

Association of Brachial Artery Flow Mediated Dilation with Cardiovascular Risk Factors in Prehypertensive Patients

Laith A. Aldabbagh
University of Kufa, Najaf, Iraq

Abstract: Endothelial dysfunction is considered as an essential role within the pathogenesis of systemic hypertension. Several factors involved in evolution of endothelial dysfunction including traditional cardiovascular risk factor had been claimed. Modulation of these factors specially the reversible factors may give us important ways for prevention of hypertension and its comorbidities in patients at risk of developing hypertension. The purpose of this study is to determine the association among brachial artery flow mediated dilation with the Cardiovascular risk factors in prehypertensive patients. In this study, 112 pre-hypertensive patients were analyzed. For each patients a full medical history including the age, gender, BMI, smoking history, physical inactivity and family history of premature CVD, followed by comprehensive physical examination was done after which a blood sample was withdrawn for estimation of FBS, total and LDL, serum cholesterol, serum HDL and TG. After that each patient had been evaluated for brachial artery flow that mediated dilation. The results show that impaired BAFMD is significantly associated with FBS, TC, LDL, Cholesterol while there was no significant association with the age, TG, nor with HDL. Impaired BAFMD is also significantly associated with gender, obesity, physical inactivity, family history of premature CV disease and smoking status. Therefore, abnormality of BAFMD as index of endothelial dysfunction is significantly associated with multiple traditional cardiovascular risk factors even in prehypertensive stage of hypertension.

Key words: Endothelial dysfunction, obesity, hypertension, CV disease, brachial artery

INTRODUCTION

Pre-hypertension has been identified as borderline hypertension in addition to high normal hypertension through the European Society of Hypertension guidelines. The new classification of prehypertension or high normal BP is a continuum to high blood pressure and is appearing as a significant and treatable risk component factor regarding cardiovascular disease (Agewall *et al.*, 2001). A marked raise in blood flow which exerts a frictional shear or force stress upon the endothelial area leading to the vessel to dilate (Pohl *et al.*, 1986). Based on this physiological phenomenon, Celermajer *et al.* (1992) created the non-invasive hyperemia method to evaluate endothelial function for the conduit artery. The method uses a transient (five min) suprasystolic forearm occlusion to create the hyperemic-induced shear pressure subsequent and stimulus vasodilation which could be detected on the brachial artery through high-resolution ultrasound. Typically the percent adjust from baseline diameter in order to post-occlusion diameter will be calculated (FMD, Flow-Mediated Dilation) and utilized as an index for endothelial function (Corretti *et al.*, 2002). In Joannides *et al.* (1995) were the first for examining the nitric oxide contributing to the FMD

reaction in humans and determined that NO blockade totally abolished FMD. At this time, it is well acknowledged that FMD, when conducted following the released guidelines (Celermajer *et al.*, 1992; Corretti *et al.*, 2002) gives a functional bioassay with regard to in vivo endothelium based NO bioavailability (Green, 2005). FMD is exhibited to be reproducible (Donald *et al.*, 2006; Sorensen *et al.*, 1995; Welsch *et al.*, 2002; West *et al.*, 2005) correlates with invasive measurements of endothelial function within the coronary arteries (Anderson *et al.*, 1995; Takase *et al.*, 1998) and predicts future cardiovascular events (Brevetti *et al.*, 2003; Widlansky *et al.*, 2003).

The prehypertension prevalence is considerably greater amongst African-Americans in comparison to whites and it is a critical factor within the racial disparity around CV and cerebrovascular disease (Brevetti *et al.*, 2003; Widlansky *et al.*, 2003). Previously, many researchers have demonstrated that BP levels for the prehypertension range have associated with circulating inflammatory markers for example High sensitivity C-Reactive Protein (hsCRP) implying that BP levels under the hypertensive range might potentially be a pro-inflammatory condition (Palinkas *et al.*, 2002).

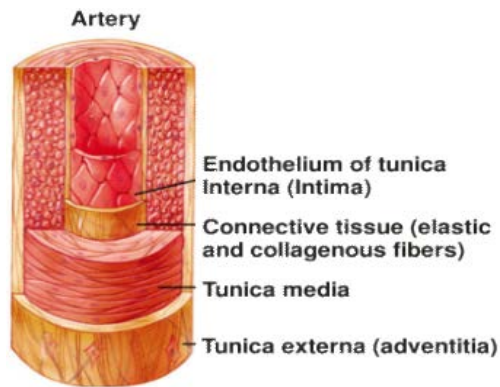


Fig. 1: Structure of an artery, the three layers of the artery; inner (intima), intermediate (media) and the outer layer (adventitia)

Previous studies also have provided compelling evidence which African Americans possess an earlier onset of decreased endothelial function (Cosio *et al.*, 2006; Venneri *et al.*, 2007) and interestingly the prehypertension prevalence is considerably higher among African Americans when compared with the white (Brevetti *et al.*, 2003; Widlansky *et al.*, 2003).

Arterial functions and properties: The organization of arterial vessel wall has three layers (Fig. 1): intima (an inner layer), media (an intermediate layer), along with adventitia (an outer layer). Typically the intima consists of endothelial cells in the luminal surface while the endothelial cells were in direct contact along with the flow blood. The last layer is Media which has a sophisticated structure of proteins (elastin and collagen matrix), SMC (Smooth Muscle Cells) can determine the artery elastic properties. The adventitia is typically the blood vessel outermost layer and is primarily composed of collagen. Typically the collagen provides for anchor of the blood vessel in order to be closed by organs and provides stability for the artery (Berry *et al.*, 2000).

The elastin fibers inside the media are carried the most of tensile load if the low mechanical stretch will be exerted at the artery. Any time the high mechanical stretch has exerted at the artery, the significantly stiffer collagen fibers reduce additional the artery deformation. Structural modifications in the matrix of elastin-collagen underlie reduction associated with arterial function. The cells smooth muscle are associated with the matrix of elastin-collagen as well as the local mechanical stresses of auto- regulate by adapting their particular contractile tone (Berry *et al.*, 2000).

Physiology for flow-mediated dilation: In the Fig. 2, it demonstrates that the artery possesses a particular diameter and also blood flow velocity throughout a

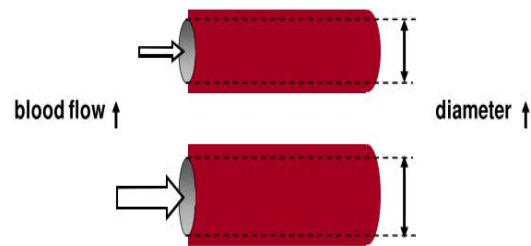


Fig. 2: Function of the artery (schematic). An increase in blood flow causes an increase in diameter

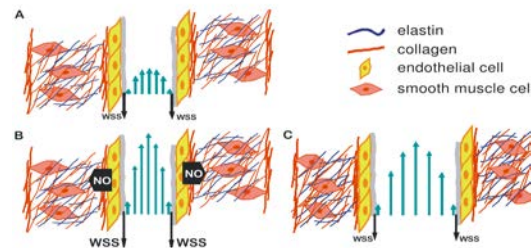


Fig. 3: Flow-mediated dilation; resting state with a normal flow: A) increased blood flow velocity (and thus higher Wall Shear Stress (WSS)) including endothelial Nitric Oxide (NO) release; B) this lead to smooth muscle cell relaxation and vessel dilation which results in lower wall shear stress but has still increased flow (C)

common resting situation. Exhibiting a closer look to the artery, the first part shows (Fig. 3A) the normal resting condition at a specific blood flow velocity. Typically this blood flow velocity applies a frictional force at the layer of endothelial. This particular frictional force is symbolized by the WSS (Wall Shear Stress). If this blood flow velocity will increase, the friction upon the layer of endothelial and therefore the WSS would increase (Fig. 3B). This can lead to more development of NO (Nitric Oxide). The cells of vascular smooth muscle for the artery responded to NO through relaxation that leads to dilation as well as a consequent reduce of the WSS. Taken together, this kind of results in a higher diameter regarding the artery (Pickering *et al.*, 2002).

Aim of study: The aim of the current study is to determine the relationship between brachial artery flow that mediated dilation and the Cardiovascular risk factor in prehypertensive patients.

MATERIALS AND METHODS

This cross-sectional study was conducted during the period from November 2014 to September 2015, at medical and echocardiography outpatient clinic in AlSader

Medical city. A total of 112 prehypertensive patients were enrolled to participate in this study and were assessed for risk factors of cardiovascular disease such as DM, smoking, age, gender, BMI, family history of prehypertensive, CVS disease, sendantary life style (Insufficient physical activity could be identified as fewer than five times for 30 min of average activity for each week or perhaps less than about 3 times in 20 min regarding vigorous activity for each week or equivalent). (Eguchi, 2010). Doppler Echo was performed in all patients to assess the FMD was normal or impaired. After taking fully informed consent about the aims and protocol of the study which was conducted according to the ethical principles of kufa medical ethics committee.

Inclusion criteria: Patients were considered as prehypertensive if they have systolic blood pressure within range of (130-139 mm Hg) or diastolic blood pressure within range of (85-89 mm Hg) (Vogel *et al.*, 2000).

Exclusion criteria:

- Patients who have past medical history of hypertension
- Patients who have chronic renal failure
- Patients who have past medical history of ischemic heart disease, endocrine disease

A full Medical history was taken from all patients including risk factors for hypertension, family history, social and past medical history followed by comprehensive physical examination after which a blood sample of 5 cc of venous blood was withdrawn for estimation of FBS, total and LDL serum cholesterol, serum HDL, TG level. For each patients a full medical history followed by comprehensive physical examination was done including the age, gender, BMI, BSA, smoking history, physical inactivity and family history of premature CVD, after which a blood sample was withdrawn for estimation of FBS (70-99 mg L⁻¹), total and LDL (<130 mg L⁻¹), serum cholesterol, serum HDL (<200 mg L⁻¹) and TG (35-160 mg L⁻¹). After that all each patient had been evaluated for brachial artery flow mediated dilation.

Measurement of BAFMD: The test was carried out in the subject's remaining arm whilst in a recumbent place in a room with quiet temperature-controlled with (22°C) after ten minute equilibration period. Making use of a Vivid 7 (general electric ultrasound echocardiography systems) the brachial artery has been longitudinally imaged just

about 5 cm proximal for the antecubital crease utilizing 15-6 MHz of linear array ultrasound prob (general electric). Brachialartery diameter has measured through the anterior in order to the particular posterior interface involving the adventitia and media in a fixed distance. Typically the mean diameter appeared to be calculated from four cardiac cycles. All measurements have been calculated in end-diastole for avoiding possible errors producing from variable arterial consent. This internal diameter is determined.

After a baseline period, some longitudinal image about 3 cm of vessel with no color flow was attained and frozen intended for 5 sec. A BP cuff placed close to the upper left arm proximal for the target artery that is inflated once the baseline level to be able to 50 mm Hg which is above the patient's systolic hypotension (or till no blood flow has been observed inside the brachial artery) in addition to held for 5 min. In this upper arm occlusion has been followed through a hyperemic state that primarily determined by metabolic local modifications in prefer of vasodilating substances as well as only partly endothelial-mediated. Improved flow was subsequently due to sudden cuff deflation, accompanied by a constant scan at deflation in 20, 40 sec and also 60, 90, 120 sec using measurements recorded with similar intervals via baseline.

Impaired BAFMD is considered when BAFMD is <5 mm from the baseline diameter. Normal BAFMD is considered when BAFMD 5 MM from the baseline diameter. All the clinical together with laboratory data were tested by using SPSS Software (Version 20, IBM, USA). The test of Chi-square was utilized for the association between categorical factors and comparison was conducted using an independent t-test using numerical variables.

RESULTS

In this study the patient's age ranges from 40-70 years with the mean of age of all patients 48(±9.4) years. Of the 112 patients analyzed 72 patients are male and 40 patients are female. Table 1 demonstrates the basic demographic characteristics regarding the study group.

The present study shows that impaired BAFMD is significantly associated with FBS, TC and LDLC while there was no significant association with the age, TG or with HDL as in Table 2.

The present study also shows that impaired BAFMD is significantly associated with gender, obesity, physical inactivity, family history of premature CV disease and smoking status as in Table 3.

Table 1: The basic demographic characteristics regarding the study population

Parameters	Factors	No.
Mean of the age (\pm SD)		48 (\pm 9.4)
Gender n (%)	Male	72 (64.29)
	Female	40 (35.71)
Obesity n (%)	Obese	87 (77.68)
	Non-obese	25 (22.32)
Smoking n (%)	Smoker	67 (59.82)
	Non-smoker	45 (40.19)
Physical inactivity n (%)	Physically inactive	77 (68.75)
	Normal activity	35 (31.25)
Family history of premature CVD n (%)	Yes	41 (36.60)
	No	71 (63.39)
Mean of FBS (mg L ⁻¹)		118
Mean of TC (mg L ⁻¹)		186
Mean of LDL-Cholesterol (mg L ⁻¹)		128
Mean of TG (mg L ⁻¹)		140
Mean of HDL (mg L ⁻¹)		43
BAFMD	Positive test result	43
	Negative test result	69
Total number of patients		112

Table 2: The association between the age, FBS, TC, LDL Cholesterol, TG, HDL and brachial artery flow mediated dilation

Parameters	Brachial artery flow mediated dilation	p-values
Means of the age		
Normal	52.6	0.300
Impaired	47.0	
FBS		
Normal	97.4 mg L ⁻¹	0.050
Impaired	122.4 mg L ⁻¹	
TC		
Normal	161.8 mg L ⁻¹	0.001
Impaired	192.4 mg L ⁻¹	
LDL C		
Normal	88.6 mg L ⁻¹	0.009
Impaired	112.2 mg L ⁻¹	
TG		
Normal	141.2 mg L ⁻¹	0.101
Impaired	132.4 mg L ⁻¹	
HDL		
Normal	44.4 mg L ⁻¹	0.500
Impaired	44.1 mg L ⁻¹	

Table 3: Shows the association between genders, obesity, physical inactivity, family history of premature CVD, smoking and brachial artery flow mediated dilation

	Brachial artery flow mediated dilation		
Parameters	Impaired	Normal	p-values
Gender			
Male	39	33	0.0200
Female	30	10	
Obesity			
Obese	49	38	0.0300
Non-obese	20	5	
Physical inactivity			
Physical inactivity	54	23	0.0050
Normal activity	15	20	
Family history of premature CV disease			
Yes	30	11	0.0500
No	39	32	
Smoking status			
Smoker	52	13	0.0002
Non-smoker	17	30	

DISCUSSION

The result of the present study shows that abnormalities of BAFMD is significantly related to cardiovascular risk factors for instance gender, obesity, physical inactivity, family history of premature CV disease, smoking status except for the age.

The result of the present study shows no significant difference with the age of the participant but this absence of difference can be readily explained by the narrow age window among study participants, although other studies showed that aging is related to endothelial dysfunction.

The latest studies that have utilized a considerably more contemporary technique reveal that the functionality of brachial artery might be preserved within old men in comparison with young men whilst elder women demonstrate attenuated brachial reactions in accordance with younger women. All these findings are recognized by Jensen-Urstad together with Johannsson that straight compared the FMD of brachial artery in both young men and old men along with in women. In general, these types of studies recommend that sex-related variations might exist within endothelial function as the age of humans, with older women representing a more obvious change throughout endothelial function.

In the present study as demonstrated in Table 2 shows that patients with higher FBS level tend to have impaired BAFMD and this reduction between the two groups was statistically significant.

It has been well known that flow-mediated dilation, regarded as a surrogate to get the evaluation for cardiovascular health and wellbeing is blunted within patients with diabetes indicating that glucose metabolism has an essential role with worsening arterial function. The flow-mediated dilation of Brachial artery assessed non-invasively provides the interaction function between endothelial cells along with smooth muscle cells as well as is shown to be adversely affected by raised blood glucose level (Bussel *et al.*, 2011).

At the level of epidemiological, an increased blood glucose level would be associated with the blunted flow-mediated expansion response. Nevertheless, the mechanisms through a raised blood glucose level leads to vascular dysfunction continues to be unraveled. Recent insights state that the functionality of vascular endothelium that hosts a substantial variety of physiological pathways represents a pivotal role within the vascular dysfunction development. Two important pathways which were addressed by available literature: firstly, the shear stress realizing; secondly, the glucose

(such as indirectly through an impact of insulin) pathways that release (NO) directly in the artery wall leading to dilation (Bussel *et al.*, 2011).

Through basic physiology, this is identified that glucose will increase blood flow around the microcirculation within the earlier postprandial phase (such as resistance arteries dilate for effect to insulin-binding towards vascular endothelium. Prior studies demonstrate that in big arteries flow dilation will be decreased after a single hour of glucose take. Nevertheless, this is unknown just how flow dilation will be impacted in the beginning phase right after glucose take in (about 30 min post-prandially). A minor pilot study indicates that the main flow-mediated dilation reaction improves in the beginning postprandial phase. Despite the fact that this particular study was small which the outcomes wall shear stress as well as an raise in blood glucose levels cause vasodilation by the relaxation of smooth muscle cell.

Another finding of note in the recent study was the significant reduction in BAFMD in patients with higher total and LDL cholesterol as shown in Table 2, this results goes along with the results of many studied dealing with this subject (Zaheditochai *et al.*, 2009).

Indeed it is well known that endothelial dysfunction provides one of the initial events inside the atherosclerosis process. Reduced endothelium-dependent vasodilation is linked to increased cholesterol, this effect can be mediated through numerous mechanisms such as impaired synthesis as well as release of NO along with raised oxidative degradation of nitric oxide.

Physical inactivity is a proven risk factor pertaining to coronary artery disease and the result of the present study as in Table 3 shows significant inverse relation between physical activity and reduction in BAFMD. Exercise training generally increases arterial function with patients using cardiovascular risk elements or diseases such as resistance vessel function within advanced age subjects. Nevertheless, earlier investigations associated with training-induced adaptations regarding conduit arteries within old healthy populations have shown inconsistent. For instance, 6 weak for knees extensor exercising training increased brachial artery FMD around old men, while an additional study in elderly sedentary men identified that 8 weak for cycles exercise caused no improvements with FMD. That is even though evidence through cross-sectional studies implying that both old fit women and men have higher FMD in comparison with elderly sedentary subjects. Typically the effect of both exercise and fitness exercising at conduit artery functionality in old humans as well as the possible sex-related variations on exercise training possess not been formerly revealed with a single study.

CONCLUSION

Abnormalitis of BAFMD as index of endothelial dysfunction is significantly associated with multiple traditional cardiovascular risk factors even in prehypertensive stage of hypertension.

RECOMMENDATIONS

Screening of prehypertensive patients for BAFMD is important as it is associated with many cardiovascular risk factors which can be modified for future prevention of hypertension and its poor cardiovascular outcomes.

Further, studies with large sample size and longer duration are highly suggestive recommendation prehypertensive.

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