



## Vascular Function in Fibromuscular Dysplasia

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### Abstract

**Background:** There have been no studies to date on the pathophysiologic mechanisms of how fibromuscular dysplasia (FMD) affects vascular function. Due to the perturbations in the blood vessel wall and the propensity for stenosis, dissection, and aneurysms seen in arteries with FMD, subjects with FMD may have impairment in endothelial function and abnormalities in arterial compliance.

**Methods:** Twenty-seven subjects with documented FMD of the renal and/or carotid arteries and ten age, gender, and ethnicity matched healthy control subjects were recruited for this study. Predictors of cardiovascular disease including endothelial function, brachial-ankle pulse wave velocities (baPWVs), ankle-brachial indices (ABIs), and carotid artery intima-media thickness (IMT) were evaluated.

**Results:** For the FMD population, endothelium dependent flow-mediated vasodilation of the brachial artery was  $15.91 \pm 8.69\%$  ( $p < 0.001$ ). Nitroglycerin produced a significant  $27.69\%$  ( $p = 0.04$ ) increase in time-averaged, volumetric flow through the brachial artery and resulted in an increase in brachial artery diameter from  $2.66 \pm 0.42$  mm to  $3.37 \pm 0.51$  mm,  $p < 0.01$ . The mean baPWV for all ages was  $1324.37 \pm 247.55$  cm/sec, the mean ABI was  $1.16 \pm 0.09$ , and the mean distal common carotid artery far wall IMT was  $0.64 \pm 0.15$  mm.

**Conclusion:** This is the first study to evaluate vascular function in FMD. In this small population, FMD was not associated with endothelial dysfunction, impaired arterial compliance, increased carotid artery IMT, or decreased ABIs. A prospective larger study will be required to confirm these findings.

**Keywords:** Fibromuscular dysplasia; Endothelium; Nitroglycerin; Brachial artery

### Introduction

#### Fibromuscular dysplasia

Fibromuscular dysplasia (FMD) is a nonatherosclerotic, noninflammatory vascular disease that primarily affects women between the ages of 18-60 years old, but may also be seen in men, older individuals, or children [1,2]. The prevalence of FMD in the general population is not known. The presence of renal artery FMD has been estimated to be as high as 4 per 100 adults [3-5]. Although recent evidence suggests that FMD is more common than previously thought [6], most physicians believe that FMD is a rare disease [7]. There are 3 pieces of evidence which suggest that there is a higher prevalence of FMD in the general population: 1) approximately 4% of healthy renal donors are found to have FMD [7-9]; 2) FMD is frequently found when imaging studies such as computed tomography angiography (CTA), magnetic resonance angiography (MRA), and duplex ultrasound are performed for reasons unrelated to FMD; 3) FMD has

been diagnosed in patients visiting a vascular office for other reasons (i.e. lower extremity swelling or venous thrombosis) [6].

FMD has been reported in almost every arterial bed, but is most commonly seen in the renal and extracranial carotid and vertebral arteries ( $\approx 65\%$  of cases) [10]. The etiology of FMD is unknown but a genetic basis is suspected [11]. When FMD affects the renal arteries, it may cause hypertension, renal artery aneurysm, dissection and renal infarction. When it affects the carotid or vertebral arteries it may cause transient ischemic attack, stroke, aneurysm, and dissection. A large number of patients with cerebrovascular FMD are asymptomatic or have only minimal symptoms such as pulsatile tinnitus due to turbulence of blood flow [12].

In contrast to atherosclerosis, which occurs at the origin or proximal portion of a given artery in older patients with typical cardiovascular risk factors, fibromuscular dysplasia occurs in the middle or distal arterial segments in patients with few or no cardiovascular risk factors [13]. There are three major types of FMD according to histopathological classification: medial fibroplasia, intimal fibroplasia, and adventitial (periarterial) fibroplasia [14-16]. In medial fibroplasia, the most common subtype of FMD accounting for 80-90% of all cases, the alterations in the vascular wall may include the

loss of internal elastic membrane, alternating areas of thinned media, extensive collagen deposition, and smooth muscle cell hyperplasia giving the angiographic appearance of a string of beads [12]. However, the recently published state of the science paper on FMD has suggested an angiographic classification scheme since histopathology is rarely available [11]. The "string of beads" type of FMD which was formally called medial fibroplasia is now called multifocal FMD. The focal concentric or tubular stenosis formerly called intimal fibroplasia is now called focal FMD [11].

There have been no studies published to date on how fibromuscular dysplasia affects vascular function. It is unknown if there are abnormalities present in sites not yet clinically or angiographically affected with FMD as there are with atherosclerosis. In order to determine if there are abnormalities in various parameters of vascular function, we assessed endothelial function, arterial compliance, ankle-brachial indices (ABIs), and carotid artery intima-media thickness (IMT) in a cohort of patients with FMD and in age and gender matched controls.

## Materials and Methods

Predictors of cardiovascular disease including endothelial function, arterial compliance, carotid artery IMT, and ABIs were evaluated in patients with documented FMD of the renal and/or carotid arteries and in age, gender, ethnicity, and blood pressure matched healthy control subjects.

## Subjects

Twenty-seven subjects with FMD and ten age, gender, and ethnicity matched healthy control subjects were recruited for this study. Subjects underwent a complete medical history and physical examination. All subjects had FMD in at least one vascular bed, typically the renal and/or carotid arteries. The FMD was diagnosed with duplex ultrasound, CT angiography, MR angiography and/or catheter based angiography.

All subjects with FMD had either multifocal FMD (more than 90%) demonstrating the typical string of beads appearance or focal FMD demonstrating a focal band like constriction or tubular narrowing of an artery. The Institutional Review Board of the Mount Sinai Hospital approved the protocol, and all participants provided written informed consent.

## Study procedures

Subjects were studied in the morning, in a quiet, temperature-controlled, dimly lit room after resting supine for a minimum of ten minutes. All subjects fasted for a minimum of 12 hours and did not use any vasoactive medications, nitrates, or caffeine for at least 12 hours prior to the test. Only non-smokers were enrolled in the study. High-resolution B-mode ultrasonography was performed using a GE Logic E9 (GE Healthcare, Wauwatosa, WI) ultrasound machine equipped with a 7-10 MHz linear array transducer. The video output signal of the ultrasound machine was connected to a computer equipped with a data translation frame-grabber video card (Dataviz, Milford, CT). A resting electrocardiogram (ECG) was performed and was directly connected onto this computer using GE's CardioSoft 12-lead ECG analysis software program (GE Healthcare, Wauwatosa, WI). The "R" wave on the electrocardiogram served as a trigger to acquire ultrasound ten consecutive frames at end-diastole. All ultrasound post-processing image analysis was performed with

commercially available software, Medical Image Analysis 5.0 (Medical Imaging Applications, Iowa City, Iowa). This software application utilizes both edge-detection and wall-tracking software, which is independent of investigator bias. For carotid artery IMT analysis, independently validated, signed error of mean IMT is  $-0.007 \pm 0.07$  mm and independently validated diameter errors for brachial artery measurements are  $0.034 \pm 0.066$  mm.

## Endothelial function

The methods used to determine endothelial function were performed according to published guidelines [17].

**Imaging technique:** Each subject's arm was positioned at an angle of 70 to 90 degrees from the torso and the wrist was placed half prone. The brachial artery was imaged longitudinally, just proximal to the antecubital fossa, with the transducer adjusted in order to obtain clear B-mode images of the near and far wall intima. During the image acquisition, anatomic landmarks such as veins and fascial planes were noted to assist in maintaining the same image of the artery throughout the study. After baseline images of the brachial artery were obtained, reactive hyperemia was induced by inflation and then deflation of a 2.5 inch wide sphygmomanometric blood pressure cuff which was placed on the upper arm (above the scanned part of the artery) and inflated to suprasystolic pressure ( $\sim 220$  mmHg) for five minutes. The ultrasound transducer remained in position over the brachial artery to ensure complete absence of blood flow through the brachial artery during cuff inflation. Upon cuff release, reactive hyperemia causes a transient increase in blood flow throughout the brachial artery below the blood pressure cuff. Flow-mediated endothelium-dependent vasodilation of the brachial artery was determined by acquiring ten sequential end-diastolic gray scale images of the brachial artery exactly one minute after cuff deflation.

After a ten-minute recovery period, nitroglycerin-mediated, endothelium-independent vasodilation was performed. All patients with a systolic blood pressure greater than 100 mmHg were eligible to receive nitroglycerin,  $n=27$ . One patient refused nitroglycerin. The brachial artery was imaged before and three minutes after administration of 0.4mg of sublingual nitroglycerin to measure peak diameter in the same segment and plane as for the endothelium-dependent portion of the study. Gray-scale longitudinal and mid vessel pulsed Doppler sample images of the brachial artery were acquired prior to and three-minutes post nitroglycerin administration.

**Analysis technique:** Two ultrasound readers (NW & IM) measured the brachial artery diameter in a blinded fashion. The inter- and intra-observer variability of this technique has previously been described [18]. Volumetric flow, Q, of the brachial artery was calculated by integrating the area under the velocity spectral waveform and dividing by the time required to arrive at the time-averaged velocity. Mean flow was calculated by multiplying the time-averaged velocity by the mean area of the brachial artery lumen.

## Carotid artery intima-media thickness

Gray-scale longitudinal images of the right and left far wall distal common carotid artery (CCA) and IMT was measured by two observers from the intima-lumen border to the media-adventitia border over a 2-centimeter segment of the distal CCA far wall [19]. The IMT was reported as an average of the ten images.

### ABI and PWV measurements

ABIs and brachial to ankle pulse-wave velocity (baPWV) were measured simultaneously using a volume-plethysmographic apparatus (form VP-1000, Omron Healthcare, Bannockburn, IL). This instrument records ABI's, PWV, blood pressure, electrocardiogram, peripheral tracings, and heart sounds simultaneously. Electrocardiogram electrodes were placed on both wrists, a microphone for detecting heart sounds was placed on the left edge of the sternum, and blood pressure cuffs were wrapped on both brachia and ankles. The blood pressure cuffs were connected to a plethysmographic sensor that determines volume pulse form and an oscillometric pressure sensor that measures blood pressure. Pulse volume waveforms were recorded using a semiconductor pressure sensor with the sample acquisition frequency set at 1,200 Hz. The sampling time for the pulse volume waveforms was 10 seconds using automatic gain analysis and quality adjustment. The distance between sampling points of the baPWV was calculated automatically according to the height and weight of the subject. The baPWV was determined in cm/sec. All pulse volume recordings were automatically stored. ABIs were calculated based on the highest systolic ankle pressure in each leg and the greatest systolic arm pressure.

### Statistical analysis

The primary endpoint was endothelium-dependent flow mediated vasodilation of the brachial artery assessed by high-resolution ultrasonography. Taking into account the study design, the sample sizes for the study were calculated using estimates of the difference in endothelium-dependent flow-mediated vasodilation between groups. Based on an estimated standard deviation of 3%, a power of 0.9, and  $\alpha$  error of 0.05 we needed 9 subjects per group in order to detect a 5% difference and 14 subjects per group in order to detect a 4% difference in vasodilation. Groups were initially defined as FMD subjects with no high blood pressure, FMD subjects with high blood pressure, healthy controls with no risk factors, and control subjects with hypertension.

Descriptive measures and experimental measures are reported as means  $\pm$  standard deviation. Experimental measures, including flow-mediated endothelium dependent and nitroglycerin mediated endothelium independent vasodilation for each subject group were compared using a paired t test. Statistical significance was accepted at the 95% confidence level ( $p < 0.05$ ). Analysis of variance (ANOVA) and Pearson correlations were used to assess the association of the primary endpoint (endothelial dependent vasodilation) with nominal and numeric confounding factors, respectively. Factors observed to have a significant or nearly significant association ( $p \leq 0.1$ ) were considered potential confounding factors allowed to compete in a multivariable regression analysis to identify independent predictors of the primary endpoint. The imaging measures were then added to the regression model containing confounding factors to assess the association of the imaging measure with the dependent variable adjusted for the confounding factors. All statistics were performed with SPSS Statistics 17 (IBM Corporation, Armonk, NY) and Minitab 15.0 (Minitab Inc, State College, PA).

## Results

### Demographics

Twenty-seven subjects with FMD were enrolled, 26 female (96.3%) with a mean age of  $49.09 \pm 9.90$  years. Patient demographics including

cardiovascular risk factors and pharmacological history are described in Table 1. Ten age, gender, and ethnicity matched healthy control female subjects with no cardiovascular risk factors were enrolled with a mean age of  $44.25 \pm 8.25$  years. All subjects with FMD had FMD of the carotid arteries ( $n=16, 59.3\%$ ) and/or renal arteries ( $n=17, 62.7\%$ ). Six (22.2%) subjects had FMD in both the carotid and renal arteries and seven (25.9%) had FMD in other blood vessels in addition to the carotid and/or renal arteries. There were 13 FMD subjects with hypertension (48.1%), 13 with hyperlipidemia (48.1%), and all subjects were non-diabetic, non-smokers. Patient medications were recorded.

Variable	N (%)
Gender (female)	26 (96.3%)
Age (years)	$49.09 \pm 9.90$
Race (Caucasian)	24 (88.9%)
Hypertension	13 (48.1%)
Hyperlipidemia	13 (48.1%)
Vessels Affected	17 (62.7%)
Renal artery	16 (59.3%)
Carotid artery	6 (22.2%)
Renal and carotid arteries	7 (25.9%)
Other vessels	
Medications	25 (92.6%)
Aspirin	9 (33.3%)
Statin	7 (25.9%)
Beta Blocker	3 (11.1%)
Ace Inhibitor	5 (18.5%)
Angiotensin II Receptor Blocker	1 (3.7%)
Calcium Channel Blocker	

Table 1: FMD study population demographics.

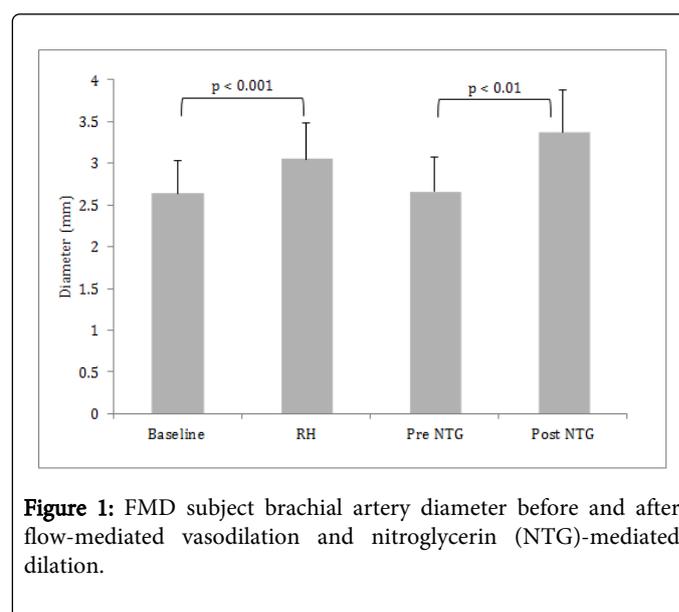
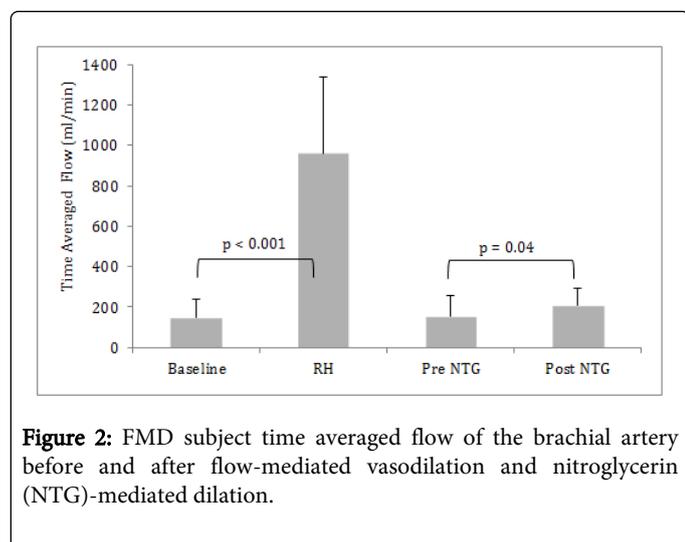


Figure 1: FMD subject brachial artery diameter before and after flow-mediated vasodilation and nitroglycerin (NTG)-mediated dilation.

### Vascular function studies

**Endothelium-Dependent and Independent Vasodilation:** For the FMD population, baseline brachial artery diameter was  $2.64 \pm 0.38$  mm and increased to  $3.05 \pm 0.44$  mm 60 seconds after deflation of the sphygmomanometric blood pressure cuff for an endothelium dependent flow-mediated vasodilation of  $15.91 \pm 8.69\%$ ,  $p < 0.001$  for the change (Figure 1). The absolute mean difference between the two ultrasound readers for measuring the brachial artery diameter at rest was  $3 \pm 0.031$  micrometers. Brachial artery volumetric flow for the FMD subjects increased from  $135.30 \pm 48.12$  ml/min at baseline to  $959.09 \pm 378.36$  ml/min ten seconds following deflation of the sphygmomanometric blood pressure cuff,  $p < 0.001$  for reactive hyperemia (Figure 2). Nitroglycerin produced a significant 27.69% ( $p = 0.04$ ) increase in time-averaged, volumetric flow through the brachial artery (Figure 2) and resulted in an increase in brachial artery diameter from  $2.66 \pm 0.42$  mm to  $3.37 \pm 0.51$  mm,  $p < 0.01$  (Figure 1). Nitroglycerin-mediated dilation was  $27.49 \pm 8.8\%$  in this cohort.



**Figure 2:** FMD subject time averaged flow of the brachial artery before and after flow-mediated vasodilation and nitroglycerin (NTG)-mediated dilation.

Endothelium dependent vasodilation was compared for FMD subjects without hypertension, FMD subjects with hypertension, and

	Age (years)	Baseline Diameter (mm ± SD)	RH Diameter (mm ± SD)	Vasodilation (% ± SD)
FMD (no HTN), n=14	43.14 ± 6.94	2.61 ± 0.43	3.00 ± 0.50	15.12 ± 10.72
FMD (HTN), n=13	55.31 ± 8.34	2.60 ± 0.39	2.98 ± 0.45	15.03 ± 9.87
Healthy, n=7	45.30 ± 8.97	3.07 ± 0.53	3.46 ± 0.60	12.86 ± 7.08

**Table 2:** Comparison of endothelial-dependent flow-mediated brachial artery vasodilation for FMD subjects without hypertension, FMD subjects with hypertension, and healthy controls.

In this study, specific markers evaluated included endothelium-dependent and independent vasodilation, arterial compliance, carotid artery IMT, and ABIs. The standard FMD population was well represented in this study. Of the 27 patients with FMD that were enrolled, 96% were women with a mean age of  $49.1 \pm 9.9$  years. 63% of subjects had FMD of the renal artery and 59% had FMD of the carotid artery. These demographics are similar to those reported in the United States FMD Registry study [10].

healthy controls (Table 2). The mean age for the FMD group without hypertension was  $43.14 \pm 6.94$  years, FMD with hypertension was  $55.31 \pm 8.34$  years, and healthy controls was  $45.30 \pm 8.97$  years. There was no difference between the resting brachial artery diameter between the two groups with FMD ( $p > 0.05$ ). There was a difference between the non-hypertensive FMD population and the healthy controls ( $p < 0.01$ ) and the hypertensive FMD population and the healthy controls ( $p < 0.01$ ). The percent vasodilation was not significant between any of the groups ( $p > 0.05$ ).

**Other Vascular Measures:** In this cohort of subjects with FMD the mean baPWV for all ages was  $1324.37 \pm 247.55$  cm/sec (Figure 3), the mean ABI was  $1.16 \pm 0.09$ , and the mean distal common carotid artery far wall IMT was  $0.64 \pm 0.15$  mm. No subjects had an ABI below 0.90, one patient had IMT measurements above 0.87 mm bilaterally, and two patients had IMT measurements above 0.87 mm unilaterally. Heterogeneous atherosclerotic plaque was visualized in the carotid arteries in four subjects.

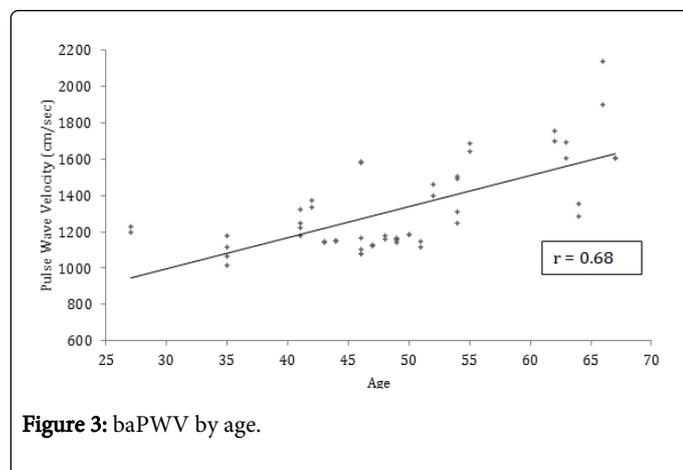
**Effect of Cardiovascular Medications on Vascular Measures:** The use of aspirin ( $p = 0.08$ ), statin ( $p = 0.1$ ) and either an ACE inhibitor or Beta blocker ( $p = 0.06$ ) were identified as potential confounding factors via ANOVA. Among numeric factors, only BMI was identified as a potential confound, showing a significant correlation with the primary endpoint ( $r = -0.42$ ,  $p = 0.035$ ). The regression identified aspirin use ( $p = 0.016$ ) and BMI ( $p = 0.007$ ) as significant independent predictors of the primary endpoint. Adjusting for BMI and aspirin use, there was no significant association between the primary endpoint and either right ABI (partial correlation:  $r = 0.19$ ,  $p = 0.376$ ), left ABI ( $r = 0.28$ ,  $p = 0.192$ ), left PWV ( $r = 0.01$ ,  $p = 0.952$ ) or right PWV ( $r = 0.02$ ,  $p = 0.916$ ).

### Discussion

This is the first study to date that has examined markers of vascular function to assess cardiovascular disease risk in patients with FMD. Atherosclerosis and its complications is the leading cause of death and disability worldwide. It is important to identify early stages of atherosclerosis using non-invasive imaging studies so that its natural progress may be delayed [20].

In this investigation both endothelium-dependent and independent vasodilation was preserved demonstrating that vascular smooth muscle function is normal in this cohort of subjects with FMD. It has been previously shown that hypertensive postmenopausal women have abnormal endothelial function [21]. There has been a considerable amount of clinical evidence that angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are effective antihypertensive agents in patients with FMD [11]. In our cohort of FMD subjects, eight (29.6%) took ACE inhibitors or ARBs

for blood pressure management. It is possible that flow mediated vasodilation and other vascular measures have normalized due to this antihypertensive therapy in this cohort of FMD subjects.



Among the non-invasive methods used to quantify the elastic properties of arteries, PWV is the most recognized and established index of arterial stiffness [22,23]. The increase of PWV with age is well established [24], and an increase in PWV in patients with atherosclerotic disease is a well-recognized phenomenon [25,26]. Mean PWV correlates well with vascular damages [27,28]. Additionally, baPWV > 1400 cm/sec serves to discriminate the patients with either stroke or coronary heart disease independent from conventional atherosclerotic risk factors [29]. In our population of patients with FMD, the average baPWV was  $1324.37 \pm 247.55$  cm/sec and 8 subjects (29.6%) had values greater than 1400 cm/sec. This finding was unexpected since we believed that the arteries in all patients with FMD would have abnormalities in arterial stiffness and compliance due a high prevalence of hypertension in patients with FMD.

There are several limitations of this study. It was difficult to identify age and gender matched control subjects who had hypertension but did not have any other cardiovascular risk factors. Additionally, the sample size was too small to detect a difference in ABI, carotid artery IMT or arterial stiffness.

## Conclusion

The present study demonstrates that in this cohort of patients, FMD was not associated with impaired overall vascular function. A prospective study with a larger sample size is required to confirm these findings.

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