Correlation Between Diastolic Impairment and Lipid Metabolism in Mild-to-Moderate Hypertensive Postmenopausal Women

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Background: Many cardiovascular risk factors are found in hypertensive patients. The aim of this study was to evaluate the correlation between cardiac abnormalities (ie, diastolic and left ventricular hypertrophy) with other cardiovascular risk factors in postmenopausal women with hypertension.

Methods: A total of 200 consecutive postmenopausal women (mean age 47.5 ± 4 years) with mild-to-moderate hypertension that had never been treated were studied. Mean systolic pressure was 163 ± 15 mm Hg and mean diastolic pressure 97 ± 75 mm Hg. All subjects underwent M-mode two-dimensional echocardiography and cardiac Doppler. The following measurements were made: peak velocity of early left ventricular filling (E); peak velocity of late ventricular filling (A), and the ratio between early and late flow velocity peaks (E/A). The E/A ratio was then normalized for heart rate (E/Ac). Left ventricular mass index normalized for body surface was also measured. In each patient, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and plasma trig-

lycerides were measured. We evaluated the correlation of E/Ac and left ventricular mass index (LVMI) with the following variables: total cholesterol, HDL, LDL, triglyceridemia, smoking status, systolic and diastolic blood pressure, and body mass index.

Results: A significant negative correlation with total cholesterol (r = −0.15, *P* < .05) and LDL (r = −0.20; *P* = .005), as well as a significant positive correlation with HDL (r = 0.20, *P* < .01) were found. No other variable was significantly correlated with E/A. There was no correlation between LVMI and any variable analyzed.

Conclusion: In postmenopausal women with mild-to-moderate hypertension, high total cholesterol levels and low HDL levels are associated with impaired diastolic function. Am J Hypertens 2002;15:615–620 © 2002 American Journal of Hypertension, Ltd.

Key Words: Essential hypertension, diastole, hypercholesterolemia.

Hypertension is a major risk factor for cardiovascular disease in both men and women. Left ventricular hypertrophy (LVH) increases cardiovascular risk in hypertensive individuals.[1,2] The effect of left ventricular mass on mortality and morbidity seems to be greater in women than in men.[3] Diastolic dysfunction is another cardiac abnormality that is often found in hypertensive patients.[4]

A cluster of several cardiovascular risk factors is common in hypertensive individuals: dyslipidemia, hyperinsulinemia, obesity, and smoking tend to characterize these patients.[5–8] In addition, hypertensive women have a more atherogenic metabolic profile than do normotensive women.[9]

The present study aimed to evaluate the correlation between cardiac abnormalities (ie, LVH and diastolic dys-

function) and cardiovascular risk factors in postmenopausal women with hypertension.

Methods
Study Population

A total of 200 consecutive women (mean age 47.5 ± 4 years) who were referred to our outpatient laboratory for mild-to-moderate hypertension were studied. Diabetic patients were excluded. All women were postmenopausal and had never been treated for hypertension. Hypertension was defined a systolic blood pressure (SBP) ≥140 mm Hg or a diastolic blood pressure (DBP) ≥90 on three different examinations. Mean systolic pressure was 163 ± 15 mm Hg and mean diastolic pressure 97 ± 8 mm Hg. All patients had a medical history taken and underwent full physical examinations as well as weight and height measurements. Body mass index (BMI) was calculated for each patient; patients with a BMI ≥30 were classified as obese. The mean menopausal age was 47.7 ± 5 years, 28 women (24%; mean age 44 ± 5 years) had had surgical menopause, whereas 172 women (86%; mean age 48 ± 3 years) had had natural menopause. Of the women, 23 (11.5%) were receiving hormone replacement therapy. A total of 27 women (13.5%) were smokers.

All patients gave informed written consent to the study.

Echocardiographic Evaluation

All subjects underwent M-mode two-dimensional echocardiography and cardiac Doppler; recordings were obtained by means of a phased-array echo-Doppler system equipped with a 2.5 and 3.5 Hz transducer. The patients were examined in the left lateral recumbent position using standard parasternal, short-axis, and apical views. M-mode recordings were obtained, and left ventricular diastolic diameter as well as septal and posterior wall thickness measured. Left ventricular mass index (LVMI) was obtained by dividing the left ventricular mass by body surface area. Left ventricular hypertrophy was defined as a LVMI >109 g/m^2.[10,11] Pulsed Doppler recordings were made from the standard apical four-chamber view; mitral inflow velocity was recorded with the sample volume at the mitral annulus level. The following measurements were made: peak velocity of early left ventricular filling (E), peak velocity of late ventricular filling (A), and the ratio between early and late flow velocity peaks (E/A). The E/A ratio was then normalized by dividing it by the heart rate (E/Ac) calculated on five cardiac cycles during Doppler evaluation. An E/Ac of <1 was considered the cut-off point for identifying patients with diastolic dysfunction.

Blood Sampling

A blood sample was drawn from each patient between 7 and 9 AM, after an overnight fast. Serum concentration of total cholesterol (TC), high-density lipoprotein (HDL), and triglycerides (TGs) were analyzed by standard methods. Low-density lipoprotein (LDL) concentrations were determined according to the Friedewald formula.[12]

Table 1. Clinical and echocardiographic characteristics of the study population

Characteristic	Mean ± SD
Age (y)	47.5 ± 4
Weight (kg)	69.7 ± 12
Height (cm)	160.6 ± 7
Body mass index (kg/m^2)	27 ± 4
Systolic blood pressure (mm Hg)	163 ± 15
Diastolic blood pressure (mm Hg)	96.8 ± 8
Total cholesterol (mg/dL)	199 ± 35
LDL (mg/dL)	120.4 ± 35
HDL (mg/dL)	53.4 ± 9
Triglycerides (mg/dL)	126 ± 47
Left ventricular mass (g)	225.7 ± 82
Left ventricular mass index LVMI (g/m^2)	130.8 ± 46
Interventricular septum thickness (mm)	11 ± 2
Posterior wall thickness (mm)	10.3 ± 2
Peak velocity of early left ventricular filling (cm/sec)	75 ± 20
Peak velocity of late left ventricular filling (cm/sec)	71 ± 20
E/A	1.12 ± 0.4
E/Ac	1.14 ± 0.4

LDL = low-density lipoprotein; HDL = high-density lipoprotein; LVMI = left ventricular mass index; E/A = ratio between early and late flow velocity peaks; E/Ac = E/A normalized for heart rate.

Statistical Analysis

Data are expressed as mean values ± standard deviations. Linear univariate correlations were analyzed by means of Pearson's moment product. Multiple regression was used for multivariate analysis, by introducing in the model variables with $P < .1$ at univariate analysis. The t test for independent sample was used when appropriate.

We evaluated the linear correlation between LVMI and E/Ac, treated as continuous variables, and the following variables: TC, HDL, LDL, TGs, SBP, DBP, and BMI. The t test was used to analyze difference of LVMI and diastolic dysfunction between obese and nonobese patients and between smokers and nonsmokers.

After dividing patients according to whether they did had or did not have LVH and diastolic dysfunction, differences in TC, LDL, HDL, TGs, BMI, SBP, and DBP were analyzed.

A value of $P < .05$ was considered to be statistically significant.

Results

Clinical and echocardiographic characteristics of study population are reported in Table 1.
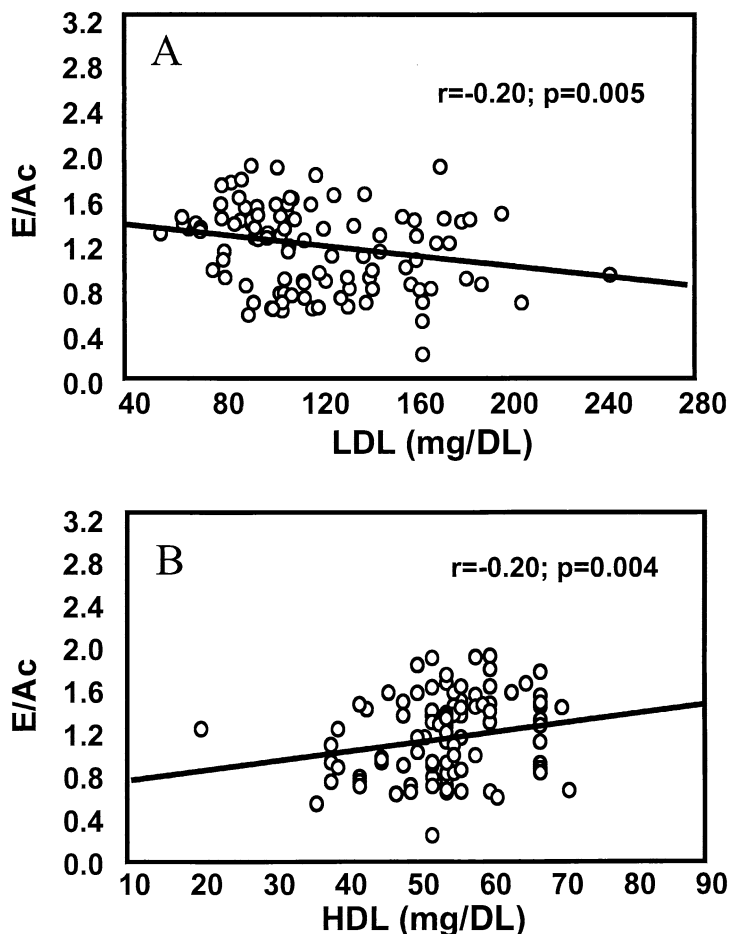
FIG. 1. **A**) Correlation between ratio of early and late flow velocity peaks, normalized for heart rate (E/Ac) and low-density lipoprotein (LDL). **B**) Correlation between E/Ac ratio and high-density lipoprotein (HDL).

Left ventricular hypertrophy was found in 115 patients (57.5%) and diastolic dysfunction in 79 (60.5%) patients.

A total of 77 patients (39%) had TC ≥200 mg/dL; 66 patients (33%) had LDL ≥130 mg/dL; 59 patients (30%) had HDL <50 mg/dL; and nine (9%) had plasma triglycerides ≥200 mg/dL. Of the patients, 51 (26%) had a BMI ≥30.

The E/Ac was significantly correlated with TC (r = −0.15, $P <$ .05), LDL (r = −0.20; $P = 0.005$) (Fig. 1A), and HDL (r = 0.20, $P =$ .004) (Fig. 1B). The E/Ac was not significantly correlated with age (r = 0.1, $P =$ .1), BMI (r = −0.03, $P =$ .6), SBP (r = −0.08, $P =$ .2), or DBP (r = −0.02, $P =$ .7). In addition, E/Ac was not different between smokers and nonsmokers (1.03 ± 0.5 v 1.16 ± 0.3, $P =$ .1). When patients were divided according to whether they did or did not have diastolic dysfunction, patients with an E/Ac <1 had significantly higher TC (206.9 ± 38 v 193.8 ± 31 mg/dL, $P =$ .009), significantly lower HDL (51.2 ± 11 v 54.9 ± 7 mg/dL; $P =$ .004), and significantly higher LDL (130.6 ± 33 v 113.6 ± 34 mg/dL, $P =$ .0008) (Fig. 2). No significant differences were found concerning TGs (125.3 ± 54 v 126.5 ± 42 mg/dL, $P =$ .85), SBP (162.6 ± 14 v 163.6 ± 15 mm Hg;

$P =$ .6), DBP (96.5 ± 8 v 97 mm Hg; 1 ± 8, $P =$ .6), and BMI (27.2 ± 5 v 26.8 ± 5, $P =$ .5).

In a multivariable model, both HDL and TC remained independently associated with E/Ac (r = −0.16, $P =$ .02; and r = 0.20, $P =$ .002, respectively), whereas no other variable was significantly correlated with E/Ac.

The LVMI was not correlated with age (r = −0.11, $P =$ .09), TC (r = −0.196, $P =$ .783), HDL (r = 0.09, $P =$ .184), LDL (r = −0.6, $P =$ .3), plasma TGs (r = 0.08, $P =$ .2), SBP (r = 0.04, $P =$ .5), DBP (r = 0.10, $P =$ 0.12), or BMI (r = −0.05, $P =$ .4). The LVMI also was not significantly different between smokers and nonsmokers (121 ± 36 v 132.3 ± 48 g/m^2; $P =$ .2).

When patients were divided according to whether they had or did not have LVH, no significant differences were found concerning age (47.6 ± 4 v 47.2 ± 4 years, $P =$ .5), TC (198.6 ± 35 v 199.5 ± 34 mg/dL, $P =$ .8), HDL (53.5 ± 9 v 53.4 ± 8 mg/dL, $P =$ .9), LDL (119.6 ± 35 v 121.4 ± 35 mg/dL, $P =$ .85), plasma TGs (128.1 ± 46 v 123.2 ± 48 mg/dL, $P =$ .4), SBP (163.5 ± 14 v 162.7 ± 15 mm Hg, $P =$ .6), DBP (97.2 ± 8 v 96.3 ± 8 mm Hg, $P =$ .4), or BMI (26.3 ± 4 v 27.2 ± 4, $P =$ .1).
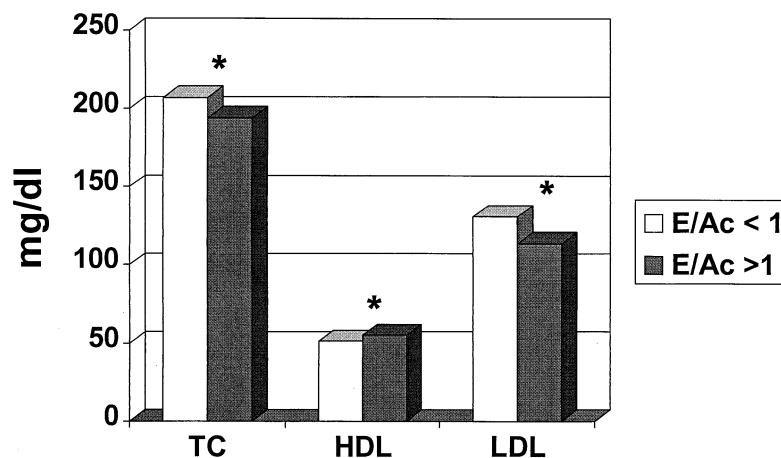
FIG. 2. Differences in total cholesterol (TC), LDL, and HDL between patients with and without diastolic dysfunction. Other abbreviations as in Fig. 1. *P < .01.

Discussion

In the present study, we aimed to evaluate the association between cardiac abnormalities and cardiovascular risk factors in women with mild-to-moderate hypertension. To avoid confounding factors, we studied a selected population of postmenopausal women with hypertension that had never been treated; consequently, the results of the present study cannot be extended to men, women of child-bearing age, and elderly subjects.

The main finding of the present study is that an impairment of diastolic function, as evaluated by Doppler methodology, is independently correlated with higher levels of TC and LDL and is associated with lower levels of HDL. No other association was found between diastolic dysfunction and other cardiovascular risk factors. Left ventricular hypertrophy was not associated with any smoking, obesity, or lipid disorders. As in previous studies, left ventricular hypertrophy was not associated with clinical blood pressure (BP).[13]

Abnormalities of glucose, insulin, and lipid metabolism are common in hypertensive patients. Hypercholesterolemia is common in hypertensive individuals, and 40% of hypercholesterolemic patients have hypertension.[5] Subjects with interrelated abnormalities of lipid, glucose metabolism, and high BP have the syndrome X or metabolic syndrome, in which the primary culprit is the insulin resistance. These patients tend to have higher concentrations of plasma TGs and lower concentrations of HDL.[14]

Metabolic abnormalities could play a role in the pathogenesis of the complications of hypertension in many patients and could increase the risk of ischemic heart disease.[15]

Diastolic dysfunction is a common finding in hypertension-related heart disease. Left ventricular diastolic filling may be abnormal even in the absence of LVH, and may represent an early marker of organ damage in hypertension.[4] Age, left ventricular mass, ambulatory BP, and autonomic control have been shown to be predictors of left ventricular filling abnormalities in previous studies.[16–18]

The correlation among diastolic dysfunction, LVH, and metabolic abnormalities has been evaluated in previous studies, with conflicting results. Diastolic dysfunction has often been associated with parameters of glucose metabolism, albeit with some differences: although some studies showed an association with glucose level after glucose load, other authors found a correlation with insulin levels and insulin resistance but not with glucose concentration.[19–22] Left ventricular hypertrophy was correlated with metabolic abnormalities in some studies, but not in others. Differences in the study population with regard to clinical, demographic, and therapeutic characteristics could account for these conflicting results.

Genetic predisposition to hypertension seems to influence the relationship between insulin sensitive and cardiac abnormalities. A family history of hypertension could affect the myocardial response to increased insulin levels, with a greater impairment of diastolic dysfunction; on the other hand, insulin sensitivity and genetic predisposition do not affect left ventricular mass response.[23]

To our knowledge, our study is the first to show that diastolic dysfunction has a positive (albeit weak) correlation with TC and LDL and a negative correlation with HDL.

In a previous study, high cholesterol levels were demonstrated to be associated with renal impairment in hypertensive patients.[24]

We did not find any correlation of E/Ac with plasma TGs. However, among patients enrolled in the study, the level of this variable was relatively low, with very few patients having TGs above the normal range. It may be that these finding reflect a common dietary factor.

Some hypotheses about the nature the association found in our study can be proposed. The main pathophysiologic feature of the metabolic syndrome in hypertensive indi-

viduals is insulin resistance and hyperinsulinemia. The effect of hyperinsulinemia could in part be mediated by an increase in sympathoadrenal system activity.[14]

Experimental studies have evaluated a growth-stimulating effect of insulin on cardiomyocytes, as well as a stimulation of collagen production by fibroblasts. Clinical studies have evaluated the possibility that insulin metabolism abnormalities could influence the development of myocardial hypertrophy and an increase in myocardial stiffness.[25,26]

Lipid metabolism abnormalities and diastolic dysfunction could be two different effects of hyperinsulinemia; however, we did not measure insulin resistance, so we cannot confirm this hypothesis.

In summary, in hypertensive patients a complex relationship exists between BP, metabolic abnormalities and sympathetic activity. Cardiovascular abnormalities may be a result of these relationships.

In hypertensive patients, hypercholesterolemia may cause endothelial dysfunction; as a consequence, this could induce a further increase of BP, with an early organ damage.[27,28] In the meantime, treatment with statins seems to be able to lower BP levels.[29] However, the observation that BP does not correlate with diastolic dysfunction, neither in this nor in other studies, opposes this hypothesis.

A great body of evidence deriving from epidemiologic studies and clinical trials supports the hypothesis that other mechanisms beside BP level may cause cardiovascular complications in hypertensive subjects.[30] Furthermore, BP level did not predict the risk of IHD in patients with high TGs and low HDL cholesterol, the peculiar dyslipidemia seen in the metabolic syndrome X.[13] Our study goes in the same direction, showing that an early abnormality as diastolic function impairment is related to metabolic abnormality, although is not associated with BP levels.

In conclusion, in postmenopausal women with mild-to-moderate hypertension, diastolic abnormality is correlated with lipid metabolism abnormality. Further studies are needed to explore the nature of this association.

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