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Responses of Plasma Norepinephrine and Heart Rate During Exercise in Patients After Fontan Operation and Patients with Residual Right Ventricular Outflow Tract Obstruction After Definitive Reconstruction

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Abstract. To determine the exercise responses of patients with congenital heart disease, 20 patients—5 who had undergone a right ventricular outflow tract reconstruction (group R; age, 15 ± 2 years), eight who had undergone a Fontan operation (group F; age, 13 ± 2 years), and seven who had a history of Kawasaki disease (group C; age, 15 ± 1 years)—performed a treadmill exercise test. Patients of group R had a significant residual right ventricular outflow obstruction. Oxygen uptake ($\dot{V}O_2$), heart rate (HR), and plasma norepinephrine (NE) concentrations were measured at rest, during warm-up, at ventilatory threshold (VT), and at peak exercise. Exercise capacity was determined as a percentage of the predicted normal peak $\dot{V}O_2$ (%$p\dot{V}O_2$). The %$p\dot{V}O_2$ for groups R and F was 65 ± 10 and 56 ± 11, respectively. Peak HR for groups R and F was 171 ± 4 and 155 ± 5, which were lower than the HR for group C ($p < 0.001$). Although NE concentrations at rest, during warm-up, and at VT were significantly greater in groups R and F ($p < 0.05$), there were no significant differences in the NE concentrations at peak exercise. Peak HR correlated with %$p\dot{V}O_2$ ($p < 0.001$). The ratio of the increase in HR to NE from rest to VT was significantly lower in groups R and F than in group C ($p < 0.001$) and correlated with %$p\dot{V}O_2$ ($r = 0.80$; $p < 0.001$). These data suggest that sympathetic nervous activity in groups R and F is increased at rest and during mild to moderate exercises, and reduced sinus node sensitivity to NE may be partly responsible for the abnormal HR response during exercise of patients with uncorrected congenital heart disease.

Key words: Exercise — Fontan — Right ventricular outflow tract reconstruction — Heart rate — Plasma norepinephrine

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Chronotropic incompetence (CI) has been reported by several investigators in patients with congenital heart disease (CHD) including tetralogy of Fallot, transposition of the great arteries, and functionally single ventricle [5, 11, 17, 22, 23–25, 33]. CI has also been documented in patients with congestive heart failure and has been considered an important factor affecting the exercise capacity of adult cardiac patients [2, 3, 7, 13, 34]. Although the definition of CI has not been well established, CI implies the inability of the heart rate (HR) to increase in proportion to metabolic demand. CI has been arbitrarily defined as a peak HR during exercise testing that is <80% of the age-predicted maximum [13, 34]. Sympathetic nervous activity, as well as parasympathetic nervous activity, plays an important role in modulating HR increases during exercise [28]. Because there are few reports in the literature concerning HR and norepinephrine (NE) responses to exercise in patients with CHD, we investigated both HR and NE responses in patients who had undergone right ventricular outflow tract reconstruction and a Fontan operation.

Materials and Methods

Patients

The study included eight patients who had undergone a Fontan operation (group F; mean age, 13 ± 5 years) for functionally single ventricle (four patients), tricuspid atresia (one patient), and other congenital cardiac anomalies (three patients). Group F included three patients who underwent atriopulmonary connection and five patients who underwent total cavopulmonary connection. The study also included five patients who had undergone a right ventricular outflow tract reconstruction (group R; mean age, 15 ± 4 years) for tetralogy of Fallot (four patients) and double outlet right ventricle (one patient). Age at definitive repair and follow-up periods in each group are shown in Table 1. Seven patients with a history of Kawasaki disease without stenotic coronary arterial lesions served as control subjects (group C; mean age, 15 ± 3 years). No patients were receiving digoxin, chronotropic agents, or diuretics at the time of inclusion in this study and no CHD patients had experienced postoperative brady- or tachyarrhythmias except for a rare single premature supraventricular or ventricular construction on

Table 1. Clinical characteristics of patients with congenital heart disease and control subjects

Characteristics	Control	Congenital heart disease	
	Group C	Group R	Group F
n	7	5	8
Age (years)	15 ± 1	15 ± 2	13 ± 2
Sex (male:female)	6;1	2;3	7;1
OP age (years)	—	8.0 ± 1.7	8.6 ± 4.2
Interval after OP (years)	—	7.5 ± 3.7	4.5 ± 2.2
CVP (mmHg)	2 ± 1	6 ± 2	10 ± 1
RVOTS (mmHg)	5 ± 1	42 ± 9	—
Systemic ventricle EF (%)	66 ± 2	56 ± 2	55 ± 4
Plasma NE (pg/ml, rest)	272 ± 34	407 ± 93	527 ± 69
VO_2 at VT (ml/kg/min) (% of normal)	23 ± 1 (102 ± 6)	17 ± 2 (78 ± 9)	16 ± 1 (67 ± 3)
Peak VO_2 (ml/kg/min) (% of normal)	44 ± 2 (98 ± 4)	27 ± 5 (65 ± 5)	27 ± 6 (56 ± 4)
R at peak exercise	1.18 ± 0.03	1.14 ± 0.02	1.14 ± 0.03
HCO_3 at peak exercise (mEq/L)	18.5 ± 0.8	19.1 ± 0.8	18.5 ± 1.0

VT, ventilatory threshold; CVP, central venous pressure; EF, ejection fraction; HCO3, bicarbonate; NE, norepinephrine; OP, definitive operation; R, gas exchange ratio; RVOTS, right ventricular outflow tract stenosis; VO_2, oxygen uptake. Values are mean ± SE.

24-hour ambulatory electrocardiographic monitoring. Routine postoperative cardiac catheterization was performed in all patients from group F as well as in two patients from group R. The severity of right ventricular outflow tract stenosis was estimated accurately in the remaining patients in group R and selective coronary angiography was performed in all patients in group C. The mean central venous pressure for group F was 10 mmHg and the mean pressure gradient across the right ventricular outflow tract for group R was 42 mmHg on average. Moderate aortic regurgitation was observed in one patient from group R and three patients in group R were supposed to undergo a repeat right ventricular outflow tract reconstruction. Cardiac catheterization and selective coronary angiography showed no hemodynamic abnormalities or stenotic coronary arterial lesions in all patients in group C. The standardized values for exercise capacity that were employed in this study were obtained from 125 subjects aged 5–24 years (65 males and 60 female patients). The weights and heights of these subjects were within the normal range for Japanese standards. This control population was categorized into two groups. One group consisted of patients with a history of Kawasaki disease and the other consisted of outpatients referred to our institute for evaluation of chest pain or discomfort. No control subjects demonstrated abnormal findings associated with cardiac lesions by physical examination, chest x-ray, electrocardiogram, two-dimensional echocardiogram, and treadmill exercise testing. These patients were therefore "healthy control subjects" and the normal values for exercise capacity from childhood to adolescence were estimated from these subjects [20, 26].

Exercise Protocol

A ramp-like progressive exercise test performed on a treadmill (Q-5000 system, Quinton, Seattle, USA) was utilized. We have previously demonstrated a high correlation between ventilatory acidosis threshold (VT) and lactate threshold using this treadmill test and have established its clinical usefulness for determining the VT as well as for evaluating cardiorespiratory tolerance in patients with CHD [19, 21]. An incremental protocol in which exercise intensity increased stepwise by 0.7 metabolic units every 30 seconds with completion of the incremental part of the exercise test in about 10 minutes was utilized. When selecting a slope of the oxygen uptake ($\dot{V}O_2$) as a function of work rate, a value of 3.5 ml/kg/min (= 1.0 metabolic unit) was used because of the difficulty determining this metabolic unit in children. After a 4-minute rest, the patients performed a 3-minute warm-up walk at a speed of 1.5 km/hr and then exercised with progressive intensity until exhausted. Twelve standard electrocardiographic leads were placed to monitor HR. Systolic blood pressure was measured every 2 minutes.

Gas Exchange Measurements

Ventilation and gas exchange were measured breath by breath. Subjects breathed through a mask connected to a hot-wire anemometer (Riko AS500, Minato Medical Science, Osaka, Japan) in order to continuously measure inspired and expired volume. A mass spectrometer (MG-300, Perkin–Elmer, St. Louis, MO, USA) was used for the continuous measurement of O_2 and CO_2 partial pressures. Two mask sizes were used: one for children between 120 and 150 cm tall, which had a dead space of 80 ml, and another for children taller than 150 cm, which had a dead space of 100 ml. In the breath-by-breath protocol, derived respiratory parameters, including respiratory rate, tidal volume, minute ventilation, ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$) and carbon dioxide ($\dot{V}E/\dot{V}CO_2$), and respiratory gas exchange ratio, were computed in real time and displayed with the HR and $\dot{V}O_2$ on a monitor. A personal computer (PC-9801, NEC, Tokyo, Japan) was used for data acquisition and storage. Breath-by-breath data were averaged for each 30-second period. The delay times and response characteristics for the O_2 and CO_2 analyzers were carefully checked before each exercise test.

The metabolic rate above which anaerobic metabolism occurs and leads to lactic acidosis corresponds to VT. This threshold was defined as the $\dot{V}O_2$ at which the $\dot{V}E/\dot{V}O_2$ and the end tidal pressure for O_2 increased without a rise in $\dot{V}E/\dot{V}CO_2$ and end tidal pressure for CO_2 [30].

Arterial Blood Gas Analyses and Plasma Norepinephrine

Arterial blood samples were taken from an indwelling 22 G angiocath placed in a brachial artery. Samples were taken at rest, 3 minutes after

warm-up walking began, at VT, and at peak exercise. Samples were held on ice until the time of analysis (≤20 minutes) for pH and HCO_3^- (ABL3 blood gas analyzer; Radiometer, Copenhagen, Denmark). These samples were then immediately spun in a refrigerated centrifuge and NE was measured by an automated catecholamine analyzer (HLC-725 CA, Tosoh, Tokyo, Japan). After sufficient explanation, all subjects had at least one experience of this exercise protocol before performing the actual test.

Informed consent was obtained from each subject and his or her parents. This protocol was in agreement with the guidelines of the Ethical Committee of the National Cardiovascular Center.

Statistical Analysis

Exercise capacity was represented as a percentage of the predicted peak $\dot{V}O_2$ (%$p\dot{V}O_2$). All data are presented as the mean ± SE. Simple linear regression analysis was used to assess the relationships between the dependent and independent variables. Differences among the groups were evaluated by the nonparametric Mann–Whitney and Kruskal–Wallis test. A p value < 0.05 was considered statistically significant.

Results

Metabolic Acidosis During Progressive Exercise

%$p\dot{V}O_2$ in groups R and F was significantly lower than that in group C ($p < 0.001$) (Table 1). Because there was no difference between the values of the gas exchange ratio and the HCO_3^- at peak exercise, all patients had performed to maximal exercise. No significant change in HCO_3^- was noted between rest and the VT exercise level.

Relationship Between $\dot{V}O_2$ and HR During Exercise

HR increased almost linearly in relation to absolute $\dot{V}O_2$ in groups R, F, and C (Fig. 1). The slope of the relationships between HR and $\dot{V}O_2$ during the period from VT to peak exercise in groups R and F was slightly steeper when compared with that of group C. Although HR in groups R and F was higher at rest and at any given $\dot{V}O_2$ during exercise, the peak HR in groups R and F was significantly lower than that in group C ($p < 0.001$). %$p\dot{V}O_2$ correlated well with the peak HR for all study subjects ($r = 0.77$, $p < 0.001$) (Fig. 2) and also when the CHD patients were analyzed separately ($r = 0.63$, $p < 0.02$).

Relationship Between $\dot{V}O_2$ and NE During Exercise

NE increased almost linearly in relation to $\dot{V}O_2$ during the period from rest to the VT exercise level (Fig. 3).

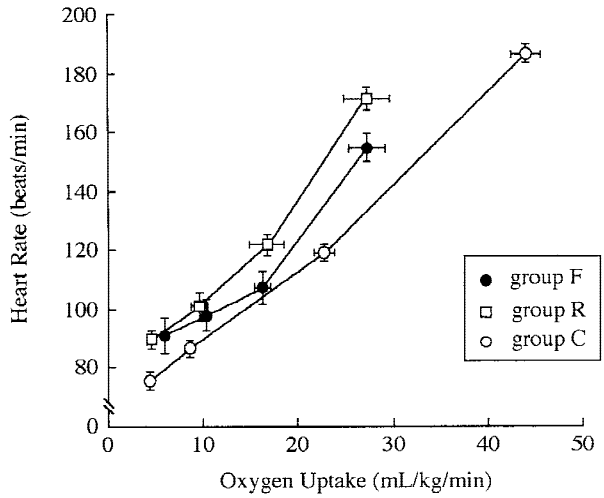

Fig. 1. Relationship between heart rate and oxygen uptake in the three study groups. Data points represent the values obtained at rest, during warm-up, at ventilatory threshold, and at peak exercise, respectively.

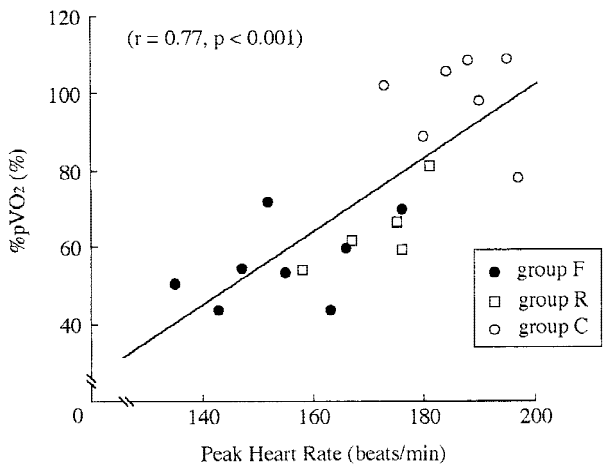

Fig. 2. Correlation between percentage of predicted normal peak oxygen uptake (%$p\dot{V}O_2$) and peak heart rate.

Above the VT level it increased rapidly in all groups. NE concentrations at rest, while warming up, and at VT in groups R and F were significantly higher than those in group C (rest; $p < 0.04$; warming up; $p < 0.02$; and VT; $p < 0.01$, respectively). However, there was no significant difference in NE concentration at peak exercise.

Relationship Between NE and HR During Exercise

HR and NE concentration increased linearly with time when the level of exercise was below the VT (Fig. 4). The slopes of the regression lines describing the association between changes in HR and NE from rest to VT

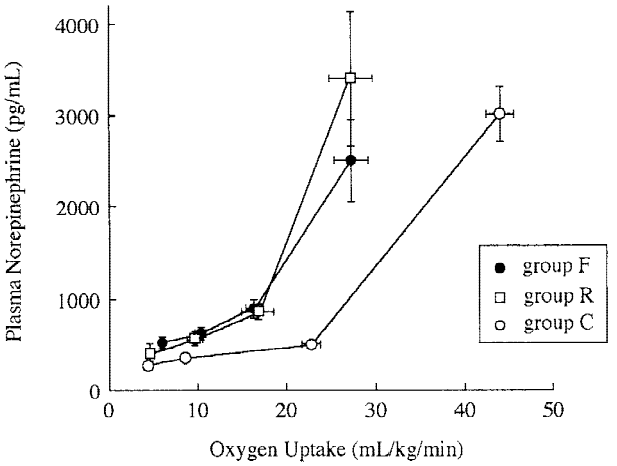

Fig. 3. Correlation between increase in heart rate (HR) and that in plasma norepinephrine (NE) concentration during the period from ventilatory threshold to peak exercise.

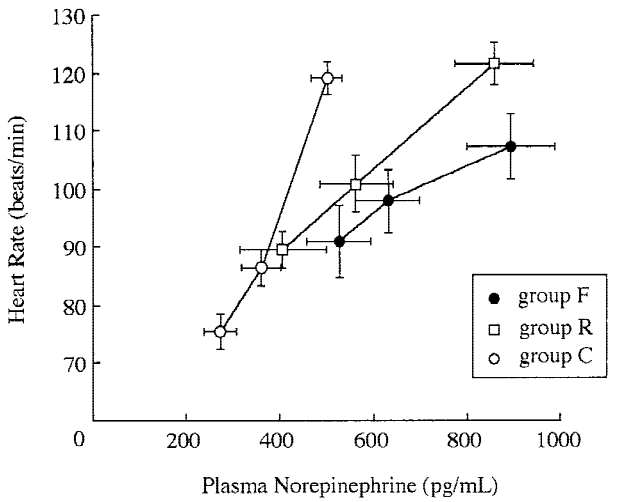

Fig. 4. Relationship between heart rate and plasma norepinephrine concentration in the three study groups. Data points represent the values obtained at rest, during warm-up, and at the ventilatory threshold exercise intensity, respectively.

were decreased in both CHD groups ($p < 0.001$; Table 2) and correlated with $\%p\dot{V}O_2$ ($r = 0.80$, $p < 0.001$). The ratios of the HR increase to the increase in NE concentration during the period from rest or VT to peak exercise were not significantly different between patients with CHD and group C. Although the increase in NE during these periods in groups R and F was not different from that of group C, the increase in HR during the period from rest to the VT tended to be less and that during the period from rest to peak exercise was significantly less than those for group C (rest to peak, $p < 0.001$; VT to peak, < 0.06, respectively; Table 2).

Discussion

The results of this study are in keeping with previous reports of CI in patients with CHD [5, 11, 17, 22, 23–25, 33]. Although a linear relationship between HR and $\dot{V}O_2$ during exercise has been demonstrated previously by several investigators [9, 27], there is great variation in the slope of the HR–$\dot{V}O_2$ relationship. In addition, this slope increases with worsening degrees of heart failure [16]. In this study, the slope of the relationship in groups R and F was similar to values reported in previous studies. If the degree of CI was evaluated using this relationship, CI was not observed. However, CI is likely to be present in these patients because the peak HR was significantly lower when compared to that of group C. Therefore, it may be impossible to quantitate the magnitude of CI based only on the HR–$\dot{V}O_2$ relationship during exercise.

Because the HR–$\dot{V}O_2$ relationship does not predict the true degree of CI, it is necessary to define CI as an inability of the sinus node to respond adequately to NE stimulation. NE release is considered an index of sympathetic nervous activity [4, 29]. Furthermore, NE concentration increases during exercise [14, 15, 31] and is augmented in patients with congestive heart failure [1, 8]. The exercise-induced increase in NE is closely related to the release of lactate and an abrupt increase in the NE concentration is observed above the lactic acidosis threshold [31]. Under acidotic conditions, an augmentation of the NE response has been reported during exercise [10, 12] despite no further increase in HR. Taking into account the linear HR–$\dot{V}O_2$ relationship above VT exercise intensities, the sinus node response to NE is impaired in the setting of the abrupt increase in NE above the VT exercise level.

In this study, the ratio of the HR increase to the increase in NE concentration during the period from VT to peak exercise in group C decreased to 14% of the ratio during the period from rest to VT. As a result, there was no significant difference in the ratio during the period from VT to peak exercise between the group of CHD patients and the control group. The ratio during the period from VT to peak exercise in groups R and F decreased to 37 and 86% of the corresponding ratios obtained during the period from rest to VT, respectively. Therefore, evaluation of CI based on data obtained at rest and peak exercise may be inadequate. Based on our findings, it may also be necessary to consider the degree of acidosis when evaluating the severity of CI during exercise.

A linear relationship between NE and HR during exercise below the level of VT has previously been reported [3, 31]. The NE–HR relationship has been demonstrated by a progressive increase in HR with isoproterenol infusion. This relationship was seen not only in

Table 2. Response of heart rate, plasma norepinephrine, and derived parameters in patients with congenital heart disease and in control subjects

Parameter	Control	Congenital heart disease		Significance
	Group C	Group R	Group F	
n	7	5	8	
Change of HR and NE below VT				
HR (rest-VT) (beats/min)	44 ± 2	32 ± 2	16 ± 2	$p < 0.001$
NE (rest-VT) (pg/mL)	231 ± 32	454 ± 47	369 ± 73	$p < 0.06$
HR (rest-VT) to NE (rest-VT) ratio	0.214 ± 0.021	0.075 ± 0.011	0.064 ± 0.016	$p < 0.001$
Change of HR and NE above VT				
HR (VT-P) (beats/min)	68 ± 3	50 ± 6	47 ± 7	$p < 0.06$
NE (VT-P) (pg/mL)	2527 ± 294	2541 ± 710	1613 ± 435	NS
HR (VT-P) to NE (VT-P) ratio	0.029 ± 0.003	0.024 ± 0.004	0.039 ± 0.008	NS
Change of HR and NE from rest to peak				
HR (rest-P) (beats/min)	111 ± 3	82 ± 6	64 ± 7	$p < 0.001$
NE (rest-P) (pg/mL)	2749 ± 303	2994 ± 688	1982 ± 424	NS
HR (rest-P) to NE (rest-P) ratio	0.044 ± 0.005	0.031 ± 0.004	0.041 ± 0.009	NS

VT, ventilatory threshold; HR, heart rate; NE, plasma norepinephrine; HR (rest-VT), increment in HR from rest to VT exercise level; HR (VT-P), increment in HR from VT to peak exercise; NE (rest-VT), increment in NE from rest to VT exercise level; NE (VT-P), increment in NE from VT to peak exercise; HR (rest-P), increment in HR from rest to peak exercise; NE (rest-P), increment in NE from rest to peak exercise. Values are mean ± SE.

normal volunteers but also in patients with heart failure [3]. It may therefore be important to evaluate the degree of CI below the VT level if CI is defined as the inability of the sinus node to respond adequately to NE. The magnitude of CI in adult patients with congestive heart failure is considered to be inversely proportional to the severity of heart failure. A reduced β-adrenergic receptor density is partially responsible for CI [7] and the decreased exercise capacity of patients with heart failure. It is therefore likely that the density of β-adrenergic receptors in patients from groups R and F was reduced as a result of increased sympathetic nervous activity.

It is also important to take into account parasympathetic nervous activity, which may participate in modulating HR increases at relatively low exercise intensities. Because parasympathetic nervous activity is minimal at the VT level of exercise [18], the increase in HR from rest to VT exercise must be influenced to a large extent by the basal parasympathetic nervous activity. The degree of parasympathetic contribution to HR variation seems to be less in patients with CHD because sympathetic nervous system activity is greater in patients with CHD of low exercise capacity when compared to control patients.

Because hypoxia or sinus node dysfunction following cardiac surgery can cause CI [5], it is possible that a surgical damage to sinus node during atriotomies or atriopulmonary connection contributes the lessened response of HR during exercise in patients of group F. Although the precise mechanism of CI remains unclear, because the peak HR in the CHD group was significantly lower than that for group C despite similar NE concentrations and similar degrees of acidosis at peak exercise, it is possible that reduced sinus node sensitivity to NE and reduced HR variation may be responsible for CI. This abnormality may also cause an inadequate cardiac output response in patients with CHD, as has been shown in experimental study in dogs with atrioventricular block [32].

Study Limitations

A normal HR response to exercise was defined, based on data obtained from patients with a past history of Kawasaki disease without stenotic coronary artery lesions. However, the patients with Kawasaki disease had similar cardiorespiratory responses to those of healthy control subjects during exercise testing [26]. We estimated sympathetic nervous activity based on NE concentrations, which is limited in terms of usefulness as a measure of sympathetic nervous activity [6]. However, it is difficult to precisely evaluate clinically the magnitude of change in sympathetic nervous activity during our progressive exercise protocol. In addition, parasympathetic nervous activity, which can be estimated by heart rate variability, was not measured in this study. Therefore, we were unable to evaluate fully the autonomic control of HR during exercise. It will be necessary to evaluate parasympathetic nervous activity in addition to sympathetic tone in future studies. However, it should be considered that the methods assessed have their limitations [6]. The study was also limited by the relatively small number of patients studied and the types of CHD that were included; however, many of the changes were statistically significant.

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