【Original Article】

Lung function and exercise capacity in adult patients late after the Fontan operation

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Abstract

Objects: We sought to investigate the clinical impact of the lung function at rest and during exercise and to elucidate its relation to exercise capacity in adult patients late after the Fontan operation.

Methods: We retrospectively reviewed 46 adult patients late after the Fontan operation. After lung function was evaluated with a spirometer, all patients underwent cardiac catheterization and cardiopulmonary exercise testing. We investigated whether age, age at operation, period after operation and number of palliative operations could have an impact as contributing factors for lung function or not, and elucidate the correlation between the clinical factors, including hemodynamics data on catheterization and parameters of lung function.

Results: Exercise disclosed restrictive pattern of lung function with low ventilatory efficiency in the adult Fontan patients. %Peak oxygen uptake had a positive correlation with % vital capacity, peak tidal volume, peak minute ventilation, increase in tidal volume during exercise and ventilation to carbondioxide production slope. In the multivariate analysis, %Vital capacity and ventilation to carbondioxide production slope were independent determinants of %Peak oxygen uptake. % Peak oxygen uptake also showed a negative correlation with patient age and age at operation, but not with number of years after Fontan operation. Peak tidal volume, peak minute ventilation and increase of tidal volume during exercise had negative correlation with age and age at Fontan operation. Patients who underwent palliative operations more than 3 times had diminished values of %peak oxygen uptake and % vital capacity.

Conclusion: In the adult patients late after the Fontan operation, despite restrictive pattern of lung function were not detected at rest, exercise disclosed the low ventilatory efficiency and the restrictive pattern of lung function. Early and minimum surgical procedure may have a beneficial effect in terms of their exercise capacity in the late after period.

Key words：Fontan operation, Lung function, Exercise, Adult congenital heart disease

The number of adult patients late after the Fontan type operation, which is functional repair for congenital complex cyanotic heart disease with single ventricle circulation is steadily increasing.[1] It is well known that cardiac output is low with a high systemic venous pressure, and pulmonary blood flow derived largely from the transpulmonary pressure gradient and by atrial contraction if the right atrium is included in the Fontan circulation. There are several late complications, such as exercise intolerance, arrhythmia, ventricular dysfunction, autonomic disturbance and others. These complications significantly influence the long term outcome. Therefore, the health outcome of the adult patients late after the Fontan operation has been increasingly important. Exercise capacity in patients after Fontan operation is low compared with normal subjects. However, the parameters of central hemodynamics do not correlate closely with their exercise capacity.[2] Recently, several reports have described restrictive impairment of lung function after Fontan operation.[3,4,5,6] However, there are not many reports regarding to

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the lung function in the late after period and it is not fully elucidated contribution of lung function to the exercise physiology in the Fontan circulation. Thus, the aim of the present study was to elucidate the relation between exercise performance and lung function and factors contributing to the impairment of lung function in adult patients late after Fontan operation.

Subjects and Methods

We retrospectively reviewed 46 adult patients late after the Fontan operation (more than 20 years of age and more than 15 years after the Fontan operation), who underwent exercise and lung function tests and cardiac catherterization in our institute from April 1999 to September 2005. Written informed consent was obtained from each patients after a detailed description of each procedure.

The baseline characteristics of the subjects are shown in Table1. Mean age of patients is 27 years old (range: 21-40) and follow-up period is 17 years in average. To evaluate the clinical impact of lung function on the Fontan circulation, we excluded the patients who have an episode of arrhythmia, cyanosis less than 90% of aortic oxygen saturation due to right-left shunt via fenestrations. Ventricular morphology was determined by both of 2-dimensioanl echocardiography and cineangiography. 28 patients have a right ventricle and 18 patients left ventricle as main systemic ventricle.

In this study, we investigated, in adult patients late after Fontan operation, whether age, age at operation, period after operation and number of palliative operations could have impact as contributing factors for lung function, and elucidated the correlation among ventilatory parameters both at rest and during exercise, hemodynamic variables and exercise capacity.

Lung function at rest: By spirometry (FUDAC-50, Fukuda Densi, Tokyo), all patients underwent a lung function test with measurements of %vital capacity (%VC) and %forced expiratory volume in 1s (%$FEV_{1.0}$), which was expressed as a sex-matched percent of the normal value predicted

Table1 Baseline characteristics

Characteristics	Fontan patients (n=46)
Age at test,years (range)	26.6+/-6.9(20-37)
Gender, female/male	21/25
Weight, Kg (range)	50.5+/-8.3(36-61)
Height, cm(range)	162+/-5(140-171)
Age at surgery, years (range)	6.5+/-6.6(2-12)
Years since surgery (range)	17.2+/-4.3(10-21)
Number of surgery (range)	1.4+/-1.0(0-3)
Exercise capacity	
Peak oxygen uptake (%) , ml/min/kg	21.8+/-5.3(73+/-15)
Ventilatory anaerobic threshold (%) , ml/min/kg	18.6+/-4.5(85+/-9)
Cardiac catheterization	
Central venous pressure, mmHg (range)	12+/-3(7-17)
Pulmonary arterial wedge pressure, mmHg (range)	8+/-2(4-12)
Systemic ventricle ejection fraction % (range)	55+/-6(45-68)
Cardiac index (range)	2.5+/-0.6(1.8-3.6)

Data are given as mean±standard deviation (maximum-minimum)
(%): % of normal value

from height.[7] Restrictive pattern of lung function was defined as 80%>%VC and 80%<%$FEV_{1.0}$.

Cardiopulmonary exercise test: At least more than 1 hour later, to evaluate exercise capacity and lung function during exercise, the patients underwent a cardiopulmonary exercise test by upright bicycle ergometer to evaluate exercise capacity and lung function during exercise. As we previously described[2)], the exercise protocol was the symptom-limited ramp method. Simultaneously, expired gas measurements were obtained using an AE-300T(CHEST, Kyoto, Japan).

We analyzed peak oxygen uptake (VO_2) and the ventilatory anaerobic threshold (VAT) as indicators of exercise capacity. The value of peak VO_2 was standardized by normal value predicted sex and age in the Japanese population.[8)] We also investigated peak respiratory rate, peak minute ventilation (VE) and peak tidal volume (VT) during exercise as indicators of lung function during exercise. Furthermore, the response of tidal volume to exercise was evaluated by peak VT-rest VT, and respiratory reserve by peak VE / maximum ventilatory volume (MVV) and peak VT /peak inspiratory capacity (IC), respectively. In addition, we calculated the ventilation to carbondioxide production slope (VE/VCO_2 slope) in a manner previously described.[9)] Each parameters were also standardized by normal value predicted sex and age in our institute.

Wasserman et al demonstrated that peak VE / MVV in normal controls were ranging from 50-80% and VT does not usually exceed approximately 70% of the IC during exercise, but it approaches a value close to 100% in patients with restrictive lung disease, suggesting that the IC may limit the increase in VT.[10)]

Cardiac catheterization: All patients underwent cardiac catheterization to assess the central hemodynamic status within 3 months of exercise and lung function testing. In the catheterization, oxygen consumption was directly measured and cardiac index was calculated by Fick principle as well as vascular and ventricular pressure measurements.

Statistical analysis: All analyses were performed using the statistical software package, Statview version4.0 (SAS Institute, Cary, North Carolina). Data were standardized by normal value and expressed as mean ± standard deviation. Parameters measured were analyzed by an unpaired or paired Student t test where appropriates. The relationship between expired gas measurements and number of palliative operations were analyzed using the Kruskal Wallis method. When differences were found among groups, the Turkey-Kramer procedure was used as a post-hoc test to determine which groups differed. For correlation analysis, univariate Pearson's correlation coefficients were calculated. Multiple regression analyses were used to define the independent predictors of peak VO_2 among the univariate predictors. All p values were two-tailed and a value of $p<0.05$ was considered to be significant.

Results

Table2 presents the parameters of exercise capacity and lung function. Low %VC and normal %$FEV_{1.0}$, restrictive pattern of lung function, were detected in 17 patients. (36%) Regarding to respiratory reserve during exercise, it appeared to be restrictive impairment in 19 patients (42%) on VE / MVV and 25 patients (53%) on VT / IC. The relationship between exercise capacity and lung function at rest is shown in Table3. Using univariate analysis, % predicted normal value of peak VO_2 (%peak VO_2) had a positive correlation with %VC, %peak VT, %peak VE and %peak VT-rest VT. In turn, %peak VO_2 had a significant inverse correlation with the %VE/VCO_2 slope. In the multivariate analysis, %peak VO_2 showed a significant correlation with %VC and the %VE/VCO_2 slope (Table4). As shown in Table5, %peakVO_2 had a negative correlation with patient age and age at operation, but not with years after Fontan operation. Similary, %VC showed a negative correlation with patient age and age at Fontan operation, whereas years after operation had no effect on %VC.

Univariate analysis between central hemodynamics variables and lung function was shown in Table6. No correlation was detected among all variables.

The effect of systemic ventricle morphology was shown in Table7. There were no difference between right and left ventricular morphology.

Table2 Respiratory variables at rest and during exercise

Variables	Fontan patients (n=46)
%Vital capacity	83+/-13
% Forced expiratory volume in 1s	98+/-11
Respiratory rate at rest ,/min (%)	21+/-6(131+/-28)
Peak respiratory rate,/min (%)	34+/-7(101+/-22)
Tidal volume at rest ,L (%)	0.50+/-0.06(77+/-9)
Peak tidal volume ,L (%)	1.24+/-0.30(76+/-14)
Peak tidal volume-rest tidal volume, L (%)	0.74+/-0.30(71+/-18)
Minute ventilation at rest,L/min (%)	11.0+/-2.7(96+/-17)
Peak minute ventilation ,L/min (%)	42.9+/-10.9(75+/-19)
Ventilation to carbon dioxide production slope (%)	33.7+/-6.6(129+/-22)
Peak minute ventilation / maximum ventilatory volume (%)	0.64+/-0.11(120+/-19)
Peak tidal volume/ inspiratory capacity (%)	0.74+/-0.13(113+/-12)

(%): % of normal value

Table3 Univariate analysis of %PeakVO2 and ventilatory variables

Variables	r	p-value
% Vital capacity	0.66	**<0.01**
% Forced expiratory volume in 1s	0.21	0.24
% Peak respiratory rate	0.25	0.139
% Peak tidal volume	0.39	**0.032**
% Peak tidal volume -rest tidal volume	0.46	**0.011**
% Peak minute ventilation	0.54	**<0.01**
% Ventilation to carbon dioxide production slope	-0.57	**<0.01**
% Peak minute ventilation / maximum ventilatory volume	0.21	0.22
% Peak tidal volume / inspiratory capacity	0.30	0.11

Table4 Multivariate analysis of %Peak VO2 and ventilatory variables.

Variables	β (95%C.I)	p-value
% Vital capacity	0.29(0.14-0.48)	**0.012**
% Ventilation to carbon dioxide production slope	-0.34(-0.49- -0.18)	**0.009**
	-	r=0.71, p<0.001

Table5 Univariate analysis of ventilatory variables and clinical factors

Variables	r	p-value
% Peak oxygen uptake		
Age	0.39	**0.019**
age at surgery	0.38	**0.024**
years after surgery	0.18	0.46
% Vital capacity		
Age	0.45	**<0.01**
age at surgery	0.38	**0.025**
years after surgery	0.13	0.41
% Peak tidal volume		
Age	0.47	**<0.01**
age at surgery	0.43	**0.017**
years after surgery	0.18	0.34
% Peak minute ventilation		
Age	0.41	**0.012**
age at surgery	0.34	**0.045**
years after surgery	0.14	0.43
% Ventilation to carbon dioxide production slope		
Age	0.42	**<0.01**
Age at surgery	0.38	**0.033**
Years after surgery	0.21	0.11

Table6 Univariate analysis of ventilatory and central hemodynamic variables.

variables	r	p-value
% Peak oxygen uptake		
Central venous pressure	0.02	0.926
Pulmonary arterial wedge pressure	0.15	0.369
Systemic ventricle ejection fraction	0.02	0.921
Cardiac index.	0.21	0.180
% Vital capacity		
Central venous pressure	-0.66	0.519
Pulmonary arterial wedge pressure	-0.05	0.576
Systemic ventricle ejection fraction	0.11	0.685
Cardiac index	0.45	0.911
% Ventilation to carbon dioxide production slope		
Central venous pressure	0.14	0.793
Pulmonary arterial wedge pressure	0.64	0.253
Systemic ventricle ejection fraction	0.02	0.894
Cardiac index	0.37	0.858

Table7 Respiratory variables and ventricular morphology

Variables	Left ventricle (n=18)	Right ventricle (n=28)	p-value
% Vital capacity	85+/-12	82+/-14	n.s.
% Forced expiratory volume in 1s	98+/-10	101+/-13	n.s.
% Peak respiratory rate	101+/-19	102+/-22	n.s.
% Peak tidal volume	76+/-8	78+/-10	n.s.
% Peak tidal volume -rest tidal volume	72+/-20	72+-18	n.s.
% Peak minute ventilation	77+/-18	75+/-21	n.s.
% Ventilation to carbondioxide production slope	134+/-19	138+/-24	n.s.
% Peak minute ventilation / maximum ventilatory volume	121+/-18	119+/-16	n.s.
% Peak tidal volume / inspiratory capacity	112+/-14	113+/-17	n.s.

Both of absolute value and % of normal predicted value, Peak VT, peak VE and increase in VT during exercise (peak VT-rest VT) showed a negative correlation with patient age and age at Fontan operation. The potential effect of the number of palliative operations is shown in Fig.1. Patients who underwent palliative operations more than 3 times had diminished values of %peakVO_2 and %VC. As shown in Fig.2, peak VT / IC had no significant correlation with % peakVO_2. Twenty-four patients (53%) had a VT exceeding 70% of the IC at peak exercise.(area I and II of Fig.2) Out of these patients, 12 patients (27%) had a low peakVO_2 which was less than the mean value of all patients (area I of Fig.2), which the restrictive impairment during exercise might have negative impact on the exercise capacity.

Discussion

Increasing number of adult patients late after the Fontan operation has been important clinical issue in the last decade. In the adult congenital heart disease unit of our hospital, also, a large part of them have been reaching in their 20s and 30s. We need to give the whole issue a second thought in terms of their late outcome. Consistence with former study[3,4,5,6], we described that restrictive pattern of lung function, which deteriorated with age, both in the rest and during exercise in the patients late after the Fontan operation. In the present study, we highlighted the findings as follows: 1) Although one thirds of the patients revealed restrictive pattern of lung function at rest, closely observing parameters of lung function during exercise, more than half of adult patients have restrictive impairment during exercise. 2) %VC and VE/VCO2 slope were independent determinants for exercise capacity in these patients. 3) Patients who underwent palliative operations more than 3 times had diminished values of %peakVO_2 and %VC. 4) Intervention for lung function, such as respiratory rehabilitation, may has a beneficial effect some part of the patients, who has high VC/IT and low peak VO2 (area I of Fig.2).

Lung function at rest

In this study, 36% of the Fontan patients demonstrated the restrictive pattern of lung function at rest. This impairment became worse with the aging of patients and was related with age at operation. Consistence with previous report, the number of surgical procedure has inversely correlated with vital capacity and peak oxygen uptake. According to these results, it is possible that an early and minimum surgical procedures improve both of their lung function and exercise capacity in the late after period.

Lung function and central hemodynamics

In this study, we do not find any clinical impact of central hemodynamics obtained by cardiac catheterization, including systemic ventricle morphology, on the lung function. As we previously

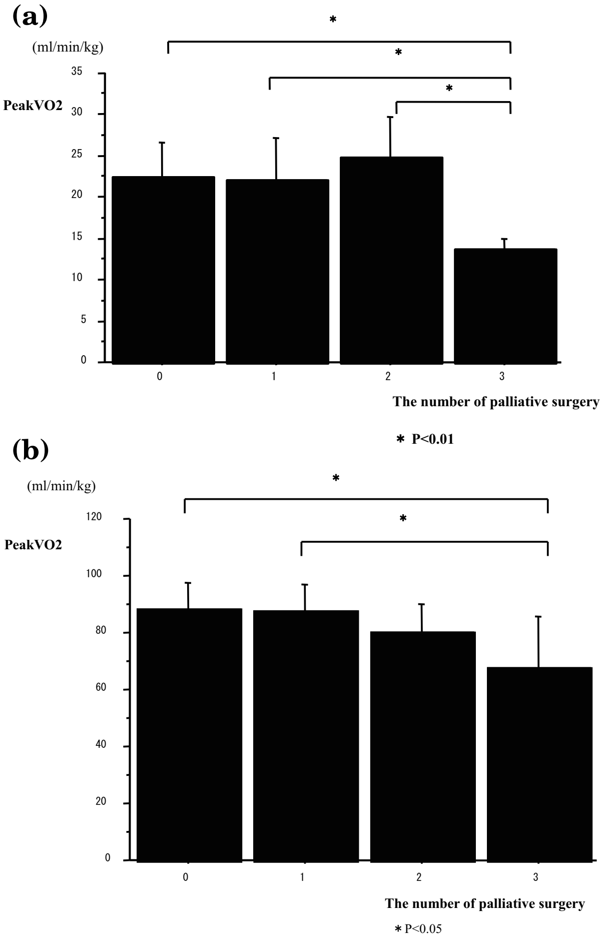

Fig.1

The potential effect of the number of palliative operations is shown in this table. Patients who underwent palliative operations more than 3 times had diminished values of both % peak oxygen uptake (a) and % vital capacity (b).

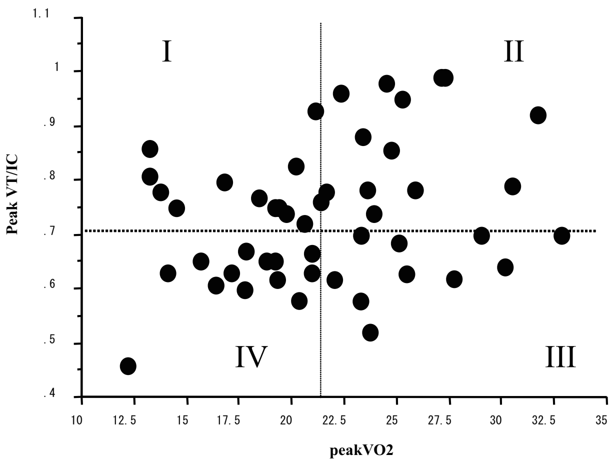

Fig.2

Peak tidal volume / inspiratory capacity had no correlation with peak oxygen uptake. However, it can be considered that lung function might limit exercise capacity in patients with a lower value of peak oxygen uptake and a higher value of tidal volume / inspiratory capacity (within area I). Patients whose tidal volume / inspiratory capacity was more than 0.7 were considered as having severely low respiratory reserve at peak exercise.

described, in the Fontan patients, central hemodynamics have less impact on exercise capacity. Because various factors could contribute to these status, the cause of exercise intolerance and the abnormal ventilatory response during exercise in Fontan patients has not been fully elucidated. This led us to attention to the peripheral factors, such as vascular function and muscle hemodynamics. Main concern in the future direction may, even in lung function study, shift to the peripheral factors, which we did not investigated in this study: chemoreceptor function and skeletal muscle afferents, such as metabo- and mechanoreceptor, may have an important effect on the ventilatory response [14,15,16] . It is reported that both patients with cyanotic heart disease and after Fontan patients have impaired chemoreceptor function, which induced excessive ventilation during exercise [14,16]. It is possible that duration and magnitude of hypoxia before Fontan operation affected the chemoreceptor function, and blunted reflex remained even after elimination of cyanosis by Fontan operation.

Lung function and exercise capacity

We demonstrated that exercise capacity in the Fontan patients decreased with age as in %VC. Fredriksen et al [4] observed no decline in aerobic capacity with age, whereas, they did not mention any change in lung function with age. The reason of this difference is uncertain. However, because of the main concern of the present study, the mean duration of follow-up was quite longer in our study. Most of the patients in our study are in 20s and 30s in age. This may emerged significant decrease exercise capacity with age.

Wasserman stated that the patients who finished exercise mainly due to respiratory limitation demonstrated more than 70% of VT / IC at peak exercise. According to this finding, it is thought that, in Fontan patients, lung function may have limited the exercise capacity in the patients with a lower value of peakVO_2 and higher value of VT / IC (12 patients, 27%), who had a low respiratory reserve at peak exercise. In turn, lung function might not have such an impact on exercise capacity in other patients (73%)

The relationship between ventilatory variables and exercise capacity, which we described in this study, was indeed detected in other type of patients such as Tetralogy of Fallot and some cyanotic heart disease. [5,17] It is uncertain that these relationship can characterize the Fontan physiology. Ohuchi et al demonstrated increase in dead space ventilation in Fontan patients, which is considered due to an increase in the high ventilation-perfusion space in the lung during exercise.[6,17] This data also indicates another possibility for low ventilatory efficiency in Fontan patients. They considered that lung compliance may be relatively high in these patients because of decreased pulmonary flow.[17] However, less is known about the lung compliance during exercise in Fontan patients . The patients with cogenital cyanotic heart disease often have small size and high resistance pulmonary vessels, so-called poor pulmonary arteries.[18] Recent study have been documented, in the Fontan circulation, it is characterized low cardiac reserve function and afterload-contractility mismatch.[19,20] In addition, it has been reported that diastolic dysfunction is presented in Fontan patients.[21,22] According to these issues, it is possible that Fontan circulation, even in normal ejection fraction in the systemic ventricle, is susceptible to elevation of pulmonary capillary wedge pressure and easily lead to pulmonary congestion during exercise. Small vital capacity and low ventilatory efficiency might influenced to cardiac output during exercise especially in Fontan physiology. To clarify these problems, further investigations , i.e. exercise catheterization , are warranted.

Conclusions

In the adult patients late after the Fontan operation, exercise disclosed the low ventilatory efficiency and the restrictive pattern of lung function. These impairment have been deteriorating with age as well as exercise capacity decreased. The patients with an early surgical procedure obtained higher values of peakVO_2, peak tidal volume during exercise and lower value of VE/VCO_2 slope. Early and minimum surgical procedure may have a beneficial effect in terms of late outcome. To provide sufficient information for adult patients late after the Fontan operation, further investigations to elucidate the relationship between Fontan physiology and lung function, and to determine the prognostic predictive value of the parameters of lung function are warranted.

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