Original Paper

Physical Exercise With Weight Reduction Lowers Blood Pressure and Improves Abnormal Left Ventricular Relaxation in Pharmacologically Treated Hypertensive Patients

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In spite of appropriate pharmacologic therapy, many hypertensive patients develop an abnormal left ventricular relaxation with preserved systolic function. This cardiac dysfunction increases the risk of cardiovascular complications. The authors assessed the therapeutic effects of an intervention with exercise training and weight reduction in patients with pharmacologically well-treated hypertension who had abnormal left ventricular relaxation with normal systolic function. Eighty-eight (44%) of 202 medically treated hypertensive patients had abnormal ventricular relaxation with normal ejection fraction. These patients were randomized to either a 6-month intervention program (cycle ergometer training twice a day for 5 days a week and a hypocaloric diet) or a control program (unchanged pharmacologic therapy without exercise and diet. Body weight, blood pressure, New York Heart Association class, glomerular filtration rate, and exercise capacity and workload were measured. Cardiac function was assessed by measuring N-terminal pro-B-type natriuretic peptide values, the electrocardiographic QT dispersion interval, and echocardiography (left atrial size, Doppler-derived E/A ratio, and mitral deceleration time). Physical exercise with weight reduction reduced blood pressure, decreased cardiovascular risks, and improved abnormal left ventricular relaxation. Measuring left atrial size is the best method for assessing changes in left ventricular relaxation with preserved systolic function. J Clin Hypertens (Greenwich). *2011;13:23–29.* ©*2010 Wiley Periodicals, Inc.*

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Manuscript received April 4, 2010; revised July 13, 2010; accepted July 24, 2010

doi: 10.1111/j.1751-7176.2010.00380.x

In spite of the remarkable advances in therapy, hypertension continues to be a major health problem whose prevalence is increasing worldwide.[1] Pharmacologically treated hypertensive patients are still at risk for future cardiac events[2] and many develop cardiac dysfunction characterized by abnormal left ventricular relaxation with preserved ejection fraction (LVEF).[3,4]

A range of systematic surveys of heart failure show that the proportions of patients with preserved LVEF range between 31% and 55%.[5–8] Heart failure with reduced LVEF has a higher mortality than that with preserved LVEF. Nonetheless, the cardiac dysfunction seen with preserved LVEF has a high 1-year mortality rate, including 27% in a study of 1720 patients from California,[5] 19% in a study of 5491 Danish patients,[6] 29% in a study of 4596 patients

from Minnesota,[7] and 22% in a study of 2801 patients from Canada.[8] The physiopathologic pattern of cardiac dysfunction with preserved LVEF is complex, and a simplistic approach using pharmacologic therapy against this type of cardiac dysfunction will most likely not be rewarding.[4]

Therefore, effective ways of decreasing the negative impact of hypertension on the cardiovascular system are needed. The therapeutic effect of regular physical activity and weight reduction has not yet been studied in hypertensive patients with abnormal left ventricular (LV) relaxation with preserved LVEF. On the other hand, increased physical activity reduces the negative effects of aging on arterial stiffness and improves age-related diastolic dysfunction.[9] In coronary patients it improves the cardiac performance[10] and reduces coronary endothelial dysfunction.[11] The same is true in patients with diabetes mellitus.[12] Weight loss improves LV diastolic function in diabetic[13] and adipose patients.[14] It is also possible, but remains unknown, whether an intervention focusing on exercise training and moderate weight loss may also be beneficial in pharmacologically treated hypertensive patients with abnormal ventricular relaxation and preserved LVEF.

METHODS

Protocol

This is an investigator-started study, without pharmacologic intervention. The study was planned according to the Good Clinical Quality standards using an intention-to-treat analysis. The protocol was approved from a local ethics committee. Analysis was performed by a single-blinded observer (who ignored the group and time of collection). The authors have no conflict of interest and there was no financial sponsoring.

Patients and Study Design

Selected patients had primary and stable arterial hypertension that was pharmacologically "well controlled." The referring physicians treated hypertension with the aim of reducing systolic blood pressure (BP) $\geq$140 mm Hg and diastolic BP $\geq$85 mm Hg. In some patients, blood reductions could not be achieved without unacceptable untoward effect and therefore we also accepted patients with a systolic BP $\geq$150 mm Hg and diastolic BP $<$86 mm Hg.

Inclusion criteria included no need to change pharmacologic therapy in the following 6 months, New York Heart Association (NYHA) class $<$III, no contraindication to physical exercise (physical work capacity $\geq$50 watts), and abnormal LV relaxation with preserved LVEF ($\geq$52%). Exclusion criteria comprised untreated or poorly treated hypertension, reduced LVEF ($<$52%), cardiac pacemaker, a history of atrial flutter or fibrillation in the past 12 months, diabetes mellitus, and pathologies affecting cardiovascular function and physical exercise (eg, pulmonary failure, peripheral arterial disease, and orthopedic pathology of the spine or legs).

According to the selection criteria, all selected patients had abnormal ventricular relaxation with normal LVEF. In this type of cardiac dysfunction, none of the symptoms of heart failure is specific[4] and many patients may have had an NYHA class $<$III. Thus, patients' selection depended on the assessment of the cardiac function. A total of 202 hypertensive patients were screened with echocardiography, of whom 101 (50%) had normal cardiac function, 13 (6%) had reduced systolic function (LVEF $\geq$52%), and 88 (44%) had abnormal ventricular relaxation with preserved LVEF. These 88 patients were selected and randomized into 2 groups: (1) an intervention program group (IG) (n=44) or (2) a control group (CG) (n=44). Patients were telephonically contacted once a month by a nurse and were seen by a physician every second month for symptoms, body weight, BP, and heart rate. NYHA class, caloric intake, laboratory and ergometric data, and electrocardiography (ECG) and echocardiography results were recorded before and at the end of the observational period.

Intervention Group. Pharmacologic therapy was left unchanged and patients were enrolled in an exercise training program, which consisted of: (1) cycle ergometer training twice a day for 5 days a week (5 minutes of warm up, 15 minutes at 80% of patients' individual maximal heart rate previously obtained during maximal ergometry, and 5 minutes of cool down), and (2) instruction to follow a hypocaloric heart diet of 1500 kcal/d. A nurse was in contact with the patients for diet and caloric intake.

Control Group. Pharmacologic therapy was left unchanged and patients were followed as in the IG, but they were neither enrolled in the exercise training program nor received a hypocaloric diet.

Assessing Heart Failure in Patients With LV Abnormal Relaxation and Preserved Ejection Fraction

In clinical settings, echocardiography is unsurpassed, especially if one measures LV systolic function.[15] However, there is uncertainty about the best

echocardiographic measurement to assess LV relaxation.[3,16,17] It is proven that in hypertensive patients, abnormal LV relaxation increases left atrial (LA) size and that this measurement is useful.[3,18] Measuring the Doppler-derived E/A ratio and the mitral deceleration time (DT E) should also be useful to the LV diastolic function.[19,20]

Furthermore, cardiac function could also be assessed by measuring N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels[21,22] and ECG QT dispersion (QTd).[23] However, the role of these measurements in assessing cardiac dysfunction in patients with abnormal relaxation and normal LVEF is largely unknown. Thus, we assessed LV relaxation function with echocardiographic, laboratory, and ECG findings. After a minimum of 8 hours of overnight fasting and 15 minutes of rest, venous blood was drawn into heparin tubes and NT-proBNP values were immediately analyzed with a Roche Cardiac reader (Nutley, NJ). The analytical range was between 60 pg/mL and 3000 pg/mL.

There is a relationship between renal function and B-type natriuretic peptide (BNP),[21] and glomerular filtration rate (GFR) was measured with the Modification of Diet in Renal Disease formula.[24]

QT interval is highly dependent on diurnal variation[23] and therefore all tracings were recorded between 8 AM and 9 AM. Standard 12-lead ECGs were recorded at 25 mm/s speed and 10 mm/mV gain using a Marquette Hellige CardioSys V6.01 (GE Medical Systems, Waukesha, WI) equipment. The tracings were scanned and 500% zoomed to increase measurement sensitivity. The beginning and end of QT and T-R intervals were detected and measured (sensitivity of 0.1 mm). QT was measured from the beginning of the QRS complex to the end of the T wave. QT had to be detected in at least 8 leads. The mean of 2 consecutive QT intervals was calculated in millimeters and then converted into seconds by multiplying the value by 0.04. Corrected QT (QTc) was calculated according to the Bazett's equation ($QTc=QT/\sqrt{R\text{-}R}$). QTd and corrected QTd were calculated by the subtraction of minimal QT and QTc from maximal QT and QTc, respectively.

Echocardiography

Scanning was performed by one experienced echocardiographer using 3-dimensional Philips iE33 equipment (Lynchburg, VA). Each patient underwent standard 2-dimensional echocardiography in the left lateral position using a standard multifrequency probe with detailed LV measurements made from the M mode in the parasternal long axis according to American Society of Echocardiography guidelines.[15] If the technical quality of the M mode was suboptimal, measurements were made from the 2-dimensional images. The E/A ratio and the DT E time were calculated with a pulse spectral Doppler echocardiography, using a 5-mm sample volume placed at the tips of the mitral leaflets parallel to inflow during diastole at end expiration, with a sweep speed of 100 mm/s. Values for each component of the DT E waveform (S′, E′, and A′) were measured and averaged over 3 consecutive cardiac cycles. While magnetic resonance imaging is the gold standard for measuring LA size, in daily practice, transthoracic echocardiography is widely used because of the feasibility and cost. Various methods are available for quantification of LA volumes using transthoracic echocardiography: the ellipsoid method and biplane area-length method use various LA diameters and volumes and the modified Simpson's rule using planimetry is considered the most accurate.[16] We, however, used real-time 3-dimensional echocardiography, which is less time-consuming and more accurate. LA volume index (LAVi) was calculated as LA volume to body surface area ratio (mL/m^2).

Statistical Analyses

Statistical analysis was performed with a Statgraphics Centurion system (Warrenton, VA). Data are expressed as mean ± standard deviation. Absolute values and percent changes in relation to baseline measurements were analyzed. The two hypotheses tested were: null hypothesis: mu1-mu2=0.0, and alternative hypothesis: mu1-mu2>>0.0. Comparisons within groups were made using paired *t* tests or the nonparametric Wilcoxon signed-rank test, where appropriate. Between-group comparisons were performed by unpaired *t* tests or the nonparametric Mann–Whitney *U* test, respectively. Chi-square test or Kruskal–Wallis test were used to compare continuous normally or not normally distributed and qualitative variables, where appropriate. Multivariate analysis of variance was performed. A *P* value of $<.05$ was considered statistically significant.

RESULTS

Patients' Characteristics

Demographic data and pharmacologic therapy are shown in Table I. At baseline, the two groups were comparable. All patients completed the study. Mean body weight decreased from 82 kg to 79 kg in the IG ($P>.0001$) and remained unchanged (81 kg and 81 kg) in the CG (Table II). At the end

Table I. Demographic Characteristics and Medications

Parameter	Intervention Group	Control Group
No.	44	44
Sex, male/female	22/22	22/22
Age, y (×±1 SD)	59±4	60±4
Height, cm (×±1 SD)	167.6±7.6	167.8±7.0
Body surface area, m^2 (×±1 SD)	1.99±0.1	1.96±0.1
Medications		
ACE inhibitors, No.	28	29
Angiotensin II antagonists, No.	13	13
β-Blocker, No.	35	36
Calcium antagonists, No.	30	29
HCT, No.	30	31
Plat, No.	18	18
HMG-CoA, No.	35	36

Abbreviations: ACE, angiotensin converting enzyme; HCT, hydrochlorothiazide and related diuretics; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors; Plat, platelets inhibitors (aspirin, clopidogrel); SD, standard deviation.

of the study, body weight was significantly different in the two groups ($P>.0001$). Mean caloric intake decreased from 2521 calories to 1669 calories ($P>.0001$) in the IG, and did not change (2618 calories and 2706 calories) in the CG (Table II). At the end of the study, the caloric intake was significantly different in the two groups ($P>.0001$). Mean systolic BP decreased from 152 mm Hg to 145 mm Hg ($P>.0001$) in the IG and from 152 mm Hg to 150 mm Hg ($P>.02$) in the CG (Table II). At the end of the study, systolic BP was significantly different in the two groups ($P>.0001$). Mean diastolic BP decreased from 88 mm Hg to 85 mm Hg ($P>.0001$) in the IG and was unchanged (88 mm Hg and 87 mm Hg) in the CG (Table II). At the end of the study, diastolic BP was significantly different in the two groups ($P>.0001$). Mean heart rate did not change during the observational period (Table II). According to the selection criteria at baseline, NYHA class was <III in all patients. In the IG at baseline, 10 patients (23%) had class I and 34 patients (77%) had class II. At the end of the study, 23 patients (52%) had class I and 21 patients (48%) had class II. In no case did the NYHA class worsen. In the CG at baseline, 10 patients (23%) had class I and 34 patients (77%) had class II. At the end of the study, 11 patients (25%) had class I, 31 patients (70%) had class II, and 2 patients (5%) had class III. Thus, in the CG, NYHA class increased in several patients.

Table II. Clinical and Hemodynamic Data and QTd

	Intervention Group			Control Group			
Parameter (×±1 SD)	Baseline	6 Months	*P* Value Baseline vs End	Baseline	6 Months	*P* Value Baseline vs End	*P* Value End Intervention vs Control Group
Body weight, kg	82±8	79±7	<.0001	81±9	81±9	NS	>.0001
Calories, kcal	2621±387	1669±147	<.0001	2618±389	2706±401	NS	>.0001
SBP, mm Hg	152±5	145±5	<.0001	152±4	150±5	>.02	>.0001
DBP, mm Hg	88±6	85±5	>.0001	88±5	87±5	NS	>.0001
Heart rate, beats/min	74±7	72±6	NS	73±6	72±7	NS	NS
NYHA class	1.8±0.4	1.4±0.3	<.005	1.8±0.4	1.8±0.5	NS	>.0001
NT-proBNP, pg/mL	719±165	526±126	<.0001	717±141	741±189	NS	>.0001
GFR, mL/min/m^2	77.6±9.6	82.5±8.6	>.0001	77.6±9.3	76.0±9.1	NS	>.0001
Ergometry							
Exercise duration, min	7±1	9±2	>.0001	7±1	7±1	NS	>.0001
Maximal exercise capacity, W	90±12	120±24	>.0001	92±15	97±21	>.09	>.0001
Electrocardiography							
QTd, ms	46±10	46±10	NS	47±9	48±9	NS	NS

Abbreviations: DBP, diastolic blood pressure; GFR, glomerular filtration rate; End, end of the observational period; NS, not significant; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; QTd, QT dispersion; SBP, systolic blood pressure; SD, standard deviation.

Table III. Echocardiographic Characteristics

Parameter (×±1 SD)	Baseline	6 Months	*P* Value Baseline vs End	Baseline	6 Months	*P* Value Baseline vs End	*P* Value End Intervention vs Control Group
LVEF, %	59.9±5.9	62.1±6.7	>.0001	61.9±4.2	61.6±5.6	NS	>.0001
LAVi, mL/m^2	28.6±1.2	26.9±2.9	>.0001	29.9±1.5	30.3±2.3	NS	>.0001
E/A ratio	1.0±0.6	1.1±0.4	>.05	1.1±0.7	1.0±0.6	NS	NS
DT E wave, ms	240±55	257±61	>.0001	247±50	255±53	NS	NS

Abbreviations: End, end of the observational period; DT E, mitral deceleration time; LAVi, left atrial volume index; LVEF, left ventricular ejection fraction; NS, not significant; SD, standard deviation.

Expressed in mean values, NYHA class decreased from 1.8 to 1.4 ($P>.005$) in the IG, and was unchanged (1.8 and 1.8) in the CG (Table II). At end of the study, NYHA class was significantly different in the two groups ($P>.0001$).

At baseline, mean NT-proBNP was elevated (>700 pg/mL) in all patients. Mean NT-proBNP decreased from 719 to 526 ($P>.0001$) in the IG, and increased from 717 to 741 in the CG (not significant) (Table II). At end of the study, NT-proBNP was significantly different in the two groups ($P>.0001$). However, NT-proBNP values showed a great interindividual variation, and there was no clear relationship between changes in NT-proBNP and NYHA class and echocardiographic data.

At baseline, mean GFR was normal in all patients. Mean GFR increased from 77.6 mL/minute/m^2 to 82.5 mL/minute/m^2 ($P>.0001$) in the IG and was unchanged (77.6 mL/minute/m^2 vs 77.0 mL/minute/m^2) in the CG (Table II). At the end of the study, GFR was significantly different in the two groups ($P>.0001$).

Mean exercise duration increased from 7 minutes to 9 minutes ($P>.0001$) in the IG and was unchanged (7 minutes and 7 minutes) in the CG (Table II). At the end of the study, exercise duration was significantly different in the two groups ($P>.0001$). Maximal exercise capacity increased from 90 W to 120 W ($P>.0001$) in the IG and from 92 W to 97 W ($P>.09$) in the CG (Table II). At the end of study, exercise capacity was significantly different in the two groups ($P>.0001$). QTd showed an extreme interindividual variation and mean QTd did not change (Table II). According to the selection criteria, LVEF was normal (≥52%) in all patients (Table III). LVEF increased from 59.9% to 62.1% ($P>.0001$) in the IG and was unchanged (61.9% and 61.6%) in the CG. At end of the study, LVEF was significantly different in the two groups ($P>.0001$). According to the selection criteria at baseline, LAVi was elevated in both groups. LAVi decreased from 28.6 mL/m^2 to 26.9 mL/m^2 in the IG ($P>.0001$) and was unchanged (29.9 mL/m^2 and 30.3 mL/m^2) in the CG (Table III). At the end of the study, LAVi was significantly different in the two groups ($P>.0001$).

At baseline, the E/A ratio was normal or slightly pathologic in both groups, with large interindividual variations. The E/A ratio improved from 1.0 to 1.1 ($P>.005$) in the IG and worsened from 1.1 to 1.0 (not significant) in the CG (Table III). At end of the study, the E/A ratio was significantly different in the two groups ($P>.0001$).

At baseline, the DT E time was higher than normal in both groups. The DT E time increased (worsened) in both groups, with large interindividual variations. At the end of the study, there was no statistical difference in the two groups (Table III).

DISCUSSION

In our study, 44% (88 cases) of 202 pharmacologically treated hypertensive patients had abnormal ventricular relaxation with normal LVEF. This percentage is similar to that of large systematic surveys of patients with heart failure.[5–8]

It seems that using pharmacologic therapy with this type of cardiac dysfunction is not rewarding,[4] and indeed pharmacologic therapy did not influence the pathology in our 6-month observational period. On the other hand, exercise training and weight reduction had several positive therapeutic effects: body weight decreased, physical work capacity (exercise duration and workload) increased, and BP and dyspnea (NYHA class) decreased. Heart rate did not change, but 81% of the selected patients were treated with β-blockers, and this therapy may have reduced the heart rate–lowering effect of regular bicycle training in the IG.

NT-proBNP is an important predictor of cardiovascular mortality[21,22] even if it is uncertain whether long-term measurements carry prognostic significance.[21] Physical exercise and weight reduction significantly decreased the high NT-proBNP values and the decrease might indicate an improved

prognosis. However, we observed large interindividual fluctuations and a lack of correlation between the changes in NT-proBNP values and NYHA class, exercise duration, and echocardiographic signs of improved LV dysfunction. Therefore, repeat measurements of NT-proBNP are of little utility to assess change of LV relaxation with preserved systolic function. Hypertension has a negative impact on renal function.[25] When the renal status is compromised, estimated GFR is a significant confounder of BNP measurements, and GFR has prognostic and therapeutic implications in cardiac patients.[22] It is known that regular exercise improves renal function in healthy persons[26] and that losing weight improves GFR in patients with severe obesity.[27] Our results show that in pharmacologically treated patients, regular physical activity and weight loss significantly increase GFR, perhaps with positive effects in long-term prognosis of hypertension.

It was suggested[28] that QTd might be useful to assess the effects of cardiac therapy. Measuring QTd is time-consuming, and it was disappointing to see that QTd is not useful in assessing the LV relaxation phase in clinical practice. Our results confirm the opinion of other authors,[29] who have shown that QTd is an approximate measure of abnormality of the complete course or repolarization.

According to the selection criteria, all patients had a preserved ($\geq$52%) LVEF. Regular exercise and weight loss increased LVEF by 2.2%, and the change was statistically significant. However, a 2.2% increase in LVEF is small and within the range of intraobserver variability. Such a small change might be easily unrecognized in individual patients, and it is uncertain that it may be clinically relevant, at least in patients with normal systolic function.

There is uncertainty about the best echocardiographic measurement to assess cardiac diastolic dysfunction,[2,16] but it was suggested that measuring the Doppler-derived E/A ratio and the mitral deceleration time (DT E) is useful.[19,20] Regular exercise and weight loss improved the E/A ratio, but the changes were marginal and might be easily unrecognized in individuals. In both groups at baseline, the DT E was higher than normal and worsened during the observational period. Furthermore, in many IG patients, LAVi and NYHA class decreased and physical work capacity increased, but the DT E time did not change or increase, showing that the DT E time does not correlate with LAVi, NYHA class, or exercise capacity. One should consider that the DT E time, and to a large extent the E/A ratio, are influenced by many factors. Measuring these two parameters, especially the DT E time, is not adequate to assess any changes of the LV relaxation phase in clinical settings. On the other hand, in hypertensive patients, abnormal LV relaxation increases LA size,[3,4] and an increased LA size was shown to be important to estimate stroke and death risks in hypertensive patients[30] and to predict outcome in patients with a mitral pathology[31] and in coronary patients.[19,32,33] Atrial dysfunction might be one of the reasons for the increased mortality observed in hypertensive patients with abnormal ventricular relaxation and preserved LVEF.[4–8] Regular physical exercise and weight loss decreased the LAVi and, in individual patients, the decreased LAVi correlated with a reduced NYHA class and an increased exercise capacity. It is proven that a decreased LAVi is a strong indicator of improved diastolic function and ventricular filling and might indicate a better cardiovascular prognosis.[30–33] Thus, we have confirmed that regular exercise and weight loss were therapeutically useful in hypertensive patients and that measuring LAVi allows for the assessment of the therapeutic effect on any intervention and the LV relaxation phase.

CONCLUSIONS

In pharmacologically well-treated hypertensive patients with abnormal LV relaxation and preserved LVEF, an intervention focusing on exercise and weight reduction reduced BP, NYHA class, and NT-proBNP values and increased physical work capacity and GFR. Furthermore, the regular physical exercise with weight loss decreased LAVi and improved the Doppler-derived E/A ratio, ie, reduced the LV relaxation dysfunction. These therapeutic effects were not seen in the CG of pharmacologically treated patients. The echocardiographic assessment of the LAVi is the best method for recognizing abnormal LV relaxation and the changes induced by a therapeutic intervention. To our knowledge, this is the first study in hypertensive patients that assessed the effect of exercise and weight loss on echocardiography.

Acknowledgment: The assistance of nurse ***Ms Hanna Brogli*** *and of the family physicians (who encouraged their patients to participate in this intervention program) is gratefully acknowledged.*

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