Improvement in Left Ventricular Diastolic Stiffness Induced by Physical Training in Patients With Dilated Cardiomyopathy

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ABSTRACT

Background: Diastolic dysfunction in long-term heart failure is accompanied by abnormal neurohormonal control and ventricular stiffness. The diastolic phase is determined by a balance between pressure gradients and intrinsic ventricular wall properties: according to a mathematical model, the latter (ie, left ventricular [LV] elastance, K_{LV}) may be calculated by the formula: $K_{LV} = (70/[DT-20])^2$ mm Hg/mL, where *DT* is the transmitral Doppler deceleration time.

Methods and Results: In 54 patients with chronic systolic heart failure (39 men, 15 women; age 65 ± 10 years; New York Heart Association [NYHA], 2.3 ± 0.9; ejection fraction [EF], 32% ± 5%), we analyzed the relationship between K_{LV} and an index of neurohormonal derangement (levels of brain natriuretic peptide [BNP]), and investigated whether 3 months of physical training could modulate diastolic operating stiffness. Patients were randomized to physical training (n = 27) or to a control group (n = 27). Before and after training, patients underwent Doppler echocardiogram and cardiopulmonary stress test. At baseline, ventricular stiffness was related to BNP levels ($P < .01$). Training improved NYHA class, exercise performance, and estimated pulmonary pressure. BNP was reduced. Ventricular volumes, mean blood pressure, and EF remained unchanged. A 27% reduction of elastance was observed (K_{LV}, 0.111 ± 0.044 from 0.195 ± 0.089 mm Hg/mL; $P < .01$), whose magnitude was related to changes in BNP ($P < .05$) and to K_{LV} at baseline ($P < .01$). No changes in K_{LV} were observed in controls after 3 months (0.192 ± 0.115 from 0.195 ± 0.121 mm Hg/mL).

Conclusions: In heart failure, left ventricular diastolic stiffness is related to neurohormonal derangement and is modified by physical training. This improvement in LV compliance could result from a combination of hemodynamic improvement and regression of the fibrotic process. (*J Cardiac Fail 2009;15:327–333*)

Key Words: Heart failure, diastolic operating stiffness, physical training, neurohormonal control.

The relevance of diastolic dysfunction in determining survival and prognosis in heart failure is being increasingly appreciated.[1–4] By influencing left atrial and capillary wedge pressures, diastolic dysfunction may also induce dyspnea in patients with normal systolic function; in addition, an abnormal diastolic phase carries an additional negative prognostic burden in the setting of systolic dysfunction.[3,4] Diastole is a sequence of interrelated events influenced by changes in loading conditions, myocardial intrinsic properties, and heart rate.[5–9] Left ventricular (LV) operating stiffness (K_{LV}), ie, the slope of the ventricular pressure-volume curve (dP/dV) is a fundamental parameter of diastole. K_{LV} is governed by a complex interplay of myocardial stiffness (related to tissue collagen content), ventricular geometry, and myocardial relaxation.[9–11] It is difficult to measure even with invasive techniques, requiring high-fidelity pressure measurements and synchronized volume assessment with high temporal resolution. For the noninvasive assessment of K_{LV}, a number of Doppler indexes have been used, one of the most useful being the deceleration time of the early mitral filling wave (DT).[6,8]

The theoretic analysis and experimental study of Little el al[12] predicted that if left atrial pressure remains relatively constant during early filling deceleration, then deceleration time will be proportional to the inverse square root of

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Manuscript received April 15, 2008; revised manuscript received October 2, 2008; revised manuscript accepted October 31, 2008.

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1071-9164/$ - see front matter

doi:10.1016/j.cardfail.2008.10.032

elastance ($1/\sqrt{K_{LV}}$), unaffected by other factors such as ejection fraction, ventricular size, and heart rate. By combining the echocardiogram and invasive hemodynamic measurements, Marino et al[13] applied this model to patients with heart disease, showing strong correlation between invasive and noninvasive K_{LV} data.

In chronic heart failure, a tight relationship may exist between diastolic dysfunction, progressive ventricular remodelling, and the unwarranted neurohormonal activation that may be revealed, among its many markers, by high levels of circulating brain natriuretic peptide (BNP) and N-terminal proBNP.[14–17] Physical exercise in heart failure patients strongly affects autonomic and neurohormonal regulation[18–21] and has also been shown to improve LV diastolic filling.[22] The effects of physical training on diastolic stiffness, on the other hand, have been so far studied only in the experimental setting.[23] The aim of the present study was to evaluate whether physical training could modify LV stiffness in patients.

Methods

Patient Population

We include data on 54 patients with chronic systolic heart failure followed up in our center. The patients were clinically stable and had been under optimal treatment for at least 3 months before being evaluated for a cycle of cardiovascular rehabilitation according to current recommendations.[24,25] Table 1 summarizes the demographic and clinical characteristics of the study groups: one-fourth of the patients were women, most patients had an ischemic etiology, and less than half of the patients had a mild to moderate functional mitral regurgitation. Exclusion criteria from the current analysis were atrial fibrillation, mitral surgery (either repair or prosthetic valve insertion), LV aneurism repair, implantable cardioverter-defibrillator or biventricular pacing implantation, or both within 6 months before. After evaluation, 27 patients were randomly assigned to a training group and 27 to an untrained control group.

Protocol

The clinical and instrumental evaluation was repeated after 12 weeks, which was at the end of the rehabilitation program for the training group. On the same day, patients underwent cardiopulmonary stress test ($V_{max}2900$, Sensor Medics, Yorba Linda, California, USA), determination of the serum levels of brain natriuretic peptide (Triage BNP test, Biosite Ltd, Belfast, United Kingdom) and Doppler echocardiography (Sequoia, Siemens, Malvern, PA). During the study period, no change in the individual drugs' treatment was allowed.

Cardiopulmonary Test

The cardiopulmonary exercise system was calibrated before every test for breath-by-breath measurements of expired volume per unit time (VE), oxygen consumption (V_{O_2}) and rate of carbon dioxide elimination (V_{CO_2}). Ventilation for O_2 and CO_2 (V_E/V_{O_2}, V_E/V_{CO_2}), the respiratory quotient ($RQ = V_{CO_2}/V_{O_2}$), and respiratory rate were derived online. A 12-lead electrocardiogram (ECG) was continuously monitored, and blood pressure was measured every 2 minutes.

Table 1. Study Population

	All	Training Group	Controls
Patients, No.	54	27	27
Age, mean ± SD, y	65 ± 10	65 ± 11	67 ± 9
Sex, No.			
Male	39	19	20
Female	15	8	7
Hear failure type, No.			
Ischemic	30	14	16
Nonischemic	24	13	11
NYHA class	2.3 ± 0.9	2.3 ± 0.5	2.2 ± 0.7
MAP, mean ± SD, mm Hg	87 ± 9	86 ± 11	87 ± 12
pV_{O_2}, mean ± SD, mL/kg/min	14.3 ± 3.5	14.1 ± 3.2	14.4 ± 3.6
Ejection fraction, %	32 ± 5	31 ± 6	33 ± 6
LVEDV, mean ± SD, mL	185 ± 40	180 ± 41	189 ± 51
LVMI, $g/m^{2.7}$	71.2 ± 11.8	73.6 ± 16.6	69.3 ± 17.9
Functional MR			
Yes	24	13	11
No	30	14	16
PAPs, mean ± SD, mm Hg	36 ± 8	36 ± 11	37 ± 9
E/A	1.56 ± 0.06	1.56 ± 0.08	1.52 ± 0.08
Restrictive filling pattern, %	11%	10%	12%
K_{LV}, mean ± SD, mL/mm Hg	0.195 ± 0.098	0.195 ± 0.081	0.195 ± 0.121
BNP, mean ± SD, pg/mL	289 ± 225	293 ± 115	318 ± 125
ICD ± biventricular pacing, No.			
Yes	25	12	13
No	29	15	14
Pharmacologic treatment, %			
ACE inhibitors	85	88	82
ARB	37	33	40
β-Blockers	80	81	78
Diuretics	70	67	71
Spironolactone	50	52	48
Digitalis	6	4	7

ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blockers; BNP, brain natriuretic peptide; E/A, ratio between velocity of the E and A wave on Doppler transmitral flow; EF, ejection fraction; ICD, implantable cardioverter-defibrillator; K_{LV}, left ventricular elastance; LVEDV, left ventricular end-diastolic volume; LVMI, left ventricular mass index; MAP, mean arterial pressure; MR, mitral regurgitation; PAPs, estimated systolic pulmonary pressure; pV_{O_2}, oxygen consumption at peak exercise; SD, standard deviation.

A ramp test with a continuous increase of workload by 10 W/min on a bicycle ergometer was chosen. The test was symptom-limited, using a Borg scale from 0 to 10 for dyspnea, fatigue, and chest pain. Patients were encouraged to exercise until exhaustion. All parameters were measured from plots over time, giving moving average values. Peak V_{O_2}, V_E/V_{O_2}, and V_E/V_{CO_2} were calculated as the average value of the last 30 seconds of exercise. The anaerobic threshold was calculated by the V-slope method. In this article, we present only data on peak V_{O_2} as the most used index of good training effect.[19,24]

Echocardiographic Measurements

Echocardiographic examination was performed following the guidelines of the American and European Society of Echocardiography.[26] The variables considered were LV ejection fraction (EF, %), LV end-systolic (LVESV) and end-diastolic volumes (LVEDV, mL), LV mass index (LVMI, $g/m^{2.7}$) and pulmonary pressure