

What determines the quality of life of adult patients after Fontan procedure?

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Abstract

Background: *Despite the low early mortality of Fontan procedures, Fontan patients are prone to various cardiac and extra-cardiac complications in the long term. This may influence patient perception of their health and outcome. The aim of the study was to assess the relationship of multi-organ complications and physical efficiency with self-reported health-related quality of life (QOL) in adult Fontan patients.*

Methods: *Quality of life was assessed with the Short Form-36 questionnaire. Laboratory tests were done together with echocardiography, plethysmography, and cardiopulmonary exercise test.*

Results: *The QOL was poorer in patients than in control subjects. The physical characteristics of patients correlated with dynamic ventilatory parameters, heart rate at the peak of exercise, alanine aminotransferase and albumin level.*

Conclusions: *Liver impairment and chronotropic incompetence during exercise are associated with poor QOL in patients after Fontan procedure. In these patient, hepatic, pulmonary and cardiac functions should be carefully monitored. (Cardiol J 2018; 25, 1: 72–80)*

Key words: adult Fontan patients, quality of life, SF-36, exercise tolerance, pulmonary function test, multiorgan complications

Introduction

The Fontan procedure, initially performed in 1971, is used to repair univentricular hearts [1]. Before 1971, less than 20% of children with cardiac malformations reached adulthood [2]. However, advances in cardiac surgery have considerably increased the life expectancy of univentricular patients. Nowadays, almost 85% of patients with congenital heart disease (CHD) reach adulthood [3]. It is predicted that 20 years from now, CHD will be seen more commonly in adult patients than in pediatric patients [4].

In spite of low early mortality after Fontan procedure, patients are prone to several complications in long term, including arrhythmias, thromboembolism, heart failure, pulmonary hypertension, cyanosis, liver dysfunction, protein-losing enteropathy, and restrictive lung diseases [5–10]. The occurrence of these complications and need for hospitalization influences the life expectancy and emotional, behavioral, and psychosocial condition of these patients. Additionally, the patients' quality of life (QOL) and perception of their health status also influence treatment outcomes [11, 12]. Therefore, patients' perceived physical and mental health should be taken

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Received: 29.11.2017

Accepted: 12.05.2017

into account to optimize treatment. There are only a few studies on patient QOL after Fontan procedure (Fontan patients) and non of them included patients with systemic complications [11–14, 40].

The aim of this study was to investigate the relationship between patient characteristics including: medical history, physical examination, hematologic, hepatic, and renal complications, physical efficiency, and pulmonary function on self-reported health-related QOL.

Methods

Study participants

Forty patients, older than 18 years, with Fontan operation, who were clinically stable in the 3 months prior to enrollment were included. Patients with any of the following were excluded: asthma, use of vasodilators for pulmonary hypertension, neoplasia, infection, inflammation, major trauma, pregnancy, diabetes, or alcohol abuse. Forty healthy volunteers, matched with patients by gender and age, were selected as controls.

Study protocol

Information on the following was recorded for each participant in the study: New York Heart Association (NYHA) functional class, vital signs, weight, height, type of cardiac malformation, history of cardiac operations, age at surgical repair, laboratory tests, echocardiography, oxygen saturation, body plethysmography, cardiopulmonary exercise test (CPET), and self-reported health-related QOL questionnaire.

The study protocol was approved by the local Ethics Committee. Each participant provided informed consent to participate in this study.

Laboratory investigations

The following laboratory tests were performed: red blood cell counts, hematocrit, hemoglobin, red blood cell distribution width, iron level, B-type natriuretic peptide, albumin level, alanine aminotransferase (ALT), creatinine level, and cystatin C.

Cardiopulmonary exercise test and echocardiography

Each participant underwent CPET with a modified Bruce protocol to evaluate exercise tolerance. The following parameters were recorded: time of exercise (T), heart rate (HR), blood pressure (BP), ventilatory equivalent (VE), maximum oxygen uptake (VO_{2max}), respiratory exchange ratio (RER), maximum ventilatory equivalent of oxygen

(VE/VO_2), maximum ventilatory equivalent of carbon dioxide (VE/VCO_2), breathing reserve (BR), and oxygen saturation. Maximum oxygen uptake (VO_{2max}) was defined as the highest value at peak workload in ml/kg/min and percentage of predicted value. Ventilatory anaerobic threshold (VAT) was measured by use of V-slope method. Oxygen pulse (pulse- O_2) was defined as the amount of oxygen consumed per systole. The ventilatory equivalent for oxygen (VE/VO_2) was defined as the amount of ventilation needed for uptake of a given amount of oxygen. The ventilatory equivalent for carbon dioxide was defined as the amount of ventilation needed for elimination of a given amount of carbon dioxide. The RER was calculated by dividing the VO_2 by VCO_2 . The HR reserve was calculated as the difference between peak and resting HR. The single ventricular ejection fraction (SVEF), valvular competence, and presence of fenestrations was noted and semi-quantified on echocardiography (Vivid 7 GE Medical System, USA).

Pulmonary function tests

Patients participating in the study underwent whole-body plethysmography. The American Thoracic Society/European Respiratory Society guidelines were followed for all lung functional measurements [15]. Pulmonary functions were expressed as absolute values and percentage of predicted values (%N) based on the age, sex, height, and race of participants. The following parameters were noted: total life capacity (TLC), vital capacity (VC), forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), tidal volume (TV), expiratory reserve volume (ERV), reserve volume (RV), peak expiratory flow (PEF); maximal expiratory flow (MEF), and total resistance (R_{tot}).

Quality of life assessment

Quality of life was assessed with the Short Form-36 questionnaire (license number: QM03-3795) [16]. It consists of 36 items divided into eight domains: physical functioning (PF), role-physical functioning (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional functioning (RE), and mental health (MH), which are created as the weighted sums of questions in their section. Then, a score between 0 and 100 is calculated for each domain on the assumption that each question carries equal weight. The physical (PCS) and mental (MCS) component summary is calculated as the average value of four clustered domains (PF+RP+BP+VT for PCS; SF+RE+MH+GH for MCS).

Table 1. Laboratory test results in Fontan patients and control.

Variable (normal value)	Fontan patients	Control	P
RBC (3.7–5.1 × 10 ⁹ /μL)	5.52 ± 0.5	4.8 ± 0.4	< 0.001
Hematocrit (37–47%)	47.6 ± 4.4	42.1 ± 3	< 0.001
Hemoglobin (12–16 g/dL)	16.2 ± 1.8	14.2 ± 1.2	< 0.001
RDW (11.5–14.5%)	14.6 ± 2.5	12.8 ± 0.5	< 0.001
Ferrum (11–28 μmol/L)	17.2 ± 7.4	19.4 ± 6.4	< 0.224
BNP (< 125 pg/mL)	493.1 ± 725.2	41.2 ± 25.9	< 0.001
Albumin (32.4–52.8 g/L)	44.3 ± 6.4	48.5 ± 2.2	0.005
ALT (< 33 U/L)	28.5 ± 12	21 ± 6	0.006
Creatynin (40–88 μmol/L)	77.6 ± 18	78.3 ± 13	0.784
Cystatin C (0.56–0.9 mg/L)	1.0 ± 0.3	0.84 ± 0.12	0.001

RBC — red blood cells; RDW — red cell distribution width; BNP — B-type natriuretic peptide; ALT — alanine aminotransferase

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 χ^2 test, Mann-Whitney U test, Student’s t-test, and Kruskal-Wallis test were performed where appropriate. Individual parameters were calculated by use of the Spearman rank test. The factors determining PF and RP were analyzed by the use of multiple logistic regression analyses. Statistical significance was set at p-value 0.05. Statistica version 10.0.1011.7 (StatSoft Inc., USA) was used to analyze data.

Results

Patients’ characteristic and laboratory test results

Forty patients with Fontan procedure (mean age 26 ± 6; 40% female) were included in this study. Mean age of patients at time of the procedure was 4.8 ± 3.2 (2–14) years, and mean postoperative time was 20.5 ± 5.3 (14–31) years. Twenty five (62%) patients had right ventricular hypoplasia, 9 (23%) had pulmonary stenosis with transposition of the great arteries, 3 (8%) left ventricular hypoplasia, 2 (5%) had double inlet right ventricle, and 1 (2%) had a complete atrioventricular canal. In addition to Fontan operation, direct right atrium–pulmonary artery connection was made in 4 (10%) patients, and total cavopulmonary connection by means of intra-atrial lateral tunnel was made in the remaining patients. The single ventricle was on the left in 37 (93%) patients and on the right in 3 (7%) patients. Fenestration was seen in 20 (50%)

patients. At the last follow-up, 9 (22%) patients were in NYHA class I, 28 (70%) were in NYHA class II, and 3 (8%) were in NYHA class III. Mean oxygen saturation, measured by pulse oximetry, was 89.1 ± 6.5%. The laboratory test results of participants are given in Table 1. Analyzing a sociodemographic status of Fontan patients, most of them (89%) were unmarried, 26% had a university diploma and 54% had a secondary school degree. Only 34% of patients were employed, 49% were unemployed, and 17% were studying.

Echocardiography and exercise performance

Patient mean ejection fraction was 51.5 ± 7.1%. Atrioventricular regurgitation was mild in 18 (45%) patients, moderate in 11 (28%) patients, and severe in 3 (7%) patients. As seen in Table 2, CPET showed significant differences between Fontan patients and controls in T, HR, maximal VO₂, VE, VE/VO₂, VE/VCO₂, BR, and RER.

Pulmonary function testing

Results of the pulmonary function tests are shown in Table 2. Restrictive lung dysfunction was seen in 61% of Fontan patients: 62% had mild, 32% had moderate, and 6% had medium-severe dysfunction. There were significant differences between Fontan patients and controls in dynamic ventilator parameters including: TLC (4.8 ± 1.3 vs. 5.74 ± 0.9 L; p = 0.01), FEV₁ (3 ± 1 vs. 3.7 ± 0.7 L; p = 0.01), FEV₁/FVC (88.4 ± 5.9 vs. 103.2 ± 8.4%; p < 0.001), VC (3.5 ± 1.2 vs. 4.3 ± 0.9 L; p = 0.025), FVC (3.4 ± 1.2 vs. 4.3 ± 0.8 L; p = 0.02), ERV (1.1 ± 0.6 vs. 1.5 ± 0.4 L; p = 0.04), and R_{tot} (0.5 ± 0.2 vs. 0.3 ± 0.09 kPa/(l/s); p = 0.007).

Table 2. Cardiopulmonary exercise test (CPET) and pulmonary function test results in Fontan patients and control.

Parameter	Fontan patients	Control	P
CPET			
T [min:s]	14:33 ± 02:43	16:52 ± 02:44	< 0.001
Heart rate [bpm]	151.2 ± 26.5	178.4 ± 22.3	< 0.001
Maximum VO ₂ [mL/kg/min]	22.9 ± 7.1	48.8 ± 7.5	< 0.001
VE [L/min]	54.4 ± 18.1	112.4 ± 28.2	< 0.001
VE/VO ₂	33.1 ± 5.8	29 ± 3.9	0.001
VE/VCO ₂	31.6 ± 3.7	26.6 ± 3.1	< 0.001
BR [L/min]	75 ± 19.4	41.4 ± 17.2	< 0.001
RER	1.05 ± 0.1	1.1 ± 0.1	0.04
Pulmonary function test			
TLC [L]	4.8 ± 1.3	5.74 ± 0.9	0.01
TLC [%N]	77.7 ± 11.8	98.5 ± 6.8	< 0.001
FEV ₁ [L]	3.0 ± 1	3.7 ± 0.7	0.01
FEV ₁ [%N]	76.9 ± 18.2	103.2 ± 8.3	< 0.001
VC [L]	3.5 ± 1.2	4.3 ± 0.9	0.025
VC [%N]	72.1 ± 19.1	98.9 ± 9.1	< 0.001
FVC [L]	3.4 ± 1.2	4.3 ± 0.8	0.02
FVC [%N]	74.4 ± 16.9	100.1 ± 8.6	< 0.001
FEV ₁ %VC [%]	88.4 ± 6.0	87.8 ± 5	0.25
FEV ₁ %VC [%N]	104.2 ± 7.4	105.6 ± 5.7	0.30
FEV ₁ %FVC [%]	88.4 ± 5.9	103.2 ± 8.4	< 0.001
FEV ₁ %FVC [%N]	103.6 ± 7.7	102.9 ± 5.8	0.92
TV [L]	0.8 ± 0.4	0.8 ± 0.4	0.98
TV [%N]	177 ± 75.1	177 ± 79.1	0.98
ERV [L]	1.1 ± 0.6	1.5 ± 0.4	0.04
ERV [%N]	75.8 ± 32.6	109.7 ± 26	0.004
RV [L]	1.3 ± 0.3	1.4 ± 0.2	0.06
RV [%N]	85.9 ± 18.3	93.5 ± 12.1	0.08
RV/TLC	28.7 ± 7.6	25 ± 4.1	0.41
RV/TLC [%N]	111.2 ± 29.6	93.5 ± 13	0.06
R _{tot} [kPa/(l/s)]	0.5 ± 0.2	0.3 ± 0.09	0.007
R _{tot} [%N]	159 ± 71.3	102.7 ± 29	0.004

T — exercise time; VO₂ — oxygen uptake; VE — ventilatory equivalent; VCO₂ — CO₂ production; BR — breath reserve; RER — respiratory exchange ratio; TLC — total life capacity; FEV₁ — forced expiratory volume in 1 s; VC — vital capacity; FVC — forced vital capacity; TV — tidal volume; ERV — expiratory reserve volume; RV — reserve volume; R_{tot} — total resistance

Quality of life

The perceived physical and mental domains of health were significantly different between Fontan patients and controls (Table 3). There were no differences between men and women in either group. PF, RP, BP, GH, and RE were significantly different in Fontan patients compared with controls. PCS and MCS were significantly lower in patients than in controls. There was no relationship of patient QOL with any of the following: age, age at Fontan

operation, time since surgery, type of operation, presence of fenestration, type of systemic ventricle (left or right), and oxygen saturation at rest. Additionally, echocardiographic data, including SVEF and atrioventricular regurgitation, and laboratory test results (other than those described below) did not correlate with QOL scores.

The relationship between hepatic dysfunction and QOL was assessed after stratification of patients based on liver tests. Serum albumin levels

Table 3. Mann-Whitney U test (χ^2 test for gender) results for the Short Form-36 questionnaire in Fontan patients and controls.

	Fontan patients	Controls	P
Age [years]	25.3 ± 6.0	26.7 ± 3.2	0.518
Gender — male	24 (60%)	20 (50%)	0.368
Physical functioning	68.8 ± 24.3	97 ± 4.6	< 0.001
Role physical	68.7 ± 38	93.7 ± 16.5	< 0.001
Bodily pain	71.7 ± 25.7	82.9 ± 20.2	0.034
General health	45.1 ± 23	78.2 ± 15	< 0.001
Vitality	58.9 ± 18.9	63.9 ± 14.8	0.177
Social functioning	80.6 ± 21.6	86.4 ± 16.4	0.069
Role emotional	74 ± 40	94.2 ± 18.3	0.009
Mental health	70 ± 19.1	73.3 ± 15.7	0.494
Mental complex status	67.4 ± 20.8	83.4 ± 11.6	< 0.001
Physical complex status	67 ± 20.5	84.4 ± 10.9	< 0.001

Table 4. Correlation test results for Short Form-36 questionnaire.

Variable	PF	RP	GH	PCS	MCS
CPET					
T	0.269	0.359	0.130	0.257	0.307
HR	0.414	0.271	0.208	0.033	0.249
VO ₂	0.064	0.131	0.021	0.044	0.140
Pulmonary function test					
FEV ₁	0.453	0.187	-0.004	0.026	0.087
FEV ₁ [%N]	0.549	0.332	0.220	0.158	0.259
VC	0.378	0.160	-0.030	-0.013	0.041
VC [%N]	0.447	0.279	0.140	0.084	0.174
FVC	0.371	0.135	-0.041	-0.042	0.031
FVC [%N]	0.513	0.305	0.183	0.099	0.220
VT	0.425	0.389	0.277	0.393	0.356
VT [%N]	0.487	0.412	0.325	0.393	0.474
ERV	0.452	0.212	0.093	-0.062	0.186
ERV [%N]	0.501	0.296	0.240	0.058	0.323
RV%TLC	-0.343	-0.467	0.214	0.266	0.026
RV%TLC [%N]	-0.290	-0.076	0.222	0.259	-0.012

CPET — cardiopulmonary exercise test; T — exercise time; VO₂ — oxygen uptake; FEV₁ — forced expiratory volume in 1 s; VC — vital capacity; FVC — forced vital capacity; VT — vitality; ERV — expiratory reserve volume; RV — receive volume; TLC — total life capacity; PF — physical functioning; RP — role physical; GH — general health; PCS — physical complex status; MCS — mental complex status

were associated with better PF and RP ($r_s = 0.399$ and 0.374 , respectively). PF and GH were negatively associated with ALT ($r_s = -0.374$ and -0.373 , respectively). QOL scores were not significantly associated with serum creatinine or cystatin C.

None of the CPET variables was correlated with QOL scores with the exception of maximal

HR at the peak of exercise which was related to PF ($r_s = 0.414$) (Table 4). There was no relation between QOL scores, including the PCS, and VO_{2max}. There was no correlation between PF and TLC, in spite of a reduced TLC in 61% of patients (Table 4). However, PF was related to dynamic lung volumes, including FEV₁ ($r_s = 0.45$), FEV₁ (%N)

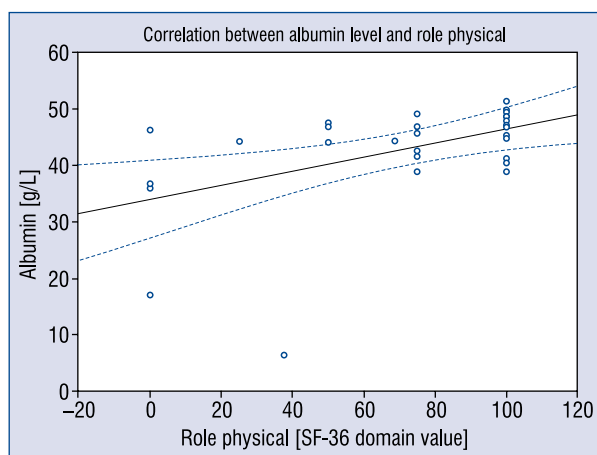


Figure 1. Correlation between heart rate level and physical functioning in Fontan patients. Blue dotted line indicates 95% confidence interval.

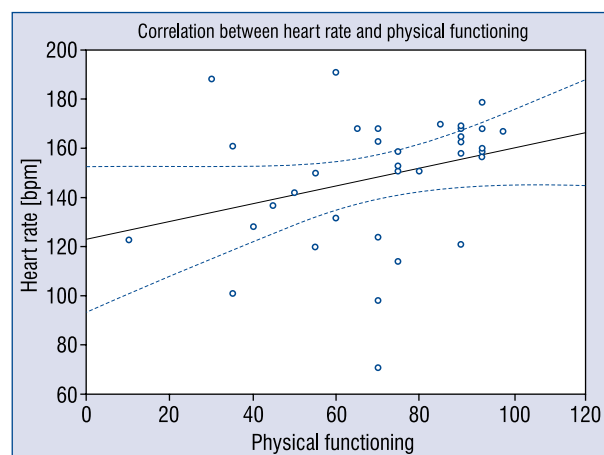


Figure 2. Correlation between albumin level and role physical in Fontan patients. Blue dotted line indicates the 95% confidence interval.

($r_s = 0.55$), VC (%N) ($r_s = 0.45$), FVC (%N) ($r_s = 0.51$), VC (%N) ($r_s = 0.447$), VT ($r_s = 0.42$), VT (%N) ($r_s = 0.49$), PEF ($r_s = 0.42$), PEF (%N) ($r_s = 0.53$), ERV ($r_s = 0.45$), and ERV (%N) ($r_s = 0.5$). PF also was significantly correlated with lung distension ratio ($r_s = -0.34$). RP was related to VT (%N) ($r_s = 0.412$), which influences the GH and PCS. Employment and social status, marital status, and level of education did not influence the perceived health-related QOL.

To determine the relationship between self-perceived QOL and cardiopulmonary function test, ventilatory parameters and liver dysfunction, a stepwise regression analysis was performed with PF and RP as dependent variables. The multivariate model showed that maximal HR at the peak of CPET ($\beta = 0.59$, $p = 0.002$) was an independent predictor of physical functioning ($r^2 = 0.35$, $p = 0.02$) (Fig. 1). Additionally, serum albumin level ($\beta = 0.47$, $p = 0.02$) was an independent predictor of RP ($r^2 = 0.22$, $p = 0.02$) (Fig. 2).

Discussion

Self-perceived QOL, in addition to long-term morbidity, is an important outcome in patients with a single ventricle. Patients with well-controlled CHD (adult and children) were reported to have QOL comparable to that in healthy individuals [17]. However, the QOL in complex or cyanotic CHD is reportedly poor [18], it was also found that patient subjective QOL assessment was corroborated by objective laboratory and imaging results.

Underlined physical functioning was positively correlated with maximal HR at the peak of exercise. Maximal HR at the peak of exercise was an independent predictor of PF. Recent data show that physical activity in patients with Fontan physiology is limited by an increased ventricular preload and inadequate cardiac output [19]. In healthy persons, cardiac output at rest depends on HR, contractility, afterload, and preload. Exercise increases the cardiac output up to 5-fold or more due to the augmentation of the above components. In Fontan circulation, the lack of a pulmonary pump reduces the return from pulmonary circulation [20]. As a result, preload reserve of the systemic ventricle is reduced or absent. Cardiac output in Fontan circulation at rest is 70% of cardiac output of the biventricular heart [21]. Additionally, chronotropic incompetence occurs during exercise in patients with Fontan circulation [20], with an HR consistently lower than in normal subjects. This situation is due to abnormal reflex control of HR and adrenergic dysfunction [20, 22]. Heart rate plays an important role in determining the cardiac output in Fontan circulation during exercise [19, 20], when autonomic dysfunction of the sinus node leads to a relatively low HR [23]. Physical functioning, including vigorous activities like running, lifting heavy objects, or strenuous sports, and mild activities like bending, kneeling, lifting, or carrying groceries, depends on maximal HR reached at the peak of exercise. In this study, a lower peak HR was associated with worse general health and role physical. Recent studies show that Fontan patients with severely impaired SVEF have decreased

cardiac output, whereas patients with moderately impaired SVEF have normal cardiac output [19]. The mean SVEF of patients was $51.5 \pm 7\%$, and SVEF and PF were not correlated.

Self-perceived PF was related to dynamic ventilatory parameters on body plethysmography. Data on respiratory dysfunction in adult Fontan patients are limited. Some studies show that Fontan patients may develop a restrictive lung disease [23–25] due to weak respiratory muscles, restrictive thoracic cage, or paralysis of the diaphragm after surgery. Previous studies have shown reduced ventilator parameters such as: TLC, FEV₁, VC, FVC, PEF, MEF₂₅, MEF₅₀, and MEF₇₅ in Fontan patients compared with those functions in healthy controls and predicted values [26]. Reduced dynamic lung volumes, which depend on respiratory muscle strength, influence the self-perceived physical functioning of patients. Respiratory muscle strength can be improved with therapeutic intervention and pulmonary rehabilitation. The impact of pulmonary rehabilitation on QOL has not been studied. Several studies report increased respiratory muscle strength and exercise capacity with resistance training in adults with Fontan circulation [27–31]. Even though exercise training is well-established as a non-pharmacologic therapy in cardiac patients, its impact on self-perceived physical functioning remains insufficiently clear in patients after CHD surgery.

In this study, PF was associated with liver impairment. Hepatic complications may develop in patients with Fontan circulation, including cholestasis, fibrosis, hepatomegaly, and cirrhosis [32]. There are limited data on QOL of patients who have liver diseases, especially end-stage liver disease, with or without cardiac disease [33–36]. This study evaluated the QOL of Fontan patients with liver dysfunction. It was found that self-perceived physical function and general health were related to ALT levels. Patients with increased ALT levels had worse physical functioning, role physical, general health and physical complex status compared with those values in patients with normal ALT levels.

Role physical component was defined as problems with work or other daily activities as a result of physical health. In the present study, role physical correlated with tidal volume measured on body plethysmography and serum albumin levels. Serum albumin level was also an independent predictor of role physical. Six percent of patients had low serum albumin levels. Protein-losing enteropathy is a rare complication of Fontan circulation with very poor diagnosis [37, 38].

Although only the role emotional domain of the Short Form-36 questionnaire was reduced in this study, the mental complex status and physical complex status were also significantly lower than in controls. This finding contrasts with that of a previous study in which the mental status of the patients was normal [13, 39]. Bordin et al. [40] concluded that Fontan patients are aware of, tolerate, and accept their physical limits, and their mental condition is influenced by their functional status only when it prevents daily life activities. The differences in these results can be explained by taking into account the NYHA class; in this study, 70% of patients were in NYHA class II and 7.5% were in NYHA class III. Therefore, severity of the disease does not influence the perceived QOL unless it interferes with the daily activities. Psychological analysis of patients may be used to explore these mental differences and ascribe a cause to limitation in daily activities. Most patients in this study had a high school diploma, and almost a quarter had a university degree. There was a high rate of unemployment (almost 50%), which is almost 5 times higher than in the general Polish population. These findings are in line with the results of a previous study [40]. Physical limitations are responsible for the inability of these patients to work; thus they may require additional social assistance. The social status of patients and their relatively young age probably explain why only 11% were married or had a partner.

Limitations of the study

The following limitations of this study are acknowledged. First, the sample size was small and heterogeneous in initial diagnoses and type of Fontan surgery. Second, the QOL was assessed by only a single standardized questionnaire, Short Form-36. Third, the liver function was assessed indirectly by commonly used markers, not by quantitative measures.

Conclusions

The study results indicate, that self-perceived QOL and physical status of patients who underwent Fontan procedure was mostly related to incompetence during exercise (as illustrated by the dynamic parameters of ventilation and maximal HR in response to physical fatigue) and to liver impairment associated with protein-losing enteropathy. Adult Fontan patients are a special, heterogeneous group requiring careful multidisciplinary and subjective assessment of their QOL.

Liver impairment and chronotropic incompetence during exercise are main factors that lead to worsening of the QOL, and should be monitored in long-term follow-up.

Funding: The study was funded by Jagiellonian University Medical College, Krakow, Poland.

Conflict of interest: None declared

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