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Left ventricular structural characteristics in Cushing's syndrome

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Summary:

The aim of the present study was to assess structural characteristics of the left ventricle by echocardiography in a group of patients with Cushing's syndrome compared with a control population. Eighteen patients with Cushing's syndrome and 18 controls, matched for sex, age, body weight, body surface area, blood pressure (BP) and duration of hypertension were investigated by M-mode (2-D derived) echocardiography. In each of the two groups, 11 of 18 subjects were hypertensive. Relative wall thickness (RWT) was above normal (> 0.45) in 11 (five normotensive and six hypertensive) of 18 patients with Cushing's syndrome and in two (hypertensive) of 18 controls. Left ventricular mass index was abnormal in three (one normotensive and two hypertensive) patients with Cushing's syndrome and in four hypertensive controls. All other systolic function indices were within normal and similar in both groups. No correlation was found between RWT and BP as well as between RWT and urinary cortisol levels in patients with Cushing's syndrome. A significant correlation was found between RWT and duration of disease. Echocardiography after successful surgery showed normalisation of RWT in five of six patients in whom it was previously abnormal. Our data suggest that time factor, i.e. long-lasting exposure to increased cortisol, rather than hormone or BP levels is the most relevant determinant of left ventricular concentric remodeling in patients with Cushing's syndrome.

Keywords: *Cushing's syndrome, echocardiography, left ventricle*

Introduction

The mortality of patients with Cushing's syndrome without effective treatment is four times that of the general population when matched for age and sex and much of this excess mortality is due to cardiovascular disease.[1] Regardless of ACTH levels, endogenous overproduction of cortisol is often associated with hypertension[2,3] resistant to conventional pharmacological treatment,[4] which is considered an important risk factor for the development of atherosclerosis. Signs of cardiovascular damage are also observed in a high proportion of normotensive patients indicating that several factors (neurohumoral, metabolic, hereditary) may be involved.[5] A high prevalence of left ventricular hypertrophy, whose pathogenesis is unclear, has been reported in Cushing's syndrome.[6–8] The aim of the present study was to assess the structural characteristics of the left ventricle by echocardiography and to relate the findings with their possible determinants in a group of patients with Cushing's syndrome compared with a control population.

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Subjects and methods

Subjects

We studied 18 consecutive patients with newly diagnosed Cushing's syndrome and 18 controls purposely matched for sex, age, body weight (BW), body surface area (BSA), BP levels and duration of hypertension, admitted to our hospital during the past three years. Hypertension was defined as SBP/DBP > 140/90 mmHg on three measurements taken by mercury sphygmomanometer at intervals of one week, in the absence of any antihypertensive treatment. According to these criteria, 11 of 18 patients (61.1%) were hypertensive in both groups. The diagnosis of Cushing's syndrome was based on

standard criteria and proven at surgery in all cases.[9] Among patients with Cushing's syndrome, 11 had pituitary-dependent bilateral adrenal hyperplasia, one had ectopic ACTH production, five had an adrenal adenoma and one had an adrenal carcinoma. Duration of disease (ranging from two to 18 months) was obtained from careful investigation of the patient's history, including early symptoms. In the 11 hypertensive patients with Cushing's syndrome, onset of hypertension was coincidental with the appearance of other clinical features. Individual clinical data, levels of urinary cortisol and duration of illness of patients with Cushing's syndrome are reported in Table I. Controls were diagnosed as having essential hypertension after extensive hormonal and instrumental work-up. BP response to therapy was unsatisfactory (i.e. supine DBP > 90 mmHg) in eight of 11 patients with Cushing's syndrome despite a combination of at least two antihypertensive drugs, including diuretics and/or calcium antagonists and/or ACE inhibitors, at full doses. To match hypertensive patients with Cushing's syndrome, hypertensive controls were selected choosing patients never treated or unsatisfactorily treated in eight of 11 cases and with similar duration of hypertension. BP values used in the analysis were the mean of three readings taken with patients in the supine position at the time of echocardiographic study. All patients were off any antihypertensive drug and were following a diet containing 120–150 mmol sodium and 60 mmol potassium for at least two weeks before echocardiograpy. None of the patients had any signs or symptoms of ischaemic heart disease, heart failure, valvular disease and/or thyroid hyperfunction. Three patients (two hypertensive and one normotensive) with Cushing's syndrome had diabetes mellitus controlled at the time of the study by oral hypoglycaemic agents. Mean values for age, BW, BSA, SBP, DBP and duration of hypertension of the two groups of subjects are reported in Table II. SBP/DBP values were 169.0 ± 5.3/108.1 ± 2.6 mmHg in the 11 hypertensive patients with Cushing's syndrome and 175.4 ± 6.4/105.4 ± 2.0 mmHg in the 11 hypertensive controls, with no statistically significant difference. Echocardiography was repeated one year after successful surgery in eight patients with Cushing's syndrome (four previously normotensive and four previously hypertensive). Informed consent was obtained in all cases.

Table II Baseline characteristics of the study groups

	Controls (n = 18)	*Cushing's syndrome (n = 18)*
Age (years)	38.6 ± 2.6	36.2 ± 3.8
Sex (female/male)	14/4	14/4
BSA (m^2)	1.7 ± 0.02	1.8 ± 0.04
BW (kg)	73.1 ± 2.9	77.4 ± 3.7
SBP (mmHg)	158.8 ± 6.4	157.9 ± 5.3
DBP (mmHg)	98.0 ± 2.6	97.6 ± 3.3
Duration of hypertension (months) ($n = 11$)	8 ± 1	9 ± 1

All values are mean ± SEM
BSA: body surface area; BW: body weight

Methods

Echocardiography From a parasternal long axis view a M-mode tracing was obtained with two-dimensional monitoring using a 2.5 or 3.5 Mhz transducer on a ALOKA-870 (Japan) echocardiographic machine. Recordings were made on photographic paper at a speed of 50 mm/s. Each patient was examined in the left lateral decubitus position. Left ventricular posterior wall thickness (PWT), interventricular septal thickness (IVST), left ventricular end-diastolic dimension (LVDd) and left ventricular end-systolic dimension (LVDs) were measured according to the American Society of

Table I Details of patients with Cushing's syndrome

Patient no.	*Age (years)*	*Sex (F/M)*	*Aetiology*	*Blood pressure (mmHg)*	*Urinary cortisol (nmol/day)*	*Duration of disease (months)*
1	33	F	Pituitary adenoma	163/116	480	2
2	43	F	Adrenal adenoma	153/105	2782	10
3	25	F	Pituitary adenoma	151/98	1328	12
4	53	F	Pituitary adenoma	146/103	651	4
5	45	F	Adrenal adenoma	173/100	1181	4
6	34	F	Pituitary adenoma	140/93	508	2
7	43	F	Ectopic ACTH	213/121	2622	18
8	29	F	Pituitary adenoma	133/83	552	16
9	45	F	Pituitary adenoma	140/81	1648	14
10	50	F	Adrenal adenoma	161/113	1250	8
11	48	F	Adrenal adenoma	181/103	1424	4
12	50	F	Pituitary adenoma	163/100	857	16
13	16	F	Pituitary adenoma	125/78	867	3
14	26	M	Adrenal carcinoma	188/116	3621	8
15	17	M	Pituitary adenoma	180/106	593	16
16	50	M	Adrenal adenoma	133/78	1982	4
17	16	M	Pituitary adenoma	138/80	883	12
18	28	M	Pituitary adenoma	151/83	1325	10

Echocardiography recommendations using leading edge methodology.[10] Fractional shortening (FS) of the left ventricle was determined as the percentage difference between systolic and diastolic internal diameter. Left ventricular mass was derived using the formula of Devereux *et al.*[11] and was indexed for BSA (left ventricular mass index (LVMI)). Relative wall thickness (RWT) was calculated at as $2 \times$ (PWT/LVDd). Increased LVMI was defined as > 135 g/m^2 for males and > 110 g/m^2 for females and increased RWT as > 0.45. Echo tracings were analysed by two independent observers in a blind manner. Measurements were obtained for at least three consecutive cardiac cycles and results were averaged. In our laboratory, the reproducibility of echocardiographic indices has been tested with the same ultrasonic technique on 10 normal and 10 hypertensive subjects, each examined three times. Coefficients of variation (CVs) are within 8%.

Statistical analysis The statistical significance of differences between the two groups was assessed by the Wilcoxon ranked sign test, or chi-square test corrected with the continuity, as appropriate. Relationships between RWT and SBP, DBP, urinary cortisol, duration of disease were investigated by calculating the rank order Spearman's coefficient. A P of < 0.05 was considered significant. Results are expressed as mean ± SEM.

Hormone measurements Urinary cortisol was measured by radioimmunoassay after extraction with dichloromethane using a kit from Diagnostic Products Co. (Los Angeles, USA). Normal range 55–330 nmol/day.

Results

The echocardiographic parameters of patients with Cushing's syndrome and matched controls are reported in Table III. No differences in heart rate were found between patients and controls. A significant difference between the two groups was found only for RWT ($P < 0.05$). Among patients with Cushing's syndrome, RWT was 0.46 ± 0.03 in the 11 hypertensive and 0.49 ± 0.03 in the seven normotensive, with no significant difference (P, NS).

The prevalence of increase in RWT was equal to 11 of 18 (61.1%) patients with Cushing's syndrome and in two of 18 (11.1%) controls (Table IV). Chi-square test revealed a significant difference (χ^2 16.94, $P < 0.001$) between these two subsets. Five of seven (71.4%) patients with Cushing's syndrome showing increased RWT were normotensive and six of 11 (54.5%) were hypertensive. Two of 11 (11.1%) hypertensive controls had increased RWT. RWT was not correlated with SBP, DBP or urinary cortisol levels. At variance, RWT was correlated with the duration of disease in patients with Cushing's syndrome ($r = 0.82$, $P < 0.01$) (Figure 1). Two of 18 (11.1%) patients with Cushing's disease, one normotensive and one hypertensive, and three of 11 (27.2%) hypertensive controls showed increased LVMI with normal RWT (i.e. eccentric hypertrophy). In one case of Cushing's syndrome and in one control, both hypertensive, increase in LVMI was associated with increase in RWT (i.e. concentric hypertrophy) (Table IV).

Six patients (three normotensive and three hypertensive) with Cushing's syndrome having abnormal RWT and two patients (one normotensive and one hypertensive) having normal RWT pretreatment, were examined in the follow-up study after surgery. RWT normalised in three of three normotensive and in two of three hypertensive patients. RWT remained normal in the other two. In all four hypertensive subjects, BP normalised soon after surgery

Table III Echocardiographic findings in the study groups

	Controls (n = 18)	*Cushing's syndrome (n = 18)*	*P value*
LVDd (mm)	47.0 ± 1.3	44.3 ± 1.3	NS
LVDs (mm)	29.3 ± 1.0	28.3 ± 1.0	NS
PWT (mm)	9.1 ± 0.4	10.1 ± 0.3	NS
IVST (mm)	10.0 ± 0.5	11.3 ± 0.6	NS
IVST/PWT	0.8 ± 0.05	0.9 ± 0.07	NS
LVMI (g.m^2)	90.5 ± 6.1	92.2 ± 6.6	NS
RWT	0.36 ± 0.02	0.47 ± 0.02	< 0.01
%FS	33.6 ± 1.0	31.1 ± 2.7	NS

All values are mean ± SEM
LVDd: left ventricular end-diastolic dimension; LVDs: left ventricular end-systolic dimension; PWT: posterior wall thickness; IVST: interventricular septal thickness; LVMI: left ventricular mass index; RWT: relative wall thickness; FS: fractional shortening

Table IV Left ventricular patterns in the study groups

	Controls (n = 18)	*Cushing's syndrome (n = 18)*
Normal pattern	12 (7 NT, 5 HT)	4 (1 NT, 3 HT)
Concentric remodelling	2 (HT)	11 (5 NT, 6 HT)
Eccentric hypertrophy	3 (HT)	2 (1 NT, 1 HT)
Concentric hypertrophy	1 (HT)	1 (HT)

NT: normotensive subjects; HT: hypertensive subjects

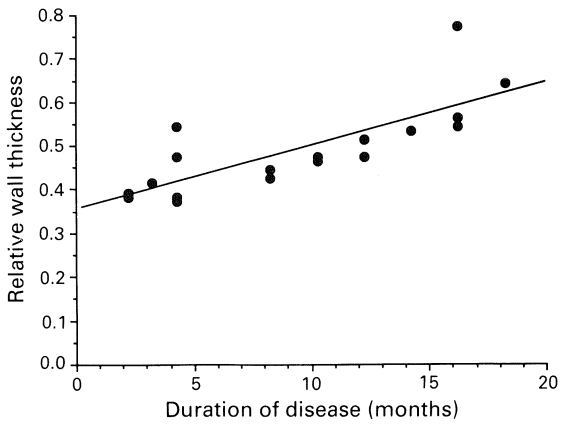

Figure 1 Scatter plot showing the correlation between duration of disease and relative wall thickness in patients with Cushing's syndrome. $r = 0.82$.

and remained normal up to the time of the study. BP and RWT data reported in Table V.

Discussion

Relation of left ventricular muscle thickness to cavity size (i.e. RWT) has been shown to be a sensitive indicator of the geometric pattern of hypertrophy,[11–13] with a potential limitation to its validity in abnormally shaped ventricles.[14] This study demonstrates a significantly higher frequency of increased RWT with normal left ventricular mass, i.e. cardiac concentric remodelling, in patients with Cushing's syndrome compared with controls. The frequency of this structural pattern increased with the duration of disease but was not related to either cortisol or BP levels.

There is little detailed information on left ventricular anatomy assessed by means of echocardiography in patients with Cushing's syndrome. Only one not case controlled study recently reported a 75% prevalence of left ventricular hypertrophy in these patients, based on the increased ratio of the thickness of interventricular septum to that of left posterior wall, but RWT values were not mentioned.[8] Discrepancy with our findings of normal left ventricular mass in the great majority of patients with Cushing's syndrome could be due to a much shorter duration of the disease (9 ± 1 vs. 47 ± 14 months) in our population.

Left ventricular concentric remodelling can be an important predictor of cardiovascular morbidity in essential hypertension[12] but is not very frequent either in essential[13] or in different forms of secondary hypertension.[15–17] This suggests that other mechanisms beside increased aortic pressure play a role in such cardiac anatomical change. Indeed, in our study hypertension *per se* does not seem to be a relevant factor in causing left ventricular concentric remodelling as its frequency was similar in both our normotensive and hypertensive patients with Cushing's syndrome. A possible interfering factor could be the effect of previous pharmacological treatment on haemodynamics or ventricular morphology.[18,19] This should not be so our case because patients with essential hypertension were carefully selected to match hypertensive patients with Cushing's syndrome as to BP duration, levels and response to treatment. The matching of our two groups of patients for sex, age, body weight and BSA also allowed us to rule out the influence of such factors in the pathogenesis of cardiac alterations.[20–22]

Regarding other possible determinants of abnormal RWT in Cushing's syndrome, no relationship was found in our patients between this parameter and urinary cortisol. A significant correlation of RWT with the duration of disease was observed, suggesting that a long-lasting exposure to abnormally high cortisol might be more relevant than the magnitude of hormone levels. It has been shown that in a hypertensive population the cardiac pattern of concentric remodelling is mainly associated with increased total peripheral resistance.[13] This haemodynamic parameter indeed characterises glucocorticoid-induced hypertension[23] and is thought to be due to direct or indirect glucocorticoid effect on peripheral vascular tone.[24] An elevated DBP at night has been considered another possible explanation for the concentric remodelling showed by subsets of patients with essential hypertension.[13] In fact, patients with Cushing's syndrome show a lack of nocturnal BP decline.[25] Another mechanism could be a direct myocardial effect of cortisol. Glucocorticoid receptors have been shown in animal heart[26] and a direct cellular effect of adrenal steroids has been reported.[27,28] Also, glucocorticoid excess has been proposed as a direct cause of hypertrophic cardiomyopathy, without hypertension, *in vivo*.[29,30] Tissue effects of cortisol could include potentiation of noradrenaline and angiotensin II responsiveness in cardiac muscle[31,32] or stimulation of the local renin-angiotensin system leading to ventricular hypertrophy by paracrine action on myocardial cells.[33,34]

Finally, our study documented the regression of left ventricular concentric remodeling in five of six patients with Cushing's syndrome one year after they were cured. RWT normalisation was also seen in the cases without hypertension, further indicating other factors rather than high BP as the possible underlying cause of cardiac abnormality in this disease. Our findings confirm reports by others[35] showing regression of left ventricular hypertrophy, unrelated to BP decrease, in patients with different forms of secondary hypertension after surgical and/or medical therapy.

Table V BP levels and relative wall thickness values of patients with Cushing's syndrome before and one year after surgical treatment. Patient numbers refer to those reported in Table I

Patient no.	*Before treatment*		*After treatment*	
	BP (mmHg)	*RWT*	*BP (mmHg)*	*RWT*
1	163/116	0.53	133/80	0.42
2	153/105	0.55	138/80	0.50
7	213/121	0.63	125/81	0.44
8	133/83	0.37	133/80	0.38
9	140/81	0.52	133/83	0.43
12	163/100	0.40	138/80	0.38
16	133/78	0.53	140/83	0.43
17	138/80	0.50	140/83	0.42

RWT: relative wall thickness

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