Abnormal Postexercise Cardiovascular Recovery and Its Determinants in Patients After Right Ventricular Outflow Tract Reconstruction

Hideo Ohuchi, MD; Hiroyuki Ohashi, MD; Jiksoo Park, MD; Johji Hayashi, MD; Aya Miyazaki, MD; Shigeyuki Echigo, MD

Background—Abnormal responses of heart rate (HR) and oxygen uptake ($\dot{V}O_2$) during exercise characterize patients after right ventricular outflow tract reconstruction (RVOTR) for congenital heart defects. However, little is known about the postexercise dynamics.

Methods and Results—We evaluated postexercise cardiovascular dynamics in 52 patients after closure of an atrioventricular septal defect (group A), 79 patients after RVOTR (group B), and 44 control subjects. HR variability, arterial baroreflex sensitivity (BRS), plasma norepinephrine, and hemodynamics were measured. Although there was no difference between group A and control subjects, declines in HR and $\dot{V}O_2$ after light and peak exercise and in systolic blood pressure (SBP) after peak exercise were delayed in group B. Age, low-frequency component of HR variability, and plasma norepinephrine were independent determinants of early HR decline. Peak SBP and $\dot{V}O_2$ had a great impact on the corresponding recoveries. When the peak values were excluded, body weight, BRS, and right ventricular ejection fraction were independent determinants of early SBP decline. BRS and the pulmonary artery resistance were independent determinants of $\dot{V}O_2$ decline throughout recovery, and age and right systolic ventricular pressure also determined the early $\dot{V}O_2$ decline. BRS and low-frequency component of HR variability were determined independently by the number of surgical procedures.

Conclusions—In RVOTR patients, in addition to metabolic and autonomic maturation, surgery-related abnormal cardiac autonomic nervous activity and impaired hemodynamics have a great impact on delayed postexercise cardiovascular recovery. (Circulation. 2002;106:2819-2826.)

Key Words: heart defects, congenital • nervous system, autonomic • exercise • blood pressure

Although abnormal cardiopulmonary responses during exercise are well documented in pediatric cardiac patients,1,2 there are few reports of postexercise dynamics and their determinants.3 In adult cardiac patients, heart rate (HR) recovery is closely related to cardiac vagal activity, and the recovery rate predicts future possible cardiac events.4 In addition, delayed recovery of systolic blood pressure (SBP) and oxygen uptake ($\dot{V}O_2$) related to the severity of heart failure, whereas increased sympathetic nervous activity delays SBP decline.5,6 A recent study demonstrated abnormal cardiac autonomic nervous activity (CANA) in patients with congenital heart disease after right ventricular outflow tract reconstruction (RVOTR), which is a common procedure in congenital heart disease.2 Our hypothesis was that abnormal CANA must have a significant impact on the postexercise dynamics in RVOTR patients; therefore, our purpose in the present study was to evaluate postexercise cardiovascular dynamics and their relation to CANA and hemodynamics in RVOTR patients.

Methods

Subjects
We studied 175 subjects, who were divided into 3 groups (Table 1). Group A consisted of 52 patients who had undergone closure of an atrial or ventricular septal defect. Group B consisted of 79 RVOTR patients (67 tetralogy of Fallot, 12 double-outlet right ventricle), 30 of whom were considered to have a hemodynamically excellent result (excellent group), whereas the other 49 patients had hemodynamic problems, as described below (impaired group). In both groups, the follow-up period from the last operation to the time of study was ≥1 year. Fourteen RVOTR patients with major aortopulmonary collateral arteries were included in this study. The control group consisted of 44 patients with a history of Kawasaki disease but no stenotic coronary arterial lesions. None of the control subjects had abnormal findings on physical examination, chest radiograph, ECG, or treadmill exercise test. Repeat RVOTR had been performed in 30 RVOTR patients. Digoxin, diuretics, and antiplatelet agents were given to 2, 12, and 14 RVOTR patients, respectively, and no patients were receiving inotropic (except digoxin), chronotropic, or antiarrhythmic medications or ACE inhibitor.
Cardiac Catheterization and Hemodynamics

Within 1 week of exercise testing, cardiac catheterization with cineventriculography was performed in 32 group A and 28 repeat RVOTR patients to evaluate postoperative hemodynamics. The remaining 31 RVOTR patients underwent this test to evaluate possible RVOT stenosis, and 34 control subjects underwent follow-up selective coronary angiography. We measured pressures in the cardiac chambers and great vessels. Oxygen consumption was determined by high-performance liquid chromatography. The plasma levels of atrial and brain natriuretic peptides were assayed by radioimmunoassay.

Measurement of Norepinephrine and Natriuretic Peptides

After ≥30 minutes rest, the plasma norepinephrine level was determined by high-performance liquid chromatography. The plasma levels of atrial and brain natriuretic peptides were assayed by radioimmunoassay.

Measurement of HR Variability and Arterial Baroreflex Sensitivity

The methodology for measuring HR variability (HRV) and arterial baroreflex sensitivity (BRS) was reported previously. Briefly, after a 10-minute supine rest, ECG signals were recorded for 5 minutes, and beat-to-beat fluctuations were transformed into frequency domain 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).

Exercise Protocol

Peak Exercise

All subjects underwent symptom-limited treadmill exercise using a 30-second incremental protocol, and endurance time (minutes) and peak VO2 (mL · kg⁻¹ · min⁻¹) were measured. After a 30-second walk-down period, the patients sat on a chair, and cardiopulmonary variables during the next 4 minutes were obtained.

A 12-lead ECG was used to determine HR. SBP was measured by palpation at rest and peak exercise and 1, 2, and 4 minutes after exercise, because it is difficult to measure SBP with a mercury

<table>
<thead>
<tr>
<th>TABLE 1. Clinical Characteristics of the Study Patients</th>
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<tbody>
<tr>
<td><strong>Patients, n</strong></td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Body weight, kg</td>
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<tr>
<td>Follow-up, y</td>
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<td>Disease (n)</td>
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<tr>
<th>Pulmonary function</th>
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<tr>
<td>Vital capacity, % of normal</td>
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<tr>
<td>Hemodynamics</td>
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<tr>
<td>Central venous pressure, mm Hg</td>
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<tr>
<td>RV systolic pressure, mm Hg</td>
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<tr>
<td>RV end-diastolic pressure, mm Hg</td>
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<tr>
<td>Pulmonary artery pressure, mm Hg</td>
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<tr>
<td>LV end-diastolic pressure, mm Hg</td>
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<tr>
<td>RV end-diastolic volume index, mL/m²</td>
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<tr>
<td>RV ejection fraction, %</td>
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<tr>
<td>LV ejection fraction, %</td>
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<tr>
<td>LV end-diastolic volume index, mL/m²</td>
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<tr>
<td>Cardiac index, L · min⁻¹ · m⁻²</td>
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<tr>
<td>Pulmonary artery resistance, U · m²</td>
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<tr>
<td>Systemic artery resistance, U · m²</td>
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<tr>
<td>Natriuretic peptides</td>
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<tr>
<td>Atrial natriuretic peptide, pg/mL</td>
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<td>Brain natriuretic peptide, pg/mL</td>
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ASD indicates atrial septal defect; VSD, ventricular septal defect; TF, tetralogy of Fallot; DORV, double-outlet right ventricle; Hx of KD, history of Kawasaki disease; LV, left ventricle; and RV, right ventricle. Values are mean ± SD.

*P < 0.05, †P < 0.01, and ‡P < 0.001 vs control; §P < 0.05, ||P < 0.01, and ¶P < 0.001 vs group A.
TABLE 2. Comparison of CANA and Exercise Variables Among the Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Group A (n)</th>
<th></th>
<th>Group B (n)</th>
<th></th>
<th>Control (n)</th>
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</thead>
<tbody>
<tr>
<td><strong>CANA</strong></td>
<td></td>
<td></td>
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<tr>
<td>log HF</td>
<td>2.0±0.4†</td>
<td>1.5±0.4§§</td>
<td>74</td>
<td>2.5±0.5</td>
<td>42</td>
</tr>
<tr>
<td>log LF</td>
<td>2.2±0.4†</td>
<td>1.8±0.5§§</td>
<td>74</td>
<td>2.6±0.4</td>
<td>42</td>
</tr>
<tr>
<td>BRS, ms/mm Hg</td>
<td>13.1±4.2‡</td>
<td>5.8±4.9§§</td>
<td>79</td>
<td>17.3±6.2</td>
<td>44</td>
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<tr>
<td>Plasma norepinephrine, pg/mL</td>
<td>140±60</td>
<td>163±96</td>
<td>79</td>
<td>162±72</td>
<td>44</td>
</tr>
<tr>
<td><strong>Exercise test</strong></td>
<td></td>
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<tr>
<td>Endurance time, min</td>
<td>9.4±0.9†</td>
<td>7.6±1.9§§</td>
<td>79</td>
<td>10.3±1.3</td>
<td>44</td>
</tr>
<tr>
<td>Peak gas exchange ratio</td>
<td>1.20±0.10</td>
<td>1.18±0.09</td>
<td>79</td>
<td>1.20±0.07</td>
<td>44</td>
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<tr>
<td>HR, bpm</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Rest</td>
<td>82±11</td>
<td>83±13</td>
<td>79</td>
<td>78±12</td>
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<tr>
<td>Peak</td>
<td>185±13</td>
<td>170±16§§</td>
<td>79</td>
<td>191±7</td>
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<tr>
<td>SBP, mm Hg</td>
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</tr>
<tr>
<td>Rest</td>
<td>106±9*</td>
<td>107±10†</td>
<td>79</td>
<td>111±9†</td>
<td>44</td>
</tr>
<tr>
<td>Peak</td>
<td>164±19</td>
<td>160±23†</td>
<td>79</td>
<td>174±19</td>
<td>44</td>
</tr>
<tr>
<td>V̇O₂, mL·kg⁻¹·min⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>5.3±1.1</td>
<td>5.0±1.0</td>
<td>79</td>
<td>5.3±1.1</td>
<td>44</td>
</tr>
<tr>
<td>Peak</td>
<td>38.5±4.8*</td>
<td>29.2±7.6§§</td>
<td>79</td>
<td>42.0±5.2</td>
<td>44</td>
</tr>
</tbody>
</table>

Groups as in Table 1.

*P<0.05, †P<0.01, and ‡P<0.001 vs control; §P<0.001 vs group A. Values are mean±SD.

Results

**Lung Volume, Hemodynamics, and Natriuretic Peptides**

Vital capacity was smaller in the patient groups, especially in group B, and most hemodynamic variables in group B were impaired compared with those of group A and control subjects. Significantly increased levels of natriuretic peptides indicated increased stress of the atria and/or ventricles in RVOTR patients (Table 1).

**Cardiac Autonomic Nervous Activity**

Although there was no significant difference in plasma norepinephrine, HRV and BRS were lower in patient groups, especially in group B, than in control subjects (Table 2). In group B, log LF and BRS were independently determined by the number of surgical procedures (BRS, P<0.001; log LF, P<0.05). Left ventricular ejection fraction and pulmonary artery pressure also determined log LF and log HF, respectively (P<0.01).

**Cardiovascular Variables During Exercise**

Endurance time and peak V̇O₂ were markedly lower in group B. Peak HR and SBP were also lower in group B than in control subjects (Table 2). Increases in HR and V̇O₂ were slightly lower in group A (P<0.05) and markedly lower in group B than in control subjects (P<0.0001). The SBP increase in group A did not differ from that of control subjects but was smaller in group B than in control subjects (P<0.01).

**HR, SBP, and V̇O₂ Recoveries After Peak Exercise**

HR, SBP, and V̇O₂ declines were lower in group B than the other 2 groups, except for the SBP decline 1 minute after exercise (Figure 1, a through c).
HR and VO₂ Recoveries After Constant-Load Exercise
Although there was no difference in HR or VO₂ at the end of exercise, the early declines in HR and VO₂ after exercise were smaller in RVOTR patients than in control subjects (Figure 2, a and b).

Respiratory Rate and Tidal Volume After Exercise
There were no differences in respiratory rate or the ratio of tidal volume to vital capacity at the end of constant-load and peak exercise tests. However, respiratory rate decline and the ratio in group B were significantly smaller (P<0.05 to 0.001) and higher (P<0.05 to 0.01), respectively, throughout the recovery period. Respiratory rate decline 30 seconds after constant-load exercise was also smaller (P<0.05) and the ratios throughout the recovery period were higher in RVOTR patients (P<0.05 to 0.001). Therefore, although a sufficient inflation of the lung occurred, faster respiration persisted because of the small vital capacity in RVOTR patients.

Comparison of Hemodynamically Excellent and Impaired Groups
Although peak HR tended to be higher in the excellent group than in the impaired group (P<0.1), there was no difference in HR or SBP decline (Figure 3, a and b). Peak VO₂ was higher in the excellent group (P<0.01), and VO₂ decline in the impaired group was slower (Figure 3c).

Comparison of Preserved and Impaired BRS Groups
The RVOTR group was divided into 39 BRS-preserved patients (BRS ≥5.3) and 40 BRS-impaired (BRS <5.3) patients. Peak HR, SBP, and VO₂ were higher in the preserved group than in the impaired group (P<0.01 to 0.001), and there were marked differences in each decline (Figure 4, a through c).

Cardiovascular Recovery and Related Factors
To investigate the major factors that determine cardiovascular recovery in 59 RVOTR patients who underwent cardiac catheterization, we compared the postexercise dynamics with clinical profiles (age at study and definitive operation, body weight, number of surgical procedures, follow-up period, HRV, BRS, plasma norepinephrine, pressures in each heart chamber and great vessel, ventricular volumes and ejection fraction, cardiac index, pulmonary and systemic vascular resistances, and vital capacity, as well as peak values of HR, SBP, and VO₂).

Figure 1. Changes in HR (ΔHR) (a), SBP (ΔSBP) (b), and VO₂ (ΔVO₂) (c) from peak to 4 minutes after exercise in groups A (closed circles), B (closed squares), and control subjects (open circles). #<0.1, *P<0.05, **P<0.01, and ***P<0.001 vs control subjects; !P<0.05, !!P<0.01, and !!!P<0.001 vs group A.

Figure 2. ΔHR (a) and ΔVO₂ (b) from peak to 4 minutes after constant-load exercise. Study groups are same as in Figure 1. *P<0.05, **P<0.01 vs control subjects.
Increases During Peak Exercise
HR increase from rest to peak exercise independently correlated positively with body weight, log LF, and left ventricular end-diastolic pressure and inversely with log HF, right ventricular systolic pressure, and pulmonary artery resistance ($P<0.05$ to $0.001$). The SBP increase correlated positively with body weight and BRS and inversely with plasma norepinephrine, right ventricular systolic pressure, and age at study ($P<0.01$ to $0.001$). The $V\dot{O}_2$ increase correlated positively with BRS and inversely with right ventricular systolic pressure and pulmonary artery resistance ($P<0.05$ to $0.001$).

Declines After Peak Exercise
Independent determinants of cardiovascular variables after peak exercise are summarized in Table 3 on the basis of a stepwise multivariate linear regression analysis.

Heart Rate
Log LF and age at exercise as well as plasma norepinephrine had a great influence on early and late HR decline. When the peak HR was excluded, the determinants of HR declines were almost the same except for log HF instead of plasma norepinephrine at 4 minutes after peak exercise.

Systolic Blood Pressure
Peak SBP independently determined SBP declines throughout the recovery period, and BRS as well as peak SBP also determined SBP declines at 2 and 4 minutes after peak exercise. When the peak SBP was excluded, although the immediate SBP decline was determined by body weight, BRS still had a significant impact on SBP declines at 2 and 4 minutes after peak exercise.

Oxygen Uptake
Peak $V\dot{O}_2$ independently determined $V\dot{O}_2$ declines throughout the recovery period. When the peak $V\dot{O}_2$ was excluded, BRS and right-sided hemodynamics (right ventricular systolic pressure, pulmonary artery resistance) determined $V\dot{O}_2$ declines throughout the recovery period. Age and body weight at study also independently determined $V\dot{O}_2$ decline at 2 minutes after exercise.

Figure 3. $\Delta$HR (a), $\Delta$SBP (b), and $\Delta$V\dot{O}_2 (c) from peak to 4 minutes after exercise in excellent (open squares) and impaired groups (closed squares). *$P<0.1$, **$P<0.05$, and ***$P<0.01$ vs excellent group.

Figure 4. $\Delta$HR (a), $\Delta$SBP (b), and $\Delta$V\dot{O}_2 (c) from peak to 4 minutes after exercise in BRS-preserved (open squares) and BRS-impaired (closed squares) groups. *$P<0.1$, **$P<0.01$, and ***$P<0.001$ vs BRS-preserved group.
Changes After Constant-Load Exercise
In the RVOTR group, HR decline 30 seconds after constant-load exercise correlated inversely with log LF (P<0.05) and tended to correlate with log HF (P<0.1). VO₂ decline 30 seconds after constant-load exercise correlated inversely with peak VO₂ (r = −0.66, P<0.05).

Discussion
HR Recovery
CANA has a great impact on HR recovery in healthy children and adults,13,14 whereas delayed recovery typifies patients with heart failure.5,14 Early HR recovery in RVOTR patients was closely associated with age and log LF in the present study. The origin of the LF component of HRV is controversial, and a tight relationship to vagal activity as it does in control subjects with normal pulmonary function. Therefore, LF rather than HF might be clinically useful to evaluate CANA status in RVOTR patients.

VO₂ Recovery
Metabolic immaturity in skeletal muscle delays VO₂ recovery in healthy children19; therefore, aging influences VO₂ recovery even in our RVOTR patients. Oxygen debt during exercise is related to VO₂ recovery,20 and the debt becomes greater in patients with heart failure because of redistribution of cardiac output to working muscle.21 Therefore, it is predictable that peak VO₂ is the main determinant of VO₂ recovery. Despite the absence of clinical symptoms, delayed VO₂ decline after even light exercise indicates that the redistribution mechanism as a compensatory adaptation always occurs, especially in RVOTR patients with impaired hemodynamics. The reason why BRS correlated with VO₂ recovery may be that this index was associated with an increase in VO₂ during exercise (P<0.0001).

SBP Response
Body weight has a great impact on SBP increase and delayed SBP decline immediately after exercise in the present walking exercise. Although the mechanism for this relationship is unclear,22 weight control is important for these RVOTR patients to reduce cardiac load during daily life.

Reduced cardiac output reserve and a contribution of plasma norepinephrine to vasoconstriction may have resulted in an inverse correlation between plasma norepinephrine and SBP increase during exercise. The mechanism of the influences of BRS and right ventricular systolic pressure on the SBP increase may be because these 2 factors are independent determinants of VO₂ increase, ie, the increase in cardiac output during exercise.
The fact that plasma norepinephrine at rest was not associated with SBP recovery as it is in patients with heart failure suggests that mechanisms other than sympathetic activation may be important in the delayed SBP decline in RVOTR patients. Arterial and cardiopulmonary baroreflex functions are important regulators of forearm and splanchnic vascular resistances, respectively, and an inhibitory cardiopulmonary–carotid cardiopulmonary interaction is also present in humans. Moreover, arterial baroreflex function may be crucial during upright posture. Probably, most RVOTR patients have impaired cardiopulmonary baroreflex function because they usually have an impaired BRS, and both impairments occur in patients with heart failure and in those after cardiac transplantation. Because body negative pressure produces a systemic vasoconstriction, a transient rise in blood pressure caused by increased cardiac venous return immediately after exercise could stimulate both arterial and cardiopulmonary baroreceptors, causing systemic vasodilation. Therefore, an inverse correlation between the SBP decline and BRS implies that an impaired baroreflex-mediated vasodilation has a significant role in the delayed postexercise SBP decline.

Another possible explanation for delayed SBP recovery is endothelial dysfunction. Because natriuretic peptides were elevated, mechanisms that occur in patients with heart failure, such as impaired nitric oxide–dependent vasodilation, may be partially responsible for the delayed SBP recovery in the RVOTR patients.

The fact that delayed SBP recovery is not related to peak VO$_2$, but is to BRS, suggests that SBP decline after exercise is determined by surgery-related CANA, not totally by pathophysiological adaptation. Because adequate postexercise perfusion pressure is crucial for oxygen delivery, impaired BRS may help prevent rapid falls in SBP after exercise in RVOTR patients.

Although mechanisms for the relationship between low right ventricular contractility and postexercise SBP delay are unclear, right-sided hemodynamic impairments also have a certain impact on postexercise SBP recovery.

**Study Limitations**

First, our control subjects cannot be considered to be entirely normal. However, when a group of post-Kawasaki patients with significant coronary artery lesions was compared with healthy subjects, no significant difference in their cardiorespiratory response to exercise was found; therefore, we believe that our present data are comparable to those from normal healthy subjects. A second limitation is the accuracy of measuring SBP during exercise; however, we believe that our data are clinically reliable because of a tight correlation with the conventional method described above. Finally, because our subjects include a large number of repeat RVOTR patients and those with major aortopulmonary collateral arteries, hemodynamic influences may be more important than in the usual RVOTR patients. If so, CANA might have much greater impact on postexercise cardiovascular dynamics in RVOTR patients with good hemodynamics. In fact, the difference in postexercise cardiovascular dynamics is more apparent when the comparison is made using BRS rather than hemodynamic status (Figure 4).

**Conclusions**

Postexercise cardiovascular recovery is delayed in most RVOTR patients. In addition to metabolic and autonomic maturation, surgery-related abnormal CANA plays an important role. In addition to right-sided impaired hemodynamics, we always should take maturity and surgery-related impaired CANA into consideration when RVOTR patients are evaluated by use of postexercise cardiovascular dynamics.

**Acknowledgments**

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**References**


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