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FACTORS ASSOCIATED WITH SERUM BRAIN NATRIURETIC PEPTIDE LEVELS AFTER THE FONTAN PROCEDURE

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Abstract

Objective—Although a useful marker of heart failure in adults, the utility of brain natriuretic peptide concentration (BNP) for children after the Fontan procedure is not well studied.

Design—BNP was measured in 510 patients aged 6–18 years in the Pediatric Heart Network Fontan cross-sectional study at a median of 8.2 years after Fontan. Patients underwent echocardiography, exercise testing, magnetic resonance imaging (MRI) and functional health status questionnaires. Associations of BNP with baseline patient characteristics, medical history and cross-sectional assessment were examined with multivariable linear regression analyses.

Results—The distribution of BNP was highly skewed, median 13.0 pg/mL (inter-quartile range: 7.1, 25.9), and was normalized with logarithmic transformation (logBNP). Among medical history variables, logBNP was greater in females ($p=0.02$) and older patients ($p<0.001$). Presence of pre-Fontan systolic ventricular dysfunction, greater number of post-Fontan complications, and thrombosis after Fontan were independently associated with higher logBNP ($R^2=0.16$). Age-adjusted logBNP was significantly related to Fontan connection type, (lower with extracardiac conduits, higher with atriopulmonary connection; $p<0.001$). Lower physical functioning health status ($R^2=0.05$), lower chronotropic index during exercise ($R^2=0.17$), indices of diastolic dysfunction measured by echocardiography ($R^2=0.15$), and higher total ventricular mass on MRI ($R^2=0.33$) were related to higher logBNP.

Conclusions—Despite a markedly abnormal circulation, BNP was variable but within a normal range in the majority of Fontan patients in this large outpatient cohort. Higher BNP was associated

with several markers of suboptimal outcome, although associations were weak. The routine use of BNP as an outpatient surveillance tool in asymptomatic Fontan patients is not warranted.

Keywords

Fontan procedure; congenital heart defects; natriuretic peptides

INTRODUCTION

Brain natriuretic peptide is a naturally occurring hormone produced by cardiac ventricular and, to a lesser extent, atrial myocytes in physiologic situations associated with ventricular or atrial wall stress. Brain natriuretic peptide concentration (BNP) has been widely used as a diagnostic tool to differentiate cardiac from respiratory illnesses in adults.^{1, 2} Studies of BNP in pediatric patients with heart disease are limited and are frequently not adjusted for factors such as age and gender that confound measurements. In small studies involving children with heterogeneous congenital heart diagnoses, elevated BNP correlated with ventricular dysfunction.³ Patients with functionally univentricular hearts had higher BNP compared to those with a biventricular circulation.⁴ There is limited published information about BNP in Fontan patients and the potential diagnostic and prognostic value of BNP in this population is currently unknown.

The Pediatric Heart Network (PHN) recently completed a multi-institutional cross-sectional study of outpatient Fontan subjects aged 6 to 18 years.^{5, 6} The purpose of the present report is to describe the profile of BNP in children and adolescents after the Fontan procedure and its relationship to subject characteristics and medical history. Furthermore, we sought to identify laboratory factors that are associated with BNP using cross-sectional tests of functional health status, exercise performance, echocardiography and cardiac magnetic resonance imaging (MRI).

METHODS

Study Subjects

The seven centers comprising the PHN performed a multicenter, prospective, cross-sectional assessment of children who had undergone a Fontan procedure.⁶ The techniques used to collect medical history data and to perform standardized echocardiography, cardiac MRI, and exercise testing have been previously described.^{5, 6} Potential study subjects were identified from medical record review, and deemed eligible if they were age 6 to 18 years at the time of enrollment; had undergone Fontan procedure at least 6 months before initial study testing; and agreed to have an echocardiogram and blood testing and to complete a parent report functional health status questionnaire within 3 months of enrollment at one of the study centers. Exclusion criteria included the presence of a non-cardiac medical or psychiatric disorder that would prevent successful completion or invalidate the results of study testing. Subjects (n=546) were evaluated at a mean age of nearly 12 years old, and at a mean interval of 8.6 years after Fontan completion.⁵ The protocol was approved by each center's institutional review board. Written informed consent and assent were obtained. The present analysis is limited to the 510 subjects with BNP measurements.

Measurements

Resting BNP in plasma was centrally measured with the Shinogi BNP-32 Human Assay (Mayo Clinical Trial Services, Rochester, MN).⁶ The samples were drawn from a venipuncture after patients had been in a sitting or supine position in a quiet room for 30

minutes. The lower detection limit was 4 pg/mL; this was used for 55 subjects whose values were denoted as below the detectable limit.

Among the 510 subjects with BNP measured, functional health status was assessed in 504 using the validated Parent Report Form of the Child Health Questionnaire (CHQ).⁷ In addition to scores for individual domains, summary scores were derived for Physical and Psychosocial Functioning. The Parent Report Form of the CHQ also required parents to identify from a list of associated health conditions those which were present in their child. A previous analysis reported associations between Physical Functioning Summary Score and patient and medical history characteristics.⁸ Exercise testing was performed in 390 of these subjects. Analysis of the 6 exercise variables was limited to the 158 subjects able to achieve maximal aerobic capacity (Peak Respiratory Exchange Ratio >1.1). Analysis of chronotropic index (maximal achieved heart rate- resting heart rate) ÷ (predicted maximal heart rate minus resting heart rate) was restricted to only the 135 non-paced subjects able to achieve maximal exercise. Among the other exercise variables, the number of missing values was small (<5 for each) and no imputation of missing values was performed. An echocardiogram was performed for 503 patients with measured BNP. Subjects were excluded from analysis of echocardiographic data if they had no available mass or volume data (n=114). Missing echocardiographic variable values were imputed in multivariable regression analyses using mean values from the subset with mass-volume data. An MRI was performed in 153 patients. Among the 7 MRI variables measured, very few values (<3 for each) were missing and imputation was not performed.

Data Analysis

Data are described as frequencies, medians with minimum and maximum values or 25th and 75th percentile values, and means with standard deviations. The distribution of BNP was highly skewed towards lower values. (Figure 1). As a result, all analyses were performed after logarithmic transformation (logBNP, natural logarithm), which resulted in a more normal distribution. Variables explored for association with logBNP were initially analyzed within associated groups (e.g., echocardiography, exercise testing, MRI) in univariable models (Table 1) and then in multivariable models (Table 2). To determine the amount of variation in logBNP explained by each group of variables, multivariable linear regression analyses were performed with all variables from each group included in the model and the R² adjusted for the number of variables are reported (Table 2). To determine which variables within each group were independently associated with logBNP, initial exploration was performed using bootstrap procedures to determine reliability for model inclusion, and then stepwise regression was performed with inclusion of gender and age at enrollment for adjustment in final models. Non-linearity was addressed by a variable transformation, as appropriate. Further adjustment for type of Fontan connection was performed by including this variable in final regression models for echocardiography, exercise testing and MRI variable groups. Given the large number of variables explored, only significant variables in multivariable regression analyses are reported (Table 3). All analyses were performed using SAS statistical software version 9 (SAS Institute, Inc, Cary, NC).

RESULTS

Study Subjects

BNP was measured in 510 of 546 subjects; 60% were male, 80% were white, 10% were black, and 10% were of another race. Subjects were a median age of 11.4 years (inter-quartile range [IQR]: 9.0 – 14.6 yrs) at the time of enrollment, and underwent their Fontan surgery at a median of 2.8 years (IQR: 2.1 – 4.0 yrs) of age. The 36 subjects without BNP measurements in the Fontan cross sectional study were significantly younger than the 510

with a measurement (10.8 ± 3.4 years versus 11.9 ± 3.4 years, $p=0.05$), likely due to reluctance to undergo venipuncture or technical difficulty. The mean BNP was 25 ± 48 pg/mL, with a median of 13 pg/mL (range 4 to 652 pg/mL; IQR 7 to 26 pg/mL). The distribution of BNP levels in the study sample is shown in Figure 1. Previous studies in patients with congenital heart disease have suggested that BNP > 40 pg/mL may be a marker of ventricular dysfunction³ and may differentiate children with congestive heart failure from those with non-cardiac causes of respiratory distress.⁹ A value of 100pg/mL has been used as a marker for heart failure in adults.² Overall, 86% of subjects ($n=438$) had BNP < 40 pg/mL and 96% ($n=489$) had BNP <100pg/mL. Values below the detection level of 4pg/mL occurred in 11% of subjects ($n=55$).

Association of Patient Variables to BNP

Table 2 shows the magnitude of the relationship of variable groups with logBNP. For all variable groups, the proportion of variance in BNP explained by the variables (adjusted R^2) was small, being highest for echocardiography at 0.14 or 14%, followed by MRI at 9%, and parent-completed CHQ associated health conditions at 8%.

The results of the multivariable analyses for each variable group are shown in Table 3. Higher logBNP was significantly and independently related to female gender and older age at enrollment. Therefore, all other multivariable analyses were subsequently adjusted for gender and age. The only pre-Fontan procedure characteristic significantly associated with higher logBNP was the presence of systolic ventricular dysfunction by echocardiography. Type of Fontan connection was the only significant Fontan procedure characteristic variable independently associated with logBNP, ($p < 0.01$, Figure 2). Mean BNP (adjusted for age and gender) among subjects with atriopulmonary connection was 8pg/mL higher than for those with intracardiac lateral tunnel, which in turn was 11 units higher than BNP in those with an extracardiac lateral tunnel, and BNP in those with an extracardiac lateral tunnel were a mean of 4 pg/mL higher than those with an extracardiac conduit. Therefore, subsequent multivariable analyses of laboratory testing were adjusted for this additional variable of Fontan connection type. Post-Fontan characteristics independently associated with higher logBNP included a greater number of complications and the presence of an episode of post-Fontan thrombosis. For the parent-completed CHQ, higher logBNP was associated with lower Physical Functioning Summary and Physical Functioning domain scores, as well as the presence of associated bone/joint/orthopedic and allergy/sinus problems.

Multivariable analyses of laboratory testing results were performed with adjustments for gender, age and type of Fontan connection (Table 3). From exercise testing, only lower chronotropic index was associated with higher logBNP. Among echocardiographic variables, indices of diastolic dysfunction were significantly related to higher logBNP. Among MRI variables, only greater total ventricular mass indexed to body surface area was associated with higher logBNP. To account for the non-linearity and improve model fit, a dichotomous variable separating observations in the 95th percentile of the indexed ventricular mass from the rest of the observations was used.

A number of variables were not associated with BNP. After adjustment for age at enrollment, gender and type of Fontan connection, the following were not independently associated with BNP: ventricular type (a dominant left, right or mixed ventricular dominance), age at Fontan completion, and post-Fontan history of arrhythmia. Protein losing enteropathy was documented in 19 subjects; median BNP was not different between those and the remaining 491 subjects, 13 vs, 10 pg/mL, $p=0.5$. The presence or magnitude of atrioventricular valve regurgitation assessed by echocardiogram was not associated with BNP. Ejection fraction (EF) assessed as a continuous variable by echocardiography and MRI was also not associated with BNP. However, when comparing subjects assessed by the

echocardiography core lab to have a normal EF (z-score ≥ -2 , which corresponds to an EF $\geq 53\%$) with those with abnormal EF (z-score < -2 , which corresponds to an EF $< 53\%$), we found logBNP to be significantly lower in those with normal EF, $p=0.01$). When adjusted for age and gender, those with normal EF continued to have a lower logBNP ($p=0.02$)

DISCUSSION

This is the largest study to date examining BNP in Fontan patients. A strength of the study is its prospective design and centralized assay for BNP concentration. In addition, the analyses were adjusted for known confounders such as age and gender. We found that BNP varied considerably in this multicenter cohort of outpatient Fontan subjects, but was relatively low in the majority of patients, especially compared to values used to define congestive heart failure in adult patients. Higher BNP (or logBNP) was associated with older age, female gender and atriopulmonary type Fontan connection, as well as selected medical history variables. Higher BNP was weakly associated with diagnostic markers of suboptimal health status and ventricular performance.

Previous studies in patients with congenital heart disease have suggested that BNP > 40 pg/mL may be a marker of ventricular dysfunction³ and may differentiate children with congestive heart failure from those with non-cardiac causes of respiratory distress.^{9, 10} Assigning specific cut-point values of BNP in pediatrics is uniquely problematic as normal values are not widely agreed upon and, similar to what we report, vary with both gender and age.^{11, 12} In a group of 67 Fontan patents, BNP was reported as normal in 81%.¹³ The data presented here suggest that the uniform and unisex cut-points for normal values for BNP may be misleading and should not be used in this population.

BNP is elevated after initial palliative operations in single ventricle patients and falls in response to subsequent volume unloading surgeries such as the cavopulmonary anastomosis (Glenn) procedure.¹⁴ In a previous study involving single ventricle patients, plasma BNP was elevated when systemic ventricular dysfunction was present but not elevated compared to normal controls for patients with Glenn or Fontan physiology without ventricular dysfunction.¹⁵ Among our subjects, ejection fraction, a marker of systolic function, was normal in 73% of subjects⁵ and those subjects had a lower logBNP when compared to those with an abnormal ejection fraction.

After controlling for age and gender, we found the type of Fontan connection was related to BNP. Similarly, BNP was higher in a small study of adult Fontan patients with atriopulmonary connections compared to those with total cavopulmonary connections.¹⁶ Although the majority of BNP is secreted from ventricular myocytes, it is also secreted from atrial myocytes, and therefore may be expected to be higher in anatomic situations of increased atrial stretch such as with the atriopulmonary connection in comparison to extracardiac connections.

We found a higher BNP to be weakly associated with lower (poorer) Physical Functioning Summary Score and lower scores for the Physical Functioning domain. This is consistent with findings in a small group of children after Fontan where higher NT-pro BNP was associated with higher New York University Pediatric Heart Failure Index scores¹⁷ and in an older Fontan population where lower BNP differentiated NYHA classification 2 from NYHA class 3 and 4.¹⁶ The association of BNP to orthopedic/bone/joint problems and allergy/sinus problems has not been previously reported and is not intuitively explained, other than speculating that these findings may co-migrate with other indicators of poor cardiac status.

In the present study, a lower chronotropic index was independently associated with higher BNP after consideration of age, gender and Fontan connection type. A lower chronotropic index has been used as a marker for chronotropic incompetence, which has been shown to be a predictor of sudden cardiac death in patients with heart failure.¹⁸ Although not previously well studied in the Fontan population, chronotropic incompetence has been associated with higher BNP in adults with congenital heart disease decades after their surgical intervention.¹⁹

The association of higher BNP with echocardiographic findings of diastolic dysfunction is consistent with a previous study involving 35 asymptomatic Fontan patients.²⁰ The association of BNP with increased ventricular mass noted in our patients undergoing MRI has not been previously reported in this population, but BNP has been associated with increased ventricular mass in adults with hypertrophic cardiomyopathy,²¹ and in pediatric patients with increased left ventricular mass as a result of aortic stenosis.²²

After adjustment for age, gender and Fontan connection type neither the presence nor magnitude of atrioventricular valve regurgitation was related to BNP. Again, this may reflect well compensated hemodynamics in this relatively healthy cross-sectional study of Fontan patients. Consistent with previous studies we found no difference in BNP related to the dominant ventricular morphology (right, left or mixed).^{16 17}

This study must be interpreted in light of some limitations. This was a cross-sectional study of pediatric Fontan outpatients, and as such, the most symptomatic Fontan patients may not have been included. This likely contributed to the rather narrow range of BNP values measured in our study and may have impeded our efforts to find strong associations. In addition, a cross-sectional study such as this cannot assess the predictive value of BNP for outcomes such as death or progressive heart failure. Not all patients were able to complete all tests, which might limit the ability to detect associations.

This study establishes a range of BNP concentrations in a large outpatient cohort of children after the Fontan procedure. Despite a markedly abnormal circulation, BNP is within the normal range for age in the majority of the subjects. Our data do not support the routine measurement of BNP in the outpatient follow up of relatively healthy patients after a Fontan procedure.

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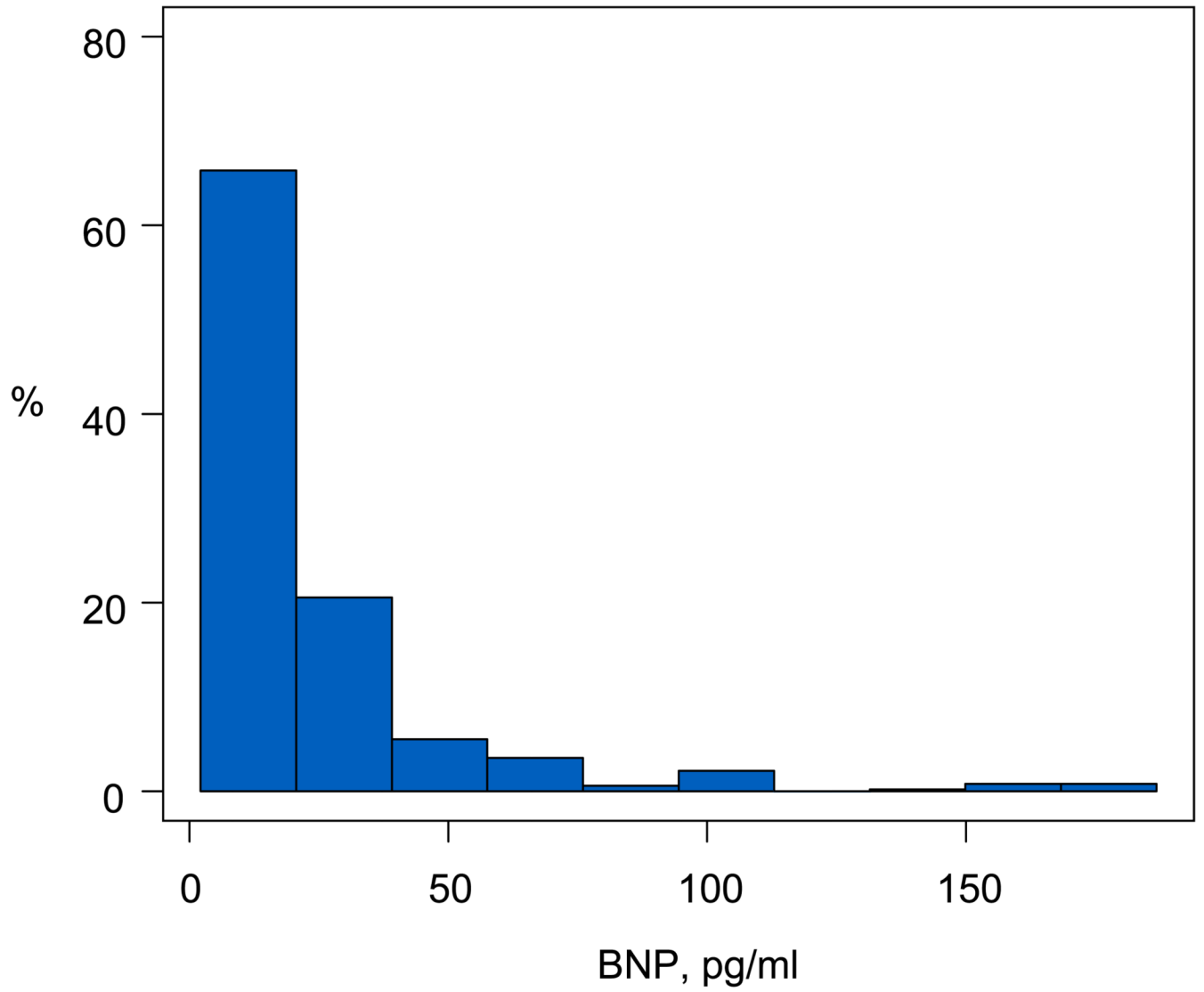


Figure 1. Distribution of Brain natriuretic peptide (BNP) concentration excluding 4 patients with values exceeding 200 pg/ml.

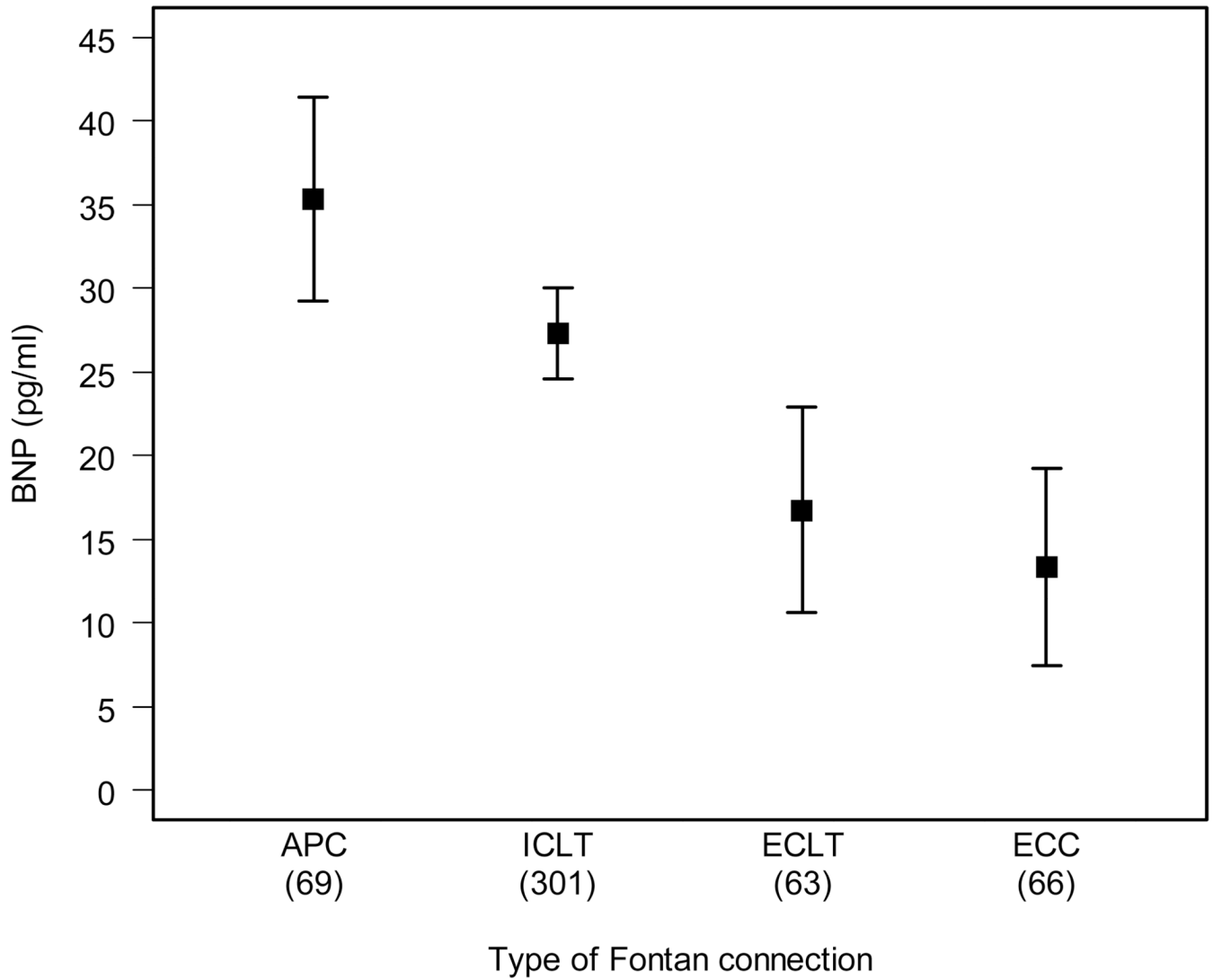


Figure 2. Subgroup analysis of serum brain natriuretic peptide concentrations (BNP) by Fontan connection type. Mean \pm SE of raw BNP adjusted for gender and age at enrollment. APC=atriopulmonary connection, ECC=extracardiac conduit, ECLT=extracardiac lateral tunnel, ICLT=intracardiac lateral tunnel.

TABLE 1

Significant Variables in Univariable Testing for Association with Log Transformed BNP concentrations

Variable	n	PE (SE)	p Value
Demographics			
Age at enrollment	510	0.05 (0.01)	<0.01
Female gender	510	0.23 (0.09)	<0.01
Race			0.02
White	406	0.23 (0.14)	
Black	49	0.51 (0.19)	
Other	54	reference	
Body mass index Z score	509	0.03 (0.01)	<0.01
Years since Fontan	510	0.04 (0.01)	<0.01
Pre-Fontan Characteristics			
History of stroke before Fontan	504	0.55 (0.22)	0.01
Systolic ventricular dysfunction before Fontan	468	0.46 (0.16)	<0.01
No Cavopulmonary staging procedure performed	510	0.33 (0.10)	<0.01
Higher ventricular end-diastolic pressure	486	0.03 (0.01)	0.04
Lower systemic oxygen saturation prior to Fontan	494	0.03 (0.01)	<0.01
Fontan Procedure Characteristics			
Type of Fontan connection			<0.01
Atriopulmonary	69	-0.37 (0.30)	
Intracardiac lateral tunnel	301	-0.76 (0.28)	
Extracardiac lateral tunnel	63	-1.08 (0.30)	
Extracardiac conduit	66	-1.22 (0.30)	
Other	11	reference	
Decreased systolic ventricular function at discharge	506	0.60 (0.23)	<0.01
Glycoside use at discharge	505	0.18 (0.09)	0.03
Post-Fontan Follow-Up Characteristics			
Total number of complications	510	0.12 (0.03)	<0.01
Post-Fontan thrombosis	510	0.60 (0.16)	<0.01
Post-Fontan arrhythmia	509	0.28 (0.10)	<0.01
Presence of other (non-cardiac) complications	510	0.21 (0.10)	0.03
Number of other (non-cardiac) complications	510	0.11 (0.04)	<0.01
Number of post-Fontan cardiac surgeries	510	0.10 (0.04)	0.02
Parent-Completed CHQ Scores			
Poorer Physical Functioning Summary score	483	0.01 (0.004)	<0.01
Poorer Physical functioning domain	503	0.01 (0.002)	<0.01
Poorer Bodily pain domain	498	0.01 (0.002)	0.01
Parent-Completed CHQ Health Conditions			
Orthopedic problems	498	0.50 (0.13)	<0.01
Allergies / sinus problems	496	0.32 (0.11)	<0.01
Sleep disturbance	498	0.36 (0.14)	0.02

Variable	n	PE (SE)	p Value
Asthma	491	0.27 (0.12)	0.03
Cardiopulmonary Exercise Testing			
Lower Chronotropic index	135	1.54 (0.61)	0.01
Echocardiography			
Ventricular mass Z score	382	0.11 (0.02)	<0.01
Ventricular end-diastolic volume Z score	389	0.11 (0.02)	<0.01
Ventricular end-systolic volume Z score	389	0.08 (0.02)	<0.01
Ventricular stroke volume Z score	389	0.09 (0.03)	<0.01
Lower AW peak late diastolic velocity	258	1.52 (0.42)	<0.01
Duration of AW late diastolic inflow	258	0.01 (0.002)	<0.01
Ratio of early to late AW diastolic velocity	258	0.31 (0.10)	<0.01
Tei Index	347	0.68 (0.29)	0.02
Magnetic Resonance Imaging			
Total ventricular mass indexed to body surface area	153	0.01 (0.003)	<0.01
Ratio of total ventricular mass to end-diastolic volume	153	0.80 (0.23)	<0.01
Lower ventricular ejection fraction	153	0.02 (0.01)	0.04

PE, parameter estimate; SE, standard error; AW, atrioventricular valve; CHQ, Child Health Questionnaire; HLHS, hypoplastic left heart syndrome; PHN, Pediatric Heart Network; SV, single ventricle

TABLE 2

The Proportion of Variance (Model R^2) in Log Transformed Brain Natriuretic Peptide Concentrations* Explained in Multivariable Analysis by Groups of Variables

Variable Group	n	Number of Variables	R^2	Adjusted R^{2**}
Demographics	510	8	0.08	0.06
Pre-Fontan characteristics	510	20	0.05	0.02
Fontan characteristics	510	31	0.15	0.10
Post-Fontan characteristics	510	14	0.05	0.03
Parent-completed CHQ summary scores	483	2	0.02	0.01
Parent-completed CHQ domain scores	504	15	0.08	0.05
Parent-completed CHQ health conditions	504	15	0.10	0.08
Cardiopulmonary exercise testing	131	6	0.06	0.02
Echocardiography [†]	389	16	0.17	0.14
Magnetic resonance imaging	151	7	0.11	0.09

* analyzed after logarithmic transformation (with the natural base) to normalize the distribution

** adjusted for the number of variables in the model

CHQ, Child Health Questionnaire

[†] Missing echocardiographic variable values were imputed from the subset with mass-volume data

TABLE 3

Final Multivariable Models for Higher Log Transformed Brain Natriuretic Peptide Concentrations*

	PE (SE)	p Value
Demographics, n=510, model R²=0.04, Adjusted R²=0.04**		
Female gender	0.21 (0.08)	0.01
Older age at enrollment	0.05 (0.01)	<0.01
Pre-Fontan Characteristics, n=466, model R²=0.06, Adjusted R²=0.06**		
Presence of systolic ventricular dysfunction on pre-Fontan echocardiography	0.52 (0.16)	<0.01
Fontan Characteristics, n=510, model R²=0.10, Adjusted R²=0.09,**		
Type of Fontan connection		<0.01
Atriopulmonary	-0.38 (0.30)	
Intracardiac lateral tunnel	-0.72 (0.28)	
Extracardiac lateral tunnel	-1.01 (0.31)	
Extracardiac conduit	-1.18 (0.30)	
Other	reference	
Post-Fontan Characteristics, n=510, model R²=0.08, Adjusted R²=0.08**		
Greater total number of complications	0.08 (0.03)	<0.01
Post-Fontan thrombosis	0.45 (0.17)	<0.01
Combined Medical History Characteristics, n=468, model R²=0.16, Adjusted R²=0.15**		
Presence of systolic ventricular dysfunction on pre-Fontan echocardiography	0.48 (0.15)	<0.01
Type of Fontan connection		<0.01
Atriopulmonary	-0.37 (0.32)	
Intracardiac lateral tunnel	-0.58 (0.30)	
Extracardiac lateral tunnel	-0.85 (0.33)	
Extracardiac conduit	-1.07 (0.32)	
Other	reference	
Greater number of post-Fontan complications during follow-up	0.11 (0.03)	<0.01
Post-Fontan thrombosis during follow-up	0.41 (0.17)	0.02
Parent-Completed CHQ Summary Scores, n=483, model R²=0.05, Adjusted R²=0.04**		
Lower Physical Functioning Summary score	0.01 (0.004)	0.02
Parent-Completed CHQ Domain Scores, n=503, model R²=0.06, Adjusted R²=0.06**		
Lower Physical Functioning Domain score	0.007 (0.002)	<0.01
Parent-Completed CHQ Health Conditions, n=494, model R²=0.07, Adjusted R²=0.06**		
Orthopedic / bone / joint problems	0.41 (0.13)	<0.01
Allergy / sinus problems	0.26 (0.11)	0.02
Cardiopulmonary Exercise Testing, n=135, model R²=0.17**, Adjusted R²=0.14*		
Lower chronotropic index	1.56 (0.60)	0.01
Echocardiography[†], n=389, model R²=0.15, Adjusted R²=0.14***		
Lower AW peak late diastolic velocity (m/sec)	1.40 (0.41)	<0.01
Longer duration of AV late diastolic inflow (msec)	0.01 (0.002)	<0.01

	PE (SE)	p Value
Magnetic Resonance Imaging, n=153, model R²=0.33, Adjusted R²=0.31^{***}		
Ventricular mass index > 95 th percentile	1.87 (0.28)	<0.01

* after logarithmic transformation (with the natural base)

** adjusted for age at enrollment and gender

*** adjusted for age at enrollment and gender, and type of Fontan connection

† Missing echocardiographic variable values were imputed from the subset with mass-volume data

AVV, atrioventricular valve; CHQ, Child Health Questionnaire; PE, parameter estimate; SE, standard error