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High-Flow Mediated Constriction in Adults Is Not Influenced by Biomarkers of Cardiovascular and Metabolic Risk

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Abstract

Purpose—During reactive hyperemia, the brachial artery in some individuals constricts prior to dilation. The aim of this study was to describe the frequency of high-flow-mediated constriction (H-FMC) in adults, and relationship of H-FMC to body composition and biomarkers of cardiovascular and metabolic risk.

Methods—246 adults (124 male, 122 female; 36±7 years) were assessed for H-FMC via ultrasound imaging of the brachial artery. Blood pressure, glucose, insulin, lipids, and body composition assessed via dual energy X-ray absorptiometer were collected for each participant. H-FMC was characterized as a 10-second average of maximal post-occlusion constriction. Independent t-tests were used to compare variables between H-FMC vs. Non-H-FMC individuals.

Results—H-FMC was observed in approximately 69% of adult participants (54 obese, 57 overweight, and 59 normal-weight). Total body mass (82.3±17.5 vs. 76.3±16.3 kg, $P=0.012$), fat mass (27.7±11.5 vs. 23.8±10.5 kg, $P=0.012$), body mass index [BMI: 27.7±4.9 vs. 26.1±5.0 kg/m², $P=0.018$], and low-density lipoprotein to high-density lipoprotein ratio [LDL/HDL: 2.41±1.03 vs. 2.09±0.72, $P=0.007$] were significantly higher in H-FMC compared to Non-H-FMC individuals. FMD (6.12±3.48 vs. 8.09±3.02%, $P<0.001$) was significantly lower in H-FMC subjects. However, when H-FMC was added to FMD there was no significant difference in brachial artery dilation between groups (7.57±3.69 vs. 8.09±3.02%, $P=0.250$).

Conclusion—Increased body mass, fat mass and BMI were associated with a greater H-FMC. When H-FMC is present, the FMD response to reactive hyperemia is significantly decreased. Since H-FMC has been observed to negatively affect FMD response to reactive hyperemia, it is suggested that H-FMC should be noted when analyzing and interpreting FMD data. H-FMC is an indicator of vascular change and may be an ancillary measure of endothelial health.

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Conflict of Interest

The authors have no conflicts of interest.

Keywords

Ultrasound; Reactive Hyperemia; Flow-Mediated Dilatation; Adults

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide.¹ In 2008 over 75% of the 17.3 million CVD deaths were attributed to manifestations of atherosclerosis, an underlying process that narrows and hardens blood vessels.¹ Endothelial dysfunction has been shown to be an important precursor in the atherosclerotic process.² Flow-mediated dilation (FMD) is widely used as a noninvasive method for measurement of endothelial health in children and adults.³

Previously, we have reported that 67% of children demonstrate vasoconstriction prior to a shear stress-induced nitric oxide (NO)-mediated dilation of the brachial artery during an FMD assessment.⁴ The opposing vasoconstrictor stimulus produces a biphasic response when plotting the diameter change of an artery in response to reactive hyperemia (Figure 1). This physiological response has been referred to as a high-flow-mediated constriction (H-FMC).^{4,5} It has been postulated that the observed vasoconstriction could result from a hemodynamic effect of increased blood flow leading to decreased transmural pressure and/or a shear stress-stimulated constrictor release, such as endothelin-1.⁴⁻⁸

This biphasic response of the brachial artery has previously been reported in adult males during reactive hyperemia.⁶ To our knowledge, no published work has reported on the frequency and magnitude of H-FMC observed at the brachial artery in a healthy adult male and female population or the impact of an H-FMC on reported peak FMD. Additionally, the relationship of biomarkers of cardiovascular and metabolic health and H-FMC has not been elucidated. The presence of an H-FMC could possibly negatively affect peak FMD such that the response to reactive hyperemia in healthy individuals appears similar to individuals with endothelial dysfunction and increased cardiovascular risk.⁹ The purpose of this study was to describe the frequency and magnitude of an H-FMC during reactive hyperemia in healthy adult males and females. In addition, we sought to examine the relationship of H-FMC to FMD, biomarkers of cardiovascular and metabolic risk as well as measures of body composition. It is hypothesized that an H-FMC affects peak FMD and is significantly correlated with body composition as well as known cardiovascular and metabolic risk factors.

Materials and Methods

Study Population

The 246 adults (124 males, 122 females) in this study were randomly sampled from two population based longitudinal studies investigating the development of obesity and insulin resistance and their interaction with associated cardiovascular risk factors.^{10,11} Subjects who smoked or were taking prescription medications, such as blood pressure, insulin, dyslipidemia or statin medication, were excluded from the study. The study protocol was

reviewed and approved by an institutional review board, and all participants gave written informed consent.

Physical Assessments

Measurements for height and weight were obtained with a standard stadiometer (Avrton, Model S100, Prior Lake, MN, USA) and electronic scale (ST Scale-Tronix, Serial No. 5022-8893, White Plains, NY, USA), respectively. Body mass index (BMI) was calculated as weight in kilograms (kg) divided by height in meters-squared (m^2).

Dual-energy X-ray Absorptiometry

Body composition was measured using a dual energy X-ray absorptiometer (DXA) (GE Healthcare Lunar iDXA, platform version 13.6, GE Healthcare Lunar, Madison, Wisconsin, USA). The total body scan was analyzed using the enCore™ CoreScan software. Standard imaging and positioning protocols were implemented while subjects were fasted and hydrated. Proprietary software algorithms from the manufacturer were used to segment and analyze the body into upper and lower extremities using the standard regions of interest (ROI) and then combined for each of the measures of interest: lean mass, fat mass, visceral adipose tissue mass (VAT), android fat, gynoid fat, subcutaneous (subQ) fat, and bone mass. Android fat was calculated between the ribs and the top of the pelvis, while the gynoid fat was determined from the upper thighs to the top of the pelvis. The subQ fat was then calculated as the android fat–VAT mass. Each subject's measure of interest was reported in kilograms (kg).

Glucose, Insulin and Lipid Profile Assessment

All assays were conducted with standard procedures at a Centers for Disease Control and Prevention-certified laboratory. Fasting blood samples were collected for glucose, insulin and lipid levels including total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL). The LDL/HDL ratio was reported for each subject, because a higher ratio has been related to increased coronary heart disease risk.¹² Homeostatic model assessment (HOMA) of insulin resistance and β -cell function were calculated using fasting plasma insulin and fasting plasma glucose.¹³

Vascular Assessments

Vascular assessment was conducted for all participants following at least 8 hours of fasting. Subjects were required to refrain from caffeine ingestion within 4 hours prior to testing and avoid strenuous exercise or physical activity 24 hours prior to the study visit. Subjects were tested in a quiet, climate-controlled room (22–23°C). Resting blood pressure was recorded using an automated sphygmomanometer (Colin BP-8800, Colin Medical Instruments Corp., San Antonio, TX, USA) on the right arm prior to FMD assessment. A specialized occlusion cuff (D.E. Hokanson, Inc., Bellevue, WA) was placed approximately five centimeters (cm) distal to the antecubital space 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 ultrasound scanner (Acuson, Sequoia 512, Siemens Medical Solutions USA, Inc., Mountain View, CA, USA) 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 occlusion cuff on the left forearm was then inflated to a suprasystolic pressure level of 200 mmHg and maintained for 5 minutes. Vascular images were captured 20-seconds prior to cuff release until 3 minutes post-cuff release and were digitized and stored on a personal computer for later analysis using an electronic wall-tracking software program (Vascular Research Tools 5, Medical Imaging Application, LLC, Iowa City, IA, USA).

A trained sonographer performed all digital ultrasound image capturing and analysis. The coefficient of variation was 11.1% in our laboratory when FMD was measured 7 days apart, demonstrating good reproducibility. Vascular images were assessed for brachial artery baseline diameter, maximal blood flow, peak shear and subsequent brachial artery constriction and dilation. The baseline brachial artery measurement was defined as a 10-second average just prior to blood pressure cuff release, i.e. occlusion baseline, to negate any low-flow mediated constriction that may occur during occlusion. Maximal blood flow (m/s) was defined as the largest 10-second average rate of blood flow following 3 seconds post-cuff release. Peak shear was used to estimate the greatest shear stress during the same timeframe as maximal blood flow. Peak shear was calculated as a 10-second average during post occlusive reactive hyperemia, which was calculated as blood flow velocity (q) divided by arterial diameter (D). High-flow-mediated constriction (H-FMC) was observed and characterized using a 10-second average of the lowest point from baseline brachial artery diameter following 3-seconds post cuff release and considered present if the percent change was less than -0.1% (Figure 1). Peak dilation during each procedure was defined as the 10-second average of the greatest percent change from baseline brachial artery diameter. The time that elapsed between cuff release and greatest constriction in H-FMC individuals was recorded as time-to-trough FMC (TTT FMC). There was no observed constriction in Non-H-FMC individuals following cuff release, so TTT FMC was not applicable for the Non-H-FMC group. The time between cuff release and peak dilation was recorded as time-to-peak FMD (TTP FMD).

Statistical Analysis

All statistical analysis was performed using IBM SPSS Statistics 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Descriptive statistics were conducted for the two groups on anthropometric, biomarkers of cardiovascular and metabolic risk, and FMD measurements. Allometric scaling was performed for H-FMC and FMD related to baseline brachial artery diameter as proposed by Atkinson et al.^{14,15} Independent t-tests were used to compare variables between subjects who demonstrated an H-FMC vs. Non-H-FMC. An alpha value of 0.05 was denoted as statistically significant. A correlation matrix was then constructed which included significant body composition, biomarkers of cardiovascular and metabolic risk, and FMD measures that were differing between H-FMC and Non-H-FMC groups at a significance of $P < 0.05$. A subgroup analysis of significant variables between groups was conducted within genders.

Results

Mean demographic characteristics of adults are presented in Table 1. Adults ranged in age from 18 to 46 years old. Of the 246 adults examined in this study, 170 (69.1%) displayed an H-FMC. A greater magnitude of H-FMC was positively associated with lower peak FMD ($r=0.238$, $P<0.001$). No differences were noted between the two groups for gender composition ($P=0.114$), however, 73% of males and 65% of females displayed an H-FMC. Height, VAT mass and body fat percentage were not different between groups. Body mass index of the study population ranged from 17.2 to 39.3, with 79.4% of obese individuals, 65.5% of overweight individuals and 64.8% of normal-weight individuals displayed an H-FMC. Total body mass, BMI, fat mass, subQ fat, android fat, gynoid fat and bone mass were significantly higher in H-FMC adults compared to Non-H-FMC adults. Total body mass ($r=-0.127$, $P=0.047$) and BMI ($r=-0.140$, $P=0.028$) were negatively associated with H-FMC. Fat mass ($r=-0.119$, $P=0.063$), subQ fat ($r=-0.123$, $P=0.059$), android fat ($r=-0.091$, $P=0.164$) and gynoid fat ($r=-0.111$, $P=0.089$) were not significantly associated with H-FMC.

A subgroup analysis within genders was conducted on significantly correlated variables between H-FMC and Non-H-FMC groups. There was not a significant correlation within males for total body mass ($r=-0.039$, $P=0.669$), BMI ($r=-0.059$, $P=0.515$), fat mass ($r=-0.023$, $P=0.802$), or subQ fat ($r=-0.053$, $P=0.567$) with H-FMC. However, significant correlations were found for total body mass ($r=-0.205$, $P=0.024$), BMI ($r=-0.205$, $P=0.024$), fat mass ($r=-0.217$, $P=0.016$), and subQ ($r=-0.202$, $P=0.030$) with H-FMC in females.

The comparison of the blood pressure and blood profile between H-FMC and Non-H-FMC groups is represented in Table 2. There was no significant difference between groups for systolic and diastolic blood pressure, glucose, insulin, HOMA, total cholesterol, triglycerides, HDL or LDL. However, LDL/HDL was significantly elevated in H-FMC subjects compared to Non-H-FMC subjects (Table 2), but not significantly correlated to H-FMC ($r=-0.111$, $P=0.087$).

Table 3 displays the study population's vascular measures. Baseline brachial artery diameter in H-FMC individuals was not significantly different from Non-H-FMC individuals. In H-FMC individuals, the average TTT FMC was 10.2 ± 4.9 seconds. Peak shear, maximal flow and TTP FMD were not significantly different between H-FMC and Non-H-FMC adults. Flow-mediated dilation response was significantly greater in Non-H-FMC individuals and did not change when using allometric scaling. However, when the magnitude of H-FMC was added to FMD in the H-FMC group, there was no longer a significant difference in response to reactive hyperemia (7.57 ± 3.69 vs. 8.09 ± 3.02 , $P=0.250$). Peak FMD was negatively correlated with total body mass ($r=-0.197$, $P=0.002$), and bone mass ($r=-0.279$, $P<0.001$). Gynoid fat ($r=0.129$, $P=0.048$) was positively associated with peak FMD.

Discussion

The purpose of the present study was to examine the prevalence of a flow-mediated constriction during reactive hyperemia in healthy adults and to investigate potential

differences of body composition, glucose, insulin, HOMA, lipids and FMD measures relative to H-FMC presence and magnitude. We observed that approximately 69% of the study population displayed H-FMC. Individuals that displayed an H-FMC had a lower peak FMD from an occlusion baseline compared to individuals not displaying an H-FMC. Also, H-FMC individuals had a significantly greater total body mass, BMI, fat mass, bone mass, android fat, gynoid fat, subQ fat and LDL/HDL compared to Non-H-FMC individuals.

Previously we demonstrated that H-FMC prevalence in children and adolescents was approximately 67%,⁴ which is very similar to the prevalence observed in adults in the present study. The significant presence of an initial constrictive response to reactive hyperemia in these studies should alert researchers utilizing FMD methodology to the possibility of a blunted peak FMD when using a baseline artery diameter measured before occlusion cuff release. However, when an addition of the percent of H-FMC to peak FMD is applied, the difference in peak FMD between the two groups is negligible. This finding is consistent with our previous research in children and adolescents.⁴ Addition of this H-FMC may be a better measure of true NO-mediated dilation, since dilation would be assessed from the lowest artery diameter. Thus, researchers could use a baseline diameter measure that occurs after the occlusion cuff has been released. It would appear that an appropriate timeframe for calculation of a 10-second average baseline diameter following occlusion would be between 5 to 15 seconds, since the average TTT FMC was at 10 seconds. This is in contrast to previous research showing that using a universal baseline diameter calculated following occlusion cuff did not produce practical differences in FMD.¹⁶ Flow-mediated dilation has been utilized as a measure of endothelial function and predictor of atherosclerotic development²⁴ and cardiovascular events in asymptomatic subjects.²⁵ A larger FMD response is generally associated with healthy endothelial function. In the current study, Non-H-FMC adults displayed brachial artery FMD levels similar to levels of healthy control subjects in other studies^{23, 26} while H-FMC individuals had a significantly lower FMD response. Even though the increased magnitude of an H-FMC was mildly associated with lower FMD response, it is unclear whether the H-FMC is an independent risk factor of endothelial dysfunction.

Age, blood pressure, peak shear, maximal flow and baseline brachial artery diameter, were not significantly different between H-FMC and Non-H-FMC groups, also consistent with prior work in children.⁴ However, contrary to the findings in children and adolescents, total body mass and BMI were significantly higher in the adult H-FMC group compared to the Non-H-FMC group. Since body composition was assessed by DXA in the current study and not in our previous research, more precise weight-related factors were found to be significantly higher in the adult H-FMC group: fat mass, android fat, gynoid fat, subQ fat and bone mass. These data would suggest that body composition has a greater influence on H-FMC in adults compared to other cardiovascular and metabolic risk factors since the LDL/HDL ratio was the only significant cardiovascular or metabolic factor significantly different between groups. However, the correlation of total body mass and BMI with H-FMC are relatively weak. Previous research has demonstrated reduced FMD in abdominally obese individuals compared to lean individuals, suggesting impaired endothelial function associated with android fat.^{17 (23)} Furthermore, modest increases, in visceral fat as opposed to subQ fat, have resulted in impaired endothelial function.¹⁸ However, android fat, gynoid

fat and subQ fat were significantly elevated in the H-FMC group in the current study. Historically, gynoid and subQ fat have been considered to be lower health risks compared to VAT and android fat.¹⁹ Lower extremity adiposity, specifically larger subQ thigh fat, has even been associated with lowering potential health risks.²⁰ A positive correlation was found between gynoid fat and FMD in the current study, which is consistent with the notion of gynoid fat lowering potential risk. An increased bone mass was also observed in the H-FMC group than the Non-H-FMC group. Since a greater percentage of obese subjects were in the H-FMC group, it would seem appropriate for there to be a significant difference in bone mass between groups due to the well-established positive effect that increased mechanical loading, via body weight, has on bone formation.²¹ Overweight and obesity has been associated with enhanced endothelin-1 mediated vasoconstriction²² and a large percentage of obese individuals in the current study displayed an H-FMC. It may be possible that an H-FMC in some adults occurs due to increased presence of a flow-mediated constriction factor following cuff release. Since H-FMC was significantly correlated to an increased BMI and body mass, it could be possible that an enhanced endothelin-1 mediated response is partially involved in the H-FMC. However, endothelin-1 was not measured and both BMI and body mass have a relatively weak correlation with H-FMC.

Another point of interest in the current research is the lack of significant differences between groups for many known cardiovascular risk factors. Previous research has reported that many of the known cardiovascular risk factors, such as dyslipidemia,²⁷ diabetes mellitus,²⁸ hypertension²⁹ and central obesity (waist circumference and VAT)^{18,30,31} can alter FMD. Of the known cardiovascular risk factors, the LDL/HDL ratio was the only non-weight-related factor statistically significant between the H-FMC and Non-H-FMC groups. However, a larger LDL/HDL ratio has been reported to have a significant associated with increasing BMI.³² Therefore, it may be possible for the development of abdominal obesity to precede a decline in lipids or presence of other cardiovascular risk factors.

In the current study, there was homogeneity of the study participants for many of the cardiovascular risk factors due to their healthy control status in the overarching study. This homogeneity of participants could be interpreted as a limitation. On the contrary, an H-FMC may be an independent factor for cardiovascular risk, because homogeneity of known cardiovascular risk did not hinder the observation of H-FMC and Non-H-FMC responses to reactive hyperemia. Instead, there were significant correlations between H-FMC, total body mass and BMI with many other weight-related factors trending toward significance. Previous research has suggested that central obesity appears to proceed the appearance of hypertension, glucose abnormalities, and dyslipidemia.³³ Thus, H-FMC could possibly be either a complimentary health assessment tool to FMD or an insignificant artifact. A greater understanding of H-FMC could be achieved with future longitudinal research that included H-FMC magnitude with FMD methodology.

Of interest, when a subgroup analysis based on gender was conducted, all of the H-FMC correlations with body composition were not significant in males, but were significant in females. This could be due to hormonal differences expected between genders. However, the significant correlations found in females between body composition and H-FMC remained weak.

It has been posed that FMD, and subsequently H-FMC, needs to be scaled to account for the reliance on baseline diameter in FMD calculation.^{14,15} However, when allometric scaling was performed in the current study, a change in significance between groups for FMD was not observed (Table 3). Furthermore, allometric scaling of H-FMC did not adhere to the criteria outlined in previous research.^{14,15}

Historically, the benefit of FMD testing is the simplistic and noninvasive nature of the procedure. Taking into account the presence of an H-FMC does complicate the analysis of FMD, as does allometric scaling,^{14,15} but it also adds to the body of FMD research. The time to reach peak dilation for both groups is similar, which seems to imply that endothelial NO and other dilating factors are secreted for a set amount of time in adults. Since body mass and BMI seem to have a significant, but weak correlation with the prevalence of vasoconstriction observed post-occlusion (Figure 2), H-FMC may be a possible independent indicator of vascular remodeling. Obesity could be an extrinsic factor associated with endothelial dysfunction, while an H-FMC may be an intrinsic sign of vascular dysfunction. However, this hypothesis will need to be examined in future studies.

The present study is subject to a few limitations. Intra-arterial pressure and vasoconstrictor mediators were not directly measured. The possibility of autonomic nervous system contribution to H-FMC was also not investigated. The cross-sectional nature of the study also does not answer the reproducibility of the H-FMC response to blood flow manipulation. Future studies could investigate both children and adult cohorts for the reproducibility in presence and magnitude of an H-FMC. Also, at-risk and diseased populations could be investigated for prevalence of an H-FMC. The investigation of inflammatory and other ancillary blood markers associated with an H-FMC would also be beneficial. A prospective study would be required to determine the reproducibility, validity, and physiological modification of an H-FMC as a risk factor for atherosclerosis and cardiovascular disease.

Conclusion

A high-flow-mediated constriction occurs in a majority of healthy adults during reactive hyperemia and FMD was lower in adults who experience H-FMC, suggesting the presence of endothelial dysfunction. Since a greater percentage of children, adolescents⁴ and adults seem to display an H-FMC following occlusion, a post-occlusion baseline may be worth consideration in future FMD technique. Increased body mass and BMI were associated with a greater H-FMC, however, it is currently unknown whether H-FMC has any clinical implications. Nevertheless, our findings suggest that this H-FMC should be considered when analyzing and interpreting FMD data. Future studies should examine the reproducibility, validity, and reliability of H-FMC and changes in body composition, specifically body mass and fat mass, on H-FMC magnitude in children and adults.

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Figure 1.

A comparison of a Flow-Mediated Dilation (percent change in brachial artery diameter from baseline) response in H-FMC (◆) and Non-H-FMC (◇) adults.

Figure 2.

A scatterplot of the relationship between BMI and H-FMC in adults.

Table 1

Physical Characteristics

	H-FMC	Non-H-FMC	P-value
<i>n</i> (% male)	170 (54%)	76 (43%)	
Age, years	36.3±7.0	36.8±6.6	0.597
Height, cm	172.0±11.7	170.9±11.7	0.483
Total body mass, kg	82.3±17.5	76.3±16.3	0.012
Body Mass Index, kg/m ²	27.7±4.9	26.1±5.0	0.018
Bone mass, kg	3.2±0.7	3.0±0.7	0.026
Lean body mass, kg	51.4±11.4	48.7±11.5	0.086
Fat mass, kg	27.7±11.5	23.8±10.5	0.012
Body fat, %	34.2±10.3	32.1±10.6	0.145
VAT mass, kg	0.89±0.71	0.74±0.68	0.122
Android fat, kg	2.5±1.3	2.1±1.2	0.029
Gynoid fat, kg	4.6±1.7	4.1±1.6	0.037
SubQ, kg	1.6±0.8	1.4±0.8	0.023

Note: Values are means±SD; *n*, number of participants/group; DXA, dual energy x-ray absorptiometry; FMC – High-Flow Mediated Constriction

Non-FMC – No High-Flow Mediated Constriction

Table 2**Blood Profile**

	H-FMC	Non-H-FMC	P-value
SBP, mmHg	113±13	113±13	0.845
DBP, mmHg	70±10	70±11	0.698
Glucose, mg·dL ⁻¹	101±13	99±11	0.205
Insulin, mU/l	7.7±7.1	6.4±5.7	0.148
HOMA1-IR	35.9±36.0	28.7±26.9	0.125
HOMA1-%B	1.5±1.3	1.3±1.1	0.201
Triglycerides, mg·dL ⁻¹	130±103	117±103	0.407
Total Cholesterol, mg·dL ⁻¹	183±36	178±39	0.306
HDL, mg·dL ⁻¹	49±14	51±12	0.235
LDL, mg·dL ⁻¹	109±32	103±29	0.125
LDL/HDL	2.41±1.03	2.09±0.72	0.007

Note: SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; H-FMC – High-Flow Mediated Constriction

Non-FMC – No High-Flow Mediated Constriction

Table 3

Measures of vascular function

	H-FMC	Non-H-FMC	P-value
Brachial Artery Diameter, mm	3.80±0.74	3.65±0.64	0.095
TTP FMD, sec	56.1±25.6	52.0±18.7	0.215
Peak Shear, sec ⁻¹	267.0±120.5	255.1±97.1	0.450
Maximal Flow, m/s	0.98±0.39	0.92±0.28	0.257
Flow-Mediated Constriction, %	-1.45±1.18	1.40±1.30	<0.001
Flow-Mediated Dilation, %	6.12±3.48	8.09±3.02	<0.001
Scaled * Flow-Mediated Dilation, %	6.56±3.73	8.67±3.23	<0.001

Note: Values are means±SD;

Maximal flow (m/s) is a measure of average blood flow following cuff release.

TTP FMD - Time-to-Peak FMD from cuff release to peak dilation

FMD – Flow Mediated Dilation

H-FMC – High-Flow Mediated Constriction

Non-FMC – No High-Flow Mediated Constriction

* Scaled Flow-Mediated Dilation, % refers to Allometric scaling^{14,15}