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ORIGINAL ARTICLE

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Alterations in cerebral blood flow in children with congestive heart failure due to ventricular septal defect

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Abstract

Objective: We aimed to investigate the effect of ventricular septal defect (VSD) and heart failure on cerebral blood flow (CBF) in children, whether heart failure treatment improves CBF, and if there is any relationship between CBF and serum N-terminal pro-brain natriuretic peptide (NT-proBNP) level.

Method: Forty children with VSD (13 with heart failure) aged between 1 and 36 months were studied. The control group comprised 25 healthy children in the same age group. Maximum, minimum, and mean blood flow velocities and pulsatility indices of the right and left middle cerebral arteries were assessed using transcranial Doppler ultrasonography. Measurements of CBF and serum NT-proBNP levels were repeated in patients with heart failure a month post–heart failure treatment initiation. The groups were also compared in terms of defect diameters, cardiac structural changes, left ventricular systolic function, and findings related to pulmonary hypertension determined by echocardiography. Correlations between echocardiographic measurements and CBF parameters were analyzed.

Results: Although no significant difference was found between patient and control groups for CBF, right and left maximum CBF velocities significantly increased post-treatment in patients with heart failure ($P = .04$ and $P = .01$, respectively). Serum NT-proBNP levels in children with VSD associated with heart failure were significantly higher than those in children with VSD alone ($P = .04$) or in healthy children ($P < .001$). NT-proBNP levels were negatively correlated with right and left maximum CBF velocities ($r = -0.39$, $P = .013$ and $r = -0.32$, $P = .043$, respectively).

Conclusion: Although no significant difference was found in CBF velocity among the study groups, increase in the CBF velocity post heart failure treatment and negative correlations between CBF velocity and both the VSD diameter and NT-proBNP levels indicate that the hemodynamic status due to VSD associated with heart failure has an effect on CBF.

KEYWORDS

cerebral blood flow, children, heart failure, NT-proBNP, ventricular septal defect

1 | INTRODUCTION

The birth prevalence of congenital heart defects is 9.1 per 1000 live births, with ventricular septal defect (VSD) being the most common type of heart defect.[1,2] Depending on the defect size, a patient with VSD may be asymptomatic or have heart failure symptoms. When heart failure occurs, compensatory mechanisms are employed, and blood circulation is redirected away from visceral organs to the heart and brain to maintain coronary blood flow and cerebral blood flow (CBF).[3,4]

CBF can be measured using various techniques. Because changes in blood flow velocity strongly correlate with changes in cranial blood flow, CBF velocity, assessed by transcranial Doppler ultrasonography, can be used as a surrogate for CBF.[5-7] Compared with other methods, it is noninvasive, inexpensive, and easily applicable with no known contraindications. In addition, it is more acceptable because it does not have radiation risk.

Brain natriuretic peptide is released from myocytes and fibroblasts in response to increased wall tension and stress caused by heart failure.[8-10] It is assessed by measuring the serum N-terminal pro-brain natriuretic peptide (NT-proBNP) level.

CBF in patients with heart failure is lower than that in controls, but it can increase with heart failure treatment.[11-13] Various neuropsychological problems associated with decreased CBF due to heart failure may regress with failure treatment.[14] A study on a 3-month-old patient with VSD associated with heart failure demonstrated a significantly lower CBF than that in the control group comprising five healthy children. However, there was no mention of whether this flow increased with heart failure treatment.[15] Reduction in CBF in adults with heart failure was negatively correlated with higher serum NT-proBNP levels.[16] We found no studies on pediatric patients that investigated the relationship between CBF and NT-proBNP levels.

We aimed to investigate the effect of VSD and heart failure on CBF in pediatric patients and to identify whether CBF improves post heart failure treatment. In addition, we assessed the relationship between CBF and serum NT-proBNP levels in patients with VSD associated with or without heart failure.

2 | METHODS

We evaluated 40 children [aged 1-36 (mean 3.8 ± 0.7) months] who were diagnosed with VSD based on clinical and laboratory findings in the Pediatric Cardiology Outpatient Clinic of Eskişehir Osmangazi University, School of Medicine, Department of Pediatric Cardiology from January 2014 to June 2015. Heart failure was diagnosed in 13 patients. A control group comprising 25 healthy children aged 1-36 (mean 5.9 ± 1.4) months, with age and gender similar to that of children in the study group, were included. These children had been referred to the Pediatric Cardiology Outpatient Clinic for evaluation of a cardiac murmur but had normal physical examination and echocardiography findings. The study was approved by the Eskişehir Osmangazi University Ethics Committee (February 1, 2014, #80558721/09); written informed consent was obtained from parents of each child.

Children were excluded if they were diagnosed with other cardiac or noncardiac pathologies that might affect their hemodynamic status or if they had already been treated for heart failure because such medications might affect CBF. The same doctor who took a detailed medical history also performed the physical examination. These findings were recorded, and the Ross score calculated to stage the heart failure. Two-dimensional and pulse-wave Doppler echocardiographic evaluation were performed by one pediatric cardiologist using a Hewlett Packard Sonos 5500 echocardiography system (Hewlet Packard, Palo Alto, California) and 3-8 MHz broadband probe. Venous blood samples were collected and sent for measurement of the NT-proBNP level. Maximum, minimum, and mean blood flow velocities and pulsatility indices of right and left middle cerebral arteries were assessed using transcranial Doppler ultrasonography (DWL Multiple Dop ×4 model; Compumedics, Singen, Germany) and a DWL linear 2 MHz probe. This examination was done in all children by the same Neurology Department technician.

Patients were scored and grouped according to the Ross scoring system for heart failure, updated in 2012,[17] with the following scores: 0-5, no heart failure; 6-10, mild heart failure; 11-15, moderate heart failure; and ≥16, severe heart failure. Thirteen patients met the criteria for heart failure. Three groups were, therefore, defined for the study.

Group 1: The 13 children with a Ross score of ≥6 were included in this group and were treated with combination heart failure therapy (digoxin, furosemide, and captopril). Approximately 1 month posttreatment initiation, initial examinations were repeated for determining if there was improvement in CBF. One patient died shortly postdiagnosis. Of the remaining 12 patients, heart failure findings improved with treatment in 10, and they underwent reassessment of CBF 1 month post treatment initiation. The other two patients did not show improvement with medication and, therefore, underwent surgery for VSD repair. These two patients underwent reassessment 1 month postoperatively.

Group 2: The 27 children with VSD but with a Ross score of ≤5, and therefore, no heart failure, were included in this group.

Group 3: This was the control group comprising 25 healthy children.

SPSS (Windows 21 software; IBM, Armonk, New York) was used for statistical analysis. When comparing independent measurements between the two groups, normally and nonnormally distributed data were analyzed with an independent sample *t* test and Mann-Whitney *U* test, respectively. For dependent measurements, normally and nonnormally distributed data were analyzed with a paired sample *t* test and Wilcoxon signed-rank test, respectively. For comparison of independent measurements among multiple groups, normally and nonnormally distributed data were analyzed with an ANOVA test and Kruskal-Wallis test, respectively. When differences were detected on ANOVA, a Tukey or Tamhan post hoc test was used for evaluating the differences. Analysis of the crosstabs was performed with chi-square test. To demonstrate relationships between variables, a Pearson test was used for normally distributed data and a Spearman correlation test was used for nonnormally distributed data. A P value $< .05$ was considered to be statistically significant.

TABLE 1 Distribution of the study groups according to gender, age, cardiothoracic ratio, defect diameter/body surface area, and NT-proBNP level

	Group 1	Group 2	Group 3	
	VSD + HF (*n* = 13)	VSD (*n* = 27)	Control (*n* = 25)	
Female/male[a]	8/5	13/14	11/14	*P* > .05
Age (month)[b]	2.1 ± 0.24	4.6 ± 1.3	5.9 ± 1.4	*P*1 = .045, *P*2 = .01, *P*3 > .05
CTR	0.59 ± 0.019	0.49 ± 0.007	0.49 ± 0.006	*P*1 = .001, *P*2 = .001, *P*3 > .05
Defect diameter/body surface area (cm/m^2)	25.17 ± 2.62	12.1 ± 0.96	–	*P*1 > .05
NT-proBNP (pg/ml)	6623 ± 1560	480 ± 81	166 ± 17	*P*1 = .04, *P*2 = .001, *P*3 = .01

[a]Chi-square test was used for comparing the groups according to gender. [b]*P* = .007 when all the groups compared with Kruskal-Wallis test. *P*1: When comparing VSD + HF group with VSD group, *P*2: When comparing VSD + HF group with control group, *P*3: When comparing VSD group with control group. CTR: cardiothoracic ratio.

3 | RESULTS

There was no statistically significant difference in gender between the groups. Mean ages were 2.1 ± 0.24, 4.6 ± 1.3, and 5.9 ± 1.4 months for groups 1, 2, and 3 respectively, with the mean age differing significantly between the three groups (*P* = .007). The mean age of group 1 was significantly lower than that of groups 2 and 3 (*P* = .045 and *P* = .01, respectively). However, there was no significant age difference between group 2 and group 3 (Table 1). Mean cardiothoracic ratios were 0.59 ± 0.019, 0.49 ± 0.007, and 0.49 ± 0.006 for groups 1, 2, and 3, respectively, with a significant difference observed between the groups (*P* < .001). On pairwise comparisons, the cardiothoracic ratio in group 1 was significantly higher than that in group 2 or 3 (*P* = .001 and *P* = .001, respectively). However, there was no significant difference between groups 2 and 3 (Table 1). On echocardiographic evaluation of the 40 children with VSD, a perimembranous defect was detected in 25 (62.5%) and a muscular defect was detected in 15 (37.5%). The distribution of VSD location did not differ significantly between groups 1 and 2. The defect diameter/body surface area (DD/BSA) ratio was 25.17 ± 2.62 cm/m^2 for group 1; this ratio was significantly higher than that for group 2 (12.1 ± 0.96 cm/m^2) (*P* < .001) (Table 1). Altough there were no significant differences in terms of left atrium and left ventricular end diastolic diameters between groups, those were higher in group 1 and group 2 than in group 3 when standardized to BSA (*P* = .001, *P* = .011, *P* = <.001 and *P* = .026, respectively). The Q_p/Q_s ratio was higher in group 1 than in group 2. Although post heart failure treatment, the Q_p/Q_s ratio in group 1 remained higher than that in the other two groups, it had significantly decreased from the pretreatment value by 1 month post treatment initiation (*P* = .043 and *P* = .001). There were no significant differences in other echocardiographic findings between any of the groups (Table 2).

Mean NT-proBNP levels were 6623 ± 1560, 480 ± 81, and 166 ± 17 pg/ml in groups 1, 2, and 3, respectively. After treatment, the mean value decreased to 989 ± 263 pg/mL in group 1. There was a significant difference in NT-proBNP levels between the groups (*P* < .001). The level in group 1 was significantly higher than in group 2 or 3 (*P* = .04 and *P* < .001, respectively). The NT-proBNP level in group 2 was also significantly higher than that in group 3 (*P* = .016). NT-proBNP levels in group 1 significantly decreased with heart failure treatment based on pre- and posttreatment assessments (*P* = .003, Wilcoxon test). However, the posttreatment levels in group 1 were still significantly higher than those in group 3 (*P* < .001, Mann-Whitney *U* test).

Based on pretreatment Ross scores in group 1, five children had mild, six had moderate, and two had severe heart failure. The mean pretreatment Ross score in group 1 was 11.6 ± 0.84, and this score significantly decreased to 2.6 ± 0.5 posttreatment (*P* < .001). The mean group 2 Ross score was 2.1 ± 0.23, which was significantly lower than the group 1 pretreatment score (*P* < .001). However, there was no significant difference between posttreatment score of groups 1 and 2.

Although the CBF velocity of group 1 was lower than that of group 3, there was no statistically significant difference in any of the measurements between the groups (Table 3). The pretreatment right maximum blood flow velocity was 94 ± 4.6 cm/s and posttreatment maximum velocity was 108 ± 5.4 cm/s, ie, a significant increase was observed with treatment (*P* = .004). The pretreatment left maximum blood flow velocity was 92 ± 3.1 cm/s, and it increased significantly to 106 ± 5.4 cm/s posttreatment (*P* = .01). There were no significant changes in other CBF velocity parameters with treatment (Table 2). Posttreatment CBF velocities in group 1 did not significantly differ in terms of any parameters from those in group 3.

3.1 | Correlation analyses

Relationships between CBF parameters and Ross score, NT-proBNP levels, and DD/BSA were investigated in all 40 patients with a VSD with correlation tests (Table 4). No significant correlation was detected between Ross score and CBF velocity, but the NT-proBNP level was negatively correlated with right and left maximum blood

TABLE 2 Echocardiographic findings of the cases

	VSD + HF (*n* = 12)	VSD (*n* = 27)	Control (*n* = 25)	*P*
LVEDd (mm)	19 ± 0.86	22 ± 0.92	21 ± 0.63	.051
LVEDd/BSA (mm/m^2)	120 ± 29.6	100 ± 28.4	78 ± 20.5	*P* < .001 *P*1 = .201 *P*2 < .001 *P*3 = .026
Ejection fraction (%)	71 ± 2.8	69 ± 1.3	73 ± 1.5	.38
Shortening fraction (%)	36 ± 1.2	37 ± 1.9	39 ± 1.3	.31
Aortic annulus diameter (mm)	10.4 ± 0.46	11 ± 0.59	10.8 ± 0.54	.69
LAd (mm)	15 ± 4.8	15 ± 3.4	14 ± 0.53	.18
LAd/BSA (mm/m$^{2)}$	97 ± 42.6	71.9 ± 23.4	51 ± 14.2	*P* = .001 *P*1 = .642 *P*2 = .001 *P*3 = .011
Q_p/Q_s	3.36 ± 0.57	1.7 ± 0.15	1.1 ± 0.001	*P* < .001 *P*1 = .033 *P*2, *P*3 < .001
Pulmonary annulus diameter (mm)	10 ± 0.62	10 ± 0.33	10 ± 0.43	.09
Right atrium diameter (mm)	16 ± 1.1	15 ± 0.88	15 ± 0.64	.92
RVEDd (mm)	18 ± 1.5	17 ± 1	18 ± 0.68	.15

Abbreviations: LVEDd, left ventricular end-diastolic diameter, LAd, left atrium diameter, RVEDd, right ventricular end-diastolic diameter, BSA, body surface area *P*1, When comparing VSD+HF group with VSD group, *P*2, when comparing VSD+HF group with control group, *P*3, when comparing VSD group with control group.

TABLE 3 Cerebral blood flow velocities of the cases[a]

	VSD + HF (pretreatment) (*n* = 12)	VSD + HF (posttreatment) (*n* = 12)	VSD (*n* = 27)	Control (*n* = 25)
Right maximum flow velocity (cm/s)	94 ± 4.6[b]	108 ± 5.4[b]	99 ± 2.5	100 ± 3.2
Right mean flow velocity (cm/s)	56 ± 3.2	64 ± 4	62 ± 2.5	62 ± 2.5
Right minimum flow velocity (cm/s)	29 ± 2.4	35 ± 3.4	32 ± 2.1	33 ± 1.9
Right pulsatile index	1.08 ± 0.09	1.14 ± 0.05	1.2 ± 0.04	1.14 ± 0.035
Left maximum flow velocity (cm/s)	92 ± 3.1[c]	106 ± 5.4[c]	102 ± 3.8	102 ± 3.2
Left mean flow velocity (cm/s)	56 ± 3.2	65 ± 3.6	59 ± 2.5	62 ± 2.5
Left minimum flow velocity (cm/s)	29 ± 2.4	36 ± 2.7	29 ± 1.8	35 ± 1.96
Left pulsatile index	1.13 ± 0.9	1 ± 0.06	1.22 ± 0.4	1 ± 0.3

[a]The pre- and posttreatment values of VSD + HF group were compared with paired samples *t* test or Wilcoxon test; posttreatment values of VSD + HF and control group were compared with independent samples *t* test or Mann-Whitney *U* test.
[b]*P* = .004. [c]*P* = .01.

flow velocities ($r = -0.39$, $P = .013$ and $r = -0.32$, $P = .043$, respectively). There was also a negative correlation between Q_p/Q_s ratio and left maximum blood flow velocity ($r = -0.31$, $P = .04$). Statistically significant negative correlations were detected between DD/BSA and right maximum CBF velocity ($r = -0.35$, $P = .023$), right mean CBF velocity ($r = -0.46$, $P = .002$), and left mean CBF velocity ($r = -0.33$, $P = .037$). A significant positive correlation was detected between Ross scores and NT-proBNP levels ($r = 0.58$, $P < .001$).

TABLE 4 Relationships of cerebral blood flow velocity with Ross score, NT-proBNP, and DD/BSA[a]

	Ross score	NT-ProBNP (pg/ml)	DD/BSA (mm/m^2)
Right maximum flow velocity (cm/s)	$r = -0.088$, $P = .58$	$r = -0.39$, $P = .013$	$r = -0.35$, $P = .023$
Right mean flow velocity (cm/s)	$r = -0.08$, $P = .58$	$r = -0.15$, $P = .32$	$r = -0.46$, $P = .002$
Right minimum flow velocity (cm/s)	$r = -0.027$, $P = .87$	$r = 0.024$, $P = .88$	$r = -0.30$, $P = .053$
Right pulsatile index	$r = -0.13$, $P = .35$	$r = -0.15$, $P = .40$	$r = 0.20$, $P = .19$
Left maximum flow velocity (cm/s)	$r = -0.11$, $P = .47$	$r = -0.32$, $P = .043$	$r = -0.27$, $P = .08$
Left mean flow velocity (cm/s)	$r = -0.005$, $P = .97$	$r = -0.17$, $P = .27$	$r = -0.33$, $P = .037$
Left minimum flow velocity (cm/s)	$r = 0.11$, $P = .50$	$r = 0.029$, $P = .85$	$r = -0.19$, $P = .22$
Left pulsatile index	$r = -0.23$, $P = .14$	$r = -0.23$, $P = .15$	$r = 0.15$, $P = .33$

[a]Values were analyzed with Spearmen correlation test.

4 | DISCUSSION

A reduction in CBF during heart failure due to low cardiac output leads to certain types of neurologic and psychological impairment that can be reversed with treatment.[11-16] However, most of these studies were conducted on adult patients; limited data is available on pediatric patients. Kojo et al[15] reported the case of a 3-month-old girl with severe heart failure due to a large VSD (DD/BSA = 37.9 mm/m^2). Her carotid artery blood flow velocity, measured by a Doppler flowmeter, was significantly lower than that of five healthy control subjects. Her Q_p/Q_s ratio detected by catheterization was 3.8. In another case report by Kojo et al,[18] impaired cardiac function as well as lower carotid artery blood flow velocity was observed on postnatal days 2 and 3 in a neonate with hypertrophic cardiomyopathy compared with those in normal neonates of the same age. Carotid artery blood flow velocity increases to normal levels when cardiac function is improved post heart failure treatment.[18] CBF velocities of eight neonates born to mothers with diabetes were compared with those of 12 healthy neonates.[19] In contrast to the aforementioned studies, six of the eight infants had ventricular hypertrophy and lower than normal cardiac output and stroke volume than the healthy neonates, but there was no significant difference in anterior cerebral artery and carotid artery blood flow velocities between the groups. Gruhn et al[11] measured CBF by SPECT and found that it was 31% below normal in 12 adults with heart failure due to cardiomyopathy and ischemic heart disease. Rajagopalan et al[20] studied nine adults with severe heart failure using SPECT and found a global decrease in CBF velocity. Recently, some investigators have attempted to demonstrate that heart failure is a risk factor for Alzheimer's disease, which may be associated with decreased CBF velocity.[21,22] Jesus et al[12] investigated an association between cognitive impairment and CBF velocity in adults with heart failure; they found a decrease in the mean flow velocity of the right middle cerebral artery and an increase in the pulsatility index. Alves et al[13] compared 17 adults with New York Heart Association class II-III heart failure with a healthy control group. CBF assessed by SPECT, particularly in the right lateral temporoparietal and posterior cingulate cortex, was lower than in the healthy control group and was associated with cognitive impairment. The same group assessed CBF by SPECT and found lower flow in patients with major depressive disorder and heart failure than in controls.[14] In a study by Loncar et al[16] CBF in 71 men with dilated cardiomyopathy and ischemic heart disease was lower than that in the healthy control group. In all these adult studies, the reduction in CBF can be explained by the decreased cardiac function.

In our study, although CBF velocities in children with a VSD and heart failure were lower than those in healthy children, the difference was not statistically significant in comparison with those with VSD alone or with healthy children. In this respect, our study results are similar to those of Wu et al,[26] who reported a statistically insignificant reduction in CBF in neonates with mothers who had diabetes. Our findings of a negative correlation between CBF and DD/BSA and Q_p/Q_s ratios support findings of Kojo et al[15] in the previously mentioned 3-month-old. A great majority of studies on this topic have investigated adults with heart failure, consistently demonstrating reduction in CBF and increase in the pulsatility index. The etiology of heart failure in such studies on adults has generally been ischemic heart disease resulting in inadequate myocardial contraction. Conversely, in pediatric patients, as our study suggests, the main cause of heart failure is congenital heart disease; the ejection fraction is preserved. Therefore, compensatory vascular responses may be more effective in pediatric patients with heart failure. Thus, our finding that CBF velocity and the pulsatility index did not differ between the groups assessed suggests that compensatory mechanisms for maintaining blood supply to the vital organs, such as CBF and coronary blood flow, function better in children (particularly in infants) than in adults.

Gruhn et al[11] evaluated CBF pretransplantation and 1 month postheart transplantation in five patients with heart failure secondary

to cardiomyopathy and ischemic heart disease. Their pretransplantation CBF was significantly lower than that in 12 healthy control subjects, but it increased posttransplantation to normal levels. This increase was secondary to an increase in cardiac output. Rajagopalan et al[20] reported that the reduced CBF in nine patients with severe heart failure improved up to that in the control group post 4-15 days of captopril therapy. Bommel et al[23] evaluated 35 adults with heart failure who received cardiac resynchronization therapy and then had significantly increased CBF measured by transcranial Doppler ultrasonography. Similar to the findings in adults,[11,20,23] we found a significant increase in CBF with a decrease in the Q_p/Q_s ratio with heart failure treatment. In the present study, all patients with VSD and heart failure were administered combined anticongestive therapy comprising digoxin, diuretics, and ACE inhibitors. It is aimed at reducing pulmonary or systemic congestion (diuretics), reducing disproportionately elevated afterload (ACE inhibitors), and increasing contractility (digoxin). In particular, increased myocardial contractility and decreased afterload were thought to reduce the Q_p/Q_s ratio by increasing systemic blood flow. These results suggest that medical treatment for symptomatic heart failure also leads to an increase in CBF velocity.

Previous studies reported that serum NT-proBNP levels in children diagnosed echocardiographically with congestive heart failure and/or left ventricular dysfunction are higher than those in healthy controls.[10,17,24] This was also found in the previously mentioned study by Loncar et al[16] studying patients with heart failure whose CBF was low and was negatively correlated with serum NT-proBNP levels. In our study, the NT-proBNP levels were significantly higher in children with heart failure than in those without heart failure. We have previously reported that heart failure treatment in children leads to a significant decrease in serum NT-proBNP levels, although they still remain higher than those in healthy children[24]; this result is consistent with that of a number of studies demonstrating that NT-proBNP can be used as a marker for monitoring heart failure treatment.[25,26] In the present study, we demonstrated a negative correlation between NT-proBNP levels and the right and left maximum CBF velocities. Similarly, Wu et al[26] found that when the NT-proBNP level increases in children with heart failure, CBF velocity decreases. Therefore, we suggest that serum NT-proBNP levels be used as a marker of changes in CBF.

In conclusion, the hemodynamic status of children with a VSD and symptomatic heart failure is associated with a reduction in CBF, which can be ameliorated by treating the heart failure. In addition to transcranial Doppler ultrasonography, serum NT-proBNP levels may also be a reliable and useful parameter for detecting changes in CBF.

5 | LIMITATIONS

There are some limitations of this study. Because we excluded patients who had already received heart failure treatment at the time of VSD diagnosis, there was a significant age difference between the three study groups. Because CBF velocities change with age, a similar study would benefit from better age-matching of patients and controls.

DECLARATION OF INTEREST

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the article.

AUTHOR CONTRIBUTIONS

Birsen Ucar, Nurdan Ozturk Tasar, and Nevzat Uzuner designed the study and wrote the protocol. Nurdan Ozturk Tasar, Nevzat Uzuner, and Pelin Kosger collected data. Pelin Kosger and Nurdan Ozturk Tasar managed literature searches and analyses. Birsen Ucar and Pelin Kosger undertook statistical analysis, and Birsen Ucar, Pelin Kosger, and Nurdan Ozturk Tasar wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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REFERENCES

1. Van der Linde D, Konings EE, Slager MA et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2011;58:2241-2247.
2. Hoffman JI, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol*. 2002;39:1890-1900.
3. Choi B-R, Kim JS, Yang YJ, et al. Factors associated with decreased cerebral blood flow in congestive heart failure secondary to idiopathic dilated cardiomyopathy. *Am J Cardiol*. 2006;97:1365-1369.
4. Meng L, Hou W, Chui J, Han R, Gelb AW. Cardiac output and cerebral blood flow: the integrated regulation of brain perfusion in adult humans. *Anesthesiology*. 2015;123:1198-1208.
5. Sharma VK, Wong KS, Alexandrov AV. Transcranial Doppler. *Front Neurol Neurosci*. 2016;40:124-140.
6. Giller CA, Hatab MR, Giller AM. Estimation of vessel flow and diameter during cerebral vasospasm using transcranial Doppler indices. *Neurosurgery*. 1998;42:1076-1081.
7. Sloan MA, Alexandrov A, Tegeler C, et al. Transcranial Doppler ultrasonography. Report of the therapeutic and tecnology assessment subcommitte of the American Academy of Neurology. *Neurology*. 2004;62:1462-1481.
8. Davis GK, Bamforth F, Sarpal A. B-type natriuretic peptide in pediatrics. *Clin Biochem*. 2006;39:600-605.
9. Baxter GF. The natriuretic peptides. *Basic Res Cardiol*. 2004;99:71-75.
10. Nasser N, Perles Z, Rein AJ, Nir A. NT-proBNP as a marker for persistent cardiac disease in children with history of dilated cardiomyopathy and myocarditis. *Pediatr Cardiol*. 2006;27:87-90.
11. Gruhn N, Larsen FS, Boesgaard S et al. Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. *Stroke*. 2001;32:2530-2533.
12. Jesus P, Melo R, Reis F et al. Cognitive dysfunction in congestive heart failure: transcranial Doppler evidence of microembolic etiology. *Arq Neuropsiquiatr*. 2006;64:207-210.

13. Alves T, Rays J, Fráguas RJ et al. Localized cerebral blood flow reductions in patients with heart failure: a study using 99mTc-HMPAO SPECT. *J Neuroimaging*. 2005;15:150-156.
14. Alves T, Rays J, Fraguaz R et al. Association between major depressive symptoms in heart failure and impaired regional cerebral blood flow in the medial temporal region: a study using 99m Tc-HMPAO single photon emission computerized tomography (SPECT). *Psychol Med*. 2006;36:597-608.
15. Kojo M, Yamada K, Maeda M, Sato K, Izumi T. Reduction of carotid arterial blood flow in ventricular septal defect associated with severe congestive heart failure. *J Neuroimaging*. 2000;10:241-243.
16. Loncar G, Bozic B, Lepic T, et al. Relationship of reduced cerebral blood flow and heart failure severity in elderly males. *Aging Male*. 2011;14:59-65.
17. Nir A, Nasser N. Clinical value of NT-ProBNP and BNP in pediatric cardiology. *J Card Fail*. 2005;11:76-80.
18. Kojo M, Ogawa T, Yamada K, Sonoda H, Saito K. Multivariate autoregressive analysis of carotid artery blood flow waveform in an infant of a diabetic mother with cardiomyopathy. *Acta Paediatr Jpn*. 1995;37:588-593.
19. Van BF, Van DM, Walther FJ. Cerebral blood flow velocity and cardiac output in infants of insulin dependent diabetic mothers. *Acta Ped Scan*. 1991;80:905-910.
20. Rajagopalan B, Raine AE, Cooper R, Ledingham JG. Changes in cerebral blood flow in patients with severe congestive cardiac failure before and after captopril treatment. *Am J Med*. 1984;76:86-90.
21. Qiu C, Winblad B, Marengoni A, Klarin I, Fastbom J, Fratiglioni L. Heart failure and risk of dementia and Alzheimerdisease: a population-based cohort study. *Arch Intern Med*. 2006;166:1003-1008.
22. Cermakova P, Eriksdotter M, Lund LH, Winblad B, Religa P, Religa D. Heart failure and Alzheimer's disease. *J Intern Med*. 2015;277:406-425.
23. Bommel RJ, Marsan NA, Koppen H et al. Effect of cardiac resynchronization therapy on cerebral blood flow. *Am J Cardiol*. 2010;106:73-77.
24. Sezgin Evim M, Uçar B, Kılıç Z, Çolak O. The value of serum N-terminal pro-brain natriuretic peptide levels in the differential diagnosis and follow-up of congestive cardiac failure and respiratory distress due to pulmonary aetiologies in infants and children. *Cardiol Young*. 2010;20:495-504.
25. Mir TS, Marohn S, Eiselt M, Grollmus O, Weil J. Plasma concentrations of N-terminal pro-brain natriuretic peptide in control children from the neonatal to adolescent period and in children with congestive heart failure. *Pediatrics*. 2002;110:e76.
26. Wu YR, Chen SB, Huang MR, Zhang YQ, Sun K, Chen S. Diagnostic value of plasma concentration of pro-brain natriureticpeptide in congestive heart failure in pediatric patients with ventricular septal defects. *Zhonghua Er Ke Za Zhi*. 2005;43:161-164.

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