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ORIGINAL ARTICLE

Relation Between Exercise Capacity and Extracardiac Conduit Size in Patients with Fontan Circulation

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Abstract

Because Fontan circulation does not have a subpulmonary ventricle, the preload is limited. In Fontan circulation with extracardiac conduit, the size of conduit could be an important factor in determining the preload. We compared exercise capacity with each conduit size and tried to search for optimal conduit size in Fontan circulation. We reviewed the medical record of 677 patients with Fontan circulation. Patients who had other type Fontan circulation (Kawashima, atriopulmonary, lateral tunnel), $SpO_2 < 85\%$, protein losing enteropathy, results of inappropriate exercise test were excluded. As a result, 150 patients were enrolled and classified according to conduit size. We compared with their exercise capacity and analyzed correlation between exercise capacity and conduit size per body surface area (BSA). 97 Males were included and mean age was 17.5 ± 5.1 years old. In cardiac catheterization, central venous pressure (CVP) was 12.4 ± 2.5 mmHg and pulmonary vascular resistance was 1.2 ± 0.5 wu m^2. In cardiopulmonary exercise test, predictive peak VO2 was $59.1 \pm 9.7\%$ and VE/VCO_2 was 36.2 ± 6.9. In analysis using quadratic model, impacts of gender, age at Fontan operation, ventricular morphology, isomerism, and fenestration on exercise capacity were excluded and conduit size per BSA had a significant curved correlation with predictive peak VO_2 and VE/VCO_2. Our results showed that patients with about 12.5 mm/m^2 conduit per BSA have the best exercise capacity. Patients with larger than smaller-sized conduit were found to be more attenuated in their ability to exercise.

Keywords Fontan · Conduit · Exercise capacity

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Abbreviations

BSA	Body surface area
CVP	Central venous pressure
HR	Heart rate
PVRi	Pulmonary vascular resistance index
Qs	Systemic blood flow
RER	Respiratory exchange ratio
SD	Standard deviation
VAT	Ventilatory anaerobic threshold
VCO_2	Minute carbon dioxide production
VE	Minute ventilation
VEDP	Ventricular end-diastolic pressure
VO_2	Oxygen consumption

Introduction

The Fontan operation is considered definitive palliation in patients with single-ventricle physiology. Since its first description in 1971 [1], several modifications have been introduced, including the lateral tunnel or fenestrated Fontan operation [2, 3]. Lacking a subpulmonic ventricle, the Fontan circulation has to maintain high systemic venous pressure and low pulmonary artery pressure and the preload is limited [4, 5]. The limitation of preload is more prominent during exercise [6]. In extracardiac conduit type Fontan circulation, conduit size can be an important factor in determining preload [6, 7].

In an extracardiac Fontan operation, a larger conduit for body size is used to allow for the patient growth. However, a large conduit causes inefficient flow due to turbulence or stagnation and might cause later problems such as thrombosis or stenosis [8, 9]. Despite improvements in surgical strategies and techniques, the optimal conduit size in the extracardiac Fontan operation has not yet been determined. We aimed to determine optimal extracardiac conduit size based on exercise capacity in patients with Fontan circulation.

Subjects and Methods

We retrospectively reviewed the medical records of 677 patients over 10 years old who underwent a Fontan operation in Seoul National University and Sejong General Hospital. Of these, 46 were mortality or heart transplantation cases, and 228 did not have extracardiac conduit type Fontan circulation (atriopulmonary, lateral tunnel type, and Kawashima type). A total of 527 patients were excluded for various causes that could limit exercise capacity (Table 1). We compared hemodynamic data from cardiac catheterization and results from cardiopulmonary exercise test. The correlation between results from cardiopulmonary exercise test and conduit diameter for body surface area was analyzed.

Patients underwent progressive exercise testing with expiratory gas analysis. Cardiopulmonary exercise testing (Quinton Q-stress®, Cardiac Science, WI, USA/Vmax®, CareFusion, CA, USA/GE Medical systems, T2100 CASE, Mexico) was performed with a modified Bruce protocol.

Table 1 Characteristics of excluded patients

Total patients who underwent Fontan operation	677
Cause	Number
Mortality or transplantation	46
Other type of Fontan circulation (atriopulmonary, lateral tunnel, Kawashima type)	228
19-mm conduit	4
Protein losing enteropathy	22
Significant cyanosis (< 85%)	10
Single-lung Fontan circulation	4
Severe ventricular dysfunction	4
Inappropriate exercise test	60
Loss of follow-up	149

RER respiratory exchange ratio

Expiratory gas analysis was performed with a Medical Graphics metabolic cart (TrueOne 2400®, ParvoMedics, Salt Lake City, UT, US). Oxygen consumption, carbon dioxide production (VCO_2), and minute ventilation (VE) were measured on a breath by breath basis and analyzed in 15-s intervals. Peak VO_2 was defined as the highest VO_2 achieved by the subject during the test. Ventilatory anaerobic threshold (VAT) was measured using the V-slope method when it could be accurately determined [10]. Values for VO_2 were indexed to body surface and expressed as percentage of predicted values for healthy age- and sex-matched subjects as reported by Cooper and Weiler-Ravell [11]. The ventilatory equivalent of carbon dioxide (VE/VCO_2) was measured at the ventilatory anaerobic threshold (VAT) determined with the V-slope method [10]. The respiratory exchange ratio (RER) (VCO_2/VO_2) was measured continuously. The pulse O_2 (VO_2/heart rate [HR]) was measured at peak VO_2 and indexed to body surface area. The pulse O_2 was equal to the product of stroke volume and the arterial-venous O_2 content difference. Because the arterial-venous O_2 content difference at peak exercise varies little among subjects, the pulse O_2 was used as a surrogate for stroke volume at peak exercise [12].

Resting 12-lead electrocardiograms were performed in sitting and standing position and during brief hyperventilation. Heart rate was monitored continuously. The chronotropic index, a measure of response that is independent of resting HR and stroke volume, was defined as: chronotropic index = (maximal achieved HR − resting HR)/(predicted maximal HR − resting HR) [13, 14].

Cardiac catheterization was performed with the patient conscious and the pressure and oxygen saturation were measured in a stable state. Calculation of systemic and pulmonary flow and their ratio (Qp/Qs) was made using the principles described by Fick, with assumed values for O_2 consumption according to data published by LeFarge and Miettinen [15]. The superior and inferior vena cava saturations were taken as the mixed venous and systemic arterial saturation in the descending thoracic aorta. Pulmonary venous saturations were obtained by pulmonary artery wedge or left ventricle indirectly. Total pulmonary vascular resistance was expressed in indexed Woods Units (WU). An oxygen delivery was calculated as the product of the cardiac index and arterial O_2 content. Because all initial hemodynamic evaluations were performed with the patient breathing room air, the contribution of dissolved O_2 was excluded from these calculations. Cardiac catheterization was performed by a pediatric cardiologist with more than 5 years of experience.

Statistical analysis was performed with SPSS 22.0 (SPSS Inc., Chicago, IL, USA) for Windows and R. Descriptive data are presented as numbers with percentage, mean with standard deviation (SD) as appropriate. Generalized additive model (GAM) is a method for finding the non-linear relationship between independent variables and response variables using nonparametric function assuming that the relationship between independent variables and response variables is not linear. Generalized additive model (GAM) is applied to identify non-linear association between conduit diameter per BSA and predicted peak VO2. We also performed GAM between conduit diameter per BSA and VE/VCO_2 with adjustment for gender, Fontan operation age, ventricular Morphology, isomerism, and Fenestration. Statistical test were two sided, and a p value ≤ 0.05 was considered statistically significant. All analyses were performed by using SPSS 25.0 (IBM Corp., Armonk, NY, USA) and R software (version 3.4.1; The Comprehensive R Archive Network: https://cran.r-project.org). This study was approved by the institutional review board in Seoul National University and Sejong General Hospital.

Results

The medical records of 677 patients were reviewed and 527 were excluded for various causes limiting exercise capacity (Table 1). The baseline patient characteristics are shown in Table 2. In correlation study between predictive peak VO_2 and hemodynamic data from cardiac catheterization such as CVP, VEDP, PVR, and Qs, only CVP had significant linear negative correlation with peak VO_2 (p value 0.026). In correlation study between VE/VCO_2 and hemodynamic data from cardiac catheterization such as CVP, VEDP, PVR, and Qs, only VEDP had significant linear negative correlation with peak VO_2 (p value 0.041).

For adjusting the impact of other factors on exercise capacity, we analyzed by quadratic model (Tables 3, 4). Analysis of the correlation between predicted peak VO_2 and conduit diameter per body surface area (BSA) showed a significant convex curved correlation ($p = 0.0387$) and a maximum peak VO_2 at about 12.7 mm/m^2 conduit diameter per BSA. (Fig. 1a) We analyzed the correlation between VE/VCO_2 and conduit diameter per BSA. These patients showed a significant concave curved correlation pattern ($p = 0.0211$) (Fig. 1b), with a lowest value at 12.4 mm/m^2 conduit diameter per BSA. Patients had maximum exercise capacity at about 12.5 mm/m^2. Even though we analyzed the significance between exercise capacity and other factors such as age at Fontan operation, ventricular morphology, isomerism, and fenestration in Fontan pathway, they did not showed the significance statistically (Tables 3, 4).

Table 2 Baseline characteristics (Mean ± SD)

Total patients: 150
Male: Female 97: 53
Mean age
  At Fontan operation (years): 4.02 ± 4.04 (1.4–29.3)
  At cardiopulmonary exercise test (years): 17.5 ± 5.1 (10.3–42.3)
Mean body surface area (m^2): 1.57 ± 0.21 (0.93–2.25)
Data of cardiac catheterization (91 patients)
  Mean age at cardiac catheterization (years): 17.4 ± 5.8 (5.77–42.8)
  Mean interval between cardiac catheterization and cardiopulmonary exercise test (years): 0.76 (0.0–6.8)
  Mean central venous pressure (mmHg): 12.4 ± 2.5 (7.0–18.0)
  Mean ventricular end-diastolic pressure (mmHg): 9.3 ± 2.8 (3.–19.0)
  Mean pulmonary vascular resistance (wu·m^2): 1.2 ± 0.5 (0.3–2.7)
  Mean systemic blood flow (L/min/m^2): 2.73 ± 0.79 (1.40–4.50)
  Mean resting saturation (%): 94.5 ± 3.0 (85.0–100.0)
Cardiopulmonary exercise test
  Peak respiratory exchange ratio: 1.12 ± 0.09 (1.60–1.12)
  VO_2 at anaerobic threshold (ml/kg/min): 21.7 ± 5.0 (8.1–35.1)
  Peak VO_2 (mL/kg/min): 28.2 ± 6.1 (16.4–51.3)
  Predicted peak VO_2 (%): 59.1 ± 9.7 (39.0–88.0)
  VE/VCO_2: 36.2 ± 6.9 (20.2–60.1)
  Predicted peak heart rate (%): 87.8 ± 7.9 (70.0–114.0)
  Chronotropic index: 0.77 ± 0.15 (0.39–1.38)

LV left ventricle, *RV* right ventricle, *SD* standard devication, *VE* minute ventilation, *VCO_2* minute carbon dioxide production, *VO_2* oxygen consumption

Table 3 The quadratic model between predicted peak VO_2 and conduit diameter per BSA

	Estimate	SE	t Value	p Value
(Intercept)	27.649	19.880	1.391	0.166
Conduit diameter per BSA	5.393	2.873	1.877	0.062
Conduit diameter per BSA^2*	−0.211	0.101	−2.087	0.038
Gender	0.957	1.698	0.564	0.574
Age at Fontan operation	0.258	0.210	1.229	0.221
Ventricle morphology (RV)	−2.835	1.960	−1.447	0.150
Ventricle morphology (LV)	−1.099	2.363	−0.465	0.642
Ventricle morphology (both)	−0.874	3.324	−0.263	0.793
Right isomerism	−0.542	3.698	−0.146	0.884
Left isomerism	−4.997	1.893	−2.639	0.009
No fenestration patency	−0.412	2.362	−0.175	0.862
Fenestration patency	1.795	3.197	0.561	0.576

*Value was adjusted by gender, Fontan operation age, ventricular morphology, isomerism, and fenestration

Discussion

Our results showed that patients with extracardiac Fontan circulation showed maximum exercise capacity at about 12.5 mm/m^2 conduit diameter per BSA. More importantly, the group with smaller conduits showed better exercise capacity than those with larger conduits. Most surgeons have determined conduit size based on the size of the inferior vena cava [9]. As an extracardiac conduit using a Gore-Tex

Table 4 The quadratic model between VE/VCO_2 and conduit diameter per BSA

	Estimate	SE	t Value	*p* Value
(Intercept)	60.70653	14.18407	4.28	3.49E−05
Conduit diameter per BSA (mm/m^2)	−4.21446	2.05056	−2.055	0.0418
Conduit diameter per BSA^2 (mm/m^2)*	0.16879	0.07235	2.333	0.0211
Gender	−2.270	1.213	−1.872	0.063
Age at Fontan operation	−0.161	0.150	−1.076	0.284
Ventricle morphology (RV)	2.534	1.402	1.807	0.073
Ventricle morphology (LV)	1.477	1.687	0.875	0.383
Ventricle morphology (both)	0.137	2.376	0.058	0.954
Right isomerism	3.719	2.638	1.410	0.161
Left isomerism	3.015	1.352	2.230	0.027
No fenestration patency	1.979	1.686	1.174	0.243
Fenestration patency	0.285	2.282	0.125	0.901

*Value was adjusted by gender, Fontan operation age, ventricular morphology, isomerism, and fenestration.

conduit does not have growth potential, there may be concern that a smaller conduit can cause hemodynamic problems as the patient grows. Particularly because of the small size of the inferior vena cava with use of a small conduit (especially a 16-mm Gore-Tex conduit), this limitation has been a concern and larger conduits have been used [16]. However, our results showed that patients with larger conduits showed a greater decrease in exercise capacity. These results suggest that flow stagnation with use of a larger conduit rather than flow disturbance with use of a smaller conduit negatively affects exercise capacity. Similar results have been reported in prior studies using computational models [8]. In this study, 16- and 18-mm conduits were found to be optimal and larger conduits had redundant space. In our study, the size of the optimal conduit was about 20 mm when considering the body surface area of the patient (BSA 1.57 $m^2 \times 12.5$ mm), and results of the previous study are almost the same considering the luminal stenosis by intimal endothelization.

The other theoretical background of this phenomenon is based on the conduit area change rate. (Fig. 2a) Based on a 20-mm conduit, although 16-mm and 24-mm conduits have the same diameter difference, the area change rate is not same. The area change rate of the 16-mm conduit is −35.9% and area change rate of the 24-mm conduit is + 43.9%. As the size of the conduit increases, the rate of change in the conduit area is greater than the rate when it increases. In addition, luminal narrowing caused by endothelization of the Gore-Tex conduit further exacerbates the difference in the area change rate between large and small conduit (Fig. 2b). Therefore, it is thought that when the conduit size is increased based on an optimal size, the change rate of the area is larger, causing a further decrease in exercise capacity.

The most difficult aspect of this study was the selection of appropriate patients. In fact, this study was not easy because there were too many factors that could affect exercise capacity [7]. Therefore, the authors analyzed patients in detail and excluded all patients with factors that could affect their exercise capacity. Only 150 of the 677 patients in both institutions were included in the study. Patients with suspected bronchial, pulmonary arterial or pulmonary parenchymal abnormalities on chest CT were excluded. Because patients with a fenestration or veno-veno collateral vessels have increased VE/VCO_2 [17], those with a fenestration on imaging or a lung/whole body ratio < 0.9 on a radioisotope scan were excluded from analysis of VE/VCO_2.

Statistical analysis was also a problem. As shown in previous results, the relationship between the predicted peak VO_2 and conduit size and the relationship between the VE/VCO_2 and conduit size showed curved correlation patterns (Fig. 1a, b). A curved correlation pattern cannot exclude the influence of other factors. Therefore, to rule out such interference, we used the quadratic model and could exclude influence by gender, age at Fontan age, ventricular morphology, isomerism, and fenestration.

As a retrospective and double-center study, this research had several limitations. Moreover, there can be a selection bias because this study included a small number of patients with heterogeneous diseases. Pulmonary function testing was not performed in many patients and airway or pulmonary parenchymal diseases were excluded by chest CT angiography. We did not directly measure preload, but estimated the value based on cardiopulmonary exercise test. However, it was difficult to measure the preload in a static state with current technology, and was even more difficult to measure during exercise. The curved correlation pattern did not completely eliminate the influence of other factors; however, we overcame this problem by quadratic model.

Despite the above limitations, our study was significant for several reasons. The optimal conduit size in Fontan circulation was found to be about 12.5 mm/m^2 conduit diameter per BSA (18 or 20 mm Gore-Tex conduit); these patients

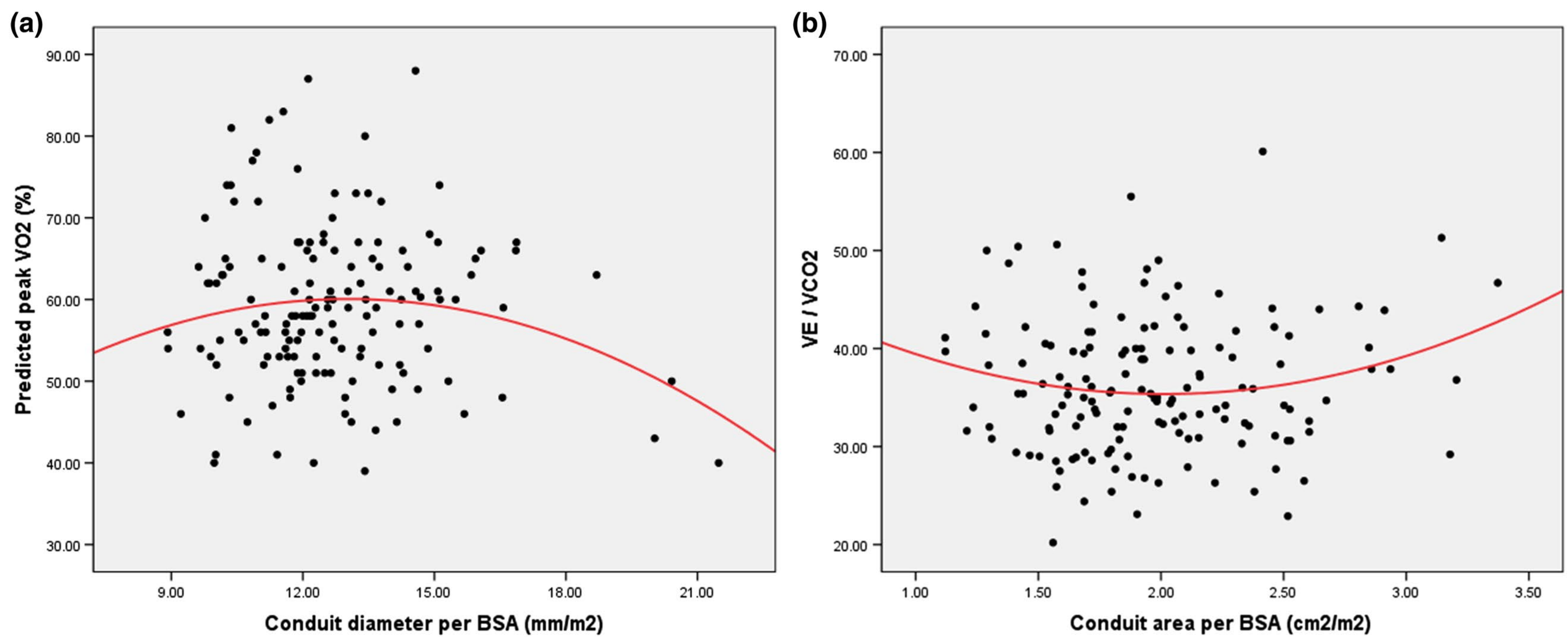

Fig. 1 Correlation analysis between predicted peak VO_2 and conduit diameter per body surface area (**a**) showed a significant convex curved pattern and a maximum peak VO_2 at about 12.7 mm/m^2 conduit diameter per BSA. Correlation analysis between VE/VCO_2 and conduit diameter per BSA (**b**) showed a significant concave curved correlation

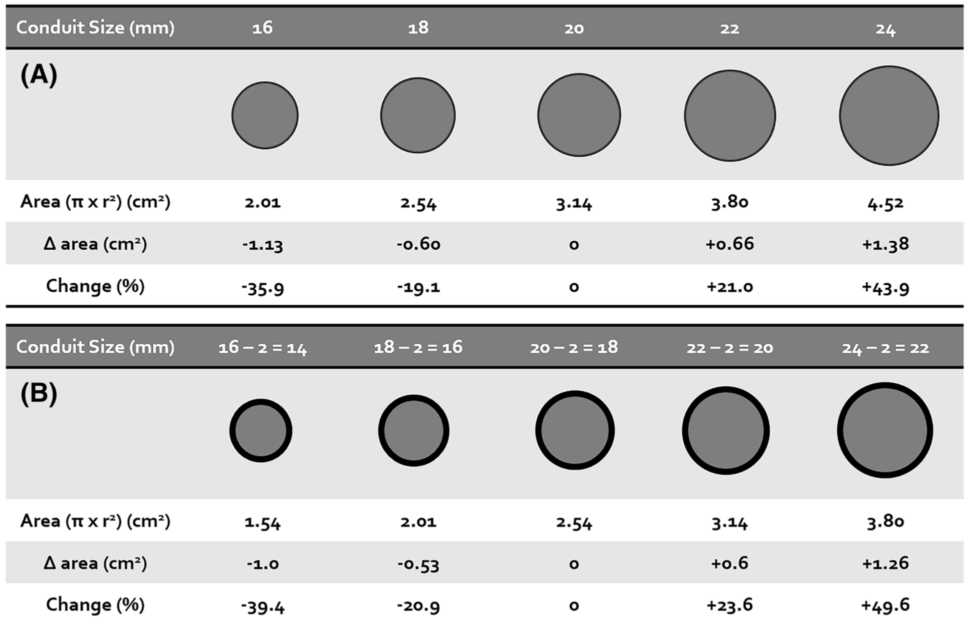

Fig. 2 The area change rate based on a 20-mm conduit (**a**) and the area change rate assuming luminal narrowing with intimal growth (**b**)

showed the best exercise capacity. Patients with larger conduits were less able to exercise. These results suggest that larger-sized conduit from optimal size may be more attenuating factor rather than smaller for supplying preload during exercise. Therefore, we need not try to put in too large sized conduit in operation room. We discussed the theoretical background using the area change rate concept.

Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was waived by this retrospective study from my hospital institutional review board.

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