Stratification of Pediatric Heart Failure on the Basis of Neurohormonal and Cardiac Autonomic Nervous Activities in Patients With Congenital Heart Disease

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Background—Stratification of pediatric patients with congenital heart disease (CHD) has been based on their hemodynamics and/or functional capacity. Our purpose was to compare cardiac autonomic nervous activity (CANA) and neurohormonal activities (NHA) with postoperative status in stable CHD patients with biventricular physiology.

Methods and Results—We divided 379 subjects (297 CHD patients, 28 dilated cardiomyopathy patient, and 54 control subjects) into 4 subgroups according to New York Heart Association (NYHA) class (1.3±0.7) and measured various CANA and NHA indices. Stepwise decreases in baroreflex sensitivity (BRS), heart rate variability (HRV), adrenergic imaging, and vital capacity (VC) were observed in proportion to functional capacity in normal to NYHA II patients (P<0.001). However, there were no differences in these indices between NYHA II and III+IV groups, whereas a stepwise proportional increase in NHA indices was observed in these groups (P<0.001). Natriuretic peptides differentiated all NYHA classes. BRS, HRV, and VC were greater in the adult patients than in the child patients (P<0.05 to 0.001), although the functional class in adult patients was lower. Cardiac surgeries resulted in low BRS and VC, and the VC reduction independently determined a small HRV. Even if functional class and ejection fraction were comparable, CANA and brain natriuretic peptide were lower in CHD patients than in dilated cardiomyopathy patients (P<0.05 to 0.001).

Conclusions—CANA and NHA indices are useful to stratify mild and severe heart failure in stable postoperative CHD patients, respectively. However, careful attention should be paid to age- and surgery-related influences on these indices. (Circulation. 2003;108:2368-2376.)

Key Words: heart defects, congenital ■ nervous system, autonomic ■ hormones ■ heart failure

The number of adults with congenital heart disease (CHD) is increasing, and their follow-up and medical treatment for residual and/or late complications are assuming great importance. Except for simple anomalies, these patients usually have residual hemodynamic abnormalities, causing volume and/or pressure overload, that may be significant future determinants of morbidity and mortality. Hemodynamics have been the main basis by which pediatric cardiologists have stratified postoperative status in CHD patients. Heart failure comprises an imbalance of cardiac autonomic nervous activity (CANA), increased neurohormonal activities (NHA), and impaired exercise capacity, and this concept is applicable to pediatric cardiac patients.1 Recent studies of adult CHD patients showed some of these abnormalities,2-4 and possible treatment using selected antagonists has been proposed.3,4 Many clinical CANA and NHA indices are available in adult heart failure patients5-10; however, little is known about these variables and their interrelationships with clinical status in pediatric patients. Therefore, the purpose of our present study was to measure various clinical parameters in a large number of postoperative CHD patients, to investigate the relationship between these variables and clinical status, and finally to propose an efficient usage of these clinical markers.

Methods

Subjects

We prospectively studied 379 clinically stable subjects (1 to 40 years old), including 297 postoperative CHD patients and 82 with acquired heart disease. They included 107 adult patients (≥18 years old; 77 CHD, 30 acquired). Postoperative patients included 70 patients after closure of an atrial or ventricular septal defect, 149 after right ventricular outflow tract reconstruction, 16 after an arterial switch operation for complete transposition of the great arteries, 29 after the Ross operation for aortic valve lesions, 30 after repair of coarctation or interruption of the aorta, and 3 after ventricular septation. Acquired heart disease included 26 young patients with idiopathic dilated cardiomyopathy (DCM), 2 patients with a history of Kawasaki disease with significant coronary stenosis who had a reduced
ventricular ejection fraction (EF), and 54 control subjects. The control subjects were being followed up at our institute because of a history of dilatation and/or aneurysm of coronary arteries caused by Kawasaki disease, and follow-up selective coronary angiography was therefore needed to evaluate possible stenosis of the coronary arteries. Our control subjects showed no significant stenotic lesions of the coronary arteries. DCM was diagnosed by myocardial biopsies in addition to hemodynamics. Patients with right ventricular outflow tract reconstruction included tetralogy of Fallot in 89 patients, double-outlet right ventricle in 16, transposition of the great arteries after Rastelli operation in 16, atrioventricular discordance in 2, and persistent truncus arteriosus in 7 (Table 1). The follow-up period after the last operation to the time of study was at least 3 months in postsurgical patients and a stable cardiac status in the DCM patients for at least 2 months. All patients were free of intravenous medications. Patients with sick sinus syndrome, Eisenmenger syndrome, primary pulmonary hypertension, and possible renal dysfunction (creatinine \( > 1.0 \)) were excluded from the study. We also excluded patients with single ventricular physiology (Fontan patients or unrepaird cyanotic complex CHD).

### Postoperative Status According to New York Heart Association Classification

Because the New York Heart Association (NYHA) classification of cardiac status applies to adult cardiac patients, a modification of the classification was used for child patients.11

### Hemodynamics

Within 1 week of exercise testing, cardiac catheterization with cineventriculography was performed in 240 patients and 51 control subjects. We measured pressures in the cardiac chambers and great arteries after a 15-minute supine rest, ECG signals were recorded for 5 minutes, and beat-to-beat fluctuations were transformed into frequency domains by use of a fast Fourier transformation. The spectral HRV was expressed as a low-frequency (LF) component (0.04 to 0.15 Hz) and a high-frequency (HF) component (0.15 to 0.40 Hz), and the logarithmic values, log LF and log HF, were used. A bolus phenylephrine method was used to measure BRS (ms/mm Hg).16

### Neurohumoral Activities

After at least 15 minutes of supine rest, the plasma norepinephrine level (NE) was determined by high-performance liquid chromatography (371 patients).12 The plasma levels of atrial and brain natriuretic peptides (ANP and BNP; 372 patients) and plasma renin activity (PRA; 368 patients) were assayed by radioimmunoassay.13–15

### HR Variability and Arterial Baroreflex Sensitivity

HR variability (HRV) and arterial baroreflex sensitivity (BRS) were measured in 341 and 343 patients, respectively. The methods have been reported previously.2,3 Briefly, after a 15-minute supine rest, ECG signals were recorded for 5 minutes, and beat-to-beat fluctuations were transformed into frequency domains by use of a fast Fourier transformation. The spectral HRV was expressed as a low-frequency (LF) component (0.04 to 0.15 Hz) and a high-frequency (HF) component (0.15 to 0.40 Hz), and the logarithmic values, log LF and log HF, were used. A bolus phenylephrine method was used to measure BRS (ms/mm Hg).16

### [123I]Metaiodobenzylguanidine Scintigraphy

The methodology for this index was identical to that reported previously.2,3 Metaiodobenzylguanidine (MBG) scintigraphy was performed in 218 patients to evaluate myocardial adrenergic nervous activity. Myocardial images were acquired 4 hours after tracer injection, and the ratio of heart to mediastinal activity (H/M) was calculated.

### Pulmonary Function Tests

Vital capacity (VC, in liters) and the percent forced expiratory volume in 1 second were measured in 346 patients (Spirosoft, SP-600, Fukuda Denso), and VC was calculated as the percentage of the body height–predicted normal value for our institute.

### Exercise Protocol

In all, 366 patients underwent symptom-limited treadmill exercise,17 and peak oxygen uptake (pVO\(_2\)) (mL · kg\(^{-1}\) · min\(^{-1}\)) and systolic blood pressure were measured and calculated as the percentage of body weight–predicted normal value for our institute. A 12-lead ECG was used to determine HR. Ventilation and gas exchange were measured with a breath-by-breath method using a hot-wire anemometer (Riko AS500, Minato Medical Science) with a mass spectrometer (MG-300, Perkins Elmer). Minute ventilation versus carbon dioxide production slope (Ve/VCO\(_2\) slope) was determined.

### Informed Consent

After adequate explanation of the purpose of the study and its clinical significance (mentioned under Clinical Implications), informed con-
sent was obtained from all patients and/or their parents. We asked control subjects and/or their parents to give permission to take part in the study as a volunteer. The study protocol was approved by the Ethical Committee of the National Cardiovascular Center.

Statistical Analysis
Differences in hemodynamics, NHA, CANA, and exercise variables were evaluated by 1-way ANOVA with Bonferroni’s post hoc test. Univariate and stepwise multivariate linear regression analysis was used to detect independent determinants of CANA, NHA, and cardiopulmonary variables. Data are expressed as the mean ± SD. A probability value of P < 0.05 was considered statistically significant.

Results
NYHA Classification
The numbers of patients in the control and NYHA I, II, and III+ IV groups were 54, 221, 60, and 16, respectively. Hemodynamics, NHA, CANA, and exercise variables for each category are shown in Table 2. Representative data according to NYHA classification and cardiac anatomy are shown in Figures 1 and 2, respectively.

Hemodynamics
Elevated central venous, right ventricular end-diastolic, and pulmonary artery pressures and low cardiac output were observed in proportion to functional severity, and a low ventricular EF with increased ventricular volumes was present in NYHA III+IV. Systemic ventricular volumes in NYHA I and II were larger (P < 0.05 to 0.01) and the contractility was lower (P < 0.1 to 0.05) in the adult CHD patients than in the child CHD patients (Figure 1).

### Table 2: Hemodynamics, Neurohormonal and Cardiac Autonomic Nervous Activities, and Exercise Variables According to Functional Capacity in Patients With Biventricular Physiology

<table>
<thead>
<tr>
<th>Group</th>
<th>Control (n=54)</th>
<th>I (n=221)</th>
<th>II (n=60)</th>
<th>III+IV (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodynamics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central venous pressure, mm Hg</td>
<td>3 ± 1</td>
<td>6 ± 3 ‡</td>
<td>7 ± 3 † ‡</td>
<td>9 ± 5 † □ #</td>
</tr>
<tr>
<td>PV-EDP, mm Hg</td>
<td>6 ± 2</td>
<td>9 ± 3 ‡</td>
<td>10 ± 4 ‡</td>
<td>12 ± 6 † □ #</td>
</tr>
<tr>
<td>PV-EF, %</td>
<td>55 ± 7</td>
<td>53 ± 9</td>
<td>52 ± 9</td>
<td>35 ± 15 † □ † ‡</td>
</tr>
<tr>
<td>PV-EDVI, ml/m²</td>
<td>85 ± 14</td>
<td>89 ± 22</td>
<td>86 ± 25</td>
<td>120 ± 42 □ † †</td>
</tr>
<tr>
<td>Pulmonary artery pressure, mm Hg</td>
<td>13 ± 2</td>
<td>16 ± 4 ‡</td>
<td>19 ± 6 † †</td>
<td>23 ± 9 † □ *</td>
</tr>
<tr>
<td>SV-EDP, mm Hg</td>
<td>10 ± 3</td>
<td>12 ± 4</td>
<td>12 ± 5</td>
<td>13 ± 6</td>
</tr>
<tr>
<td>SV-EF, %</td>
<td>64 ± 8</td>
<td>65 ± 10</td>
<td>58 ± 12 † †</td>
<td>37 ± 16 □ † †</td>
</tr>
<tr>
<td>SV-EDVI, ml/m²</td>
<td>80 ± 15</td>
<td>91 ± 24 *</td>
<td>99 ± 33 ‡</td>
<td>131 ± 45 □ † †</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>3.6 ± 0.7</td>
<td>3.3 ± 0.7 †</td>
<td>3.0 ± 0.7 † □</td>
<td>2.6 ± 0.6 □</td>
</tr>
<tr>
<td>Arterial oxygen saturation, %</td>
<td>98 ± 1</td>
<td>98 ± 1</td>
<td>98 ± 2 *</td>
<td>96 ± 31 □ † †</td>
</tr>
<tr>
<td>NHA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NE, pg/mL</td>
<td>157 ± 70</td>
<td>154 ± 68</td>
<td>182 ± 80 †</td>
<td>319 ± 211 † □ † □</td>
</tr>
<tr>
<td>ANP, pg/mL</td>
<td>19 ± 10</td>
<td>45 ± 31 ‡</td>
<td>77 ± 49 † †</td>
<td>125 ± 111 † □ † †</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>4 ± 4</td>
<td>23 ± 25 †</td>
<td>53 ± 59 † †</td>
<td>150 ± 144 □ † †</td>
</tr>
<tr>
<td>PRA, ng/ml·L⁻¹·h⁻¹</td>
<td>3.0 ± 2.1</td>
<td>3.5 ± 3.0</td>
<td>10.2 ± 13.5 †</td>
<td>18.5 ± 17.8 □ † †</td>
</tr>
<tr>
<td>CANA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>log LF</td>
<td>2.5 ± 0.4</td>
<td>2.0 ± 0.5 ‡</td>
<td>1.6 ± 0.5 † ‡</td>
<td>1.3 ± 0.5 † □</td>
</tr>
<tr>
<td>log HF</td>
<td>2.5 ± 0.5</td>
<td>1.8 ± 0.5 ‡</td>
<td>1.4 ± 0.5 † ‡</td>
<td>1.2 ± 0.4 †</td>
</tr>
<tr>
<td>BRS</td>
<td>17.6 ± 6.3</td>
<td>9.2 ± 5.6 ″</td>
<td>4.0 ± 3.4 † †</td>
<td>1.0 ± 1.5 †</td>
</tr>
<tr>
<td>H/M</td>
<td>2.9 ± 0.5</td>
<td>1.9 ± 0.5 ‡</td>
<td>1.7 ± 0.4 † †</td>
<td>1.5 ± 0.3 †</td>
</tr>
<tr>
<td>Exercise variables</td>
<td>(n=54)</td>
<td>(n=216)</td>
<td>(n=59)</td>
<td>(n=14)</td>
</tr>
<tr>
<td>Peak V̇O₂, % predicted</td>
<td>96 ± 13</td>
<td>77 ± 13 †</td>
<td>52 ± 6 † †</td>
<td>41 ± 5 † □</td>
</tr>
<tr>
<td>Vo₂-ECO₂ slope, % predicted</td>
<td>99 ± 13</td>
<td>104 ± 17</td>
<td>115 ± 21 † †</td>
<td>132 ± 38 † □ †</td>
</tr>
<tr>
<td>Pulmonary function</td>
<td>(n=49)</td>
<td>(n=207)</td>
<td>(n=55)</td>
<td>(n=14)</td>
</tr>
<tr>
<td>VC, % predicted</td>
<td>101 ± 15</td>
<td>83 ± 16 †</td>
<td>66 ± 18 † †</td>
<td>61 ± 18 †</td>
</tr>
<tr>
<td>Forced expired volume in 1 second, %</td>
<td>90 ± 7</td>
<td>88 ± 7</td>
<td>87 ± 12 *</td>
<td>82 ± 10 □</td>
</tr>
</tbody>
</table>

Values are mean ± SD. EDP indicates end-diastolic pressure; EDVI, end-diastolic volume index; PV, pulmonary ventricle; SV, systemic ventricle; and Vo₂-ECO₂ slope, ventilation vs bicarbonate dioxide production slope.

*P < 0.05, †P < 0.01, ‡P < 0.001 vs Control.

$P < 0.05, ||P < 0.01, ††P < 0.001 vs I.

#P < 0.05, **P < 0.01, †††P < 0.001 vs II.
Neurohormonal Activities

Although NE and PRA did not increase until NYHA II, ANP and BNP could differentiate all groups from each other ($P<0.001$). The increase in all NHA was stepwise, and the difference was much greater between NYHA II and III/IV (Figure 1).

Figure 1. Relationship between categorized groups according to NYHA classification and clinical variables. SVEF indicates systemic ventricular EF; SVEDVI, systemic ventricular end-diastolic volume index; and VO2, oxygen uptake. White and black bars represent child and adult patients, respectively; *, **, and *** $P<0.05$, 0.01, and 0.001 vs child CHD patients, respectively.

Significant inverse correlation between natriuretic peptides and age was observed in control subjects ($r=-0.46$, $P<0.001$ and $r=-0.32$, $P<0.05$, for ANP and BNP, respectively). Normal values for ANP and BNP were 19±10 and 4±4, respectively. In the control and NYHA I groups, ANP was higher in the child CHD patients than in the adult CHD patients. In contrast, in NYHA III+IV, NE was higher in the adult CHD patients.

Cardiac Autonomic Nervous Activity

All CANA indices were reduced, even in the NYHA I group, compared with control subjects. Significant decreases in all CANA indices in proportion to functional severity were observed from control subjects to NYHA II, whereas no differences were observed in these variables between NYHA II and III+IV, except for log LF.

In NYHA I and II, BRS was significantly greater in the adult CHD patients than in the child CHD patients ($P<0.05$),...
and HRV was also greater in the adult CHD patients with NYHA II \( (P < 0.05) \).

**Vital Capacity**
The there was a significant proportional decrease from control subjects to NYHA II, whereas no difference was observed between NYHA II and III/IV. The maintained forced expiratory volume in 1 second in all patient groups indicated that most of our CHD patients had restrictive ventilatory impairment.

**Exercise Variables**
p\( \dot{V}O_2 \) decreased in proportion to NYHA classification. A stepwise increase in V\( \dot{E} / V\dot{C}O \) slope was observed in the NYHA II and III/IV groups.

**Correlation Between NHA and CANA**
All NHA indices correlated with each other and also correlated with CANA and p\( \dot{V}O_2 \) except for the relationship between NE and HRV or BRS and that between natriuretic peptides and H/M (Table 3). Tight correlations were observed between ANP and BNP and between HRV and BRS. p\( \dot{V}O_2 \) correlated with all NHA and CANA indices, especially with BRS.

**Determinant Factors**
To determine the independent factors, the following parameters were used; age at tests and definitive repair, follow-up period, number of surgeries, hemodynamics, VC, and medications (Table 4).

**Neurohormonal Activities**
A high NE was multifactorially determined (high age, female sex, small ventricular volume, low arterial saturation, small VC, and use of ACE inhibitor and antiarrhythmic agent, \( P < 0.05 \) to 0.001). BNP was determined by pulmonary and systemic ventricular function \( (P < 0.05 \) to 0.001). ANP was determined by pulmonary ventricular end-diastolic pressure, and a small VC had a significant impact on high ANP \( (P < 0.001) \). In contrast, PRA was determined by the use of diuretics and ACE inhibitor, not by hemodynamics.

**Cardiac Autonomic Nervous Activity**
A small VC and low systemic ventricular contractility determined low HRV \( (P < 0.001) \). In addition to use of diuretics, high pulmonary ventricular systolic pressure determined low H/M \( (P < 0.001) \). Surgeries and high central venous pressure determined BRS \( (P < 0.001) \). In addition, small VC determined low BRS \( (P < 0.001) \).

**Vital Capacity**
In addition to female sex, shorter follow-up period and a large number of surgical procedures independently determined a low VC \( (P < 0.05 \) to 0.001).
Subgroup Analysis

**CHD Versus DCM**

When 20 CHD patients with low EF (≤45%) were compared with 18 DCM patients with low EF (≤45%), central venous and right ventricular end-diastolic pressures were higher in CHD than in DCM patients. However, although there were no differences in NYHA class (2.2±0.2 versus 2.1±0.2), pV̇O₂ (52±3% versus 58±5%), or EF (35±2% versus 35±2%), BNP, HRV, and H/M were lower in the CHD patients (Figure 3). Thus, even if the pV̇O₂ and EF were comparable, BNP and CANA were lower in CHD than in DCM patients.

**Normal Versus Abnormal Natriuretic Peptides, BRS in NYHA I**

Of 214 CHD patients in NYHA I, 97, 110, and 54 patients showed high ANP (>40 pg/mL), high BNP (>13 pg/mL), and low BRS (<5.0 mm/s/mm Hg). Peak HR, systolic blood pressure, pV̇O₂, and VC were lower in the high-natriuretic-peptide (P<0.05 to 0.001) and in the low-BRS patients (P<0.0001) than in the normal-range patients. The percentage of patients receiving diuretics was greater in the high-natriuretic-peptide and/or impaired BRS patients than in the normal-range patients (P<0.05 to 0.001).

### Table 3: Correlation Coefficients Between Neurohumoral and Cardiac Autonomic Nervous Activities in Patients With Biventricular Physiology

<table>
<thead>
<tr>
<th>NHA</th>
<th>ANP</th>
<th>BNP</th>
<th>PRA</th>
<th>CANA</th>
<th>log LF</th>
<th>log HF</th>
<th>BRS</th>
<th>H/M</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE</td>
<td>0.15*</td>
<td>0.25†</td>
<td>0.30‡</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>-0.19*</td>
<td>-0.31†</td>
<td>Peak V̇O₂, %</td>
</tr>
<tr>
<td>ANP</td>
<td>...</td>
<td>0.79‡</td>
<td>0.24‡</td>
<td>-0.29‡</td>
<td>-0.28‡</td>
<td>-0.34‡</td>
<td>NS</td>
<td>-0.41†</td>
<td></td>
</tr>
<tr>
<td>BNP</td>
<td>...</td>
<td>0.38‡</td>
<td>...</td>
<td>-0.25‡</td>
<td>-0.24‡</td>
<td>-0.25‡</td>
<td>NS</td>
<td>-0.41†</td>
<td></td>
</tr>
<tr>
<td>PRA</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>-0.27†</td>
<td>-0.18*</td>
<td>-0.24‡</td>
<td>-0.20*</td>
<td>-0.40†</td>
<td></td>
</tr>
<tr>
<td>CANA</td>
<td>log LF</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.82‡</td>
<td>0.58‡</td>
<td>0.26‡</td>
<td>0.42†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>log HF</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.56‡</td>
<td>0.19*</td>
<td>0.37†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BRS</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.54†</td>
<td>0.60†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>H/M</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.43†</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.001, †P<0.0001.

### Discussion

Our major findings are as follows: in postoperative CHD patients with biventricular physiology, (1) natriuretic peptides can differentiate all NYHA classes from each other, and BNP is sensitive to systemic ventricular function and especially useful to differentiate patients with symptomatic heart failure. However, (2) there is no obvious difference in HRV or BRS between patients in NYHA II and III+IV, although these are useful for stratification of asymptomatic patients. (3) HRV and BRS are greater in adult patients in NYHA I and II than those in comparable child patients and are closely related to VC. In addition, surgeries have a great impact on HRV and BRS, and (4) BNP and CANA indices are lower in CHD patients than in the DCM patients when the functional capacity is comparable.

### Table 4: Independent Determinants and Their β-Coefficients for Neurohumoral and Cardiac Autonomic Nervous Activities

<table>
<thead>
<tr>
<th>Hemodynamics</th>
<th>Pulmonary Ventricle</th>
<th>Systemic Ventricle</th>
<th>Lung VC</th>
<th>Medications: Diuretics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natriuretic peptides</td>
<td>ANP</td>
<td>0.26‡</td>
<td>-0.37‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BNP</td>
<td>0.29*</td>
<td>0.16†</td>
<td>-0.23‡</td>
</tr>
<tr>
<td>CANA</td>
<td>log LF</td>
<td>0.27‡</td>
<td>0.36‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>log HF</td>
<td>0.26‡</td>
<td>0.37‡</td>
<td></td>
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<tr>
<td></td>
<td>BRS</td>
<td>-0.22‡</td>
<td>-0.18‡</td>
<td>0.30‡</td>
</tr>
<tr>
<td></td>
<td>H/M</td>
<td>-0.39‡</td>
<td>-0.32‡</td>
<td></td>
</tr>
</tbody>
</table>

CVP indicates central venous pressure; SP, systolic pressure. Other abbreviations as in Table 2.

*P<0.05, †P<0.01, ‡P<0.001.
Neurohormonal Activities
NE and natriuretic peptides are good guides for stratification and prognosis in adult heart failure patients. Bolger et al reported on the NHA indices and their association with hemodynamics and functional capacity in adult CHD. Our study confirms their findings and expands them into child CHD. Moreover, significant elevation of natriuretic peptides could identify the decreased cardiovascular reserve in asymptomatic patients. However, we should pay attention to the significant inverse correlation between age and natriuretic peptide levels and a significantly high value of ANP in the child NYHA I patients compared with the comparable adult patients. A possible beneficial role of ANP on pulmonary gas exchange may work as a compensatory mechanism in child CHD patients with a small VC. In addition, we should be aware that the magnitude of increase in natriuretic peptides may be lower in CHD patients than those in functionally comparable DCM patients or levels reported in adult heart failure patients. High central venous and right ventricular end-diastolic pressures without significant difference in functional class or EF implies that postoperative CHD patients have some restrictive hemodynamics. In addition to restrictive change in the pericardium because of adhesions and pericardial fibrosis, myocardial fibrosis caused by hypoxia and volume and/or pressure overload existing before definitive repair cause ventricular diastolic abnormalities. These conditions may result in a high central venous and both ventricular end-diastolic pressures without a proportional increase in ventricular wall stress.

Although NE differentiates adult CHD patients in NYHA II from those in NYHA III+IV, the difference in NE was not significant in the child CHD patients. Sympathetic nervous activation may be more important in regulating severely impaired hemodynamics in the adult than in the child patients. PRA is not related to the severity of functional class but is related to the use of diuretics as in adult heart failure patients.

Cardiac Autonomic Nervous Activity
CANA indices are prognostic guides in patients after myocardial infarction and with heart failure. However, the benefit of HRV in patients with severe disease may be small, and our data support this idea because CANA did not stratify the symptomatic groups, especially in the child CHD patients. In contrast, CANA indices are useful to classify asymptomatic to moderately ill patients, and cardiac surgeries had a significant influence on BRS. Interestingly, HRV was associated with not only EF but also VC. Surgery-related restrictive ventilatory change is inevitable, although the magnitude varies widely. A smaller tidal volume reduces HRV because of reduced respiratory cyclic inhibition of the central parasympathetic outflow to the heart and may result in a sympathoexcitation even in CHD patients as it does in adult heart failure patients.

Greater HRV and BRS in the adult CHD patients in NYHA I and II imply that a possible future parasympathetic reinnervation and larger VC may also contribute to greater HRV and BRS. However, according to the comparison of postoperative CHD and DCM patients, surgeries have a greater impact on CANA abnormalities than do hemodynamics.

Exercise Variables and VC
We confirmed the value of pV̇O₂ in both child and adult CHD patients. VC classifies asymptomatic and moderate patients and the V̇E/V̇CO₂ slope for relatively severe patients.

Clinical Implications
Natriuretic peptides, HRV, and BRS are useful to stratify CHD patients in NYHA classes I and II, including mass screening for control subjects, and the latter parasympathetic indices are especially useful for asymptomatic patients with reduced cardiac reserve. The clinically significant difference between HRV and BRS may be small in normal subjects and cardiac patients without a history of surgeries. However, BRS may be more advantageous than HRV in child postoperative CHD patients, especially those with restrictive pulmonary physiology. The parasympathetic indices are, to some extent, useful when they are applied to symptomatic adult CHD patients. Conversely, NHA indices, especially BNP, are more valuable to stratify severe symptomatic patients because they sometimes show no significant change in EF or CANA despite significant improvement of clinical symptoms. However, MIBG imaging is not an appropriate measure to classify CHD patients because of frequent denervation caused by cardiac surgeries. Our present study is summarized in Figure 4. We should always keep these relationships in mind and
choose the appropriate measurement in the right patients. Special attention should also be paid to the shaded area, ie, the influence of “cardiopulmonary restrictive physiology,” resulting from cardiac surgeries and/or the nature of CHD itself on these measurements, especially the CANA indices. Adding CANA and NHA indices to conventional parameters is very advantageous for objective assessment of stable postoperative CHD patients.

Another clinical implication is that an enhancement of HRV and BRS because of some intervention like exercise training may reduce the risks of future cardiac events, including the preventive role of parasympathetic modulation for the cardiac arrhythmias that are now becoming of great concern in adult CHD patients.28

Study Limitations
The diversity of the patient groups may be our major limitation. For example, CANA damage after the Ross or arterial switch operation is obviously different from that after right ventricular outflow tract reconstruction, because the former procedures include a direct cut of the cardiopulmonary nerves. Therefore, it would be ideal and important to analyze each specific CHD condition, and the analysis should provide us with good guides to plan sophisticated strategies to manage CHD patients. Another limitation is that our control subjects are not entirely normal and that microangiitis may exist even when there is no overt aneurysm, and this may have some influence on CANA and/or NHA.

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References


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