Presence of a High-Flow-Mediated Constriction Phenomenon Prior to Flow-Mediated Dilation in Normal Weight, Overweight, and Obese Children and Adolescents

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ABSTRACT: Purpose. When assessing vasomotor endothelial function by reactive hyperemia, the brachial artery, in some individuals, constricts immediately before beginning to dilate following cuff release. We call this response high-flow-mediated constriction (H-FMC). The aim of this study was to describe the rate of the H-FMC during reactive hyperemia in children and adolescents throughout a range of body mass index (BMI) values, and to investigate differences in flow-mediated dilation (FMD), cardiovascular, and anthropometric measures between subjects with and without H-FMC.

Methods. FMD was assessed in 136 children and adolescents (61 male, 75 female; 13 ± 3 years) by sonographic imaging of the brachial artery. H-FMC was characterized as the lowest point from the baseline brachial artery diameter immediately following reactive cuff release. Independent t tests were used to compare subjects with and without H-FMC.

Results. H-FMC was observed in 91 of the 136 participants (66.9%). No significant difference was found between H-FMC and non-H-FMC subjects for age (p = 0.602), gender (p = 0.767), height (p = 0.227), or weight (p = 0.171). BMI percentile was nonsignificantly higher (91.8 ± 14.9th versus 84.6 ± 22.8th percentile, p = 0.057) and FMD was significantly lower (5.43 ± 3.41% versus 8.05 ± 3.97%, p < 0.001) in H-FMC than in non-H-FMC subjects. Adding H-FMC to FMD produced no significant difference between H-FMC and non-H-FMC individuals (8.03 ± 3.27% versus 8.05 ± 3.97%, p = 0.977).

Conclusions. Approximately 67% of participants demonstrated an H-FMC during reactive hyperemia. BMI percentile was nonsignificantly higher and FMD was significantly lower in children and adolescents who displayed this phenomenon. © 2015 Wiley Periodicals, Inc. J Clin Ultrasound 43:495–501, 2015; Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/jcu.22267

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INTRODUCTION

Flow-mediated dilation (FMD) is widely used as a noninvasive method for measurement of endothelial function through sonographic imaging of the brachial artery following reactive hyperemia.1 Endothelial dysfunction has been associated with cardiovascular events2 as well as increasing age,3 gender,4,5 cigarette smoking,6 and obesity.7,8 An increase in shear stress via increased flow has been thought to initiate endothelial nitric oxide (NO) synthase production and subsequent release of NO.9,10 A delayed arterial dilatory response to shear stress has been observed in radial,11 brachial,1 and femoral12 vascular beds. In the radial artery, a relatively recent study11 concluded that, during high blood flow, an opposing vasoconstrictor stimulus conceals the shear stress-induced NO-mediated dilation. It was postulated that vasoconstriction could result from the
decrease in transmural pressure produced by the sudden fall in downstream flow resistance and/or by a shear stress-stimulated constrictor release such as endothelin-1.\textsuperscript{11,13}

A delayed dilation response is regularly observed in humans.\textsuperscript{1,14,15} However, immediately following the cuff release, the arteries of some individuals constrict before they begin to dilate. This physiologic response has been referred to as a flow-mediated constriction (FMC) (Figure 1).\textsuperscript{11,16–18} An alternative method for assessing the vascular function has been proposed by measuring the radial artery constriction during distal occlusion.\textsuperscript{18} This procedure has been termed low-flow-mediated constriction (L-FMC).\textsuperscript{18} In contrast, a high-flow-mediated constriction (H-FMC) has been observed in healthy adults at the radial artery following occlusion.\textsuperscript{11} However, we found no report in the literature regarding the occurrence of brachial artery H-FMC in children and adolescents. The aim of the present study was to assess the rate of brachial artery H-FMC during reactive hyperemia in children and adolescents throughout a large range of body mass index (BMI) values, and to investigate differences in FMD, and hemodynamic and anthropometric measures, between subjects who experience this phenomenon and those who do not.

**MATERIALS AND METHODS**

**Study Population**

One hundred thirty-six children and adolescents (61 males, 75 females) were assessed for peak FMD. Subjects were recruited from a pediatric weight management clinic (patients and siblings) and from the community via flyers and advertisements. The study protocol was reviewed and approved by the University of Minnesota Institutional Review Board and all participants, along with parents/guardians, gave written informed assent and consent. The procedures followed in the study were in accordance with the institutional review board and HIPAA guidelines. Subjects fasted for at least 8 hours prior to vascular assessment and were asked to abstain from caffeine for at least 4 hours on the morning of testing. Avoidance of strenuous exercise or physical activity was also required for 24 hours prior to the study visit.

**Physical Assessments**

Measurements for height and weight were obtained with a standard stadiometer (Avrton, Model S100, Prior Lake, MN) and electronic scale (ST Scale-Tronix, Serial No. 5022–8893, White Plains, NY), respectively. BMI was calculated as weight in kilograms divided by height in meters-squared. Tanner stage was assessed by a trained pediatrician or registered nurse. Waist and hip circumferences (in centimeters) were obtained with a Gulick measuring tape (Creative Health Products, Ann Arbor, MI).

**Vascular Assessments**

Vascular testing was performed in the Vascular Biology Laboratory of the Clinical and Translation Science Institute at the University of Minnesota. Subjects were tested in a quiet, climate-controlled room (22–23°C). Resting blood pressure was recorded using an automated sphygmomanometer (Colin Medical Instruments Corp., San Antonio, TX) on the right arm prior to FMD assessment. A blood pressure cuff was also placed on the left forearm. Following 15 minutes of quiet rest in the supine position, vascular images of the left brachial artery were obtained proximal to the antecubital fossa in the longitudinal plane using a conventional sonographic scanner (Acuson, Sequoia 512; Siemens Medical Solutions USA, Inc., Mountain View, CA) with a 8–15-MHz linear array probe held at a constant pressure on the skin and at a
fixed point over the imaged artery by a stereotactic arm.

The blood pressure cuff on the left forearm was inflated to a suprasystolic pressure level of 200 mmHg and maintained for 5 minutes. Vascular images were captured from 20 seconds prior to cuff release until 3 minutes post-cuff release and were digitized and stored on a personal computer for later off-line analysis using an electronic wall-tracking software program (Vascular Research Tools 5; Medical Imaging Application, LLC, IA City, IA). Vascular images were assessed and baseline brachial artery measurements were recorded as a 10-second average just prior to blood pressure cuff release (ie, occlusion baseline), and a 10-second average immediately following blood pressure cuff release. Peak dilation was defined as the 10-second average of the greatest percentage change from baseline brachial artery diameter. Shear rate was used to estimate shear stress and calculated as blood flow velocity divided by arterial diameter. The maximal 10-second average blood flow after cuff release was reported as maximal flow. The H-FMC was characterized using a 10-second average of the lowest point from baseline brachial artery diameter following cuff release and considered present if the diameter increased by less than −0.1% or decreased (Figure 1). A trained sonographer performed all digital sonographic image analysis. When FMD was measured 7 days apart, the coefficient of variation was 11.1% in our laboratory, demonstrating good reproducibility.

**Statistical Analysis**

Statistical analysis was performed using IBM SPSS Statistics 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0; IBM Corp., Armonk, NY). Descriptive statistics were conducted for the two groups on anthropometric and hemodynamic measurements. Independent t tests were used to compare differences between subjects who demonstrated an H-FMC and those who did not. A correlation matrix between analyzed parameters was implemented among significant anthropometric and vascular measures. A one-way analysis of variance was conducted for the degree of H-FMC for BMI percentile. An α value of 0.05 was denoted as statistically significant.

**RESULTS**

Mean demographic characteristics of children are presented in Table 1. Of the 136 children and adolescents examined in this study, 91 (66.9%) displayed an H-FMC. Children and adolescents ranged in age from 8 to 17 years old, with a mean age of 13 ± 3 years. When classified by BMI percentile, 70.6% of the study population was considered obese, 9.5% were overweight, and 19.9% were normal weight for their age and gender. When grouped by the presence or absence of H-FMC according to BMI percentile, 70.8% of obese and 76.9% of overweight children and adolescents displayed an H-FMC versus 48.1% of normal weight children and adolescents. Comparing BMI percentile within the H-FMC group and degree of H-FMC, average constriction was significantly greater in normal weight individuals than in both overweight and obese combined (−3.53 ± 1.88% versus −2.45 ± 1.59%, p = 0.03). No differences were observed for composition of gender, levels of systolic and diastolic blood pressure, heart rate, height, weight, BMI, Tanner stage, or hip and waist circumference (Table 1). BMI percentile was nonsignificantly higher in H-FMC than in non-H-FMC children and adolescents (Table 1). Table 2 displays the vascular measures for the study population. Baseline brachial artery diameter, average shear, peak shear, and maximal flow were not significantly different between H-FMC and non-H-FMC children and adolescents. Peak FMD was significantly lower in H-FMC than in non-H-FMC individuals.

A correlation matrix was constructed using FMD, H-FMC, BMI, and BMI percentile values. A greater H-FMC was associated with lower peak FMD (r = 0.455, p < 0.001). Peak FMD was positively correlated with BMI (r = 0.243,
have been shown to suppress endothelin-1 release in cultured endothelial cells. However, in the present study, there was no significant difference in shear stress or maximal flow between subjects who displayed an H-FMC and those who did not.

Another possible explanation may be that H-FMC children have a higher sensitivity to endothelin-1. Research by Weil et al in adults supports the notion that overweight and obesity are associated with enhanced endothelin-1-mediated vasoconstriction. Enhanced constriction could contribute to endothelial vasodilator dysfunction and to the increased risk of hypertension in these subjects. In the present study, 85.7% of H-FMC children and adolescents were categorized as overweight or obese versus 68.8% of the non-H-FMC. Those demonstrating H-FMC had a nonsignificantly greater BMI percentile, which may support the hypothesis of the release of an FMC factor following cuff release. However, H-FMC and BMI percentile were not significantly correlated.

A significant drop in intra-arterial pressure may also be responsible for H-FMC. Reactive tissue hyperemia is due to the buildup of metabolic by-products during ischemia, inducing vasodilation of “resistance” arteries (at the microcirculation level). The resulting fall in circulatory resistance led to increased blood flow in the “conduit” artery upstream, so that its own resistance to flow may become significant (at least until its own vasodilation occurs) and create a pressure loss, which may cause its passive mechanical constriction (recoil). However, all things being equal, this response should have been observed in all subjects because the methodology was identical for H-FMC and non-H-FMC children and adolescents. Differences in the amplitude of tissue hyperemia and/or in baseline conduit artery diameter might explain various degrees of imbalance between these opposite mechanisms, with H-FMC occurring when greater hyperemia and/or smaller conduit artery baseline diameter led to a larger pressure drop. This, in turn, would result in a greater, although delayed, FMD, which we could not observe in the present study. Moreover, we found no significant difference in shear stress or maximal flow between subjects who displayed an H-FMC and those who did not, and children and adolescents with an H-FMC had a significantly lower FMD than those without. Therefore, some release of endothelin-1 cannot be ruled out.

FMD has been utilized as a predictor of cardiovascular events in asymptomatic subjects.

### DISCUSSION

The aim of this study was to examine the prevalence of early FMC during reactive hyperemia in normal weight, overweight, and obese children and adolescents and investigate potential differences of anthropometric and hemodynamic measures in relation to its presence. We found that approximately 67% of the population displayed H-FMC. Those individuals who displayed H-FMC had a lower peak FMD compared with those that did not.

Jiang et al suggested two explanations for this transient initial constriction following cuff release: (1) an FMC factor, or (2) a reduction in intra-arterial pressure resulting from the fall in downstream resistance that, in turn, led to increased flow. An argument could be made that non-H-FMC children and adolescents could possibly have a blunted shear-stimulated release of a constrictor agent, such as endothelin-1. If this were true, one would expect a difference in the time to peak between H-FMC and non-H-FMC groups, which there was not. A blunted shear stress release of vasoconstrictors such as endothelin-1 could, theoretically, be due to a higher level of shear stress in non-FMC before cuff release, since high levels of shear stress...
Overweight and obese children have displayed impaired FMD values\textsuperscript{21} and are at increased risk for developing coronary heart disease risk factors.\textsuperscript{22} Higher FMD is generally associated with healthy endothelial function, and in the present study, non-H-FMC children and adolescents displayed brachial artery FMD levels similar to those of healthy control subjects in other studies.\textsuperscript{23} Even though the presence of an H-FMC was associated with lower FMD response, it is unclear whether the H-FMC is associated with other cardiovascular risk factors. This will need to be examined in future studies.

Of interest, when an addition of the percentage of H-FMC to peak FMD was applied to those displaying a vasoconstriction, the difference in peak FMD between the two groups disappeared. It seems that there is a limited timeframe during which peak dilatory response to reactive hyperemia occurs. Therefore, if the initial response to cuff release is constriction, the result will lower the overall dilation of the brachial vessel relative to the initial baseline diameter. Statistical difference has been observed in the current study between the two groups for the composite end point and FMD values (Table 2). H-FMC may have a similar complementary value to FMD as L-FMC, which was shown to have further value than a composite value (FMD + L-FMD) by reducing false-positive and false-negative results when used independently of FMD in clinical applications.\textsuperscript{24,25} Not only does the presence of an H-FMC complicate the analysis of FMD but also it adds to the body of FMD research. The time course for dilation for both groups was similar, which seems to imply that NO and other dilating factors are secreted for a set amount of time in children and adolescents. BMI may also have an effect on the prevalence of vasoconstriction observed after occlusion, with H-FMC being a possible independent indicator of vascular change. Since obesity is often associated with endothelial dysfunction,\textsuperscript{7,8} the presence of an H-FMC may be an initial sign of vascular dysfunction, as there was a moderate correlation between H-FMC and FMD but not with BMI or BMI percentile. However, this hypothesis will need to be examined in future studies.

Previous research has investigated ancillary measures to FMD. L-FMC has been documented as a response of the radial artery during distal occlusion.\textsuperscript{18,25} This provides an accurate measure of resting arterial tone as it assesses the arterial response to resting shear stress.\textsuperscript{18,25} However, the technique reported for measuring L-FMC is vastly different compared with H-FMC. Weissgerber et al\textsuperscript{26} reported that L-FMC was observed in the radial artery but not in the brachial artery of healthy pregnant and non-pregnant women. It would appear that L-FMC in the brachial artery is not as uniform a response as the radial artery. A significant increase in brachial artery diameter during cuff occlusion was observed in healthy children and young adults.\textsuperscript{27} Not only does the imaged vascular bed differ but also the time course of the constriction is different. L-FMC measures constriction during blood flow restriction while H-FMC is the constriction observed immediately following occlusion release. Brachial artery H-FMC may have a comparable benefit on cardiovascular health assessment as L-FMC of the radial artery.

The present study is subject to a few limitations. Intra-arterial pressure and vasoconstrictor mediators were not directly measured. Since many of the participants were recruited from a pediatric weight management clinic (in addition to the community), the percentage of overweight and obese children in this study was much higher than in the general pediatric population. Future studies should investigate children with lower BMI values for the presence and rate of an H-FMC as well as the prevalence of an H-FMC in different adult populations. Investigation of health risk factors possibly associated with an H-FMC would also be beneficial. In addition, assessment of L-FMC would be beneficial when assessing FMD and H-FMC in future studies. A prospective study would be required to determine the validity and reliability of H-FMC as a risk factor for atherosclerosis and cardiovascular disease.

**CONCLUSION**

We observed an H-FMC in a majority of overweight and obese children and adolescents during reactive hyperemia. FMD was lower in children and adolescents who experienced this phenomenon, suggesting the presence of endothelial dysfunction. Whether H-FMC has any clinical implication is currently unknown. However, our findings suggest that this phenomenon should be considered when analyzing and interpreting FMD data. Future studies should examine the relationship of the presence of H-FMC with cardiovascular risk factors in children and adults.

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