Aortic Elastic Properties in Patients With Hypertensive Response to Exercise

Atila Bitigen, MD; Erdem Türkyılmaz, MD; Irfan Barutcu, MD;
Gökhan Kahveci, MD; Ibrahim Halil Tanboğa, MD; Soe Moe Aung, MD;
Nihal Özdemir, MD; Cihangir Kaymaz, MD

Background The aim of this study was to evaluate whether there is a relationship between aortic elastic properties in patients with a suggestive response to treadmill exercise testing.

Methods and Results The study group comprised 32 patients suggesting hypertensive response to exercise and 20 patients suggesting normal blood pressure response to treadmill exercise testing. Baseline demographic characteristics were similar in both groups. However, the mean aortic stiffness index of patients suggesting hypertensive response to treadmill exercise testing was significantly higher (4.8 ± 1.26 vs 2.36 ± 1.09 ; $p=0.001$) whereas aortic distensibility was significantly lower (12.82 ± 5.84 vs 22.64 ± 14.54 ; $p=0.001$) than the control group. The aortic strain of patients with hypertensive response to exercise was lower than the control group ($12 \pm 3\%$ vs $19.2 \pm 5\%$, $p<0.001$). The left ventricular mass (LVM) of these patients was also higher than control group (206.5 ± 46.3 vs 134.2 ± 19.97 ; $p=0.01$). A negative correlation between LVM and distensibility was found ($r=-0.64$; $p=0.001$) well as a positive correlation between LVM and aortic stiffness index ($r=0.51$; $p=0.004$) in patients suggesting hypertensive response to exercise. Pressure–rate product was also found to be correlated with LVM ($r=0.47$; $p=0.006$).

Conclusion Elastic properties of the aorta may be impaired in subjects showing exaggerated blood pressure response to exercise long before clinically manifest hypertension, particularly if the LVM is increased. (*Circ J* 2007; 71: 727–730)

Key Words: Aortic stiffness; Exercise testing; Hypertensive response; Left ventricular mass; Treadmill

Treadmill exercise testing is generally accepted as an important diagnostic tool for coronary artery disease. It can also provide accurate estimates of blood pressure (BP) reactivity to physical exertion! It has been shown that latent hypertension can be exacerbated by exercise^{2–5} It has also been shown that physiopathological changes indicating hypertension and its complications have occurred in those suggesting hypertensive response to exercise even in clinically normotensive states⁶

Recently, the identification of a close relationship between aortic stiffness and cardiovascular mortality has aroused the interest of investigators to carry out studies related to aortic stiffness^{7–9} In many diseases, aortic stiffness has been studied to show whether the great vessels are involved and to obtain information about the pathophysiology of the great arteries.^{10–14} Accordingly, it has been shown that aortic stiffness is increased in patients with hypertension, diabetes and in postmenopausal women!^{11,12} Although it is well known that hypertension causes stiff arteries, there is insufficient data regarding aortic elastic properties in patients suggesting hypertensive response to treadmill exercise testing before hypertension has manifested clinically. Therefore, the aim of this study was to evaluate aortic elastic properties in patients suggesting

hypertensive response to treadmill exercise testing.

Methods

Patients

A total of 52 patients who underwent treadmill exercise testing with the suspicion of coronary artery disease but showing no ischemic changes during exercise were included in the study. They were divided into 2 groups according to their test results; those suggesting hypertensive responses to exercise (group-1) and those suggesting normal BP responses to exercise (group-2).

All subjects underwent treadmill exercise testing using the modified Bruce protocol. Prior to testing, all subjects were instructed to not eat, drink any beverages, or smoke for 3 h before the testing. Heart rate (HR), ECG, and BP were recorded at the onset and at the end of each stage. BP was measured automatically by sphygmomanometry (Tango Stress BP, Morisville NC, USA). Also, pressure–rate product (PRP) at peak exercise of treadmill test was calculated as follows: $PRP = \text{systolic arterial pressure} \times HR (\text{beats/min}) \times 10^{-2}$.

All subjects also underwent echocardiographic evaluation in order to exclude left ventricular wall motion abnormality, systolic dysfunction and valvular disorders. Hypertensive response to treadmill exercise testing was defined as $\geq 210/105$ mmHg and $\geq 190/105$ mmHg at peak exercise in males and females, respectively.^{5,15} Exclusion criteria were resting BP $\geq 140/90$ mmHg, those taking antihypertensive medications, those with moderate to severe valvular regurgitation or stenosis, diabetes mellitus, congenital heart disease,

(Received August 28, 2006; revised manuscript received February 7, 2007; accepted February 15, 2007)

Department of Cardiology, Kartal Kosuyolu Yüksek İhtisas Education and Research Hospital, Istanbul, Turkey

Mailing address: Atila Bitigen, MD, TRT-Marmara Sitesi E-Blok No:10, P.K: 80840 Ulus/Beşiktaş, Istanbul, Turkey. E-mail: bitigen@yahoo.com

Table 1 Demographic and Biochemical Variables

	Group I (32)	Group II (20)	p value
Age (years)	48.7±7	47.8±5	NS
Sex	15 F, 17 M	9 F, 11 M	NS
BMI (kg/m ²)	24±5	25±4	NS
TC (mg/dl)	198±34	185±34	NS
LDL-C (mg/dl)	122±32	115±30	NS
HDL-C (mg/dl)	45±11	46±11	NS
TG (mg/dl)	140±40	133±39	NS
Plasma glucose (mg/dl)	100±11	99±19	NS
Creatinine (mg/dl)	0.95±0.12	0.90±0.14	NS

NS, not significant; BMI, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; TG, triglycerides.

atrial fibrillation, left ventricular systolic dysfunction, renal disease, the presence of familial hypercholesterolemia, obesity, smoking habit, the use of oral contraceptives or estrogen replacement therapy, the presence of aortic disease such as aneurysm, Marfan's syndrome, coarctation or previous aortic surgery and insufficient echocardiographic evaluation due to poor echocardiographic windows. Informed consent was given by all participants and the local ethics committee approved the study protocol.

Echocardiographic Measurements

Transthoracic echocardiography was performed by an experienced echocardiographer, using a System-Five Performance instrument (General Electric, Vingmed, Norway) with a 2.5 MHz phased-array transducer. The right brachial artery was used to calculate systolic and diastolic pressures during echocardiographic evaluation. At least 3 consecutive measurements were obtained and the results were averaged. Recordings were taken with patients positioned in the left lateral decubitus position. The M-mode traces were recorded at a speed of 50 mm/s and the Doppler signals were also recorded at a speed of 100 mm/s.

Simultaneous electrocardiographic recordings were also taken. The average of 3 consecutive cycles were calculated for each parameter. Measurement of the left ventricle (LV) diameters and the left atrial systolic diameter was performed on M-mode traces recorded in the parasternal long axis view according to established standards.¹⁶ Diameter of the ascending aorta was measured from the same view on the M-mode tracing at 3 cm above the aortic valve.¹⁷ The systolic diameter was measured at the maximal anterior motion of the aorta, whereas the diastolic diameter was measured at the peak of the QRS complex on the simultaneously recorded electrocardiogram.

Calculation of the Elastic Parameters of the Aorta

The aortic strain, index and aortic distensibility were used as aortic elasticity parameters.^{17–21} The formulae used in the calculation of these parameters were as follows: aortic strain (%)=(aortic systolic diameter–diastolic diameter)×100/diastolic diameter; aortic stiffness index=ln(systolic pressure/diastolic pressure)/aortic strain; distensibility (cm²/dyn)=(2×aortic strain)/(systolic pressure–diastolic pressure). In addition, the left ventricular mass (LVM) was calculated by using the Devereux formula: LVM=0.8×1.04 [(interventricular septum thickness in diastole+LV internal diameter in diastole+posterior wall thickness in diastole)³–LV internal diameter in diastole³]+0.6, as described previ-

Table 2 Comparison of the Echocardiography of Both Groups Values

	Group I (32)	Group II (20)	p value
LA (cm)	3.4±0.2	3.2±0.3	NS
EF (%)	68±7	65±6	NS
FS (%)	39±5	44±6	NS
AO (cm)	3.06±0.3	3.1±0.3	NS
RA (cm)	3.2±1.8	2.9±1.9	NS
LV systolic diameter (cm)	3.1±0.3	2.9±0.4	NS
LV diastolic diameter (cm)	5.1±0.4	4.9±0.5	NS
Aortic systolic diameter (cm)	3.1±0.4	3.0±0.5	NS
Aortic diastolic diameter (cm)	2.9±0.3	2.6±0.3	0.001
SBP (mmHg)	118.9±4	118.3±3	NS
DBP (mmHg)	77±5	75±4	NS
Heart rate (beats/min)	73±9	70±4	NS

LA, left atrial diameter; EF, ejection fraction; FS, fractional shortening; AO, aortic root diameter; RA, right atrial diameter; LV, left ventricular; SBP, systolic blood pressure; DBP, diastolic blood pressure. Other abbreviation see in Table 1.

ously?²²

Biochemical Analysis

Venous blood samples were obtained from all subjects after an overnight fast and serum glucose, total cholesterol, triglyceride, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels were immediately measured by an autoanalyzer (Olympus AU 5200, Japan).

Statistical Analysis

Statistical analysis was performed with SPSS for Windows version 10.0 (SPSS Inc Chicago, IL, USA). Data are presented as mean±SD. For continuous variables the Mann-Whitney U test and for categorical changes the chi-square test was used.

Relationships between various variables were examined with Pearson correlation coefficients. A p-value <0.05 was considered to indicate statistical significance.

Results

Baseline demographic properties were similar in both groups (Table 1). There was no significant difference between the 2 groups with regard to serum total cholesterol, HDL-cholesterol (C), LDL-C, triglyceride and serum glucose levels (Table 1). Comparison of transthoracic echocardiographic parameters is shown in Table 2. The mean aortic stiffness index of patients suggesting hypertensive response to treadmill exercise testing was significantly higher (4.8±1.26 vs 2.36±1.09; p=0.001) whereas aortic distensibility was significantly lower (12.82±5.84 vs 22.64±14.54; p=0.001) than the control group. The aortic strain of patients with hypertensive response to exercise was lower than the control group (12±3% vs 19.2±5%, p<0.001). The LVM of these patients was also higher than control group (206.5±46.3 g/m² vs 134.2±19.97 g/m²; p=0.01). We also found a negative correlation between LVM and distensibility (r=–0.64; p=0.001) as well as a positive correlation between LVM and aortic stiffness index (r=0.51; p=0.004) in patients suggesting hypertensive response to exercise.

Relationship Between Hemodynamic Response to Treadmill Test and Cardiac Mass

We formed 2 groups (Group-1: BP >210/105 mmHg, males and >190/105 mmHg in females) and compared the

Table 3 Aortic Stiffness Index, LV Mass and Aortic Distensibility Values of Both Groups

	Group I	Group II	p value
Aortic stiffness index	4.8±1.26	2.36±1.09	0.001
Aortic distensibility	12.82±5.84	22.64±14.54	0.001
Aortic strain (%)	12.5±3	19.2±5	0.001
LV mass (g/m ²)	206.5±46.3	134.2±19.97	0.001

Abbreviation see in Table 2.

parameters; however, the degree of hemodynamic response to treadmill test and amounts of cardiac mass might be continuously and widely distributed. Therefore, the relationship between PRP (which was calculated at the peak of the treadmill test) and cardiac mass (which was evaluated by the echocardiographic study) was evaluated in all of the patients in Group-1 and Group-2. PRP was found to correlate with LVM ($r=0.47$; $p=0.006$) (Fig 1). Among LVM, aortic stiffness and distensibility, LVM was best correlated with exercise-induced BP increase ($r=0.51$; $p=0.004$). However, we found no correlation between pulse pressure and exercise-induced BP increase.

Discussion

The principle findings of this study are (1) aortic stiffness is higher and distensibility is lower in patients suggesting hypertensive response to treadmill exercise testing when compared to those with normal BP response to exercise; (2) the patients suggesting hypertensive response to treadmill exercise testing have higher LVM when compared to those with normal BP response to exercise; and (3) LVM is inversely correlated with aortic distensibility, but is positively correlated with aortic stiffness in patients suggesting hypertensive response to exercise.

Several different techniques to evaluate arterial compliance have been described. Segers et al²³ used ultrasound and magnetic resonance imaging to measure central pressure and flow waveforms in 26 patients with Marfan's syndrome and 26 age- and gender-matched controls. Aortic systolic and diastolic cross-sectional areas were measured at the ascending aorta, diaphragm, and lower abdominal aorta. From these measurements, local characteristic impedance and local reflection coefficients were calculated. Calculated global wave reflection indexes were defined as augmentation index and the ratio of backward to forward pressure wave. They concluded that the major determinants of augmentation index were pulse wave velocity and the effective length of the arterial system.²³ Lind et al²⁴ compared 3 different methods to determine arterial compliance in a population-based study. Assessment of arterial distensibility by ultrasound in the carotid artery, by pulse wave analysis (augmentation index) and the stroke volume to pulse pressure ratio by echocardiography were inter-related and only carotid artery distensibility and the stroke volume to pulse pressure ratio were independently related to coronary risk. Also, Tanriverdi et al²⁵ using M-mode echocardiography measured elastic properties of aorta in 40 patients with obstructive sleep apnea and respiratory disturbance index showed a positive correlation with aortic stiffness and a negative correlation with distensibility. In our study we used the same technique to measure aortic elastic properties.

Previous studies have shown that aortic compliance decreases in hypertensive subjects.^{26,27} A long follow-up

Fig 1. Relationship between left ventricular (LV) mass and pressure-rate product (PRP).

study showed that the increase in stiffness over a period of 6 years is more marked in treated hypertensives than in normotensives, indicating accelerated arterial aging among treated hypertensives.²⁷ Three factors were identified as being responsible for accelerated progression of arterial stiffness in treated hypertensive patients, as follows: uncontrolled BP values, increased HR, and increased serum creatinine.²⁷

Tomiya et al²⁸ assessed the clinical significance of the LV geometry and physical fitness in 192 patients with borderline and mild hypertension. They found that patients with concentric hypertrophy exhibited slightly impaired levels of physical fitness and cardiac work efficiency, and the progression of concentric hypertrophy demonstrated further impairments of these conditions. The authors concluded that not only lowering BP, but also improving LV hypertrophy (LVH), cardiovascular hemodynamics, and physical fitness might be required in patients with concentric hypertrophy.²⁸ Even in the absence of hypertension, exaggerated BP responses during exercise testing suggest a probability of LVH, a finding associated with the cardiac "end-organ" manifestations of hypertension.²⁹ Change in BP due to exercise may act as a mechanical stimulus to the myocytes, activating protein synthesis and hypertrophy.³⁰ Cardiac sympathetic nervous activity may also affect myocyte development.³¹

Study Limitations

In a small number of patients, we did not measure the relationship between the indices of target organ damage such as renal, vascular and cardiac changes and elastic properties of aorta, although none of the patients had apparent renal, cardiac or other systemic disease. On the other hand, prospective studies have demonstrated that target organ damage in essential hypertension is more closely associated with ambulatory BP than it is with clinical BP and the incidence of cardiovascular events is correlated with BP occasional as well as ambulatory measurement.^{32,33} We did not perform ambulatory BP monitoring to assess long-term course of BP.

Conclusions

In the present study we have found a relationship between arterial stiffness and LVM in patients with hypertensive response to exercise. These findings may indicate that elastic properties of the aorta may be impaired in subjects showing exaggerated BP response to exercise long before clinically manifest hypertension, particularly if the LVM is increased. However, these results need to be validated with further large-scale studies and long-term follow-up.

References

1. Franz IW. Exercise hypertension: Its measurement and evaluation. *Herz* 1987; **12**: 99–109.
2. Manolio TA, Burke GL, Savage PJ, Sidney S, Gardin JM, Oberman A. Exercise blood pressure response and 5-year risk of elevated blood pressure in a cohort of young adults: The CARDIA study. *Am J Hypertens* 1994; **7**: 234–241.
3. Wilson MF, Sung BH, Pincomb GA, Lovullo WR. Exaggerated pressure response to exercise in men at risk for systemic hypertension. *Am J Cardiol* 1990; **66**: 731–736.
4. Matthews CE, Pate RR, Jackson KL, Ward DS, Macera CA, Kohl HW, et al. Exaggerated blood pressure response to dynamic exercise and risk of future hypertension. *J Clin Epidemiol* 1998; **51**: 29–35.
5. Singh JP, Larson MG, Manolio TA, O'Donnell CJ, Lauer M, Evans JC, et al. Blood pressure response during treadmill testing as a risk factor for new-onset hypertension. *Circulation* 1999; **99**: 1831–1836.
6. Kamarck TW, Eranen J, Jennings JR, Manuck SB, Everson SA, Kaplan GA, et al. Anticipatory blood pressure responses to exercise are associated with left ventricular mass in Finnish men: Kuopio Ischemic Heart Disease Risk Factor Study. *Circulation* 2000; **102**: 1394–1399.
7. Arnett DK, Evans GW, Riley WA. Arterial stiffness a new cardiovascular risk factor. *Am J Epidemiol* 1994; **140**: 669–682.
8. Blacher J, Asmar R, Djane S, London GM, Safar ME. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. *Hypertension* 1999; **33**: 1111–1117.
9. Shokawa T, Imazu M, Yamamoto H, Toyofuko M, Tasaki N, Okimoto T, et al. Pulse wave velocity predicts cardiovascular mortality: Findings from the Hawaii-Los Angeles-Hiroshima study. *Circ J* 2005; **69**: 259–264.
10. Gorgulu S, Uslu N, Eren M, Celik S, Yildirim A, Dagdeviren B, et al. Aortic stiffness in patients with cardiac syndrome X. *Acta Cardiol* 2003; **58**: 507–511.
11. Eren M, Gorgulu S, Uslu N, Celik S, Dagdeviren B, Tezel T. Relation between aortic stiffness and left ventricular diastolic function in patients with hypertension, diabetes, or both. *Heart* 2004; **90**: 37–43.
12. Gorgulu S, Eren M, Celik S, Dagdeviren B, Uslu N, Suer N, et al. The effects of hormonal therapy on aortic stiffness and left ventricular diastolic function. *Acta Cardiol* 2003; **58**: 1–8.
13. Fukuhara M, Yoshida A, Fuji K, Iide M, Takehara T. Prediction of cognitive function by arterial stiffness in the very elderly. *Circ J* 2006; **70**: 756–761.
14. Park SM, Soe HS, Lim HE, Shin SH, Park CG, Oh DJ, et al. Assessment of arterial stiffness index as a clinical parameter for atherosclerotic coronary artery disease. *Circ J* 2005; **69**: 1218–1222.
15. Lauer MS, Levy D, Anderson KM, Plehn JF. Is there a relationship between exercise systolic blood pressure response and left ventricular mass?: The Framingham Heart Study. *Ann Intern Med* 1992; **116**: 203–210.
16. Henry WL, DeMaria A, Gramiak R, King DL, Kisslo JA, Popp RL, et al. Report of the American Society of Echocardiography Committee on nomenclature and standards in two dimensional echocardiography. *Circulation* 1980; **62**: 212–217.
17. Stratos C, Stefanidis C, Kallikazaros I, Boudoulas H, Toutouzas P. Ascending aorta distensibility abnormalities in hypertensive patients and response to nifedipin administration. *Am J Med* 1992; **93**: 505–512.
18. Lacombe F, Dart A, Dewar E, Jennings G, Cameron J, Laufer E. Arterial elastic properties in man: A comparison of echo-Doppler indices of aortic stiffness. *Eur Heart J* 1992; **13**: 1040–1045.
19. Hirai T, Sasayama S, Kawasaki T, Yagi S. Stiffness of systemic arteries in patients with myocardial infarction: A noninvasive method to predict severity of coronary atherosclerosis. *Circulation* 1989; **80**: 78–86.
20. Stefanadis C, Wooley CF, Bush CA, Kolibash AJ, Boudoulas H. Aortic distensibility abnormalities in coronary artery disease. *Am J Cardiol* 1987; **59**: 1300–1304.
21. Stefanadis C, Wooley CF, Bush CA, Kolibash AJ, Boudoulas H. Aortic distensibility in post stenotic aortic dilatation: The effect of co-existing coronary artery disease. *Am J Cardiol* 1988; **18**: 78–82.
22. Devereux RB. Detection of left ventricular hypertrophy by M-mode echocardiography: Anatomic validation, standardization, and comparison to other methods. *Hypertension* 1987; **9**: 19–26.
23. Segers P, De Backer J, Devos D, Rabben SI, Gillebert TC, Van Bortel LM, et al. Aortic reflection coefficients and their association with global indexes of wave reflection in healthy controls and patients with Marfan's syndrome. *Am J Physiol Heart Circ Physiol* 2006; **290**: H2385–H2392.
24. Lind L, Fors N, Hall J, Marttala K, Stenborg A. A comparison of three different methods to determine arterial compliance in the elderly: The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. *J Hypertens* 2006; **24**: 1075–1082.
25. Tanriverdi H, Evrengul H, Kaftan A, Kara CO, Kuru O, Tanriverdi S, et al. Effect of obstructive sleep apnea on aortic elastic parameters: Relationship to left ventricular mass and function. *Circ J* 2006; **70**: 737–743.
26. Kuwajima I, Suzuki Y, Shimomura T, Kanemaru A, Hoshino S, Kuramoto K. Diminished nocturnal decline in blood pressure in elderly hypertensive patients with left ventricular hypertrophy. *Am Heart J* 1992; **123**: 1307–1311.
27. Benetos A, Adamopoulos C, Bureau JM, Temmar M, Labat C, Bean K, et al. Determinants of accelerated progression of arterial stiffness in normotensive subjects and in treated hypertensive subjects over a 6-year period. *Circulation* 2002; **105**: 1202.
28. Tomiyama H, Doba N, Kushihiro T, Yamashita M, Kanmatsuse K, Kajiwaru N, et al. Prospective studies on left ventricular geometric patterns and exercise tolerance in unmedicated men with borderline and mild hypertension. *J Hypertens* 1996; **14**: 1223–1238.
29. Julius S, Li Y, Brant D, Krause L, Buda AJ. Neurogenic pressor episodes fail to cause hypertension, but do induce cardiac hypertrophy. *Hypertension* 1989; **13**: 422–429.
30. Ostman-Smith I. Cardiac sympathetic nerves as the final common pathway in the induction of adaptive cardiac hypertrophy. *Clin Sci* 1981; **61**: 265–272.
31. Bouthier JD, De Luca N, Safar ME, Simon AC. Cardiac hypertrophy and arterial distensibility in essential hypertension. *Am Heart J* 1985; **109**: 1345–1352.
32. Verdecchia P, Reboldi GP. Hypertension and microalbuminuria: The new detrimental duo. *Blood Press* 2004; **13**: 198–211.
33. Verdecchia P, Clement D, Fagard R, Palatini P, Parati G. Blood Pressure Monitoring Task force III: Target-organ damage, morbidity and mortality. *Blood Press Monit* 1999; **4**: 303–317.