Cardiac Function in Congenital Adrenal Hyperplasia: A Pattern of Reversible Cardiomyopathy

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Objective To evaluate cardiac function in infants with congenital adrenal hyperplasia (CAH) before and after corticosteroid replacement therapy.

Study design This prospective, case-control study included 9 infants with CAH. Cardiac function was assessed by echocardiography at presentation and after corticosteroid replacement therapy. Six term infants underwent 2 echocardiograms each and served as the control group. Data on fractional shortening (FS), rate-corrected velocity of circumferential fiber shortening (V_{cf}), wall stress, tissue Doppler indices, myocardial performance index, left ventricular mass, and V_{cf}/wall stress were obtained.

Results The infants with CAH exhibited myocardial dysfunction at baseline and lower systolic blood pressure (SBP) compared with the control group. FS, a measure of systolic contractility, differed significantly from before to after corticosteroid treatment (mean, 32.3% ± 4.7% pretreatment, 39.9% ± 5.0% posttreatment). V_{cf}, a preload-independent measure of cardiac contractility, also differed significantly before and after treatment (mean, 1.23 ± 0.16 circumferences/second pretreatment, 1.45 ± 0.22 circumferences/second posttreatment). SBP was also lower (mean, 84 ± 9.3 mmHg) and improved with treatment (mean, 95 ± 4.8 mmHg). The control group demonstrated no statistically significant changes in FS, V_{cf}, or SBP. There was a change in left ventricular mass in the control group between the 2 studies.

Conclusion Newborns with CAH have evidence for cardiac dysfunction at baseline that reverses with corticosteroid replacement therapy. These data suggest that corticosteroids play a direct role in modulating cardiac function in the newborn. *(J Pediatr 2013;162:1193-8)*.

Patients with congenital adrenal hyperplasia (CAH) have enzymatic defects in corticosteroid synthesis pathways. The most common form of CAH, 21-hydroxylase deficiency, leads to inadequate cortisol production (simple virilizing form) or both inadequate cortisol and aldosterone production (salt-wasting form). Before the widespread use of newborn screening for 21-hydroxylase deficiency, infants with unrecognized CAH frequently came to medical attention in shock that resolved after glucocorticoid replacement therapy.[1] The etiology of shock in CAH is not completely understood, but proposed explanations include hypovolemia from sodium wasting and decreased cortisol-potentiated vasoconstriction.[2]

A potential cause of shock or cardiac symptoms in patients with CAH may be a deficiency of direct steroid action on the myocardium. We previously reported an infant who initially presented with cardiogenic shock secondary to dilated cardiomyopathy.[3] This infant was subsequently diagnosed with CAH and started on corticosteroid replacement therapy, and demonstrated improved cardiac function within 4 days. Published case reports have described similar findings in other settings of glucocorticoid deficiency, including Addison's disease and adrenocorticotropic hormone deficiency.[4-9]

These individual case reports describing reversible cardiac dysfunction after glucocorticoid replacement suggest a direct role for cortisol modulation of cardiac function. Some previous research has supported the importance of mineralocorticoid excess in cardiac function,[10] but less is known about conditions involving glucocorticoid and mineralocorticoid deficiency in adults or children. We hypothesized that patients with cortisol-deficiency may exhibit altered cardiac function regardless of symptoms. To investigate this hypothesis, we performed a prospective study of the effects of corticosteroid replacement on cardiac contractility in newborns diagnosed with adrenal insufficiency.

CAH	Congenital adrenal hyperplasia
FS	Fractional shortening
MPI	Myocardial performance index
SBP	Systolic blood pressure
V_{cf}	Rate-corrected velocity of circumferential fiber shortening

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Methods

Infants with CAH secondary to 21-hydroxylase deficiency were identified through the Northwest Regional Newborn Screening Program or by the presence of ambiguous genitalia noted at birth. Control subjects were identified from among healthy infants. Written informed consent was obtained from the parents of all infants before enrollment in the study, which was approved by the Oregon Health & Science University Institutional Review Board. Infants with a family history of primary cardiomyopathy were excluded. No subject in either group had congenital heart disease, including ductus arteriosus. A health history was obtained and physical examination performed in all subjects. Serum electrolyte and confirmatory serum 17-hydroxyprogesterone levels were obtained for all subjects with CAH.

Echocardiography was performed using a Philips 5500, 7500, or IE 33 machine (Philips, Andover, Massachusetts). The initial echocardiogram was obtained after a brief physical examination. In the CAH group, echocardiography was performed before blood samples were drawn. M-mode measurements of the left ventricle, mitral inflow and aortic valve Doppler velocities, and tissue Doppler indices were obtained following American Society of Echocardiography standards.[11,12] Resting automated blood pressure measurements were obtained when the subjects were calm. Appropriate corticosteroid therapy was subsequently initiated in all subjects with CAH. All subjects with CAH and control infants returned for a second echocardiogram and another resting blood pressure measurement.

All echocardiographic measurements were made using syngo Dynamics 7.0 software (Siemens Medical Solutions, Ann Arbor, Michigan). All echocardiograms were read together as a group by a single, blinded reviewer to eliminate bias. Each variable was measured 3 times, and the mean value was reported and used for all calculations. Fractional shortening (FS) was calculated using the equation (left ventricular internal dimension in diastole - left ventricular internal dimension in systole)/left ventricular internal dimension in diastole. The rate-corrected velocity of circumferential fiber shortening (V_{cf}) was calculated using FS × 1/(ejection time/√intervalfrom R wave to R wave).[13,14] Meridional wall stress was calculated using the equation (1.35 × mean blood pressure × left ventricular internal dimension in systole)/(4 × thickness of the posterior wall in systole (1 + thickness of the posterior wall in systole/left ventricular internal dimension in systole).[13,15-18] The V_{cf}–wall stress relationship was evaluated and compared with published values for healthy infants.[13,17,19] The myocardial performance index (MPI) was calculated as (isovolumic contraction time + isovolumic relaxation time)/ejection time.[20] All results were compared using the 2-tailed unpaired Student *t* test assuming equal variances using Prism software (GraphPad Software, San Diego, California).

Results

Nine infants with CAH secondary to 21-hydroxylase deficiency were enrolled, including 5 males identified by newborn screening and 4 females by the presence of ambiguous genitalia at birth (Table I). Eight infants were diagnosed with salt-wasting CAH; 6 of these infants presented with hyponatremia and hyperkalemia at the initial examination. Two subjects with salt-wasting CAH had normal electrolyte levels but nonetheless were started on glucocorticoid and mineralocorticoid replacement, owing to significantly elevated plasma renin activity levels. One subject diagnosed with simple virilizing CAH received glucocorticoid replacement only.

All subjects were asymptomatic at the initial examination. All subjects with CAH were started on appropriate corticosteroid replacement therapy immediately after the first

Table I. Profile of the CAH and control groups

Patient	Age at study 1, days	Age at study 2, days	Sex	Na^+/K^+, mmol/L	17-Hydroxy-progesterone, ng/dL	Corticosteroid replacement
CAH group						
1	4	13	F	133/6.8	23 000	GC, MC
2	8	20	M	124/8.4	12 550	GC, MC
3	8	21	M	124/6.0	12 572	GC, MC
4	7	20	M	129/8.7	12 010	GC, MC
5	7	20	F	140/5.9	35 010	GC, MC
6	6	17	M	131/6.4	3943	GC, MC
7	3	13	F	144/4.9	1445	GC
8	2	15	F	147/5.0	11 000	GC, MC
9	8	22	M	130/6.6	12 500	GC, MC
Mean	6	18				
Control group						
1	6	20	F	NA	NA	NA
2	14	34	F	NA	NA	NA
3	8	18	M	NA	NA	NA
4	10	19	M	NA	NA	NA
5	7	21	F	NA	NA	NA
6	8	33	M	NA	NA	NA
Mean	9	24				

F, female; *GC*, glucocorticoid; *M*, male; *MC*, mineralocorticoid; *NA*, not applicable.