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Laboratory Measures of Exercise Capacity and Ventricular Characteristics and Function Are Weakly Associated With Functional Health Status After Fontan Procedure

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Background—Patients after the Fontan procedure are at risk for suboptimal functional health status, and associations with laboratory measures are important for planning interventions and outcome measures for clinical trials.

Methods and Results—Parents completed the generic Child Health Questionnaire for 511 Fontan Cross-Sectional Study patients 6 to 18 years of age (61% male). Associations of Child Health Questionnaire Physical and Psychosocial Functioning Summary Scores (FSS) with standardized measurements from prospective exercise testing, echocardiography, magnetic resonance imaging, and measurement of brain natriuretic peptide were determined by regression analyses. For exercise variables for maximal effort patients only, the final model showed that higher Physical FSS was associated only with higher maximum work rate, accounting for 9% of variation in Physical FSS. For echocardiography, lower Tei index (particularly for patients with extracardiac lateral tunnel connections), lower indexed end-systolic volume, and the absence of atrioventricular valve regurgitation for patients having Fontan procedure at age <2 years were associated with higher Physical FSS, accounting for 14% of variation in Physical FSS. For magnetic resonance imaging, ratio of lower mass to end-diastolic volume and midquartiles of indexed end-systolic volume (nonlinear) were associated with higher Physical FSS, accounting for 11% of variation. Lower brain natriuretic peptide was significantly but weakly associated with higher Physical FSS (1% of variation). Significant associations for Psychosocial FSS with laboratory measures were fewer and weaker than for Physical FSS.

Conclusions—In relatively healthy Fontan patients, laboratory measures account for a small proportion of the variation in functional health status and therefore may not be optimal surrogate end points for trials of therapeutic interventions. (*Circulation*. 2010;121:34-42.)

Key Words: Fontan procedure ■ heart defects, congenital ■ pediatrics

A long-term concern for patients after the Fontan procedure for palliation of functional single ventricle is the preservation and improvement of suboptimal functional health status. Important cardiac morbidities, including arrhythmia, ventricular dysfunction, protein-losing enteropathy, and thrombosis, remain difficult to predict, prevent, and treat.¹ Changes in the specific venous anastomoses performed during the Fontan procedure have improved exercise capacity

and decreased arrhythmias.^{2,3} Strategies aimed at preventing thrombosis have been proposed that are only partially effective and not evidence based.⁴ Strategies to preserve ventricular function, such as the use of angiotensin-converting enzyme inhibitors, have not shown benefit in limited study.⁵ Improved exercise capacity has been noted with exercise training programs, but the impact on functional health status and activity levels is not known.^{6,7} A rationale for

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A list of the members of the Pediatric Heart Network Investigators appears in the online-only Data Supplement.

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intervention strategies is incomplete because associations between laboratory measures and functional health status are not well characterized, making it difficult to plan clinical trials likely to answer important management questions.

Clinical Perspective on p 42

The Fontan Cross-Sectional Study was designed by the Pediatric Heart Network (PHN) to identify a quantifiable measure of cardiovascular performance that is associated with clinical outcome assessed by a validated functional health status instrument in children and adolescents after the Fontan procedure.⁸ The study enrolled Fontan patients who were 6 to 18 years of age and included assessment of patient characteristics and medical history, functional health status, and standardized assessment with cardiopulmonary exercise testing, echocardiography, magnetic resonance imaging (MRI), and measurement of brain natriuretic peptide (BNP).^{8,9} The purpose of the present analysis was to determine associations between laboratory measures and functional health status in children and adolescents after the Fontan procedure, as well as interactions with a prespecified set of patient characteristics.

Methods

Study Design

The Fontan Cross-Sectional Study was performed by the PHN, consisting of 7 pediatric cardiac centers in the United States and Canada, a data coordinating center at the New England Research Institutes, a PHN chair, and staff from the National Heart, Lung, and Blood Institute of the National Institutes of Health.¹⁰ The design and methods of the study have been described previously.⁸ Institutional ethical review and approval were obtained from each participating institution, and written informed consent or assent was obtained for all study participants or their legal guardians.

Study Subjects

Study subjects were eligible if they were 6 to 18 years of age at enrollment, had had a Fontan procedure at least 6 months before initial testing, and agreed to complete the functional health status questionnaire and undergo study laboratory testing within 3 months of enrollment. Patients with important noncardiac or psychiatric conditions precluding or influencing testing, pregnancy or planned pregnancy, or current or planned participation in another conflicting research study, or whose primary caregiver lacked reading fluency in English or Spanish, were deemed not eligible. A detailed medical record review for eligible and consenting participants was performed.

Functional Health Status Questionnaire

Functional health status was assessed by having a parent complete the parent report version of the Child Health Questionnaire (CHQ-PF50).¹¹ The CHQ assesses functional health status in 12 domains of physical, behavioral, social, and emotional well-being and has been validated for use in children 5 to 18 years of age. Domain scores contribute to a Physical and a Psychosocial Functioning Summary Score (FSS), which was used for analysis in the present report.

Laboratory Testing

Details of the laboratory testing procedures have been reported elsewhere.⁸ Resting serum BNP concentration was determined in a single laboratory by standardized methods. Echocardiography and MRI were performed according to standardized protocols and transmitted to core reading laboratories for central measurement, interpretation, and data completion. Maximal cardiopulmonary ex-

ercise testing was performed with the use of cycle ergometry and a standardized protocol. Measurements from exercise testing were made locally and transmitted to the Data Coordinating Center.

Data Analysis

Data are described as frequencies, medians with 25th and 75th percentile values, and means with standard deviations as appropriate. Given the skewed distribution of BNP values, a normalizing logarithmic transformation was performed. The study population used for analysis was restricted to those patients with both Physical and Psychosocial FSS from the parent-completed CHQ. Because not all tests were performed in all patients (Figure 1), analyses were restricted to individual test data sets, and no overall analysis incorporating all tests was performed.

Because data derived from exercise testing performed with submaximal effort are of questionable validity and without normative values, analysis of associations with cardiopulmonary exercise variables was restricted to those patients who had a maximal effort, defined as a respiratory exchange ratio ≥ 1.1 . Furthermore, analysis of chronotropic index was also restricted to those patients without a pacemaker. Analyses of echocardiographic and MRI variables were restricted to those tests for which suitable ventricular mass and volume data were obtained. MRI variables for ventricular end-systolic and end-diastolic volume and mass were indexed to body surface area^{1.3} (BSA^{1.3}), and echocardiographic quantitative variables were converted to Z scores based on BSA with the use of published normal values and methods.¹² Separate analyses were performed for the Physical and the Psychosocial FSS. Univariable associations between the scores and each testing variable were first performed without any imputation of missing values. BNP values demonstrated a nonnormal distribution, and a normalizing logarithmic transformation was performed (logBNP); associations were determined with this variable. Missing values were minimal for the exercise testing and MRI data sets but were more frequent in the echocardiography data set. Mean imputation of the missing values in the echocardiography data set was performed before multivariable regression analyses. Multivariable linear regression analysis of each testing data set was performed initially with all testing variables included to determine overall R^2 adjusted for the number of included variables. Stepwise multivariable regression was performed for both scores, with further testing for nonlinear associations. Variable selection for final models was also guided by bootstrap bagging (1000 random sample data sets) to assess reliability (percentage of random sample data sets for which the variable was selected) for inclusion. Interactions with testing variables were sought only for 6 prespecified categorical patient characteristics, which included sex, dominant ventricular morphology, staging with a cavopulmonary anastomosis, age at Fontan procedure, type of Fontan connection, and age at enrollment. Given the large number of potential interaction terms, only interactions with $P \leq 0.01$ were considered significant for inclusion in final regression models. Data analyses were performed with the use of SAS statistical software version 9.1 (SAS Institute Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Study Participation

Medical records were screened for 1078 patients, with 831 potentially eligible for participation. After being contacted, 637 patients were fully eligible, and consent was obtained for 546 (86%). Of these, 511 had a fully completed parent-report CHQ and were included in the present analysis. Only 118 patients (23%) completed all laboratory tests, and 275 (54%) completed all tests except MRI. The number of patients who underwent each type of test is shown in Figure 1.

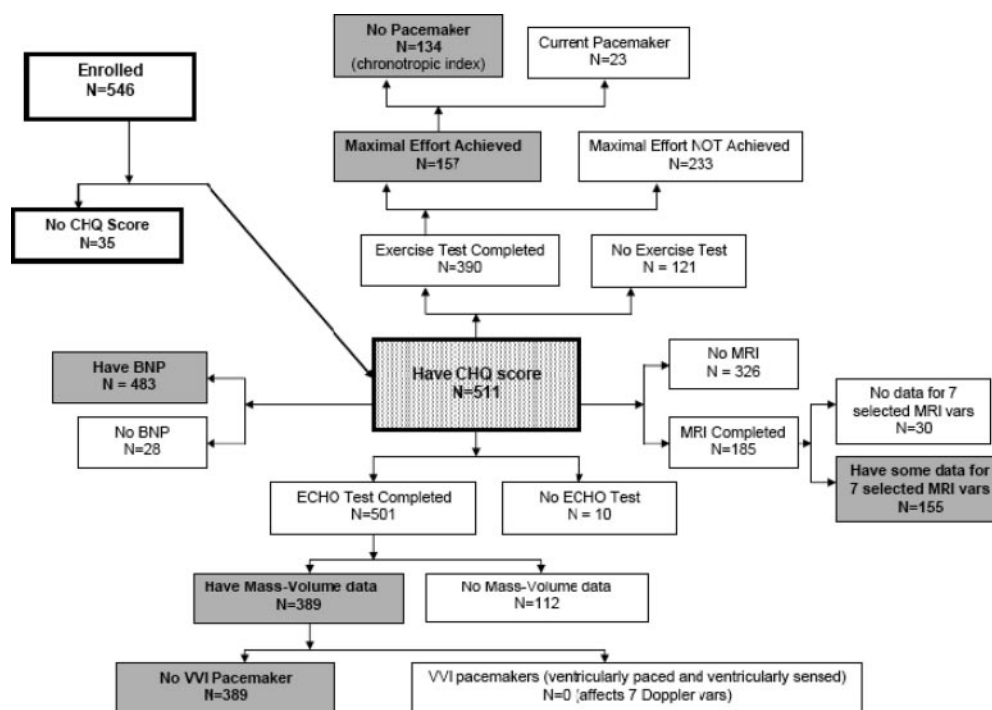


Figure 1. Level of participation of PHN Fontan Cross-Sectional Study enrolled subjects. ECHO indicates echocardiography; vars, variables.

Patient Characteristics

Patient and medical characteristics together with their associations with parent-completed CHQ Physical and Psychosocial FSS have been reported previously.¹³ Selected characteristics of the 511 subjects included in the present analysis are shown in Table I in the online-only Data Supplement, as well as results from the CHQ and laboratory testing. Mean Physical and Psychosocial FSS were 45 ± 12 and 47 ± 11 , respectively.

Associations With CHQ Summary Scores

Brain Natriuretic Peptide

BNP concentration was measured in 483 of the 511 study subjects. Higher logBNP was significantly but weakly related to lower CHQ Physical FSS (parameter estimate = -1.50 ; $P=0.009$; $R^2=0.01$; parameter estimates represent the degree of change in the summary score associated with a 1-integer unit change in the laboratory testing variable). There were no significant interactions with the 6 prespecified patient characteristic variables. BNP was not significantly associated with CHQ Psychosocial FSS, and there were no significant interactions with the 6 prespecified patient characteristic variables.

Cardiopulmonary Exercise Testing

Of the 511 study subjects, 390 had cardiopulmonary exercise testing. Of these, only 157 (40%) achieved a maximal effort as indicated by a respiratory exchange ratio >1.1 . The number of missing values was very small on the maximal effort subset (only 4 missing values for all the variables under consideration), and therefore imputation of missing values was not performed. Chronotropic index was not considered for 23 patients who had a pacemaker at testing.

For CHQ Physical FSS, when all 6 exercise testing variables were included in a multivariable model, the R^2 was 0.094 (adjusted $R^2=0.049$) with $P=0.06$ ($n=130$). In univariable analyses, higher CHQ Physical FSS was significantly associated with higher percent predicted maximum work rate, higher percent predicted $\dot{V}O_2$ at peak exercise, higher percent predicted $\dot{V}O_2$ at anaerobic threshold, and higher percent predicted maximum oxygen pulse. The relationship between score and percent predicted $\dot{V}O_2$ at anaerobic threshold appeared to be nonlinear, but various transformations did not improve the model fit. In multivariable analysis, only higher percent predicted maximum work rate was significant, with a model R^2 of 0.086 and $P<0.001$ (Table 1). There were no significant interactions between the 6 prespecified patient characteristic variables and any of the exercise testing variables.

For CHQ Psychosocial FSS, when all 6 exercise testing variables were included in a multivariable model, the R^2 was 0.05 (adjusted $R^2=0.01$) with $P=0.31$ ($n=130$). In univariable analyses, there were no significant linear or nonlinear associations. A stepwise multivariable analysis showed that higher CHQ Psychosocial FSS was significantly associated with higher percent predicted maximum work rate ($P<0.05$), but the inclusion in the data set of chronotropic index restricted the analysis to 130 patients with available data, with no significant univariable association noted over the full exercise testing data set ($P=0.40$). Exploration for interactions with the 6 prespecified patient characteristics showed a significant interaction between sex and resting oxygen saturation ($P=0.007$). Higher CHQ Psychosocial FSS was associated with higher resting oxygen saturation for female subjects (parameter estimate = 0.825 ; $P=0.006$) and no association for male subjects (parameter estimate = -0.271 ;

Table 1. Association Between CHQ Physical FSS and Cardiopulmonary Exercise Testing*

Variable	Univariable		Multivariable†		Reliability, %‡
	Parameter Estimate	P	Parameter Estimate	P	
Percent predicted maximum work rate, %	0.216	<0.001	0.216	<0.001	79
Percent predicted $\dot{V}O_2$ at peak exercise, %	0.198	<0.001			
Percent predicted $\dot{V}O_2$ at anaerobic threshold, %	0.108	0.003			
Percent predicted maximum oxygen pulse, %	0.079	0.03			
Resting oxygen saturation, %	0.134	0.49			
Chronotropic index	1.699	0.77			

Parameter estimates represent the degree of change in the Summary Score associated with a 1-integer unit change in the laboratory testing variable. $\dot{V}O_2$ indicates oxygen consumption.

*Analysis limited to 157 subjects with maximal effort indicated by a respiratory exchange ratio >1.1. Additionally, analysis of chronotropic index was further limited to those 134 subjects who did not have a current pacemaker.

† $R^2=0.086$ (adjusted $R^2=0.079$); $P<0.001$; $n=157$.

‡From bootstrap bagging (presented for the variables included in the multivariable model).

$P=0.32$; model $R^2=0.06$; adjusted $R^2=0.04$; $P<0.001$; $n=156$).

Echocardiography

Of the 511 study subjects with CHQ summary scores, 501 underwent echocardiography, with 389 subjects having suitable mass-volume data available. None of the patients with pacemakers were being paced in VVI mode at testing, and thus diastolic function parameters were considered valid.

For CHQ Physical FSS, when all 16 echocardiography variables were included in a multivariable model ($n=63$), the model R^2 was 0.29 (adjusted $R^2=0.04$) with $P=0.49$. With mean imputation of missing values, the multivariable model R^2 was 0.07 (adjusted $R^2=0.03$) with $P=0.12$ ($n=388$). In univariable analyses without mean imputation, higher CHQ Physical FSS was significantly associated with lower end-systolic and end-diastolic volume Z scores, lower ventricular mass Z score, and lower atrioventricular valve peak late diastolic velocity. In multivariable analysis with imputation of missing values, only lower end-systolic volume Z score and lower Tei index were significantly and independently related to higher score, with a model $R^2=0.03$ (adjusted $R^2=0.02$) and $P=0.005$ ($n=389$) from a data set with mean imputation of missing values (Table 2). Tei index was included in the final model despite borderline statistical significance because it was more reliable than other variables in bootstrapping. When Tei index was excluded from the model, only end-systolic volume Z score was selected for inclusion in a final model.

Interactions with the 6 prespecified patient characteristics were explored with mean imputation of missing values. There was a significant interaction between Tei index and type of Fontan connection ($P=0.001$). The negative relationship between a lower Tei index and higher score was largest and most significant for patients with an extracardiac lateral tunnel connection versus all other connection types. In addition, there was a significant interaction between the presence of moderate or severe atrioventricular valve regurgitation and age at Fontan procedure ($P=0.005$). The presence of moderate or severe regurgitation appeared to have a particularly detrimental effect on Physical FSS only for

patients who had their Fontan procedure at <2 years of age (Figure 2). When these 2 interactions were included in the final multivariable model, the R^2 increased to 0.15 (adjusted $R^2=0.14$) with $P<0.001$ ($n=388$).

For CHQ Psychosocial FSS, when all 16 echocardiography variables were included in a multivariable model, the model R^2 was 0.12 (adjusted $R^2<0.01$) with $P>0.99$ ($n=63$). With mean imputation of missing values, the multivariable model R^2 was 0.07 (adjusted $R^2=0.03$) with $P=0.11$ ($n=388$). In univariable analyses, higher CHQ Psychosocial FSS was significantly associated with higher Tei index and lower total ventricular mass Z score. A stepwise multivariable regression analysis from a data set with mean imputation included both of these variables in a final model, with a parameter estimate for Tei index of 8.83 per integer unit increment ($P=0.01$) and for total ventricular mass Z score of -0.57 ($P=0.02$), with a model R^2 of 0.03 (adjusted $R^2=0.02$) ($P=0.004$). When interactions with the 6 prespecified patient characteristics were explored, the only significant interaction was between dominant ventricular morphology and ratio of early to late atrioventricular valve diastolic velocities (E/A ratio) ($P=0.006$). It appeared that the positive relationship between increasing Psychosocial FSS and increasing E/A ratio was restricted to those patients with non-left ventricular morphology. When this interaction term was included in the final multivariable model, the model R^2 increased to 0.07 (adjusted $R^2=0.06$) with $P<0.001$.

Magnetic Resonance Imaging

Of the 511 study subjects, 185 had MRI, with 155 having sufficient data for the 7 studied variables. Because there were only 2 missing values for these 7 variables over 155 subjects, imputation was not performed. Subjects who underwent MRI were comparable to the remaining subjects with regard to demographics and non-MRI study test results (data not shown; no significant differences). For Physical FSS, when all 7 MRI variables were included in a multivariable model, the R^2 was 0.13 (adjusted $R^2=0.09$) with $P=0.004$ ($n=153$). In univariable analyses, higher CHQ Physical FSS was significantly associated with lower mass/end-diastolic volume ratio and lower total ventricular mass indexed to BSA^{1.3}.

Table 2. Association Between CHQ Physical FSS and Echocardiography*

Variable	Univariable		Multivariable†		Reliability, %‡
	Parameter Estimate	P	Parameter Estimate	P	
Overall atrioventricular valve regurgitation		0.27			
None	Reference				
Mild	1.214				
Moderate or severe	-1.448				
Semilunar valve regurgitation		0.77			
None	Reference				
Mild	0.615				
Moderate	1.910				
End-systolic volume Z score	-0.718	0.005	-0.689	0.007	43
End-diastolic volume Z score	-0.810	0.02			
Total stroke volume Z score	-0.488	0.16			
Total ejection fraction Z score	0.423	0.17			
Total ventricular mass Z score	-0.700	0.02			
Total mass/end-diastolic volume ratio	0.225	0.89			
Tei index	-7.160	0.08	-6.422	0.10	48
dP/dt, mm Hg/s	0.000	0.63			
Atrioventricular valve peak late diastolic velocity, m/s	-11.02	<0.05			
Early/late atrioventricular valve diastolic velocity (E/A)	1.580	0.23			
Duration of atrioventricular valve late diastolic inflow, ms	-0.026	0.33			
Absolute systemic ventricular flow propagation rate, cm/s	0.040	0.40			
Ratio of AV to tissue Doppler early diastolic flow velocity	-0.158	0.41			
Tissue Doppler peak early diastolic flow velocity (cm/sec)	-0.122	0.56			

Parameter estimates represent the degree of change in the Summary Score associated with a 1-integer unit change in the laboratory testing variable.

*Analysis limited to 389 subjects. Of those with a current pacemaker, none were being paced in a VVI mode. Missing values were not imputed for univariable analyses and were imputed for multivariable analyses.

† $R^2=0.03$ (adjusted $R^2=0.02$); $P=0.005$.

‡From bootstrap bagging (presented for the variables included in the multivariable model).

Total end-systolic volume indexed to BSA^{1,3} appeared to have a nonlinear relationship to score from nonparametric analysis, and several transformations were explored. The variable became significant when a quadratic term was included in addition to the linear term in the model (Figure 3). In multivariable analysis, lower mass/end-diastolic volume ratio and lower and higher total end-systolic volume indexed to

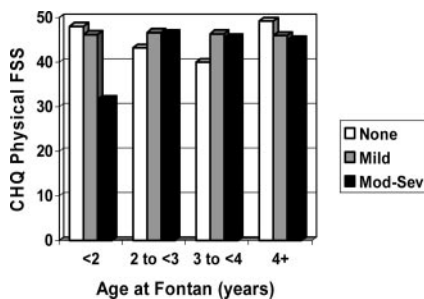


Figure 2. Interaction of subjective grade of atrioventricular valvar regurgitation from echocardiography with age at Fontan procedure and association with Physical FSS. The detrimental impact of moderate or severe atrioventricular valve regurgitation appears to be limited to patients who had Fontan procedure at <2 years of age. Mod-Sev indicates moderate to severe.

BSA^{1,3} were significantly and independently related to higher score, with a model $R^2=0.12$ (adjusted $R^2=0.11$) with $P<0.001$ (n=153) (Table 3). There were no significant interactions between the 6 prespecified patient characteristic variables and any of the MRI variables.

For Psychosocial FSS, when all 7 MRI variables were included in a multivariable model, the R^2 was 0.02 (adjusted $R^2<0.01$) with $P=0.85$ (n=153). In univariable analyses,

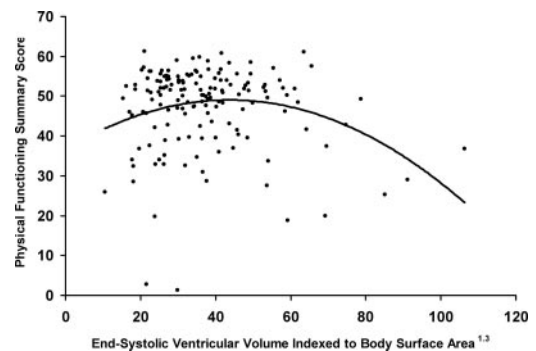


Figure 3. Nonlinear relationship between MRI-assessed end-systolic ventricular volume indexed to BSA (mL/m^{1.3}) and Physical FSS.

Table 3. Association Between CHQ Physical FSS and MRI*

Variable	Univariable		Multivariable†		Reliability, %‡
	Parameter Estimate	P	Parameter Estimate	P	
Total ESV indexed to BSA ^{1,3} , mL/m ²	-0.057	0.30	0.437	0.03	36
(Total ESV/BSA ^{1,3}) ²			-0.006	0.004	56
Total EDV indexed to BSA ^{1,3} , mL/m ²	-0.006	0.87			
Total stroke volume, mL	0.045	0.19			
Total ejection fraction, %	0.075	0.43			
Cardiac output, L/min	0.326	0.52			
Total ventricular mass indexed to BSA ^{1,3} , g/m ²	-0.099	0.02			
Total mass/EDV ratio, g/mL	-7.068	0.02	-8.366	0.004	56

Parameter estimates represent the degree of change in the Summary Score associated with a 1-integer unit change in the laboratory testing variable. ESV indicates end-systolic volume; EDV, end-diastolic volume.

*Analysis limited to 155 subjects with values for the 7 variables. Missing values were not imputed.

†R²=0.12 (adjusted R²=0.11); P<0.001 (n=153). Final multivariable model includes a significant quadratic term for total end-systolic volume indexed to BSA^{1,3}, indicating a nonlinear relationship.

‡From bootstrap bagging (presented for the variables included in the multivariable model).

CHQ Psychosocial FSS was not significantly associated with any of the MRI variables. For the 6 prespecified patient characteristics, there was a significant interaction between total end-diastolic volume indexed to BSA^{1,3} and age at Fontan procedure (P=0.005). A multivariable model with the interaction term and both variables had a model R² of 0.12 (adjusted R²=0.10) with a P=0.02. The interaction showed that lower Psychosocial FSS was significantly related to higher total end-diastolic volume indexed to BSA^{1,3} for patients who had their Fontan procedure at <2 years of age (parameter estimate=-0.19; P=0.02) and ≥4 years of age (parameter estimate=-0.16; P<0.05) versus those at age 2 years (parameter estimate=0.01; P=0.83) or age 3 years (parameter estimate=0.13; P=0.08).

Discussion

Summary Score Measures

Summary Score measures of both physical and psychosocial functional health status were only weakly associated with objective laboratory measures reflecting various physiological and pathophysiological parameters. Some associations are of interest. Higher Physical FSS was weakly associated with more optimal measures of exercise capacity, most significantly with higher maximum work rate. A weak but statistically significant association was noted between lower BNP levels and higher Physical FSS. Physiological assessment from imaging modalities showed weak but statistically significant associations of higher Physical FSS with more optimal ventricular size, mass, and indices of both systolic and diastolic function. Some of these associations were modified by other factors, such as age at Fontan procedure and Fontan connection type. For example, the presence of moderate or severe grade of atrioventricular valvar regurgitation was associated with lower Physical FSS only for those having Fontan procedure at <2 years of age. Psychosocial FSS was weakly associated with limited variables from laboratory testing, usually in relation to interactions with the 6 prespecified categorical patient characteristics, and the

possibility that these associations may be spurious cannot be excluded.

Functional Health Status and Relationship to Patient and Medical Characteristics

CHQ Summary Scores in this cohort were lower than published scores from subjects with other types of chronic health conditions.¹³ A previous focused analysis showed that lower Physical FSS was significantly associated with higher patient weight at Fontan procedure, no fenestration performed, other surgical procedures performed at Fontan procedure, arrhythmias during follow-up, and higher number of current medications.¹³ In addition, associated noncardiac medical conditions, including asthma, non-asthma respiratory problems, and orthopedic problems, were independently associated with lower scores. Psychosocial factors, including learning problems, lower family income, and parent not working because of patient’s health, were also independently associated with lower scores. These factors accounted for 40% of the variation in Physical FSS, much more than any combination of laboratory variables in the present analysis. Lower Psychosocial FSS was associated only with psychosocial factors, including lower family income and problems with behavior, learning, anxiety, attention, and depression, accounting for 34% of the variation in scores. The present analysis showed limited and weak associations between Psychosocial FSS and laboratory variables. Current medical and psychosocial conditions appear to be more strongly associated with functional health status than Fontan-specific factors, including those measured objectively.

Relationship to BNP

BNP level explained only 1% of the variation observed in Physical FSS, with patients with higher BNP having lower Physical FSS. Our findings are consistent with smaller single-center reports using less specific health status indices. In patients evaluated in the outpatient setting a median of 9 years after Fontan procedure, those in New York Heart

Association class I (n=55) had lower BNP than those in class II (n=12).¹⁴ Similarly, amino-terminal pro-BNP has been correlated with a higher index of heart failure with the use of the New York University Pediatric Heart Failure Index in 59 children and adolescents at a median of 8 years after Fontan procedure.¹⁵ Among adults after Fontan procedure, higher BNP differentiated patients in New York Heart Association class II from those in New York Heart Association class III and IV.¹⁶ In a single-center study of heterogeneous adult patients with a systemic right ventricle, BNP was elevated and was related to New York Heart Association class but not to exercise capacity or echocardiography-assessed function.¹⁷ The BNP values noted in our study were within an age-adjusted normal range in the majority of patients. This likely reflects the compensated state of the relatively healthy outpatient cohort that was enrolled. The relationship of BNP to functional health status may be stronger among symptomatic Fontan patients.

Relationship to Exercise Capacity

Although patients who achieved maximal effort had diminished exercise capacity, exercise variables were not strongly associated with functional health status. A previous focused analysis of this cohort has shown that peak oxygen consumption was 65% of normal, with only 40% achieving maximal capacity.¹⁸ Oxygen consumption at ventilatory anaerobic threshold was better preserved, and associations with echocardiographic indices of ventricular function were weak. Better exercise capacity was associated with higher oxygen pulse at peak exercise, probably a surrogate for higher stroke volume.

The majority of subjects failed to achieve maximal aerobic capacity, and pulmonary and musculoskeletal deconditioning and motivational factors may be important determinants. Deconditioning may be related to poor levels of physical activity,¹⁹ possibly reflective of increased parental and patient anxiety and uncertainty around physical activity. Many patients in this cohort were reported to have asthma or non-asthma respiratory conditions, and abnormalities of pulmonary function have been reported previously.²⁰ Pulmonary function abnormalities and musculoskeletal deconditioning may have at least as important an impact on perceived physical functioning in this population as aerobic capacity. The limited association (only 9% of the variation in Physical FSS explained) between the measures of aerobic capacity and functional health status in the present study population for those who achieved a maximal aerobic effort would support this notion. This would suggest that interventions designed to improve physical functioning should address these issues as well as aerobic capacity.

Rehabilitation through exercise training programs results in improved exercise capacity^{7,21} and muscle function.²² Although exercise training programs have shown modest improvements in aerobic capacity, these programs are resource intensive, and interventions aimed at improving physical activity levels may prove more feasible. Improved control of asthma or improved muscle strength may result in a more significant enhancement of physical functioning than attempts to improve aerobic capacity. Limited data are

available on pharmacological interventions. Sildenafil treatment has been shown to be associated with improvements in exercise capacity,²³ whereas no effect has been noted with treatment with enalapril.⁵ Improvements in the surgical management of single-ventricle patients have been associated with better exercise capacity, including earlier volume unloading surgery²⁴ and avoidance of and conversion from atriopulmonary Fontan connection type.² The role of fenestration closure is less clear.²⁵ The development and study of interventions aimed at improving exercise capacity might include measures of functional health status.

Valvar Function, Ventricular Size and Performance, and Relationship to Functional Health Status

Measures of valvar function, ventricular volumes, mass, and mass/volume relationships were weakly associated with Physical FSS, accounting for only 14% of the variation in scores (6% for Psychosocial FSS) in the final multivariable model for echocardiographic variables and 11% (10% for Psychosocial FSS) for MRI variables. Both systolic and diastolic functional abnormalities have been reported after the Fontan procedure, with diastolic functional abnormalities of both compliance and relaxation reported to worsen with time.^{26,27} Effective interventions to reduce ventricular volumes, preserve systolic function, manage diastolic dysfunction, and prevent or treat inappropriate hypertrophy have not been developed or studied. There is some evidence that earlier volume unloading is beneficial.²⁶ The relationship of neurohumoral activation to these abnormalities is unclear, although it is present and does not appear to be related to functional health status.¹⁶

Study Limitations

The results of this study should be viewed in light of some limitations. The subjects represented a subgroup of available current survivors, although enrolled versus nonenrolled eligible subjects did not differ in important ways.⁸ The level of participation of enrolled subjects was not uniform for all laboratory tests and may have been influenced by factors associated with functional health status. In addition, analysis of associations with cardiopulmonary exercise variables was restricted to those with maximal effort. These factors may have introduced some selection bias, although the focus of the present analysis was on determining associations. The study population was relatively well, and this may have contributed to the lack of strong associations noted. Many interventions proposed for study in Fontan patients have been aimed at primary prevention (preventing ventricular dysfunction, arrhythmias, thrombosis, exercise intolerance); thus, the population we studied would be the target population, and the associations explored would be the ones of interest. Functional health status was determined from parent or proxy report, which may differ from that reported by the child or adolescent, although the age range of the subjects precluded uniform administration of the Child Report form of the CHQ. A few of the variables reported, such as subjective grade of valvar regurgitation, may have been less valid and reliable, although no gold standard currently exists for use in a

heterogeneous group of functional single-ventricle patients. Given the large number of variables tested, we may have observed spurious associations arising from multiple comparisons. For this reason, only results from multivariable analyses are emphasized, and variable selection was confirmed with bootstrapping for reliability. Finally, the clinical meaning of the observed associations is unclear, given their relatively small magnitude.

Conclusion

In a spectrum of Fontan patients, variation in exercise capacity and ventricular characteristics and performance explains only a small proportion of the variation in functional health status. Laboratory measures may not be optimal surrogate end points in trials of therapeutic interventions aimed at improving functional health status for Fontan patients, and functional health status assessment should be included. Our supposition is that patients would be more likely to benefit from interventions aimed at psychosocial and behavioral factors in terms of improving functional health status. Preventive medical interventions have not been shown to be of benefit, and treatment interventions might be effective once the patient passes a certain pathophysiological threshold. Potential strategies and initiatives suggested by the PHN Fontan Cross-Sectional Study that may influence sub-optimal functional health status and its assessment for Fontan patients and that might be the topics of further study include the following: coordinated and effective management of noncardiac medical conditions¹³; coordinated and effective prevention, identification, and management of learning, behavior, and emotional problems¹³; specific targeting of interventions for patients from low-income households¹³; development and evaluation of cardiovascular rehabilitation programs; development of a disease-specific assessment tool for functional health status that is responsive to laboratory measures; and ongoing study of laboratory abnormalities and their association with functional health status, particularly longitudinal changes into adulthood.

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Disclosures

None.

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CLINICAL PERSPECTIVE

As mortality rate has declined dramatically for repair of even the most complex congenital heart disease patients, clinical care will focus increasingly on preventing and treating morbidities and improving functional health status. Patients with a functional single ventricle who have had the Fontan procedure are at high risk for suboptimal functional health status. Determination of associations of functional health status with laboratory measures, which may suggest pathophysiological mechanisms, are important for planning interventions and outcome measures for clinical trials. We performed a cross-sectional assessment of patients 6 to 18 years of age who had undergone the Fontan procedure. Our results showed that laboratory measures of exercise capacity and ventricular characteristics and function, as assessed objectively by brain natriuretic peptide levels, exercise testing, echocardiography, and magnetic resonance imaging, were only weakly associated with results from a validated questionnaire measure of physical and psychosocial functional health status. This suggests that strategies aimed at preserving indices of ventricular form and function as assessed by laboratory testing may have little effect on current functional health status. The impact of treatment strategies targeted toward those with important laboratory abnormalities in the pathological range may influence functional health status to an unknown degree but should be an important component of future studies. Strategies targeting functional health status and its noncardiac determinants directly, such as through rehabilitation programs and by addressing psychosocial morbidities, may have a greater impact on health-related quality of life. Such programs should be developed and evaluated for these high-risk and complex patients.