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Hypokalemia, Diabetes Mellitus, and Hypercortisolemia are the Major Contributing Factors to Cardiac Dysfunction in Adrenal Cushing's Syndrome

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Abstract. Although cardiovascular complications are the major determinant of the prognosis of Cushing's syndrome (CS), factors contributing to the cardiovascular lesions are still unclear. We investigated clinical factors determining cardiac function in patients with adrenal CS. Fifty patients with adrenal CS were studied. Patients were divided into 3 groups based on their NYHA classification and electrocardiographic (ECG) findings: group A with NYHA grade 0 and normal ECG, group B with NYHA grade I and abnormal ECG, and group C with NYHA grade II or higher. Clinical and echocardiographic findings were compared between the groups. Heart failure of grade I or higher was seen in 40% and grade II or higher was seen in 8% of the patients. Age, HbA1c, and prevalence of diabetes mellitus were positively correlated and serum potassium levels were negatively correlated with the severity of cardiac dysfunction. Decreased ejection fraction (EF) and the ratio of the peak to late transmittal filling velocities (E/A), and increased left ventricular mass index (LVMI) were frequently observed. Multivariate analysis demonstrated that serum potassium and HbA1c levels were independent factors contributing to EF, while serum potassium and cortisol levels were independent factors contributing to LVMI. These results clearly demonstrated that hypokalemia, diabetes mellitus, and hypercortisolemia are the major contributing factors to cardiac dysfunction in adrenal CS. Strict control of these conditions is warranted for the prevention of cardiac dysfunction in adrenal CS.

Key words: Cushing's syndrome, Heart failure, Hypokalemia, Cardiac hypertrophy, Cortisol

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CUSHING'S SYNDROME is one of the classic causes of secondary hypertension. Excessive secretion of cortisol causes not only characteristic physical features but also hypertension, impaired glucose metabolism and serum electrolyte imbalance, including hypokalemia. Most patients with Cushing's syndrome are biochemically cured by early diagnosis followed by appropriate surgical therapy. However, it has been reported that the prevalence of cardiovascular disease in Cushing's syndrome patients is high [1-3] and persists even after normalization of endocrine abnormalities [4, 5].

The mortality rate due to cardiovascular complications is 4 times as high in Cushing's syndrome patients as in the age- and gender-matched general population [2, 6]. Hypertension can persist even after complete removal of adrenal adenomas and normalization of hypercortisolism. The survival rate in patients with adrenal Cushing's syndrome, if hypertension is not controlled, is approximately 50% of that seen in patients with well-controlled blood pressure [7]. Cardiovascular complications are therefore important factors determining prognosis in Cushing's syndrome. Cardiac dysfunction is one of the most important cardiovascular complications affecting mortality. Cardiac hypertrophy [8-11] and congestive heart failure [3, 12-14] are the major forms of cardiac dys-

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function in Cushing's syndrome. Hypertension and impaired glucose and lipid metabolism due to chronic hypercortisolism and the direct effects of cortisol on the heart have been reported as risks for cardiovascular complications [9, 10]. However, there has to date been no detailed analysis of the factors involved in cardiac dysfunction in patients with Cushing's syndrome and their related mechanisms. In addition, previous studies have mainly focused on pituitary Cushing's disease with a smaller number of adrenal Cushing's syndrome [5, 10, 15]. Analyses of the patients group with heterogeneous causes may modify the relationship between the clinical factors and cardiac function, while no studies of the cardiac function and contributing clinical factors in adrenal Cushing's syndrome have been reported.

In this study, we have investigated cardiac function and its correlation with clinical and echocardiographic findings in 50 patients with adrenal Cushing's syndrome.

Patients and Methods

Subjects

Fifty patients with adrenal Cushing's syndrome (44 females and 6 males; average age 46.6±14.3 years) in the active stage were studied. Patients had been referred to Tokyo Women's Medical University Hospital between 1994 and 2007 for evaluation of Cushing's syndrome. All patients showed typical Cushing's feature. The diagnosis of adrenal Cushing's syndrome was based on endocrine findings including suppressed plasma ACTH with normal or elevated serum cortisol concentration, absence of physiological circadian rhythms of serum cortisol, failure of cortisol suppression by 1 mg and 8 mg dexamethasone, visualization of an adrenal tumor in imaging studies, and pathological findings after surgery. This study has been conducted in accordance with the Helsinki Declaration on human experimentation and guideline of epidemiologic study of Japanese Ministry of Health, Labor and Welfare.

These patients were on a normocaloric, low sodium (6-10 g/day), normopotassuim diet regimen. The duration of the disease was estimated based on the appearance either of Cushing's feature, hypertension or impaired glucose metabolism. The estimated mean duration of the disease was 5.9±5.8 years (mean ±SD). Blood pressure was measured between 0830 h and 0900 h with a mercury sphygmomanometer after at least 30 minutes spine-position and diagnosis of hypertension was defined according to the Guideline of JNC7. Blood biochemistry was measured at the time of diagnosis in patients without heart failure and before administration of diuretics in the patients with heart failure. Diagnosis of diabetes mellitus was defined as having FPG higher than 126 mg/dL [16] and/or HbA1c higher than 6.5% according to the report by the International Expert Committee in 2009 [17], or if the patient was taking antiglycemic medication.

Subgroup classification for cardiac dysfunction

Cardiac function was clinically assessed using the classifications of the New York Heart Association (NYHA) for heart failure [18] and electrocardiogram (ECG) results. Patients were divided into three groups: Group A without symptoms of heart failure and normal electrocardiograms, Group B with class I NYHA classification and/or abnormal electrocardiographic findings (conduction disorder, ischemic change, and/or arrhythmia), and Group C with class II-IV NYHA classification. Clinical demographics compared between the three groups were as follows: age, gender, estimated mean duration of the disease, blood pressure, fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), serum potassium concentration, serum creatinine concentration, serum cortisol concentration (early morning, midnight, after 1-mg overnight dexamethasone suppression test [1-mg DST]), and urinary free cortisol excretion (total excretion, normalized by urine creatinine), smoking status, presence of diabetes mellitus, dyslipidemia and hypertension, antihypertensive medications, and antidiabetic agents.

Echocardiography

Thirty-seven patients were subjected to echocardiography [19] using Sonos 500 echo machines (YHP International Co. Ltd., Tokyo, Japan). End-diastolic left ventricular (LV) internal dimensions (LVDd), end-systolic LV internal dimensions (LVDs), interventricular septum thickness (IVST), and posterior wall thickness (PWT) were measured using two-dimensional targeted M-mode echocardiography, using the criteria of the American Society of Echocardiography [20]. The ejection fraction (EF) was calculated using the following formula: $(LVDd^2\text{-}LVDs^2)/ LVDd^2 \times 100$

(%) and systolic function was defined as being impaired if the EF was less than 60%. The ratio of peak (E) to late (A) transmittal filling velocities (E/A) and E-wave deceleration time (DcT) as markers for diastolic dysfunction were evaluated by two-dimensional, pulsed-wave Doppler. E/A≥1.0 and E-wave DcT ranging from 150 to 250 msec were defined as normal [21, 22]. LV mass was calculated using the Penn Convention [23]. LV mass index (LVMI) was calculated by correcting LV mass with body surface area [24] and was defined as left ventricular hypertrophy if LVMI was more than 125 g/m^2 [24]. End-diastolic RWT was calculated using the following formula: PWT×2/LVDd and was defined as wall thickening if it was greater than 0.45 [24].

To identify patterns of left ventricular hypertrophy, patients with left ventricular hypertrophy were classified into the following three groups according to the geometric pattern of their hypertrophy: concentric left ventricular remodeling (increased RWT without increased LVMI), eccentric left ventricular hypertrophy (increased LVMI without increased RWT), and concentric left ventricular hypertrophy (increased LVMI with increased RWT) [24]. Asymmetric septal hypertrophy (ASH) was defined as having IVST/PWT greater than 1.3 or IVST greater than 15 mm.

Echocardiographic findings were compared between the three groups. In addition, the correlations between echocardiographic parameters (EF, E/A, RWT, LVMI) and clinical findings (age, estimated mean duration of the disease, blood pressure, FPG, HbA1c, serum potassium concentration, serum cortisol concentration (early morning, midnight, after 1-mg DST), and urinary free cortisol excretion) were investigated using simple correlation and multivariate analysis.

Of the 4 patients in the group C with severe heart failure, one patient died of heart failure 3 weeks after adrenalectomy and autopsy disclosed the presence of severe dilated cardiomyopathy. Echocardiographic and biochemical findings one year after the surgery were compared to those before the surgery in 3 patients of the group C with heart failure.

Hormone assay

Serum cortisol was measured by radioimmunoassay in commercial laboratories using radioimmunoassay kits (Amerlex RIA; Ortho-clinical Diagnostics Co., Tokyo).

Statistical analyses

All values are expressed as mean±SD. The Mann-Whitney U test and Kruskal Wallis test were used to compare mean values between 2 groups and 3 groups, respectively. The $\chi 2$ test was used for comparison of the prevalence of each geometric pattern in the 3 groups. Simple correlation analysis was performed to assess the correlation between echocardiographic parameters and clinical findings. Multivariate analysis was performed to assess the independent effects of clinical parameters on echocardiographic parameters. All analyses were carried out using the SPSS 11.0.1 statistical package. A value of $P < 0.05$ was considered to be statistically significant.

Results

Although 30 patients did not show any clinical manifestation of heart failure, 16 patients had class I, and 4 patients had class IV of NYHA classification. Accordingly, the prevalence of decompensated heart failure was 8%. Patients were divided into three groups based on their NYHA classification and ECG findings: 30 patients in Group A, 16 patients in Group B, and 4 patients in Group C. There was no statistical difference in gender composition, estimated mean duration of the disease, blood pressure, fasting plasma glucose concentration, serum creatinine concentration, serum cortisol concentration (early morning, midnight, after 1-mg DST), and urinary free cortisol excretion, or smoking status between the three groups (Table 1). Average age was highest in Group C followed by groups B and A with a significant difference between the groups (Table 1, Fig. 1a). Three of 4 patients in Group C were less than 65 years of age (44, 57, 64, and 72 y.o.).

Patients were treated with antidiabetic agents including insulin in 6 of 30 patients (20%) of group A, 4 of 16 patients (25%) of group B, and 4 of 4 patients (100%) of group C. HbA1c in Group C were however significantly higher than that in Group A (Table 1, Fig. 1b). Serum potassium concentration was lowest in Group C followed by groups B and A with a significant difference between the groups (Table 1, Fig. 1c). The prevalence of diabetes mellitus in Group C (100%) was significantly higher than that in groups A and B (Table 1). There was no significant difference in the

Table 1. Clinical demographics of all subjects and of each of the 3 groups of adrenal Cushing's syndrome patients classified by NYHA classification and ECG findings

		All subjects[a]	Group A[a]	Group B[a]	Group C[a]	*P*[b]
N		50	30	16	4	
Age (y.o)		46.6±14.3	41.5±13.0	52.9±13.2	59.3±11.9	*P*<0.005
Gender (F/M)		44/6	26/4	14/2	4/0	*P*=0.741
Duration of the disease (yrs)		5.9±5.8	5.2±5.1	6.0±5.7	10.5±10.2	*P*=0.419
Mean blood pressure (mmHg)		102.1±19.7	103.4±23.6	101.1±13.5	96.0±2.2	*P*=0.262
Systolic blood pressure (mmHg)		145.2±22.3	146.7±23.8	146.4±20.9	128.5±5.7	*P*=0.159
Diastolic blood pressure (mmHg)		84.0±13.7	87.2±15.0	78.8±11.2	80.5±1.0	*P*=0.093
Fasting plasma glucose (mg/dL)		104.6±32.8	100.0±27.5	110.3±39.2	116.5±45.5	*P*=0.662
HbA1c (%)		6.2±1.6	5.9±1.1	6.4±2.3	7.5±1.5*	*P*=0.090
Serum potassium concentration (mEq/L)		3.8±0.6	3.9±0.5	3.8±0.6	2.8±0.3	*P*<0.05
Serum creatinine concentration (mg/dL)		0.80±0.16	0.79±0.14	0.80±0.17	0.90±0.19	*P*=0.44
Serum cortisol concentration (μg/dL)		24.3±16.6	21.9±5.4	29.9±28.7	21.0±7.9	*P*=0.886
Urinary cortisol excretion (μg/day)		330.7±195.6	356.2±215.1	309.0±159.0	276.7±149.5	*P*=0.775
Prevalence (%)	Smoking habit	35	31	46	25	*P*=0.580
	Diabetes mellitus	50	53	31	100	*P*<0.05
	Dyslipidemia	76	73	75	100	*P*=0.499
	Hypertension	82	83	81	100	*P*=0.617
Rate of antihypertensive medication treatment (%)	ACEI/ARB	52	52	46	75	*P*=0.599
	Ca antagonist	79	80	77	75	*P*=0.960
	β blocker	21	16	31	25	*P*=0.565
	α blocker	26	32	15	0	*P*=0.261

[a] Values are the mean±SD, [b] *P*: comparison between the 3 groups by Kruskal-Wallis test, *$P<0.05$ *vs*. Group A

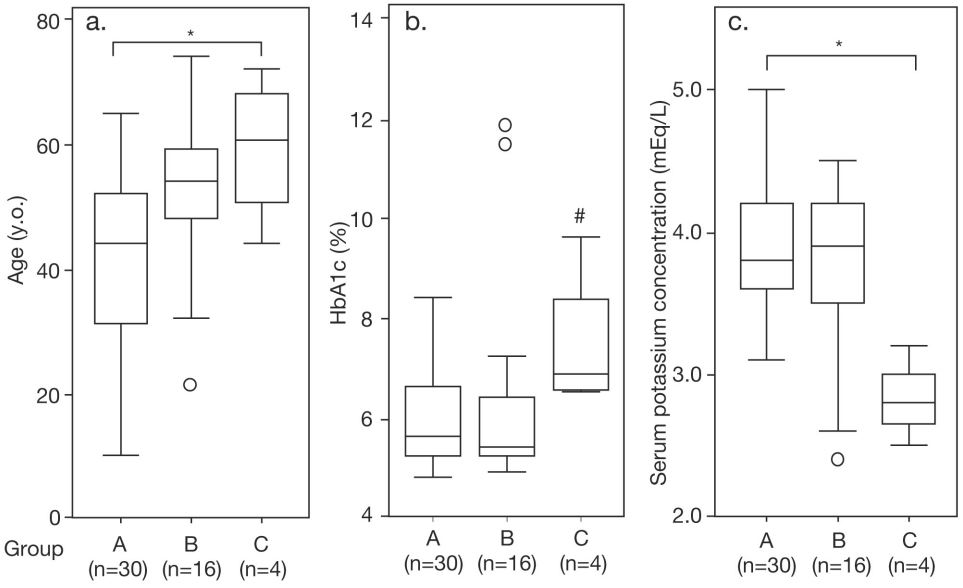

Fig. 1. Comparison of age (a), HbA1c levels (b), and serum potassium concentration (c) between the 3 groups of adrenal Cushing's syndrome patients classified by NYHA classification and ECG findings.
*$p<0.05$ between the 3 groups, # $p<0.05$ *vs.* Group A

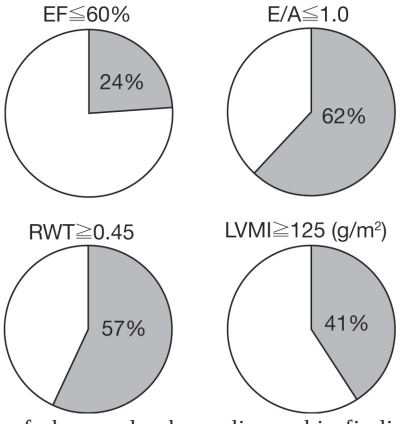

Fig. 2. Rate of abnormal echocardiographic findings in 50 patients with adrenal Cushing's syndrome.
EF: ejection fraction, E/A: ratio of the peak (E) and late (A) transmittal filling velocity, RWT: left ventricular relative wall thickness, LVMI: left ventricular mass index.

Table 2. Echocardiographic findings of the 3 groups of adrenal Cushing's syndrome patients classified by NYHA classification and ECG findings

	Group A[a]	Group B[a]	Group C[a]	*P*[b]
N	22	11	4	
EF (%)	71.0±7.1	67.0±11.7	41.5±8.4	*P*<0.005
E/A	1.1±0.5	0.9±0.4	0.7±0.3*	*P*=0.06
DcT (msec)	195.9±58.9	177.7±39.0	195.0±38.5	*P*=0.684
LVDd (mm)	43.6±4.7	45.2±4.2	45.4±4.4	*P*=0.891
LVDs (mm)	25.2±3.6	28.9±7.4	34.3±5.9	*P*<0.05
IVST (mm)	10.3±2.1	11.2±2.7	11.0±2.2	*P*=0.447
PWT (mm)	10.7±1.8	11.5±2.2	11.5±3.4	*P*=0.279
RWT	0.5±0.1	0.5±0.1	0.5±0.2	*P*=0.579
LVMI (g/m²)	103.6±31.6	135.1±71.5	157.8±24.3	*P*<0.05

[a] Values are the mean±SD
[b] *P*: comparison between the 3 groups by Kruskal-Wallis test
*$P<0.05$ *vs.* Group A

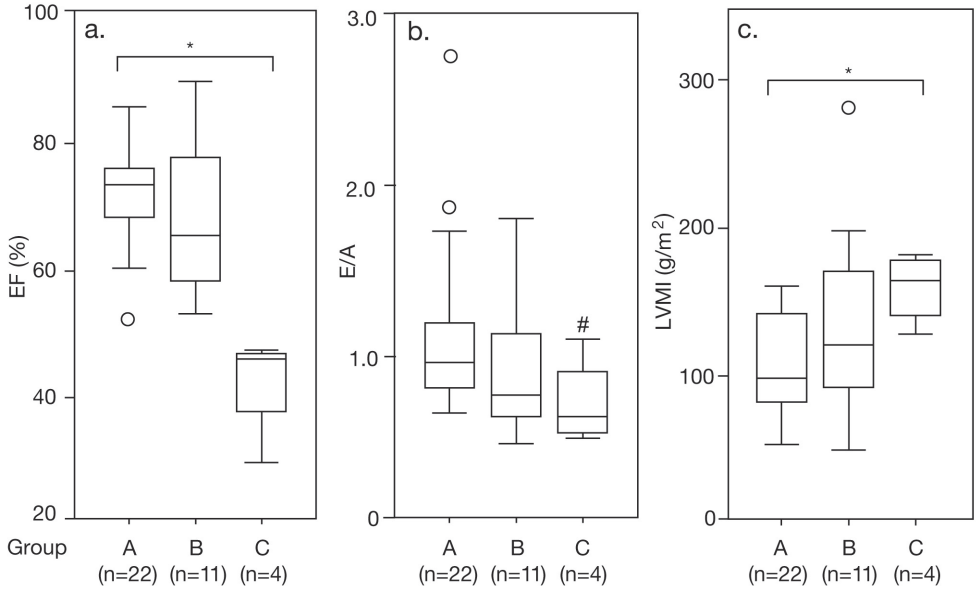

Fig. 3. Comparison of EF (a), E/A (b), and LVMI (c) between the 3 groups of adrenal Cushing's syndrome patients classified by NYHA classification and ECG findings.
*$p<0.05$ between the 3 groups, # $p<0.05$ *vs.* Group A

prevalence of dyslipidemia and hypertension. None of the patients was given diuretics for hypertension and/or heart failure at the time of the present study. There was no significant difference in the classes of antihypertensive medications between the groups (Table 1).

In the 37 patients subjected to echocardiography, EF was decreased in 24%, E/A was decreased in 62%, RWT was increased in 57% and LVMI was increased in 41% of the whole patients (Fig. 2). Twenty-two, 11, and 4 patients were classified in Group A, Group B, and Group C, respectively. EF was lowest in Group C followed by groups B and A (Table 2, Fig. 3a). E/A was significantly lower in Group C than that in Group A (Table 2, Figure 3b). There was no significant difference in E-wave DcT between the groups. LVDs was significantly greater in Group C than in Groups A and B (Table 2). Although there was no significant difference in LVDd, IVST, PWT, and RWT between the groups, ventricular wall thickening (RWT greater than 0.45) was more prevalent in Groups B (50%) and C

(50%) than in Group A (36.7%). LVMI was greatest in Group C followed by groups B and A with a significant difference between the groups (Table 2, Fig. 3c).

The geometric pattern of cardiac morphology is shown in Fig. 4. A normal geometric pattern was seen in 35.1% of 50 patients. However, concentric remodeling, eccentric hypertrophy, and concentric hypertrophy were seen in 24.4%, 8.1% and 32.4% of patients, respectively. The overall prevalence of an abnormal geometric pattern was 64.9% of the patients (Fig.4a). Although not statistically significant, the prevalence of concentric hypertrophy in groups B and C (Fig. 4b) was twice as high as in group A (Fig. 4c). ASH was not seen in any of the patients in this study.

There was a significant positive correlation between serum potassium concentration and EF (r^2=0.467, P<0.005) (Fig.5a) and a significant negative correlation between serum potassium concentration and LVMI (r^2=-0.439, P<0.01) (Fig. 5b). In contrast, there was no significant correlation of age, systolic and diastolic blood pressure, estimated mean duration of the disease, or any of the cortisol measurements with the echocardiographic parameters including EF, E/A and LVMI.

Multivariate analysis of clinical factors contributing to the echocardiographic parameters revealed that serum potassium concentration and HbA1c were independent explanatory variables for EF. Age was shown to be an independent explanatory variable for E/A. Serum potassium concentration and serum cortisol concentration in the morning were shown to be independent explanatory variables for LVMI (Table 3). By contrast, serum cortisol concentration at midnight and after 1 mg DST, and urinary free cortisol excretion were not independent explanatory variables for EF or LVMI.

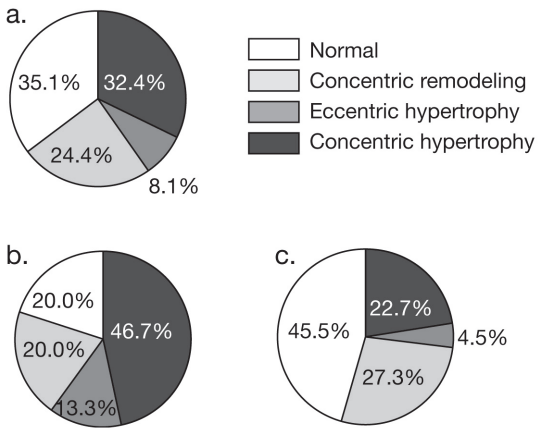

Fig. 4. Geometric pattern of left ventricular hypertrophy by echocardiography in all subjects (a), groups B and C (b), and group A (c). Geometric patterns were classified based on RWT and LVMI.

Changes in cardiac function and biochemical measurements were compared before and one year after adrenal surgery in 3 patients of Group C. EF, LVMI, serum potassium, and HbA1c were all significantly improved as well as the plasma cortisol concentration (data not shown) in those 3 patients after surgery (Table 4).

Discussion

We have investigated cardiac function and its contributing factors in 50 patients with adrenal Cushing's

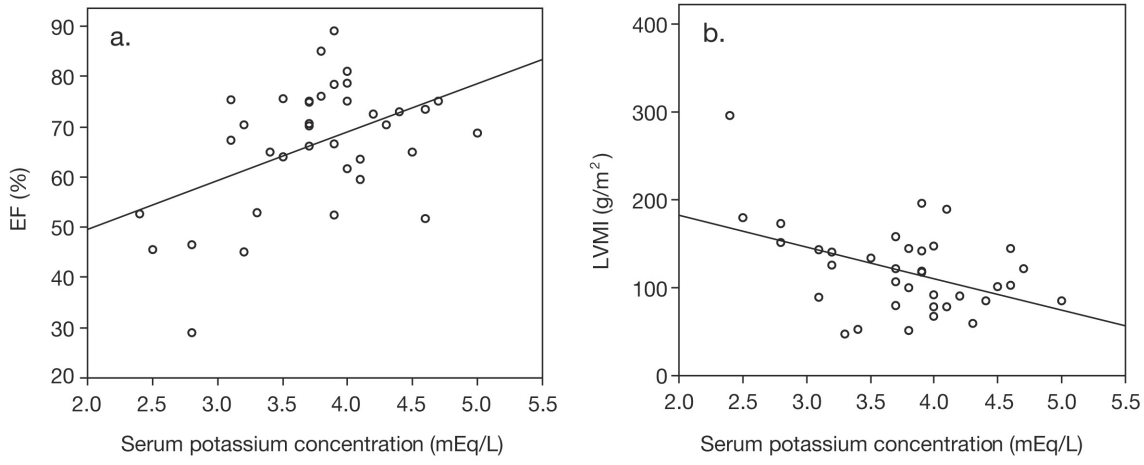

Fig. 5. Correlation between serum potassium concentration and EF (a) and LVMI (b) in patients with adrenal Cushing's syndrome.

Table 3. Multivariate analysis of the clinical factors contributing to echocardiographic parameters in patients with adrenal Cushing's syndrome

Dependent variables	Independent variables	r^2	P
EF	HbA1c	0.529	$P<0.05$
	Serum potassium		$P<0.05$
E/A	Age	0.477	$P<0.05$
LVMI	Serum potassium	0.647	$P<0.01$
	Serum cortisol		$P<0.05$

Table 4. Changes in cardiac function and serum potassium (K), and HbA1c in three patients of group C with severe cardiac failure before and one year after adrenalectomy

Case No.	EF (%)		LVMI (g/m^2)		serum K (mEq/L)		HbA1c (%)	
	before	after	before	after	before	after	before	after
1	46.6	72.2	152.0	96.1	2.8	4.0	6.5	5.1
2	45.0	70.0	164.0	126.0	2.8	4.0	9.6	6.3
3	29.0	69.0	176.0	134.3	2.8	4.0	6.6	5.0

EF; ejection fraction, LVMI; left ventricular mass index,
before; before adrenalectomy, after; one year after adrenalectomy

syndrome. We demonstrated that 8% of patients had decompensated heart failure according to the NYHA classification. To investigate the factors contributing to cardiac dysfunction in this population, patients were divided into three groups based on their NYHA heart failure classification and electrocardiographic findings. We found that age, HbA1c levels, serum potassium concentration, and diabetes mellitus status are correlated with severity of the cardiac dysfunction.

The average age of patients in group C, who had the most severe cardiac dysfunction, was higher than that of patients in groups A and B. These results are consistent with a previous study showing that age is the most important predictive factor for complications of heart failure [25]. However, the average age of group C, 59.3 years, was significantly younger than the average age of 70 years seen in patients with chronic heart failure in the general population [26]. Mancini *et al*. [3] reported that the prevalence of heart failure was 8.2% in a group of Cushing's syndrome patients with a mean age of 43.6 years. Taking these results into account, it appears that heart failure develops at a younger age in Cushing's syndrome patients than in the general population. Serum potassium concentration was significantly lower in group C than in groups B and A. In agreement with previous findings [3], 50% of the 50 patients with adrenal Cushing's syndrome also had diabetes mellitus. HbA1c was highest in group C, the group with the most severe cardiac dysfunction, and all of the patients in this group also had diabetes mellitus. These results suggest that serum potassium concentration and abnormal glucose metabolism are closely related to cardiac dysfunction.

Cardiac function was more quantitatively ascertained by echocardiography in 37 patients with adrenal Cushing's syndrome. Both EF, a marker of systolic function, and E/A, a marker of diastolic function, were low in many patients, and low cardiac function coincided with the clinical subgroups established based on NYHA classification and ECG. Multivariate analysis demonstrated that HbA1c was an independent explanatory factor for decreased EF. Treatments of diabetes may affect the correlation between HbA1c levels and cardiac function through their effects on the diabetic control. However, HbA1c levels were highest in group C compared to other groups despite of the most intensive antidiabetic treatments in this group. It is therefore suggested that elevated HbA1c levels is an explanatory factor for cardiac dysfunction regardless the antidiabetic treatments. Even a 1% increase in HbA1c doubles the risk for heart failure [27], and the diabetes is closely related to later development of heart failure [28]. In addition, hyperglycemia induces diabetic cardiomyopathy through its direct cardiotropic effects [29]. All of these findings suggest that abnormal glucose metabolism is an important risk factor for cardiac dysfunction in Cushing's syndrome patients.

Thickening of the RWT was seen in many patients in this study in agreement with previous findings [15]. Increases in LVMI were also frequently observed and the extent of the changes coincided with the clinical subgroupings. Increased LVMI has been demonstrated to be a risk factor for myocardial ischemia and impairment of the heart conduction system leading to the development of heart failure [30]. Analysis of the geometric pattern of the heart showed concentric hypertrophy with the worst prognosis [31] in 32.4% of the patients with adrenal Cushing's syndrome. In ad-

dition, the frequency of concentric hypertrophy was higher in groups B and C than in group A. These results suggest that Cushing's syndrome is associated with left ventricular hypertrophy with a poor geometric pattern. Although Sugihara *et al*. [9] demonstrated that ASH is the characteristic pattern of hypertrophy in Cushing's syndrome, none of the patients in our study showed that type of hypertrophy.

Details of the mechanisms responsible for cardiac hypertrophy in Cushing's syndrome are still unclear. Hypertension is one of the most crucial factors involved in cardiac hypertrophy. However, there was no significant difference in blood pressure or duration of the disease between the 3 groups. In addition, simple correlation and multivariate analysis did not show a significant relationship between blood pressure and LVMI. Most of the patients studied were under treatment for hypertension, which may explain the lack of correlation between blood pressure and cardiac hypertrophy. Expression of the angiotensin II type 1 receptor and the vascular response to angiotensin II are increased in patients with Cushing's syndrome [32], suggesting upregulation of the activity of the renin-angiotensin system. We therefore hypothesized that certain types of antihypertensive medications, especially those that affect the renin-angiotensin system, might modify cardiac function and morphology. However, the use of different classes of antihypertensive medications was not significantly different between the 3 groups, suggesting that this is not the case.

Serum potassium concentration was shown to be inversely correlated with EF and LVMI and to be an independent explanatory variable for these functional and morphological parameters. Hypokalemia is known to be a risk factor for acute heart failure, ventricular arrhythmia, and sudden death [33, 34]. Since serum potassium concentration has a key role in determining the cell membrane resting potential of cardiac myocytes, decreased serum potassium concentration causes arrhythmia [35] by affecting the impulse-conduction system and cardiac contraction [36]. Hypokalemia has also been shown to induce dilated cardiomyopathy [37] and cardiac hypertrophy by direct mechanisms [38].

Hypercortisolism, the major pathophysiological condition in Cushing's syndrome, has been suggested to contribute to cardiac hypertrophy [9, 10, 14]. Duprez *et al*. [39] have shown evidence of a significant relationship between cortisol production and LVMI independent of arterial blood pressure in essential hypertension. In this study, we demonstrated by multivariate analysis that serum cortisol is an independent explanatory variable for the increase in LVMI in adrenal Cushing's syndrome. Cortisol has been demonstrated to be involved in left ventricular hypertrophy through diverse mechanisms including hypertension [40], potentiation of the hypertrophic effects of noradrenalin and angiotensin II [41], and activation of the local renin-angiotensin-aldosterone system in the heart [42]. More recently, cortisol was shown to stimulate both the entry of cardiomyocytes into the cell cycle leading to cardiomyocyte proliferation [43] and expression of angiotensinogen mRNA leading to cardiomyocyte hypertrophy [44]. These results suggest that cortisol acts directly on the heart through glucocorticoid receptors.

Serum cortisol concentrations at midnight and after 1 mg DST, and urinary cortisol excretion are expected to reflect the excessive secretion of cortisol in Cushing's syndrome. There was however no significant correlation between these parameters and cardiac function in this study. Although the exact reasons for the lack of significant correlation remain to be elucidated, accuracy of collecting 24 hours urine as well as the sensitivity of the cortisol assay, especially that in the lower concentration range, may be responsible for the dissociation. By contrast, serum cortisol concentration in the morning was shown to significantly correlate to the cardiac function in the present study. Although not many studies described the pathophysiological significance of serum cortisol concentration in the morning in Cushing's syndrome, Bonnin R *et al.* [45] clearly demonstrated a significant correlation between morning serum cortisol concentrations and urinary free cortisol excretion in Cushing's syndrome. Serum cortisol concentration even determined in the morning therefore could reflect hypercortisolism.

We have investigated the post-operative course of the 4 patients in group C with severe heart failure. Besides the one patient who died of heart failure after surgery, three patients showed a significant improvement of cardiac function associated with normalization of serum potassium, HbA1c, and hypercortisolemia. These results demonstrated the reversibility of the cardiac dysfunction and provided rational for an early diagnosis and treatments in patients with Cushing's syndrome.

In conclusion, we have investigated cardiac function in 50 patients with adrenal Cushing's syndrome.

Heart failure with Class I or higher NYHA classification and/or abnormal ECG findings was seen in 40% of the patients and was correlated with age, serum potassium concentration, and abnormal glucose metabolism. Echocardiography demonstrated a high prevalence of cardiac systolic and diastolic dysfunction and an increase in ventricular wall thickness and LVMI in these patients. Multivariate analyses demonstrated that serum potassium, HbA1c, and cortisol levels are independent factors determining EF and LVMI, EF, and LVMI, respectively. Taken these results and those of the postoperative changes indicate that hypokalemia, diabetes mellitus, and increased serum cortisol levels are important factors in the development of cardiac dysfunction in patients with adrenal Cushing's syndrome. Strict treatments of these complications before ultimate surgical treatment are warranted for the prevention of cardiovascular lesions in adrenal Cushing's syndrome.

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