Neurohormonal Activation and the Chronic Heart Failure Syndrome in Adults With Congenital Heart Disease

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Background—Neurohormonal activation characterizes chronic heart failure, relates to outcome, and is a therapeutic target. It is not known whether a similar pattern of neurohormonal activation exists in adults with congenital heart disease and, if so, whether it relates to common measures of disease severity or whether cardiac anatomy is a better discriminant.

Methods and Results—Concentrations of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), endothelin-1 (ET-1), renin, aldosterone, norepinephrine, and epinephrine were determined in 53 adults with congenital heart disease, comprising 4 distinct anatomic subgroups (29 female; 33.5±1.5 years of age; New York Heart Association class 2.0±0.1, mean±SEM) and 15 healthy control subjects (8 female; 32.3±1.3 years of age). Systemic ventricular function was graded by a blinded echocardiographer as normal or mildly, moderately, or severely impaired. Adults with congenital heart disease had elevated levels of ANP (56.6 versus 3.1 pmol/L), BNP (35.8 versus 5.7 pmol/L), ET-1 (2.5 versus 0.7 pmol/L, all $P<0.0001$), renin (147 versus 16.3 pmol/L), norepinephrine (2.2 versus 1.6 pmol/L, both $P<0.01$) and aldosterone (546 versus 337 pmol/L, $P<0.05$). There was a highly significant stepwise increase in ANP, BNP, ET-1, and norepinephrine according to New York Heart Association class and systemic ventricular function, with even asymptomatic patients having evidence of significant neurohormonal activation. In contrast, there was no direct relationship between the 4 anatomic subgroups and any of the neurohormones studied.

Conclusions—Neurohormonal activation in adult congenital heart disease bears the hallmarks of chronic heart failure, relating to symptom severity and ventricular dysfunction and not necessarily to anatomic substrate. Neurohormonal antagonism across this large and anatomically diverse population should be considered. **(*Circulation*. 2002;106:92-99.)**

Key Words: heart diseases ■ heart failure ■ heart defects, congenital

Chronic heart failure (CHF) in adults is characterized by high circulating levels of several chemical messengers of cardiac and extracardiac origin, collectively referred to as neurohormones.[1] It is well established that the degree of neurohormonal activation in CHF relates to functional capacity,[2,3] the degree of left ventricular dysfunction,[4,5] and mortality.[6–8] Contemporary evidence-based therapy for CHF involves pharmacological manipulation of neurohormonal pathways and has resulted in substantial improvements in morbidity[9] and prognosis for patients with this condition.[10]

Neurohormonal activation has been observed in some manifestations of congenital heart disease,[11–14] although reports have, in the main, been confined to small numbers of pediatric patients, have focused on specific types of cardiac lesions, and have been limited to the assessment of a single neurohormone system. After major advances in diagnosis and treatment in children, however, there are now as many as 1 million adults with congenital heart disease in the United States[15] and comparable prevalence in the United Kingdom.[16] Very little is known about neurohormonal activation in adults with congenital heart disease. The few published studies in this patient group have considered only the natriuretic peptides in specific anatomic groups.[17–19] Activation of the sympathoadrenergic, renin-angiotensin-aldosterone, and endothelin systems has not been described in adults with congenital heart disease. Furthermore, it is not known whether neurohormonal activation in such patients relates to common measures of disease severity such as functional class, exercise capacity, and measures of ventricular function (as in CHF) or whether specific patterns of cardiac anatomy are more important discriminants. The identification of clinical and neurohormonal characteristics shared by an otherwise heterogeneous population would provide important insight into our understanding of the congenital heart disease phenotype and might have important implications in the pharmacological management of the condition.

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Methods

We performed a prospectively designed detailed assessment of clinical and neurohormonal variables in 53 adult patients with stable congenital heart disease and 15 sex- and aged-matched healthy control subjects. Patients were consecutively recruited from a specialist congenital heart disease outpatient clinic of the Royal Brompton Hospital between September 2000 and April 2001. Control subjects were staff and students at the Royal Brompton Hospital. All participants gave written informed consent, and the local ethics committee approved the study. At recruitment, all subjects had their weight, height, heart rate, and blood pressure recorded.

Patients were subgrouped according to the New York Heart Association (NYHA) functional class, systemic ventricular function, and cardiac anatomy. There were 20 patients with tetralogy of Fallot (TOF), of whom 4 had undergone palliative and 16 had undergone reparative surgery. Sixteen patients had single-ventricle physiology (7 with tricuspid atresia, 7 with common atria or double-inlet left ventricles, and 2 with single ventricles of right ventricular morphology). Fifteen of this group had undergone palliative surgery, and the remaining patient no surgery. Four had dextrocardia, 3 with associated situs inversus. A third group comprised 7 patients with morphologically right-sided systemic ventricles (all had transposition of the great arteries), of whom 6 had undergone atrial baffle surgery (5 Mustard procedures and 1 Senning procedure) and the remaining patient no surgery. The final group included all other lesions and embraced 4 patients with either atrial or ventricular septal defects (of whom 3 had undergone successful reparative surgery), 2 patients with repaired patent ductus arteriosus, and 4 additional patients with repaired left atrial (LA) isomerism, anomalous left coronary artery (reimplanted), surgically corrected type I truncus arteriosus, and congenital pulmonary hypertension, respectively. Cyanosis, as defined by oxygen saturation <85%, was present in 14 patients.

Patients with clinically decompensated cardiac disease or evidence of concurrent systemic infection or malignancy were excluded from the study. No patients screened for the study fulfilled the other exclusion criteria of chronic renal impairment (serum creatinine >200 μmol/L, 2.26 mg/dL) or liver aspartate transaminase twice the upper limit of normal (82 IU/L). Medical therapy at the time of the study and the clinical, biochemical, and hematologic characteristics of all participants are listed in Table 1.

Clinical Investigation Protocols

Indices of disease severity, related to neurohormonal activation in CHF, were quantified in the patient population. A standard 12-lead

TABLE 1. Clinical Characteristics of Study Subjects

	Congenital Heart Disease Patients (n=53)	Control Subjects (n=15)	*P*
Age, y	33.5 (1.5)	32.3 (1.3)	0.67
Sex, male/female	24/29	7/8	0.93
Weight, kg	64.1 (1.9)	73.0 (2.6)	**0.022**
NYHA functional class I/II/III/IV	11/31/10/1	...	
Anatomy			
Single-ventricle physiology	16	...	
Surgery: none/palliative/reparative	1/15/0	...	
Tetralogy of Fallot	20	...	
Surgery: none/palliative/reparative	0/4/16	...	
Systemic right ventricle	7	...	
Surgery: none/palliative/reparative	1/0/6	...	
Other lesions (see text)	10	...	
Surgery: none/palliative/reparative	3/0/7	...	
Cyanotic heart disease: single ventricle/tetralogy/other	8/4/2	...	
Existing therapy			
ACE inhibitors	14	...	
Angiotensin receptor blockers	3	...	
β-Blockers	7	...	
Digoxin	4	...	
Spironolactone	6	...	
Diuretics	17	...	
Heart rate, bpm	73.9 (1.7)	68.8 (2.3)	0.26
Systolic blood pressure, mm Hg	117.0 (1.6)	113.2 (3.9)	0.42
Diastolic blood pressure, mm Hg	68.8 (1.6)	73.5 (2.3)	0.17
Sodium, mmol/L	137.1 (0.2)	137.4 (0.5)	0.60
Creatinine, μmol/L	82.2 (3.1)	76.8 (2.5)	0.38
Aspartate transaminase, IU/L	29.4 (1.5)	25.4 (1.6)	0.18
Hemoglobin, g/dL	15.2 (0.3)	14.2 (0.3)	0.13
Hematocrit, %	46.1 (1.0)	41.8 (0.8)	**0.023**
Platelet count, 10^9/L	199.8 (8.9)	239.3 (15.7)	**0.038**

Values are mean (±SEM).

P values are for unpaired *t* tests between patients and control subjects. Significant differences are shown in bold.

TABLE 2. Clinical Results of Patients Grouped According to Functional Severity

	All Patients (n=53)	NYHA Class I (n=11)	NYHA Class II (n=31)	NYHA Class III/IV (n=11)	*P* by ANOVA
Oximetry					
Oxygen saturation, %	91.1 (1.4)	94.8 (2.6)	94.0 (1.2)	85.2 (2.9)*†	**0.006**
ECG					
QRS duration, ms	123.4 (4.2)	123.8 (9.9)	123.2 (5.1)	123.6 (12.0)	1.0
Corrected QT interval, ms	453.6 (6.8)	441.3 (11.9)	447.1 (8.1)	488.7 (19.2)*‡	**0.041**
Radiology					
Cardiothoracic ratio	0.58 (0.01)	0.53 (0.02)	0.57 (0.02)	0.66 (0.02)†§	**0.003**
Echocardiography					
Systemic ventricular function: normal/mild/moderately to severely impaired	17/19/7/3	3/6/0/0	11/11/4/1	3/1/4/2	0.06
RA length, cm	5.6 (0.2)	4.8 (0.2)	5.6 (0.3)	6.4 (0.6)	0.09
RA width, cm	5.3 (0.2)	4.5 (0.3)	5.3 (0.3)	6.1 (0.6)	0.12
RA volume, cm^3	136.2 (22.0)	61.2 (9.2)	147.0 (32.1)	177.3 (44.8)	0.22
LA length, cm	5.4 (0.2)	5.2 (0.7)	5.4 (0.3)	5.7 (0.4)	0.72
LA width, cm	3.9 (0.2)	4.1 (0.8)	3.8 (0.3)	4.3 (0.5)	0.74
LA volume, cm^3	82.2 (10.2)	96.2 (44.3)	72.3 (7.8)	97.9 (15.6)	0.51
Exercise physiology					
Peak $\dot{V}O_2$, $mL \cdot kg^{-1} \cdot min^{-1}$	22.0 (1.2)	25.4 (23.1)	21.7 (1.5)	17.0 (2.8)	0.11
$VE/\dot{V}CO_2$ slope	35.4 (1.9)	27.5 (1.7)	37.3 (2.4)	40.7 (6.9)	0.06

Values are mean (±SEM).

*$P<0.05$ vs NYHA class I; †$P<0.01$ vs NYHA class II; ‡$P<0.05$ vs NYHA class II; and §$P<0.01$ vs NYHA class I. Significant differences are shown in bold.

ECG was recorded (Hewlett Packard PageWriter XLi) to obtain measurements of the QRS width and the QT interval corrected for heart rate (QTc). Posteroanterior chest x-rays were captured using phosphor plate technology, digitally processed (Siemens Digiscan), and the cardiothoracic ratio (CTR) was calculated with the use of on-screen calipers. Transcutaneous pulse oximetry was performed at rest (NPB-40, Nellcor Puritan Bennett).

Echocardiography was performed by a single experienced operator (W.L.), blinded to all other results, via a transthoracic approach using a Hewlett Packard Sonos 5500 echocardiograph interfaced with a multifrequency MHz transducer. Because of the heterogeneity of cardiac anatomy, we used a qualitative, subjective assessment of systemic ventricular function from multiview 2-dimensional echocardiography, grading it as normal or mildly, moderately, or severely impaired,[20] while accounting for significant AV valve regurgitation by similarly grading the systemic ventricular end-systolic diameter. Right atrial (RA) and LA length and width were measured from an apical 4-chamber view, as previously described,[21] and atrial volumes were quantified by tracing the atrial endocardial border at end-systole and applying the biplane area-length method.[22]

Cardiopulmonary exercise testing was performed in a subgroup of 28 patients according to the modified Bruce protocol. These patients were typical of patients as a whole, being similar (nonsignificant differences) to the group who were not tested in all the clinical variables studied, including systemic ventricular function. Peak oxygen consumption ($\dot{V}O_2$) and the slope of ventilatory rate over carbon dioxide production ($VE/\dot{V}CO_2$) were derived.

Neurohormone Assessment

Peripheral venous blood samples were obtained from all participants after they had rested for at least 20 minutes. Blood was collected into tubes containing EDTA, EDTA and aprotinin (50 KIU/mL of blood), or no additive. The samples were centrifuged at 3000 rpm for 15 minutes at 4°C. Plasma and serum aliquots were stored at −75°C until analysis. Atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and active renin were determined using immunoradiometric assays, ANP and BNP from EDTA/aprotinin plasma (Shionogi, Osaka, Japan), and active renin from EDTA plasma (Nichols Institute Diagnostics). Aldosterone was determined in serum by radioimmunoassay (EuroDPC). Endothelin-1 (ET-1) was determined in EDTA/aprotinin plasma by enzyme-linked immunosorbent assay (Bachem). Norepinephrine and epinephrine levels were measured in EDTA plasma using high-performance liquid chromatography with electrochemical detection, as previously described.[23] For all subjects, the full blood count, renal function, and liver function were determined using routine laboratory methods.

Analysis and Statistics

All results are reported as mean±SEM. Groups were assessed using unpaired Student's *t* test or ANOVA and then Fisher's post hoc test, as appropriate. Simple linear regression analysis was performed to correlate clinical variables with neurohormone levels and to correlate neurohormone levels with each other (Statview 5, Abacus Concepts). Results for each variable were tested for normality using the Kolmogorov Smirnov method. Results not normally distributed were log-transformed for statistical analysis (ANP, BNP, and renin). All *P* values <0.05 are referred to in the text as having statistical significance.

Results

Clinical Variables

As NYHA functional class increased, systemic ventricular function tended to worsen ($P=0.06$), and mean NYHA class was greater in patients with severely and moderately impaired ventricular function than in those with mildly impaired ventricular function (both $P<0.05$). According to the NYHA classification, patients in class III or IV had the lowest oxygen saturations (8.8% lower than NYHA II, $P<0.01$; 9.6% lower than NYHA I, $P<0.05$; see Table 2). Oxygen

TABLE 3. Clinical Results of Patients Grouped According to Systemic Ventricular Function

	Normal	Mildly Impaired	Moderately Impaired	Severely Impaired	*P* by ANOVA
NYHA functional class					
I/II/III/IV	3/11/2/1	6/12/1/0	0/4/3/0	0/1/2/0	...
Mean	2.1 (0.2)	1.7 (0.1)	2.4 (0.2)*	2.7 (0.3)*	**0.030**
Oximetry					
Oxygen saturation, %	92.9 (2.5)	94.1 (0.9)	91.1 (2.3)	81.3 (8.3)†‡§	**0.034**
ECG					
QRS duration, ms	129.7 (7.9)	118.8 (5.3)	112.3 (5.9)	142.3 (43.9)	0.37
Corrected QT interval, ms	446.5 (12.8)	447.7 (9.6)	453.7 (9.7)	527.0 (41.5)‡§‖	**0.044**
Radiology					
Cardiothoracic ratio	0.54 (0.02)	0.57 (0.02)	0.65 (0.05)*‖	0.69 (0.03)*‖	**0.006**
Echocardiography					
RA length, cm	5.4 (0.3)	5.4 (0.4)	6.1 (0.8)	6.7 (0.20)	0.41
RA width, cm	4.9 (0.3)	5.1 (0.4)	6.4 (0.9)	6.2 (0.3)	0.13
RA volume, cm^3	113.8 (24.7)	107.7 (24.1)	247.5 (99.7)	140.3 (21.7)	0.14
LA length, cm	5.1 (0.3)	5.6 (0.4)	5.1 (0.7)	6.5 (0.5)	0.41
LA width, cm	3.4 (0.3)	4.0 (0.4)	4.9 (1.0)	4.3 (0.2)	0.24
LA volume, cm^3	63.4 (9.0)	91.8 (23.0)	85.0 (13.0)	120.0 (19.4)	0.47
Exercise physiology					
Peak $\dot{V}O_2$, $mL \cdot kg^{-1} \cdot min^{-1}$	22.9 (1.8)	22.7 (2.0)	17.9 (2.6)	18.9	0.41
$VE/\dot{V}CO_2$ slope	36.8 (3.0)	30.5 (2.6)	43.9 (4.9)	34.9	0.09

Values are mean (±SEM).

*$P<0.05$ vs mildly impaired group; †$P<0.05$ vs normal ventricular function group; ‡$P<0.01$ vs mildly impaired group; §$P<0.05$ vs moderately impaired group; and ‖$P<0.01$ vs normal ventricular function group. Significant differences are shown in bold.

saturations were 9.8%, 12.8%, and 11.6% lower in patients with severely impaired systemic ventricular function than in those with moderately impaired, mildly impaired, or normal systemic ventricular function, respectively ($P<0.05$, $P<0.01$, and $P<0.05$, see Table 3). The QTc interval was 41.6 and 47.4 ms longer and CTR was 9% and 13% greater in patients in NYHA class III or IV than in patients in class II or I, respectively (both $P<0.05$ for QTc, both $P<0.01$ for CTR). The QTc was prolonged by 73.3, 79.3, and 80.5 ms in patients with severely impaired systemic ventricular function versus those with moderately impaired, mildly impaired, or normal systemic ventricular function, respectively ($P<0.05$, $P<0.01$, and $P<0.05$). CTR was 12% and 15% greater in patients with severely impaired systemic ventricular function and 8% and 11% greater in patients with moderately impaired systemic ventricular function than in those with mildly impaired or normal ventricular function, respectively (both $P<0.05$ and $P<0.01$ versus each group). Peak $\dot{V}O_2$ fell and the $VE/\dot{V}CO_2$ slope became steeper as symptoms worsened, although these just failed to reach significance ($P=0.11$ and $P=0.06$, respectively).

Patients with TOF had a wider mean QRS width than did the systemic right ventricle group (138.0±8.6 versus 103.4±5.0 ms, $P<0.05$) and a trend toward a longer QTc (ANOVA, $P=0.06$), reflecting the large proportion of this group who had right bundle-branch block related to surgical ventriculotomy. Otherwise, no relationship was found between any of the clinical indices and the anatomic groups (all ANOVA $P>0.10$).

Neurohormone Levels

Taken as a whole, adult patients with congenital heart disease had significantly higher circulating levels of ANP, BNP, ET-1 (all $P<0.0001$), norepinephrine, renin (both $P=0.003$), and aldosterone ($P=0.024$) than did control subjects (see Table 4). The ANP, BNP, ET-1, and norepinephrine levels for patients subgrouped according to NYHA functional class and systemic left ventricular function are given in Figure 1.

TABLE 4. Neurohormone Levels in Adults With Congenital Heart Disease and Healthy Controls

	Congenital Heart Disease Patients (n=53)	Control Subjects (n=15)	*P*
ANP, pmol/L	56.6 (17.5)	3.1 (0.6)	**<0.0001**
BNP, pmol/L	35.8 (7.7)	5.7 (0.9)	**<0.0001**
ET-1, pmol/L	2.52 (0.21)	0.72 (0.08)	**<0.0001**
Norepinephrine, nmol/L	2.19 (0.09)	1.63 (0.13)	**0.003**
Epinephrine, nmol/L	0.52 (0.03)	0.43 (0.05)	0.12
Renin, pmol/L	147.5 (28.1)	16.3 (1.9)	**0.003**
Aldosterone, pmol/L	546.3 (47.3)	337.4 (22.9)	**0.024**

Values are mean (±SEM).

P values are for unpaired *t* tests between patients and control subjects. Significant differences are shown in bold.

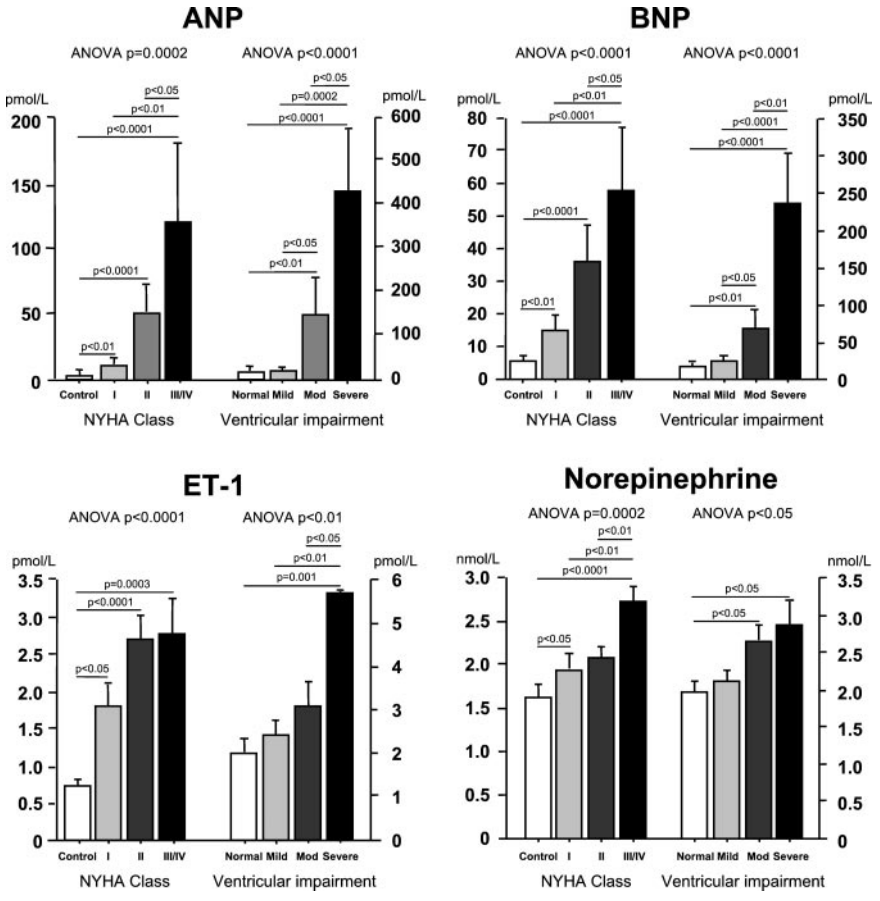

Figure 1. Neurohormone levels in all subjects according to NYHA functional class and in adults with congenital heart disease according to systemic ventricular function. Note differing *y*-scales for each measure.

There was a highly significant stepwise increase in the concentrations of all 4 neurohormones with increasing disease severity, as quantified by both measures. Neurohormonal activation was evident even in patients with asymptomatic disease compared with control subjects. In addition, activation of the renin-aldosterone axis was apparent in symptomatic patients versus control subjects or versus those without symptoms (Figure 2). In contrast, none of the 7 neurohormones assessed were higher in any particular anatomic group (ANP, $P=0.30$; BNP, $P=0.48$; ET-1, $P=0.12$; norepinephrine, $P=0.24$; epinephrine, $P=0.50$; renin, $P=0.89$; and aldosterone, $P=0.85$).

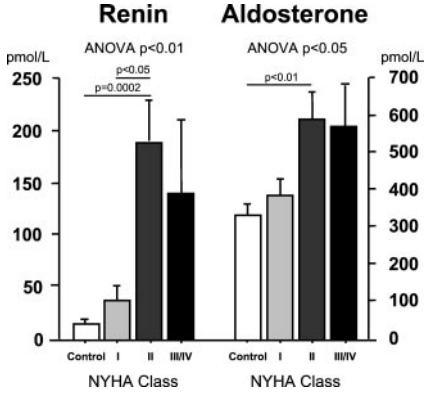

Figure 2. Renin and aldosterone levels in all subjects according to NYHA functional class.

Table 5 gives the correlation coefficients of the neurohormones with the clinical variables. QRS width and QTc in patients with surgically created bundle-branch block, RA, and LA volumes, and CTR all correlated well with ANP, BNP, and ET-1 (QRS, $r=0.74$, 0.74, and 0.69; QTc, $r=0.71$, 0.66, and 0.63; RA volume, $r=0.52$, 0.45, and 0.40; LA volume, $r=0.58$, 0.55, and 0.60; CTR, $r=0.59$, 0.62, and 0.44, respectively). In addition, RA and LA volumes correlated with aldosterone levels ($r=0.45$ and $r=0.40$, respectively) and LA volume with norepinephrine ($r=0.56$). Of the 2 cardiopulmonary exercise measures, peak $\dot{V}O_2$ was most closely (and inversely) associated with neurohormonal activation (ANP, $r=-0.54$; BNP, $r=-0.46$; and ET-1, $r=-0.42$). There was also a modest correlation between QTc and ANP ($r=0.37$) and ET-1 levels ($r=0.33$).

The natriuretic peptides were very closely correlated with one another ($r=0.91$, Table 6) and demonstrated strong relationships to ET-1 levels (ANP/ET-1, $r=0.83$; BNP/ET-1, $r=0.71$). As a group, ANP, BNP, ET-1, norepinephrine, and epinephrine levels were well associated with each other. This was in marked contrast to renin and aldosterone levels, which correlated only with each other ($r=0.76$) and with none of the other 5 neurohormones measured.

Medication and Neurohormone Levels

There was no difference in neurohormone levels between patients taking and not taking ACE inhibitors (including when matched for NYHA class, systemic ventricular func-

TABLE 5. Correlation Coefficients of Neurohormones With Clinical Variables in Adult Patients With Congenital Heart Disease

	Sa_{O_2}	QRS, No Surgical BBB	QRS, Surgical BBB	QTc, No Surgical BBB	QTc, Surgical BBB	CTR	RA Volume	LA Volume	Peak $\dot{V}_{O_2}$	$VE/\dot{V}_{CO_2}$
ANP										
P	**0.037**	0.24	**0.002**	**0.04**	**0.006**	**<0.0001**	**0.0009**	**0.0002**	**0.004**	0.10
r	**−0.38**	0.20	**0.74**	**0.36**	**0.71**	**0.59**	**0.52**	**0.58**	**−0.54**	−0.33
BNP										
P	0.23	0.34	**0.003**	0.17	**0.01**	**<0.0001**	**0.005**	**0.0005**	**0.017**	0.11
r	−0.23	0.17	**0.74**	0.25	**0.66**	**0.62**	**0.45**	**0.55**	**−0.46**	−0.32
ET-1										
P	0.42	0.05	**0.007**	0.05	**0.02**	**0.003**	**0.013**	**0.0001**	**0.031**	0.44
r	−0.15	0.33	**0.69**	0.35	**0.63**	**0.44**	**0.40**	**0.60**	**−0.42**	−0.16
Norepinephrine										
P	0.10	0.13	0.08	0.19	0.14	**0.010**	0.06	**0.0002**	0.07	0.18
r	−0.30	0.25	0.47	0.23	0.41	**0.37**	0.30	**0.56**	−0.34	−0.26
Epinephrine										
P	**0.006**	0.59	0.49	0.46	0.88	0.11	0.11	0.38	0.25	**0.048**
r	**−0.48**	0.09	0.20	0.13	0.05	0.23	0.25	0.15	0.22	**−0.37**
Renin										
P	0.54	0.60	0.78	0.16	0.78	0.69	0.07	0.48	0.85	0.30
r	−0.11	0.09	0.08	0.25	0.08	0.06	0.29	0.12	−0.04	−0.20
Aldosterone										
P	0.29	0.43	0.46	0.87	0.70	0.12	**0.003**	**0.012**	0.44	0.75
r	−0.19	0.14	0.20	0.03	0.11	0.23	**0.45**	**0.40**	−0.15	−0.06

Sa_{O_2} indicates oxygen saturation and BBB, bundle-branch block.
Significant correlations are shown in bold.

tion, and clinical variables). Similarly, neurohormone levels, NYHA class, and systemic ventricular function did not differ between those taking and not taking β-blockers. ANP, BNP, ET-1, aldosterone, and norepinephrine levels were significantly higher in patients taking diuretics, but this group also had a higher mean NYHA class (1.8 ± 0.1 versus 2.5 ± 0.2, $P<0.001$) and worse systemic ventricular function ($P<0.05$).

Discussion

Adults with congenital heart disease have elevated circulating levels of the natriuretic peptides, ET-1, norepinephrine, renin, and aldosterone, and neurohormonal activation is present even in asymptomatic individuals. The degree of neurohormonal activation relates closely to NYHA functional class, systemic ventricular function, and other clinical indices typically used to assess the patient with CHF. As such, the congenital heart disease phenotype per se, with apparent independence from anatomy, bears all of the hallmarks of the syndrome of CHF.

NYHA functional class and measures of left ventricular function have become fundamental to the initial diagnosis of CHF, in assessing the response to treatment and in estimating prognosis. In recent years, the realization that activation of several neurohormonal pathways parallels the development of CHF, relates closely to clinical indices of disease severity, and is instrumental in perpetuating disease progression has resulted in the incorporation of neurohormonal activation into the very definition of heart failure.[24] Crucially, the pharmacological manipulation of neurohormonal pathways has revolutionized the management of CHF, leading to substantial improvements in morbidity and prognosis, an important feature of which has been a relative independence from etiology. Activation of neurohormonal systems in children with congenital heart disease has been described,[11–14] but the broader relevance of these individual findings to congenital heart disease populations as a whole has been difficult to gauge because common clinical denominators have been difficult to apply to this anatomically heterogeneous population. Patterns of neurohormonal activation and clinical measures of disease severity are even less well understood in those patients surviving into adulthood, a large population that may number >1 million in the United States alone and that is growing by as much as 5% per annum.[15]

Taking the routine assessment of CHF as a model, the present study clearly demonstrates that in adult patients with congenital heart disease, important clinical measures of heart failure severity, including the QT interval[25] and CTR,[26] relate well to both NYHA functional class and systemic ventricular function and not necessarily to anatomic substrates. NYHA class itself increases as systemic ventricular function worsens. In addition, taken as a group, adults with congenital heart disease have marked activation of the natriuretic, endothelin, sympathoadrenergic, and renin-aldosterone systems. The magnitude of neurohormonal activation is equivalent to that

TABLE 6. Correlation Coefficients of Neurohormones With Each Other in Adult Patients With Congenital Heart Disease

	BNP	ET-1	Norepinephrine	Epinephrine	Renin	Aldosterone
ANP						
P	**<0.0001**	**<0.0001**	**<0.0001**	**0.0002**	0.66	0.44
r	**0.91**	**0.83**	**0.68**	**0.50**	0.06	0.11
BNP						
P		**<0.0001**	**<0.0001**	**0.008**	0.71	0.33
r		**0.71**	**0.58**	**0.37**	0.06	0.14
ET-1						
P			**<0.0001**	**0.003**	0.90	0.32
r			**0.53**	**0.42**	0.02	0.02
Norepinephrine						
P				**0.003**	0.80	0.92
r				**0.40**	0.04	0.01
Epinephrine						
P					0.25	0.43
r					0.16	0.11
Renin						
P						**<0.0001**
r						**0.76**

Significant correlations are shown in bold.

found in CHF with good concordance between NYHA class in the 2 populations.[2,27]

Neurohormone levels were found to increase in a stepwise manner across functional class, with even patients with asymptomatic disease having significantly elevated levels of ANP, BNP, ET-1, and norepinephrine compared with controls. Anatomic group again did not distinguish between patients with differing degrees of neurohormonal activation, a finding consistent with that of Ross et al,[28] who reported that infants and children (mean age, 3.3 years) with congenital heart disease and severe congestive heart failure had elevated plasma norepinephrine levels regardless of etiology. Systemic ventricular function, although not relating to neurohormonal activation when impairment was mild, seems to be an extremely sensitive discriminant in this regard when severely impaired. Although accounting for only 3 patients, mean levels of ANP (434 pmol/L), BNP (235 pmol/L), ET-1 (5.66 pmol/L), and norepinephrine (2.86 ± 0.32 nmol/L) were higher in this group than in any other group by systemic ventricular function or NYHA class.

The correlations found between neurohormones and clinical variables (Table 5) demonstrate that relatively simple and routine noninvasive cardiac investigations (chest x-ray, measurement of atrial volume by echocardiography, and cardiopulmonary exercise testing stand out) could help identify which patients with congenital heart disease are likely to have significant neurohormonal activation. These associations may also point toward mechanisms underlying neurohormonal activation in congenital heart disease, with cardiac size, and in particular RA and LA size, seeming to be important. Atrial volume[29] and atrial size indexed by body surface area[30] rather than pressure have been found to relate to natriuretic peptide production in children with congenital heart disease, and right ventricular ejection fraction seems important in patients with chronic right ventricular pressure overload.[19] These findings are in keeping with present knowledge regarding the distribution, synthesis, and release of natriuretic peptides in the context of heart failure.[31] The design of the present study did not allow for the determination of pulmonary flow or pressure, extracardiac factors that are also known to influence natriuretic peptide and ET-1 production. However, the natriuretic peptides, ET-1, norepinephrine, and epinephrine correlate very closely as a group, perhaps reflecting the importance of changes in central pressure-volume relationships to activation of these systems. Therefore, it is intriguing that renin and aldosterone levels were found to relate only to one another and not to systemic ventricular function, suggesting that activation of these neurohormones is under alternative influence.

By aligning the phenotype of congenital heart disease with the syndrome of CHF, we are not seeking to deny that cardiac anatomy can have an important influence on clinical and neurohormonal measures in the former. Given greater numbers of patients, anatomy-specific differences (particularly relating to cyanotic heart disease) may have emerged, and this certainly requires additional investigation. Similarly, the influence of surgery cannot be overlooked. In our study, of the patients with TOF, those who had undergone reparative surgery had lower levels of all 7 neurohormones measured compared with those who had had palliative operations, and in the case of aldosterone, this difference was significant ($P=0.001$). This is not an isolated finding. There are several reports of neurohormone levels falling, sometimes to normal levels, after surgical repair of congenital heart disease,[32–34] and earlier surgery is known to favorably influence the risk of sudden death in patients with TOF.[35]

However, this study and that of Iivainen et al,[18] demonstrating that *N*-terminal ANP levels are elevated 2 decades after routine closure of atrial septal defects, suggest that this situation may not endure. Subtle and persistent abnormalities of cardiac or extracardiac structure and function may continue to drive neurohormonal activation, albeit to a lesser extent than in surgically naive disease.

Built on the principles used for defining CHF, our findings provide a framework for diagnosis and disease characterization that has applicability to an anatomically diverse population of adult patients with congenital heart disease. Evidence of significant neurohormonal activation relating strongly to functional class, systemic ventricular function, and other routine measures of heart failure severity additionally validates this approach. It now remains to be seen what the prognostic implications of neurohormonal activation are for adults with congenital heart disease and whether pharmacological manipulation of neurohormonal systems in such patients with reference to this paradigm translates into meaningful clinical benefit.

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