Relationships between Physiologic and Neuropsychologic Functioning after Fontan

Kelly R. Wolfe, PhD[1], Deborah R. Liptzin, MD[2], Dania Brigham, MD[3], Sarah L. Kelly, PsyD[4], Carey Rafferty, RN[4], Megan Albertz, MD[5], Adel K. Younoszai, MD[4], and Michael V. Di Maria, MD[4]

Objective To investigate potential relationships between neuropsychologic functioning and cardiac, gastroenterologic/hepatologic, and pulmonary complications in the single ventricle heart disease (SVHD) post-Fontan population.

Study design Following the initiation of a Fontan Multidisciplinary Clinic, patients with SVHD were evaluated systematically according to a clinical care pathway, and data from multiple subspecialty evaluations were collected prospectively from 2016 to 2019. Biomarkers of cardiology, pulmonary, and hepatology/gastroenterology functioning were abstracted, along with neuropsychologic testing results. Bivariate correlations and regression analyses examined cross-sectional relationships between physiologic predictors and neuropsychologic outcomes.

Results The sample included a cohort of 68 youth with SVHD age 3-19 years, after Fontan palliation. Sleep-disordered breathing was related to poorer visual-motor integration skills ($r = -0.33$; $P < .05$) and marginally related to poorer executive functioning ($r = -0.33$; $P = .05$). Lower arterial blood oxygen content was related to poorer executive functioning ($r = .45$; $P < .05$). Greater atrioventricular valve regurgitation was related to lower parent-rated adaptive functioning ($\rho = -0.34$; $P < .01$). These results were maintained in regression analyses controlling for history of stroke and/or seizures.

Conclusions We demonstrated associations between neuropsychologic functioning and potentially modifiable aspects of physiologic functioning in a prospectively evaluated cohort of patients with SVHD with Fontan physiology. Our findings emphasize the importance of multidisciplinary screening and care after a Fontan procedure and suggest avenues for intervention that may improve patient outcomes and quality of life. *(J Pediatr 2020;227:239-46)*.

Single ventricle heart disease (SVHD) affects approximately 9 in 100 000 live births worldwide.[1] Palliative surgical advances, such as the Fontan procedure, have improved life expectancy, which has been accompanied by an increase in morbidities across various organ systems as a result of "downstream" consequences of the Fontan circulation.[2-5] Although the success of a single ventricle clinical program has historically been defined by a low short-term mortality rate, outcomes are now being redefined in the framework of both quantity and quality of life. Children with Fontan physiology are at risk for ventricular dysfunction and arrhythmias, hepatic fibrosis and portal hypertension, protein-losing enteropathy, sleep-disordered breathing, and neuropsychologic impairments.[6-10] These Fontan-related comorbidities confer increased risk for mortality and poorer quality of life.[11-13] However, relationships between physiologic and neuropsychologic outcomes have not been explored. Understanding any potential links between sequelae could help clinicians to offer more appropriate anticipatory guidance to families and recognize constellations of symptoms more quickly, which could result in more timely intervention and optimized long-term outcomes.

The general profile in SVHD has been described to include an IQ approximately 1 SD below the general population mean and particular impairments in executive functions and visual-spatial/visual-motor skills.[6,14-16] These cognitive symptoms are thought to contribute to academic learning difficulties and underemployment and reduced independence in adulthood.[17,18] The underlying neural pathophysiology for neuropsychologic impairments in SVHD includes reduced brain growth and slowed neuronal maturation starting in the third trimester of gestation, increased risk for punctate foci of brain microinjury related to cardiopulmonary bypass, and a higher base rate of neurological comorbidities such as stroke and seizures.[19-21]

Previous research exploring the etiology of neurological injury and concomitant neuropsychologic impairments in complex congenital heart disease (CHD), including SVHD, has mostly focused on risk factors around the time of the first

AVVR	Atrioventricular valve regurgitation
CHD	Congenital heart disease
MDC	Fontan Multidisciplinary Clinic
SVHD	Single ventricle heart disease

From the [1]Section of Neurology, [2]Section of Pulmonology, [3]Section of Gastroenterology, [4]Section of Cardiology, Department of Pediatrics, and the [5]Section of Anesthesiology, University of Colorado School of Medicine, Aurora, CO

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palliative surgery as predictors for early developmental delays.[22-29] Less is known about later, potentially modifiable risk factors after Fontan or predictors for long-term neuropsychologic functioning across domains of cognition.[15,20,30] We hypothesized that the following aspects of physiologic functioning would be related to poorer neuropsychologic functioning: higher atrioventricular valve regurgitation (AVVR), higher Fontan pressures, longer Fontan length of stay, higher estimates of hepatic fibrosis, diagnosis of protein-losing enteropathy, diagnosis of sleep-disordered breathing, and lower arterial blood oxygen content. We also sought to examine whether these relationships were unique predictors above and beyond neurologic complications, including a history of stroke and/or seizure.

Methods

Study Design

In 2015, our quaternary care center created a Fontan Multidisciplinary Clinic (MDC) to increase access for patients with SVHD to subspecialty care, offer a standardized model of multiorgan surveillance and testing, and increase patient engagement with the medical team and other SVHD families. Proximal to each patient's MDC visit, he or she completed some or all of the following tests according to a prospectively applied, previously published clinical care pathway for ages 4 years to adulthood.[31] Recommended testing at various, standardized, intervals included bloodwork, echocardiogram and pulmonary function testing annually, liver ultrasound examination with elastography and cardiopulmonary exercise testing every 2 years starting at 8 years of age, cardiac catheterization at 10 years of age, and neuropsychologic assessment every 3 years. Referrals for a formal sleep study were placed by a pediatric pulmonologist when clinically indicated.

Data from the MDC visits and associated subspecialty testing for this cross-sectional study were collected prospectively, from 2016 to 2019, with Colorado Multiple Institution Review Board approval, including a waiver of informed consent. Inclusion criteria for the present study were status post Fontan Interdisciplinary evaluation in the MDC and completion of a neuropsychologic assessment between the ages of 3 and 18 years of age. Exclusion criteria were an identified genetic syndrome, a non-English-speaking patient (because this would introduce additional variability to the neuropsychologic testing results) and status post heart transplantation (ie, failed Fontan). Parents of Fontan patients were involved in the design of the MDC, but were not directly involved in the conduct, reporting, or dissemination plans of this research.

Data Acquisition

Demographic and Physiologic Variables of Interest. Demographic and physiologic information was abstracted from the clinical database. Physiologic predictors were chosen a priori by physicians in each subspecialty with expertise in the SVHD population, based on hypothesized relationships with neuropsychologic functioning. Cardiac predictors included Fontan operation length of stay and data obtained from post-Fontan cardiac catheterization and echocardiogram proximal to neuropsychologic testing including Fontan pressures and degree of AVVR (as rated by the cardiologist: none/trivial, mild; moderate and above per published guidelines[32]). Specifically, we only included data from cardiac catheterizations in our analyses if the catheterization occurred less than 36 months from the time of the participant's neuropsychologic evaluation. Pulmonary predictors included arterial blood oxygen content at the same post-Fontan cardiac catheterization and presence of sleep-disordered breathing (yes/no) as noted on a formal sleep study. Hepatologic/gastroenterological predictors included degree of liver fibrosis measured via liver ultrasound examination and elastography and presence of protein-losing enteropathy (yes/no). History of stroke and history of seizure were obtained from the medical record for follow-up analyses, because these risk factors are known for poorer neuropsychologic outcomes.[25]

Neuropsychologic Variables of Interest. Neuropsychologic testing data were also abstracted from the clinical database. Neuropsychologic outcomes in several major cognitive domains were chosen based on clinical relevance and literature identifying these risks in SVHD, and specific measures were selected based on literature demonstrating their sensitivity to neuropsychologic impairment in pediatric CHD.[6] Overall intellectual functioning was measured with the Full-Scale IQ score from the age-appropriate Wechsler Intelligence Scale (Wechsler Intelligence Scale for Children, 5th edition, the Wechsler Adult Intelligence Scale, 4th edition, or the Wechsler Preschool and Primary Scales of Intelligence, 4th edition).[33-35] Overall parent-rated adaptive functioning was obtained from the General Adaptive Composite score from the Adaptive Behavior Assessment System, 3rd edition.[36] Adaptive functioning is a measure of a child's day-to-day functioning; it is distinct from direct neuropsychologic testing in that it assesses what a child usually does in her daily routine rather than her ability in an optimized testing setting. Visual-motor integration (ie, copying line drawings) was measured with the Beery-Buktenica Test of Visual-Motor Integration.[37] Attention was measured using the Hit Reaction Time Inter Stimulus Interval from the age-appropriate version of the Conners Continuous Processing Test (3rd edition[38] or Kiddie version, 2nd edition[39]), a computerized task assessing sustained attention and responding. Executive functioning, an umbrella term for a set of cognitive skills that are involved in planning, problem-solving, and self-monitoring, was measured with the Total Moves score from the Tower of London-Drexel,[40] a task assessing spatial planning and problem-solving. Reading and math achievement were measured with the Word Reading and Numerical Operations subtests, respectively, of the Wechsler Individual Achievement Test, 3rd edition.[41] All scores were standardized according to age-based normative means specific to each test.

Statistical Analyses

Continuous data were examined for normality using the Shapiro-Wilk test. Missing data were examined for bias. Because missing data were due to either differences by age in recommended testing on the clinical care pathway (eg, very young children did not have routine liver fibrosis testing) or restricted age ranges on neuropsychologic tests (eg, the executive function tests are used starting at age 7 years per test manual guidelines), pairwise deletion was used for analyses.[31] Despite our care pathway recommending catheterization and liver elastography prospectively for all patients at certain ages, we wanted to evaluate for any potential selection bias. As such, we used independent sample t tests to determine whether there were any differences in neuropsychologic functioning between participants who had undergone cardiac catheterization and those who had not, as well as for any differences between participants who had undergone liver elastography, and those who had not.

Bivariate Pearson correlations were obtained to investigate relationships between neuropsychologic outcomes and continuous or dichotomous medical predictors. Spearman correlations were used to evaluate relationships between neuropsychologic variables and ordinal-level data (ie, degree of AVVR).

Statistically significant correlations were followed by hierarchical regression analyses using the general linear model to evaluate the unique predictive usefulness of the physiologic variables, controlling for clinical history of stroke or seizure. In these models, history of stroke and history of seizure were entered in the first step of the regression analysis, and physiologic predictors of interest were entered in the second step. A 2-tailed alpha value of P of less than .05 was used for all hypothesis testing. Statistical analyses were performed using SPSS version 26 (IBM, Armonk, New York).[28]

A priori power calculations using a α of 0.05 and a β of 0.20 indicated adequate power for detecting medium to large effect sizes ($d \geq 0.3$), but that our sample may have been underpowered to detect small effects ($d < 0.3$). We ultimately decided against using a Bonferroni correction because of the reduced risk of committing a type I error given our decreased statistical power (common when studying clinical populations), and our substantial associated increased risk for making type II errors, to which our analyses were already vulnerable given the sample size.[43]

Post hoc analyses using partial bivariate Pearson correlations were conducted to assess for possible residual confounders including socioeconomic status (using maternal education as a proxy), time between Fontan operation and neuropsychologic evaluation, and time between Fontan operation and cardiac catheterization for correlations involving physiologic variables obtained from catheterization.

Results

The final sample for data analysis included 68 youth with SVHD, status post Fontan, age 3-19 years (Table I). Across neuropsychologic tests of overall IQ, adaptive functioning, visual-motor integration, attention, executive functions, reading, and math, the overall sample's mean scores ranged from 0.5 to 1.0 SD below population means. Forty-four participants (65%) had cardiac catheterizations within 2.5 years of their neuropsychologic evaluation; there were no group differences on any of the neuropsychologic measures between children who had and had not had a cardiac catheterization within this timeframe (all $P > .05$). Twenty-eight patients had liver ultrasound elastography data available, and there were no group differences on any of the neuropsychologic measures between children who had and had not completed liver elastography (all $P > .05$).

Relationships between theoretically identified aspects of physiologic and neuropsychologic functioning are presented in Table II and the Figure. Higher arterial blood oxygen content at the most recent post-Fontan cardiac catheterization was associated with better executive functioning ($r = 0.45$; $P = .03$). Presence of sleep-disordered breathing was associated with poorer visual-motor integration ($r = -0.33$; $P = .01$). and marginally associated with poorer executive functioning ($r = -0.33$; $P = .05$). Greater degree of AVVR was associated with lower parent-rated adaptive functioning ($\rho = -0.34$; $P = .009$).

These relationships with executive functioning and visual-motor integration were each shown to account for unique variance in follow-up hierarchical linear regression analyses controlling for patient history of stroke and/or seizure (Table III). Neither stroke nor seizure history was related to executive functioning, visual-motor integration, or adaptive functioning when entered into the model alone. Arterial blood oxygen content and sleep-disordered breathing were related to executive functioning when included together in the second step of the regression analysis, indicating the unique predictive usefulness of each variable, above and beyond any variance explained by history of stroke or seizure. A history of stroke was strongly related to lower adaptive functioning, and in our sample, history of stroke was also related to greater AVVR ($\rho = 0.31$; $P = .02$); as a result, the relationship between adaptive functioning and AVVR became no longer statistically significant after accounting for variance explained by clinical history of stroke and/or seizure.

Fontan operation length of stay, Fontan pressures, liver elastography, and protein-losing enteropathy were not related to neuropsychologic variables. IQ, visual attention, word reading, and math calculation skills were not related to physiologic variables. A post hoc analysis to evaluate the potential residual confounders revealed no changes in the significance or nonsignificance of the results in Table II when controlling for maternal education level or time between Fontan operation and neuropsychologic evaluation for all comparisons, and time between Fontan operation and cardiac catheterization for correlations involving physiologic variables obtained via catheterization.

Table I. Sample demographic, medical, and neuropsychologic descriptive data (n = 68)

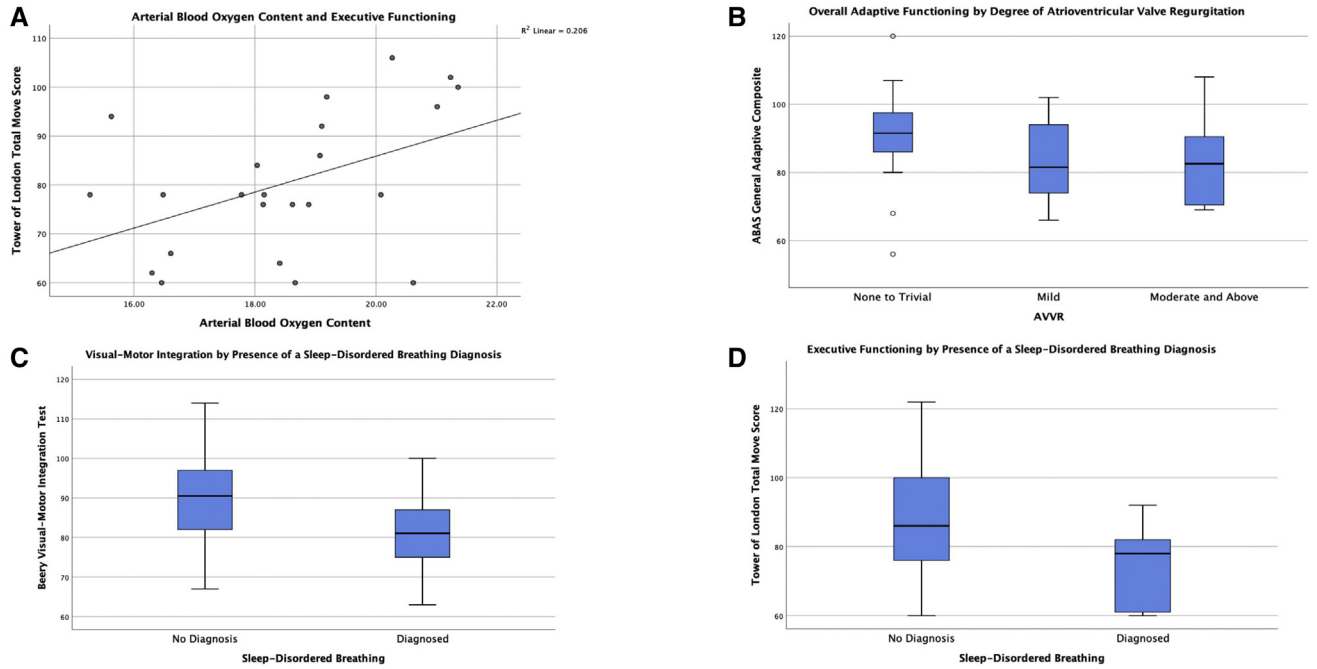
Variables	No. (%) or mean ± SD (range)	No. reporting
Sex (female)	34 (50)	68
Age (years)	9.55 ± 4.31 (3.08-19.34)	68
Race		68
African American	2 (3)	
Asian	3 (4)	
Multiracial	3 (4)	
Caucasian	60 (88)	
Ethnicity		68
Hispanic	17 (25)	
Non-Hispanic	51 (75)	
Maternal education (years)	13.71 ± 2.45 (7-18)	68
HLHS diagnosis	28 (41)	68
History of clinical stroke	8 (12)	68
History of clinical seizures	4 (6)	68
Fontan length of stay (days)	14.04 ± 10.46 (5-49)	41
AVVR		68
None/trivial	38 (56)	
Mild	21 (31)	
Moderate and above	9 (13)	
Fontan pressures (mm Hg)	12.34 ± 2.17 (9-18)	44
Sleep-disordered breathing	10 (15)	68
Arterial O_2 content (mL O_2/dL)	17.82 ± 2.01 (12.15-21.36)	44
Liver elastography (kPa)	8.21 ± 5.80 (1.24-25.50)	28
Protein-losing enteropathy	7 (10)	68
Time between catheterization and neuropsychologic testing (months)	3.02 ± 14.06 (0-27)	44
Time between Fontan operation and catheterization (months)	66.54 ± 53.58 (0-183)	48
Time between Fontan operation and neuropsychologic testing (months)	76.54 ± 50.66 (2-194)	68
Wechsler Full-Scale IQ SS	90.02 ± 14.98 (55-122)	66
ABAS-3 Global Adaptive Composite SS	87.86 ± 12.19 (56-120)	58
Beery Visual-Motor Integration SS	88.68 ± 10.73 (63-114)	60
CPT Hit Reaction Time ISI T-score	57.33 ± 13.19 (39-90)	41
Tower of London Total Moves SS	84.00 ± 16.55 (60-122)	34
WIAT-III Word Reading SS	93.23 ± 19.05 (55-138)	41
WIAT-III Numerical Operations SS	85.00 ± 16.87 (57-120)	44

ABAS, Adaptive Behavior Assessment System, 3rd edition; z-score distribution has a mean of 0 and a SD of 1 and higher scores indicate better performance); *CPT*, Connors Continuous Processing Test, (3rd edition or Kiddie version, 2nd edition; T-score distribution has a mean of 50 and SD of 10, and higher scores indicate worse performance); *CVLT*, California Verbal Learning Test (Children's version, 2nd or 3rd edition); *HLHS*, hypoplastic left heart syndrome; *SS*, standard score, which has a normative mean of 100 and SD of 15 and higher scores indicate better performance; *WIAT-III*, Wechsler Individual Achievement Test, 3rd edition.
Wechsler tests include Wechsler Intelligence Scale for Children (WISC, 5th edition), Wechsler Adult Intelligence Scale (WAIS, 4th edition), or the Wechsler Preschool and Primary Scales of Intelligence (WPPSI, 4th edition).
Sample n indicates number of subjects for which the information was available.

Table II. Relationships between physiologic and neuropsychologic functioning

Variables	Wechsler Full-Scale IQ SS	ABAS-3 Global adaptive SS	Beery visual-motor integration SS	CPT Hit reaction time ISI T-score	Tower of London total moves SS	WIAT-III word reading SS	WIAT-III numerical operations SS
Fontan length of stay	$r = -0.11$	$r = -0.16$	$r = -0.00$	$r = 0.26$	$r = -0.08$	$r = -0.03$	$r = -0.32$
AVVR	$\rho = -0.10$	$\rho = -0.34$*	$\rho = -0.05$	$\rho = 0.00$	$\rho = -0.19$	$\rho = 0.12$	$\rho = -0.04$
Fontan pressures	$r = -0.06$	$r = -0.01$	$r = 0.09$	$r = -0.10$	$r = -0.05$	$r = -0.19$	$r = -0.03$
Sleep disordered breathing	$r = -0.16$	$r = -0.09$	$r = -0.33$†	$r = -0.19$	$r = -0.33$‡	$r = -0.11$	$r = 0.04$
Arterial blood O_2	$r = -0.20$	$r = -0.18$	$r = -0.20$	$r = -0.28$	$r = 0.45$†	$r = -0.21$	$r = 0.02$
Liver elastography	$r = -0.22$	$r = -0.12$	$r = -0.15$	$r = 0.00$	$r = 0.05$	$r = -0.11$	$r = -0.16$
Protein-losing enteropathy	$r = -0.02$	$r = -0.14$	$r = 0.06$	$r = -0.06$	$r = 0.13$	$r = -0.13$	$r = -0.02$

r, Pearson bivariate correlation coefficient; ρ, Spearman rho correlation coefficient; *VMI*, visual-motor integration.
Fontan length of stay is measured in days. AVVR is coded by a cardiologist as: 0 = none/trivial; 1 = mild; 2 = moderate and above. Sleep-disordered breathing and protein-losing enteropathy are coded as yes/no. Arterial blood O_2 units are mL O_2/dL. Liver elastography units are kPa.
Wechsler tests include Wechsler Intelligence Scale for Children (WISC, 5th edition), Wechsler Adult Intelligence Scale (WAIS, 4th edition), or the Wechsler Preschool and Primary Scales of Intelligence (WPPSI, 4th edition).
*$P < .01$.
†$P < .05$.
‡$P = .05$.



Note. Higher scores indicate better functioning on the Tower of London, Adaptive Behavior Assessment System, and Beery Visual-Motor Integration Test. AVVR = atrioventricular valve regurgitation.

Figure. Relationships between physiologic and neuropsychological variables. Higher scores indicate better functioning on the Tower of London, Adaptive Behavior Assessment System, and Beery Visual-Motor Integration Test.

Discussion

In this cohort of 68 children and adolescents with SVHD after Fontan operation, we found significant associations between physiologic and neuropsychologic functioning. Poorer executive functioning was predicted independently by lower arterial blood oxygen content and the presence of sleep-disordered breathing. Executive functioning difficulties have been associated with lower quality of life in adolescence and increased reliance on disability benefits in adulthood for individuals with complex CHD.[17,37-44]

In infants with CHD, lower regional cerebral oxygen saturations have been associated with poorer neurodevelopmental outcomes and decrease cerebral oxygen delivery has been shown to predict impaired development of the cerebral cortex.[44-49] In contrast, pulse oximetry readings during the interstage period have been found to not predict developmental status in SVHD.[50] We extended this literature by demonstrating that post-Fontan arterial blood oxygen content is an important predictor of executive functioning in children with SVHD. Implications include consideration of interventions to maximize blood oxygen content after the Fontan procedure. For example, a fenestration in the Fontan conduit is often created in an attempt to optimize the postoperative course by providing a means for cavopulmonary flow to bypass the lungs and reenter the heart; this procedure has the effect of marginally decreasing cavopulmonary pressures at the expense of systemic oxygen saturations, and arterial blood oxygen content by extension. There is significant practice variability surrounding whether or not to routinely close Fontan fenestrations in the years after Fontan surgery. If the association between blood oxygen content and executive functioning appear robust and reproducible, this could provide a strong impetus to optimize blood oxygen content, including consideration of routine fenestration closure.

Sleep-disordered breathing was related to poorer visual-motor integration skills. Visual-motor integration is involved in academic learning and has been found to be correlated with school readiness, nonverbal reasoning, and visual attention.[45,46,51,52] Previous research has identified relationships between sleep-disordered breathing, executive functioning, and visual-motor integration in healthy populations.[47,48,53,54] We extend these findings to the SVHD post-Fontan population, a group with myriad additional risk factors for cognitive sequelae. Although 15% of our sample had a diagnosis of sleep-disordered breathing, up to 33% of the SVHD post-Fontan population may have symptoms of primary snoring and/or obstructive sleep apnea.[9] Notably, a retrospective chart review indicated that none of the patients in our sample with sleep-disordered breathing were receiving an intervention (eg, continuous positive airway pressure therapy) at the time of the neuropsychologic evaluation. The implications for executive functioning impairment warrant careful screening and treatment of sleep-disordered breathing in SVHD.

Table III. Relationships between physiologic and neuropsychologic functioning after controlling for history of stroke or seizure

Predictors	β	R^2	ΔR^2	F	P value
Dependent variable: executive functioning					
Step 1		0.04	0.04	0.44	.65
History of stroke	−0.18				.42
History of seizures	−0.07				.74
Step 2		0.40	0.36	2.98	.04
History of stroke	−0.15				.41
History of seizures	0.07				.73
Sleep disordered breathing	−0.42				.01
Arterial O_2 content	0.52				.04
Dependent variable: visual-motor integration					
Step 1		0.03	0.03	0.99	.37
History of stroke	−0.14				.28
History of seizures	0.13				.33
Step 2		0.16	0.13	3.58	.01
History of stroke	−0.11				.36
History of seizures	0.22				.09
Sleep-disordered breathing	−0.37				.00
Dependent variable: adaptive functioning					
Step 1		0.16	0.16	5.38	.000
History of stroke	−0.41				.002
History of seizures	0.07				.57
Step 2		0.21	0.05	4.80	.000
History of stroke	−0.35				.007
History of seizures	0.04				.75
AVVR	−0.22				.07

Executive functioning measured by the Tower of London Total Moves Standard Score (a higher score indicates better executive functioning). Sleep-disordered breathing is coded as dichotomous (yes/no). Visual motor integration measured by the Beery Visual-Motor Integration Standard Score (higher score indicates better visual-motor integration). Adaptive Functioning measured by the Adaptive Behavior Assessment System, Third Edition General Adaptive Composite Standard Score (higher score indicates better adaptive functioning). AVVR coded as none/trivial (0), mild (1), moderate, and above (2).

We also found that a greater degree of AVVR was associated with poorer parent-rated adaptive functioning. Adaptive functioning has been shown to be impaired in adolescents with CHD, and it has direct implications for an individual's eventual level of educational attainment, independence, and employment status. −0. Of note, more significant AVVR may be a marker of more problematic single ventricle physiology writ large, because it is more common to see higher-grade AVVR in the setting of single right ventricle morphology or common atrioventricular canal defect, which are well-established risk factors for adverse outcomes. From a mechanistic standpoint, more severe AVVR may result in decreased cardiac output, in that some of the stroke volume is directed retrograde into the atrium. In this conceptual framework, there may be implications for oxygen and nutrient delivery to the brain, which may be reflected in this broad index of a child's day-to-day functioning. This relationship was only marginally significant when controlling for history of stroke because of a strong correlation in our sample between AVVR and stroke history. It is unclear why children with history of a stroke would have a higher AVVR; we suspect this collinearity is spurious and maintain the importance of the primary relationship between AVVR and adaptive functioning. Implications include consideration of proactive management of moderate and above AVVR, such as atrioventricular valvuloplasty or replacement.

In addition to these findings, our data suggest that several neuropsychologic domains may not be related to physiologic functioning in this population, including overall IQ, visual attention, reading, and math. These particular neuropsychologic domains are broad, and future research into their component parts (eg, verbal vs visual IQ, sustained vs focused attention, and particular aspects of reading and math skill) may be helpful in elucidating any potential relationships with physiologic functioning.

Strengths of this study include the size of the sample and the comprehensiveness of the multidisciplinary evaluation. One important limitation is the clinical nature of our dataset. We collected data prospectively according to our clinical care pathway, which meant that not all participants had every data point available concurrently.[31] For example, our clinical care pathway advocates for regular post-Fontan cardiac catheterizations for all patients with SVHD starting at age 10. The cross-sectional nature of our analyses precludes direct assumptions of causality, and although our post hoc tests addressed 3 potential residual confounders, it is certainly possible that other, unstudied variables impacted our results. Additionally, we made a number of comparisons and, given our sample size, we may have been underpowered to detect relationships with a small to medium effect size. We endeavored to limit the number of comparisons a priori by limiting medical and neuropsychologic variables and maximizing our sample size by using a wide age range in the post-Fontan population. Although using an inclusive age range increased our sample size, it also may have introduced additional variability in our study given differences in neuropsychologic assessment from young childhood to adolescence. We did not perform subgroup analyses owing to the number of comparisons presented herein, but future studies might investigate relationships between physiologic and neuropsychologic functioning in more circumscribed cohorts.

Our findings include the impact of sleep-disordered breathing on executive functions and visual-motor skills, the influence of arterial blood oxygen content on executive functions, and the link between AVVR and adaptive functioning in the post-Fontan SVHD population. Broad implications include the critical need for long-term, prospective, multidisciplinary surveillance and intervention in SVHD, including subspecialists from cardiology, pulmonology, gastroenterology/hepatology, and psychology. Furthermore, it is important to consider risk factors for neuropsychologic difficulties from outside the central nervous system to optimize the neurodevelopmental trajectories of individuals with SVHD and Fontan physiology. ■

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Reprint requests: Kelly R. Wolfe, PhD, 13123 E 16th Ave, B155, Aurora, CO 80045. E-mail: kelly.wolfe@childrenscolorado.org

Data Statement

Data sharing statement available at www.jpeds.com.

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