Cardiac dysfunction is reversed upon successful treatment of Cushing’s syndrome

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Abstract

Objective: In patients with active Cushing’s syndrome (CS), cardiac structural and functional changes have been described in a limited number of patients. It is unknown whether these changes reverse after successful treatment. We therefore evaluated the changes in cardiac structure and dysfunction after successful treatment of CS, using more sensitive echocardiographic parameters (based on two-dimensional strain imaging) to detect subtle changes in cardiac structure and function.

Methods: In a prospective study design, we studied 15 consecutive CS patients and 30 controls (matched for age, sex, body surface area, hypertension, and left ventricular (LV) systolic function). Multidirectional LV strain was evaluated by two-dimensional speckle tracking strain imaging. Systolic (radial thickening, and circumferential and longitudinal shortening) and diastolic (longitudinal strain rate at the isovolumetric relaxation time (SR IVRT)) parameters were measured.

Results: At baseline, CS patients had similar LV diameters but had significantly more LV hypertrophy and impaired LV diastolic function, compared to controls. In addition, CS patients showed impaired LV shortening in the circumferential (K16.5 G3.5 vs K19.7 G3.4%, P<0.013) and longitudinal (K15.9 G1.9 vs K20.1 G2.3%, P<0.001) directions and decreased SR IVRT (0.3 G0.15 vs 0.4 G0.2/ s, P=0.012) compared to controls. After normalization of corticosteroid excess, LV structural abnormalities reversed, LV circumferential and longitudinal shortening occurred, and SR IVRT normalized.

Conclusion: CS induces not only LV hypertrophy and diastolic dysfunction but also subclinical LV systolic dysfunction, which reverses upon normalization of corticosteroid excess.

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Introduction

Cushing’s syndrome (CS) is a very rare disorder that results from endogenous hypercortisolism. CS is a fatal condition in the absence of adequate treatment (1), but even many years after successful cure, the patients remain at increased risk for cardiovascular disease (2, 3).

In patients with active CS, cardiac structural and functional changes have been described in a limited number of patients. These changes were characterized by left ventricular (LV) hypertrophy and concentric remodeling, and reduced midwall systolic performance with diastolic dysfunction (4). It is unknown whether these changes reverse after normalization of corticosteroid excess. Currently, two-dimensional speckle tracking strain imaging constitutes a highly sensitive technique to detect subclinical LV systolic and diastolic dysfunction, which may enable the detection of subclinical LV systolic dysfunction in CS patients. In addition, subtle changes in LV structure and function after normalization of corticosteroid excess can be monitored.

Therefore, the aim of the present study was first to evaluate cardiac structural and functional changes in CS patients with two-dimensional speckle tracking strain imaging. Secondly, we also evaluated potential reversibility of these changes after normalization of corticosteroid levels using this novel imaging technique.

Methods

Study design

In a prospective study design, patients with CS underwent echocardiography at baseline (during the untreated, active phase of the disease), at short-term follow-up after surgical treatment during a period of stable cortisol status, and at long-term follow-up after final remission. It was anticipated i) that successful surgery would result in a glucocorticoid withdrawal syndrome and hydrocortisone dependency, and ii) that not all patients would be in remission directly after...
surgery. Therefore, the timing of the post-surgical evaluations was as follows: the first post-surgical evaluation was planned at short-term follow-up at least 2 weeks after surgery on a stable physiological hydrocortisone dose for those who were in remission, and between 2 and 6 weeks after surgery in those patients who were not in remission before additional therapy (i.e. radiotherapy) was instituted. The second post-surgical evaluation was planned at least 1 year and maximum 18 months after documented remission. LV dimensions and function were evaluated with standard two-dimensional echocardiography and, in addition, subclinical LV systolic and diastolic dysfunction was evaluated with two-dimensional speckle tracking strain analysis. The time course for LV structural and functional changes was also studied to determine whether changes occur at short- or long-term follow-up.

**Patient population and evaluation of disease status**

We evaluated 15 consecutive patients with CS. The diagnosis was made on clinical grounds together with biochemical confirmation of CS based on the following tests: increased 24-h urinary free cortisol (UFC) excretion (criterion > 220 nmol), failure of serum cortisol to suppress after the administration of low-dose dexamethasone (one evening dose of 1 mg), and loss of diurnal rhythm. In case of ACTH-dependent CS, we also evaluated the suppression of serum cortisol during a 7-h i.v. dexamethasone suppression test as described by Biemond et al. (5), and the response of serum cortisol and ACTH on i.v. CRH stimulation (6). Pituitary imaging by magnetic resonance imaging with i.v. contrast was performed in all patients with ACTH-dependent hypercortisolism. In patients with ACTH-independent CS, adrenal imaging was performed with computed tomography scanning.

The effect of treatment on biochemical control of CS has been extensively described previously (7). After surgery, and if necessary after pituitary irradiation, patients were considered in remission according to normal 24-h urinary cortisol excretion rates (< 80 µg/24 h or < 220 nmol/24 h) and normal overnight suppression of serum cortisol (< 1.8 µg/dl or < 50 nmol/l) after the administration of 1 mg dexamethasone. With these stringent criteria for cure, persistence of (sub-clinical) CS in these patients is unlikely. Moreover, these tests were performed regularly during follow-up to detect possible recurrence, which was not found in the present series of patients. All patients were seen at least twice yearly by an endocrinologist, with adequate evaluation and treatment of possible deficits of pituitary hormones. In patients who were glucocorticoid dependent after surgery, recovery of the pituitary–adrenal axis was tested every 3 months. The hydrocortisone dose was on average 20 mg/d divided into three dosages. After withdrawal of hydrocortisone replacement for 24 h, a fasting morning blood sample was taken for the measurement of serum cortisol concentration. Patients with a serum cortisol concentration < 100 nmol/l were considered glucocorticoid dependent, and hydrocortisone treatment was restarted. Patients with a serum cortisol level between 100 and 500 nmol/l were tested by an ACTH stimulation test (250 µg). Normalization of cortisol production was defined as stimulated cortisol that is more than 500 nmol/l.

In addition, 30 individuals whose frequency was matched by age, sex, body surface area, LV ejection fraction, and blood pressure were included as the control group. These controls were recruited from an echocardiographic database, as previously described (8). We controlled for LV ejection fraction to avoid inclusion of patients with mitral regurgitation due to LV enlargement, with subsequent incomplete mitral leaflet closure. In addition, those controls who were referred for echocardiographic evaluation of known valvular disease, murmur, hypertrophic cardiomyopathy, or heart failure were also excluded. Accordingly, the control group comprised individuals referred for atypical chest pain, palpitations, or syncope without murmur, and showed normal structural heart on echocardiography. The study was approved by the local institutional ethics committee, and written informed consent was obtained from all subjects.

**Echocardiography**

Patients were imaged in the left lateral decubitus position using a commercially available system equipped with a 3.5-MHz transducer (Vingmed Vivid-7, General Electric Vingmed, Horten, Norway). Standard M-mode, two-dimensional, and color-Doppler data were acquired triggered to the QRS complex and saved in cine-loop format for off-line analysis (EchoPac 7.0.0, General Electric/Vingmed Ultrasound). The frame rate of the two-dimensional gray-scale data ranged between 80 and 100 frames/s.

LV dimensions (end-diastolic and end-systolic diameters, end-diastolic interventricular septum thickness, and posterior wall thickness) were measured from M-mode recordings obtained at the parasternal long-axis views, according to the American Society of Echocardiography guidelines (9). LV mass was calculated by Devereux’s formula and indexed to body surface area (10). In addition, relative wall thickness was calculated as previously described to characterize LV geometry (a relative wall thickness > 0.44 indicates LV concentric remodeling) (11). End-diastolic and end-systolic LV volumes were calculated from the apical two- and four-chamber views, and LV ejection fraction was derived according to Simpson’s method (9).

Diastolic function was evaluated by measuring the following parameters: E-wave, A-wave, E/A ratio, deceleration time of the E-wave, and isovolumetric relaxation time obtained from the pulsed-wave Doppler...
recordings (12). In addition, E' velocity was measured at the septal and lateral mitral valve annulus from color-coded tissue Doppler imaging data, and E/E' ratio was derived, reflecting the LV filling pressures (13). Finally, left atrial volume was measured from the apical two- and four-chamber views as a morphologic marker of diastolic function. A left atrial volume indexed to body surface area > 28 ml/m² was considered abnormally dilated, according to current guidelines (9).

**Two-dimensional speckle tracking strain imaging**

Multidirectional LV myocardial strain and strain rate were measured by two-dimensional speckle tracking strain imaging. This novel imaging tool enables the assessment of the LV mechanical properties by tracking frame-to-frame natural acoustic markers (the so-called speckles), equally distributed within the myocardium and visible in the standard gray-scale two-dimensional images (14, 15). Accordingly, LV deformation can be studied along the cardiac cycle in three orthogonal directions: radial, circumferential, and longitudinal (14, 15).

From the LV mid-ventricular short-axis images, the thickening/thinning of the myocardial wall can be assessed with radial strain, whereas the myocardial shortening/lengthening along the curvature of the LV can be evaluated with circumferential strain. The mid-ventricular short-axis of the LV is divided into six segments, and the global values of radial and circumferential strains are derived from the average of the six segmental peak systolic strain values (Fig. 1, panels A and B).

From the apical two- and four-chamber and long-axis views, longitudinal strain evaluates the shortening/lengthening of the myocardial wall, resulting from the movement of the mitral annulus plane upward/downward the LV apex. Each LV apical view is divided into six segments, and the global longitudinal strain value is derived from the average of the 18 segmental peak systolic strain values (Fig. 1, panel C) (15).

Finally, as a marker of global myocardial relaxation, global peak longitudinal strain rate at the isovolumetric relaxation time (SRIVRT) is measured at the three apical views and averaged for final analysis (Fig. 1, panel D), as previously described (16).

Therefore, in the present study, LV mechanical properties were evaluated through three systolic parameters (global radial, circumferential, and longitudinal strains) and one diastolic parameter (SRIVRT), all of them derived with two-dimensional speckle tracking strain imaging.

Intra and interobserver reproducibility for multidirectional strain measurements has been previously reported (17). The intraclass correlation coefficients for radial, circumferential, and longitudinal strain measurements performed by the same observer were 0.97, 0.96, and 0.98 respectively, whereas the inter-observer intraclass correlation coefficients for radial, circumferential, and longitudinal strain measurements performed by two independent observers were 0.81, 0.9, and 0.9 respectively.

**Assays**

Plasma cortisol was measured by RIA (GammaCoat; DiaSorin, Stillwater, MN, USA). The detection limit of the assay was 25 nmol/l, and the interassay variation ranged from 2 to 4%. UFC levels were measured by the same assay after purification over a C18 SPE-10 column (Baker, Phillipsburg, NJ, USA).

![Figure 1](https://www.eje-online.org)
Statistical analysis

Continuous variables are presented as mean ± s.d., and categorical variables are presented in number and frequencies. Comparisons between the group of CS patients at baseline and the control group were performed with the Mann–Whitney U test for unpaired data. Comparisons within the group of CS patients along the follow-up were performed with Friedman’s test for repeated measurements. LV dimensions and function were compared at three different stages: i) baseline versus short-term follow-up after surgery, ii) baseline versus long-term follow-up after surgery, and iii) short-term versus long-term follow-up after surgery. To adjust for inflation of the type I error with multiple tests, a post-hoc analysis was applied; consequently, a P value <0.017 was considered significant (0.05 divided by three different stages). Finally, the independent determinants of multidirectional LV strain and strain rate were evaluated in univariable and multivariable linear regression analyses. All statistical analyses were performed with SPSS software (version 16.0, SPSS Inc., Chicago, IL, USA). A P value < 0.05 was considered statistically significant.

Results

Patient characteristics

Baseline clinical characteristics of CS patients and controls are summarized in Table 1. Six patients were on anti-hypertensive agents (valsartan (n = 2), enalapril (n = 1), atenolol (n = 1), metoprolol (n = 1), and doxazosin (n = 2)). The underlying causes of CS were ACTH dependent (n = 12): ACTH-producing pituitary adenoma (Cushing’s disease, ten microadenomas and two macroadenomas), and ACTH independent (n = 3): bilateral macronodular adrenal hyperplasia (n = 1), bilateral micronodular hyperplasia, secondary to primary pigmented adrenocortical disease (PPNAD) (n = 1), and adrenal adenoma (n = 1). All patients were treated surgically: transsphenoidal adrenalectomy (n = 12), and unilateral (n = 2) and bilateral (n = 1) adrenalectomy. The patient with bilateral macronodular hyperplasia underwent bilateral adrenalectomy. The second patient with ACTH-independent CS was diagnosed with bilateral micronodular hyperplasia, secondary to PPNAD, as part of the Carney complex. Although PPNAD is bilateral, it is unknown whether both adrenal glands are equally affected with respect to autonomous cortisol production. Therefore, the patient underwent bilateral selective adrenal vein sampling, which documented much higher cortisol concentrations in the left adrenal vein. Consequently, a unilateral adrenalectomy of the presumably most affected adrenal was performed. After surgery, 24-h UFC excretion (4.2 times ULN before surgery), ACTH (suppressed before surgery), and the dexamethasone suppression test were all normalized. The third patient, with a unilateral adenoma, underwent unilateral adrenalectomy. Histological investigations confirmed the clinical diagnosis in all cases. Anti-hypertensive and anti-diabetic medication was used in six and five patients respectively.

Table 1 Baseline characteristics and changes in clinical status after surgical treatment (n = 15) and radiotherapy (n = 6).

<table>
<thead>
<tr>
<th>(A) Baseline characteristics</th>
<th>Patients (n = 15)</th>
<th>Controls (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41 ± 12</td>
<td>44 ± 11</td>
<td>0.329</td>
</tr>
<tr>
<td>Sex (male, %)</td>
<td>6 (40%)</td>
<td>13 (43%)</td>
<td>0.832</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.9 ± 0.2</td>
<td>1.9 ± 0.1</td>
<td>0.316</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.6 ± 4.9</td>
<td>24.5 ± 4.0</td>
<td>0.038</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>135 ± 13</td>
<td>134 ± 17</td>
<td>0.635</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>88 ± 12</td>
<td>82 ± 12</td>
<td>0.071</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(B) Changes in clinical status after surgical treatment (n = 15) and after radiotherapy (n = 6)</th>
<th>Baseline</th>
<th>Short-term follow-up</th>
<th>Long-term follow-up</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>135 ± 13</td>
<td>129 ± 15</td>
<td>127 ± 12</td>
<td>0.057</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>88 ± 12</td>
<td>85 ± 10</td>
<td>81 ± 7</td>
<td>0.125</td>
</tr>
<tr>
<td>Median (IQR) 24-h UFCa (nmol)</td>
<td>880 (550, 3454)</td>
<td>586 (195, 940)</td>
<td>165* (122, 220)</td>
<td>0.015</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.7 ± 1.1</td>
<td>5.7 ± 0.8</td>
<td>5.9 ± 1.1</td>
<td>0.502</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.6 ± 4.9</td>
<td>28.7 ± 5.6</td>
<td>28.7 ± 5.6</td>
<td>0.905</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Patients on anti-hypertensives (%)</td>
<td>6</td>
<td>6</td>
<td>4b</td>
<td></td>
</tr>
<tr>
<td>Patients on anti-diabetics/insulin (%)</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Patients on HC replacement (%)</td>
<td>NA</td>
<td>8</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

HC, hydrocortisone; IQR, interquartile range; NA, not applicable. *P = 0.002 versus baseline.  
a24-h UFC, 24-h urinary free cortisol excretion.  
bReduction of dose in one patient versus short-term follow-up.
Changes in clinical status at short- and long-term follow-up after surgery

At short-term follow-up after surgery (median 1 month), at the time of the second echocardiography, 9/15 patients (60%) were in remission. Eight of these nine patients were hydrocortisone dependent. The six patients with Cushing’s disease and persistent disease were treated by pituitary irradiation (using a conventional linear accelerator (8 MeV) in a rotating field; total tumor dose: 40–45 Gy, fractionated in 20 sessions over a period of 4 weeks). During long-term follow-up (median 14 months), at the time of the third echocardiography, all patients were in biochemical remission. Six patients were still dependent on hydrocortisone.

After short-term follow-up after surgical treatment, systolic blood pressure decreased from 135±13 to 129±15 mmHg (P=0.168) and remained stable at long-term follow-up (127±12 mmHg, P=0.468 versus short-term follow-up; Table 1). Similarly, diastolic pressure decreased progressively from 88±12 to 85±10 mmHg at short-term follow-up (P=0.347) and to 81±7 mmHg at long-term follow-up (P=0.090 versus short-term follow-up; Table 1). There were no significant changes in body mass index (BMI; Table 1) or smoking status (n=4, 27%). The number of patients using anti-hypertensive or anti-diabetic medication reduced from 6 to 4 and from 5 to 3 patients respectively after long-term follow-up. Before treatment, all six premenopausal female patients had secondary amenorrhea, and another two patients (both with pituitary macroadenoma) had additional hormone pituitary rhea, and another two patients (both with pituitary premenopausal female patients had secondary amenorrhoea after long-term follow-up. Before treatment, all six patients with Cushing’s disease and persistent disease were treated by pituitary irradiation (using a conventional linear accelerator (8 MeV) in a rotating field; total tumor dose: 40–45 Gy, fractionated in 20 sessions over a period of 4 weeks). During long-term follow-up (median 14 months), at the time of the third echocardiography, all patients were in biochemical remission. Six patients were still dependent on hydrocortisone.

Other treatment-induced deficiencies, besides hydrocortisone dependency, were not documented during the follow-up period.

Baseline echocardiography and two-dimensional speckle tracking strain analysis: comparison between patients with active CS and controls

At baseline, there were no differences in LV diameters, volumes, and ejection fraction between patients with CS and controls (Table 2). However, patients with CS had significantly more LV hypertrophy, with significantly higher values of interventricular septum and posterior wall thickness. LV mass index, and relative wall thickness. In addition, patients with CS had impaired early LV relaxation, with significantly lower values of transmural E-wave velocity and E/A ratio and significantly longer isovolumetric relaxation time (Table 2). Mitral annular E’ velocity was also significantly reduced in CS patients, resulting in a significantly higher E/E’ ratio.

Two-dimensional speckle tracking strain imaging analysis demonstrated that LV shortening in the circumferential and longitudinal directions was significantly impaired in CS patients, with significantly less negative values of global circumferential strain and global longitudinal strain, compared to controls (Table 3). In contrast, there were no differences in LV global radial strain between both groups. Finally, SRivert was significantly lower in CS patients compared to controls, indicating impaired global myocardial relaxation (Table 3).
Univariable and multivariable linear regression analyses were performed to evaluate the independent determinants of circumferential and longitudinal strains and SR IVRT. CS, BMI, and LV mass index were included as independent variables. As shown in Table 4, CS was the strongest independent determinant of circumferential and longitudinal strains and SR IVRT.

Changes in LV dimensions and function after surgery

After surgical treatment, there were no changes in LV internal dimensions, volumes, or systolic function. Importantly, there was a regression of LV hypertrophy, with a significant reduction in interventricular septum thickness, LV mass index, and relative wall thickness (Table 5). In addition, LV diastolic function improved with significant increases in E-wave and E' velocities and a significant reduction in indexed left atrial volume. Of note, all these significant changes were observed at long-term follow-up, whereas at short-term follow-up, significant changes were not yet noted.

Changes in time in multidirectional LV strain after surgery

A gradual improvement in LV shortening in the circumferential and longitudinal directions was observed after surgical treatment, whereas no changes were noted in global radial strain (Fig. 2). Importantly, significant improvements in global circumferential and longitudinal strains were noted early at short-term follow-up after surgery and were sustained at long-term follow-up. These early improvements were observed

### Table 3 Baseline LV multidirectional strain assessed with two-dimensional speckle tracking (A) and differences between patients with and without complete remission at follow-up in longitudinal and circumferential shortening time course evolution.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CS patients ( (n=15) )</th>
<th>Controls ( (n=30) )</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global radial strain (%)</strong></td>
<td>33.8 ± 12.8</td>
<td>42.1 ± 17.1</td>
<td>0.144</td>
</tr>
<tr>
<td><strong>Global circumferential strain (%)</strong></td>
<td>−16.5 ± 3.5</td>
<td>−19.7 ± 3.4</td>
<td><strong>0.013</strong></td>
</tr>
<tr>
<td><strong>Global longitudinal strain (%)</strong></td>
<td>−15.4 ± 1.9</td>
<td>−20.1 ± 2.3</td>
<td>&lt; <strong>0.001</strong></td>
</tr>
<tr>
<td><strong>SR IVRT (per s)</strong></td>
<td>0.3 ± 0.1</td>
<td>0.4 ± 0.2</td>
<td><strong>0.012</strong></td>
</tr>
</tbody>
</table>

### Table 4 Determinants of multidirectional left ventricular strain and strain rate.

<table>
<thead>
<tr>
<th>Variable</th>
<th>( \beta )</th>
<th>( P ) value</th>
<th>( \beta )</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Circumferential strain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>0.413</td>
<td>0.005</td>
<td>0.402</td>
<td>0.006</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.240</td>
<td>0.116</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LV mass index</td>
<td>0.358</td>
<td>0.018</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Longitudinal strain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>0.717</td>
<td>&lt; 0.001</td>
<td>0.717</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.380</td>
<td>0.010</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LV mass index</td>
<td>0.379</td>
<td>0.011</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>SR IVRT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>−0.343</td>
<td>0.023</td>
<td>−0.338</td>
<td>0.027</td>
</tr>
<tr>
<td>Body mass index</td>
<td>−0.293</td>
<td>0.054</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LV mass index</td>
<td>−0.273</td>
<td>0.076</td>
<td>—</td>
<td>—</td>
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</tbody>
</table>

LV, left ventricular; SR IVRT, global peak longitudinal strain rate at the isovolumetric relaxation time.

(A M Pereira and others)

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only in patients who were in remission directly after surgery, whereas in patients with persistent hypercortisolism, no significant changes were observed at short-term follow-up (Table 3). Furthermore, these significant improvements in circumferential and longitudinal strains were observed at a similar extent in patients who remained under hydrocortisone therapy and in patients who were not, and no significant differences were observed between both groups of patients at follow-up (Table 3).

Similarly, global myocardial diastolic relaxation improved significantly with an increase in SRIVRT (Fig. 2). However, this improvement was only noted at long-term follow-up.

**Discussion**

This study has demonstrated for the first time that the abnormalities in LV structure and function in patients with CS are reversible upon normalization of corticosteroid excess. This has important implications for
the treatment of patients exposed to persistent corticosteroid excess.

Two previous studies, involving a total of 82 patients, have evaluated cardiac function in CS (4, 18). These reports evaluated cardiac function only in the active phase of the disease and demonstrated that patients with CS commonly have abnormal LV geometry (with increased LV mass index and relative wall thickness) and LV diastolic dysfunction (impaired relaxation LV filling pattern), but preserved LV ejection fraction (4, 18). The use of more sensitive echocardiographic parameters (such as mid-wall fractional shortening or strain imaging) may enable the detection of subtle LV systolic dysfunction, yielding important clinical implications for the risk stratification and clinical management of these patients (4, 19). In this regard, Muiiesan et al demonstrated the presence of subclinical LV systolic dysfunction in patients with active CS by evaluating the LV mid-wall fractional shortening (4). Compared to controls, patients with CS showed more LV concentric remodeling and diastolic dysfunction, whereas LV ejection fraction was preserved. In contrast, LV mid-wall fractional shortening was significantly reduced, indicating the presence of subclinical LV systolic dysfunction (4). However, CS per se and other related clinical conditions such as obesity or diabetes may induce ultrastructural changes that are not identified by conventional echocardiography. The mineralocorticoid receptor and 11β-hydroxysteroid dehydrogenase type 2, the enzyme that converts cortisol to the inactive cortisone, are co-expressed in human heart. Glucocorticoid excess impairs the conversion of cortisol leading to glucocorticoid-mediated mineralocorticoid effects, finally resulting in increased myocardial fibrosis (20, 21). The presence of increased fibrosis and lipid content may induce metabolic and functional myocardial changes that can be detected with more sensitive and sophisticated imaging modalities (magnetic resonance spectroscopy and two-dimensional speckle tracking imaging) (22, 23).

The present study extends the previous observations by providing full evaluation of LV diastolic function and by studying, for the first time, myocardial deformation properties with two-dimensional speckle tracking strain imaging. Although the present cohort of patients had normal LV dimensions, LV mass index and relative wall thickness were increased. In addition, LV diastolic function was characterized by an impaired relaxation filling pattern in the majority of the patients, with increased LV filling pressures, indicated by the relatively increased E/E′ ratio and enlarged left atrium. In accordance with the previous studies, LV ejection fraction was preserved. However, by applying two-dimensional speckle tracking strain imaging. LV systolic dysfunction was detected, with deterioration in LV circumferential and longitudinal shortening. Furthermore, LV filling pressures were elevated, reflected by a decreased SRIVRT value. These findings add more insight into the cardiac pathophysiology of corticosteroid excess.

After surgical treatment for CS, the present study demonstrated, for the first time, that there is a significant reduction in LV mass and relative wall thickness together with a normalization of LV diastolic function. In addition, two-dimensional speckle tracking strain imaging demonstrated subtle changes in LV mechanics, with a normalization of LV circumferential and longitudinal shortening and an improvement in SRIVRT indicating normalization of LV filling pressures. Importantly, cardiac structural and functional changes assessed with conventional two-dimensional echocardiography were observed at long-term follow-up. In contrast, two-dimensional speckle tracking strain imaging enabled an earlier detection of subtle changes in LV systolic performance, with a significant improvement in LV circumferential and longitudinal shortening after one-month follow-up. Of note, these changes in myocardial mechanical properties were independent of changes in blood pressure. After normalization of corticosteroid levels, no significant changes in blood pressure were observed along the follow-up. Apparently, restoration of eucortisolemia can completely normalize cardiac dysfunction, whereas cardiovascular risk factors, including hypertension or dyslipidemia, persisted in some patients despite optimal medical treatment (2).

However, we have to keep in mind that immediate surgical remission will not be obtained in a significant number (up to 40%) of the patients with CS (7). This was also the case in the present series. Radiation therapy is an effective treatment for patients with persistent disease, but normalization of cortisol secretion only occurs after a prolonged period of time, usually after 1–3 years. In the mean time, the patient is exposed to persistent corticosteroid excess, and thus, to persistent alterations in LV mass and impairments in LV function.

Increased LV mass constitutes an independent risk factor for the development of heart failure, and concentric remodeling is related to adverse cardiovascular events and increased mortality despite preserved LV ejection fraction (24, 25). The presence of impaired LV circumferential and longitudinal shortening in patients with LV hypertrophy and preserved LV ejection fraction has been previously demonstrated using tagged magnetic resonance imaging (26). With an increasing degree of LV hypertrophy and concentric remodeling, the subendocardial myocardial layer, responsible for the longitudinal and circumferential shortening, becomes more susceptible to ischemia, apoptotic, and fibrosis phenomena, resulting in reduced LV longitudinal and circumferential shortening at an early stage of the disease. Instead, mid-wall myocardial layer, responsible for the radial thickening, is only affected at a late stage, when the cardiac afterload exceeds the compensatory LV hypertrophy (26). Therefore, unlike LV longitudinal and circumferential shortening, LV radial strain and ejection fraction will remain preserved during a longer time. The onset of intensive therapies at this early stage reverses the structural cardiac abnormalities and restores the LV performance as demonstrated by the current study.
However, in case of persistent hypercortisolism despite optimal treatment, we advocate additional treatment with angiotensin-converting enzyme inhibitors in agreement with the treatment guidelines for patients with increased cardiovascular morbidity and mortality (27).

Some limitations have to be acknowledged. The presence of hypertension or diabetes may influence the results of the present study, since these cardiovascular risks may have a detrimental effect on LV performance. However, the inclusion of patients with CS and hypertension or diabetes strengthens the study since these patients represent a substantial part of the clinical spectrum of the disease and the daily clinical practice. In addition, the limited number of patients may have precluded us to observe significant changes in LV radial strain. Finally, the control group was not matched by BMI, a potential confounder factor. However, the multivariable regression analyses demonstrated that CS was the strongest determinant of impaired multidirectional LV strain and strain rate.

In conclusion, patients with CS have abnormalities of LV structure and function that are reversible upon normalization of corticosteroid excess. These LV abnormalities reverse with an early improvement in longitudinal and circumferential shortening and a late regression of LV hypertrophy. Two-dimensional speckle tracking strain imaging is a valuable tool to detect subtle LV dysfunction in patients and to monitor the changes in LV performance after normalization of corticosteroid excess. Considering the increased cardiovascular morbidity and mortality in Cushing syndrome, these findings have potentially important implications for all patients exposed to persistent corticosteroid excess.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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