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Impact of central hypercapnic chemosensitivity on enhanced ventilation in patients after the Fontan operation

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Abstract

Background: Central hypercapnic chemosensitivity (Chemo) influences the enhanced ventilatory and sympathetic responses in heart failure patients; however, its influence on these responses in Fontan patients is unknown.
Objectives: To measure Chemo and compare the results with rest and exercise ventilatory characteristics in Fontan patients.
Methods and results: We measured Chemo (l/min/mmHg), hemodynamics, pulmonary function, cardiac autonomic nervous and neurohumoral activities and compared the results with the ventilatory response during exercise in 42 Fontan patients and 12 referents. Chemo did not differ significantly between the Fontan patients (1.5 ± 0.9) and referents (1.3 ± 0.4). However, a higher Chemo in addition to lower resting arterial oxygen saturation (SaO_2) and higher dead space ventilation (Vd/Vt) independently determined a higher resting minute ventilation (VE) and, except for the Chemo, these factors also independently determined the higher resting ventilatory equivalent for carbon dioxide output (VE/VCO_2) ($p<0.05$–0.001). At peak exercise, the higher Chemo as well as the higher peak Vd/Vt and aerobic exercise capacity independently determined the higher peak VE and VE/VCO_2 ($p<0.01$–0.001). Among cardiac autonomic and neurohumoral activities, only the higher plasma norepinephrine concentration was associated with higher Chemo in Fontan patients ($r=0.40$, $p<0.01$) and age was correlated positively with Chemo in the high Chemo (≥ 2.1) Fontan patients ($n=10$).
Conclusions: In addition to lower SaO_2 and higher Vd/Vt, an increased Chemo associated with sympathetic activation has a significant impact on accelerated rest and exercise ventilation in some Fontan patients, especially in adult patients.

Keywords: Fontan; Ventilation; Exercise; Dead space; Oxygen saturation; Hypercapnic chemosensitivity

1. Introduction

Accelerated rest and exercise ventilation characterizes Fontan patients [1–3]. There are multiple responsible factors including; ventilation–perfusion mismatch due to lack of the pulmonary ventricle, mild but significant lower arterial oxygenation (SaO_2) and restrictive ventilatory impairment secondary to open cardiac surgeries [1,2]. In addition, ergoreceptor overactivity and central and peripheral chemosensitivities are believed to be important determinants of the accelerated ventilatory response to exercise seen in patients with chronic heart failure [4–7]. In particular, enhanced central hypercapnic chemosensitivity (Chemo) has been highlighted as a pivotal factor responsible for the enhanced ventilatory and sympathetic responses and has a significant pathophysiologic role in chronic heart failure patients [8]. Fontan patients exhibit similar hemodynamic and clinical characteristics i.e., low cardiac output and impaired exercise capacity. However, there has been no study addressing Chemo in Fontan patients. We hypothesized that the accelerated rest and exercise ventilation were associated with increased Chemo and/or impaired cardiac autonomic

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nervous activity and the increased Chemo had some relationship to clinical status in Fontan patients.

2. Methods

2.1. Subjects

We studied a consecutive cohort of 42 clinically stable Fontan patients (9 to 30 years) and 12 referents (9 to 22 years). The postoperative follow-up period was at least 1 year. Of the Fontan patients, a total cavopulmonary connection was created in 26 and an atriopulmonary connection in 16 (Table 1). Medications included digoxin (5), diuretics (13), anticoagulant agents (19), and angiotensin converting enzyme inhibitors (3). No patients were taking antiarrhythmics, including β blockers. Operations prior to the Fontan included, systemic to pulmonary shunt(s) (26); pulmonary arterial banding (6); Glenn anastomosis (6); atrioventricular valvuloplasty or valve replacement (5). No patients had undergone a fenestration at the time of the Fontan operation. The age-matched referents were being followed at our institute because of a history of coronary artery dilatation, aneurysm or both, due to Kawasaki disease and all underwent follow-up selective coronary angiography to evaluate possible stenosis of the coronary arteries. Our referents showed no significant stenotic lesions of the coronary arteries, nor did they have lung or hemodynamic abnormalities [1,3]. Modified New York Heart Association classification of cardiac status was used for the Fontan patients [9].

Table 1
Clinical characteristics of the study patients

Group	Fontan (n=42)	Referent (n=12)
Age (yrs)	15±4	15±4
Body weight (kg)	46±13	52±13
Follow-up (years)	10±4	–
Disease	TA (14), UVH (14)	Hx of KD (12)
	DORV (3), MA (4)	–
	PA (3), Others (4)	–
APC/TCPC	16/26	–
Hemodynamics		
Central venous pressure (mmHg)	12±3***	4±1$^{\$}$
Pulmonary artery pressure (mmHg)	12±3	14±2$^{\$}$
SV end-diastolic pressure (mmHg)	9±3**	11±3
SV end-diastolic volume index (ml/m^2)	80±30	87±19
SV ejection fraction (%)	53±14**	65±7
Cardiac index (l/min/m^2)	2.4±0.6***	3.5±0.5$^{\$}$
Arterial oxygen saturation (%)	95±3***	98±1
Natriuretic peptides		
Atrial natriuretic peptide (pg/ml)	83±70***	19±7
Brain natriuretic peptide (pg/ml)	54±67**	5±3

APC = atriopulmonary connection, TCPC = total cavopulmonary connection, DORV = double outlet right ventricle, Hx of KD = history of Kawasaki disease, MA = mitral atresia, PA = pulmonary atresia UVH = univentricular heart, SV = systemic ventricle, TA = tricuspid atresia. **p<0.01 and ***p<0.001 vs. referent. $^{\$}n$=4. Values are mean±SD.

2.2. Hemodynamics

Cardiac catheterization was performed in all patients and the 12 referents. We estimated oxygen consumption from the age, sex, and heart rate (HR) and measured cardiac index (l/min/m^2) using the Fick principle with the assumption that right and left pulmonary arterial saturations were equal in patients with either a Glenn or a total cavopulmonary connection because it is clinically difficult to measure accurate flow distribution in the bilateral pulmonary arteries. 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 and systemic ventricular ejection fraction was calculated [10].

2.3. Neurohumoral activities

After at least 15 min supine rest, the plasma norepinephrine concentration (NE, by high-performance liquid chromatography [11]), atrial and brain natriuretic peptides were determined in all Fontans and referents [12,13]. Endothelin-1 was determined in 24 Fontan patients and 9 referents [14].

2.4. Heart rate variability and arterial baroreflex sensitivity

Heart rate variability and arterial baroreflex sensitivity were measured in all subjects [15]. The spectral heart rate variability was expressed as a low frequency component (0.04 to 0.15 Hz) and a high frequency component (0.15 to 0.40 Hz) and the logarithmic values were used. We used a bolus phenylephrine method to measure arterial baroreflex sensitivity (ms/mmHg) [15,16].

2.5. Pulmonary function tests

We measured vital capacity (l); the percent forced expiratory volume in 1 s (%) (Spirosift, SP-600, Fukuda Denshi, Tokyo). Vital capacity was calculated as the percentage of the body height predicted normal value for our institute.

2.6. Exercise protocol

All subjects underwent symptom-limited treadmill exercise within 1 week of cardiac catheterization [17]. Cardiorespiratory variables, including peak oxygen uptake (VO_2), were measured and calculated as the percentage of gender and body weight predicted normal value for our institute. We used a twelve lead ECG to determine HR and pulse oximeter (PULSOX-M2, Teijin, Tokyo) to measure SaO_2 during exercise test.