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Endothelial Dysfunction in Prehypertension and Associated Factors

ORIGINAL

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Abstract

Background: Endothelial dysfunction precedes structural abnormalities and atherosclerosis clinical manifestations, and thus it is considered an early marker of cardiovascular diseases. The objectives of this cross-sectional study were to determine the frequency of endothelial dysfunction in prehypertensive subjects and its association with demographic, anthropometric and clinical characteristics of the population studied.

Methods and Results: Endothelial function was assessed by flow-mediated vasodilation (FMD) of the brachial artery in 60 non-smoking and non-diabetic prehypertensive subjects aged 30-70 years who were recruited from the community. Variables analyzed were gender, age, race, sedentary lifestyle, dyslipidemia, body mass index, abdominal circumference and blood pressure. In order to evaluate the relationship between endothelial dysfunction and study variables, Student t, Mann-Whitney and chi-square tests were used. Multivariate logistic regression of variables analyzed with respect to endothelial dysfunction was applied in unadjusted as well as adjusted models ($p<0.20$). Significance level was set at 5%. Mean age of prehypertensive subjects was 42.6±9.2 years; 60% were females, 33.3% were Black, 61.6% were overweight, and 68.3% had a sedentary lifestyle. Endothelial dysfunction was detected in 36.7% of the population; its frequency was higher for Black subjects (45%). Association was established between endothelial dysfunction and males as well as obesity, the latter even after adjustment of the model ($p=0.010$).

Conclusions: In conclusion, frequency of endothelial dysfunction as determined by FMD was high in the population under study, even

though subjects were young, non-smoking and non-diabetic, and association was established between endothelial dysfunction and obesity.

Keywords
Endothelial Dysfunction; Prehypertension; Flow-Mediated Vasodilation; Associated Factors.

Introduction

Endothelial dysfunction is associated with atherosclerosis progression and complications, and thus it is an early marker of cardiovascular disease (CVD). [1]

Endothelial dysfunction as detected by flow-mediated vasodilation (FMD) of the brachial artery was related to the presence of coronary artery disease in 122 subjects undergoing coronary angiography, with 71% sensitivity and 81% specificity. [2] The positive predictive value of abnormal brachial dilation with respect to coronary endothelial dysfunction is 95%. [3] Therefore, assessment of endothelial function can help in the identification of early changes in asymptomatic subjects with CVD risk factors, such as prehypertension.

Despite controversies over the use of the term 'prehypertension', studies have demonstrated that this clinical condition is an independent risk factor for the development of systemic arterial hypertension (SAH) and arteriosclerotic vascular disease. [4-7]

Weil et al [8] have shown that, regardless of other CVD risk factors, prehypertension is associated with decreased blood flow in the forearm in response to acetylcholine infusion, suggesting less endothelium-dependent vasodilation. Moreover, it is known that increased age is associated to decreased endothelium-dependent vasodilation in humans and such reduction occurs earlier in males than females. [9, 10]

Nevertheless, data on the influence of clinical and epidemiological profile of prehypertensive subjects on endothelial function is lacking and little is known about the relationship between intermediate cardiovascular phenotypes and race differences. Pulse wave velocity seems to be greater in Africans than in Europeans. [11] Plavnik et al [12], when comparing the endothelial function of prehypertensive and normotensive subjects, have showed no impact of body weight on FMD in either group.

This study aimed at evaluating the endothelial function of prehypertensive subjects by FMD and investigating the association of demographic, anthropometric and clinical characteristics with endothelial dysfunction.

Methods

Study Design

This is an analytical cross-sectional study evaluating 60 male and female subjects aged 30-70 years, recruited from the community, with prehypertension: systolic blood pressure (SBP) 120-139 mmHg and/or diastolic blood pressure (DBP) 80-89 mmHg. [13] Subjects with diabetes mellitus or known CVD, on daily anti-inflammatory drugs within the last 30 days, smokers (subjects smoking any number of cigarettes per day) and pregnant females were not enrolled in the study.

Data Collection and Analysis

Subjects who consented to participating in the study were asked to fill out a form regarding de-

mographics (gender, age and race as reported by subject), past medical history and living habits, and then underwent physical examination for collection of anthropometric measures (weight and height for body mass index (BMI) calculation, and abdominal circumference (AC).

Previous diagnosis of SAH, diabetes mellitus, dyslipidemia, heart diseases and stroke was based on information provided by subjects or administration of drugs intended to treat such diseases. Sedentary lifestyle was defined as less than 150 minutes of aerobic physical activity per week. [14]

Weight (kg) and height (m) were measured using a calibrated and standardized digital scale (G-tech® BALGL200, Providence, RI, USA) and standard measuring tape, in subjects in the standing position and barefoot. BMI calculation was based on the equation: BMI (kg/ m2) = weight (kg)/(height × height) (m), and results were presented according to categories (underweight, normal weight, overweight and obesity class I, II and III). [15]

AC (midpoint between the last rib and iliac crest) measurement was also carried out using standard measuring tape and results were sorted according to values adopted by the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III): >88 cm for females and >102 cm for males. [16]

Blood pressure was measured by oscillometry with a validated automatic digital device (Omron® HEM-7200, Song Jiang Road, China) and cuff adjusted for mid-upper arm circumference, with subjects in the sitting position and measurement of the dominant arm; results were expressed as average of four measurements (two at each visit, considering an interval of 7-15 days between them).

In order to evaluate the influence of blood pressure on FMD, subjects were divided into two groups according to pressure values: 120 × 80 to 129 × 84 mmHg (Stage I) and 130 × 85 to 139 × 89 mmHg (Stage II), given that in the Framingham Heart Study, risk of adverse cardiovascular events was higher in the category previously known as high-normal pressure (Stage II). [4]

For FMD evaluation, patients were instructed not to consume caffeine and not to perform physical exercises on the day of examination. Women were also instructed to have the examination conducted outside their menstrual period. Tests were conducted in peaceful setting and temperature at around 20 °C.

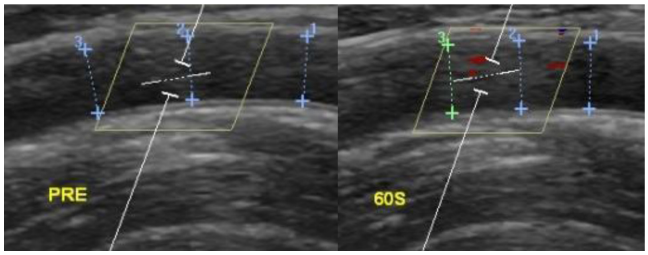
The technique used for analysis of FMD was the one proposed by Celermajer et al [17] and modified by Montenegro et al [18].

Patients were placed in the supine position, with slight abduction of the right arm. Continuous electrocardiographic monitoring was performed for synchronization of brachial artery measurements with electrocardiographic R wave. Linear transducer was placed on the medial aspect of the arm for B-mode longitudinal image of the brachial artery 5-10 cm above the antecubital fossa. In order to attest to the location of the artery, color flow mapping was used and mid-vessel maximum diameter of the brachial artery was measured lengthwise in scans of proximal and distal lumen-to-intima interfaces. Baseline brachial artery diameter (BBAD) was measured three times.

Following BBAD measurement, transducer location on the skin was marked to measure post-occlusion brachial artery diameter (POBAD) at the same location. Artery occlusion for 5 minutes was obtained with pneumatic cuff placed on the arm and adjustment of pressure at 50 mmHg above individual SBP. Brachial artery diameter was recorded continuously for 90 s after deflation of cuff. Flow rate was obtained before and 15 s after cuff deflation and three POBAD measurements were performed at each time point: 30, 60 and 90 s after cessation of insufflation **(Figure 1)**.

FMD was calculated by means of the equation: FMD (%) = [(POBAD (mm) – BBAD) (mm)/BBAD (mm)] × 100. Values >10% were considered normal. [19-21]

Figure 1: Scans for baseline (PRE) and post-occlusion (60S) brachial artery diameter for flow-mediated vasodilation calculation.



The measure considered as POBAD for FMD calculation was the one obtained at 60 s after the cuff deflation.

FMD testing was conducted in a two-dimensional color and spectral Doppler ultrasound device and linear probe transducer with frequency 8-11 MHz (GE® LOGIQ VP3, Fairfield, CT, USA).

All tests were performed by the same vascular surgeon who was blind to clinical characteristics of subjects in the study.

Statistical Analysis

Data were analyzed using the software IBM SPSS Statistics 20.0 (2011). Significance level was set at 5%. First, descriptive analysis was conducted. Normality of quantitative variables was analyzed by Lilliefors test. Qualitative variables are presented by frequency and percentage whereas quantitative variables are presented as mean±s.d. and median. In order to evaluate the relationship between endothelial dysfunction and study variables, independent Student t (normality), Mann-Whitney (asymmetry) and independent chi-square tests were employed. Finally, multivariate logistic regression was applied, at first as unadjusted model with respect to FMD for odds ratio (OR) and 95% confidence interval (CI) estimates, then as adjusted model with $p<0.20$.

Consent and Approval

Study procedures, methods and objectives were considered in accordance with ethical standards of the Research Ethics Committee of University Hospital Presidente Dutra, Federal University of Maranhão, from which approval was received in Unified Opinion # 249 218 (Attachment A). Study participation was only possible for subjects who signed the Informed Consent Form written according to provisions in the Brazilian National Health Council (CNS) Resolution # 466/12, et seq.

Results

From February 2013 to December 2014, 361 prehypertensive subjects were recruited in SAH collaborative efforts and prevention actions. Of these, 134 met study inclusion criteria and 84 agreed to participate in it. There was a loss of 28% of subjects, totaling a population of 60 prehypertensive subjects.

Demographic, anthropometric and clinical characteristics of the study population are presented in **Table 1**.

Table 1. Demographic, anthropometric and clinical characteristics of the study population.

Variables	Values
Gender (%)	
Male	40.0
Female	60.0
Mean age (years)	42.6±9.2
Age group (%)	
30-39 years	40.0
40-49 years	40.0
50-59 years	15.0
>59 years	5.0
Race (%)	
Black	33.3
Brown	33.3
White	33.3
Median BMI (kg m^2)	26.1
Overweight (%)	43.3
Obesity (%)	18.3
Mean AC (cm)	90.6±11.4

Variables	Values
Increased AC (%)	43.3
Dyslipidemia (%)	20.0
Sedentary lifestyle (%)	68.3

BMI: body mass index; AC: abdominal circumference. Data are percentage (%), median, or mean±s.d.

Mean blood pressure was 126.7±5.9 × 77.1±6.5 mmHg and 63.3% of subjects had stage I prehypertension, with statistically significant difference in SPB values between genders, as shown in **Table 2**.

Endothelial dysfunction was detected in 36.7% of the population. When assessing the frequency of endothelial dysfunction according to the race, it can be inferred that 45% of Black subjects had endothelial dysfunction when compared to 35% of Brown and 30% of White ones (p=0.605) **(Table 3)**.

Table 2. Blood pressure levels and prehypertension stages in the study population.

Blood pressure levels	mmHg	p value*
Mean blood pressure	126.7±5.9 × 77.1±6.5	<0.01
Median SBP		
All subjects	125.6	
Males	131.7	
Females	123.5	
Prehypertension stages (%)		
I (120 × 80 to 129 × 84)	63.3	
II (130 × 85 to 139 × 89)	36.7	
Total	100.0	

SBP: systolic blood pressure. *: According to Mann-Whitney test. Data are percentage (%), median, or mean±s.d

Table 4 presents BBAD and POBAD values as well as percent change after vessel occlusion (FMD) in males and females.

Association was established between endothelial dysfunction and male subjects (p=0.022), as shown

Figure 2: Shows mean FMD values for subjects with and without endothelial dysfunction.

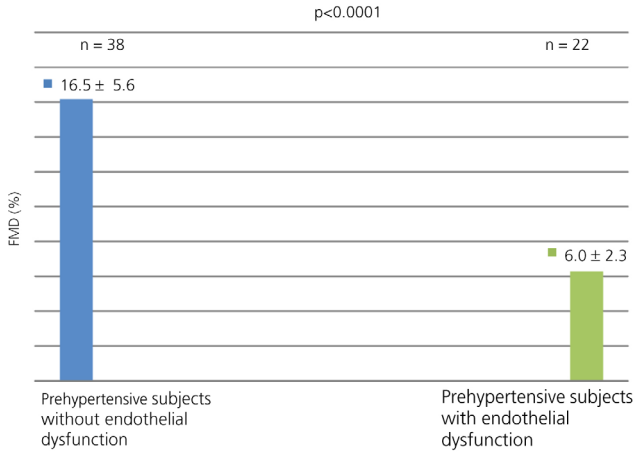


Table 4. Baseline and post-occlusion brachial artery diameter and flow-mediated vasodilation of the brachial artery according to gender in prehypertensive subjects.

Variables	Males	Females	p value
Median BBAD (mm)	3.7	3.0	<0.001[a]
Median POBAD (mm)	4.0	3.4	<0.001[a]
Mean FMD (%)	10.3±5.6	14.2±7.7	0.038[b]

BBAD: baseline brachial artery diameter; POBAD: post-occlusion brachial artery diameter; FMD: flow-mediated vasodilation of the brachial artery. [a]:According to Mann-Whitney test; [b]:According to Student t test. Data are median or mean±s.d.

Table 3. Flow-mediated vasodilation of the brachial artery and endothelial dysfunction frequency per race in the study population.

FMD	Race						Total	p value
	White	%	Black	%	Brown	%		
Median	11.9	----	12.3	----	12.2	----	----	0.865[a]
Q1/Q3 (%)	8.8/14.3		5.0/16.2		7.8/16.3			
> 10%	14	70.0	11	55.0	13	65.0	38	0.605[b]
≤ 10%	6	30.0	9	45.0	7	35.0	22	

FMD: flow-mediated vasodilation of the brachial artery. [a]:According to Kruskal-Wallis test; [b]:According to chi-square test

in **Table 5**. However, such association lost its statistical significance following model adjustment with respect to other variables.

On the other hand, in the multivariate logistic regression, endothelial dysfunction was associated to obesity in the unadjusted model (p=0.012) as well as in the adjusted one (p=0.010) **(Table 6)**.

Table 5. Association between study variables and flow-mediated vasodilation of the brachial artery.

Variables	FMD*				Total *	p value
	>10%	%	≤10%	%		
Gender						
Male	11	28.9	13	59.1	24	0.022†
Female	27	71.1	9	40.9	36	
Age group						
30-39	15	39.5	9	40.9	24	0.983†
40-49	15	39.5	9	40.9	24	
50-59	6	15.8	3	13.6	9	
>59	2	5.3	1	4.5	3	
Mean age (years)	42.4±9.5	----	42.9±8.7	----	-----	0.861‡
Race						
White	14	36.8	6	27.3	20	0.605†
Black	11	28.9	9	40.9	20	
Brown	13	34.2	7	31.8	20	
Prehypertension stages						
I	25	65.8	13	59.1	38	0.604†
II	13	34.2	9	40.9	22	
Sedentary lifestyle	26	68.4	15	68.2	41	0.788†
Dyslipidemia	9	23.7	3	13.6	12	0.546†
Median BMI (kg m^2)	25.3	----	27.5	----	----	0.055§
Mean AC (cm)	88.9±11.5	----	93.4±11	----	----	0.147‡

FMD: flow-mediated vasodilation of the brachial artery; BMI: body mass index; AC: abdominal circumference.
*: Data are numbers (n), median, or mean±s.d.

Discussion

Endothelial dysfunction plays a fundamental role in all stages of atherogenesis, from initial injury to plaque rupture, leading to acute coronary events. [21] It is also known that endothelial dysfunction is a generalized process. Therefore, to test nitric oxide-mediated vasomotor function of the brachial artery allows stratifying asymptomatic individuals at increased risk for CVD complications. [22] Approximately 50% of blood pressure-related deaths occur in individuals with SBP 115-140 mmHg, suggesting that prehypertension accounts for a significant proportion of CVD-related mortality. [23] Thus, it is important to identify endothelial dysfunction in this population, as this condition could constitute

Table 6. Multivariate logistic regression of study variables with respect to flow-mediated vasodilation of the brachial artery.

Variables	Unadjusted model			Adjusted model		
	OR	CI 95%	p value	OR	CI 95%	p value
Male	3.03	0.82-11.29	0.098	3.04	0.88-10.51	0.078
Age >45 years	1.05	0.26-4.30	0.942	-	-	-
Black race	1.53	0.40-5.92	0.534	-	-	-
Dyslipidemia	0.70	0.12-4.25	0.701	-	-	-
Sedentary lifestyle	1.30	0.31-5.52	0.724	-	-	-
BMI (obese)	11.83	1.72-81.43	0.012	12.10	1.81-80.83	0.010
Increased AC	0.25	0.04-1.77	0.166	0.29	0.05-1.56	0.19

OR: odds ratio; CI: confidence interval; BMI, body mass index; AC, abdominal circumference.

a key mechanism for the development of SAH and arteriosclerotic vascular disease. [8]

This study evaluated non-smoking and non-diabetic prehypertensive subjects of both genders and identified the presence of endothelial dysfunction in 36.7% of the population under analysis. Prehypertensive subjects were mainly female, non-White, overweight and had a sedentary lifestyle.

In 2007, Plavnik et al [12] have analyzed the nitrate-mediated endothelium-dependent and -independent vasodilation response (FMD) in 33 normotensive subjects compared to 28 normal-high blood pressure subjects with age and BMI similar to those of the present study and the authors have demonstrated a flow-mediated vasodilation response about 30% lower in the first group, suggesting endothelial dysfunction at prehypertension levels. Nevertheless, there subjects were mainly males, and race and sedentary lifestyle were not study variables.

Gender frequency differences between both studies could be explained by recruitment locations of individuals such as malls, churches and health centers in the present study. In both studies, FMD was higher in females. It is known that hyperemic stimuli are greater in smaller arteries because of their smaller radius. Thus, low BBAD values as observed in females compared to males may result in higher FMD values. [24] Juonala et al [22] have studied cardiovascular risk in 2 265 subjects aged 24-39 years and have also found higher FMD values among females that were believed to be due to lower BBAD values.

Brown and Black subjects accounted for two-thirds of the study population. Although there was no statistical significance probably due to the sample size, endothelial dysfunction frequency was higher among Black prehypertensive subjects compared to White ones. This finding is particularly important as most of the local population is non-White and can be at greater risk for developing CVD complications.

It is noteworthy the percentage of overweight and obese subjects, which may reflect an unhealthy lifestyle. Two-thirds of prehypertensive subjects in the study reported having a sedentary lifestyle, and an Israeli study [25] has shown that high BMI was the main predictive factor of prehypertension.

There was a tendency of association between endothelial dysfunction and increased BMI. And according to multivariate analysis, obese subjects were more likely to have endothelial dysfunction even after adjustment to other variables. Plavnik et al [12], when comparing endothelial function of prehypertensive and normotensive subjects, showed no impact of body weight on FMD in all groups. However, it is known that obesity is a risk factor for coronary heart disease. Adipose tissue, particularly in the visceral compartment, is an endocrine and paracrine organ, a source of pro-inflammatory substances and mediators capable of causing vascular injury and endothelial dysfunction. [26]

Regarding blood pressure, the mean of the study population was lower than the one described by Plavnik et al [12], and it is noteworthy that 63.3% of subjects fall within stage I of prehypertension. The predominantly young population, with 80% of subjects being 30-49 years old and females, may explain this finding.

In the initial analysis, there was association between endothelial dysfunction and males, which could be explained by differences in SBP values between genders. SBP level in males was significantly higher than in females, even though both genders had similar age and BMI. Plavnik et al12, when stratifying levels of SBP and diastolic blood pressure in their groups, have demonstrated a 29% reduction in FMD with increasing SBP from 125 mmHg to 139 mmHg. Nonetheless, this association was not maintained after adjustment for the remaining variables.

Regarding FMD among prehypertensive subjects, Plavnik et al [12] have found values lower than those detected in this study, considering both total population and prehypertensive subjects without

endothelial dysfunction. This difference can be explained by time points for POBAD measurement (90 s × 60 s) in the studies. Maximum increase in brachial diameter seems to occur approximately 60 s after release of blood flow, when 70% of dilation is believed to be due to nitric oxide synthesis. [27] Repeated measurements must be performed to capture maximum response. [22] Another fact that may explain this finding is the difference between samples with respect to gender.

It is also known that stimuli should be consistent and FMD must be related to the change in blood flow. [27] To exclude inconsistencies of ischemic stimuli, peak hyperemic flow was measured 15 s after cuff deflation, showing that the real increase in flow is responsible for vasodilation.

Regarding FMD in prehypertensive subjects with endothelial dysfunction, values detected in this study are lower than mean values in prehypertensive subjects in the study by Plavnik et al [12]. It is noteworthy that authors have compared normotensive and normal-high pressure subjects and have identified a FMD reduction in groups without a cut-off value for endothelial dysfunction diagnosis, as carried out in this study.

Currently, wrist or forearm occlusion is used to assess endothelial function [28], because it seems to express dilation promoted exclusively by nitric oxide. However, location of the cuff does not appear to affect method reliability. Most importantly, time length between release of flow and post-occlusion diameter measurements should be 60 s [24], as performed in this study.

The mechanism responsible for endothelial dysfunction in prehypertensive subjects is not yet known. However, inflammation, oxidative stress and increased endothelin-1 activity may be involved in this process. [8] Additionally, there is evidence of a lower capacity for repair of endothelial progenitor cells contributing to endothelial dysfunction. [28]

The study design (cross-sectional) is one of its limitations, once it doesn´t provide the causal relationship between prehypertension and endothelial dysfunction, besides the sample size.

Conclusively, this study confirms the presence of endothelial dysfunction in young, non-smoking and non-diabetic prehypertensive subjects with blood pressure values lower than those described in other studies, especially in Black subjects, which ultimately means increased risk for development of CVD. Such findings reinforce recent arguments in favor of earlier intervention and treatment of prehypertension.

Since 40% of prehypertensive subjects present SAH within two years [29] and conversion risk is 35% higher in Black individuals compared to White ones [30], conducting clinical trials designed to better assess racial differences in prehypertension prevalence, evolution and prognosis should be considered.

Disclosures

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Conflict of interests

None.

Abbreviations

AC: abdominal circumference
BBAD: baseline brachial artery diameter
BMI: body mass index
CI: confidence interval
CVD: cardiovascular disease
DBP: diastolic blood pressure
FMD: flow mediated dilation
OR: odds ratio
POBAD: post-occlusion brachial artery diameter
SAH: systemic arterial hypertension
SBP: systolic blood pressure

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