, atrial filling fraction. See Table 1 for other abbreviations.

*$P<.005$ vs before training; †$P<.005$ BT vs AT, CT vs AT, BNT vs ANT, CNT vs ANT; ‡$P<.005$ CT vs BT, CNT vs BNT; §$P<.05$ BNT vs BT, CNT vs CT. Data are mean±SD.

subgroups, the most significant changes before and after training were observed in subgroup C, those with initial abnormal relaxation (Fig 2). In this subgroup, peak early filling velocity was significantly increased (+26%; $P<.005$), whereas peak atrial filling velocity was significantly reduced (−23%; $P<.005$) by training, so that the E/A ratio was increased (+70%; $P<.005$). The deceleration time of peak early filling velocity was significantly reduced only in this subgroup (−21%; $P<.005$). The isovolumic relaxation time was significantly shorter after training in the patients with the restrictive pattern (subgroup A) and those with abnormal relaxation (subgroup C) and was unchanged in those with a "normal" pattern (subgroup B). Diastolic filling time increased significantly in all trained subgroups, and the increase was greatest in the patients with abnormal relaxation compared with the other two subgroups. After training, the rapid filling fraction increased (+35%; $P<.005$) and atrial filling fraction decreased (−30%; $P<.005$) only in the patients with abnormal relaxation. No changes were observed in untrained subgroups.

Measurements from Doppler echocardiography and radionuclide technique were similar (Table 4). Correlation coefficients computed in all subjects (before and after exercise training) were as follows: rapid filling fraction, r=.71, .75; atrial filling fraction, r=.85, .83; time from aortic valve closure to peak early filling velocity, r=.69, .70; time from aortic valve closure to atrial filling velocity, r=.82, .74. P values were <.0001 for all correlations.

Exercise Training

No significant cardiovascular events were observed during the training sessions, and no patients were withdrawn from the study. One patient had a self-limited episode of atrial fibrillation during cycling, spontaneously converting to sinus rhythm after 10 minutes of rest. Sporadic ventricular extrasystoles were observed in 11 patients during cycling and in 5 patients during early recovery. Two patients had hypotension at the end of cycling, which promptly resolved by resting supine for a few minutes.

Outcome

Table 5 shows a summary of cardiac events during the follow-up. Of the 55 patients, 23 overall (41.8%) had cardiac events (cardiac death, worsening heart failure, and/or worsening angina pectoris) during the follow-up. Eight patients (14.5%) had worsening of angina pectoris. In 6 patients, angina was classified as Canadian class III and in 2 patients as Canadian class IV. Nine patients (16%) had heart failure, but hospitalization was required in only 4 of them. Six patients died, 2 of them suddenly. There were no significant differences between

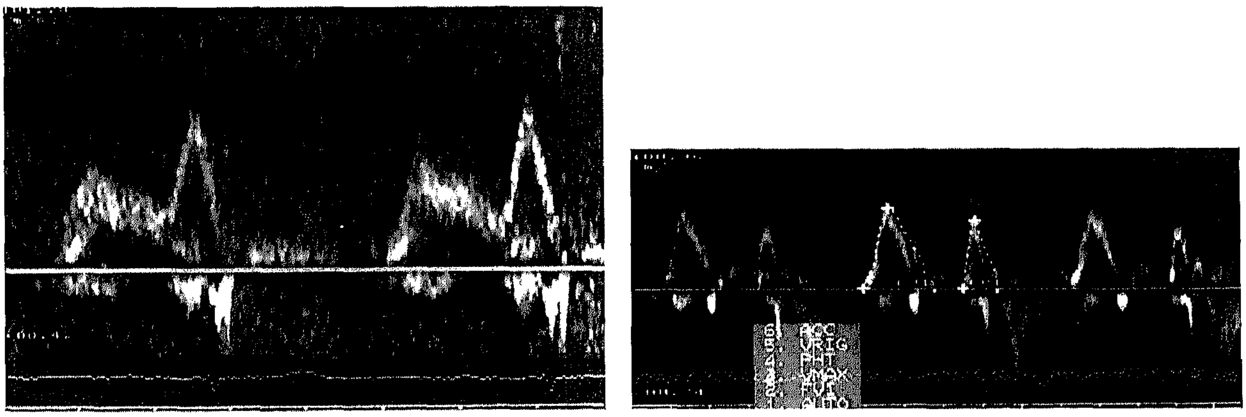

FIG 2. Changes in Doppler diastolic filling pattern after training. Left, Before exercise training, a diastolic filling pattern of abnormal relaxation is evident, with a reduced peak early filling velocity, a prolonged deceleration time of peak early filling velocity, a greater peak atrial filling velocity, and a reduced E/A ratio (0.7). The isovolumic relaxation time, not shown here, was also prolonged. Right, After exercise training, there was a radical change in diastolic filling pattern, with an increased peak early filling velocity with shorter deceleration time, a reduced peak atrial filling velocity, and a greater E/A ratio (1.44).

TABLE 4. Changes in Radionuclide Left Ventricular Diastolic Filling Parameters in All Subgroups Before and After Exercise Training

	T						NT					
	A (n=12)		B (n=6)		C (n=9)		A (n=6)		B (n=4)		C (n=5)	
Variable	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
PEFR, EDV/s	1.90±0.7	1.85±0.6	1.53±0.5†	1.57±0.4†	1.48±0.6†	1.68±0.7*†	1.81±0.5	1.80±0.5	1.55±0.3†	1.59±0.5†	1.46±0.6†	1.41±0.6†‡§
PAFR, EDV/s	0.80±0.6	0.82±0.5	0.74±0.5	0.71±0.5	1.62±0.5†‡	1.1±0.4*†	0.84±0.6	0.81±0.7	0.65±0.4	0.61±0.6	1.71±0.5†‡	1.68±0.7†‡§
PFR, EDV/s	2.2±0.3	2.1±0.3	2.15±0.4	2.5±0.4	2.7±0.3†‡	3.0±0.3*†	2.3±0.4	2.25±0.5	2.35±0.5	2.4±0.6	2.8±0.5†‡	2.7±0.9§
TPEFR, ms	142±60	146±12	163±6†	163±5†	168±7†	162±7†	145±52	140±16	161±14†	155±11	171±17†	165±12
TPAFR, ms	155±43	248±68*	184±26†	290±47*	213±60†	260±80*	152±63	172±54§	189±16†	201±36§	202±45†	210±66§
TPFR, ms	125±6	133±13	138±7	134±13	142±8	133±15	131±11	126±14	141±12	136±11	144±11	139±18
DFP, ms	298±89	431±92*	308±71	454±66*	324±55	532±102*†‡	312±71	341±102§	325±51	311±57§	330±38	345±92§
RFF, %	62±12	61±14	59±12	61±13	51.0±12†‡	60.0±16*	60.0±6	61.5±8	59.2±8	58.3±10	49.0±6†‡	50.0±16†‡§
AFF, ms	31±11	33±15	28±14	29±12	39.1±14†‡	31.3±15*	33.0±5	3.02±4	31.0±9	34.2±11	41.2±12†‡	40.4±9†‡§

PEFR indicates peak early filling rate; EDV, end-diastolic volume; PAFR, peak atrial filling rate; PFR, peak filling rate; TPEFR, time to PEFR; TPAFR, time to PAFR; and TPFR, time to PFR. See Tables 1 and 3 for other abbreviations.

**P*<.005 vs before training; †*P*<.005 vs AT, CT vs AT, BNT vs ANT, CNT vs ANT; ‡*P*<.005 CT vs BT, CNT vs BNT; §*P*<.05 ANT vs AT, BNT vs BT, CNT vs CT. Data are mean±SD.

the trained and untrained groups in the frequency of cardiac events during the following period. However, 16 of 23 patients in both groups who had complications had the restrictive filling pattern (subgroup A). Thus, 70% (16 of 23) of the patients with this finding had a poor outcome. Only 2 of 11 patients with a "normal" pattern (subgroup B) and 5 of 19 patients with impaired relaxation (subgroup C) had a poor outcome. In 6 patients, a Doppler restrictive pattern was initially present that was not modified by training. Six patients of the trained group (16.6%) and 3 patients of the untrained group (15.7%) had heart failure. Canadian class IV angina was present in the 2 patients of the trained subgroup A. In the others, angina was classified as Canadian class III. Table 6 shows the clinical and Doppler echocardiographic variables in patients with and without cardiac events during the follow-up.

Univariate Cox Model Analysis

Table 7 shows the results of univariate analysis performed using all clinical, echocardiographic, and Doppler variables in decreasing order of strength for predicting baseline peak oxygen uptake and change in peak oxygen uptake at the follow-up examination. Pretraining peak oxygen uptake was significantly correlated with all Doppler variables except for peak atrial filling velocity, diastolic filling period, and resting LVEF. The best predictor was the change in the lactic anaerobic threshold (r=.95; P≤.0001). The change in peak Vo_2 was correlated with changes in peak atrial filling velocity, isovolumic relaxation time, peak heart rate, and E/A ratio.

Multivariate Analysis

Stepwise multiple regression was performed to assess the independent predictors of peak oxygen uptake at

TABLE 5. Cardiac Events During Follow-up

T (n=36)				NT (n=19)			
Patient No.	Subgroup (A, B, C)	Events	Time, mo	Patient No.	Subgroup (A, B, C)	Events	Time, mo
2	A	Aa	6	37	A	HF	4
4	A	Aa	3	38	A	HF	6
6	A	HF	7	39	A	D	8
7	A	HF	10	43	A	HF	12
10	A	HF	3	48	A	D	10
12	A	D	5	50	A	Aa	7
14	A	D	8	51	C	Aa	9
17	A	SD	9	54	C	Aa	10
20	A	HF	4	55	C	Aa	12
24	A	SD	7				
33	B	Aa	3				
36	B	HF	11				
16	C	HF	8				
31	C	Aa	10				

Aa indicates angina pectoris; HF, heart failure; D, death; and SD, sudden death. See Table 1 for other abbreviations.

Table 6. Clinical and Doppler Echocardiographic Variables in Patients With and Without Cardiac Events During Follow-up

Variable	Cardiac Event-Free (n=32)	Cardiac Event (n=23)	*P*
Clinical			
Age, y	53±7	56±8	NS
Sex (M/F)	27/5	20/3	NS
Etiology			
DCM	9	9	NS
ICM	23	14	NS
Peak $\dot{V}O_2$, mL·kg^{-1}·min^{-1}	15.7±1.4	16.4±1.3	<.05
HR, rest, beats per minute	89±6	93±9	<.04
HR, peak, beats per minute	138±12	135±10	NS
Echocardiographic			
LVEDD, mm	63±20	67±18	NS
LVESD, mm	52±22	56±20	NS
LVEDV, mL	187±41	194±32	NS
LVESV, mL	136±41	143±28	NS
LVFS, %	17.5±18	16.2±21	NS
LVEF, %	27±16	26±18	NS
Doppler			
E, cm/s	77±21	99±24	<.0008
A, cm/s	72±24	65±18	NS
E/A	1.25±0.7	1.7±0.6	<.02
IVRT, ms	68±22	55±22	<.03
EDT, ms	192±45	159±52	<.02
RFF, %	55.5±14	64.9±15	<.02
AFF, %	35.5±13	29.1±14	NS
DFP, ms	356±137	305±104	NS

LVEDD indicates left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVFS, left ventricular fractional shortening; and LVEF, left ventricular ejection fraction. See Tables 1 and 3 for other abbreviations.

baseline and after exercise training using the univariate variables, with $P \leq .10$. As shown in Table 8, multivariate analysis demonstrated that peak heart rate and E/A ratio were the most significant pretraining independent predictors of peak $\dot{V}O_2$. Changes in exercise tolerance and E/A ratio were the best predictors of change in peak $\dot{V}O_2$. Stepwise logistic regression analysis showed an overall effect of Doppler pattern on predicting overall

Table 7. Univariate Analysis of Peak Oxygen Uptake at Baseline and as Change After Exercise Training

Peak Oxygen Uptake, mL·kg^{-1}·min^{-1}	Correlation Coefficient	*P*
Correlation with baseline peak $\dot{V}O_2$		
LAT before, mL·kg^{-1}·min^{-1}	.72	≤.0001
E/A before	.68	≤.0001
HR, peak before, beats per minute	.49	≤.0001
IVRT before, ms	.37	≤.005
E before, cm/s	−.37	≤.006
EDT before, ms	.36	≤.006
pWL before, W	−.36	≤.007
HR, resting before, beats per minute	.30	≤.03
RFF before, %	−.29	≤.03
Correlation with change in peak $\dot{V}O_2$		
ΔLAT, mL·kg^{-1}·min^{-1}	.95	≤.0001
ΔE/A	.61	≤.0001
ΔIVRT, ms	−.28	≤.04
ΔRFF, %	.27	≤.04

See Tables 1, 2, and 3 for abbreviations.

Table 8. Multivariate Analysis of Peak Oxygen Uptake at Baseline and as Change After Exercise Training

Peak Oxygen Uptake, mL·kg^{-1}·min^{-1}	β-Coefficient	*P*
Correlation with baseline peak $\dot{V}O_2$		
E/A before	.08±.01	≤.0001
HR, peak before, beats per minute	.06±.01	≤.0002
Correlation with change in peak $\dot{V}O_2$		
ΔpWL, W	.09±.01	≤.0001
ΔE/A	.17±.01	≤.0001

See Tables 2 and 3 for abbreviations.

cardiac events ($P=.02$). Contrasts showed significant differences between subgroup A, with the restrictive Doppler pattern, and subgroup B, with the "normal" pattern ($P=.04$), and between subgroups A and C, with the abnormal relaxation Doppler pattern ($P=.007$), indicating a worse prognosis in patients with baseline Doppler pattern of restrictive filling. Exercise training did not reach statistical significance ($P=.54$) as a predictor of cardiac events. Stepwise logistic regression with event as the outcome produced the following results: Subjects who had cardiac events had significantly higher values on E, RFF, and resting heart rate and significantly lower values on IVRT, EDT, and peak $\dot{V}O_2$ than patients who had no events. The results were similar when patients who died were compared with those who survived, with the exception that the former also had lower peak atrial filling velocity and higher heart rates.

The survival model (log rank test) showed lower event-free survival for patients with pattern A ($\chi^2=11.53$; $P=.003$) than for either B or C (Fig 3). The trend of survival curves was similar when patients were separated by etiology (idiopathic or ischemic cardiomyopathy). However, there was no significant difference between survival functions when separated by exercise training (Fig 4).

Discussion

These data show that LV diastolic filling patterns assessed by Doppler echocardiography can identify patients with DCM who will increase their peak $\dot{V}O_2$ with exercise training. In this population, the most significant improvement in aerobic capacity was observed in patients with a baseline Doppler pattern of abnormal LV relaxation. However, in this study, there was no signifi-

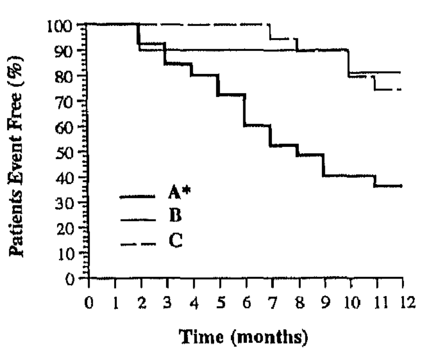

Fig 3. Graph of event-free rates as assessed by the influence of Doppler pattern of left ventricular diastolic dysfunction (A, B, C) on cardiac events. Patients with pattern A have a 1-year probability of cardiac events significantly greater than pattern B and pattern C. *$P<.003$.

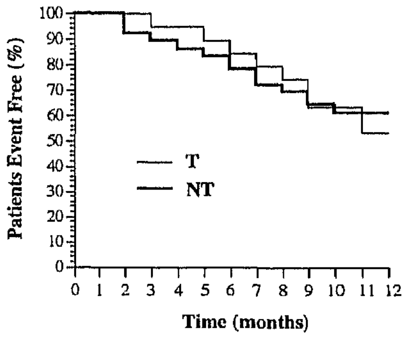

FIG 4. Graph of event-free rates as assessed by the influence of exercise training on cardiac events. The 1-year probability to avoid cardiac events with exercise training is not statistically significant between training (T) and nontraining control (NT) groups.

cant association between improved exercise capacity and prognosis.

The best independent predictors of morbidity and mortality were pretraining Doppler variables of LV restrictive filling. Patients with cardiac events during the follow-up had significantly higher values on E and RFF and significantly lower values on IVRT and EDT than patients who had no events. All the patients who died had the restrictive filling pattern and no improvement in aerobic capacity after training. Patients with a baseline Doppler pattern of abnormal LV relaxation had the best outcome compared with the other two patterns.

Exercise Training and Left Ventricular Diastolic Filling in Dilated Cardiomyopathy

Abnormalities of LV diastolic function that often precede systolic dysfunction have been demonstrated in patients with DCM by contrast LV angiography[8] and radionuclide angiography.[35] Recently, pulsed Doppler echocardiography has been shown to correlate with both angiographic[21-23] and radionuclide[24,25] techniques in assessing diastolic filling in patients with DCM[36-38] and other cardiac diseases.[12,37-39] Moreover, Doppler recordings have proven to be accurate in evaluating serial changes in LV diastolic function[40,41] as well as in defining prognosis in patients with DCM[12,13] and cardiac amyloidosis.[42]

Although the Doppler pattern of diastolic mitral inflow directly reflects LV filling, it is influenced by multiple related factors such as LV relaxation,[43] cardiac motion,[44] intrinsic myocardial properties, heart rate, and loading conditions. Thus, it is not surprising that different inflow patterns have been identified in patients with DCM, reflecting different clinical and hemodynamic profiles.[8] In the restrictive pattern, hemodynamic comparisons have shown an increase in mean left atrial pressure with a greater atrioventricular pressure gradient. This causes a more prominent early diastolic filling velocity and a more rapid deceleration rate due to a faster equalization between left atrial and LV pressures. By contrast, when impaired relaxation is present, the early diastolic pressure gradient between the left atrium and LV is small, resulting in a decreased rate of early filling velocity with a prolonged deceleration time as well as a greater residual atrial volume. A third pattern of mixed abnormalities resulting in a "normal" pattern involving both restrictive and impaired relaxation conditions may sometimes be evident in patients with DCM. In this case, it is possible that an initially abnormal relaxation pattern may be present, which later can progress to a restrictive pattern when left atrial pressure rises.

In this study, 45% of patients had a restrictive pattern, 25% had a pattern of abnormal relaxation, and 20% had a "normal" pattern. In our patients with the abnormal relaxation pattern, functional capacity was improved after training and the A wave was reduced. Because we observed no significant changes in LV chamber dimensions, loading conditions, and heart rate after training, the increase in transmural gradient may be related to a decrease in the LV minimal pressure, possibly produced by an increase in ventricular relaxation rate. These data are consistent with the findings of Levy et al,[45] who found a significant correlation between a training-induced increase in early filling and peak V_{O_2} in both young and old normal subjects. They suggested that the improvement in aerobic capacity could be explained through the increase in early diastolic filling, resulting in an increase in stroke volume and cardiac output. In this study, the increase in aerobic capacity was not associated with changes in echocardiographic indexes of systolic performance. This suggests that the improved aerobic capacity may be due to peripheral adaptations.

The observation that exercise training positively influences only patients with a Doppler pattern of abnormal LV relaxation has not been described before and needs further confirmation. Various mechanisms may play a role, such as a lower LV filling pressure, a lower transmitral left atrioventricular gradient, as well as a lower incidence of mitral insufficiency.

In our patients, the increase in early diastolic filling was accompanied by a significant reduction in the isovolumic relaxation time (Table 3). Since isovolumic relaxation time is the most energy-requiring phase of excitation-contraction coupling[46] and is primarily influenced by sympathetic tone, its reduction after training probably reflects a greater calcium reuptake from myofilaments. An increase in myocardial distensibility can contribute to an increase in cardiac output and oxygen supply to skeletal muscles. We hypothesize that this mechanism may play a role in explaining the changes in LV diastolic filling in patients with DCM and abnormal LV relaxation.

The absence of significant changes in exercise capacity and LV diastolic filling in patients with Doppler restrictive "normal" patterns has not been previously described. Both hemodynamic and anatomic factors may be involved. Patients with restrictive LV filling may have a greater LV end-diastolic pressure and a stiffer ventricle. Such factors could limit the capacity of the left ventricle to adapt to exercise training, which may be caused by interstitial fibrosis and collagen abormalities. However, recent data have shown that the amount of interstitial fibrosis does not correlate with the Doppler pattern of LV diastolic filling.[43] In this study, the absence of significant changes in LV diastolic filling as well as peak V_{O_2} after training was similar in patients with "normal" and with Doppler restrictive patterns.

Prognostic Significance of the Effects of Exercise Training

Previous studies have attempted to define prognostic indicators in patients with DCM. One report suggested that a significant Doppler predictor of outcome was the early to atrial filling velocity (E/A).[47] A ratio of 2.3 was associated with a greater capillary pulmonary wedge pressure, a lower cardiac index, and a lower functional capacity. Our data confirm that pretraining E/A ratio and posttraining change in E/A ratio, primarily due to a reduction in the amplitude of the A wave, were independent predictors of peak V_{O_2}. Stepwise logistic regression analysis showed an overall effect of pretraining patterns on predicting overall cardiac events. Patients with a baseline restrictive pattern of LV diastolic dysfunction had a higher morbidity and mortality compared with the other subgroups. However, exercise training did not significantly modify the outcome of patients with DCM (Fig 4). Patients with abnormal relaxation did have a greater increase in exercise capacity and a lower incidence of overall cardiac events compared with the patients with a restrictive pattern during follow-up (P=.007). This trend was independent of the etiology of the heart failure, confirming that the identification of these specific patterns by Doppler echocardiography is very important in identifying patients with DCM with a poor outcome.

Limitations of the Study

The number of patients studied was relatively small, especially since they were further subdivided into three subgroups. Of interest, other investigators recently reported similar results[13] on the prognostic significance of Doppler patterns in similar numbers of patients. However, they did not exercise their patients. We are the first to describe the prognostic significance of the posttraining changes in LV diastolic filling in patients with dilated cardiomyopathy. A single load of exercise training was chosen. The effects of different intensities of exercise training in patients with DCM are not known and will need further study. But the fact that the trained group demonstrated an increase in lactic acid threshold, peak V_{O_2}, and work capacity compared with the control group indicates that the exercise program was vigorous enough to produce a training effect. Invasive studies such as muscle biopsies and arterial venous O_2 differences during exercise might help to clarify some of the mechanisms by which DCM patients can improve their functional capacity, but those were not part of the design of this study. Left ventricular diastolic filling patterns assessed by Doppler are influenced by a variety of factors, such as valvular insufficiency, loading conditions, viscoelastic properties of the myocardium, ventricular compliance, pericardial restraint, and left and right ventricular interaction. However, Doppler LV filling variables were highly correlated with radionuclide LV filling variables both before and after exercise training, indicating the applicability of Doppler measurements of LV filling. The training-induced reduction in resting heart rate, evident in all trained subgroups, may have increased the magnitude of LV filling. However, resting heart rate was only modestly reduced after training (Table 2). By contrast, changes in filling fractions, observed only in the trained subgroup with abnormal relaxation pattern, were more pronounced, suggesting that factors other than the mechanism of training-induced bradycardia can be involved. Changes in loading conditions induced by training could also account for the changes in LV diastolic filling. We found no changes in LV end-diastolic diameter or diastolic blood pressure, suggesting that both preload and afterload were scarcely involved in training-induced changes of diastolic filling. Although mitral insufficiency was present in two thirds of the trained patients, in particular in patients with restrictive pattern, its degree was mild in all patients and was not modified by exercise training. Finally, the accuracy of Doppler echocardiography for prognostic evaluation may be decreased by the variability of LV diastolic filling. This variability could be increased by exercise training. In our study, however, loading conditions were not significantly modified by training except for the pattern of abnormal relaxation.

Conclusions

Some patients with DCM can improve their functional capacity with training, whereas patients who do not exercise have a tendency to further reduce their exercise capacity. The improvement in peak exercise V_{O_2} is significantly correlated with the increase in early filling rate as well as a decrease in atrial filling rate. Since the increase in exercise tolerance is statistically significant only in patients with the initial Doppler pattern of abnormal relaxation, and since this pattern has a better prognosis compared with the other two patterns studied, we believe that the Doppler pattern of abnormal LV relaxation may represent a useful criterion for the identification of patients with DCM who will benefit the most from exercise training and for the assessment of outcome. Furthermore, Doppler echocardiography can identify patients with restrictive LV diastolic filling as well as "normal" pattern who will not benefit from exercising and will not have an amelioration in prognosis by exercise training.

The results indicate that Doppler echocardiograpy is a valuable tool in the prognostic assessment of patients with DCM involved in exercise training programs. However, the small number of observations prevents us from reaching definitive conclusions about the clinical and prognostic significance of exercise-induced changes in LV diastolic filling patterns. The prognostic significance of these data should be confirmed in larger studies with a longer follow-up.

Acknowledgment

The secretarial assistance of Edward Murray is greatly appreciated.

References

1. Jetté M, Heller R, Landry F, Blümchen G. Randomized 4-week exercise program in patients with impaired left ventricular function. *Circulation*. 1991;84:1561-1567.
2. Shabetai R. Beneficial effects of exercise training in compensated heart failure. *Circulation*. 1988;78:775-776.
3. Sullivan MJ, Higginbotham MB, Cobb FR. Exercise training in patients with chronic heart failure delays ventilatory anaerobic threshold and improves submaximal exercise performance. *Circulation*. 1989;79:324-329.
4. Sullivan MJ, Higginbotham MB, Cobb FR. Exercise training in patients with severe left ventricular dysfunction: hemodynamic and metabolic effects. *Circulation*. 1988;78:506-515.
5. Bonow RO, Bacharach SL, Green MV, Kent KM, Rosing DR, Lipson LC, Leon MB, Epstein SE. Impaired left ventricular diastolic filling in patients with coronary artery disease: assessment with radionuclide angiography. *Circulation*. 1981;64:315-323.
6. Grossman W, McLaurin LP, Rolett EL. Alterations in left ventricular relaxation and diastolic compliance in congestive cardiomyopathy. *Cardiovasc Res*. 1979;13:514-522.

7. Ehsani AA, Martin WH, Heath GW, Coyle EF. Cardiac effects of prolonged and intense exercise training in patients with coronary artery disease. *Am J Cardiol.* 1982;50:246-254.
8. Arvan S. Exercise performance of the high risk acute myocardial infarction patient after cardiac rehabilitation. *Am J Cardiol.* 1988;62:197-201.
9. DeMaria AN, Wisenbaugh TW, Smith MD, Harrison MR, Berk MR. Doppler echocardiographic evaluation of diastolic dysfunction. *Circulation.* 1991;84(suppl I):I-288-I-295.
10. Taylor R, Waggoner AD. Doppler assessment of left ventricular diastolic function: a review. *J Am Soc Echocardiogr.* 1992;5:603-612.
11. Nishimura RA, Housmans PR, Hatle LK, Tajik AJ. Assessment of diastolic function of the heart: background and current applications of Doppler echocardiography, I: physiologic and pathophysiologic features. *Mayo Clin Proc.* 1989;64:71-81.
12. Oh JK, Ding ZP, Gersh BJ, Bailey KR, Tajik AJ. Restrictive left ventricular diastolic filling identifies patients with heart failure after acute myocardial infarction. *J Am Soc Echocardiogr.* 1992;5:497-503.
13. Weener GS, Schaefer C, Dirks R, Figulla HC, Kreuzer H. Prognostic value of Doppler echocardiographic assessment of left ventricular filling in idiopathic dilated cardiomyopathy. *Am J Cardiol.* 1994;73:792-798.
14. Lavine SJ, Campbell CA, Held AC, Johnson V. Effect of nitroglycerin-induced reduction of left ventricular filling pressure on diastolic filling in acute dilated heart failure. *J Am Coll Cardiol.* 1989;13:233-241.
15. Choong CY, Abascal VM, Thomas JD, Guerrero JL, McGlew S, Weyman AE. Combined influence of ventricular loading and relaxation on the transmitral flow velocity profile in dogs measured by Doppler echocardiography. *Circulation.* 1988;78:672-683.
16. Zile MR, Blaustein AS, Gaasch WH. The effect of acute alterations in ventricular afterload and β-adrenergic tone on indexes of early diastolic filling rate. *Circ Res.* 1989;65:406-416.
17. Gardin JM, Dabestani A, Takenaka K, Rohan MK, Knoll M, Russel D, Henry WL. Effect of imaging view and sample volume location on evaluation of mitral flow velocity by pulsed doppler echocardiography. *Am J Cardiol.* 1986;57:1335-1339.
18. Iskandrian AS, HamidHakki A. Age-related changes in left ventricular diastolic performance. *Am Heart J.* 1986;112:75-78.
19. Harrison MR, Clifton GD, Pennel AT, DeMaria AN. Effect of heart rate on left ventricular diastolic transmitral flow velocity patterns assessed by Doppler echocardiography in normal subjects. *Am J Cardiol.* 1991;67:622-627.
20. Gaasch WH, Cole JS, Quinones MA, Alexander JK. Dynamic determinants of left ventricular diastolic pressure-volume relation in man. *Circulation.* 1975;51:317-323.
21. Rokey R, Kuo LC, Zoghbi WA, Limacher MC, Quinones MA. Determination of parameters of left ventricular diastolic filling with pulsed Doppler echocardiography: comparison with cineangiography. *Circulation.* 1985;71:543-550.
22. Appleton CP, Hatle LK, Popp RL. Relation of transmitral flow velocity patterns of left ventricular diastolic function: new insights from a combined hemodynamic and Doppler echocardiographic study. *J Am Coll Cardiol.* 1988;12:426-440.
23. Stoddard MF, Pearson AC, Kern MJ, Ratcliff J, Mrosek DG, Labovitz AJ. Left ventricular diastolic function: comparison of pulsed Doppler echocardiographic and hemodynamic indexes in subjects with and without coronary artery disease. *J Am Coll Cardiol.* 1989;12:327-336.
24. Spirito P, Maron BJ, Bonow RO. Noninvasive assessment of left ventricular diastolic function: comparative analysis of Doppler echocardiographic and radionuclide angiographic techniques. *J Am Coll Cardiol.* 1989;12:327-336.
25. Friedman BJ, Drinkovic N, Miles H, Shih WJ, Mazzoleni A, DeMaria AN. Assessment of left ventricular diastolic function: comparison of Doppler echocardiography and gated blood pool scintigraphy. *J Am Coll Cardiol.* 1986;8:1348-1354.
26. Feigenbaum H. *Echocardiography.* Philadelphia, Pa: Lea & Febiger; 1986:212-234.
27. Henry WL, DeMaria AN, Gramak R, King DL, Kisslo JA, Popp RL, Sahn DJ, Schiller NB, Tajik A, Teicholz LE, Weyman AE. Report of the American Society of Echocardiography Committee on Nomenclature and Standards in Two-Dimensional Echocardiography. *Circulation.* 1980;
28. Spain MG, Smith MD, Grayburn PA, Harlamert EA, DeMaria AN. Quantitative assessment of mitral regurgitation by Doppler color flow imaging: angiographic and hemodynamic correlations. *J Am Coll Cardiol.* 1989;13:585-590.
29. Broadhurst XJ, Liu PMM, Cashman EB, Raftery EB, Lahiri A. Spontaneous variability of left ventricular ejection fraction assessed with the Cardioscint. *Nucl Med Comm.* 1992;13:312-320.
30. Broadhurst P, Cashman PMM, Crawley J, Raftery EB, Lahiri A. Clinical validation of a miniature nuclear probe system for continuous monitoring of left ventricular function and ST segment. *J Nucl Med.* 1991;32:37-43.
31. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol.* 1986;60: 2020-2027.
32. Armitage P. *Statistical Methods in Medical Research.* London, UK: Blackwell Scientific Publications; 1971:456-460.
33. Carlson KJ, Lee DCS, Goroll AH, Leahy M, Johnson RA. An analysis of physicians' reasons for prescribing long-term digitalis therapy in outpatients. *J Chronic Dis.* 1985;38:733-739.
34. Campeau L. Grading of angina pectoris. *Circulation.* 1976;54: 522-531.
35. Packer M. Abnormalities of diastolic function as a potential cause of exercise intolerance in chronic heart failure. *Circulation.* 1990; 8(suppl III):III-78-III-86.
36. Takenaka K, Dabestani A, Gardin JM, Russell D, Clark S, Allfie A, Henry W. Pulsed Doppler echocardiography study of left ventricular filling in dilated cardiomyopathy. *Am J Cardiol.* 1986;58: 143-147.
37. Lavine SJ, Arends. Importance of the left ventricular filling pressure on diastolic filling in idiopathic dilated cardiomyopathy. *Am J Cardiol.* 1989;64:61-65.
38. Klein AL, Hatle LK, Burstow DJ, Seward JB, Kyle RA, Bailey KR, Luscher TF, Gertz MA, Tajik AJ. Doppler characterization of left ventricular diastolic function in cardiac amyloidosis. *J Am Coll Cardiol.* 1989;13:1017-1026.
39. Pearson AC, Labovitz AJ, Mrosek D, Williams GA, Kennedy HL. Assessment of diastolic function in normal and hypertrophied hearts: comparison of Doppler echocardiography and M-mode echocardiography. *Am Heart J.* 1987;113:1417-1425.
40. Myreng Y, Myhre E. Effects of verapamil on left ventricular relaxation and filling dynamics in coronary artery disease: a study by pulsed Doppler echocardiography. *Am Heart J.* 1989;117:870-875.
41. Wind E, Snider AR, Buda AJ, O'Neill WW, Topol EJ, Dilworth LR. Pulsed Doppler assessment of left ventricular diastolic filling in coronary artery disease before and immediately after coronary angioplasty. *Am J Cardiol.* 1987;59:1041-1046.
42. Klein AL, Hatle LK, Taliercio CP, Oh JK, Kyle RA, Gertz MA, Bailey KR, Seward JB, Tajik AJ. Prognostic significance of Doppler measures of diastolic function in cardiac amyloidosis: a Doppler echocardiographic study. *Circulation.* 1991;83:808-816.
43. Pinamonti B, DiLenarda A, Sinagra G, Camerini F. Restrictive left ventricular filling pattern in dilated cardiomyopathy assessed by Doppler echocardiography: clinical, echocardiographic and hemodynamic correlations and prognostic implications. *J Am Coll Cardiol.* 1993;22:808-815.
44. Cao T, Shapiro SM, Bersohn M, Lin SC, Ginzton LE. Influence of cardiac motion on Doppler measurements using in vitro and in vivo models. *J Am Coll Cardiol.* 1993;22:271-276.
45. Levy WC, Cerqueira MD, Abrass IB, Schwartz RS, Stratton JR. Endurance exercise training augments diastolic filling at rest and during exercise in healthy young and older men. *Circulation.* 1993;88:116-126.
46. Stehno-Bittel L, Laughlin MH, Sturek M. Exercise training depletes sarcoplasmic reticulum Ca in coronary smooth muscle. *J Appl Physiol.* 1991;71:1764-1773.
47. Vanoverchelde JLJ, Raphael DA, Robert AR, Cosyns JR. Left ventricular filling in dilated cardiomyopathy: relation to functional class and hemodynamics. *J Am Coll Cardiol.* 1990;15:1288-1295.