Journal of Rare Cardiovascular Diseases 2016; 2 (8): 254–258
www.jrcd.eu

ORIGINAL PAPER
Rare congenital cardiovascular diseases

Exercise capacity in adult patients after Fontan procedure (RCD code: IV-5B.1)

Monika Smaś-Suska*[1], Piotr Weryński[2], Natalia Dłużniewska[1], Maria Olszowska[1], Piotr Podolec[1], Lidia Tomkiewicz-Pająk[1]

[1] Department of Cardiac and Vascular Diseases, Institute of Cardiology, Jagiellonian University Medical College, Krakow, Poland; [2] Department of Pediatric Cardiology, Polish-American Institute of Pediatrics, Jagiellonian University Medical College, Krakow, Poland

Abstract

Background: The aim of Fontan procedure is to restore a balance between pulmonary and systemic circulation and improve or nearly normalize arterial saturation in patients with functionally univentricular heart. Nevertheless, due to the lack of subpulmonary pump, the circulatory system becomes haemodynamically less efficient, what can lead to the impairment of exercise capacity. **Aim**: The aim of the study was to investigate exercise capacity by means of cardiopulmonary exercise test and pulmonary function tests, of 37 adult Fontan patients with regard to the time passed from the index procedure. The patients were divided into 3 groups: group I – up to 15 years post procedure; group II – 16–20 years, group III – more than 20 years after Fontan procedure). **Results**: 37 Fontan patients (mean age was 24.4 ±5.7 years, 40% of women) were enrolled in the study. The mean postoperative time was 19.4 ±5.1 (13–30) years. Mean, peak oxygen consumption ($VO_{2peak)}$ was 22.7 ±7.1 ml/kg/min (64.2 ±18.5% of predicted value). According to postoperative time a significant increase of ventilatory equivalent of carbon dioxide (VE/VCO_2) ($p = 0.033$) and significant decrease of forced expiratory volume in 1 s/vital capacity (FEV_1%VC) between group 2 and 3 ($p = 0.026$) were observed. Additionally, the age of the patients correlated negatively with and heart rate (HR) ($r = -0.360$, $p < 0.05$) and peak oxygen consumption ($VO_{2peak)}$ ($r = -0,337$, $p < 0.05$). Moreover, age at Fontan operation and time after Fontan procedure was related to ventilator equivalent of oxygen (VE/VO_2) ($r = -0,343$, $p < 0.05$, and $r = 0.393$, $p < 0.05$). Single ventricle ejection fraction (SVEF) and atrioventricular regurgitation degree did not corresponded with cardiopulmonary exercise test (CPET) values. **Conclusions:** Results highlight the complex problem of diminished exercise capacity of Fontan patients depending on the time passed from the procedure. Exercise tolerance deteriorates in time: VE/VCO_2 increases, FEV1/VC markedly lowers in a group of Fontan patients at 20 years follow-up. JRCD 2016; 2 (8): 254–258

Key words: rare disease, Fontan procedure, cardiopulmonary exercise test, pulmonary function test

Introduction

Univentricular heart constitutes 8% of congenital heart diseases. The Fontan procedure firstly introduced 40 years ago, still remains a preferable operative method in this group of patients [1]. The aim of Fontan procedure is to restore a balance between pulmonary and systemic circulation and improve or nearly normalize arterial saturation in patients with functionally univentricular heart. Nevertheless, due to the lack of subpulmonary pump, circulatory system becomes haemodynamically less efficient, what can lead to impairment of exercise capacity [2–5]. Reduction in exercise capacity can be caused by many factors, including an increase in pulmonary artery systolic pressure with a reduction of preload of single ventricle, impairment of autoregulation of systemic vascular resistance, and the absence of a prepulmonary pump [6–12].

This study aimed to investigate exercise capacity of 37 adult Fontan patients, by means of cardiopulmonary exercise test and pulmonary function tests, with regard to the time passed from the index procedure.

Material and methods

Thirty seven adult patients after staged Fontan operation (Fontan patients), aged between 18–42 years were included in the study. According to postoperative time patients were divided into three groups: up to 15 years, between 16 and 20 years and above

Conflict of interest: none declared. Submitted: March 16, 2016. Accepted: August 18, 2016.

* Corresponding author: Department of Cardiac and Vascular Diseases, Institute of Cardiology, Jagiellonian University Medical College, Centre for Rare Cardiovascular Diseases, John Paul II Hospital, ul. Prądnicka 80, 31-202 Krakow, Poland; tel. 0048 12 614 22 87, fax 0048 12 423 43 76; e-mail: monikasmas@gmail.com

20 years after surgery. Clinical, demographic and anatomical data were studied by a retrospective analysis of the clinical records. All patients underwent clinical assessment including physical examination and functional status (NYHA class). Systolic fraction of systemic ventricle (SV) was assessed semi-quantitatively. Furthermore semi-quantitative assessment of atrioventricular valve regurgitation was provided using a following scale: none, mild, moderate, severe. To evaluate an exercise tolerance cardiopulmonary exercise test (CPET) was performed, using a modified Bruce protocol. Results of the test were interpreted according to guidelines described by Knap et al [13]. To access a ventilatory efficiency Fontan patients underwent whole-body plethysmography. Pulmonary functions were expressed as absolute values and percentage of predicted values (%N) based on the age, sex, height, and race of participants. The parameters were interpreted according to the previous study [14].

Statistical analysis

Categorical variables were expressed as frequency and percentage; continuous variables were expressed as mean and standard deviation. The conformity of continuous variables to the normal distribution was analyzed with the Shapiro-Wilk test. The $\chi 2$ test, Mann-Whitney U test, student's t-test, and ANOVA with Tukey post-hoc test were performed where appropriate. Parameters correlations were calculated by use of the Spearman rank test. Statistical significance was set at p-value 0.05. Statistica version 10.0.1011.7 (StatSoft Inc., USA) was used to analyze data.

Results

In total, 37 Fontan patients (mean age was 24.4 ±5.7 years, 40% of women) were enrolled to the study. The mean age at Fontan procedure was 5.1 ±3.3 (2–14) years. The mean postoperative time was 19.4 ±5.1 (13–30) years.

The group of patients with anatomically univentricular heart consisted of: 35% (13 patients) with tricuspid atresia, 32% (12 patients) with ventricular septal defect and pulmonary atresia, three patients (8%) were diagnosed a double outlet right ventricle with hypoplasia of left ventricle, 8 patients (22%) had right ventricle hypoplasia and one (3%) with complete atrioventricular canal. Among patients with univentricular heart, 89% underwent total cavopulmonary anastomosis (TCPC), while rest of them (11%) underwent atriopulmonary anastomosis (APC). The morphology of SV was left in 34 (92%) and right in 3 (8%) patients. The fenestration was present in 17 (46%) of patients. At the last follow-up, the NYHA class was assessed as I in 9 (25%) patients, II in 26 (75%) and III in 2 (5%) subjects. Mean oxygen saturation (SaO2), measured by pulse oximetry was 89.8 ±5.9%.

Mean ejection fraction of SV was 51.3 ±7.3%. Atrioventricular valve regurgitation was assessed as mild in 17 (46%) patients, moderate in 10 (27%) and severe in 3 (8%) subjects.

In our study maximum VO_2 at the peak of exercise in Fontan patients was 22.7 ±7.1 ml/kg/min (64.2 ±18.5% of predicted value).

Table 1. Values of the CPET and bodyplethysmography parameters depending on follow-up duration

Parameter	Sub-group	Mean	SEM	ANOVA	Tukey test
	<15	23.67	2.55		
VO_2	16–20	23.32	1.75	0.683	
	>20	21.22	2.08		
	<15	57.42	8.21		
VO_2 % Pred	16–20	50.52	5.27	0.270	
	>20	41.08	6.27		
	<15	68.14	7.10		
Max % Pred VO_2	16–20	65.00	4.56	0.699	
	>20	60.83	5.42		
	<15	57.42	8.21		
AT % Pred VO_2	16–20	50.52	5.27	0.270	
	>20	41.08	6.27		
	< 15	159.87	9.72		
HR	16 – 20	149.23	6.67	0.564	
	> 20	146.91	7.94		
	< 15	36.12	9.19		
HRR	16 – 20	48.93	6.49	0.685	
	> 20	49.16	7.50		
	< 15	51.75	6.31		
VE	16 – 20	60.11	4.33	0.273	
	> 20	49.75	5.15		
	< 15	29.10	1.95		
VE/VO_2	16 – 20	33.61	1.37	0.053	
	> 20	35.40	1.59		
	< 15	29.77	1.27		ab
VE/VCO_2	16 – 20	31.21	0.87	0.048	a
	> 20	33.66	1.03		b
	< 15	35.75	2.74		
Bf	16 – 20	39.00	1.88	0.568	
	> 20	39.75	2.24		
	< 15	67.70	6.63		
BR	16 – 20	78.78	4.54	0.372	
	> 20	79.76	5.65		
	< 15	104.16	2.90		ab
FEV_1%VC	16 – 20	107.09	2.14	0.017	a
	> 20	100.62	2.37		b

CPET – cardiopulmonary exercise test, VO_2 – oxygen uptake, AT – anaerobic threshold, HR – heart rate, HRR – heart rate reserve, VE – ventilator equivalent, VE/VCO_2 – ventilatory equivalent of carbon dioxide, VE/VO_2 – ventilatory equivalent of oxygen, Bf – breathing frequency, BR – breath reserve, FEV_1 – forced expiratory volume in 1 s, VC – vital capacity

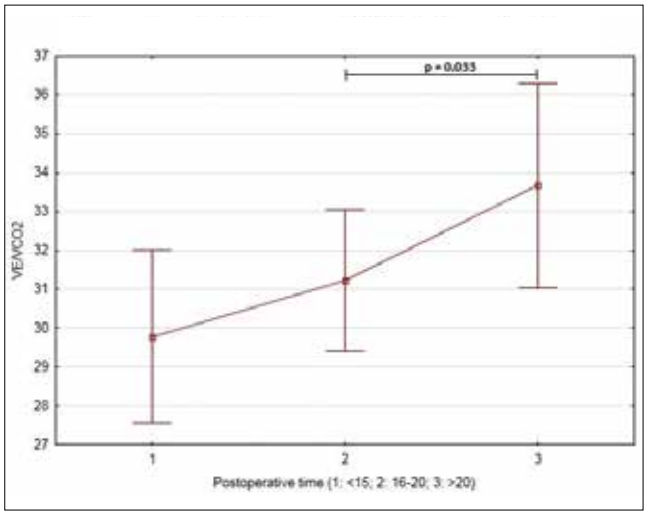

Figure 1. Mean values of VE/VCO_2 grouped by the Postoperative Time

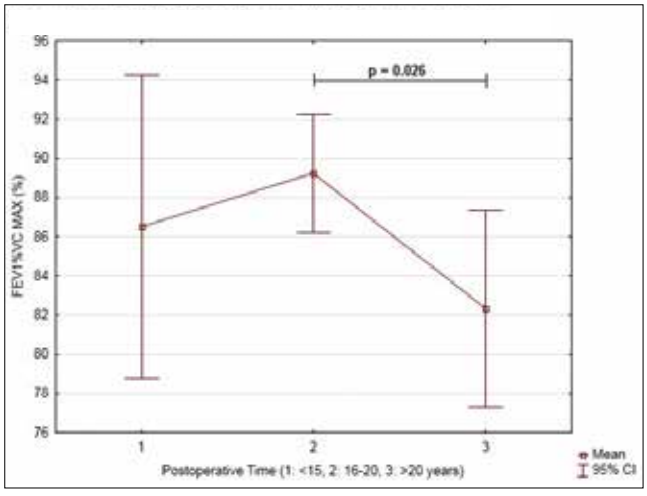

Figure 2. Mean values of FEV1%VC MAX groupedby the Postoperative Time

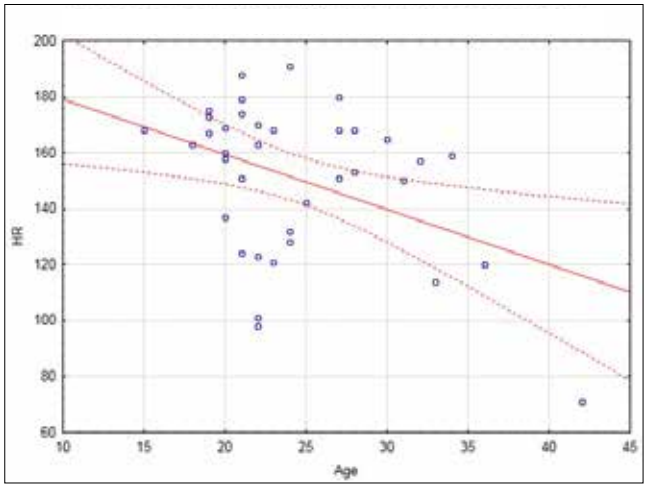

Figure 3. Correlation plot of Heart Rate (HR) with the age of the Fontan Patients

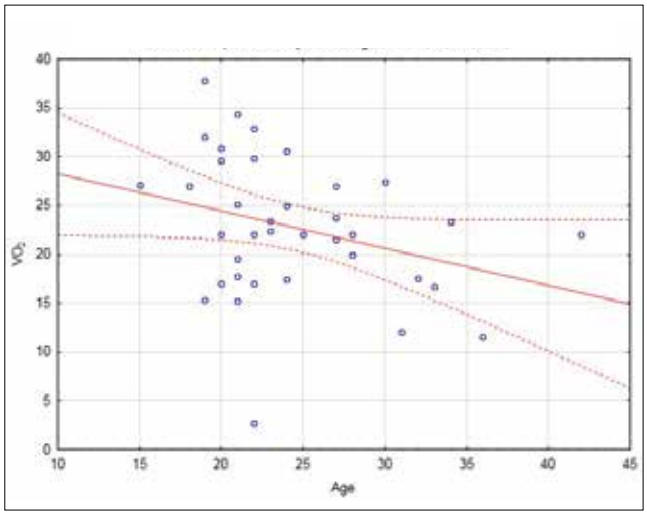

Figure 4. Correlation plot of VO_2 with the age of the Fontan Patients

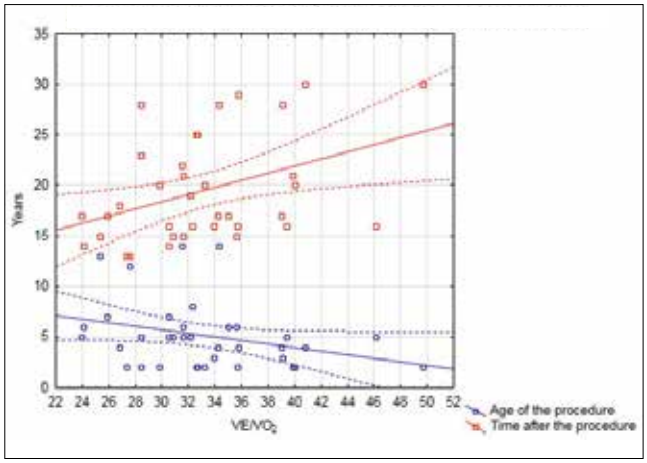

Figure 5. Correlation plot of VE/VO_2 with the age of the Fontan procedure and time after Fontan procedure

Values of the CPET and bodyplethysmography parameters depending on follow-up duration are listed in Table 1.

In our study there were no significant differences in peak oxygen consumption (VO_{2peak}) according to postoperative time: up to 15 years, between 16 and 20 years and above 20 years after surgery, as well as VO_2% of predicted value, oxygen uptake at anaerobic threshold (VO_{2AT}) however there was a trend towards the reduction of oxygen uptake during exercise between groups up to 15 years, 16–20 and above 20 years after surgery.

Maximum heart rate (HR) reached at the peak of exercise was 151 ±27 beats per minute and heart rate reserve (HRR) was 46 ±26 beats per minute. Moreover a trend towards the decrease of maximum HR and increase of HRR between compared groups of Fontan patients was observed.

Ventilatory parameters: ventilatory equivalent of oxygen (VE/VO_2) and breath reserve (BR) increased with postoperative time. We observed significant difference (increase) in the ventilatory equivalent of carbon dioxide (VE/VCO_2) parameter value between group 2 and 3 ($p = 0.033$) (Figure 1).

Additionally we observed a significant association between postoperative time and dynamic ventilatory parameter: forced expiratory volume in 1 s (FEV_1%VC), which statistically significantly decreased between group 2 and 3 ($p = 0.026$) (Figure 2).

Moreover, we found a negative correlation between age at the test and maximum HR reached at the peak of exercise ($r = -0.360$, $p < 0.05$) and maximum VO_2 ($r = -0,337$, $p < 0.05$) (Figure 3,4). Age at Fontan operation and time after Fontan procedure was related to VE/VO_2 ($r = -0,343$, $p < 0.05$, and $r = 0.393$, $p < 0.05$, respectively) (Figure 5).

Echocardiographic parameters did not reveal correlation between single ventricle ejection fraction, severity of the valve regurgitation and cardiopulmonary exercise parameters in studied patients.

Discussion

In presented study we describe the results of cardiopulmonary exercise test and pulmonary function test in patients after Fontan procedure in the long term observation. In spite of the fact that Fontan operation significantly counteracted the mortality of patients with hemodynamically single ventricle, they develop many complications including the impairment of exercise capacity [2,3,5,10].

Our study shows that Fontan patients exhibit a decreased exercise capacity which is in line with previous studies concerning the adult patients with Fontan circulation [12,15,16]. In our group of Fontan patients maximum VO_2 was decreased.

Recent studies show that patients after Fontan operation have lower hemodynamic parameters including: maximum VO_2, HR, cardiac index and stroke volume index at rest and during all stages of exercise compared to healthy, age-matched controls [3]. During exercise in healthy population, to match the metabolic demands, VO_2 and cardiac output (CO) increase [3,17]. A CO depends on HR, contractility of the ventricle, afterload and preload. Physiologically an increase of the heart rate will increase the output of a ventricle with preload reserve. Moreover in the biventricular physiological circulation, right ventricle ensures to increase pulmonary blood flow and left ventricular preload. Recent studies showed that CO in a Fontan circulation at rest is about 70% lower as compared to the biventricular heart [18]. In the Fontan circulation, due to the lack of a pulmonary pump, the pulmonary blood flow is restriced and as a result the return from the pulmonary circulation is limited [19], what causes the reduction or even absence of preload reserve. In Fontan patients the pulmonary blood flow depends on skeletal muscle pump, central venous pressure, inspiration and on pulmonary vascular resistance [17].

Moreover in Fontan patients a 'chronotropic incompetence' during exercise is observed [19], when a heart rate is consistently lower than in normal subjects. Those observations are in line with our study – we observed a trend towards a decrease of maximum HR and increase of HRR in Fontan patients according to postoperative time. A chronotropic incompetence can be related to an abnormal reflex control of heart rate or adrenergic dysfunction [2,16]. The HR plays an important role in controlling a CO in Fontan circulation during exercise [20]. It is also believed that abnormal autonomic control with a dysfunction of the sinus node can attribute to lower heart rate response to exercise in Fontan patients [21].

In our study, according to postoperative time, Fontan patients had increased VE/VCO_2 with significance after 20 years follow up after Fontan procedure. We observed an increase of VE/VO_2 and BR in postoperative time. In several studies describing patients with congenital heart diseases, a high slope of the ventilation vs carbon dioxide relationship (VE/VCO2 slope) during exercise has been reported [15,22,23]. What is more, several studies showed that impaired ventilatory response to exercise assessed with inceased VE/VCO_2 slope is a predictor of mortality in patients with congenital heart diseases, even stronger than peak VCO_2. Furthermore, a value of elevated VE/VCO_2 has been described as a prognostic marker in a patients with heart failure [23]. Changes in ventilatory efficiency assessed by increase of VE/VCO_2 peak has had the predictive value to identify exercise-induced myocardial ischaemia. The study provided by Mezzani et al. demonstrated that the most dominant cause of low VE/VCO_2 and VE/VO_2 could be a reduction of lung perfusion and systemic circulation rather than excessive ventilation in adolescent and adult patients with CHD.

In our study we observed a significant reduction in FEV_1%VC according to postoperative time. Recent studies show that abnormal lung function is present in adult patients with congenital heart diseases and its severity is related with worse outcome. Moreover a severity of ventilator abnormalities corresponded with a complexity of heart defects and surgical history. Previous cardiac surgeries may lead to inadequate development of the thorax, diaphragmatic nerve palsy and abnormal respiratory muscle function [24,25,14]. Another cause of ventilatory abnormality in Fontan patients could be a pulmonary embolism. According to Varma et al. an asymptomatic pulmonary embolism was present in 17% of patients, what was detected on CT and ventilation/perfusion lung scintigraphy [26]. A pulmonary embolism impairs blood flow in the lung and may aggravate the ventilatory abnormalities in adult Fontan patients. Importantly, moderate to severe lung dysfunction could be an independent predictor of mortality in the medium term [27].

Conclusions

Adult patients after Fontan procedure have significantly reduced VO_2 and HR at the peak of exercise. Furthermore exercise capacity deteriorates in time: VE/VO_2, VE/VCO_2 increases. Also FEV1/VC is markedly reduced in a group of patients at 20 years follow-up.

References

1. Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax 1971;26:240–248.
2. Zając A, Tomkiewicz L, Podolec P, et al. Cardiorespiratory response to exercise in children after modified Fontan operation. Scand Cardiovasc J SCJ 2002;36:80–85.
3. Hebert A, Jensen AS, Mikkelsen UR, et al. Hemodynamic causes of exercise intolerance in Fontan patients. Int J Cardiol 2014; 175: 478–483.
4. Matthews IL, Fredriksen PM, Bjørnstad PG, et al. Reduced pulmonary function in children with the Fontan circulation affects their exercise capacity. Cardiol Young 2006; 16: 261–267.

5. Tomkiewicz-Pajak L, Podolec P, Drabik L, et al. Single ventricle function and exercise tolerance in adult patients after Fontan operation. Acta Cardiol 2014; 69: 155–160.
6. Bidart CM, Abbas AE, Parish JM, et al. The noninvasive evaluation of exercise-induced changes in pulmonary artery pressure and pulmonary vascular resistance. J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr 2007; 20: 270–275.
7. Douglas PS, O'Toole ML, Hiller WD, et al. Different effects of prolonged exercise on the right and left ventricles. J Am Coll Cardiol 1990; 15: 64–69.
8. Argiento P, Chesler N, Mulè M, et al. Exercise stress echocardiography for the study of the pulmonary circulation. Eur Respir J 2010; 35: 1273–1278.
9. Bidart CM, Abbas AE, Parish JM, et al. The noninvasive evaluation of exercise-induced changes in pulmonary artery pressure and pulmonary vascular resistance. J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr 2007; 20: 270–275.
10. Ohuchi H. Cardiopulmonary response to exercise in patients with the Fontan circulation. Cardiol Young 2005; 15: 39–44.
11. Senzaki H, Masutani S, Ishido H, et al. Cardiac rest and reserve function in patients with Fontan circulation. J Am Coll Cardiol 2006; 47: 2528–2535.
12. Loomba RS, Danduran ME, Dixon JE, et al. Effect of Fontan fenestration on regional venous oxygen saturation during exercise: further insights into Fontan fenestration closure. Pediatr Cardiol 2014; 35: 514–520.
13. Knap K, Dłużniewska N, Tomkiewicz-Pająk L, et al. Cardiopulmonary exercise tests in rare cardiovascular diseases. J Rare Cardiovasc Dis 2015; 2: 139–143.
14. Tomkiewicz-Pajak L, Olszowska M, Komnata K, et al. Lung function and exercise tolerance in adults after Fontan procedure. Exp Clin Cardiol 2014; 20: 2606–2614.
15. Dimopoulos K, Okonko DO, Diller GP, et al. Abnormal ventilatory response to exercise in adults with congenital heart disease relates to cyanosis and predicts survival. Circulation 2006; 113: 2796–2802.
16. Tomkiewicz-Pająk L, Hoffman P, Trojnarska O, et al. Long-term follow-up in adult patients after Fontan operations. Pol J Cardio-Thorac Surg 2013; 4: 357–363.
17. Shafer KM, Garcia JA, Babb TG, et al. The importance of the muscle and ventilatory blood pumps during exercise in patients without a subpulmonary ventricle (Fontan operation). J Am Coll Cardiol 2012; 60: 2115–2121.
18. Khairy P, Poirier N, Mercier LA. Univentricular heart. Circulation 2007; 115: 800–812.
19. Takken T, Tacken MHP, Blank AC, et al. Exercise limitation in patients with Fontan circulation: a review. J Cardiovasc Med Hagerstown Md 2007; 8: 775–781.
20. Gewillig M, Brown SC, Eyskens B, et al. The Fontan circulation: who controls cardiac output? Interact Cardiovasc Thorac Surg 2010; 10: 428–433.
21. Fredriksen P, Therrien J, Veldtman G, et al. Lung function and aerobic capacity in adult patients following modified Fontan procedure. Heart 2001; 85: 295–299.
22. Buys R, Cornelissen V, Van De Bruaene A, et al. Measures of exercise capacity in adults with congenital heart disease. Int J Cardiol 2011; 153: 26–30.
23. Mezzani A, Giordano A, Moussa NB, et al. Hemodynamic, not ventilatory, inefficiency is associated with high VE/VCO2 slope in repaired, noncyanotic congenital heart disease. Int J Cardiol 2015; 191: 132–137.
24. Hawkins SMM, Taylor AL, Sillau SH, et al. Restrictive lung function in pediatric patients with structural congenital heart disease. J Thorac Cardiovasc Surg 2014; 148: 207–211.
25. Troutman WB, Barstow TJ, Galindo AJ, et al. Abnormal dynamic cardiorespiratory responses to exercise in pediatric patients after Fontan procedure. J Am Coll Cardiol 1998; 31: 668–673.
26. Varma C, Warr MR, Hendler AL, et al. Prevalence of "silent" pulmonary emboli in adults after the Fontan operation. J Am Coll Cardiol 2003; 41: 2252–2258.
27. Alonso-Gonzalez R, Borgia F, Diller GP, et al. Abnormal lung function in adults with congenital heart disease: prevalence, relation to cardiac anatomy, and association with survival. Circulation 2013; 127: 882–890.