TRANSCRANIAL DOPPLER SONOGRAPHY IN CHILDREN WITH CONGENITAL HEART DISEASE UNDERGOING CARDIAC CATHETERIZATION

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ABSTRACT

Background: *Children with congenital heart disease (CHD) remain at high risk for long-term neurodevelopmental disabilities. Acute neurologic complications, such as seizures, transient ischemic attack, intracranial hemorrhage, and ischemic stroke may occur in the setting of cardiac surgery and cardiac catheterization.*

Objective: *to evaluate the effect of cardiac catheterization on cerebral hemodynamics assessed by transcranial Doppler (TCD) sonography in children with congenital heart disease.*

Methods: *This was an observational cohort study included forty children aged from 1 month to 18 years who were scheduled for cardiac catheterization at Ain Shams University Children's hospital in the period from January 2020 to January 2021. Clinical data, neurologic examination and TCD parameters were done before and after cardiac catheterization.*

Results: *In the present study, 33 patients (82.5%) had interventional catheterization and 7 (17.5%) had diagnostic catheterization. A history of previous cardiac catheterization were found in 11 (27.5%), 4 (36.4%) had previous failed catheterization, 3 (27.3%) had previous diagnostic catheterization out of 40 patients;. Middle cerebral artery TCD parameters of the patients in the diagnostic group showed statistically significant lower peak systolic (PS), and time average mean of the maximal velocities (TAMX) pre catheterization and statistically significant lower PS, end diastolic, and TAMX post catheterization. All patients showed statistically significant lower TAMX post catheterization.*

Conclusion: *Transcranial Doppler sonography is a noninvasive physiologic monitor of cerebral hemodynamics that can be performed at the bedside. In our experience derangements in cerebral hemodynamics were recorded. However, the practical implications of these findings remain uncertain.*

Keywords: *Cardiac Catheterization; Congenital Heart Disease; Transcranial Doppler Sonography.*

INTRODUCTION

Congenital heart disease is considered the most common congenital malformation, present in about 1% of live birth **(Khoshnood et al., 2012)**.

Cardiac catheterization is an important diagnostic and therapeutic tool, that includes two types of procedures diagnostic (DGN), and interventional (INTV). INTV studies consists of procedures involving manipulative therapy (e.g., valvuloplasty, angioplasty, embolization, etc.), while all other studies performed to evaluate anatomic structure, assess hemodynamic (e.g., drug studies for pulmonary hypertension) or for diagnosis, including myocardial biopsy, is classified as DGN procedures. Although in the last decade, there have been significant improvements in technology and equipment, the risk for complications remains, adversely effecting outcomes **(Mehta et al., 2008)**.

A reported incidence of 0.38% acute neurologic complications (14 children of a total of 3,648 cardiac catheterization procedures) performed for acyanotic or cyanotic congenital heart disease. Neurologic complications were convulsion, stroke, intracranial hemorrhage, extrapyramidal features, paraplegia, visual impairment, hearing impairment, and brachial plexus injury. The possible mechanisms causing brain injury were cerebral embolism and hypoxia as complications during the procedure. Intracranial hemorrhage secondary to anticoagulation and peripheral plexopathy due to prolonged fixed posture during anesthesia. Neurologic sequelae, such as global developmental delay or epilepsy, occurred in those with hypoxic-ischemic encephalopathy **(Liu et al., 2001)**. Seizures were the most common presenting symptom of stroke and more often than a focal neurologic signs in periprocedural period **(Asakai et al., 2015)**.

Bed side neuroimaging strategies such as near infrared spectroscopy, continuous electroencephalogram and transcranial Doppler (TCD) may hold some promises in early detection of stroke. The non-invasive nature and bed side facility of cranial ultrasound makes it frequently relied on for screening of intracranial events **(Sinclair et al., 2015)**.

Multifrequency transcranial Doppler was used during transcatheter closure of patent ductus arteriosus (PDA) to monitor cerebral blood flow velocity (CBFV) and detect microembolic signals (MES) in the middle cerebral artery **(Wallace et. al., 2016)**.

AIM OF THE STUDY

The aim of this study is to evaluate the effect of cardiac catheterization on transcranial Doppler sonography (TCD) in correlation with clinical data during the procedure in children with congenital heart disease and to monitor any short-term neurologic outcome.

PATIENTS AND METHODS

I. Ethical considerations:

1. Prior to conducting the study, the ethical approval of Ain Shams University ethical committee was obtained ensuring that the work complies with the principles of the Declaration of Helsinki in 1975.
2. Written informed consent was signed by caregivers before enrolment.
3. All patients' data were kept confidential and care givers had the right to keep them.
4. No conflict of interests existed regarding the research or the publications.
5. No Funds were received to conduct the research.

II. Sample size:

The sample size estimation was done using the Epi Info7 program for sample size calculation, setting the confidence level at 95% and margins of error at 10% and based on the work done by **Wallace et. al., (2016)**, a total of 40 patients was estimated to be sufficient sample size.

III. Inclusion Criteria:

This observational cohort study included 40 Infants and children aged from 1 month to 18 years of both gender who had various CHD who performed diagnostic or interventional catheterization attending the cardiac catheterization unit at Children's hospital, Ain shams university they were randomly selected during the period from January 2020 to January 2021.

IV. Exclusion Criteria: Any patients who had

1. Intracardiac masses and/or infective endocarditis in their

initial or follow up echocardiographic studies.

2. Congenital malformation of the nervous system.
3. Complex multiple congenital anomalies.
4. Bleeding diathesis and suspected inborn error of metabolism.
5. Patients who failed to have TCD prior to and/or after the catheterization procedure due to unavailability of the radio-diagnosis consultant, refusal to be examined, death or discharge immediately post catheterization were excluded from the study.

V. Methods: This was an observational cohort study included forty children aged from 1 month to 18 years who were scheduled for cardiac catheterization at Ain Shams University Children's hospital. They were randomly selected period from January 2020 to January 2021.

All patients under study who were scheduled for cardiac catheterization at Ain Shams University Children's hospital catheterization laboratory were subjected to:

I. Full medical history and examination e.g., (vital data, anthropometric parameters, cardiac examination and neurological assessment)

II. Transcranial Doppler sonography (TCD): which is performed preoperatively and within 24 hours post catheterization. All TCD recordings were performed by the radiodiagnosis investigator to all patients while being awake. Bilateral monitoring and recording of the middle cerebral artery (MCA) through the temporal bone acoustic window. The bifurcation of the MCA (M1 segment, antegrade flow) and anterior cerebral artery (A1 segment, retrograde flow) was initially identified, ensuring a reproducible window. 3MHz, multifrequency TCD probe was used through (LOGIQ P9, Norway) ultrasound device. All real-time recordings were saved for further off-line analysis.

III. Cardiac catheterization procedure: The procedure was explained to the parents and the informed consent was signed. General anesthesia was used for all patients either by laryngeal mask or endotracheal intubation. The patients were sterilized using betadine from the umbilicus to the knees bilaterally, and then covered with sterile drapes. The vascular access was obtained using the usual Seldinger's technique.

IV. **Post-catheterization assessment:** Clinical neurological assessment was done within 24hrs post catheterization and before discharge. Further examination was done at one week, and one month after catheterization.

Vi. Statistical Analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when parametric and median, inter-quartile range (IQR) when data found non-parametric. Also, qualitative variables were presented as number and percentages. Then the appropriate statistical analysis was applied and the confidence interval was set to 95% and the margin of error accepted was set to 5%.

RESULTS

The results of the current study is demonstrated in the following tables:

Table (1): Demographic and anthropometric data of the studied patients **before catheterization**

		Total no. = 40
Age (years)	Median (IQR)	3.75 (1.85 – 8)
	Range	0.16 – 16
Sex	Females	29 (72.5%)
	Males	11 (27.5%)
Weight (kg)	Mean ± SD	19.02 ± 12.13
	Range	5.7 – 55
Height (cm)	Mean ± SD	98.84 ± 26.38
	Range	58.5 – 149
BMI (kg/m2)	Mean ± SD	18.01 ± 3.21
	Range	12.1 – 24.8
BSA	Mean ± SD	0.71 ± 0.32
	Range	0.31 – 1.51

Age: 0.16 = 2 months.
BMI: body mass index, BSA: body surface area.

Table (2): Clinical data of the studied patients before catheterization

SBP (mmHg)	Mean ± SD	99.90 ± 10.18
	Range	77 – 122
SBP centile	<=50th	27 (67.5%)
	90th	9 (22.5%)
	>= 95th	4 (10.0%)
DBP (mmHg)	Mean ± SD	61.20 ± 9.72
	Range	40 – 84
DBP centile	<=50th	28 (70.0%)
	90th	7 (17.5%)
	>= 95th	5 (12.5%)
SPO2 (mmHg)	Mean ± SD	94.20 ± 7.57
	Range	70 – 100
HR	Mean ± SD	104.28 ± 16.47
	Range	72 – 136
Signs of heart failure	No	25 (62.5%)
	Yes	15 (37.5%)

DBP: diastolic blood pressure, HR: heart rate, SPO2: oxygen saturation, SBP: systolic blood pressure.

Table (3): Comparison between transcranial Doppler parameters (TCD) of middle cerebral artery (MCA) of patients before and after catheterization

		MCA Before cath.	MCA After cath.	Test value	P-value	Sig.
PS	Median (IQR)	98.63 (78.83 – 113.2)	93.58 (62.46 – 113.48)	-0.860≠	0.390	NS
	Range	20.6 – 141.65	25.2 – 129.05			
ED	Median (IQR)	35.7 (28.63 – 44.43)	34.7 (24.97 – 48.08)	-0.121≠	0.904	NS
	Range	4.3 – 63.45	5.65 – 58.5			
TAMX	Median (IQR)	63.15 (51.63 – 76.18)	54.7 (35.21 – 69.08)	**-2.137≠**	**0.033**	**S**
	Range	13.15 – 100.2	19 – 89.4			
PI	Mean ± SD	0.95 ± 0.18	0.93 ± 0.20	0.678•	0.502	NS
	Range	0.49 – 1.35	0.55 – 1.52			
RI	Mean ± SD	0.61 ± 0.08	0.59 ± 0.08	1.020•	0.314	NS
	Range	0.36 – 0.77	0.43 – 0.81			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
•: Paired t-test; ≠: Wilcoxon Rank test.
Wilcoxon rank test was used for parametric values (ED, PS, TAMAX).
Paired t-test was used for non-parametric values (PI, RI).
ED: end diastolic velocity, PS: peak systolic velocity, PI: pulsatility index, RI: resistive index, TAMAX: time average mean of the maximal velocities.

Table (3) shows that TAMX of MCA was statistically higher before catheterization [63.15(51.63-76.18)] compared to TAMAX after catheterization [54.7(35.21-69.08] (p-value=0.033), with no statistically significant difference found between before and after catheterization as regard the remaining TCD parameters of MCA.

Table (4): Correlation between TCD parameters of MCA before catheterization and some clinical and procedural data of the studied patients

	MCA before catheterization									
	PS		**ED**		**TAMX**		**PI**		**RI**	
	R	**P-value**	**r**	**P-value**	**R**	**P-value**	**r**	**P-value**	**r**	**P-value**
O2 sat. at enrolment	**0.404****	**0.010**	**0.361***	**0.022**	**0.404****	**0.010**	-0.060	0.714	-0.020	0.904
HR	-0.085	0.600	-0.234	0.146	-0.173	0.285	0.278	0.082	0.214	0.184
Duration of anesthesia	**-0.326***	**0.040**	-0.301	0.060	-0.305	0.056	-0.048	0.770	-0.015	0.928
O2 sat. during cath.	**0.404****	**0.404**	**0.437****	**0.005**	**0.476****	**0.002**	-0.130	0.424	-0.015	0.925

Table (4) shows a positive correlation between oxygen saturation at enrolment and PS (r= 0.404**, p-value= 0.010), ED (r=0.361, p-value= 0.022) and TAMX (r=0.404, p-value= 0.010) of MCA before catheterization.

Another positive correlation was found between oxygen saturation during catheterization and PS (r=0.404, p-value=0.404), ED (r=0.437, p-value=0.476) and TAMX (r=0.476, p-value=0.002) of MCA before catheterization while There is a negative correlation between duration of anesthesia and PS of MCA before catheterization (r=-0.326, p-value=0.040).

Table (5): Correlation between TCD parameters of MCA after catheterization and some clinical and procedural data of the studied patients

	MCA after catheterization									
	PS		ED		TAMX		PI		RI	
	r	P-value	r	P-value	R	P-value	r	P-value	r	P-value
O2 sat. at enrolment	**0.444****	**0.004**	**0.427****	**0.006**	0.285	0.075	-0.161	0.322	-0.222	0.168
HR	-0.078	0.632	-0.125	0.443	-0.109	0.502	0.051	0.755	0.062	0.704
Duration of anesthesia	0.047	0.773	0.091	0.575	0.040	0.806	-0.057	0.728	-0.158	0.330
O2 sat. during cath.	**0.556****	**0.000**	**0.607****	**0.000**	**0.467****	**0.002**	-0.189	0.244	-0.277	0.084

Table (5) shows a positive correlation between O2 saturation at enrolment and PS (r=0.444, p-value=0.004) and ED (r=0.427, p-value= 0.006) of MCA after catheterization. Another positive correlation was found between O2 saturation during catheterization and PS (r=0.556, p-value=0.000), ED (r=0.607, p-value=0.467) and TAMX (r=0.467, p-value= 0.002) of MCA after catheterization.

DISCUSSION

The primary aim of the current study is to evaluate the effect of cardiac catheterization on transcranial sonography and to study TCD parameters value in correlation with clinical data during cardiac catheterization. For this purpose, 40 children; 29 females (72.5%) and 11 males (27.5%) with median age 3.75 years (range: 2 months - 16 years) was enrolled.

In the present study, the mean systolic blood pressure (SBP) was 99.90 ±10.18 mmHg while mean diastolic blood pressure (DBP) was 61.20 ± 9.72. Diagnostic group showed significantly higher systolic and diastolic blood pressure despite insignificant difference as regard centiles.

Conversely, as the mean arterial BP increases, the brain arterioles constrict. With impaired autoregulation, cerebral blood flow becomes pressure passive, and the ICP can rise and fall in the same direction as the mean arterial BP. **(Figaji et al., 2009**; **LaRovere and O'Brien, 2015)**. As our MAP did not exceed 150 mmHg, therefore autoregulation mechanism was intact preserving adequate cerebral blood flow. In a multivariable analysis of MAP and cardiac output on middle cerebral artery velocity (MCAV) **Lie et al (2021)** states that the estimated effect of a change of 10 mmHg in MAP corresponding to a change in MCAV of 3.11 cm/s (95% CI 2.51–3.71; P<0.001).

In the present study, TCD parameters of MCA showed that TAMX after catheterization showed statistically significance lower value in all the studied patients. In agreement with our data, **Cheng et al. (2014)** found that TAMX was higher in interventional group than diagnostic group. Velocity in systole (Vs) was 97.1 ± 36.2 cm/s and 94.7 ± 29.8 cm/s in TOF and VSD in interventional group, respectively post-induction compared to 55.0 ± 17.9 cm/s in diagnostic group, they were statistically highly significant (P <0.001). The velocity decrease to 73.7 ± 30.5 cm/s and 93.0 ± 22.7 cm/s in TOF and VSD, respectively, 18 hours post-catheter, but still significant compared to diagnostic group.

This finding could be explained by the fact, velocity (V) in a rigid vessel equals the volume of fluid per time (Q) divided by the cross-sectional area (A) of the pipe, V = Q / A. Thus, the CBFV in an artery depends on two factors: the cross-sectional area of the vessel and the blood flow through it. In a narrowed vessel, as long as the blood volume flow is constant, the velocity increases at, and immediately downstream from, the stenosis. An increased velocity can also reflect increased flow volume without a change in luminal diameter, e.g., in anemia, arteriovenous malformation, in a vessel functioning as a collateral for another occluded artery, or a combination of these. As proximal segments of intracranial arteries have limited vasodilatation capacity, low velocity always reflects low blood flow, e.g., downstream from a stenosis, or in case of increased vascular resistance (as in cerebral oedema). TCD parameters are influenced by different physiological and pathological factors, and by vasoactive substances **(Verlhac, 2011)**. A reduction in CBF during reduced cardiac output has been found in several studies **(Ogoh et al. 2005, 2015**; **Brown et al. 2003**; **Ogawa et al. 2007**; **Bronzwaer et al. 2017)**. **Lie et al (2021)** in a multivariable analysis stated that a 1 L/min change in cardiac output corresponding to a change in MCAV of 3.41 cm/s (95% CI 2.82–4.00; P<0.001).

In the present study, there is a positive correlation between oxygen saturation at enrolment and during catheterization and PS, ED and TAMX of MCA before catheterization. Another positive correlation was found between O2 saturation at enrolment and PS and ED after catheterization, while oxygen saturation during catheterization had a positive correlation with PS, ED and TAMX after catheterization. Also, there was a lower PS and TAMX of MCA before catheterization and lower PS, ED and TAMX after catheterization in patients with cyanosis than those who hadn't (p = 0.015 and 0.021) respectively. **Lagunju et al. (2014)** on the contrary, found significantly negative correlation between SaO2 and TAMMV (r = 20.171, p = 0.023). Cerebral blood flow velocities were significantly higher in children with sickle cell disease who showed evidence of arterial oxygen desaturation, SaO2 <95% at baseline. TAMX decreased by about1.8 cm/s when the SaO2 increased by 1% (96% CI -3.12 to -0.38).

In the present study, duration of anesthesia showed a negative correlation with PS before catheterization. **Saxena et al 1997** stated that the incidence of arterial thrombosis was 8.2%, when the procedure lasted less than 30 minutes as compared with 15% when the duration exceeded 50 minutes. The duration of catheterization was prolonged in interventional cardiac catheterization (P = 0.018), indicating that prolonged duration of interventional cardiac catheterization was an important risk factor for the development of neurologic complications **(Liu et al., 2001)** showed that elevated cerebral blood flow velocities measured by TCD are highly predictive of significant vessel narrowing and of an increased risk of stroke in children with SCD.

In the present study, there wasn't any neurological affection detected by examination neither pre- catheterization nor post-catheterization. Only painful limitation of movement of the limbs from the puncture site that was disappeared in the one week follow up.

From April 1986 to April 1998 (12 years), Liu et al 2001 studied 3,648 cardiac catheterizations (2,953 diagnostic procedures alone and 695 interventional with or without diagnostic procedures) for acute neurologic complications that may present after cardiac catheterization. Only 14 children of a total of 3,648 (0.38%) catheterization procedure developed neurological complication within 48 hours after catheterization (seven of 2,953 children, or 0.24%, with diagnostic cardiac catheterization; seven of 695 children, or 1.01%, with interventional cardiac catheterization). Agha et al 2021, studied 1200 patients, 895 (74.6%) were cardiac catheterizations either diagnostic or intervention, 167 (13.9%) were open-heart surgery, and 138 (11.5%) were closed heart surgery to assess their neurological sequelae within 30 days of cardiac intervention. According to the previous studies, neurological complications was a complication that needs a large sample size to be detected. As our study included only 40 patients that could be the reason why there wasn't any neurological complication found in our study group. For that we recommend to establish the same study but with a larger sample size.

Earlier studies suggests that younger children may experience more complications during cardiac catheterization **(Yılmazer et al., 2012)**. Also, studies had described that complications occur more commonly in children under 10 kg or 5 kg in **Mehta et al. (2008)** and **Yılmazer et al. (2012)**, respectively. Mortality was most common in children with younger age, lower weight and interventional procedures **(Bennett et al., 2005**; **Yılmazer et al., 2012)**.

CONCLUSIONS

Transcranial Doppler sonography is a noninvasive physiologic monitor of cerebral hemodynamics that can be performed at the bedside. In our experience derangements in cerebral hemodynamics were recorded. However, the practical implications of these findings remain uncertain.

RECOMMENDATION

Future research using transcranial Doppler sonography may elucidate underlying cerebrovascular pathophysiology, identify markers of increased risk of further neurologic injury, influence the choice of additional testing and treatment, and ultimately impact patient outcomes.

LIMITATIONS

As our study included only 40 patients that could be the reason why there wasn't any neurological complication found in our study population. For that we recommend to establish the same study but with a larger sample size. In addition to the intra-observer variability encountered in using TCD which could affect its parameters.

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