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ORIGINAL ARTICLE

Cognitive dysfunction is associated with abnormal responses in cerebral blood flow in patients with single ventricular physiology: Novel insights from transcranial Doppler ultrasound

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Abstract

Objectives: Improvements in the management of complex congenital heart disease, including those with single ventricle physiology, have resulted in increased survival. As this population ages, the recognition of cognitive impairment is increasingly important. At present, little is known about the potential mechanisms of cognitive dysfunction. In this cross-sectional study, we aimed to characterize the nature of abnormalities in cerebral blood flow and the relationship to cognitive deficits in adults with single ventricular physiology.

Patients: Ten adults with single ventricular physiology (age 18-40 years) and 12 age- and gender-matched controls underwent transcranial Doppler ultrasound and accompanying cognitive assessment.

Outcome Measures: Patients underwent neuropsychological testing that assessed differing cognitive domains, with subjective cognitive decline determined from a 24-question survey. Transcranial Doppler ultrasound was used to assess baseline cerebral blood flow as well as change in cerebral blood flow velocities from baseline and during cognitive testing. Age, ethnicity, individual, and parental education levels were considered in the multivariate analyses.

Results: On assessment of cognitive function, the patient group performed more poorly across each of the measured domains. The control group had a significantly greater increase in cerebral blood flow in response to cognitive stimuli compared to the patient cohort; these differences in response to cognitive stimuli were seen to a similar extent across each of the measured cognitive domains.

Conclusion: Adults with Fontan physiology are underperforming in assessments of executive function with associated abnormalities in cerebral perfusion potentially contributing to cognitive deficits.

KEYWORDS

cerebral blood flow, cognitive function, congenital heart defects, Fontan procedure

1 | INTRODUCTION

Patients born with congenital heart disease now can expect excellent survival into adulthood, as the number of adults with congenital heart disease now exceeds the number of affected children.[1] With the survival into adult life being excellent, there is increasing understanding of adverse sequelae complicating the complex forms of congenital heart disease, which influence late morbidity and quality of life. In particular, recognition of cognitive impairment is increasingly relevant, yet our understanding of the possible mechanisms is limited among various congenital cardiac diseases.[2] Patients undergoing Fontan palliation typically undergo multiple surgical procedures resulting in the creation of single ventricular physiology. This cohort is subject to the consequences of chronic hypoxemia, central venous hypertension, arrhythmia, and a tendency to thromboembolic complications.[3] This is reflected in patients with Fontan circulation who are noted to have more pronounced cognitive deficits in association with cerebral structural abnormalities when compared to normal controls.[4]

Abnormalities of cerebral blood flow in response to cognitive stimuli may potentially contribute to the increasingly recognized impairment in cognitive function. Under normal conditions, local cerebral blood flow is closely related to the metabolic activity of the local brain region (neurovascular coupling). This relationship forms the basis of the signal changes used in functional magnetic resonance imaging to localize brain activation regions associated with specific tasks. We hypothesized that adaptive cerebrovascular responses in patients following Fontan procedure may impair local neurovascular coupling, and that this may underlie some of the cognitive deficits observed in these patients. Furthermore, utilization of methods with the ability to detect subclinical abnormalities of cerebral blood flow may be important as these tools may allow for early intervention where appropriate, document changes after interventional procedures, and measure the efficacy of the interventions designed to minimize cerebral injury during complex cardiac surgical procedures.

2 | AIMS

In this cross-sectional study, we aimed to characterize the nature of the cognitive deficits in adults with single ventricular physiology (Fontan circulation) and document correlations with abnormalities in cerebral blood flow using transcranial Doppler ultrasound. We hypothesized that abnormalities in cognitive performance would be associated with impaired cerebrovascular responsiveness (neurovascular coupling).

3 | METHODS

The primary end point was change in cerebral blood flow cerebrovascular responsiveness (CVR) between baseline and during cognitive testing at the level of the middle cerebral artery (MCA) in patients with single ventricular physiology compared to controls. Participants underwent the transcranial Doppler ultrasound assessment of the MCA at baseline and then changes in blood flow velocities during cognitive were continuously recorded.

Secondary outcomes included comparison of cognitive function between the patient and control groups, basal cerebrovascular hemodynamics, and gait speed.

Patients underwent 10 neuropsychological tests that assessed 6 cognitive domains (ie processing speed, language, attention, working memory, episodic memory and cognitive flexibility—Appendix A). The overall cognitive performance was determined by averaging the composite Z-scores from each domain. Subjective cognitive decline (SCD) was determined from a previously validated 24-question survey,[5] with SCD expressed as a percentage of the number of positive responses (yes/no) to the list of 24-item questions pertaining to everyday memory complaints experienced in the last two years. Perceived mental fatigue and stress levels are determined by placing a mark on a 10-cm e-Visual Analogue Scale, and expressed as a percentage. We present the pre–post difference in perceived fatigue and stress in response to the cognitive test battery. The higher the percentage means, the greater the levels of fatigue and stress following testing.

Basal cerebral hemodynamics included pulsatility and resistive indices of the middle cerebral arteries which reflect the degree of arterial stiffness; previous studies have demonstrated these measures to be abnormal in patients with aortic coarctation,[6] with deficits similar to those seen in patients with established vascular disease.[7]

The measure of the gait speed requires volunteers walk at a normal pace for 4 and 20 m which may reflect early cognitive dysfunction.

Cognitive performance was fully adjusted for age, ethnicity, and individual and parental education levels. Clinical characteristics were used as covariates if they were significantly correlated with the outcome measures. A two-sample *t* test was used to compare the group differences in outcome measures. Linear regressions were used to determine the relationships between gait speed and cerebrovascular function and cognitive performance. Bonferroni adjustments were made to allow for multiple comparisons of secondary outcomes, where the adjusted level of significance was set at .017.

The study was conducted according to International Conference on Harmonization guidelines for Good Clinical Practice and national guidelines. The study was approved by the Human Ethics Committee of University of Newcastle and Hunter New England Local Health District. After written informed consent, anthropometric measurements of height, weight, and waist circumference were obtained along with baseline blood pressure.

4 | RESULTS

A total of 12 patients with single ventricular physiology underwent assessment of cerebral blood flow at rest and during cognitive testing and were compared with 12 healthy control subjects. Two patients had unreliable transcranial Doppler signals with ultrasound data excluded from the primary outcome. Baseline characteristics of the two groups are outlined in Table 1. The single ventricle group was more likely to describe SCD, mental fatigue, and mental stress during cognitive testing. A summary of the relevant congenital heart disease diagnoses in the group with single ventricular physiology is outlined in Table 2.

TABLE 1 Baseline characteristics

	Patient (*n* = 12)	Control (*n* = 12)	*P* value
Female/male	5/7	6/6	-
Age (years)	28 ± 2	28 ± 2	.937
Years of completed education (years)	15 ± 1	22 ± 0	<.001
BMI (kg/m^2)	28.1 ± 1.6	25.1 ± 1.1	.133
Waist circumference (cm)	96.8 ± 4.2	80.6 ± 3.6	.008
Systolic BP (mm Hg)	126 ± 5	120 ± 4	.338
Diastolic BP (mm Hg)	73 ± 3	72 ± 3	.861
Mean BP (mm Hg)	91 ± 3	89 ± 3	.621
Pulse pressure (mm Hg)	53 ± 4	47 ± 3	.293
Subjective cognitive decline (%)	24 ± 7	2 ± 1	.005
Perceived mental fatigue (%)	20 ± 10	13 ± 6	.564
Perceived mental stress (%)	10 ± 10	0 ± 10	.170
Gait speed from 4 m track (m/s)	0.97 ± 0.10	1.20 ± 0.06	.104
Gait speed from 20 m track (m/s)	1.05 ± 0.07	1.22 ± 0.04	.036

TABLE 2 Summary of congenital heart disease diagnoses

Congenital heart disease diagnoses [N (%)]	
Double inlet left ventricle	3 (25%)
Ebstein's anomaly	1 (8.3%)
Mitral valve atresia	1 (8.3%)
Tricuspid atresia	5 (41.5%)
Ventricular septal defect	2 (16.6%)
Fontan type [N (%)]	
Extracardiac conduit	9 (75%)
Lateral tunnel	1 (8.3%)
Atrio-pulmonary	0 (0%)
Glenn Shunt (hemi-Fontan)	2 (16.6%)
Mean age at Fontan completion [years (SD)]	7 (8)
Abnormal systemic ventricular function [*N* (%)]	3 (25)
History arrhythmia [*N* (%)]	4 (33.3%)
Anticoagulation use [*N* (%)]	4 (33.3%)

On formal assessment of cognition, the patient group performed more poorly across each of the six measured domains, with the differences in Z-scores outlined in Figure 1. When comparing the change in blood flow during assessment, the control group had a significantly greater increase in cerebral blood flow compared to the patient cohort (Figure 2); these differences in response to cognitive stimuli were seen to a similar extent across each of the measured cognitive domains.

In addition to impaired cerebral blood flow responses to cognitive stimuli, the patient group demonstrated abnormal cerebral blood flow parameters at baseline, with the patient group demonstrating increasing vessel stiffness as measured by resistive and pulsatility indices (Figure 3).

5 | DISCUSSION

This study confirms the presence of deficits in cerebral blood flow in patients with complex congenital heart disease as measured by transcranial Doppler ultrasound at rest and in response to cognitive testing. Patients with single ventricular physiology were noted to have abnormalities of resting cerebral blood flow with impairment in cerebral perfusion at baseline. Furthermore, we note reduced cerebral blood flow in these patients compared to controls in response to cognitive stimuli. Reduced baseline perfusion and an inadequate response to appropriate cognitive stimuli may be potentially important mechanisms in the pathogenesis of cognitive dysfunction in this patient cohort.

Cognitive dysfunction in patients with congenital heart disease has been attributed to the effects of surgery, genetic abnormalities, and the effect of the underlying cardiac lesions on neurodevelopment; however, poor cerebral perfusion has also been associated with cognitive impairment.[8] Neuronal activation promotes the endothelium to release nitric oxide, resulting in the dilatation of local arterioles, which is reflected in increased blood flow in larger vessels (neurovascular coupling). Impaired vasodilation may reduce the normal perfusion increase during neuronal activation potentially contributing to poor cognitive performance in patients with congenital heart disease; in healthy older women, early deficits in cerebral blood responses predicted cognitive dysfunction,[9] with altered neurovascular coupling associated with cognitive deficits in patients with diabetes mellitus.[10] Impaired cerebral blood flow response to cognitive stimulus has also been associated with abnormal gait patterns, in keeping with differences in gait speed observed between the two cohorts.[11] Our previous cross-sectional comparison between patients with previous surgical repair of aortic coarctation and controls has shown impairment of CVR, reflecting abnormal cerebral blood flow.[6] The detection of cognitive dysfunction and accompanying perturbations in cerebral blood flow is an important insight into the late morbidity associated with single ventricular physiology.

Patients with congenital heart disease are well documented to have cognitive deficits,[8] with deficits more notable in complex forms of congenital heart disease, such as single ventricular physiology.[12]

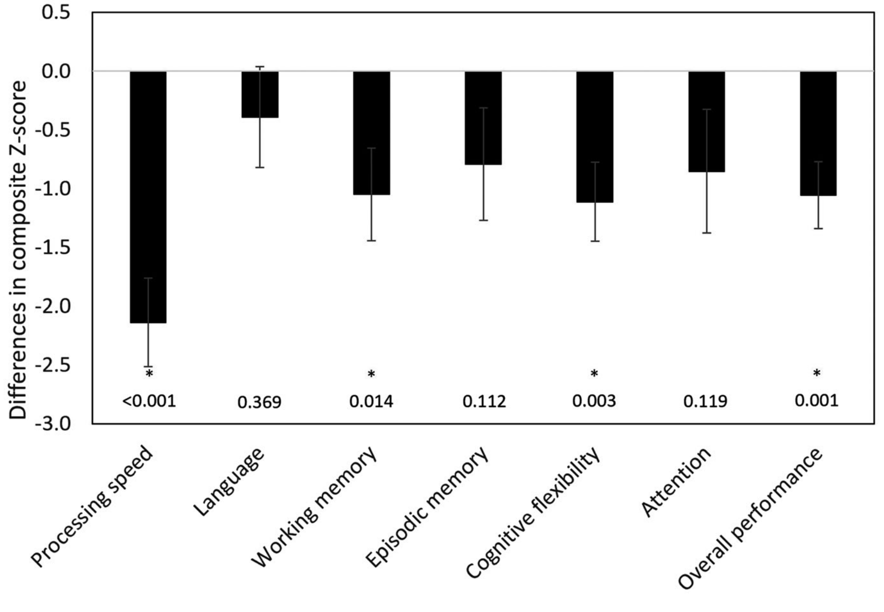

FIGURE 1 Differences in cognitive domains between patients with single ventricular physiology compared to normal controls fully adjusted for education level, gender, ethnicity, and age. Data are mean ± SEM

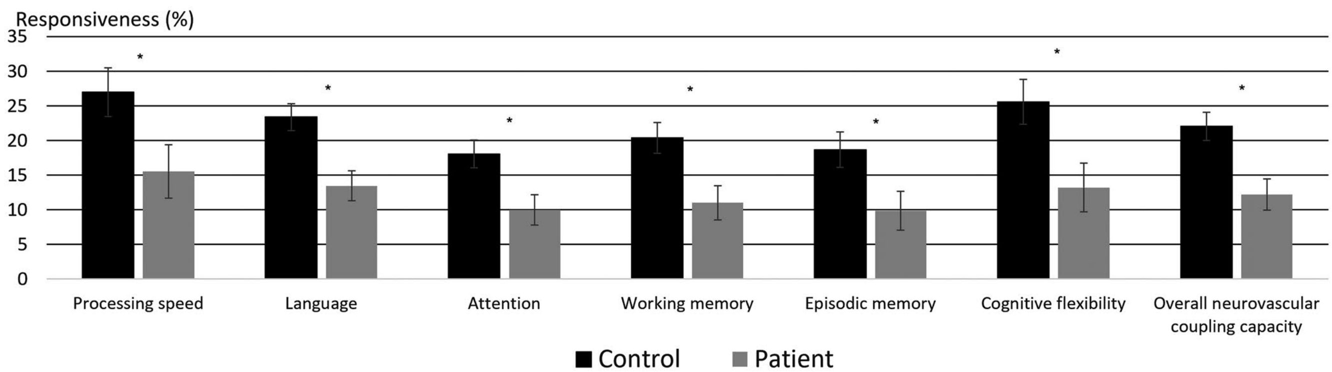

FIGURE 2 Pooled analysis of cerebrovascular responsiveness expressed as an increase from baseline between groups according to cognitive domains and overall neurovascular coupling capacity

In particular, cognitive limitation in areas essential for social and academic performance, referred to as executive function, are deficient in these patients with congenital heart disease.[13] It is now recognized that impairment in cognitive function is an important influence on the quality of life and a target for treatment in this cohort.[2] Early identification of patients with impaired executive function is critical to permit a focused approach to the initiation of strategies designed to facilitate neurodevelopment.[14,15] Serial assessment is therefore suggested to identify the presence of cognitive impairment.[16] As abnormal executive function is an area where neurocognitive function may be improved,[15] objective imaging markers which parallel cognitive function may serve to document the efficacy of such interventions.

Patients with complex congenital heart disease are noted to be prone to ischemic cerebral injury,[17] with progressive risk complicating the development of traditional cardiovascular risk factors with aging, resulting in ongoing risks to cognitive performance.[2] The development of atherosclerotic disease is now recognized to progress from childhood, with ultrasound measures to assess vascular function identified as an important modality.[18] Abnormal carotid artery resistance is associated with increased stroke risk[19]; transcranial Doppler techniques have identified abnormal resistance in cerebral arteries in patients with diabetes,[7] a group prone to adverse cerebral vascular events, as well as in adult patients with a background of aortic coarctation repair,[6] similarly documented to be at risk of adverse cerebral events.[20] This study demonstrates that similar abnormalities of measures of vascular resistance are seen in patients with single ventricular physiology. While there is a documented increased risk of stroke seen in adult patients with severe congenital heart disease, this has been attributed to consequences of previous surgery, arrhythmia, thrombosis risk, and ventricular dysfunction.[8,17] Increased carotid artery resistance is associated with an increased risk of incident stroke[19] with cerebral vascular abnormalities, as seen in this study, potentially an important contributor to the increased risk of stroke seen in this patient population.

	Patient (n=10)	Control (n=12)	P-value	
Peak systolic blood flow velocity (cm/s)	81.2±6.0	88.3±5.5	0.404	↓7%
Mean blood flow velocity (cm/s)	48.5±3.7	60.0±3.4	0.035*	↓19%
End diastolic blood flow velocity (cm/s)	33.3±2.7	44.0±2.5	0.011*	↓24%
Pulsatility index	0.97±0.04	0.74±0.03	<0.001*	↑31%
Resistive index	0.58±0.01	0.50±0.01	<0.001*	↑16%
Pulsatility index: mean flow velocity	2.2±0.2	1.3±0.2	0.001*	↑68%
Cerebrovascular resistance index	2.01±0.18	1.54±0.12	0.073	↑30%

FIGURE 3 Baseline cerebral blood flow characteristics as measured by transcranial Doppler ultrasound

The study is limited by the small sample size, noting it does reflect a well-defined subset, and while corrected in multivariate analysis, there was a difference in education level between the two groups.

6 | CONCLUSIONS

Patients with a history of complex congenital heart disease have demonstrable abnormalities of cerebral blood flow using transcranial Doppler ultrasound in response to cognitive stimuli. Changes in resting cerebral blood flow and resistance, as noted in this cohort, are consistent with previous observations of impaired cerebral perfusion during development and increased stroke risk seen in this unique patient population. An important novel observation is the impairment in CVR, which may also be a contributing factor to cognitive dysfunction. Aside from mechanistic insights, the results of the imaging modalities that parallel cognitive performance may allow for the objective assessment of cerebral function, facilitate serial monitoring with development, and document responses to interventions designed to improve executive and other cognitive functions in this complex patient group.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to the research design, the acquisition, analysis, and interpretation of the data, drafting the paper, and obtaining approval of the submitted and final versions.

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APPENDIX A

The neuropsychological examination consisted of the National Institute of Health (NIH) Toolbox battery of cognitive function, with additional tests of the executive function (Trail Making Task) and working memory (N-back Test and Spatial Span Test).

The NIH test battery and Spatial Span Test was delivered via an iPad and assessed domains of language, attention, information processing speed, working and episodic memory. This test included the following components:

PICTURE VOCABULARY TEST

The participant is presented with four pictures on the iPad screen and an audio recording saying a word. The participant is instructed to touch the picture that most closely shows the meaning of the word. After the participant makes a choice, another set of pictures automatically appears with the next item and associated audio files. The specific words presented depend on the participants' performance. For most participants, the measure will last approximately five minutes and will contain 25 items. The iPad will administer each item one by one, in an untimed fashion, until the test is completed.

FLANKER INHIBITORY CONTROL AND ATTENTION TEST

This test is a measure of inhibitory control and attention. The Flanker requires the participant to focus on a particular stimulus while inhibiting attention to the stimuli flanking it. Participants are instructed to choose one of two buttons on the screen that corresponds to the direction in which the middle arrow is pointing. On congruent trials, all the arrows are pointing in the same direction. On incongruent trials, the flanking arrows are pointing in the opposite direction of the middle arrow. Congruent and incongruent trials are mixed. The word middle will appear on the screen. Participants will be instructed to select the button that matches the way the MIDDLE arrow is point and place their index finger on the Home Base after they have responded. There will be 20 trials in this test.

LIST SORTING WORKING MEMORY TEST

This task assesses working memory and will require participants to recall and sequence differences to visually and orally presented stimuli. Picture of different foods and animals are displayed with both an accompanying audio recording and written text that names the item. In the1-list condition, the participant is asked to say the item back to the examiner in size order from smallest to largest. The test begins with two objects. The participant must succeed at one of the first two object items to continue. In the 2-list condition, participants are presented both food and animals and are first asked to say the food objects in size order and then the animal objects in size order.

DIMENSIONAL CHANGE CARD SORT TEST

This task is a measure of cognitive flexibility and attention. Two target pictures are presented that vary along two dimensions (e.g. shape and colour). Participants are asked to match a series of bivalent test pictures (e.g. yellow balls and blue trucks) to the target pictures, first according to one dimension (e.g. colour) and then, after a number of trials, according to the other dimension (e.g. shapes). The relevant dimension for sorting is indicated by a cue word (e.g. 'shape' or 'colour') that appears on the screen for all participants. Participants must get at least three out of four practice trials correct to advance to the test. There will be a total of 30 mixed items.

PATTERN COMPARISON PROCESSING SPEED TEST

This test is designed to measure processing speed. The test itself takes less than 9-s and requires participants to discern whether two side-by-side pictures are the same or not by pressing ‘yes’ or ‘no’ on the buttons on the screen. There are a maximum of 130 items or a maximum response time of 85 seconds.

PICTURE SEQUENCE MEMORY TEST

In this measure of episodic memory, sequences of pictured objects and activities are presented in a particular order. The participants are asked to reproduce the sequence of pictures that is shown on the screen. Participants will respond by dragging the pictures from the yellow box on the screen to the grey boxes on the screen.

ADDITIONAL TESTS OF COGNITIVE FUNCTION ARE OUTLINED BELOW

Trail Making Task will be assessed by pen-paper modality and will comprised of part A and part B. Trail Making Task, Part A, measures the ability to scan and to connect 25 numbers/letters consecutively that are placed randomly on a page (i.e. 1-2-3-4… or A-B-C-D…). This process requires both working memory and processing speed, which is found to be less efficient with age. Part B of the task assesses cognitive flexibility and processing speed, a process generally referred to as executive control, while alternating between connecting a number and letters in sequence with speed and accuracy (e.g. 1-A-2-B-3-C…). Time taken to complete Parts B and A forms an interference ratio score (B:A).

N-Back task will be presented on a computer screen. Targets and non-targets of digits will appear at a fast rate. The participant has to press a button whenever they see the target. In the 1-back condition, the target is any number identical to the trial preceding it. In the 2-back condition, the target is any number identical to the one presented two trials back. In the 3-back condition, the target is any number identical to the one presented three trials back. The task will consist out of 6 randomized blocks, each condition has 2 blocks. The blocks will last for 1.5 minutes and consist out of 30 trials. Errors and missed targets will be scored.

SPATIAL SPAN TEST

This test assesses working memory capacity. A random number of white squares are presented on the screen, some of which will briefly change colour in a variable sequence. The participant must then touch the boxes, which changed colour, in the same order that they were displayed by the iPad. The number of boxes increases from two at the start of the test to nine at the end. The longest sequence successfully recalled and time taken will be recorded.