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ASSESSING GLYMPHATIC SYSTEM FUNCTION USING DTI-ALPS IN ADOLESCENTS WITH CONGENITAL HEART DISEASE

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ASSESSING GLYMPHATIC SYSTEM FUNCTION USING DTI-ALPS IN ADOLESCENTS WITH CONGENITAL HEART DISEASE

by

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THESIS

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Dedicated to Thomas Alexander & Amalorpava Mary for being role models in faith who made me who I am today, and to Jerome Lawrence James & Agnes Sagaya Rani for being my pillars in life.

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ASSESSING GLYMPHATIC SYSTEM FUNCTION USING DTI-ALPS IN ADOLESCENTS WITH CONGENITAL HEART DISEASE

Linda Angelina Jerome

ABSTRACT

Congenital heart disease (CHD), a structural malformation of the heart or great vessels, is associated with brain abnormalities and an elevated risk of neurodevelopmental deficits. The mechanisms underlying these abnormalities remain incompletely characterized. The glymphatic system, the primary waste clearance system for the central nervous system, is driven by arterial pulsatility and dependent on systemic venous pressure. The glymphatic system may be impaired in CHD due to altered vascular pulsatility and systemic venous pressure resulting from abnormal cardiac physiology and surgical palliations. Diffusion tensor imaging analysis along the perivascular space (DTI-ALPS) is an MRI-based non-invasive metric that is used to evaluate glymphatic function and has not been previously applied to adolescents with CHD. This study includes 34 adolescents with critical CHD (Transposition of great arteries (TGA): n = 17, Single-ventricle physiology (SVP): n = 9, Other CHD: n = 8) and 99 healthy adolescent controls. DTI-ALPS indices were calculated using a publicly available diffusion MRI processing pipeline (alps.sh). The expected results of this study included lower DTI-ALPS indices in subjects with CHD compared to controls, with subjects with SVP expected to have significantly lower ALPS indices compared to those with TGA. Statistical analysis included Bland-Altman analysis, group comparisons using two-tailed t-tests, and multivariable linear regression adjusting for age. DTI-ALPS mean indices were significantly lower in the CHD group compared to controls (1.348 vs. 1.499; β = -0.152, 95% CI: -0.216 - -0.089, $p < 0.001$), and this difference remained significant after adjusting for age (β = -0.083, 95% CI: -0.118 - -0.049, $p < 0.001$). Additionally, each CHD sub-type demonstrated

significant reduction in DTI-ALPS mean indices compared against healthy controls. No significant difference was found between TGA and SVP subgroups ($p = 0.671$). No significant relationship was found between DTI-ALPS index and age or sex within either CHD or control group. Overall, these findings represent preliminary evidence of potential glymphatic dysfunction in CHD patients, with DTI-ALPS being a novel non-invasive biomarker for brain health and potential future neuroprotective interventions. Further research with larger cohorts and neurodevelopmental outcomes is needed to determine the clinical implications of these findings.

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LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
AQP4	Aquaporin-4
CHD	Congenital Heart Disease
CI	Confidence Interval
CSF	Cerebral Spinal Fluid
DTI	Diffusion Tensor Imaging
DTI-ALPS	Diffusion Tensor Imaging Analysis Along the Perivascular Space
FA	Fractional Anisotropy
SD	Standard Deviation
SVP	Single Ventricle Physiology
TGA	Transposition of the Great Arteries

INTRODUCTION

1.1 Brain Development in Congenital Heart Disease

Congenital heart disease (CHD) refers to structural malformations of the heart and great vessels during fetal development and has a frequency of 0.3 to 0.6 per 1,000 births (1). Survival has considerably improved (>90% survive well into adulthood) with advances in surgical techniques and perioperative care though neurological impairments in behavioral, emotional, motor and cognitive domains have become more prominent in survivors across the lifespan (1,2). Adolescents with CHD have a higher prevalence of brain MRI abnormalities by approximately 16 times compared to healthy peers (2). In older children and adolescents, reduced fractional anisotropy across multiple white matter regions and reduced total and regional brain volumes have been associated with poorer cognitive outcomes including deficits in memory and executive functioning (2). Prior studies have demonstrated that neonates with complex forms of CHD also have evidence of brain dysmaturity (1,3). Additionally, maturation delays have been demonstrated in fetal life starting as early as late gestation, including simplified cortical gyrification, reduced brain volume, less white matter tract organization, and immature biochemistry and electrical activity (1).

1.2 The Glymphatic System & Its Function

The glymphatic system is the primary waste clearance system for the central nervous system via interstitial and cerebrospinal fluid (CSF) movement and supports critical functions including clearance of excess fluid and metabolic waste. Unique features pertaining to the glymphatic system include directionality of fluid transport, dependence on the aquaporin-4 (AQP4) water channels for fluid transport in the vascular end feet of astrocytes, and upregulation of fluid transport during sleep paralleled by an increase in clearance of metabolic waste (4,5).

Prior studies have established that the glymphatic system is critically implicated in Alzheimer's Disease (AD) pathogenesis where dysregulation causes the accumulation of tau and amyloid-beta proteins. This

accumulation is thought to be driven by the imbalance of these neurotoxic protein production and clearance caused by an impaired glymphatic system (5).

CSF is produced in the choroid plexus driven by arterial pulsatility from cardiac cycles which then circulates into the brain parenchyma along the periarterial spaces. CSF, in the brain parenchyma, mixes with interstitial fluid which enables waste clearance and nutrient distribution. Efflux routes of interstitial fluid include exiting the CNS along the perivenous space and along the cranial/spinal nerves (5).

For non-invasive evaluation of glymphatic clearance function, a novel diffusion-based MRI method, Diffusion Tensor Imaging analysis along the perivascular space (DTI-ALPS) has been recently developed (4,6). The perivascular space, at the lateral ventricle level, runs in the right-left direction (x-axis), while the projection fibers run in the superior-inferior direction (z-axis), and association fibers run in the anterior-posterior direction (y-axis) (Figure 1). As these fiber tracts run perpendicular to the perivascular space, x-axis diffusivity serves as a potential indication for glymphatic activity. DTI-ALPS is therefore calculated as the ratio of the mean x-axis diffusivity in the area of projection fibers and x-axis diffusivity in the area of association fibers to the mean y-axis diffusivity in the area of projection fibers and z-axis diffusivity in the area of association fibers (4).

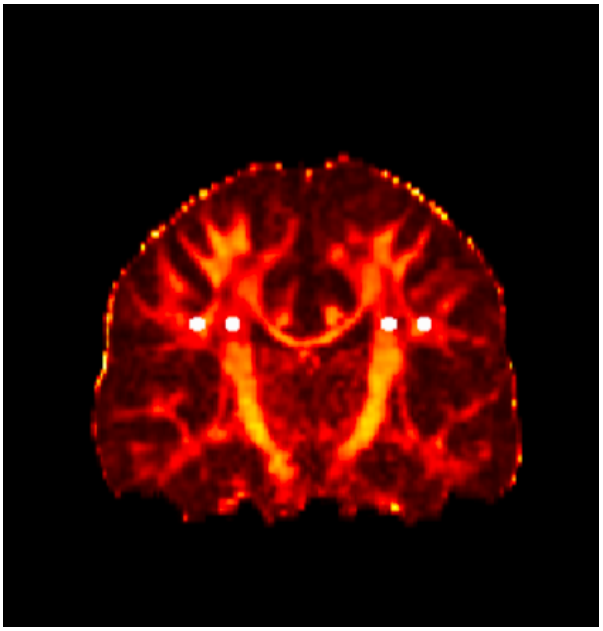

Figure 1 *Fractional anisotropy map with ROI*

Fractional anisotropy (FA) map at the level of the lateral ventricles for one representative subject with CHD. The white spherical ROIs indicate placement in the superior corona radiata region (projection fibers) and superior longitudinal fasciculus region (association fibers) bilaterally, used for DTI-ALPS index calculation.

1.3 Systemic Lymphatic Dysfunction in Congenital Heart Disease

The lymphatic system functions to maintain homeostasis by transporting fluid back to central veins. The fluid is collected by lymphatic capillaries and ascends in the mediastinum via the thoracic duct which eventually carries the majority of the lymphatic fluid to the left venous angle and subclavian vein. Individuals with CHD can experience perturbations in cardiac physiology including increased intracardiac pressures and altered blood flow patterns (7).

One of the most severe forms of CHD is single ventricle CHD. Patients with this type of CHD undergo a 3-stage palliation. While the first stage does not cause a major perturbation to the lymphatic physiology, the second stage elevates the superior vena cava pressure from atrial to pulmonary arterial levels. This increase in pressure results in an increased afterload on the thoracic duct leading to lymphatic congestion

and can cause major perturbation to the lymphatic system. The final stage of palliation results in all veins in the extracardiac systemic circulation facing increased venous pressure as they are no longer draining into the right atrium. This leads to increased production of lymph in the tissues causing an increased preload and afterload on the lymphatic system (7,8).

Lymphatic dysfunction in CHD can cause plastic bronchitis, protein losing enteropathy, chylothorax, and lymphedema. It is further compounded in patients with associated genetic syndromes including Trisomy 21, Turner syndrome, and Noonan syndrome (7).

1.4 Glymphatic System Dysfunction in Congenital Heart Disease

Glymphatic drainage is thought to be dependent on vascular pulsatility and systemic venous pressure and hence may be altered in CHD (5,9). In single ventricle CHD, surgical palliation results in loss of pulsatile blood flow and elevated systemic venous pressure (7,10). Similarly, patients with transposition of the great arteries (TGA) may experience altered glymphatic function to a lesser degree due to abnormal cardiovascular physiology and surgical repair which affects vascular pulsatility (8). Impairment of the glymphatic system caused by CHD palliation may lead to incomplete clearance of protein aggregates and therefore a heightened potential for neurodegeneration, potentially contributing to the brain abnormalities observed in this population (9).

Direct evidence from cardiovascular disease animal models further demonstrates the association between impaired cardiac function and disruption of glymphatic homeostasis, thus impairing clearance (9). These findings suggest CHD-related cardiovascular dysfunction may represent a mechanism underlying glymphatic impairment and the neurodevelopmental deficits observed in CHD patients (9,10).

1.5 Hypothesis

Adolescents with CHD will demonstrate lower DTI-ALPS indices compared to healthy peers, with the most significant reductions in subjects with single ventricle CHD.

METHODS

2.1 Study Population

This study includes 34 adolescents between ages 8-18 years with critical CHD who underwent corrective cardiac surgery as neonates. This includes children with prenatal/neonatal diagnosis of transposition of great arteries (TGA) or single ventricle physiology (SVP). This is part of a longitudinal institutional cohort of children with critical CHD who have been followed since birth and have been brought back for brain MRI as adolescents. The control group includes baseline MRI in 99 healthy adolescents enrolled in the Brain Change Study (Table 1), an institutional study on non-pharmaceutical intervention such as mindfulness training on adolescent brain function.

Table 1 *Study Population Demographics*

	TGA (N=17)	**SVP (N=9)**	**Other CHD (N=8)**	**Normal Control (N=99)**	P~
Sex, n (%)					0.162
Female	4 (24%)	3 (33%)	3 (37.5%)	52* (56%)	
Male	13 (76%)	6 (67%)	5 (62.5%)	41* (44%)	
Age, Mean (SD)	14.06 (4.06)	14.63 (4.24)	13.33 (3.83)	15.92* (1.30)	0.008

**Sex and age not available for 6 control subjects (n=93/99)*

~P value for all CHD vs. Control groups

2.2 MRI Acquisition

Data were collected using a 3T GE SIGNA Premier MRI at the University of California, San Francisco (UCSF) QB3 imaging facility. Diffusion tensor imaging was performed using the multishell ABCD protocol with 96 diffusion gradient directions, seven b = 0 volumes, and four b-values (6 directions with b = 500 s/mm^2, 15 directions with b = 1000 s/mm^2, 15 directions with b = 2000 s/mm^2, and 60 directions with b = 3000 s/mm^2 (11).

2.3 Distortion Correction

Distortion correction was performed using Synb0-DISCO, a deep learning-based method that synthesizes an undistorted b0 image from the subject's T1-weighted structural scan, which allows FSL's TOPUP-based distortion correction without a reverse phase-encoding acquisition (12,13).

2.4 DTI-ALPS Pipeline

Diffusion-weighted images were preprocessed using MRtrix3 for denoising and Gibbs ringing artifact removal. This was followed by eddy current correction and brain extraction using FSL's BET tool. Diffusion tensor fitting was performed using FSL to generate fractional anisotropy (FA) and diffusivity maps. The FA map was then registered to the JHU-ICBM-FA template using FSL, with spherical ROIs automatically placed in the superior corona radiata and superior longitudinal fasciculus bilaterally (4). The ALPS index was calculated for each participant, including left, right, and mean ALPS values.

2.5 Statistical Analysis

Statistical analyses included Bland-Altman analysis to assess agreement between left and right ALPS indices and correlation between left and right ALPS. The relationship between age and DTI-ALPS index was assessed separately within the CHD and control groups using linear regression, and sex-based differences in DTI-ALPS index were evaluated within each group similarly using two-tailed t-tests. The mean DTI-ALPS (average of right and left hemispheric ALPS) was compared between groups (TGA vs. Control, SVP vs. Control, Other CHD types vs. Control, all combined CHD vs. Control and TGA vs.

SVP) using two-tailed t-tests. Given the difference in age between the CHD and control cohorts, a multivariable linear regression was run with DTI-ALPS index as the dependent variable where group (CHD vs Control) and age were set as independent variables to assess whether the difference between CHD and control remained significant after adjusting for age. JMP and Microsoft Excel were used for calculations and for creating graphs.

RESULTS

3.1 Study Demographics

Age differed significantly between CHD and controls (14.0 ± 4 yrs in CHD vs. 15.9 ± 1.3 yrs in controls, p = 0.008), with control participants being slightly older on average than CHD participants. No significant difference was found in sex distribution between CHD and controls (Male 70.6 % in CHD vs 44% in controls, p = 0.162) (Table 1).

3.2 Bland-Altman Analysis

Bland-Altman analysis demonstrated good agreement between the left and right DTI-ALPS mean indices with a mean bias of 0.022, limits of agreement ranging from -0.305 to 0.349, and SD difference of 0.167 (Figure 2).

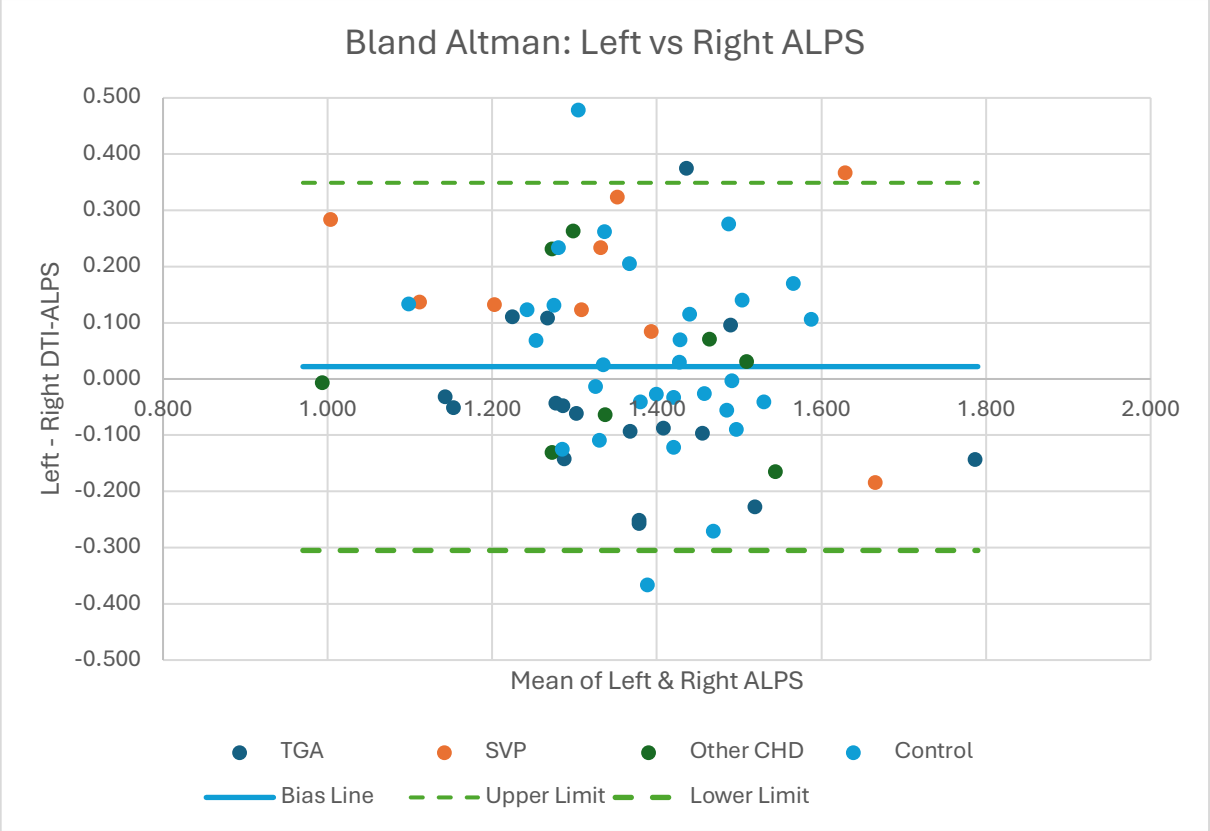

Figure 2 *Bland-Altman Analysis graph*

3.3 Association with Age

No significant relationship was found between age and DTI-ALPS index within the CHD group (p = 0.279, R^2 = 0.037). Similarly, no significant relationship was found between age and DTI-ALPS index within the control group (p = 0.639, R^2 = 0.002).

3.4 Association with Sex

No significant relationship was found between the sex and DTI-ALPS index within the CHD group (p = 0.375). Similarly, no significant relationship was found between sex and DTI-ALPS index within the control group (p = 0.058).

3.5 Group Comparisons

The mean DTI-ALPS index was significantly lower in the combined CHD group compared with the controls (Controls average mean: 1.499, All CHD average mean: 1.348, p < 0.001) (Figure 3).

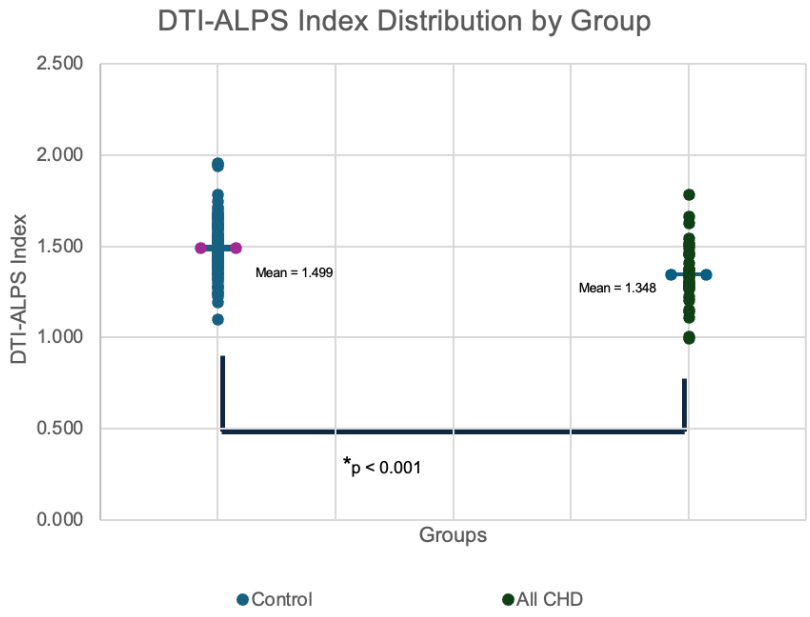

Figure 3 *DTI-ALPS Index distribution in all CHD vs controls*

While examining the subgroups, all three CHD subtypes (TGA, SVP, and other CHD group) demonstrated significantly reduced DTI-ALPS compared to controls: TGA (1.364 vs. 1.499, p = 0.003), SVP (1.328 vs. 1.499, p = 0.046), and Other CHD (1.336 vs. 1.499, p = 0.035). Although SVP showed the numerically lowest mean of all groups, the difference did not reach significance (SVP vs. TGA, 1.328 vs. 1.364, p = 0.671) (Figure 4).

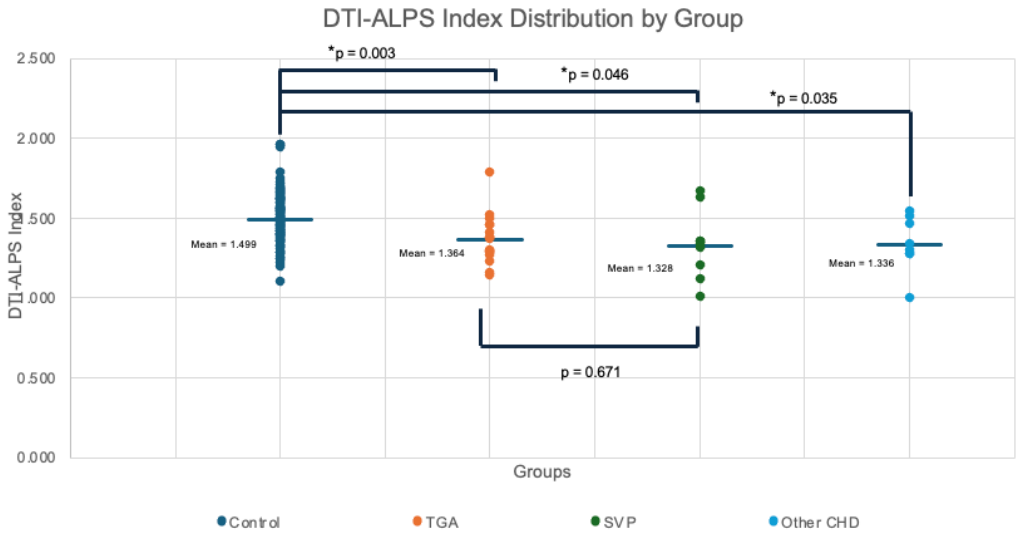

Figure 4 *DTI-ALPS Index distribution between sub-types of CHD and controls*

3.6 Multivariable Regression

After adjusting for age in a multivariable linear regression, the difference in DTI-ALPS index between CHD and control groups remained statistically significant (β = -0.083, 95% CI: -0.118- -0.049, p < 0.001). Age was not an independent predictor (p = 0.219).

DISCUSSION

4.1 Discussion

The data in this study demonstrate a significantly lower DTI-ALPS index in adolescents with critical CHD compared to controls after adjusting for age. Each CHD sub-type also demonstrated a statistically significant lower DTI-ALPS index compared to the control group.

Though DTI-ALPS has not been studied previously in adolescent CHD populations to assess glymphatic function, reduced DTI-ALPS has been reported across several pediatric brain conditions compared to healthy controls, including acute lymphoblastic leukemia without clinical central nervous system infiltration (14), periventricular leukomalacia-related cerebral palsy (15), and cognitively impaired pediatric multiple sclerosis (16). In both the leukemia and multiple sclerosis cohorts, DTI-ALPS indices were not significantly associated with age, similar to the findings in this study (14,16). Beyond pediatric populations, glymphatic dysfunction has been assessed in adult populations with coronary artery disease, where reduced DTI-ALPS indices were observed with worsening disease progression. The reduction in DTI-ALPS indices demonstrated partial improvement following coronary revascularization (17). While these are not direct comparisons, these studies collectively support that glymphatic impairment assessed with DTI-ALPS is seen in other disease processes, and cardiovascular dysfunction specifically has an emerging link to reduced glymphatic function.

Glymphatic clearance is driven by arterial pulsatility from cardiac cycles and the interstitial fluid then circulates through the brain parenchyma along the periarterial spaces (5). Reduced cardiac output and diminished arterial pulsatility are potential mechanisms that link cardiovascular dysfunction to impaired glymphatic clearance in adults with coronary artery disease (17). This mechanism may extend to CHD where there are alterations in physiology are observed based on the specific hemodynamic alterations. In SVP, the Glenn and Fontan palliation stages redirect the systemic venous return to the pulmonary arteries bypassing the subpulmonary ventricle, thus eliminating pulsatile pulmonary blood flow (7,10). These

palliation stages elevate systemic venous pressures as venous blood must be driven passively into the pulmonary arteries without the assistance of the subpulmonary ventricle, rather than draining into the right atrium under normal low-pressure conditions (7). The elevated systemic venous pressure would be expected to impair both the influx and efflux of glymphatic circulation as glymphatic circulation is dependent on a favorable pressure gradient between the periarterial and perivenous compartments (5). In TGA, the arterial switch operation restores the two-ventricle circulation. TGA post-operative patients may experience altered glymphatic function to a lesser degree as a result of their previously abnormal cardiovascular physiology and surgical repair (8). Despite differences in hemodynamic severity, all CHD subtype groups in this study demonstrated significant DTI-ALPS reductions relative to the healthy-control group, indicating a potential link between glymphatic function and congenital heart disease.

We hypothesized that SVP subjects will have significant reductions in glymphatic function compared to TGA. However, this was not supported by our data. While statistically significant reductions were not found between SVP and TGA, SVP did have the lowest group DTI-ALPS mean value compared against all other sub-types. The small number of subjects per sub-type may have contributed to the results not being statistically significantly different.

This study has several limitations, including the use of DTI-ALPS as a measure of glymphatic function. The biological specificity of DTI-ALPS remains uncertain. Reduced DTI-ALPS indices should not be assumed as a direct measure of glymphatic clearance, as similar reductions could arise from underlying white matter microstructural differences between groups rather than from perivascular fluid dynamics (17). This is especially a concern with assessing glymphatic function in CHD subjects with DTI-ALPS as white matter microstructural abnormalities are independently well documented, potentially confounding the interpretations of the DTI-ALPS findings (2,3). Alternative techniques to directly assess glymphatic and CSF dynamics exist including intrathecal or intravenous contrast-enhanced MRI, phase-contrast MRI for bulk CSF flow quantification, and MR encephalography for real-time assessment of cardiac driven or respiratory driven brain tissue pulsations (18). Although most of these techniques are direct measures for

glymphatic function, they require contrast administration or prospective specialized imaging acquisition, which may not always be feasible or available. The DTI-ALPS index is a local measure limited to areas of ROI placement and it is unclear if there are regional differences in glymphatic function, which would not be assessed using this technique. This study cannot determine if the observed reductions reflect a pre-existing developmental vulnerability, a consequence of surgery, or due to ongoing hemodynamic alterations, particularly since it was only analyzed one time point during adolescence. Additionally, this study had a small CHD cohort which may have limited the SVP vs. TGA comparison. Finally, while statistically significant, the absolute difference in DTI-ALPS means between CHD groups and controls was small.

CONCLUSION

5.1 Conclusion

The findings of this study suggest glymphatic dysfunction may be present in adolescents with CHD compared to healthy peers, which may be an additional mechanism for abnormal brain development and neurodevelopmental impairment in CHD.

FUTURE DIRECTION

6.1 Future Direction

In future studies, longitudinal assessment of DTI-ALPS could provide insight into how the glymphatic dysfunction changes with age and following cardiac intervention. Also, examining the relationship between DTI-ALPS indices and structural brain volume as well as neurodevelopmental outcomes would help understand how glymphatic impairment contributes to neurodevelopmental deficits and brain abnormalities observed in this population (2). Additionally, future exploratory analyses could be done to test association of cardiac physiologic parameters such as cardiac output and SVC flow from transthoracic echocardiogram with DTI-ALPS index.

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