Abnormalities of Neurohormonal and Cardiac Autonomic Nervous Activities Relate Poorly to Functional Status in Fontan Patients

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Background—Impaired cardiac autonomic nervous activities and increased neurohumoral activities (CANA, NHA) characterize Fontan patients. However, the clinical significance of these changes is not clearly understood. Our purpose was to clarify the clinical significance of the CANA and NHA in stable Fontan patients.

Methods and Results—We divided 22 atriopulmonary connection (APC) and 75 total cavopulmonary connection (TCPC) patients into 4 subgroups according to New York Heart Association (NYHA) class (1.8±0.6) and measured various CANA and NHA indices. All NHA indices were elevated in the symptomatic patients (P<0.001). Natriuretic peptides were higher in the APC than in the TCPC patients, and the hemodynamics showed no correlation with brain natriuretic peptide in the APC patients. Low arterial oxygen saturation and impaired hemodynamics greatly influenced all elevated NHA indices (P<0.01), except for plasma renin activity, in the TCPC patients. Impaired CANA indices did not relate to NYHA class, although surgeries were associated with lower heart rate variability. In addition to poor correlation between NHA and CANA, age and ventricular morphology had no impact on all CANA and NHA indices, except for high norepinephrine in right ventricular Fontan patients.

Conclusions—Although symptomatic Fontan patients exhibit higher NHA, CANA is not related to either NYHA class or NHA. APC itself is responsible for higher natriuretic peptides, and arterial oxygen desaturation has a great impact on elevated NHA in the TCPC patients. These characteristics of the NHA and CANA differ from those of heart failure patients with biventricular physiology. (Circulation. 2004;110:2601-2608.)

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

activated neurohumoral activity (NHA), impaired cardiac autonomic nervous activity (CANA), and low cardiac output and reduced exercise capacity characterize Fontan patients.1–4 These changes resemble those in adult patients with chronic heart failure (CHF) and NHA and CANA have been useful in stratifying these adult CHF patients and predicting their prognosis.5–10 These 2 indices are also, to some extent, applicable to postoperative patients with congenital heart disease after biventricular repair, especially in adult patients.11 However, comprehensive evaluation of Fontan patients using NHA and CANA has not been undertaken. Our hypothesis was that relationships between these 2 indices and clinical status in Fontan patients with unique single-ventricular physiology might differ from those in biventricular physiology. In addition, we thought that the type of repair and ventricular morphology and surgery-related damage might influence these 2 indices. Therefore, the purpose of the present study was to measure various NHA and CANA indices and compare the results with clinical status, including hemodynamic and cardiopulmonary capacity.

Methods

Subjects
We studied prospectively 97 clinically stable Fontan patients (2 to 34 years old) and 48 control subjects. Clinical stability meant that patients were free from intravenous medications with no major change of oral medications, and the postoperative follow-up period was at least 4 months. Of the Fontan patients, a total cavopulmonary connection (TCPC) was created in 75 and an atriopulmonary connection (APC) in 22 (Table 1). All patients had undergone cardiac catheterization within the previous 1 year. Recently, our follow-up policy has included cardiac catheterization every 5 years after the operation to evaluate hemodynamics and exercise performance unless the patient had significant neurological or orthopedic complications. Of the present Fontan patients, there were no patients with sick sinus syndrome or possible renal dysfunction (creatinine >1.0). A patient with tricuspid atresia (20 years old) who had a ventricular tachycardia easily induced during exercise was excluded from the study. We divided our patients into 2 groups according to age <16 years (low-age group, 11±3 years old, n=63) and age ≥16 years (high-age group, 19±5 years old, n=34). Medications included digoxin (n=11), diuretics (n=49), anticoagulant agents (n=56), ACE inhibitors (n=8), antiarrhythmics (n=2), and

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2601
The total number of surgical procedures including the Fontan operation ranged from 1 to 6 (mean, 2.6 operations per patient). Operations before the Fontan included systemic-to-pulmonary shunt(s) (n=59), pulmonary arterial banding (n=23), Glenn anastomosis (n=22), and atrioventricular valvuloplasty or valve replacement (n=13). Fenestration was created in 5 patients at the time of the Fontan operation and spontaneously closed in 2 patients 1 year after the operation. The age-matched control subjects were being followed up at our institute because of a history of coronary artery dilatation, aneurysm, or both because of Kawasaki disease, and all underwent follow-up selective coronary angiography to evaluate possible stenosis of the coronary arteries. Our control subjects showed no significant stenotic lesions of the coronary arteries.1,5

Postoperative Status Based on 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.12
Hemodynamics, Ventricular Morphology, and Calculation of Volume
Cardiac catheterization was performed in 95 patients and 46 control subjects within 1 week of exercise testing. We measured pressures in the cardiac chambers and great vessels. We estimated oxygen consumption from the age, sex, and heart rate (HR) and measured cardiac index (L · min⁻¹ · m⁻²) using the Fick principle with the assumption that right and left pulmonary arterial saturations were equal in patients with either a Glenn anastomosis or a TCPC, because it is clinically difficult to measure accurate flow distribution of the bilateral pulmonary arteries. Ventricular morphology was determined angiographically, and patients were divided into 3 groups,¹ ie, those with (1) a dominant left ventricle with or without a rudimentary right ventricle, (2) presence of both right and left ventricles, and (3) a dominant right ventricle with or without a rudimentary left ventricle. In this study, the groups consisted of 43, 19, and 35 patients, respectively. Patients with 2 ventricles in whom the volume of the smaller ventricle was either >30% of the main ventricle or was >50% of the predicted normal value were included in the biventricular group.¹ We used Simpson’s rule to estimate morphological right and left ventricular volumes. End-diastolic ventricular volume was divided by body surface area to obtain end-diastolic volume index (EDVI), and systemic ventricular ejection fraction (EF) was calculated.¹ ⁵

Neurohumoral Activities
After at least 15 minutes of supine rest, the plasma norepinephrine (NE) level,¹³ atrial and brain natriuretic peptides (ANP, BNP), and renin activity (PRA) were determined in 95, 96, and 94 Fontan patients, respectively, and in all control subjects.¹⁴–¹⁶ Plasma endothelin-1 (ET-1) was determined by radioimmunoassay in 62 Fontan patients and 22 control subjects.¹⁷

Heart Rate Variability and Arterial Baroreflex Sensitivity
Heart rate variability (HRV) and arterial baroreflex sensitivity (BRS) were measured in 138 and 132 patients, respectively. The methods have been reported previously.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. We used a bolus phenylephrine method to measure BRS (ms/mm Hg).¹⁸

[^123I]Metaiodobenzylguanidine (MIBG) Scintigraphy
The methodolgy for this index was identical to that previously reported.³ Metaiodobenzylguanidine (MIBG) scintigraphy was performed in 70 patients to evaluate myocardial adrenergic nervous activity. Myocardial images were acquired 4 hours after tracer injection, and the heart-to-mediastinal activity ratio (H/M) was calculated.

Pulmonary Function Tests
We measured vital capacity (VC, in liters) and percent forced expiratory volume in 1 second in 134 patients (Spirosif, SP-600, Fukuda Denshi), and VC was calculated as the percentage of the body height–predicted normal value for our institute.

Exercise Protocol
One hundred forty-two patients underwent symptom-limited treadmill exercise,¹⁹ and peak oxygen uptake (pV˙O₂) (m L · kg⁻¹ · min⁻¹) and systolic blood pressure were measured and calculated as the percentage of body weight–predicted normal value for our institute. We used a 12-lead ECG to determine HR. Ventilation and gas exchange were measured by use of a breath-by-breath method using a hot-wire anemometer (Riko AS500, Minato Medical Science) with a mass spectrometer (MG-300, Perkin Elmer). Minute ventilation versus carbon dioxide production slope (V˙E-V˙CO₂ slope) was determined and expressed as the percentage of our age- and sex-matched predicted normal values.

Informed Consent
Informed consent was obtained from all patients and/or their parents. We asked control subjects and/or their parents to participate as volunteers. The Ethics Committee of the National Cardiovascular Center approved the study protocol.

Statistical Analysis
Differences in hemodynamics, NHA, CANA, and exercise variables were evaluated using 1-way ANOVA with Bonferroni 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 categories were 48, 29, 58, and 10, respectively. Hemodynamics, NHA, CANA, and exercise variables for each category are shown in Table 2. Representative data according to NYHA classification are shown in the Figure.

Hemodynamics
Low cardiac output was observed in proportion to functional severity, whereas a low EF with increased EDVI and elevated central venous and pulmonary artery pressures was present in NYHA III+IV. When symptomatic patients (NYHA II–IV) were compared with asymptomatic patients (NYHA I), there was no difference in any index between low- and high-age groups, except for a lower cardiac index in the high-age group (P<0.05) (Figure). Cardiac index was higher and arterial oxygen saturation (SaO₂) was lower in the TCPC than in the APC patients (P<0.01).

Neurohumoral Activity
All NHA indices were elevated in proportion to functional capacity (P<0.001). BNP and NE in particular differentiated NYHA II from NYHA III+IV (P<0.01 to 0.001). Although all NHA indices were higher in the symptomatic patients than in the asymptomatic patients, no differences in these indices were observed between the asymptomatic patients and control subjects, except for ANP. Natriuretic peptides were higher in the APC than in the TCPC patients (P<0.001). There were no differences in NHA indices between low- and high-age groups.

Cardiac Autonomic Nervous Activity
All CANA indices were markedly abnormal; however, they could not differentiate these patients on the basis of their functional classification, except for H/M in NYHA class III+IV. Moreover, there was no difference in CANA indices between symptomatic and asymptomatic patients, between low- and high-age groups, or between the APC and the TCPC patients.
**TABLE 2.** Hemodynamics, Neurohormonal and Cardiac Autonomic Nervous Activities, and Cardiopulmonary Variables According to NYHA Functional Status in Fontan Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Control (n=48)</th>
<th>I (n=29)</th>
<th>II (n=58)</th>
<th>III+IV (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemodynamics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central venous pressure, mm Hg</td>
<td>3±1</td>
<td>11±3‡</td>
<td>12±3‡</td>
<td>14±4‡†‡</td>
</tr>
<tr>
<td>Pulmonary artery pressure, mm Hg</td>
<td>13±2</td>
<td>10±2‡</td>
<td>11±3‡</td>
<td>13±4‡</td>
</tr>
<tr>
<td>EDP, mm Hg</td>
<td>11±2</td>
<td>7±3‡</td>
<td>8±3‡</td>
<td>9±4</td>
</tr>
<tr>
<td>EF, %</td>
<td>65±8</td>
<td>55±11‡</td>
<td>52±11‡</td>
<td>38±16‡¶‡‡</td>
</tr>
<tr>
<td>EDVI, mL/m²</td>
<td>80±15</td>
<td>77±20</td>
<td>79±27</td>
<td>115±47‡¶‡‡</td>
</tr>
<tr>
<td>Cardiac index, L/min⁻¹·m⁻²</td>
<td>3.6±0.6</td>
<td>2.7±0.7‡</td>
<td>2.4±0.6‡§</td>
<td>2.1±0.5§</td>
</tr>
<tr>
<td>Arterial oxygen saturation, %</td>
<td>98±1</td>
<td>95±2‡</td>
<td>95±3‡</td>
<td>90±8‡¶‡‡</td>
</tr>
<tr>
<td><strong>Neurohormonal activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>158±71</td>
<td>205±76</td>
<td>256±130‡¶§</td>
<td>365±195‡¶‡‡</td>
</tr>
<tr>
<td>ANP, pg/mL</td>
<td>20±10</td>
<td>45±4*</td>
<td>68±53‡¶¶</td>
<td>95±83¶</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>5±4</td>
<td>24±27</td>
<td>43±62‡</td>
<td>127±148‡¶‡‡</td>
</tr>
<tr>
<td>PRA, ng·mL⁻¹·h⁻¹</td>
<td>3.0±2.2</td>
<td>5.3±3.2*</td>
<td>8.3±11.1‡</td>
<td>12.1±8.2‡†</td>
</tr>
<tr>
<td>ET-1, pg/mL</td>
<td>3.2±1.4</td>
<td>3.7±1.1</td>
<td>5.4±2.8‡§</td>
<td>7.2±5.6‡</td>
</tr>
<tr>
<td><strong>Cardiac autonomic nervous activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>log LF</td>
<td>2.6±0.4</td>
<td>1.7±0.5‡</td>
<td>1.5±0.6‡</td>
<td>1.5±0.4‡</td>
</tr>
<tr>
<td>log HF</td>
<td>2.5±0.5</td>
<td>1.4±0.6‡</td>
<td>1.2±0.5‡</td>
<td>1.3±0.6‡</td>
</tr>
<tr>
<td>BRS</td>
<td>17.5±5.9</td>
<td>3.8±3.5‡</td>
<td>3.0±3.0‡</td>
<td>1.9±2.2‡</td>
</tr>
<tr>
<td>H/M</td>
<td>2.9±0.5</td>
<td>1.8±0.3‡</td>
<td>1.7±0.4‡</td>
<td>1.4±0.5§</td>
</tr>
<tr>
<td>Exercise variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak VO₂, % predicted</td>
<td>96±13</td>
<td>60±8‡</td>
<td>50±7‡¶</td>
<td>36±61¶‡‡‡</td>
</tr>
<tr>
<td>Ve-VO₂ slope, % predicted</td>
<td>99±13</td>
<td>125±21‡</td>
<td>135±24‡¶§</td>
<td>168±54‡¶‡‡</td>
</tr>
<tr>
<td><strong>Pulmonary function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital capacity, % predicted</td>
<td>99±14</td>
<td>76±16‡</td>
<td>70±17‡</td>
<td>57±10‡¶</td>
</tr>
<tr>
<td>Forced expired volume in 1 sec, %</td>
<td>91±8</td>
<td>89±6</td>
<td>88±7</td>
<td>86±9</td>
</tr>
</tbody>
</table>

Vital Capacity
VC was small in all Fontan groups, especially in the III+IV patients, whereas their percent forced expiratory volume in 1 second was maintained. However, no significant difference in pulmonary function was observed between low- and high-age groups or between the APC and TCPC patients.

Exercise Variables
Although there was no difference between the low- and high-age groups or the APC and the TCPC patients, pVO₂ decreased and Ve-VO₂ slope increased in proportion to NYHA classification (P<0.001).

Correlation Between NHA and CANA
Relationships between NHA and CANA indices are shown in Table 3. NE correlated weakly with PRA and H/M. Natriuretic peptides and ET-1 correlated well with each other; however, relationships between NHA and CANA indices were either weak or nonexistent. BRS correlated closely with HRV, whereas no correlation between H/M and HRV or BRS was observed, except for log LF. Although NE, BNP, and ET-1 correlated inversely with pVO₂, only H/M showed a weak positive correlation with pVO₂.

Multivariate Analysis
To determine the independent factors, the following parameters were used: age at tests and definitive repair, sex, follow-up period, number of surgeries, hemodynamics, VC, medications (diuretics), and exercise capacity (Table 4).

New York Heart Association
High BNP and low EF were major determinants of low NYHA class in all Fontan patients (P<0.0001). When the TCPC patients were analyzed separately, ANP and EF were the major determinants of NYHA classification.
**Neurohumoral Activity**
A high NE was determined by high age at operation and large EDVI ($P<0.01$). Both high natriuretic peptides were determined by the repair of APC, large EDVI, low Sao$_2$, and low cardiac output ($P<0.0001$). Male sex also determined high ANP. High PRA depended on the use of diuretics and low aortic blood pressure ($P<0.0001$) and high ET-1 on low cardiac output and low VC ($P<0.01$).

When the APC patients were analyzed, although low cardiac output and high ventricular end-diastolic pressure correlated with high ANP ($P<0.01$), no other indices were associated with high natriuretic peptides, except for use of diuretics for high PRA and ET-1 ($P<0.05$). When the TCPC patients were analyzed, high age at exercise and low Sao$_2$ correlated with high NE ($P<0.005$). Low Sao$_2$ also correlated with high natriuretic peptides and ET-1. In addition, low cardiac output and large EDVI were associated with high ANP and BNP, respectively. High PRA was determined by low arterial pressure and the use of diuretics ($P<0.0001$). Higher age at repair, short follow-up duration, and the use of diuretics were associated with high ET-1.

**Autonomic Nervous Activity**
A large number of surgical procedures, APC type repair, and low cardiac output correlated with low log LF and HF ($P<0.005$ for both). BRS was determined by low cardiac output and VC ($P<0.005$). Only the use of diuretics correlated with low H/M ($P<0.01$).

In APC patients, a high EDP correlated with a low BRS ($P<0.05$), and a low H/M was determined by a large number

---

**Figure Legends**

1. **EF (%)**
   - Control
   - Asymptomatic
   - Symptomatic

2. **CI (l/min/m$^2$)**
   - Control
   - Asymptomatic
   - Symptomatic

3. **pVO$_2$ (%)**
   - Control
   - Asymptomatic
   - Symptomatic

4. **NE (pg/ml)**
   - Control
   - Asymptomatic
   - Symptomatic

5. **ANP (pg/ml)**
   - Control
   - Asymptomatic
   - Symptomatic

6. **BNP (pg/ml)**
   - Control
   - Asymptomatic
   - Symptomatic

7. **Log HF**
   - Control
   - Asymptomatic
   - Symptomatic

8. **H/M (%)**
   - Control
   - Asymptomatic
   - Symptomatic

9. **BRS (ms/mmHg)**
   - Control
   - Asymptomatic
   - Symptomatic

Relationship between categorized groups according to symptom-based classification and clinical variables. Abbreviations as in Table 2. CI indicates cardiac index. White, shaded, and black bars represent control subjects, APC, and TCPC patients, respectively. *$P<0.05$, **$P<0.01$, and ***$P<0.001$ versus APC patients.
of surgical procedures and high central venous pressure \( (P<0.001) \). For the TCPC patients, only a large number of surgical procedures correlated with low HRV and BRS \( (P<0.001) \), whereas a longer follow-up period was associated with high H/M \( (P<0.05) \).

**Vital Capacity**

In addition to low \( \text{Sa}_O_2 \) and higher age at Fontan repair, a large number of surgical procedures correlated with a low VC \( (P<0.0001) \).

**\( V\dot{E}/V\dot{CO}_2 \) Slope**

High NE and low EF and \( \text{Sa}_O_2 \) correlated with a high \( V\dot{E}/V\dot{CO}_2 \) slope \( (P<0.001) \).

**Subgroup Analysis**

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

Of 29 Fontan patients in NYHA I, 9 and 14 patients showed high ANP (>40 pg/mL) and BNP (>13 pg/mL), respectively. However, no differences in cardiovascular reserve (peak HR, systolic blood pressure, \( \text{pVO}_2 \), including VC) were observed between the high natriuretic peptide and the normal-range patients. The percentage of patients receiving diuretics was not different between the 2 groups.

**Influence of Ventricular Morphology on CANA and NHA**

NYHA class, EF, \( \text{Sa}_O_2 \), and \( \text{pVO}_2 \) were lower and \( V\dot{E}/V\dot{CO}_2 \) slope was higher in the right ventricular type than the left ventricular type Fontan patients (Table 5, \( P<0.05 \) to 0.0001). However, ventricular morphology had no influence on the CANA or NHA indices, except for higher NE in the right ventricular type group \( (P<0.05) \).

**Discussion**

We found that, in Fontan patients, (1) natriuretic peptides and EF were major determinants of NYHA status; (2) all NHA indices were elevated, although there was no difference between asymptomatic patients and control subjects; (3) APC

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**TABLE 3. Correlation Coefficients Between Neurohumoral and Cardiac Autonomic Nervous Activities in Fontan Patients**

<table>
<thead>
<tr>
<th>Neurohormonal Activity</th>
<th>Cardiac Autonomic Nervous Activity</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ANP</td>
<td>BNP</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>ANP</td>
<td>...</td>
<td>NS</td>
</tr>
<tr>
<td>BNP</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>PRA</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>ET-1</td>
<td>...</td>
<td>...</td>
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</table>

**Cardiac autonomic nervous activity**

<table>
<thead>
<tr>
<th>log LF</th>
<th>log HF</th>
<th>BRS</th>
<th>H/M</th>
<th>Peak ( \text{VO}_2 ), %</th>
</tr>
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<tbody>
<tr>
<td>...</td>
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<td>...</td>
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</tbody>
</table>

**TABLE 4. Major Determinants and Their Standard \( \beta \)-Coefficients for Neurohumoral and Cardiac Autonomic Nervous Activities**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Surgery</th>
<th>Hemodynamics</th>
<th>Medications</th>
<th>Lung</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Sex</td>
<td>Number</td>
<td>Age at Fontan</td>
<td>APC/TCPC</td>
</tr>
<tr>
<td>NE</td>
<td>0.23</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANP</td>
<td>−0.21</td>
<td>−0.60</td>
<td>−0.24</td>
<td>−0.34</td>
</tr>
<tr>
<td>BNP</td>
<td>−0.52</td>
<td>0.24</td>
<td></td>
<td>−0.34</td>
</tr>
<tr>
<td>PRA</td>
<td>−0.33</td>
<td>0.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ET-1</td>
<td>−0.35</td>
<td>0.24</td>
<td></td>
<td>0.24</td>
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<tr>
<td>log LF</td>
<td>−0.33</td>
<td>0.26</td>
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<td>0.22</td>
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<tr>
<td>log HF</td>
<td>−0.33</td>
<td>0.29</td>
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<td>0.31</td>
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<tr>
<td>BRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H/M</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>VC</td>
<td>−0.68</td>
<td>0.17</td>
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<td>0.17</td>
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<tr>
<td>( \dot{V}/\dot{CO}_2 )</td>
<td></td>
<td></td>
<td></td>
<td>−0.53</td>
</tr>
</tbody>
</table>

MAO indicates mean aortic pressure. Other abbreviations as in Table 2.
TABLE 5. Hemodynamics, Neurohormonal and Cardiac Autonomic Nervous Activities, and Cardiopulmonary Variables According to Systemic Ventricular Morphology

<table>
<thead>
<tr>
<th>Group</th>
<th>LV (n=43)</th>
<th>BV (n=19)</th>
<th>RV (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>14±5</td>
<td>14±6</td>
<td>14±5</td>
</tr>
<tr>
<td>NYHA class</td>
<td>1.6±0.5</td>
<td>1.9±0.7</td>
<td>2.0±0.7†</td>
</tr>
<tr>
<td>APC/TCPC</td>
<td>14/29</td>
<td>3/16</td>
<td>5/30</td>
</tr>
</tbody>
</table>

Hemodynamics

- Central venous pressure, mm Hg: 11±3, 12±3, 12±3
- EF, %: 55±12, 49±12, 48±13*<sup>†</sup>
- Cardiac index, L⋅min<sup>-1</sup>⋅m<sup>-2</sup>: 2.6±0.7, 2.5±0.5, 2.3±0.6
- Arterial oxygen saturation, %: 95±2, 95±2, 93±5*<sup>†</sup>

Neurohormonal activity

- Norepinephrine, pg/mL: 228±121, 234±112, 291±148*<sup>†</sup>
- ANP, pg/mL: 72±62, 51±48, 61±52
- BNP, pg/mL: 52±70, 38±60, 44±85

Cardiac autonomic nervous activity

- log HF: 1.2±0.6, 1.3±0.7, 1.3±0.5
- BRS: 2.9±3.3, 3.7±3.2, 3.0±3.0
- H/M: 1.7±0.3, 1.7±0.5, 1.7±0.4

Exercise variables

- Peak VO<sub>2</sub>, % predicted: 56±8, 50±12*<sup>†</sup>, 48±10‡

LV, BV, and RV indicate left, biventricular, and right ventricular type ventricle as a systemic ventricle, respectively. Other abbreviations as in previous tables. Values are mean±SD.

*<sup>P</sup>≤0.05, †<sup>P</sup>≤0.01, ‡<sup>P</sup>≤0.001 vs LV.

itself was responsible for high natriuretic peptides, and decreased SaO<sub>2</sub> had a great impact on the elevated NHA in the TCPC patients; and (4) although cardiac surgeries were related to CANA, impaired CANA had no influence on NHA or NYHA status.

Neurohormonal Activities

Bolger et al<sup>20</sup> described the clinical use of NHA to stratify adult patients with congenital heart disease. However, it is not clear whether the relationship between NHA abnormalities and functional status applies to Fontan patients because of the wide variety of their diseases. Our study demonstrates that stratification based on the abnormal NHA is less significant in Fontan patients than has been reported in biventricular physiology patients, although symptomatic patients exhibit a high NHA. In fact, we could not find any difference in hemodynamics and cardiovascular reserve between asymptomatic patients with elevated NHA and those without. APC itself, rather than the hemodynamics, has a great impact on higher natriuretic peptides and ET-1. An increased secretion of BNP and ANP from the hypertrophied atrial myocardium in the APC patients may be responsible for the high natriuretic peptides.<sup>21</sup> Interestingly, SaO<sub>2</sub> has a significant impact on the elevated NHA in the TCPC patients. Resting (and maybe exercise-induced) decreased SaO<sub>2</sub> also causes sympathetic nervous activation<sup>22</sup> and excess ventilation,<sup>23</sup> and these are related to poor prognosis in adult heart failure patients.<sup>10</sup>

Moreover, in addition to sympathetic dominant CANA,<sup>24</sup> high natriuretic peptides may worsen the Fontan patients’ hypercoagulable state because of their diuretic effect.<sup>25</sup> The mechanism responsible for high ET-1 is unidentified in the present study, but the low pulmonary arterial oxygen saturation because of low cardiac output in addition to nonpulsatile flow may be an explanation.<sup>26</sup> The presence of a low systemic blood pressure and the use of diuretics imply that the renin-angiotensin system is important to maintaining perfusion pressure in these patients.

Cardiac Autonomic Nervous Activity

CANA indices are prognostic guides in patients after myocardial infarction<sup>8</sup> and with heart failure.<sup>9,27</sup> However, the benefit of HRV in severe patients may be slight,<sup>28</sup> and this is especially true in Fontan patients because of their severely impaired CANA.<sup>11</sup> In addition, the lack of a relationship between CANA and exercise capacity also makes clinical classification difficult. In contrast to biventricular patients,<sup>11</sup> the prolonged lack of reinnervation after the Fontan procedure may explain the absence of a difference in CANA indices between child and adult patients.<sup>5</sup> In addition to the influence of surgical technique, low cardiac output is associated with a lower HRV and BRS and high NHA; consequently, maintaining a good cardiac output is important in patients with Fontan physiology. Alternatively, the Fontan circulation per se may cause a low H/M, because even the NYHA I patients without significant elevation in NE showed a low value, and no correlation between surgical procedures and H/M was observed. The reason why the use of diuretics had a significant impact on the low H/M, as observed in the biventricular patients, is unclear in the present study.<sup>11</sup>

Exercise Variables and VC

Exercise capacity by definition determines the NYHA classification. VC distinguished the asymptomatic from the symptomatic patients, and the V<sub>En</sub>/V<sub>CO<sub>2</sub></sub> slope identified relatively severe patients.<sup>29</sup> Mismatched ventilation-perfusion in the lung and elevated dead space ventilation have been considered to be major determinants of the excess ventilation in Fontan patients. However, the significant arterial desaturation also has a great impact on the excess ventilation in these patients, as demonstrated in the present study.

Clinical Implications

Although natriuretic peptides and ventricular function stratify patients in line with their NYHA classification, we should be aware of the discrepancy between NHA and functional status, especially the lack of relationship between BNP and EF in the APC patients and the decreased sensitivity of NHA and CANA for detecting a reduced cardiovascular capacity. These present results imply that the diagnostic information from NHA and CANA indices cannot be applied to Fontan patients in the same manner as for patients with biventricular physiology.<sup>11</sup>

Nevertheless, considering the many clinical findings in adult cardiac patients, the abnormal physiological and biochemical findings in Fontan patients, even when they are asymptomatic, imply that they have a poor prognosis and suggest the need for treatment for these patients. In addition to congenitally determined factors (ventricular morphology,
function of the atrioventricular valve) and surgery-associated issues such as age at operation, functional status (NYHA class) is a possible determinant of their poor long-term prognosis. In this respect, nonsurgical interventions that focus on maintaining physical fitness through exercise training and medication to prevent deterioration in EF and NHA are rational. Furthermore, we need to follow the unique contributions of NHA and CANA to the long-term prognosis in these patients.

**Study Limitations**

Although we focused on Fontan patients, their surgical procedures varied from patient to patient. In addition, the structural anatomic variability in our study population is marked. However, a prospective randomized trial in these patients is clinically difficult and would require a very large number of patients. Another limitation is that our control subjects are not entirely normal; microangiitis may exist even when there is no apparent radiographic abnormality, and this may influence CANA or NHA or both.

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**References**

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