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ORIGINAL ARTICLE

The relationship between aortic stiffness and left ventricular function in patients with Cushing's disease

Aortic stiffness in Cushing's disease

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Abstract We aimed to investigate the aortic function and to evaluate the relationship between aortic stiffness and systolic and diastolic functions of the left ventricle in patients with Cushing's disease (CD). Fourteen women and one man with newly diagnosed CD, and 17 control cases were enrolled in this study. All subjects underwent echocardiography and systolic and diastolic aortic measurements were noted from M-mode aortic root. Aortic elastic parameters, aortic strain, and distensibility were calculated. Left ventricle functions were measured using echocardiography including, two-dimensional, M-mode, conventional Doppler, and tissue Doppler imaging. Aortic strain (7.4 ± 1.9 vs. $12.3 \pm 2.4\%$; $P < 0.001$), and aortic distensibility ($3.2 \pm 1.1 \times 10^{-6}$ vs. $5.6 \pm 1.4 \times 10^{-6}$ cm^2 dyn^{-1}; $P < 0.001$) were significantly decreased in patient group compared with control group. Mitral E velocity and the ratio of E/A were significantly lower and deceleration time of E was significantly prolonged in patients with CD. We also observed that patients with CD had markedly lower early diastolic myocardial peak velocity (Em) and Em/Am ratio and higher Tei index than in control group. Aortic elastic parameters are deranged in patients with CD and there is a significant correlation between left ventricular parameters determined by tissue Doppler echocardiography and aortic elastic parameters in these patients. We think that patients with CD should also be evaluated with aortic stiffness known to be an early marker for atherosclerosis.

Keywords Cushing's disease · Aortic stiffness · Left ventricular function · Tissue Doppler imaging

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Introduction

Epidemiological studies have shown that cardiovascular complications in patients with Cushing syndrome (CS) cause a mortality rate of fourfold higher than that expected in the normal population [1, 2]. Cardiovascular risk associated with CS is caused either by clinical and metabolic complications or by the vascular alterations resulting from chronic glucocorticoid excess. In CS, the main vascular alteration is atherosclerosis [3]. High prevalence of atherosclerosis due to visceral obesity, systemic arterial hypertension, impairment of glucose tolerance, hyperlipidemia, and hypercoagulability is known to occur in hypercortisolism [3–5].

Aortic elastic properties and aortic stiffness are important determinants of increased cardiovascular morbidity and mortality in different diseases [6–8] and can be evaluated by transthoracic echocardiography (TTE) [8]. Aortic stiffness may influence the structure of the heart and cardiac systolic and diastolic functions, and in recent years it is used as a noninvasive method to identify atherosclerosis in subclinical phase. However, to our knowledge, there is no study evaluating aortic stiffness in patients with CS in the literature.

The current study was designed to investigate the aortic function in patients with Cushing's disease (CD) and to evaluate the relationship between aortic stiffness and

systolic and diastolic functions of the left ventricle in these patients.

Materials and methods

The study was conducted in the Department of Cardiology, and the Department of Endocrinology and Metabolism of Ankara Ataturk Education and Research Hospital, Turkey. All patients and control group gave written informed consent to participate in the study according to the protocol approved by the local ethic committee and in accordance with the ethical standards of Helsinki declaration.

Study population

Fourteen women and one man with newly diagnosed CD were enrolled in this study. The diagnosis of CD was based on the presence of the following criteria [9, 10]: (1) increase in daily urinary cortisol excretion with inappropriately high plasma adrenocorticotrophic hormone (ACTH) concentrations; (2) increase in basal serum cortisol concentrations with lack of the physiological circadian rhythm; (3) failure of urinary and serum cortisol suppression after low-dose dexamethasone test but greater than 50% decrease after high-dose dexamethasone test. In all patients, imaging of the pituitary was obtained by magnetic resonance and an adenoma was observed. Inferior petrosal sinus sampling (IPSS) with CRH stimulation was performed in all patients. All patients underwent selective surgical resection of an ACTH-secreting pituitary adenoma by transsphenoidal approach, and the diagnoses were confirmed immunohistochemically. Patient profiles at the time of diagnosis are summarized in Table 1.

Four out of 15 patients had no additional disease. Two patients had merely diabetes mellitus (DM), 3 patients had merely hypertension (HT), 1 patient had DM and hyperlipidemia, 3 patients had DM and hypertension, and 2 patients had DM, HT, and hyperlipidemia.

Patients with CD were compared with 17 control cases matched for age, gender, body mass index (BMI), and concomitant diseases (HT, hyperlipidemia, impaired glucose tolerance or DM). Controls with concomitant diseases were selected among hypertensive and/or diabetic and/or hyperlipidemic patients seen at our outpatient clinic. Five out of 17 patients in the control group had DM, 3 patients had HT, 1 had hyperlipidemia, 2 patients had DM and hyperlipidemia, 1 patient had hyperlipidemia and HT, and 1 patient had DM, HT, and hyperlipidemia.

In 8 patients with CD and 8 controls, DM was well controlled by at least one oral hypoglycemic agent (including sulfonylurea, metformin and/or acarbose) and/or insulin at the time of study. Also, 8 patients with CD and 5 controls had arterial HT well controlled by at least one antihypertensive drug (including diuretics, calcium antagonists, angiotensin-converting enzyme inhibitors, and angiotensin II receptor antagonists). Three patients and 4 subjects in the control group were receiving 10–40 mg statin therapy for hyperlipidemia.

Table 1 Profile of patients with Cushing's disease

No	Sex	Age	Adenoma (mm)	IPSS	Localization	Serum cortisol 08.00	Serum cortisol 24.00	Urinary cortisol	Therapy
1	F	51	8 × 4	+	R	27.4	18.6	976	TS
2	F	32	6 × 5	+	L	31.8	12.0	1271	TS
3	F	28	7 × 4	+	R	14.9	16.8	245	TS
4	F	52	6 × 4	+	R	22.9	18.6	387	TS
5	F	49	8 × 5	+	L	50.0	22.8	164.6	TS
6	F	46	9 × 5	+	L	50.0	37.0	245.0	TS
7	F	24	8 × 7	+	L	18.6	17.2	210.0	TS
8	F	44	5 × 3	+	L	21.4	15.1	368	TS
9	F	45	7 × 4	+	R	41.0	20.9	316	TS
10	F	36	6 × 5	+	L	24.3	15.8	164.6	TS
11	F	47	6 × 4	+	L	50.0	27.6	634	TS
12	F	58	7 × 5	+	R	37.6	21.2	149.2	TS
13	F	54	7 × 6	+	L	32.7	22.5	1772.0	TS
14	M	56	6 × 4	+	L	27.6	22.4	88.9	TS
15	F	35	4 × 5	+	M	42.0	35.0	1848	TS

Normal hormone ranges at 08.00 serum cortisol: 8–25 μg/dl, at 24.00 serum cortisol: 4–12.5 μg/dl, free urinary cortisol: 35–135 nmol/24 h

F female, *IPSS* inferior petrosal sinus sampling, *R* right, *L* left, *M* medial, *TS* transsphenoidal surgery

All patients and controls were non-smokers. Those with a previous history of heart failure, ischemic heart disease, valvular heart disease, peripheral artery disease, pulmonary hypertension, respiratory disease, malignancy, hepatic or renal dysfunction were not included in the study.

Echocardiography

In all subjects, echocardiographic images were obtained with a scanner (Vivid 7; GE, Horten, Norway) using a 2.5–3.5 MHz probe. Echocardiographic measurements were made with patient in the left lateral decubitis position. All echocardiographic measurements were performed by a single experienced cardiologist who was unaware of the clinical and laboratory variables of the cases. M-mode traces were recorded at a speed of 50 mm/s and the Doppler signals at 100 mm/s. Three cardiac cycles were averaged for all measurements.

Left ventricle end diastolic diameter (LVEDD; mm), left ventricle end systolic diameter (LVESD; mm), interventricular septum diameter at end diastole (IVSd; mm), posterior wall diameter at end diastole (PWd; mm) were obtained from the M-mode echocardiographic tracing under the guide of two-dimensional imaging. The measurements were made based on the standard of the American Society of Echocardiography [11].

Mitral inflow velocities were measured by pulsed wave Doppler recording in apical 4-chamber view placing the sample volume at the tips of the mitral valve leaflets. The peak early diastole (E; m/s) and late diastole (A; m/s) transmitral flow velocity, deceleration time of E (DT; ms), isovolumetric relaxation time (IVRT; ms), and a combined myocardial performance index (isovolumic contraction time plus isovolumic relaxation time divided by ejection time; Tei-index) were measured.

Tissue Doppler measurements were obtained from the apical four-chamber view, and a 3-mm sample volume was placed at the level of the lateral corner of the mitral annulus. The peak systolic velocity (Sm; cm/s), early diastolic myocardial peak velocity (Em; cm/s), late diastolic myocardial peak velocity (Am; cm/s) were measured. The time interval from the end to the onset of the mitral annular velocity pattern during diastole (a) and the duration of the Sm wave (b) were measured from the Tissue Doppler Imaging (TDI) recordings. The modified Tei index obtained by the pulse wave TDI was calculated as $(a - b)/b$.

The diameter of ascending aorta was recorded by M-mode echocardiography at a level 3 cm above the aortic valve [12]. An aortic systolic diameter (AoSD) was measured at the time of full opening of the aortic valve, and aortic diastolic diameters (AoDD) were measured at the peak of QRS complex on a simultaneously recorded electrocardiogram.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) values were measured with an external sphygmomanometer. Pulse pressure (PP) was calculated as SBP minus DBP. Aortic strain (%) was calculated as AoSD − AoDD/AoDD, and aortic distensibility (10^{-6} cm^2 dyn^{-1}) was calculated as (2 × aortic strain)/PP.

Statistical analysis

For the statistical analysis of the study, SPSS 13.0 packet program (SPSS Inc., Chicago, IL) was used. Descriptive statistics were shown as mean ± standard deviation. The statistical significances between two groups were assessed by Mann–Whitney *U* test. Chi-square test was used to assess differences of categorical variables between groups. Pearson's analysis was used to calculate the correlation coefficients. Values of $P < 0.05$ were accepted as statistically significant.

Results

The clinical and laboratory characteristics of the subjects are summarized in Table 2. There was no statistically significant difference ($P > 0.05$) between groups in terms of age, SBP, DBP, BMI, serum lipid parameters, fasting blood glucose, and heart rate.

The results of two dimensional echocardiographic measurements and pulsed Doppler study of transmitral flow velocities are presented in Table 3. IVSd (10.6 ± 1.0 vs.

Table 2 Clinical characteristics of the patients with Cushing's disease and control group

	Patients ($n = 15$)	Controls ($n = 17$)	*P*
Age (years)	43.8 ± 10.4	45.1 ± 11.5	NS
Gender (female)	14/15	16/17	NS
BMI (kg/m^2)	33.8 ± 5.3	31.6 ± 2.6	NS
SBP (mmHg)	130.0 ± 20.4	125.6 ± 6.8	NS
DBP (mmHg)	80.7 ± 12.8	77.1 ± 6.6	NS
Heart rate (beats/min)	86.5 ± 13.1	80.2 ± 8.7	NS
Fasting blood glucose (mg/dl)	121.5 ± 17.8	117.1 ± 19.9	NS
Cholesterol (mg/dl)	192.5 ± 32.0	192.7 ± 37.0	NS
LDL-cholesterol (mg/dl)	116.6 ± 31.8	112.5 ± 23.8	NS
HDL-cholesterol (mg/dl)	43.6 ± 11.0	40.1 ± 3.2	NS
Triglyceride (mg/dl)	155.7 ± 113.5	142.1 ± 24.6	NS
Diabetes mellitus	8/15	8/17	NS
Hypertension	8/15	5/17	NS
Hyperlipidemia	3/15	5/17	NS

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *NS* no significant

Table 3 Conventional echocardiographic results in study groups

	Patients ($n = 15$)	Controls ($n = 17$)	P
LVEDD (mm)	46.7 ± 3.8	45.5 ± 2.4	NS
LVESD (mm)	29.5 ± 5.4	28.9 ± 1.4	NS
IVSd (mm)	10.6 ± 1.0	9.7 ± 1.0	0.02
PWd (mm)	10.1 ± 1.0	9.3 ± 1.0	0.03
E wave (m/s)	0.70 ± 0.11	0.86 ± 0.16	0.004
A wave (m/s)	0.82 ± 0.10	0.76 ± 0.09	NS
E to A ratio	0.87 ± 0.18	1.1 ± 0.20	<0.001
DT (ms)	215.3 ± 17.1	196.2 ± 21.2	0.009
IVRT (ms)	90.5 ± 11.9	82.8 ± 10.8	NS

A mitral late diastolic velocity, *DT* deceleration time of E, *E* mitral early diastolic velocity, *IVSd* interventricular septum diameter at end diastole, *LVEDD* left ventricle end diastolic diameter, *LVESD* left ventricle end systolic diameter, *PWd* posterior wall diameter at end diastole, *IVRT* isovolumetric relaxation time, *ms* millisecond, *NS* no significant

Table 4 Tissue Doppler imaging findings of patients and control group

	Patients ($n = 15$)	Control group ($n = 17$)	P
Sm (cm/s)	8.9 ± 1.4	9.8 ± 1.9	NS
Em (cm/s)	9.0 ± 1.9	11.5 ± 3.3	0.01
Am (cm/s)	10.1 ± 2.0	9.1 ± 2.4	NS
Em/Am	0.90 ± 0.13	1.32 ± 0.40	0.001
Tei index	0.66 ± 0.10	0.54 ± 0.08	0.001

Am late diastolic myocardial peak velocity, *Em* early diastolic myocardial peak velocity, *Sm* peak systolic myocardial velocity, *Tei-index* isovolumic contraction time plus isovolumic relaxation time divided by ejection time, *NS* no significant

9.7 ± 1.0 mm; $P = 0.03$), PWd (10.1 ± 1.0 vs. 9.3 ± 1.0 mm; $P = 0.03$) were significantly higher, mitral E velocity (0.7 ± 0.1 vs. 0.9 ± 0.2 m/s; $P = 0.004$) and the ratio of E/A were significantly lower (0.87 ± 0.18 vs. 1.1 ± 0.20; $P < 0.001$) and DT (215.3 ± 17.1 vs. 196.2 ± 21.2 ms; $P = 0.009$) was significantly prolonged in patients with CD compared with control group. However, LVESD, LVEDD, mitral A velocitiy, and IVRT were found to be similar in both groups ($P > 0.05$ for all).

TDI variables are shown in Table 4. We observed a significantly lower Em (9.0 ± 1.9 vs. 11.5 ± 3.3 cm/s; $P = 0.02$) and Em/Am ratio (0.90 ± 0.13 vs. 1.32 ± 0.40; $P = 0.001$), and a significantly higher Tei index (0.66 ± 0.10 vs. 0.54 ± 0.08; $P = 0.001$) in patients with CD than control group. Sm and Am did not differ between the two groups ($P > 0.05$ for both).

Echocardiographic aortic elastic parameters are presented in Table 5. Aortic strain (7.4 ± 1.9% vs. 12.3 ± 2.4%; $P < 0.001$), aortic distensibility (3.2 ± 1.1 × 10^{-6} vs. 5.6 ± 1.4 × 10^{-6} cm^2 dyn^{-1}; $P < 0.001$) and pulse

Table 5 Aortic elastic echocardiographic parameters of patients with CD and control group

	Patients ($n = 15$)	Control group ($n = 17$)	P value
AoSD (mm)	31.5 ± 2.4	31.0 ± 3.0	0.63
AoDD (mm)	29.3 ± 2.1	27.4 ± 2.9	0.03
PDC (mm)	2.2 ± 0.6	3.5 ± 0.8	<0.001
Aortic strain (%)	7.4 ± 1.9	12.3 ± 2.4	<0.001
Aortic distensibility (10^{-6} cm^2 dyn^{-1})	3.2 ± 1.1	5.6 ± 1.4	<0.001

AoSD aortic systolic diameter, *AoDD* aortic diastolic diameter, *PDC* pulsatile diameter change

Table 6 Correlations between aortic elastic parameters and left ventricle tissue Doppler echocardiographic parameters

	Aortic strain coefficient	Aortic strain P value	Aortic distensibility coefficient	Aortic distensibility P value
Sm	0.49	0.004	0.41	0.02
Em	0.53	0.002	0.29	0.11
Am	−0.02	0.92	−0.14	0.45
Em/Am	0.51	0.003	0.38	0.03
Tei index	−0.45	0.01	−0.29	0.11

Am late diastolic myocardial peak velocity, *Em* early diastolic myocardial peak velocity, *Sm* peak systolic myocardial velocity, *Tei-index* isovolumic contraction time plus isovolumic relaxation time divided by ejection time

diameter change (PDC) were significantly decreased in CD patients compared to control group. Patients with CD had significantly increased AoDD (29.3 ± 2.1 vs. 27.4 ± 2.9 mm; $P = 0.03$), while there was no significant difference in terms of AoSD between the two groups.

Correlations between the LV echocardiographic measurements and aortic elastic parameters are shown in Table 6. A significant negative correlation between aortic strain and Tei index ($r = -0.45$, $P = 0.01$) and positive correlations between aortic strain and Sm ($r = 0.49$, $P = 0.004$), Em ($r = 0.53$, $P = 0.002$), and Em/Am ratio ($r = 0.51$, $P = 0.003$) were detected. Aortic strain and Am was not correlated. Aortic distensibility was correlated with Sm ($r = 0.41$, $P = 0.02$) and Em/Am ($r = 0.38$, $P = 0.03$) but not with Em, Am, and Tei index.

Discussion

Demonstration of vascular connective tissue changes in animal studies [13] and in patients on long-term glucocorticoid treatment [14] has raised the possibility that hypercortisolism may be related with development of

atherosclerosis. This suggestion has been supported strongly by studies reporting higher serum cortisol levels in coronary heart disease patients who underwent coronary angiography because of angina or stroke [15]. Also, in patients with connective tissue diseases, long-term glucocorticoid usage was shown to be associated with atherosclerosis and coronary heart disease [16, 17].

Although cardiac structure and function have been widely investigated in CS, the studies dealing with vascular consequences of CS are limited to its effects on carotid artery. Increased carotid intima-media thickness (IMT) and atherosclerotic plaques, compared to the general population, was reported in a cohort of patients with CD evaluated while in remission [9]. In another study, the same authors demonstrated that in patients with active CD, carotid artery IMT decreased after 1 year of disease remission, nevertheless it was still abnormal compared to controls, indicating a persistent cardiovascular risk [3]. The results of these studies also suggested that beyond a direct effect of glucocorticoid excess on the vascular system, metabolic syndrome may play a pivotal role in carotid atherosclerosis associated with CS. Similar findings were reported also by others [18].

Aortic stiffness is an early marker for atherosclerosis. In addition to blood circulating feature of aorta as an elastic artery, systolic and diastolic diameter change in proximal aorta during left ventricle systole and diastole constitute the aortic wall movement. Increase in aortic stiffness cause increased left ventricle mass and systolic blood pressure consequently influencing left ventricle functions and coronary blood flow [19, 20]. In recent years aortic stiffness is used as a noninvasive method for determining subclinical atherosclerosis. Decrease in elasticity and increase in stiffness of aorta are considered to be indicative for atherosclerotic change [21]. As atherosclerosis involves coronary arteries and aorta at the same time, changes in aortic stiffness and elasticity were supposed to reflect coronary diseases [12]. Various studies have reported aortic stiffness as an independent predictor for cardiovascular morbidity and mortality in different diseases [6, 7].

In the present study, our aim was to investigate the aortic function in patients with CD. We also evaluated the relationship between aortic stiffness and systolic and diastolic functions of the left ventricle. In a previous study, we have examined left ventricle functions using TDI in patients with CD and demonstrated change in diastolic and systolic functions in these patients [22]. In the present study, we showed decreased aortic elastic distensibility and aortic strain in CD compared with control group. Additionally, we observed significant correlation between aortic elastic properties and left ventricular parameters obtained by tissue Doppler echocardiography. However, there were some limitations of our study. Firstly this study involves a small number of patients. Secondly, it is well known that DM and HT have significant effects on development of atherosclerosis and left ventricle functions. Although, we tried to match patient group and control group for metabolic parameters and presence of coexistent diseases, this may have contributed to our results. Also, because we did not perform noninvasive stress test or coronary angiography in our patients, a likely underlying coronary artery disease was not excluded. However, we evaluated patient and control group clinically and with electrocardiographic and echocardiographic findings and did not include cases with any sign of ischemic heart disease.

Our study is the first to examine aortic properties and relation of these with left ventricle functions in patients with CD. A recent review has emphasized the importance of cardiovascular evaluation in patients with CS [23]. It is recommended to screen these patients with routine physical examination (including anthropometric measures and blood pressure measurement) and laboratory tests (including blood chemistry and electrocardiogram) as well as oral glucose tolerance test, 24 h ambulatory blood pressure monitoring, echocardiography, and carotid artery ultrasonography. In addition to these investigations, we suggest evaluation of aortic stiffness which is an early marker for atherosclerosis in patients with CS.

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