

Cardiac Findings in Cushing's Syndrome

Left Ventricular Structural and Functional Characteristics in Cushing's Syndrome

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OBJECTIVES	This study was designed to evaluate left ventricular (LV) anatomy and function in patients with Cushing's syndrome.
BACKGROUND	A high prevalence of LV hypertrophy and concentric remodeling has been reported in Cushing's syndrome, although no data have been reported on LV systolic and diastolic function.
METHODS	Forty-two consecutive patients with Cushing's syndrome and 42 control subjects, matched for age, gender, and blood pressure, were studied. Left ventricular mass index (LVMI) and relative wall thickness (RWT) were measured by echocardiography, endocardial and midwall fractional shortening (FS) were assessed, and diastolic filling was measured by Doppler transmitral flow.
RESULTS	The RWT was significantly greater in Cushing patients than in controls. Left ventricular hypertrophy and concentric remodeling were observed in 10 and 26 patients with Cushing's syndrome, respectively. In Cushing patients, midwall FS was significantly reduced compared with controls ($16.2 \pm 3\%$ vs. $21 \pm 4.5\%$, $p = 0.01$). The ratio of transmitral E and A flow velocities was reduced and E deceleration time was prolonged in Cushing patients compared with controls ($p = 0.03$ and $p < 0.001$, respectively).
CONCLUSIONS	In patients with Cushing's syndrome, cardiac structural changes are associated with reduced midwall systolic performance and with diastolic dysfunction that may contribute to the high risk of cardiovascular events observed in these patients. (J Am Coll Cardiol 2003;41:2275-9) © 2003 by the American College of Cardiology Foundation

Cardiovascular complications of Cushing's syndrome cause a mortality rate that is fourfold higher than that expected in the normal population (1). Cortisol hypersecretion causes central obesity, hypertension, impairment of glucose tolerance or diabetes, hyperlipidemia, and a pro-thrombotic state. Altogether, these abnormalities contribute to the high cardiovascular risks, such as myocardial infarction and stroke, associated with this disease (2,3). We previously documented in Cushing's syndrome a characteristic alteration of cardiac structure, that is, a high relative wall thickness (RWT), which was not related to blood pressure (BP) levels (4). We therefore indicated the exposure to increased cortisol per se as the determinant of left ventricular (LV) concentric remodeling, proposing that this feature may contribute to high cardiovascular morbidity (2,3,5). The aim of this study was to further investigate, in a larger group of patients with Cushing's syndrome, LV structural and functional characteristics. For this purpose, we evaluated LV systolic performance by the measurement of endocardial and midwall fractional shortening (FS) and diastolic filling by pulsed Doppler echocardiography. In

fact, midwall systolic dysfunction seems a more reliable measure of myocardial contractility and may represent a predictor of an adverse outcome in arterial hypertension (6,7). Very recently, diastolic filling abnormalities have also been shown to influence the occurrence of heart failure and cardiovascular events (8-10).

METHODS

Study population. We studied 42 consecutive patients with newly diagnosed Cushing's syndrome. The diagnosis of Cushing's syndrome was based on standard criteria and proved at surgery in all cases (1); 24-h urinary cortisol values were 1.522 ± 1.044 nmol/day. Among patients with Cushing's syndrome, 36 had pituitary-dependent bilateral adrenal hyperplasia, one had ectopic adrenocorticotrophic hormone production, six had an adrenal adenoma, and one had an adrenal carcinoma. Duration of disease (ranging from 2 to 50 months) was obtained from careful investigation of the patient's history, including early symptoms. In 32 patients with Cushing's syndrome, onset of hypertension was coincidental with the appearance of other clinical features and BP values at diagnosis were $156 \pm 22/97 \pm 11$ mm Hg, whereas in 10 patients BP values were always within normal limits. Five patients (three hypertensive and two normotensive) with Cushing's syndrome had diabetes mellitus well controlled by oral hypoglycemic agents at the time of the study.

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Abbreviations and Acronyms

BP	= blood pressure
ESS	= end-systolic stress
FS	= fractional shortening
LV	= left ventricle/ventricular
LVMI	= left ventricular mass index
RWT	= relative wall thickness

Patients with Cushing's disease were compared with 42 control cases, purposely matched for gender, age, body mass index, smoking habit, lipid levels, BP levels, and duration of hypertension. Controls were selected among hypertensive patients seen at our outpatient clinic and from a general population cohort under evaluation for cardiovascular risk stratification (11).

In 21 of 32 hypertensive patients with Cushing's syndrome, despite a combination of at least two antihypertensive drugs (including diuretics and/or calcium antagonists and/or angiotensin-converting enzyme inhibitors and/or angiotensin II receptor antagonists), BP response to therapy was unsatisfactory (i.e., supine diastolic BP >90 mm Hg), in agreement with previous findings (12). For this reason we included in the group of control cases 21 patients previously treated with at least two drugs, matched for BP values, and 11 never-treated hypertensive patients; these patients were selected after extensive hormonal and instrumental workup for the exclusion of secondary hypertension and other diseases (ischemic heart disease, heart or renal failure, valvular disease, and/or thyroid hyper- or hypofunction) (13). All patients and controls underwent the echocardiographic examination after a short period (10 to 15 days) of antihypertensive treatment withdrawal. Mean values of age, body mass index, systolic and diastolic BP, and duration of hypertension of the two groups of subjects are reported in Table 1. The local ethics committees approved the study.

Echocardiographic examination. Echocardiography was performed by standardized procedures with two Sonos 1500 echo machines (Agilent Technologies). The echocardiographic study protocol recorded at least 10 cycles of two-dimensional parasternal long- and short-axis LV views with optimal orientation of the M-mode cursor beam.

Table 1. Demographic Characteristics of Cushing Patients and Controls

	Cushing Patients	Controls	p
Age (yrs)	39 ± 12	40.5 ± 11	NS
Gender (F/M)	30/12	30/12	NS
Body mass index (kg/m ²)	28 ± 4.8	28 ± 4.0	NS
Hypertensive/normotensive patients	32/10	32/10	NS
Duration of hypertension, months	10.8 ± 14	11.8 ± 11	NS
Systolic BP (mm Hg)	153 ± 21	151 ± 19	NS
Diastolic BP (mm Hg)	96 ± 13	95 ± 12	NS
Total cholesterol (mmol/l)	6.01 ± 0.82	5.5 ± 0.98	NS
Fasting glucose (mmol/l)	5.7 ± 1.07	5.45 ± 1.1	NS

BP = blood pressure.

The LV internal dimensions, interventricular septum, and posterior wall thickness were measured according to the recommendations of the American Society of Echocardiography (14). End-diastolic RWT (i.e., the ratio of posterior wall thickness to one-half LV internal dimension) was calculated as index of LV geometric pattern; values higher than 0.44 were considered to indicate LV concentric geometry (15). The Penn Convention was used to calculate LV mass by an anatomically validated formula (16); LV mass was indexed by body height to the 2.7 power, and the partition value of 51 g/m^{2.7} was used to define LV hypertrophy in both genders (17).

Left ventricular systolic function was estimated by both endocardial FS and midwall FS, as previously reported (7,18). Endocardial FS was defined as [(LVDd - LVDs)/LVDd] × 100. Midwall FS was calculated by taking into account epicardial migration of the midwall during systole according to the following formula:

$$\text{Midwall FS} = \frac{(\text{LVDd} + \text{PWTd}/2 + \text{IVSTd}/2) - (\text{LVDs} + \text{hs}/2)}{(\text{LVDd} + \text{PWTd}/2 + \text{IVSTd}/2)}$$

where LVD = left ventricular diameter, PWT = posterior wall thickness, IVST = interventricular septum thickness, h = combined thickness of interventricular septum and posterior wall, s = end-systole, and d = end-diastole.

Myocardial contractile efficiency is usually examined by the relation of systolic shortening to end-systolic stress (ESS). In order to identify deviations from normal in contractile performance, endocardial FS was also expressed as a percentage of the value predicted for meridional ESS on findings in normal subjects (18). Meridional ESS was calculated by the standard method of Reichek et al. (19). Accordingly, midwall shortening was related to circumferential ESS, calculated at the midwall by the method of Gaasch et al. (20). Observed midwall FS was expressed as a percent of the value predicted from circumferential ESS with an equation derived from normal adults (18).

In 22 patients (17 hypertensive and 5 normotensive) with Cushing's syndrome and in 22 matched controls, pulsed Doppler recordings at the level of the mitral valve tips from apical four-chamber two-dimensional views were obtained in order to measure early (E) and late (A) wave diastolic filling velocities, their ratio (E/A ratio), and E-wave deceleration time (18,21).

Two different readers, unaware of the patients' or controls' identity, performed all echocardiographic and Doppler measurements.

All the echocardiographic and Doppler parameters were selected before the initiation of the investigation, in order to evaluate abnormalities of LV structure by LV mass and geometry, of systolic performance by endocardial and midwall FS, and of diastolic filling by the E/A ratio and E-wave deceleration. All these parameters' abnormalities are known to occur in arterial hypertension and may influence clinical outcome (4-10,18).

Table 2. Echocardiographic Features of Cushing Patients and Controls

	Cushing Patients	Controls	p
Left atrium diameter (mm)	32 ± 5.6	34 ± 5.4	0.14
LVDd (mm)	43.7 ± 4.0	49.5 ± 4.1	< 0.001
LVDs (mm)	26.5 ± 4.2	31 ± 4.6	< 0.001
LV IVSd (mm)	10.1 ± 2.2	8.8 ± 1.3	0.05
LV PWd (mm)	9.8 ± 1.71	7.8 ± 1.15	0.005
RWT	0.46 ± 0.1	0.32 ± 0.05	0.008
LV mass (g)	155.4 ± 47	145 ± 39	0.18
LV mass index (g/m ^{2.7})	41 ± 12.7	34.8 ± 8	0.021

LV = left ventricular; LVDd = left ventricular end-diastolic diameter; LVDs = left ventricular end-systolic diameter; LV IVSd = left ventricular interventricular septum diameter; LV PWd = left ventricular posterior wall diameter.

Hormone measurement. Twenty-four-hour urinary cortisol was measured by radioimmunoassay using a kit from Diagnostic Products Co. (Los Angeles, California). The intra-assay coefficient of variation was 6%, and the inter-assay coefficient of variation was 8.2%. The normal range was 55 to 330 nmol/day.

Statistical analysis. The statistical significance of differences between the two groups (Cushing patients and controls) was assessed by unpaired *t*-test, with Bonferroni correction for multiple comparisons. Chi-square statistic was used to assess differences of categorical variables between groups.

Relationships between echocardiographic indices (LVMI, RWT, E/A ratio, E-wave deceleration, midwall FS) and urinary cortisol or duration of disease were investigated calculating the rank order Spearman's coefficient. Multivariate analysis was performed to assess the independent effect of hypertension and presence or absence of Cushing's syndrome diagnosis on RWT, midwall FS, E/A ratio, and E-wave deceleration time. All statistical tests were two-tailed at the *p* value of 0.05. Results are expressed as mean ± SD. All analyses were carried out with the SPSS 10.01 statistical package.

RESULTS

LV structure. The echocardiographic parameters of patients with Cushing's syndrome and matched controls are reported in Table 2. No difference in heart rate or in atrial size was found between patients and controls.

End-diastolic diameter was significantly lower in Cushing patients, suggesting the absence of volume overload in these patients. Left ventricular mass index and RWT were significantly higher in Cushing patients than in controls. Left ventricular hypertrophy was observed in 10 of 42 Cushing patients and in 3 of 42 controls; concentric remodeling was observed in 26 of 42 Cushing patients and in none of the controls.

Among patients with Cushing's syndrome, LVMI was 42 ± 12 g/m^{2.7} and 38 ± 14 g/m^{2.7}, and RWT was 0.47 ± 0.10 and 0.40 ± 0.09 in the 32 hypertensives and in the 10 normotensives, respectively.

Left ventricular mass index was independently associated

Table 3. Systolic Performance and Diastolic Filling Parameters

	Cushing Patients	Controls	p
Endocardial FS (%)	39 ± 7.6	39 ± 7.5	0.88
Predicted endocardial FS, % (mESS adjusted)	39 ± 3.8	35.4 ± 2.3	
Endocardial FS (% of predicted value)	99.6 ± 14	110 ± 18	0.001
Midwall FS (%)	16.2 ± 3	20.5 ± 4.5	< 0.01
Predicted midwall FS (%) (cESS adjusted)	17.9 ± 0.6	17.6 ± 0.7	
Midwall FS (% of predicted value)	89 ± 17	115 ± 15	< 0.0001
Ejection fraction (%)	75 ± 6	74 ± 10	0.12
E velocity (cm/s)	55.6 ± 12	78 ± 21	0.005
A velocity (cm/s)	62 ± 13	65 ± 22	0.21
E/A ratio	0.94 ± 0.27	1.18 ± 0.32	0.03
E-wave deceleration time (ms)	205 ± 36	150 ± 30	< 0.001

ESS = end-systolic shortening; FS = fractional shortening.

with hypertension (*F* = 7.12, *p* = 0.006) and Cushing's syndrome (*F* = 6.59, *p* = 0.012). Left ventricular RWT was also independently associated with hypertension (*F* = 14.2, *p* < 0.001) and Cushing's syndrome (*F* = 49.2, *p* < 0.001).

In patients with Cushing's syndrome, RWT but not LVMI was related with the duration of disease (*r* = -0.32, *p* = 0.05) but not with urinary cortisol levels.

LV systolic function. No significant differences between Cushing patients and controls were observed for endocardial FS, whereas stress-adjusted endocardial FS was significantly lower in Cushing patients than in controls (Table 3).

In Cushing patients, midwall FS (absolute and stress-adjusted values) was significantly reduced compared with controls (Table 3), with no significant difference between hypertensives and normotensives (18 ± 3 vs. 16 ± 3, *p* = 0.62). Midwall FS was independently associated with Cushing's syndrome (*F* = 22.6, *p* < 0.001) and with hypertension (*F* = 5.78, *p* = 0.012).

LV diastolic function. The ratio of E/A velocities was reduced and the E-wave deceleration was prolonged in Cushing patients compared with controls (Table 3). The E/A ratio was independently associated with hypertension (*F* = 17.3, *p* < 0.001) and Cushing's syndrome (*F* = 12.9, *p* = 0.001), whereas the duration of E-wave deceleration was independently associated with Cushing's syndrome (*F* = 23.3, *p* < 0.001) but not with hypertension (*F* = 1.93, *p* = 0.18).

In patients with Cushing's syndrome, the E/A ratio (*r* = -0.39, *p* = 0.01) and the E-wave deceleration time (*r* = 0.31, *p* = 0.05) were significantly related with the duration of the disease. No correlation was observed between the urinary cortisol levels and Doppler parameters of diastolic filling.

DISCUSSION

This study has demonstrated for the first time that in patients with Cushing's syndrome the abnormalities of LV anatomy are associated with important functional conse-

quences: a decrease of LV systolic performance measured at the midwall and a change of diastolic filling toward abnormal relaxation pattern.

In addition, our results expand previous data (4), confirming a significantly higher frequency of concentric remodeling (normal LV mass and concentric geometry) in patients with Cushing's syndrome than in controls, accurately matched not only for demographic characteristics but also for BP values, previous antihypertensive treatment type, and duration.

The use of echocardiographic determination of midwall LV performance is considered a more appropriate method of evaluating ventricular systolic function (6,7), because the inward movement by the thickened inner layer of a hypertrophic ventricle is greater than the movement of the inner layer of a normal ventricle. Therefore, it has been possible to identify a subgroup of asymptomatic hypertensive patients who exhibit hemodynamic characteristics associated with an increased cardiovascular risk (15,22-27) and a reduction of LV myocardial performance at rest (25-27). The presence of depressed midwall shortening is a predictor of an adverse outcome in arterial hypertension (6,7), and the combination of higher LV mass and lower midwall shortening identifies patients with a marked increase of risk (6).

The impact of diastolic dysfunction on cardiac morbidity and mortality is becoming increasingly understood (8-10,28,29), and diastolic filling abnormalities may be identified by the use of non-invasive, simple and repeatable Doppler transmitral flow velocities measurements (28).

In Cushing's syndrome, the frequency of concentric remodeling and of diastolic dysfunction parameters increased with the duration of disease and was not related to cortisol levels. This suggests that a long-lasting exposure to high cortisol levels might be more relevant than the magnitude of hormone levels. Duration of disease has been also seen as the determinant of persistent high BP levels after successful surgery in hypertensive patients with Cushing's syndrome (30).

Obesity has been associated per se with abnormalities of both midwall systolic performance and diastolic filling, possibly influencing, at least in part, our findings (31). However, truncular fat distribution in Cushing patients is different from traditional obesity, and the appropriateness of body mass index correction for obese patients with Cushing's disease is unknown.

The mechanism(s) by which cortisol may determine an increase in LV wall thickness in our patients is not clear. The rise in BP seems not to be essential for the development of initial structural changes in LV wall, because an increase in RWT was demonstrated in normotensive patients compared with controls. Cardiac structure may be influenced by endocrine abnormalities through hemodynamic changes, and in Cushing patients a volume overload would have been expected. At variance, we have observed a smaller cavity size of the LV, suggesting the absence of an increase in preload. Because all echocardiographic studies were performed a short time after withdrawal from treatment in previously

treated patients, the possible influence of antihypertensive drugs on LV dimensions (such a decrease in LV cavity size and a concomitant increase in RWT) can be reasonably ruled out.

Cortisol is thought to have a range of effects on cardiovascular regulation (5). In addition to inducing hypertension by a number of mechanisms, cortisol may act directly on myocardial tissue. Indeed, glucocorticoid receptors have been shown in animal (32) as well as in human heart (33). Tissue effect of cortisol could also include potentiation of cardiac noradrenaline and angiotensin II responsiveness (34,35) or stimulation of the local renin-angiotensin system (36). Similar findings were obtained also in different forms of secondary hypertension; in fact, in our previous work (37) and in that of Rossi et al. (38) an increase in RWT was observed in patients with primary aldosteronism, at an early stage of the disease, when hypervolemia is usually not yet evident, suggesting a direct action of aldosterone on both vascular and cardiac growth and remodeling. The lack of correlation between echo-Doppler parameters of systolic or diastolic performance and cortisol urinary concentrations may render less justifiable the findings observed in Cushing patients. However, it is possible that the long-lasting exposure to increased cortisol levels, in addition to hormone circulating amount or BP increase, is the most relevant determinant of structural and functional characteristics described in patients with Cushing's syndrome.

Some potential limitations of the present study need to be discussed. First, the impact of BP on cardiac anatomy and function in Cushing patients may be underestimated because we have no data on 24-h ambulatory BP values (39), which may show an altered day-to-night variability in this disease (40). However, we made an effort by matching patients with Cushing's disease not only for BP values and known duration of hypertension but also for previous antihypertensive treatment type.

Second, we have evaluated only transmitral early and late diastolic filling velocities and E wave deceleration time, and data on isovolumic relaxation time (measured at the LV outflow tract) are lacking (21,28,29). It has been proposed that this parameter may more precisely indicate the influence of hypertension (and other cardiovascular risk factors) on early abnormalities of diastolic function. However, recent data from the Cardiovascular Health Study have clearly demonstrated that the E/A ratio may have a predictive value for the occurrence of subsequent cardiovascular events or heart failure (8-10).

Lastly, in the group of Cushing patients, five patients (three hypertensives and two normotensives) had diabetes mellitus, and we cannot exclude a possible influence of diabetes per se on cardiac structure and function; however, in all patients diabetes was well controlled at the time of the study by oral hypoglycemic agents, and mean fasting glucose levels were similar in Cushing patients and in controls.

In conclusion, the presence of a low midwall systolic performance as well as of a diastolic dysfunction has been observed in patients with Cushing's syndrome. These ab-

normalities may contribute to the high risk of cardiovascular events observed in these patients

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