

Positive pediatric exercise capacity trajectory predicts better adult Fontan physiology rationale for early establishment of exercise habits

Hideo Ohuchi^{a,b,*}, Jun Negishi^a, Hikari Miike^a, Yuka Toyoshima^a, Hitomi Morimoto^a, Midori Fukuyama^a, Toru Iwasa^a, Heima Sakaguchi^a, Aya Miyazaki^a, Isao Shiraishi^a, Kenichi Kurosaki^a, Michikazu Nakai^c

^a Departments of Pediatric Cardiology, National Cerebral and Cardiovascular Center, Osaka, Japan

^b Adult Congenital Heart Disease, National Cerebral and Cardiovascular Center, Osaka, Japan

^c Preventive Medicine and Epidemiologic Informatics, Center for Cerebral and Cardiovascular Center, National Cerebral and Cardiovascular Center, Osaka, Japan

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ABSTRACT

Objective: Exercise training is recommended for its possible favorable effects on Fontan pathophysiology. This study aimed to elucidate the impact of pediatric exercise capacity trajectory, which may mimic the effect of exercise training, on late adult Fontan pathophysiology.

Methods: Since 1990, 97 Fontan patients had consecutively undergone two serial cardiopulmonary exercise tests (CPX1 and CPX2) during childhood (ages 8 ± 2 and 14 ± 2 years) and one during adulthood (CPX3; age 23 ± 5 years). The changes in peak oxygen uptake (PVO₂: % of normal value) from CPX1 to CPX2 (1-dPVO₂) and from CPX2 to CPX3 (2-dPVO₂) were calculated, and then the patients were divided into four subgroups according to the 1-dPVO₂ and 2-dPVO₂.

Results: In their adulthood, when compared with groups with negative 1-dPVO₂, the central venous pressure, plasma brain natriuretic peptide level, and renal resistive index were lower, whereas liver synthetic function, body fat-free percentage, and PVO₂ were higher in those with positive 1-dPVO₂ ($p < 0.05$ – 0.0001). However, these favorable associations of 2-dPVO₂ with adult Fontan pathophysiology were not observed, except for the PVO₂. After CPX3, 13 unexpected events occurred, and the risk was 76% lower in the groups having positive 1-dPVO₂ than in those with negative 1-dPVO₂ (hazard ratio, 0.24; 95% confidence interval, 0.09–0.62; $p = 0.0035$).

Conclusions: A positive exercise capacity trajectory during childhood predicts better adult Fontan pathophysiology, including better prognosis. Thus, prescription of exercise could be a promising strategy in the management of pediatric Fontan patients.

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1. Introduction

A majority of pediatric patients who underwent Fontan operation have reached adulthood owing to recent medical advancements [1]. However, the chronic congestion and hypoperfusion in multiple organs ultimately lead to high morbidity and mortality [2]. Several clinical interventions aimed at establishing a better management strategy have been attempted, and the interventions consisted of two main approaches, one was medication and the other was exercise training. Although the efficacy of medications has been controversial [3–7], the efficacy of short-term exercise training has been generally positive in terms of the improvement in exercise capacity and safety [8–12]. Since exercise capacity is a powerful predictor of mortality in Fontan patients [13], it has been thought that establishing an active lifestyle, i.e., exercise habits, may guarantee a better long-term outcome [14].

However, it has been unclear whether an improved exercise capacity during childhood has a favorable influence on late adult Fontan pathophysiology, and it may be difficult to conduct a long-term randomized clinical trial to demonstrate a direct association between improved exercise capacity through pediatric exercise training and its later benefits on adult Fontan pathophysiology. In this context, investigating the association between long-term serial assessment of exercise capacity, specifically the trajectory of exercise capacity in childhood, and late adult Fontan pathophysiology could give us important information on the possible impact of pediatric long-term exercise training based on our assumption that pediatric exercise capacity trajectory reflects exercise habits during childhood.

2. Methods

2.1. Subjects

From August 31, 1990 to September 13, 2017, a total of 998 cardiopulmonary exercise tests (CPX) have been performed, and the derived peak oxygen uptake (PVO₂) was measured in 351 patients who underwent Fontan operations. Of these patients, 131 had

* Corresponding author at: Department of Pediatric Cardiology, National Cardiovascular Center, 5-7-1, Fujishiro-dai, Suita, Osaka 565-8565, Japan.
E-mail address: hohuchi@ncvc.go.jp (H. Ohuchi).

undergone at least two serial CPXs in their childhood (<16 years old) and at least one CPX in their adulthood (≥ 16 years old). We used the values of PVO₂ from the first CPX (CPX1) during childhood, from the last CPX performed at nearly 16 years of age (CPX2), and from the latest CPX during adulthood (CPX3). The interval from one CPX to another CPX was at least >2 years. Since the present study aimed to evaluate the association between trajectory of exercise capacity, which might reflect exercise habits and mimic an effect of “exercise training”, and late adult Fontan pathophysiology, we excluded two children incapable of undergoing exercise training, one with severe AV valve regurgitation and the other with hypoxia (resting arterial oxygen saturation $\leq 80\%$). In addition, we excluded 32 children from the assessment due to surgical ($n = 19$), catheter ($n = 11$), and/or device intervention ($n = 2$) between CPXs. Finally, the remaining 97 Fontan patients were included as subjects of the present study. A comparison of clinical characteristics between the 97 Fontan patients and those excluded ($n = 34$) revealed that there was no difference in their characteristics, except for the rate of diuretic usage. The study protocol was approved by the Ethical Committee of the National Cerebral and Cardiovascular Center.

2.2. Exercise protocol and PVO₂

All patients underwent symptom-limited treadmill exercise with expired gas analysis [15]. A 12-lead ECG was used to determine the heart rate, and the PVO₂ (mL/kg/min) was measured. The predicted PVO₂ was estimated according to our gender- and body weight-derived formulas based on 160 children and 49 adult volunteers [16], and the percentage of the predicted PVO₂ was calculated as the ratio of the actual value divided by the predicted value.

2.3. Subgroups according to trajectory of PVO₂

Initially, the patients were divided into four groups according to the difference in the percentage of the predicted value of PVO₂ at the time of CPX1 and CPX2 (1-dPVO₂) testing and CPX2 and CPX3 (2-dPVO₂) testing. If both the 1-dPVO₂ and 1-dPVO₂ were ≥ 0 , (% positive), the patients were categorized as belonging to group PP. If the 1-dPVO₂ was positive and the 2-dPVO₂ was < 0 (% negative), the patients were categorized as belonging to group PN. If the 1-dPVO₂ was negative and the 2-dPVO₂ was positive, the patients were categorized as belonging to group NP. If both the 1-dPVO₂ and 2-dPVO₂ were negative, the patients were categorized as belonging to group NN. Therefore, we assumed that positive 1-dPVO₂ and 2-dPVO₂ reflected a relatively active life during their childhood and during childhood to young adulthood, respectively, which might mimic the effect of long-term “exercise training” during the corresponding period.

2.4. Assessment of adult Fontan pathophysiology

The following investigations were performed at the time of CPX3 testing as part of the clinical practice.

2.4.1. Hemodynamics

Cardiac catheterization was performed in 93 patients with an interval of 1 week between each CPX test, and the hemodynamic variables were obtained as previously described [17]. Ventricular morphology was determined using echocardiography and/or cine ventriculography, and the patients were divided into three groups: those with a dominant left ventricle with or without a rudimentary right ventricle; the presence of both right and left ventricles; and a dominant right ventricle with or without a rudimentary left ventricle [17]. In this study, each group consisted of 31, 23, and 29 patients, respectively, and the latter two groups were categorized as non-left ventricle patients for the analysis. We used Simpson's rule to estimate right and left ventricular volumes with biplane cineventriculography. The end-diastolic ventricular volume was divided by the body surface area to obtain the end-diastolic volume index (mL/m²), and the ventricular ejection fraction (%) was calculated. AV valve regurgitation was estimated by the use of color flow mapping and categorized as none to mild, moderate, or severe.

2.4.2. Brain natriuretic peptide (BNP)

After at least 15 min of rest in supine position, BNP plasma levels were assayed using radioimmunoassay.

2.4.3. Pulmonary function

We measured the vital capacity (VC; l) and the percentage of forced expiratory volume in 1 s (FEV1) among the 88 adult patients (Spirosift, SP-600, Fukuda Denshi, Tokyo), and we calculated the VC as the percentage of the body-height-predicted normal value for Japanese children and adults [18].

2.4.4. Hepatorenal function

We measured the plasma levels of albumin (g/L), total bilirubin (mg/dL), creatinine (mg/dL), and cholinesterase (U/L) and calculated the modified model for end-stage liver disease excluding the INR (MELD-XI) score. Renal resistive index was measured as previously described [19].

2.4.5. Body composition

Fat mass and fat-free mass (kg) were estimated using bioelectrical impedance analysis performed with an InBody 720 (Biospace Co., Ltd., Seoul, Korea) [20] in 72 patients, and the ratios (%) of the fat and fat-free masses to total body weight were calculated. Patients with pacemaker implantation were excluded from this analysis.

2.4.6. Clinical events after CPX3

Cardiac events related to Fontan pathophysiology were defined as those requiring unscheduled hospitalization (USH) included arrhythmias; heart failure; protein-losing enteropathy and its relapse; hemostatic complications, such as thromboembolism and hemoptysis; catheterization and/or surgical intervention; and all-cause death. Patients were categorized as having heart failure if at least one of the following was present: orthopnea, nocturnal dyspnea, pulmonary edema, increasing peripheral edema, or radiological signs. Decisions for emergent catheter and/or surgical intervention for hemodynamic abnormalities were made during our clinical conferences. Therefore, scheduled catheterization, such as coil embolization for venous collaterals, was not considered as USH.

2.5. Statistical analysis

Data are expressed as the mean \pm standard deviation. Due to a skewed data distribution for the plasma BNP level, the natural logarithmic value was used for some statistical analyses. The differences in patients' clinical characteristics, hemodynamics, and end-organ functions were evaluated using an unpaired *t*-test or a one-way ANOVA with Tukey's post hoc test, as appropriate. Repeated ANOVA was used to assess the serial change in PVO₂ from childhood to adulthood. Comparisons of the prevalence of pre-Fontan procedures, diagnosis, and medication usage were analyzed using chi-square or Fisher's exact test. We employed simple regression analysis to determine the correlations of 1-dPVO₂ and 2-dPVO₂ with adult Fontan hemodynamics, pulmonary function, hepatorenal function, and body composition. Logistic regression model was used to determine predictors of patients belong to group PP. We used Cox's proportional hazards model to predict the associations of these clinical factors with morbidity and mortality in adult Fontan patients after CPX3 testing. USH-free and all-cause mortality-free statuses were estimated using the Kaplan–Meier method, and differences in the status between groups were assessed using log-rank tests. All analyses were performed using the statistical software JMP 12 (SAS Institute, Cary, NC, USA). A two-sided $p < 0.05$ was considered statistically significant.

3. Results

After the exclusion of 34 patients, the value of PVO₂ values during CPX1, CPX2, and CPX3 testing were $54.3 \pm 9.2\%$, $61.6 \pm 13.1\%$, and $59.7 \pm 12.9\%$, respectively. The values of 1-dPVO₂ and 2-dPVO₂ were $7.3 \pm 11.8\%$ and $2.0 \pm 11.0\%$, respectively. PVO₂ increased significantly from CPX1 to CPX2 and from CPX1 to CPX3 ($p = 0.01$), whereas PVO₂ tended to decrease from CPX2 to CPX3 ($p = 0.059$). A positive 1-dPVO₂ was observed in 74 patients (group P) with a mean of $11.7 \pm 9.2\%$, whereas a negative 1-dPVO₂ was observed in 23 patients (group N) with a mean of $-7.1 \pm 6.5\%$. Further group subdivision was made, and the numbers of patients in groups PP, PN, NP, and NN were 38, 36, 13, and 10, respectively. Comparisons of clinical variables among these four subgroups are shown in Table 1. The time interval from CPX2 to CPX3 was significantly longer in the group with negative 1-dPVO₂, i.e., group N.

3.1. Associations of trajectory of PVO₂ with adult Fontan pathophysiology

Comparisons of clinical variables between groups P and N based on 1-d-PVO₂ and 2-d-PVO₂ are shown in Table 2.

3.1.1. PVO₂

In both subgroup analyses based on 1-dPVO₂ and 2-dPVO₂, the PVO₂ at CPX3 testing was higher in group P than in group N ($p < 0.0001$). 1-dPVO₂ and 2-dPVO₂ were positively correlated with PVO₂ at CPX3 testing ($r = 0.50$, $p < 0.0001$ and $r = 0.36$, $p = 0.0004$, respectively, Fig. 1).

3.1.2. Hemodynamics

In the subgroup analysis based on 1-dPVO₂, the central venous pressure (CVP) and log BNP were lower in group P than in group N, and arterial blood oxygen saturation (Sat) tended to be higher in group P, whereas no significant difference was observed among other hemodynamic variables. 1-dPVO₂ was inversely correlated with CVP and log BNP at the time of CPX3 ($r = -0.21$, $p = 0.0419$ and $r = -0.50$, $p < 0.0001$, respectively) and was positively correlated with Sat ($r = 0.25$, $p = 0.0154$). However, no such associations were observed in the subgroup analysis based on 2-dPVO₂ (Fig. 2).

Table 1
Clinical characteristics of all subjects and the four subgroups according to trajectories of peak VO₂ at CPX1.

Group	All	PP	PN	NP	NN	p
Cases (male)	97 (62)	38 (29)	36 (20)	13 (7)	10 (6)	
Era of 1st Fontan operation (year)	1996 ± 4	1997 ± 3	1997 ± 5	1995 ± 6	1992 ± 4*!	0.0074
Age at 1st Fontan operation (years)	4 ± 3	4 ± 2	3 ± 2	7 ± 3*!	5 ± 3!	< 0.0001
<i>Age at CPX (years)</i>						
Child: CPX1 (years)	8.4 ± 1.8	8.2 ± 1.6	7.9 ± 1.6	9.9 ± 2.1*!	8.6 ± 1.9	0.0044
Child: CPX2 (years)	13.5 ± 1.8	13.2 ± 1.5	13.3 ± 1.7	14.8 ± 2.1*!	13.3 ± 2.3	0.0397
Adult: CPX3 (years)	22.3 ± 5.0	20.7 ± 3.9	21.6 ± 5.1	26.8 ± 4.9*!	25.1 ± 5.7*	0.0003
Interval from CPX1 to CPX2	5.1 ± 1.6	5.0 ± 1.4	5.4 ± 1.5	4.9 ± 2.4	4.8 ± 1.4	0.5649
Interval from CPX2 to CPX3	8.8 ± 4.8	7.4 ± 4.0	8.3 ± 4.4	11.9 ± 5.2*	11.7 ± 5.8*	0.0036
<i>Type of 1st Fontan procedure</i>						
APC/IAR/ECR	7/43/47	1/17/20	2/13/21	1/8/4	3/5/2	0.0893
<i>Disease</i>						
Heterotaxy (%)	34 (35%)	14 (37%)	12 (33%)	6 (46%)	2 (20%)	0.6002
Non-LV (%)	64 (66%)	11 (29%)	12 (33%)	7 (54%)	3 (30%)	0.4456
<i>Hemodynamics</i>						
CVP (mm hg)	11 ± 3	10 ± 3	10 ± 2	13 ± 3*!	12 ± 2	0.0174
CI (L/min/m ²)	3.1 ± 0.7	3.4 ± 0.8	3.0 ± 0.6	2.8 ± 0.7	2.6 ± 0.6*	0.0041
EDVI (ml/m ²)	79 ± 24	77 ± 22	78 ± 26	79 ± 22	86 ± 30	0.8197
EF (%)	54 ± 10	55 ± 9	54 ± 12	51 ± 8	57 ± 10	0.6062
Sat (%)	94 ± 3	93 ± 4	94 ± 3	93 ± 3	94 ± 3	0.6389
BNP (pg/ml) (n: cases measured)	20 ± 44 (66)	13 ± 14 (27)	15 ± 10 (31)	17 ± 6 (4)	109 ± 165 (4)*!†	0.0002
NYHA class	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.3 ± 0.5	1.1 ± 0.3	0.239
<i>Exercise capacity</i>						
Peak VO ₂ (mL/kg/min)	29 ± 5	27 ± 5	30 ± 5*	28 ± 3	32 ± 6*	0.0075
Peak VO ₂ (% of normal)	54 ± 9	50 ± 9	57 ± 9*	55 ± 7	60 ± 9*	0.0008
<i>Medications (%) at 1st CPX</i>						
Diuretics	38 (39%)	12 (32%)	14 (39%)	8 (62%)	4 (40%)	0.3089
Anti-coagulant	71 (73%)	28 (74%)	26 (72%)	11 (85%)	6 (60%)	0.6133
ACEI/ARB	11 (11%)	1 (3%)	7 (19%)	2 (15%)	1 (10%)	0.1017
Beta blocker	4 (4%)	1 (3%)	2 (6%)	1 (8%)	0 (0%)	0.6611
Anti-arrhythmia	6 (6%)	2 (5%)	2 (6%)	1 (8%)	1 (10%)	0.9514

Subgroups of PP, PN, NP, and NN are defined in the text. BNP = brain natriuretic peptide, CI = cardiac index, CVP = central venous pressure, EDVI = ventricular end-diastolic volume index, EF = ventricular ejection fraction, NYHA = New York Heart Association, Sat = arterial Oxygen saturation, VO₂ = oxygen uptake. *, ! and † indicate statistically significant ($p < 0.05$) vs. groups PP, PN and NP, respectively.

3.1.3. Pulmonary function

In the subgroup analysis based on 1-dPVO₂, FEV1 was significantly greater and VC tended to be greater in group P than in group N. 1-dPVO₂ was positively correlated with VC and FEV1 ($r = 0.32$, $p = 0.0018$ and $r = 0.28$, $p = 0.0083$, respectively). However, no such associations were observed in the subgroup analysis based on 2-dPVO₂ (Fig. 2).

3.1.4. Hepatorenal function

In the subgroup analysis based on 1-dPVO₂, plasma levels of albumin and cholinesterase were higher and the renal resistive index was lower in group P than in group N. 1-dPVO₂ was positively correlated with plasma levels of albumin and cholinesterase and inversely correlated with the renal resistive index ($r = 0.31$, $p = 0.0023$; $r = 0.25$, $p = 0.0136$; and $r = -0.45$, $p < 0.0001$; respectively). However, no such associations were observed in the subgroup analysis based on 2-dPVO₂ (Fig. 3).

3.1.5. Body composition

In the subgroup analysis based on 1-dPVO₂, the body fat percentage was lower and the fat-free percentage was higher in group P than in group N. 1-dPVO₂ was inversely correlated with fat percentage and positively correlated with fat-free percentage ($r = -0.25$, $p = 0.033$ and $r = 0.30$, $p = 0.0089$, respectively). However, no such associations were observed in the subgroup analysis based on 2-dPVO₂ (Fig. 3).

3.1.6. Impact of peak VO₂ trajectory on prognosis of adult Fontan patients

After CPX3, 13 USHs (cardiac surgery in 3 patients; catheter intervention in 3; thromboembolic events in 3; and heart failure, arrhythmia,

hepatocellular carcinoma, and sudden death with 1 patient each) including 5 deaths (sudden death in 2 patients, heart failure in 2, and hepatocellular carcinoma in 1 patient) occurred.

The hazard risk for USH was significantly lower in groups of positive 2-dPVO₂ than in groups of negative 2-dPVO₂ (hazard ratio [HR], 0.25; 95% confidence interval [CI], 0.09–0.69; $p = 0.0075$). Interestingly, the hazard risk for USH was also significantly lower in group P than in group N (HR, 0.24; 95% CI, 0.09–0.62; $p = 0.0035$; Fig. 4: a, b). The survival rate also tended to be higher in group P (HR, 0.18; 95% CI, 0.01–1.45; $p = 0.108$). When compared with group NN, the hazard risks for USH and mortality were much lower among non-NN groups (HR, 0.12; 95% CI, 0.05–0.34; $p = 0.0002$ for USH and HR, 0.07; 95% CI, 0.00–0.64; $p = 0.0188$ for mortality). Furthermore, the HR for USH was also significantly lower in groups PN and NP than in group NN (HR, 0.18; 95% CI, 0.06–0.54; $p = 0.003$), indicating a certain period of positive PVO₂ trajectory had a significant favorable impact on prognosis. The USH-free rates of all subgroups are shown in Fig. 4 (c).

3.1.7. Predictors of the PP Fontan group

Among the patient profiles at initial CPX1, including age and time of Fontan operation, type of repair, pre-Fontan procedures, ventricular morphology, hemodynamics, %-predicted PVO₂, use of medications, higher cardiac index (OR: 3.74 per L/min/m²), lower PVO₂ (OR: 0.88 per 1%), and the absence of angiotensin-converting enzyme inhibitors or angiotensin receptor antagonist (OR: 0.07) independently predicted the group of PP patients ($p < 0.01$ – 0.0001). Thus, these PP patients with low exercise capacity, despite having well-perfused organs during childhood, could enjoy a better adult Fontan pathophysiology.

Table 2
Impact of trajectories of peak VO₂ on adult (current) Fontan pathophysiology.

Group	1-d-PVO ₂			2-d-PVO ₂		
	P (Positive)	N (Negative)	p	P (Positive)	N (Negative)	p
Cases (n)	74	23		51	46	
Current age	21 ± 5	26 ± 5	<0.0001	22 ± 5	22 ± 5	0.9083
Age at 1st Fontan	3.2 ± 2.1	6.2 ± 2.9	<0.0001	4.5 ± 2.9	3.2 ± 2.1	0.016
Year at 1st Fontan	1994 ± 5	1997 ± 4	0.0014	1996 ± 4	1996 ± 5	0.6413
Years between CPX1 and CPX2	4.8 ± 2.0	5.2 ± 1.5	0.3721	5.0 ± 1.7	5.3 ± 1.5	0.3554
Years between CPX2 and CPX3	7.8 ± 4.2	11.9 ± 5.4	0.0003	8.6 ± 4.7	9.0 ± 4.9	0.651
<i>Functional capacity</i>						
NYHA class	1.1 ± 0.4	1.8 ± 0.8	<0.0001	1.3 ± 0.5	1.3 ± 0.6	0.7179
Peak VO ₂ (%)	63 ± 12	50 ± 12	<0.0001	62 ± 13	57 ± 12	0.0314
<i>Hemodynamics</i>						
CVP (mm Hg)	9.3 ± 2.2	10.7 ± 3.3	0.0221	10.0 ± 2.7	9.1 ± 2.3	0.1045
CI (L/min/m ²)	2.8 ± 0.6	2.8 ± 0.9	0.9677	2.9 ± 0.7	2.7 ± 0.7	0.2953
EDVI (ml/m ²)	77 ± 20	80 ± 22	0.5056	77 ± 23	78 ± 17	0.8654
EF (%)	52 ± 8	52 ± 8	0.9881	51 ± 7	53 ± 9	0.2395
Sat (%)	95 ± 3	93 ± 4	0.0556	95 ± 3	94 ± 3	0.443
log BNP (pg/ml)	2.6 ± 0.8	3.2 ± 0.9	0.0018	2.6 ± 0.7	2.9 ± 1.0	0.1854
<i>Pulmonary function</i>						
Vital capacity (%)	82 ± 17	75 ± 15	0.0709	79 ± 17	83 ± 16	0.3447
FEV1.0 (%)	88 ± 6	83 ± 7	0.0054	87 ± 7	86 ± 5	0.5186
<i>Hepato-renal function</i>						
Albumin	4.6 ± 0.4	4.1 ± 0.8	<0.0001	4.4 ± 0.6	4.4 ± 0.6	0.1647
Ch-E	279 ± 70	233 ± 78	0.0116	262 ± 63	277 ± 85	0.3359
MELD-XI	9.9 ± 0.7	10.0 ± 0.9	0.3588	9.9 ± 0.7	9.9 ± 0.9	0.7969
RRI	0.66 ± 0.06	0.73 ± 0.09	0.0003	0.67 ± 0.07	0.68 ± 0.08	0.3245
<i>Body composition</i>						
Fat (%)	20 ± 8	27 ± 8	0.0057	20 ± 9	23 ± 8	0.2272
Non-Fat (%)	43 ± 5	39 ± 5	0.0026	43 ± 5	42 ± 5	0.2416

BNP = brain natriuretic peptide, Ch-E = cholinesterase, CI = cardiac index, CVP = central venous pressure, EDVI = systemic ventricular volume index, EF = ejection fraction of the systemic ventricle, FEV1 = forced expired volume in one second, MELD-XI = modified model for end-stage liver disease excluding INR, RRI = renal resistive index, VO₂ = oxygen uptake, Sat = arterial oxygen saturation. Values are mean ± SD. Groups of P and N consisted of patients with positive and negative change in peak VO₂ during childhood (1-d-PVO₂) and from childhood to young adult (2-d-PVO₂), respectively.

4. Discussion

This study provided us with the following novel and important thought-provoking information. First, the positive trajectory of PVO₂ during childhood (8–13 years old) was closely associated with better late adult Fontan pathophysiology, including higher PVO₂, preserved pulmonary and hepatorenal functions, favorable body composition, and an even better prognosis. Second, interestingly, associations of 1-dPVO₂ with better adult Fontan physiology

were much stronger than those of 2-dPVO₂. Thus, in pediatric Fontan patients, early establishment of exercise habits could prevent the progression of end-organ dysfunction and predict better prognosis, including low mortality, in their adulthood. Finally, we reconfirmed that a favorable impact of improved exercise capacity on patient outcomes could be anticipated, to some extent, at any postoperative stage, including the post-pediatric period. All these findings might support the rationale that a pediatric exercise training program should be part of all management strategies.

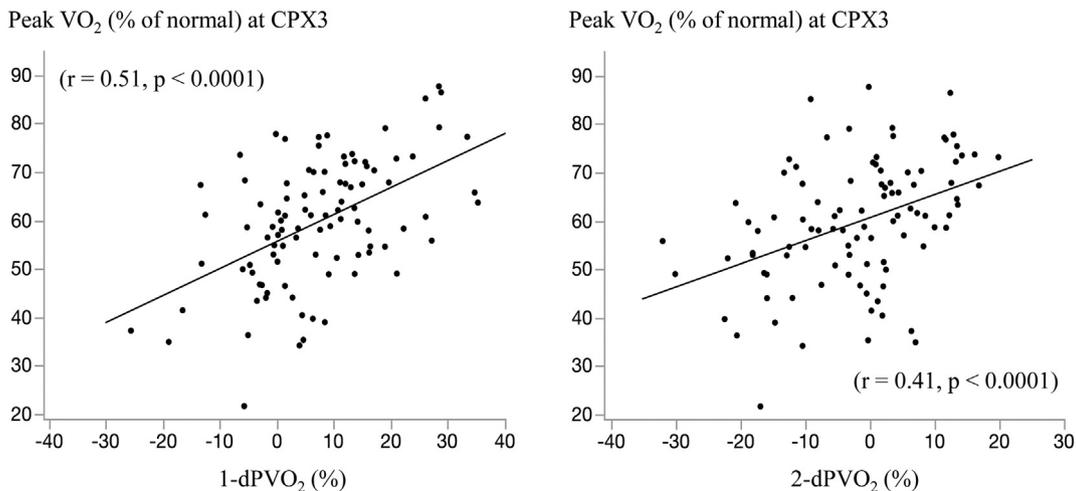


Fig. 1. Associations of 1-dPVO₂ (left) and 2-dPVO₂ (right) with peak VO₂ at CPX3 during adulthood.

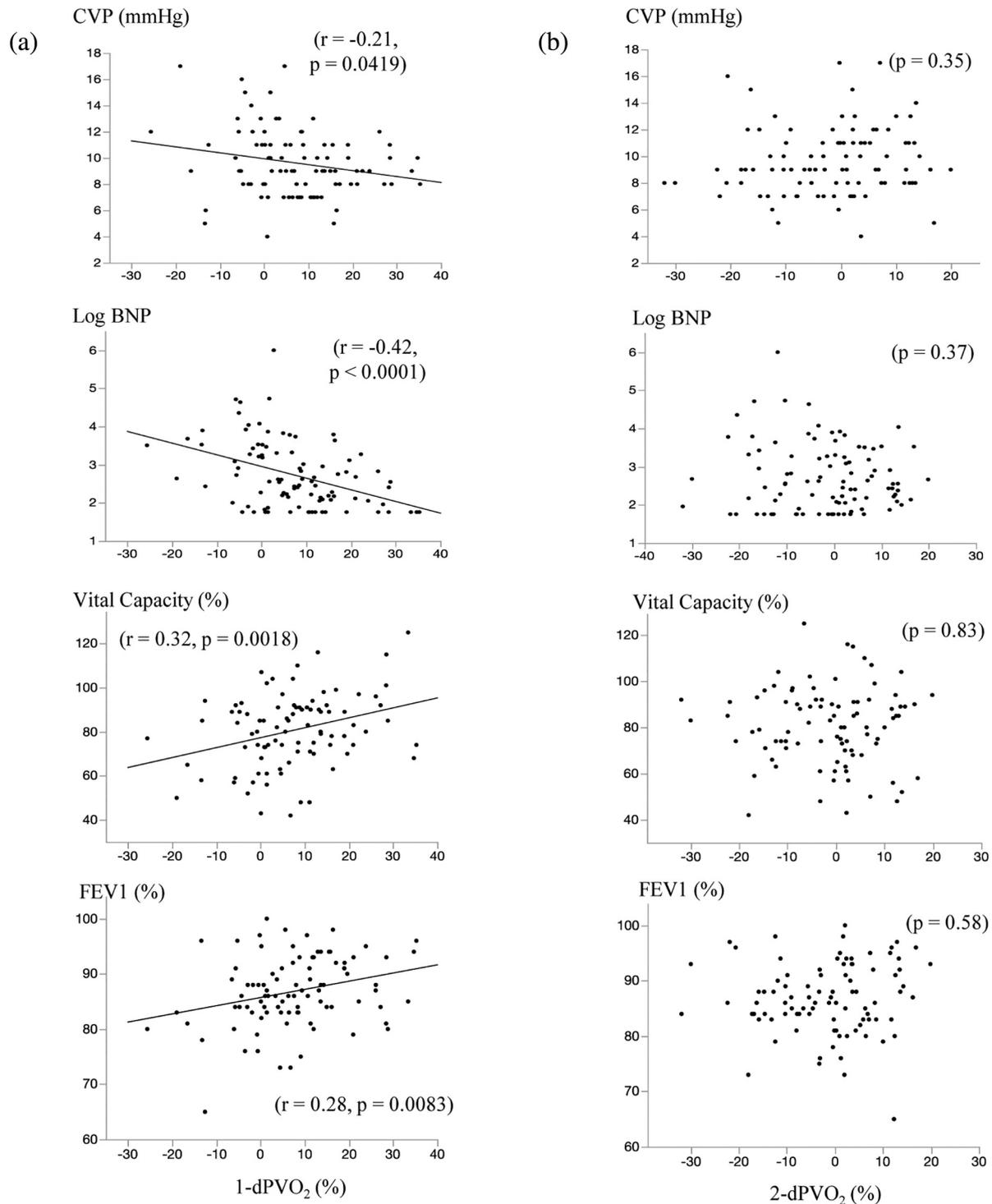


Fig. 2. Associations of 1-dPVO₂ (left, a) and 2-dPVO₂ (right, b) with central venous pressure (CVP), log BNP, vital capacity, and forced expired volume in one second (FEV1) at the time of CPX3 (adulthood).

4.1. Pulmonary function

Restrictive ventilatory impairment characterizes the main pulmonary dysfunction in Fontan patients and determines exercise capacity, even prognosis [21,22]. Inspiratory muscle training improved inspiratory muscle strength and ventilatory efficiency as described in patients with chronic heart failure [23]. This study demonstrated a significant positive correlation of 1-dPVO₂ with VC and FEV1, the latter being associated with mortality [22], indicating the close association of pulmonary function with aerobic exercise capacity and the importance of exercise

training for better pulmonary function. In fact, pulmonary pump function plays a critical role in Fontan pulmonary circulation [24]. However, whether inspiratory muscle training can improve exercise capacity in Fontan patients still remains uncertain [23].

4.2. Cardiac and hemodynamics

Exercise training prevents the progression of cardiac remodeling and improves cardiac function in patients with ischemic and/or chronic heart failure with reduced left ventricular contractility [25]. Short-term

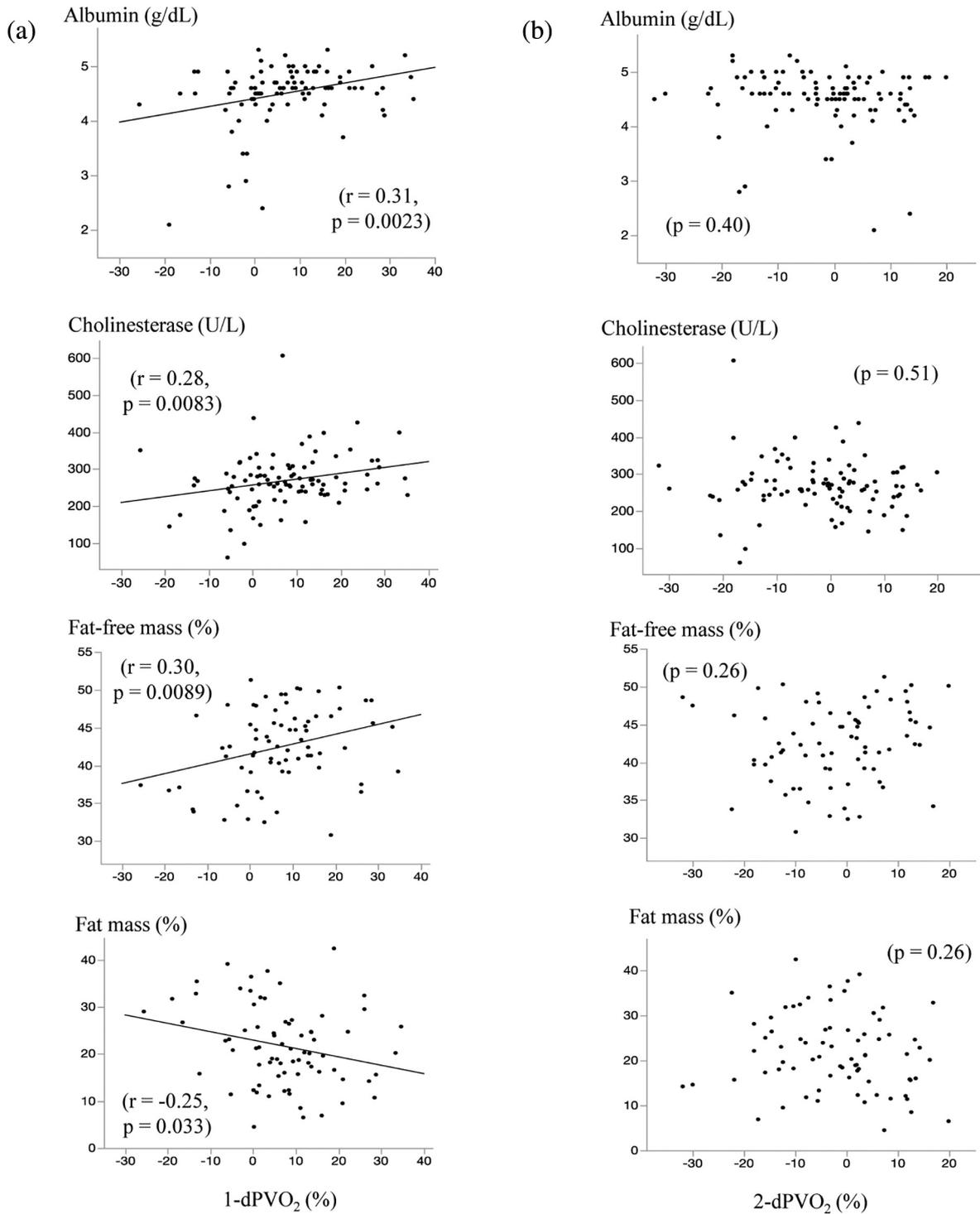


Fig. 3. Associations of 1-dPVO₂ (left, a) and 2-dPVO₂ (right, b) with plasma levels of albumin and cholinesterase, fat-free mass, and fat mass at the time of CPX3 (adulthood).

(median, 3 months) exercise training with programs of exercise intensity at 50–80% of peak heart rate could improve exercise capacity by 7–26% in most studies on Fontan patients [8–12]. The group P patients demonstrated a 12% increase in the percentage of predicted PVO₂. In our study, a positive 1-dPVO₂ was associated with lower CVP, higher Sat, and lower BNP, all of which are predictors of all-cause mortality in Fontan patients [26]. The underlying mechanisms of these associations are unclear. EF decreased from CPX1 to CPX3 (54.2% vs. 51.8%, $p = 0.02$), as previously demonstrated [27], and no association was observed between changes in EDVI or EF and those in CVP or BNP (all $p > 0.05$). However, CVP is multifactorially determined, along with the

functions of the ventricle and AV valve, water balance, and the status of pulmonary circulation. Further studies on the effect of exercise training on cardiac function as well as on the hemodynamics in Fontan circulation should be conducted.

4.3. Hepatorenal function

Fontan-associated liver disease (FALD), particularly liver cirrhosis and hepatocellular carcinoma, is one of the important emerging pathophysiologicals, which ultimately determine the long-term outcome among these patients [28]. Although the precise mechanisms of FALD

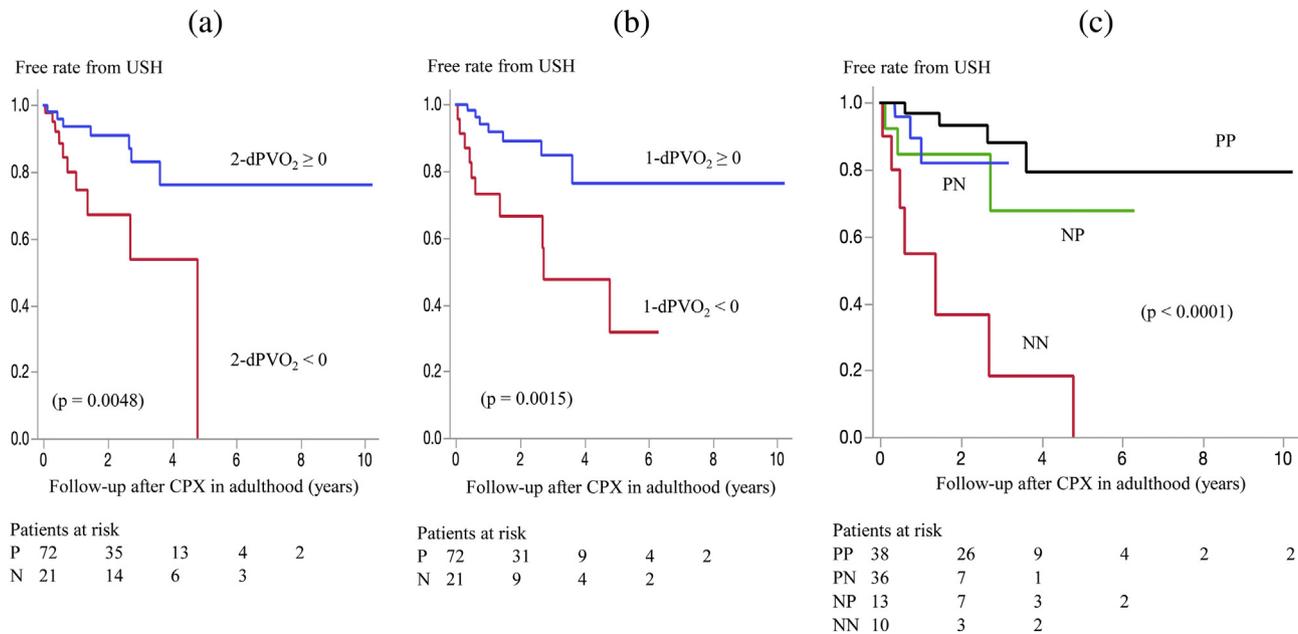


Fig. 4. The Kaplan-Meier unscheduled hospitalization (USH) free rate curves were divided by positive or negative value of 2-dPVO₂ (a) and 1-dPVO₂ (b). The Kaplan-Meier USH free rate curves were divided by four groups according to the history of peak VO₂ trajectory during childhood and post-childhood. Definitions of groups PP, PN, NP, and NN are defined in the text.

progression are not well understood, a pathophysiologic congested liver with hypoperfusion due to Fontan hemodynamics may result in FALD progression [29]. The association of 1-dPVO₂ with higher plasma levels of albumin and cholinesterase indicates a favorable influence of exercise training on hepatic synthetic function. The hepatic synthetic capacity is impaired in patients with liver cirrhosis [30]; however, this study was not able to clarify whether positive 1-dPVO₂ was associated with the less hepatic fibrotic change.

Renal dysfunction strongly predicts poor prognosis in patients with cardiovascular disease, including adults with congenital heart disease [31]. In the present study, 1-dPVO₂ was closely associated with renal resistive index, indicating well-preserved renal hemodynamics and better survival [19]. The absence of an association between 1-dPVO₂ and MELD-XI score implies that liver damage was not severe in our patients, compared with that seen in end-stage liver cirrhosis.

4.4. Body composition

In heart failure patients, activation of the renin-angiotensin-aldosterone system, inflammation, and disuse of the skeletal muscle result in the muscle wasting known as sarcopenia [32,33]. At the same time, muscle structural change (type I to type II transformation) occurs and mitochondrial function is impaired [34]. In Fontan patients, a decrease in skeletal muscle mass and changes in muscle characteristics have also been observed, and these abnormalities determined the exercise capacity [35]. Preserved leg muscle mass is an important determinant of cardiac preload during exercise, particularly in Fontan patients, through the pump function of the skeletal muscle [24]. Hence, resistance training can help increase muscle mass in Fontan patients [11]. According to this evidence, the significant association of 1-dPVO₂ with higher fat-free mass and lower fat mass implies that early establishment of an active lifestyle can guarantee an ideal body composition for Fontan circulation in the future, which is specifically beneficial during dynamic exercise.

4.5. Stronger impact of 1-dPVO₂ on adult Fontan pathophysiology

The reasons for the different influences of 1-dPVO₂ and 2-dPVO₂ on the adult Fontan pathophysiology are unclear. Increase in organ weight is considerably greater during childhood than during post-childhood. For instance, percent weight increase of the heart, lungs, liver,

and kidneys is approximately 60%–140% during childhood (age 8–14 years), whereas it is only 10%–15% during post-childhood (age 14–20 years) [36]. The rapidly growing and developing organs might be more sensitive to exercise training than the grown and developed ones.

4.6. Study limitations

First, the retrospective nature of the present study cannot clarify causal relationships; for instance, whether greater 1-dPVO₂ leads to a higher percentage of fat-free mass. Second, the direct association of 1-dPVO₂ with daily active life during childhood might be speculative. However, our previous study demonstrated a close association between individual daily activity (total time required for them to go to and from school on foot or by bicycle and time spent in physically active play and/or habitual exercise training in 1 week determined by a questionnaire) and PVO₂ ($r = 0.43$, $p = 0.0003$) [17]. Thus, we believe that 1-dPVO₂ reflects individual exercise habits during childhood, which could mimic the effect of long-term exercise training on exercise capacity. Considering the relatively high dropout rate of participants (10–31%) even in prospective short-term exercise training programs (median, 3 months) [8–12], the long-term benefits have been largely unproven. Furthermore, it may be practically and/or ethically difficult to conduct a long-term randomized controlled trial to prove the benefits of pediatric exercise training on late adult Fontan pathophysiology.

5. Conclusions

A positive exercise capacity trajectory during childhood predicted better adult Fontan pathophysiology in terms of exercise capacity, hemodynamics, pulmonary function, hepatorenal function, and body composition. However, a positive post-childhood exercise capacity trajectory had less significant benefits on end-organ function. Therefore, an early exercise training program may be one of the promising strategies in the management of pediatric Fontan patients.

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Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

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