Cardiology in the Young

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Impaired systolic and diastolic left ventricular function in children and adolescents with congenital adrenal hyperplasia receiving corticosteroid therapy

Hale Tuhan[1], Tülay Demircan[2], Ayca Altıncık[3], Gönül Çatlı[4], Özgür Kızılca[2], Tuğba Egeli[1], Mustafa Kır[2], Şule Can[5], Bumin Dündar[4], Ece Böber[1] and Ayhan Abacı[1]

[1]Department of Pediatric Endocrinology, Dokuz Eylül University, Faculty of Medicine, Izmir, Turkey, [2]Department of Pediatric Cardiology, Dokuz Eylül University, Faculty of Medicine, Izmir, Turkey, [3]Pediatric Endocrinology Unit, State Hospital of Denizli, Denizli, Turkey, [4]Department of Pediatric Endocrinology, Izmir Katip Celebi University, Faculty of Medicine, Izmir, Turkey and [5]Division of Pediatric Endocrinology, Tepecik Training and Research Hospital, Izmir, Turkey

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Author for correspondence:
H. Tuhan, MD, Department of Pediatric Endocrinology, Dokuz Eylul University, Faculty of Medicine, Balcova, Izmir 35340, Turkey. Tel: +90 232 4126080; Fax: +90 232 4126001; E-mail: halenvr@hotmail.com

Abstract

Aim: The present study aimed to evaluate systolic and diastolic myocardial function in children and adolescents with congenital adrenal hyperplasia. *Methods:* The study included 44 children with the diagnosis of classic congenital adrenal hyperplasia and 39 healthy children whose age, pubertal status, and gender were similar to those of the patient group. Anthropometric parameters and 17-hydroxyprogesterone levels were measured, and bone age was calculated. The average daily hydrocortisone dose was calculated over the last 1-year file records. Hyperandrogenic state was defined according to bone age SD score (⩾2) and 17-hydroxyprogesterone levels (>10 ng/ml). Echocardiographic examinations were assessed by conventional two-dimensional Doppler echocardiography and tissue Doppler imaging. *Results:* Patients had higher morphological parameters, such as left ventricular end-systolic diameter, interventricular septal thickness at end diastole, left ventricular posterior wall thickness at end diastole, left ventricular mass and index, than the control group ($p < 0.05$). On pulsed-wave and tissue Doppler echocardiography, significant subclinical alterations were observed in systolic (isovolumic contraction time), diastolic (isovolumic relaxation time), and global left ventricular functional (myocardial performance index) parameters in the congenital adrenal hyperplasia group compared to the control group ($p < 0.05$). In partial correlation analyses, after controlling the effect of hyperandrogenism, the mean hydrocortisone dosage was positively correlated with isovolumic relaxation time in congenital adrenal hyperplasia group ($p < 0.05$). *Conclusion:* This study demonstrated that the patients with congenital adrenal hyperplasia are at risk for left ventricular hypertrophy, systolic and diastolic myocardial subclinical alterations. Overtreatment may be responsible for the increased risk of myocardial dysfunction in patients with congenital adrenal hyperplasia.

The most common type of congenital adrenal hyperplasia, which accounts for 90–95% of all cases, is 21-hydroxylase deficiency. It is an autosomal recessive disorder due to the mutations in *CYP21A2* gene. The disease is characterised by glucocorticoid and mineralocorticoid deficiency and androgen excess. Nearly 70% of the patients with classic congenital adrenal hyperplasia have salt-wasting type, while 20–30% of the patients have simple virilising type.[1]

The aim of the treatment in congenital adrenal hyperplasia is to prevent adrenal crisis, to allow normal growth and development, and to reduce adrenal androgens by replacing the deficient hormones such as cortisol and aldosterone. For this purpose, hydrocortisone and fludrocortisone are used in the treatment. However, the therapeutic window of glucocorticoids is narrow where overtreatment can lead to hypercortisolism and undertreatment can lead to hyperandrogenism. Therefore, replacement therapy cannot always meet the physiological requirements in patients with congenital adrenal hyperplasia.[2]

For some time, it has been thought that elevated androgen levels and/or side effects of glucocorticoid therapy may cause cardiovascular diseases in patients with congenital adrenal hyperplasia. Obesity, insulin resistance, hypertension, and lipid abnormalities in children with congenital adrenal hyperplasia have often been studied in order to evaluate cardiovascular risk factors.[3–5] However, there is only a limited number of studies conducted to evaluate myocardial function in children and adolescents with congenital adrenal hyperplasia.[1,6,7] The aim

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of the present study was to evaluate systolic and diastolic myocardial function in children and adolescents with congenital adrenal hyperplasia.

Materials and methods

Subjects

A total of 44 children with a diagnosis of classic congenital adrenal hyperplasia on regular glucocorticoid treatment for ⩾3 years and 39 healthy children were enrolled in the study. Age, pubertal status, and sex-matched healthy controls were recruited from the General Pediatric Outpatient Clinic. The salt-wasting type of congenital adrenal hyperplasia represented 68% (n = 30) of the studied patients while simple virilising type represented 22% (n = 14). All patients were receiving glucocorticoid substitution therapy with hydrocortisone, while 31 were receiving fludrocortisone additionally. At the time of the analyses, none of the patients were receiving lipid-lowering therapy or additional medication. Patients were recruited to their regular follow-up appointments every 3 months in the three outpatient paediatric endocrinology clinics, in Izmir, Turkey. Cardiovascular and respiratory diseases, hepatic or renal dysfunction, diabetes mellitus, and malignancy were excluded from both congenital adrenal hyperplasia and control groups.

This study was approved by local ethics committee of Dokuz Eylül University (approval number: 2012/02-24) and Ministry of Health (Turkey). Besides, written informed consent was obtained from all participants and/or their parents.

Methods

Demographic and clinical data including age, gender, type of congenital adrenal hyperplasia, mean hydrocortisone dosage (mg/m^2/day) in the last year, weight, weight SD score, height, height SD score, body mass index, body mass index SD score, blood pressure, heart rate, and pubertal status whether pre-pubertal or pubertal were collected.

Height was measured using a Harpenden stadiometer with a sensitivity of 0.1 cm and weight was measured using a scale with a sensitivity of 0.1 kg (SECA, Hamburg, Germany). The weight of each subject was measured with all clothing removed except undergarments. Body mass index was calculated by dividing weight (kg) by the square of height (m^2). Pubertal development of subjects was evaluated according to Tanner staging. A testicular volume of ⩾4 ml in males and stage 2–5 of breast development in females were considered to be consistent with puberty.

Blood pressure was measured by one of the investigators using a validated protocol. Systolic blood pressure and diastolic blood pressure were measured twice in the right arm after a 10-minute rest in the supine position using a calibrated sphygmomanometer. Hypertension was defined as blood pressure values above the 95th percentile for height, age, and gender.[8]

Bone age was evaluated according to the Greulich–Pyle method and bone age SD score was calculated using the tables of Greulich and Pyle.[9] A bone age SD score of ⩾+2 was accepted as advanced bone age, which is an indirect effect of hyperandrogenism.

After an overnight fast, serum 17-hydroxyprogesterone and androstenedione levels were measured in the morning between 08:00 and 09:00 hours for all patients with congenital adrenal hyperplasia. Androstenedione and 17-hydroxyprogesterone measurements were performed with commercially available radioimmunoassay kits. To assess the effect of hydrocortisone treatment on myocardial parameters, we calculated the mean hydrocortisone dosage (mg/m^2/day) in the last year before the study.

The patients were divided into two groups according to the mean hydrocortisone dosage. One group is the low-dose group, <17 mg/m^2/day, consisting of 33 patients out of 44 (75%), and the other is the high-dose group, ⩾17 mg/m^2/day, of 11 patients (25%) from a total of 44 patients.

Poor control, hyperandrogenic state, was defined as the presence of a high morning 17-hydroxyprogesterone level (>10 ng/ml) in patients with closed growth plates or the presence of an advanced bone age with bone age SD score > +2 in patients with open growth plates.[10]

Echocardiographic measurements

Echocardiographic examinations were performed with an ultrasound machine (model iE33, Philips Medical Systems, Netherlands) with an S5-1 MHz transducer by the same observer (T.D.), who had been blinded to the clinical condition of the patients. Conventional echocardiographic measurements were made according to the American Echocardiography Society standards.[11] All subjects rested for 10 minutes before imaging and then underwent echocardiographic studies in left lateral decubitus position.

Images of two-dimensional ultrasound were obtained in parasternal long-axis and short-axis views and apical two- and four-chamber views using standard transducer positions. The following end-diastolic and end-systolic parameters were measured in M-mode echocardiography in a parasternal long-axis view: interventricular septal thickness at end diastole, interventricular septal thickness at end systole, left ventricular posterior wall thickness at end diastole, left ventricular posterior wall thickness at end systole, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, left ventricular ejection fraction, and percent fractional left ventricular shortening, relative wall thickness, end-diastolic volume, and end-systolic volume. Each of these parameters was calculated using the mean of five readings over consecutive cardiac cycles. Left ventricular systolic function was assessed from left ventricular ejection fraction using the Teichholz rule. Left ventricular mass was calculated using standard formulas from the M-mode echocardiogram.[12] Transmitral flow velocities were measured using pulsed-wave Doppler in the apical four-chamber view, the Doppler sample being placed between the tips of the mitral leaflets. The peak transmitral flow velocity in early diastole and late diastole was measured, and peak transmitral flow velocity in early diastole/late diastole ratio was calculated. Diastolic function was assessed by calculating peak transmitral flow velocity in early diastole/late diastole ratio. Mitral deceleration time was measured in milliseconds.

Colour tissue Doppler images were obtained in the apical view. At least four consecutive cardiac cycles were recorded for each parameter. A Doppler frame scanning rate of 100–140 Hz with 40–80 frames/second was used. Early diastolic myocardial wave, atrial diastolic myocardial wave, and systolic myocardial wave were measured by the baseline pulsed-wave colour tissue Doppler images examination of the left ventricular free wall and of the interventricular septum. Pulsed-wave Doppler-derived early transmitral flow velocity/tissue Doppler echocardiography-derived early diastolic wave velocity ratio was also calculated.

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Diastolic function was assessed by calculating the early transmitral flow velocity/early diastolic wave velocity ratio. Isovolumic contraction time was measured as the time between the end of the systolic wave and the beginning of the diastolic wave. Isovolumic relaxation time was measured as the time between the end of the systolic wave and the beginning of the diastolic wave. Myocardial performance index was calculated as the sum of isovolumic contraction time and isovolumic relaxation time divided by ejection time.[13]

Statistical analysis

A commercially available statistical software package (SPSS 21.0 for Windows, Chicago, IL, United States of America) was used for all statistical analyses. The values are presented as mean ± SD. To test the normality of the data, the one-sample Kolmogorov–Smirnov test was used. Student's t-test and Mann–Whitney U-test were used to compare the difference between means for parametric and non-parametric data, respectively. Pearson's χ^2-test was used for comparison of categorical variables. Relation of mean hydrocortisone dosage and cardiac parameters was evaluated with Spearman's and hyperandrogenic state-adjusted partial correlation analysis. A p-value <0.05 was considered statistically significant.

Results

The demographic and clinical characteristics of the studied groups are shown in Table 1. A total of 44 children with classic congenital adrenal hyperplasia (mean age of 10.3 ± 4.3 years, 22 male, 24 pre-pubertal) and 39 healthy children (mean age of 9.8 ± 4.0 years, 17 male, 19 pre-pubertal) were enrolled in the study. No difference was found between congenital adrenal hyperplasia patients and control subjects regarding age, sex, puberty, weight, height, height SD score, heart rate, systolic and diastolic blood pressure ($p > 0.05$) (Table 1). Compared to the control group, the congenital adrenal hyperplasia patients had higher weight SD scores, body mass index, and body mass index SD scores ($p = 0.022$, $p < 0.001$, $p = 0.001$, respectively). None of the children in the congenital adrenal hyperplasia and the control groups had systemic hypertension, while 10 (22.7%) patients in the congenital adrenal hyperplasia group were obese. Mean age at diagnosis of congenital adrenal hyperplasia was 1.8 ± 2.1 years. At study entry, the mean duration of hydrocortisone therapy was 8.9 ± 4.0 years with a mean dose of 13.4 ± 4.0 mg/m^2/day. The mean serum 17-hydroxyprogesterone and androstenedione levels were 11.7 ± 7.1 and 2.9 ± 2.8 ng/ml, respectively, for the congenital adrenal hyperplasia group.

Of 44 patients, 19 (43.2%) were well controlled and 25 (56.8%) were poorly controlled and defined as hyperandrogenic group. In the well-controlled group, four patients (21.0%) received high-dose and 15 patients (79.0%) received low-dose treatment. In the poorly controlled group, seven patients (28.0%) received high-dose and 18 patients (72.0%) received low-dose treatment. There was no statistical difference between the two groups according to the treatment dose ($p > 0.05$).

The results of pulsed-wave Doppler and M-mode echocardiographic measurements are shown in Table 2. Patients had higher left ventricular end-systolic diameter, interventricular septal thickness at end diastole, left ventricular posterior wall thickness at end diastole, left ventricular mass, left ventricular mass index than the control group ($p = 0.032$, $p = 0.001$, $p = 0.045$, $p = 0.009$, $p = 0.001$, respectively); however, other parameters were similar in both groups.

Table 1. Demographic and clinical characteristics of the study groups.

	CAH group ($N = 44$)	Control group ($N = 39$)	p
Age (years)	10.3 ± 4.3	9.8 ± 4.0	0.571[a]
Sex (M/F)	22/22	17/20	0.716[c]
Puberty (pre-pubertal/pubertal)	24/20	19/18	0.774[c]
Weight (kg)	42.4 ± 18.4	35.5 ± 14.5	0.068[a]
Weight SDS	0.6 ± 1.1	0.1 ± 0.9	0.022[a]
Height (cm)	137.2 ± 22.6	137.8 ± 23.0	0.905[a]
Height SDS	−0.3 (2.1)	0.2 (1.4)	0.165[b]
BMI (kg/m^2)	21.2 ± 3.9	17.7 ± 2.8	<0.001[a]
BMI-SDS	1.2 (1.2)	0.3 (2.5)	0.001[b]
Heart rate (beat/minute)	90.6 ± 12.4	86.0 ± 8.6	0.06[a]
SBP (mmHg)	100 (20)	100 (15)	0.273[b]
DBP (mmHg)	60 (14)	64 (12)	0.939[b]

BMI = body mass index; BMI-SDS = standard deviation score of body mass index; CAH = congenital adrenal hyperplasia; DBP = diastolic blood pressure; SBP = systolic blood pressure
[a]Student's t-test
[b]Mann–Whitney *U*-test
[c]χ^2-test. Data are given as mean ± SD or median (IQR)

Pulsed-wave and tissue Doppler imaging parameters of the study groups are shown in Table 3. In the lateral localisation of the mitral annulus, patients with congenital adrenal hyperplasia exhibited significantly impaired systolic (longer isovolumic contraction time), diastolic (longer isovolumic relaxation time), and global left ventricular functional parameters (higher myocardial performance index) when compared to the control group. In the interventricular septum, patients exhibited significantly impaired systolic (longer isovolumic contraction time), diastolic (longer isovolumic relaxation time, higher atrial diastolic wave, lower early diastolic wave/atrial diastolic wave ratio), and global left ventricular functional parameters (higher myocardial performance index) when compared to the control group.

Regarding the pulsed tissue Doppler imaging parameters, there was no significance difference between the congenital adrenal hyperplasia patients with high and low hydrocortisone doses ($p > 0.05$). Spearman correlation analysis revealed that the mean hydrocortisone dosage was significantly positively correlated with isovolumic relaxation time and early transmitral flow velocity/early diastolic wave ratio in congenital adrenal hyperplasia group ($p < 0.05$) (Table 4). The mean hydrocortisone dosage was still positively correlated with isovolumic relaxation time after adjustment for hyperandrogenic state ($p < 0.05$) (Table 4). In the high-dose group, the mean hydrocortisone dosage was significantly positively correlated with isovolumic relaxation time ($r = 0.776$, $p = 0.04$). In the low-dose group, there was no correlation between the mean hydrocortisone dosage and myocardial parameters ($p > 0.05$). There were no correlations between serum 17-hydroxyprogesterone and androstenedione concentrations with myocardial parameters ($p > 0.05$).

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Table 2. M-mode and pulsed-wave Doppler echocardiographic measurements of the study groups.

	CAH group ($N = 44$)	Control group ($N = 39$)	*p
Morphological parameters			
LVEDD (cm)	3.99 ± 0.67	3.85 ± 0.49	0.275[a]
LVESD (cm)	2.55 (0.60)	2.40 (0.60)	0.032[b]
IVSD (cm)	0.70 (0.20)	0.60 (0.01)	0.001[b]
IVSs (cm)	0.90 (0.30)	0.80 (0.20)	0.297[b]
LVPWD (cm)	0.70 (0.20)	0.60 (0.10)	0.045[b]
LVPWS (cm)	0.98 ± 0.26	0.83 ± 0.15	0.052[a]
LVM (g)	84.17 ± 42.54	63.30 ± 21.70	0.009[a]
LVMI (g/m 2.7)	33.73 ± 9.09	23.70 ± 7.80	0.001[a]
Systolic parameters			
FS (%)	37.29 ± 4.36	37.83 ± 5.38	0.827[a]
EF (%)	68.20 ± 5.34	68.45 ± 5.04	0.617[a]
ET (ms)	255.55 ± 36.11	272.00 ± 29.67	0.062[a]
EDV (ml)	72.74 ± 29.18	62.70 ± 22.90	0.116[a]
ESV (ml)	22.00 (14.00)	20.00 (11.00)	0.279[b]
Diastolic parameters			
RWT	0.35 ± 0.07	0.33 ± 0.04	0.141[a]
Peak *E* (cm/s)	91.74 ± 13.46	91.85 ± 11.01	0.962[a]
Peak *A* (cm/s)	58.00 (14.10)	58.00 (15.00)	0.818[b]
E/A ratio	1.44 (0.45)	1.53 (0.27)	0.845[b]
MDT (ms)	106.00 (19.00)	104.00 (21.00)	0.387[b]

CAH = congenital adrenal hyperplasia; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; ET = ejection time; FS = fractional shortening; IVSD = interventricular septal thickness at end diastole; IVSs = interventricular septal thickness at end systole; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; LVM = left ventricular mass; LVMI = left ventricular mass index; LVPWD = left ventricular posterior wall end diastole; LVPWS = left ventricular posterior wall end systole; MDT = mitral deceleration time; MPI = myocardial performance index; RWT = relative wall thickness; Peak *E*, early transmitral flow velocity; Peak *A*, late transmitral flow velocity.
[a]Student's t-test
[b]Mann–Whitney U-test. Data are given as mean ± SD or median (IQR)

Table 3. Pulsed-wave Doppler and tissue Doppler imaging parameters of the study groups.

	CAH group ($N = 44$)	Control group ($N = 39$)	*p
Lateral localisations of the mitral annulus			
Systolic parameters			
S_m (cm/s)	10.00 (3.00)	9.50 (2.95)	0.824[b]
$IVCT_m$ (ms)	39.00 (6.50)	35.00 (4.00)	0.001[b]
ET (ms)	280.11 ± 39.19	294.02 ± 29.51	0.052[a]
Diastolic parameters			
E'_m (cm/s)	17.64 ± 4.39	16.94 ± 2.71	0.264[a]
A'_m (cm/s)	8.20 (2.90)	8.30 (3.00)	0.626[b]
E'_m/A'_m ratio	1.92 (0.81)	1.96 (0.66)	0.420[b]
$IVRT_m$ (ms)	49.00 (10.00)	46.00 (7.00)	0.028[b]
E/E'_m	5.47 ± 1.40	5.53 ± 0.99	0.821[a]
Global ventricular performance			
MPI	0.33 ± 0.06	0.28 ± 0.03	<0.001[a]
Interventricular septum			
Systolic parameters			
S_m (cm/s)	8.00 (2.18)	7.40 (2.00)	0.053[b]
$IVCT_m$ (ms)	39.00 (7.00)	37.00 (5.50)	0.045[b]
ET (ms)	278.72 ± 27.09	286.76 ± 29.55	0.206[a]
Diastolic parameters			
E'_m (cm/s)	12.90 (3.90)	12.45 (2.40)	0.579[b]
A'_m (cm/s)	7.00 (2.00)	5.85 (1.63)	0.011[b]
E'_m/A'_m ratio	1.89 (0.57)	2.01 (0.43)	0.038[b]
$IVRT_m$ (ms)	50.68 ± 7.01	46.64 ± 5.34	0.005[a]
Global ventricular performance			
MPI	0.32 (0.06)	0.30 (0.04)	0.005[b]

CAH = congenital adrenal hyperplasia; $IVRT_m$ = isovolumic relaxation time; $IVCT_m$ = isovolumic contraction time; MPI = myocardial performance index.
A'_m = atrial diastolic wave; E = early transmitral flow velocity; $E'_{m,}$ = early diastolic wave; $S_{m,}$ = myocardial systolic wave
[a]Student's t-test,
[b]Mann–Whitney U-test. Data are given as mean ± SD or median ± IQR

Discussion

Inability to mimic the physiological cortisol secretion may cause endogenous hyperandrogenism or iatrogenic hypercortisolism during the treatment in patients with congenital adrenal hyperplasia. In previous studies, obesity, dyslipidaemia, hypertension, and insulin resistance have been associated with inadequate treatment or overtreatment. However, the cause of the increased risk of cardiovascular disease is still not fully understood in patients with congenital adrenal hyperplasia.[14,15] Little is known about myocardial function of patients with congenital adrenal hyperplasia. In our study, consistent with the literature, values of morphological parameters showing left ventricular hypertrophy, such as left ventricular mass, left ventricular mass index, interventricular septal thickness at end diastole, left ventricular end-systolic diameter and left ventricular posterior wall thickness at end diastole, were significantly higher in the congenital adrenal hyperplasia group compared with the control group.[6] In the study conducted by Metwalley et al,[6] left ventricular hypertrophy with higher values of left ventricular mass and left ventricular mass index was identified in patients with congenital adrenal hyperplasia. However, in some studies[1,7] no difference was reported in left ventricular mass between congenital adrenal hyperplasia patients and control subjects. In the study by Metwalley et al,[6] a significant positive correlation was also reported between testosterone level and left ventricular mass index, which suggests a harmful cardiac effect of hyperandrogenism in patients with

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Table 4. Bivariate correlation analyses and hyperandrogenic state-adjusted partial correlation analyses between mean hydrocortisone dosage and cardiac parameters in congenital adrenal hyperplasia group.

	Spearman's ρ	p*	Partial correlation	p**
M-mode echocardiographic parameter				
LVMI	0.143	0.361	0.128	0.434
Pulsed tissue Doppler imaging parameters Lateral localisations of the mitral annulus				
$IVCT_m$ (ms)	0.162	0.294	0.156	0.357
E'_m/A'_m ratio	0.122	0.435	0.120	0.452
$IVRT_m$ (ms)	0.411	0.006	0.423	0.007
E/E'_m	0.341	0.029	0.302	0.070
MPI	0.238	0.121	0.188	0.221
Interventricular septum				
$IVCT_m$ (ms)	0.277	0.069	0.306	0.065
E'_m/A'_m ratio	−0.670	0.670	−0.720	0.674
$IVRT_m$ (ms)	0.338	0.012	0.356	0.026
MPI	0.120	0.278	0.189	0.263

*Spearman's correlation analysis; mean hydrocortisone dosage as dependent variable
**Partial correlation coefficient; after adjusting for hyperandrogenemic state
$IVCT_m$ = isovolumic contraction time; $IVRT_m$ = isovolumic relaxation time; IVSD = interventricular septal thickness at end diastole; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; LVMI = left ventricular mass index; MPI = myocardial performance index
E = early transmitral flow velocity; E'_m = early diastolic wave; A'_m = atrial diastolic wave

congenital adrenal hyperplasia. In previous studies, the relationship between serum androgen levels and myocardial function has been reported to be controversial.[6,16–18] Wang et al[19] reported high left ventricular mass index values in patients with hyperandrogenism, whereas Ozdemir et al[7] did not report any relationship between left ventricular mass index values and serum androgen levels in patients with congenital adrenal hyperplasia. It was reported that cardiac muscle cells have receptors for androgens which act directly on these cells and lead to proliferation of proteins as a mechanism of cardiac muscular hypertrophy in hyperandrogenism.[20] In addition, some clinical and experimental studies remarked that androgenic anabolic steroids lead to myocardial hypertrophy.[21,22] However, in our study, despite higher left ventricular mass index values in patients with congenital adrenal hyperplasia, no correlation was detected between serum androgen levels and left ventricular mass index values. The contradictory results from different studies may be explained by genetic factors and ethnicity, administration of steroid treatment, and measuring serum androgen levels only once in the morning, which cannot reflect continuous androgen exposure.

In our study, pulsed tissue Doppler imaging parameters showed significantly longer isovolumic relaxation time, both in the lateral localisation of the mitral annulus and interventricular septum indicating diastolic filling impairment, significantly higher atrial diastolic wave values and a lower early diastolic wave/atrial diastolic wave ratio in the interventricular septum – markers of diastolic dysfunction, as well as a significantly higher myocardial performance index value both in the lateral localisation of the mitral annulus and interventricular septum – markers of global left ventricular dysfunction in the congenital adrenal hyperplasia group. There is only one recent study evaluating the presence of left ventricular dysfunction by using pulsed tissue Doppler imaging in children with congenital adrenal hyperplasia in the literature.[7] In this study, which is consistent with our results, children with congenital adrenal hyperplasia were reported to have impaired left ventricular diastolic function with decreased early diastolic wave/atrial diastolic wave ratio.[7] We also reported significant positive correlations of the mean hydrocortisone dosage with isovolumic relaxation time and early transmitral flow/early diastolic wave ratio (index of left ventricular relaxation), which suggest the detrimental effect of overtreatment on myocardial function. Furthermore, after controlling for hyperandrogenic state, the mean hydrocortisone dosage was still positively correlated with isovolumic relaxation time. These findings may support the idea that overtreatment can lead to left ventricular diastolic dysfunction. However, in our study, the isovolumic relaxation time and myocardial performance index values of congenital adrenal hyperplasia and control groups were within the normal ranges and the differences between them were very small. Thus, these results were considered to be subclinical alterations. Furthermore, there was a weak correlation between the mean hydrocortisone dosage and isovolumic relaxation time in the congenital adrenal hyperplasia group. Even though the positive correlation was still maintained after controlling for the hyperandrogenic condition, we cannot definitely say that hydrocortisone therapy is responsible for diastolic alterations in congenital adrenal hyperplasia patients. There are no studies that evaluate the relation between the hydrocortisone dosage and myocardial function in children with congenital adrenal hyperplasia. Results from previous studies regarding the relationship between cortisol excess and myocardial function are contradictory in Cushing's syndrome.[23,24] In a study conducted by Bayram et al,[24] no significant difference was found in isovolumic relaxation time and early transmitral flow/early diastolic wave ratio values between the patients with Cushing's syndrome and healthy subjects. In contrast, the study conducted by Baykan et al[23] demonstrated a significant increase in isovolumic relaxation time value and a positive correlation between serum cortisol levels and early transmitral flow/early diastolic wave ratio in patients with Cushing's syndrome. This study of 22 patients with Cushing's syndrome supports our findings.[23] The effect of cortisol on cardiac muscle is supported by the facts that cortisol could act directly on myocardial tissue, cortisol may stimulate local renin–angiotensin system, and cortisol may increase the angiotensin II and noradrenaline response of cardiac muscle.[23,25] We also reported the presence of subclinical left ventricular systolic dysfunction – prolonged isovolumic contraction time and increased myocardial performance index – for the first time in children with congenital adrenal hyperplasia. A study conducted by Poulsen et al[26] demonstrated that the myocardial performance index was significantly more sensitive than the ejection fraction in determining left ventricular dysfunction. On the contrary, our findings can be explained by the predominance of diastolic dysfunction, which was shown by the alterations in myocardial performance index and isovolumic contraction time but not in the ejection fraction and myocardial systolic wave.

The main limitation of our study was that we could not exclude the effect of related metabolic factors such as obesity and blood pressure changes. Left ventricular hypertrophy and myocardial dysfunction were reported in patients with obesity and hypertension earlier.[27] Although there was no difference in blood pressures between the groups in our study, intermittent elevated

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blood pressure may cause endothelial dysfunction and lead to a reduced left ventricular myocardial compliance in the congenital adrenal hyperplasia group.[17] Therefore, it would be more appropriate to perform 24-hour blood pressure monitoring in congenital adrenal hyperplasia patients. The other limitation of our study is the use of the stress hormone 17-hydroxyprogesterone and bone age SD score, which are indirect indicators, to determine hyperandrogenism. An additional limitation is the lack of file records such as the average androstenedione and 17-hydroxyprogesterone levels over the last one year to evaluate the hyperandrogenism group in the congenital adrenal hyperplasia patients; moreover, serum androstenedione levels are not routinely performed in all centres.

In conclusion, this study demonstrated that patients with congenital adrenal hyperplasia are at risk of left ventricular hypertrophy, and subclinical systolic and diastolic myocardial alterations. More importantly, our findings suggested that overtreatment may be one of the factors related to an increased risk of myocardial alterations in patients with congenital adrenal hyperplasia. To our knowledge, this is the first report evaluating the relationship between hydrocortisone dosage and diastolic dysfunction in patients with congenital adrenal hyperplasia. Physicians should keep in mind that unnecessarily high doses of hydrocortisone to prevent hyperandrogenism may also be harmful on cardiac function, as well as on body mass index, insulin resistance, and blood pressure.

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Conflicts of interest. None.

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