Flow-Mediated Dilatation of the Brachial Artery for Assessing Endothelial Dysfunction in Children with Moyamoya Disease

Eun-Hee Kim Hyung-Chul Lee Jaeyeon Chung Sang-Hwan Ji
Young-Eun Jang Ji-Hyun Lee Jin-Tae Kim Hee-Soo Kim

Department of Anesthesiology and Pain Medicine, College of Medicine, Seoul National University,
Seoul, Republic of Korea

Keywords

Flow-mediated dilatation · Moyamoya disease · Pediatric neurosurgery

Abstract

Background: Moyamoya disease is a progressive, steno-occlusive arteriopathy involving the internal carotid artery and its branches and causing recurrent stroke episodes in children. Patients with moyamoya disease may be more susceptible to influences that cause endothelial dysfunction. We evaluated whether flow-mediated dilatation (FMD) of the brachial artery is useful for assessing endothelial dysfunction in children with moyamoya disease. **Methods:** This prospective observational study included 30 children with moyamoya disease and 30 controls. After anesthesia induction, a blood pressure cuff was applied to the forearm and inflated to a pressure that was 50 mm Hg above the baseline systolic blood pressure for 5 min. From 30 s before to 2 min after deflation, the brachial artery diameter was recorded on ultrasound. The increase in internal diameter was expressed as the percentage of the baseline diameter. **Results:** Fifty-nine patients were analyzed. Baseline brachial artery diam-

eters in the moyamoya and control groups were 3.00 and 3.37 mm, respectively ($p = 0.004$; difference, 0.38; 95% CI 0.12–0.63), while those after deflation were 3.06 and 3.48 mm, respectively ($p = 0.003$; difference, 0.42; 95% CI 0.15–0.68). The percent change of the baseline diameter value was 4.0% in the disease group and 8.3% in the control group ($p = 0.10$). There was a group and time interaction for brachial artery diameter ($p = 0.01$; main effect of group, $p = 0.009$; main effect of time, $p = 0.007$). **Conclusion:** FMD of the brachial artery may not be enough for determining endothelial dysfunction under general anesthesia in children with moyamoya disease.

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Introduction

Vascular disease is not common in children. Previous studies involving children showed that in children, impaired flow-mediated dilatation (FMD) was related to several pathological conditions including sickle cell anemia, diabetes, low birthweight, Henoch-Schönlein purpura, and sleep-disordered breathing [1–6].

Fig. 1. Endothelium-derived flow-mediated dilatation of the brachial artery measurement using ultrasound.

FMD is used to measure the change in the diameter of conduit arteries, such as the brachial artery, in response to a shear stress stimulus that produces a nitric oxide-dependent response. FMD can be easily determined by ultrasound; thus, this technique is used as a standard method for noninvasive evaluation of endothelial dysfunction [7]. Previous studies have shown that impaired endothelial function in the brachial artery is an independent predictor of postoperative cardiovascular events in patients undergoing vascular surgery [8]. In addition, impaired FMD in adult patients with ischemic stroke is reportedly associated with a poor outcome and a predictor of new-onset vascular events after the first ischemic stroke [9, 10].

Moyamoya disease is a progressive, steno-occlusive arteriopathy involving the internal carotid artery and its branches and causing recurrent stroke episodes in children [11]. Thus far, the exact etiology of moyamoya disease remains unknown. Given that endothelial dysfunction is associated with thrombus formation and vessel wall inflammation, patients with moyamoya disease may be more susceptible to influences that cause endothelial dysfunction [12].

Accordingly, we hypothesized that endothelial function would be impaired in pediatric patients with moyamoya disease and conducted the present study to evaluate whether endothelium-dependent FMD of the brachial artery is useful for assessing endothelial dysfunction in pediatric patients with moyamoya disease.

Table 1. Patient characteristics

	Moyamoya disease	Healthy controls	<i>p</i> value
Age, years	9.5 (6.2–11)	8.0 (6–10)	0.18
Height, m	1.3 (1.2–1.4)	1.2 (1.1–1.4)	0.81
Weight, kg	30.0 (23.5–43.7)	31.4 (21.4–41.7)	0.37
BMI	18.3 (16.1–19.6)	18.6 (15.7–20.8)	0.69

Values are presented as median (interquartile range). BMI, body mass index.

Subjects and Methods

Patients

We prospectively enrolled children aged 3–12 years who were scheduled to undergo surgery under general anesthesia at a tertiary care children's hospital between March and August 2017. In total, there were 30 patients with moyamoya disease who were scheduled to undergo encephaloduroarteriosynangiosis and 30 patients without moyamoya disease who required orthopedic surgery (control group). Children with cardiovascular disease and those with a body mass index >25 kg/m² were excluded.

Anesthesia Protocol

None of the patients received premedication. On arrival in the operating room, noninvasive blood pressure monitoring, pulse oximetry, and electrocardiography were initiated via a patient monitor (Solar 8000; GE Medical, Milwaukee, WI, USA). Baseline blood pressure was measured using an appropriately sized cuff placed on the right arm in the supine position. The mean of three consecutive measurements was recorded. Anesthesia was induced with propofol 2 mg/kg and maintained with sevoflurane 2–3 vol% and continuous infusion of sufentanil 0.5–1.0 µg/kg/h. Muscle relaxation was achieved with rocuronium 0.6 mg/kg.

Study Protocol

Before the initiation of the surgery, endothelium-derived FMD of the brachial artery was measured using ultrasound (Fig. 1), which was performed by an experienced pediatric anesthesiologist. The E-CUBE i7 device (Alpinion Medical Systems Co., Korea) with a linear hockey stick-shaped IO8-17T (Alpinion Medical Systems Co.; 8–17 MHz) probe exhibiting a small footprint (31 × 6 mm) was used for all assessments. The brachial artery of the left arm was visualized and scanned in a longitudinal section 2 cm above the elbow. The internal diameter, defined as the distance between the boundaries of the intima, was measured at baseline. Then, arterial occlusion at the forearm was achieved by insufflation of a blood cuff (Welch Allyn FlexiPort reusable blood pressure cuff size 9 or 10) to a pressure that was

Table 2. Blood pressures of included patients

	Moyamoya disease (<i>n</i> = 29)	Healthy controls (<i>n</i> = 30)	<i>p</i> value
Ward SBP, mm Hg	116.1 (12.9)	107.5 (11.0)	0.01
Ward DBP, mm Hg	66.0 (16.1)	60.7 (12.2)	0.16
Ward MBP, mm Hg	82.7 (14.1)	76.2 (11.1)	0.05
Baseline SBP, mm Hg	115.4 (18.9)	111.2 (16.8)	0.37
Baseline DBP, mm Hg	61.1 (14.7)	64.4 (14.4)	0.38
Baseline MBP, mm Hg	80.0 (17.4)	80.2 (15.3)	0.96
Pre FMD SBP, mm Hg	112.1 (13.3)	100.7 (11.6)	0.00
Pre FMD DBP, mm Hg	58.3 (7.6)	51.5 (7.6)	0.00
Pre FMD MBP, mm Hg	76.6 (8.6)	68.5 (10.0)	0.00
Post FMD SBP, mm Hg	108.5 (13.1)	99.1 (17.4)	0.02
Post FMD DBP, mm Hg	57.5 (9.9)	51.7 (11.8)	0.02
Post FMD MBP, mm Hg	74.6 (9.4)	68.3 (13.0)	0.04

Values are presented mean (standard deviation). SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; FMD, flow-mediated dilatation.

at least 50 mm Hg above the baseline systolic pressure for 5 min. The longitudinal image of the brachial artery was continuously recorded from 30 s before to 2 min after cuff deflation. The increase in internal diameter as a consequence of reactive hyperemia was expressed as the percentage of the baseline diameter (%FMD).

Once the image for analysis had been selected, the boundaries for diameter measurements (the lumen-intima or the media-adventitia interfaces) were automatically identified by an edge detection program created by one of the authors (H.-C. Lee) using the MATLAB software. Variability in the diameter measurement is maximum with point-to-point measurement in a single frame. In contrast, it is least when an average is derived from multiple measurements obtained along a segment of the vessel. Diameter measurement along a longitudinal segment of a vessel is dependent on the alignment of the image.

Statistical Analysis

FMD in healthy school-going children is reportedly 8.34–8.77% [13], and no previous study has used this technique in children with moyamoya disease. We considered that FMD would decrease by 50% in patients with moyamoya disease and determined that 25 patients would be required in each group, considering an alpha error of 5% and a power of 0.8. After considering the dropout rate, we determined that 60 patients would be required in total. Normality of the data distribution was tested with the Kolmogorov-Smirnov test. Continuous variables were evaluated using the Student *t* test or the Mann-Whitney test, as appropriate, while categorical variables were evaluated using the χ^2 test. Generalized linear mixed model analysis was performed to compare the brachial artery diameters at different time points between the two groups. All statistical analyses were performed using MedCalc version 18.11.3 (MedCalc, Mariakerke, Belgium) and SPSS version 23.0 (IBM Corp., Armonk, NY, USA). We reported statistical significance at *p* < 0.05.

Results

All recruited participants completed the study. However, one moyamoya patient with insufficient data was excluded, and the data of 59 patients were included in the final analysis. There were no significant differences in patient characteristics between the two groups (Table 1).

Blood pressures were measured and compared in the ward and after anesthesia induction (Table 2). The baseline systolic blood pressure measured in the ward was higher in the moyamoya disease group than in the control group. After anesthesia induction, there were no significant differences in blood pressure values for the two groups. Before and after FMD, blood pressure was significantly higher in the moyamoya disease group than in the control group. There were no adverse events during the study procedure.

Mean baseline brachial artery diameters in the moyamoya disease and control groups were 3.00 (2.85–3.15) and 3.37 (3.17–3.59) mm, respectively (*p* = 0.004; difference, 0.38; 95% CI 0.12–0.63). After deflation, these diameters were 3.06 (2.92–3.20) and 3.48 (3.24–3.71) mm, respectively, with a significant difference between groups (*p* = 0.003; difference, 0.42; 95% CI 0.15–0.68).

The %FMD values for the moyamoya disease and control groups were 4.0% (0–16.2%) and 8.3% (4.0–14.7%), respectively (*p* = 0.10). However, there was a significant group and time interaction (*p* = 0.01; main effect of group, *p* = 0.009; main effect of time, *p* = 0.007) for brachial artery diameter (Fig. 2).

Fig. 2. Changes in brachial artery diameter from the beginning of flow-mediated dilatation in the moyamoya and healthy control groups.

Discussion

In the present study, we found that endothelial function assessed by FMD under general anesthesia was comparable between pediatric patients with moyamoya disease and those with expected normal endothelial function, although the brachial artery diameter at baseline and in the dilated phase was smaller in the former group than in the latter.

Several studies of endothelial function in pediatric patients without vascular disease [13–15] and those with vascular disease [16] are available. However, to our knowledge, no study has used FMD to investigate endothelial function in patients with moyamoya disease. Moreover, the association between endothelial dysfunction and moyamoya disease has not been fully elucidated, with the few available studies presenting conflicting results. A small cohort study showed increased nitric oxide metabolites in cerebrospinal fluid, which was thought to reflect the development of an abnormal collateral circulation [17]. However, another study reported that serum levels of nitric oxide metabolites in patients with moyamoya disease did not differ from those in healthy controls [12]. Moreover, researchers found no difference in polymorphisms in endothelial nitric oxide synthase, a key molecule for producing nitric oxide, between control and moyamoya disease groups [18]. However, all these studies included a small number of patients and did not perform direct measurements of clinical endothelial function.

In the present study, the %FMD value was 4.0% in the presence of moyamoya disease and 8.3% in the absence of this condition. Reported %FMD values for normal Asian

children in the awake state range from 8.29 to 8.80%; these values are similar to that for our control group (8.3%) [6]. Although the %FMD value for our moyamoya disease group was almost half the value for the control group, the difference was not statistically significant. One possible explanation for this result is that FMD was evaluated under general anesthesia. A previous study reported that recovery of endothelial function was impaired by sevoflurane-based anesthesia, and that decreased endothelial function could be associated with reduced blood pressure and inhibited sympathetic nerve activity, which are unavoidable during general anesthesia [19]. Similar findings were reported in a previous animal study [20]. In addition, volatile anesthetics induce vasodilation, and this phenomenon may have interfered with the results of FMD in the present study. Therefore, the vascular response to FMD may have been attenuated, which resulted in the absence of a significant difference. Pediatric patients in previous studies of FMD were mostly awake; however, 5 min of tourniquet time can cause significant discomfort, numbness, and occasionally pain, even in adult patients [21]. Therefore, we performed the FMD procedure after the induction of general anesthesia and maintenance of a stable sevoflurane concentration.

The baseline brachial artery diameter in the control group in our study was relatively larger than those reported in previous studies [13, 14]. The mean diameter in children aged 6 years was found to be 2.62 mm, with an increase to 3.18 mm at the age of 18 years [13]. Accordingly, the mean diameter of the brachial artery in the patients recruited in our study, who were aged 3–12 years, should have been approximately 2.9 mm. In our study,

the brachial artery diameter in the control group was considerably larger (3.37 mm) than the reported diameter, while that in the moyamoya disease group was only slightly larger (3.0 mm). This finding could be partially attributed to the vasodilation induced by volatile anesthesia. If the normal values reported in the previous study are accepted, the values derived in the present study may be attributed to the response of the vessels to the volatile anesthetics, and there could be a difference between the control and moyamoya disease groups, although the brachial artery diameter was not measured in the awake state in either group. In other words, vasodilation of the brachial artery in response to sevoflurane anesthesia was greater in the control group than in the moyamoya disease group.

In a previous study, postoperative temporary hypertension was frequently observed in pediatric patients with moyamoya disease [22], while another study found that renovascular hypertension was associated with moyamoya disease, partly because of the proliferative characteristics of the intima in these patients [23]. A correlation between blood pressure and FMD in children has been reported in a previous study [24], where children with essential and white-coat hypertension showed lesser FMD than controls. This could be a result of endothelial dysfunction and imbalance of the sympathovagal nervous system in patients with hypertension. Similarly, in the present study, patients with moyamoya disease showed relatively high systolic blood pressure at baseline and during the FMD procedure. We speculate that the underlying mechanism may be similar to that in patients with hypertension.

Another unique finding in the present study was the difference between the two groups in changes in brachial artery diameter over time during the FMD procedure (Fig. 2). This implies the presence of differences in the vascular response to the procedure. FMD represents the difference in brachial artery diameter between two different time points; however, the present study demonstrated the dynamic vascular response during the procedure. Even though this is not a standard method of interpretation of FMD, we believe the findings are clinically meaningful and valuable.

Impaired FMD can be used as a predictor of future cardiovascular events in older patients [21] or a prognostic factor in adult patients with stroke [9, 10]. The presence of impaired FMD in children with moyamoya disease might be helpful in predicting clinical outcomes in these patients.

This study has several limitations. First, the measurements were obtained under general anesthesia. Most pre-

vious studies involved awake patients, so it was difficult to make direct comparisons with their findings. Second, this was an observational study, and our sample size was not large enough for obtaining a statistically significant difference in FMD between the two groups. Third, FMD was not evaluated in the pre- and postoperative periods. According to previous studies, surgical trauma and stress may affect endothelial function and result in potential vascular dysfunction [25, 26]. Further studies should evaluate FMD in the perioperative period for patients with moyamoya disease. Finally, information regarding the severity of moyamoya disease was lacking, and it was difficult to associate impaired FMD with worse clinical outcomes.

Conclusions

Our findings suggest that children with moyamoya disease might have endothelial dysfunction. However, FMD of the brachial artery may not be enough for determining endothelial dysfunction in children with moyamoya disease under general anesthesia.

Statement of Ethics

This case-control, prospective, observational study was approved by the institutional review board of Seoul National University (<http://cris.snuh.org/ncris>; approval No.: H-1512-092-728) and is registered at cris.nih.go.kr (ref. No. KCT0001790). The parents/legal guardians or children (if older than 7 years) provided informed consent before participation.

Conflict of Interest Statement

The authors declare no competing interests.

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Author Contributions

E.-H. Kim: methodology, writing of the original draft. H.-C. Lee and J.-H. Lee: formal analysis. J. Chung, S.-H. Ji, Y.-E. Jang, and J.-T. Kim: investigation, data curation. H.-S. Kim: supervision, writing, review, editing.

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