

Assessment of endothelial dysfunction by flow mediated dilatation in patients with Coronary Artery Disease

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Abstract:

Background: Endothelial dysfunction is thought to be a key event in the development of atherosclerosis. It is a systemic process that simultaneously affects different vascular territories including coronary arteries. It is recommended that noninvasive approaches assessing endothelial function in peripheral vessels like flow mediated dilatation are indirectly representative of coronary vascular function.

Objectives: This study is aimed to assess endothelial dysfunction by using flow mediated dilatation in patients with coronary artery disease

Patients and methods: 82 patients of either sex with an age range of 40-65 years are involved in this study. Each patient was subjected to two tests; first test was the flow mediated dilatation percentage (FMD%) measurement to assess endothelial functional integrity and second one was coronary computerized tomography angiography for measuring the percentage of coronary artery stenosis.

Results: the results of this study revealed that FMD% is inversely correlated with the percentage of coronary artery stenosis (p value <0.01). FMD% in patients having a single coronary vessel atheromatous stenosis (9.9±3.5) % was significantly lower than that of control subjects (15.3±7) %, p<0.0001.

Conclusion: this study concludes that FMD% of brachial artery could be used as a marker for systemic endothelial functional integrity including that of coronary arteries.

Keywords: endothelial dysfunction, flow mediated dilatation (FMD %).

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Introduction:

Endothelial dysfunction is thought to be a key event in the development of atherosclerosis (1). It is a systemic process that simultaneously affects different vascular territories. Coronary endothelial dysfunction is assessed using invasive methods, such as the infusion of acetylcholine (ACh) into the coronary artery that produces vasoconstriction in vessels with impaired endothelial function and atheroma (muscarinic effect) in the absence of nitric oxide release. Recently, it is recommended to use noninvasive approach to assess endothelial function in the peripheral vessels that is indirectly representative of coronary vascular function. Testing involves pharmacological and/or physiological stimulation of endothelial release of NO in these vessels with its subsequent influence on vascular tone. Currently the main noninvasive technique to assess endothelial functions is flow-mediated vasodilation (FMD) of the brachial artery as measured by using external vascular ultrasound (2) Flow-mediated dilatation (FMD) is a process that increases blood flow through an artery. This increase in the blood flow produces shear forces on the endothelium and

subsequently stimulates endothelial cells to release NO (3). Reduced vasodilatation following an increase in shear forces is representative of impaired NO bioavailability (4). Therefore, FMD is a good marker of NO bioavailability. However, the FMD protocol involves a 5 minute occlusion of an artery, which causes tissue ischemia and when the cuff is released, a sudden increase in bloodflow (reactive hyperaemia) increases laminar shear forces parallel to the long axis of the vessel which is transduced via luminal mechanoreceptors to the endothelial cell. This event increases G-protein expression of phosphokinase A, signaling an increase of endothelial nitric oxide synthase (eNOS) activity which catalyzes the conversion of L-arginine to NO (5). NO then diffuses into the tunica media where it activates soluble guanylate cyclase which converts guanosine triphosphate into guanosine monophosphate to induce relaxation of the smooth muscle and subsequent vasodilation. FMD is expressed as the maximum percentage change in vessel diameter after cuff release relative to baseline vessel diameter (% FMD) (6), with a low percentage indicating poor endothelial function.

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Patients and Methods:

This observational study was carried out in the Radiology Department at Al-Yarmook Teaching Hospital, Baghdad, Iraq

from October 2013 till March 2015). 82 Participants of either sex with an age range (40-65years) were involved in this study. The participants were divided into two groups:

- Patient group with Single coronary vessel lesion (n=51).
- Control group with normal coronary CT angiography (n=31).

Systolic and diastolic blood pressures were measured for the right arm in a supine position after 10 minutes of rest using a standard mercury sphygmomanometer. Two readings were recorded and the average was considered. (7). The Flow mediated dilatation FMD test was performed in the morning (8–9 am) after a minimum 8-hour overnight fasting. Sonographic scans were performed after blood pressure measurements with a High Resolution, Multi-frequency (3- 12-MHz) Linear array Ultrasound Doppler Probe equipped with HD11XE machine (Philips) with an attached electrocardiograph. (8). External vascular ultrasound imaging was performed by positioning Ultrasound probe longitudinally at approximately 5 cm proximal to the antecubital crease of the supinated and abducted right arm where the clearest image was obtained to measure brachial artery baseline diameter during systole and diastole according to the recommendations of the International Brachial Artery Task Force (9). The ultrasound Doppler system has an integrated electrocardiogram to synchronize the assessment of arterial diameter with the cardiac cycle, where a three-lead ECG system was used to ensure the timing and sequence of events in the brachial artery relative to the cardiac cycle. After a baseline measurement of brachial artery diameter synchronized with R wave which represents end-diastolic diameter, the sphygmomanometer cuff was inflated to about 50 mm Hg above systolic arterial pressure and this pressure was held for five minutes to induce ischemia in the forearm (10). Then, after 5 minutes occlusion, cuff was deflated. It is essential that the probe is held in the same position during the scan which is achieved by pen marking the exact site where the brachial artery was visualized during the baseline diameters measurements. Blood flow was re-established by rapidly deflating the cuff, causing a reactive hyperemia following deflation, while brachial artery diameter is measured as soon as possible within 30-60 seconds while recording the FMD diameter, where FMD was defined as the maximal diameter seen within 60 seconds after cuff deflation. Determination of the diameter was performed at end-diastole synchronized with the R-wave of the electrocardiogram. All previous measurements were taken in freeze B mode of doppler sonography after identification of the artery versus the vein using a pulse wave (PW) and colour wave (CW) doppler. The angle of probe positioning is essential for better visualization of anterior and posterior arterial walls which ensures accurate measurement of the diameter. In addition to intimal thickness. (11).

Calculation of FMD

The calculation of FMD as a % change considers the peak diameter in response to reactive hyperemia in respect to the baseline diameter according to the following equation:

$$\text{FMD (\%)} = \frac{(\text{PeakDiameter} - \text{BaselineDiameter})}{\text{Baseline Diameter}} \times 100$$
 (12). Coronary arteries were visualized by coronary CT angiography by using the 64 slice type (Philips, Holland, 2010). Reducing a patient's heart rate before a scan was performed by administration of an oral β -blocker (50–100 mg) of oral metoprolol is administered 1 h before the scan or (5–20 mg) of intravenous metoprolol administered immediately before the scan. While sublingual nitroglycerin was administered to dilate the coronary arteries and increases side branches visualization (12). Three ECG leads are attached to obtain an adequate ECG tracing. Viscous intravenous contrast agent which is iodine (Omnipaque. Healthcare. Ireland) of (300–400 mg/mL) concentration at a high flow rate (4–6 mL/s) was injected. A special computer program creates two-dimensional cross-sectional images, which are then displayed on the monitor. A CT dataset for the coronary arteries covers the entire heart from the proximal ascending aorta to the diaphragmatic surface of the heart. (13). Maximum percent luminal stenosis was measured as: $100 - \left\{ \frac{\text{the area of residual patent lumen}}{\text{the area of the normal adjacent vessels}} \times 100 \right\}$. In this study, the data were analyzed using Microsoft Excel 2010. P-value <0.05 was considered to be statistically significant. The data were presented as mean \pm SD. Statistical comparisons between two means were performed using unpaired Student's t-test. Pearson's correlation analysis was used to assess the possible relationships between study parameters.

Results:

In the current study, the functional marker (FMD %) revealed an inverse correlation with a percentage of coronary artery stenosis as a structural marker of atherosclerosis in patients with single coronary vessel involvement by atherosclerotic lesion (p value <0.01) (figure 1). FMD in patients having a single coronary vessel atheromatous stenosis (9.9 \pm 3.5) % was significantly lower than that of control subjects (15.3 \pm 7) %, p<0.0001.

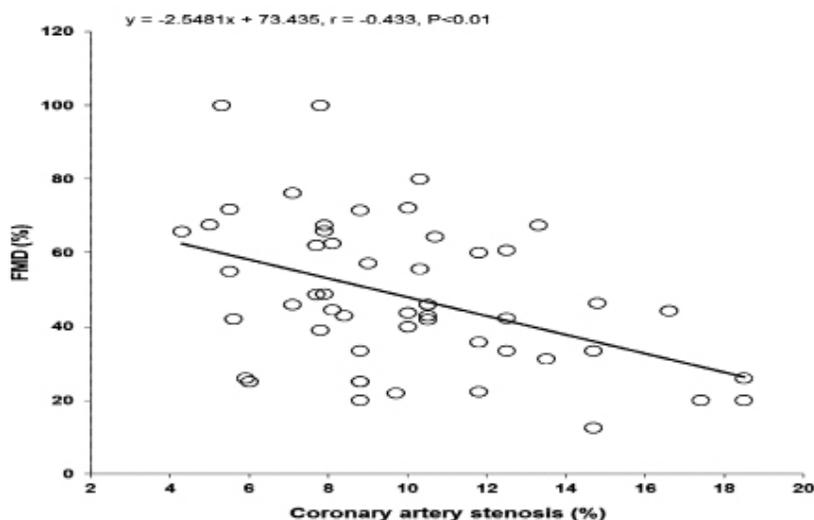


Figure 1: Correlation between brachial artery FMD and Coronary artery stenosis in SCL group (n=51).

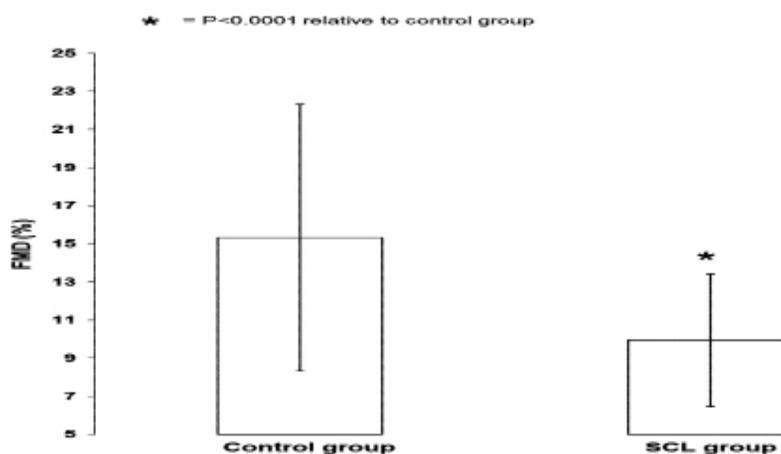


Figure 2: FMD (%) in control group (n=31) and SCL group (N=51).

Discussion:

Endothelial-dependent vascular consequences are important medical issues in the initiation, progression of atherosclerosis and in the transition from a reversible to irreversible disease status. The flow-mediated dilatation not only reflects the integrity of the vascular endothelium, but also extends beyond that to reflect the coronary structural changes which are proved, in the current study, by an inverse correlation between the FMD% with the percentage of coronary artery stenosis in SCL patients. These findings are in agreement with the two studies performed by Mulukutla et al., 2010 (14) and Schnabel et al., 2012 (15) who proved that FMD reflects the functional physiology of the coronary endothelium and the impairment of FMD could proceed to the coronary structural changes revealed by atheroma. The biological link between vascular endothelial damage and the pathogenesis of atherosclerosis

may be due to the diminished arterial bioavailability of NO, which may be the predisposing factor to leucocyte and platelet adhesion, smooth muscle cell proliferation and vasoconstriction because under normal conditions, endothelial NO not only produces vasodilatation, but it also reduces migration and growth of vascular smooth muscle cells, platelet aggregation and subsequent thrombosis, monocyte and macrophage adhesion and inflammation (Bonetti, Lerman and Lerman, 2003) (16). Therefore, this impairment in endothelial function plays a principal role in the pathophysiology of coronary artery atherosclerotic diseases. The lower mean brachial artery FMD percentages in patients with coronary artery stenosis when compared with that of controls are in accordance with a previous study performed by Yeboah et al., 2009 (17) who concluded that brachial FMD is considered as a predictor of coronary artery disease.

Conclusion:

Endothelial dysfunction reflected by decreased FMD% is an important peripheral marker of coronary artery atherosclerosis.

Author's contribution:

Study conception and design: Dr Najeeb Hassan Mohammed.

Acquisition of data: Dr. Saba Fawzi Salih, Dr. Sarab Hilal

Analysis and interpretation: Dr. Saba Fawzi Salih, Dr Najeeb Hassan Mohammed.

Drafting of manuscript: Dr. Saba Fawzi Salih, Dr Najeeb Hassan Mohammed.

Critical revision: Dr. Najeeb Hassan Mohammed. Dr. Abbas Naji Muslim.

References:

1. Eren EI, Yilmaz N, Aydin O. Functionally Defective High-Density Lipoprotein and Paraoxonase: A Couple for Endothelial Dysfunction in Atherosclerosis. *CHOLESTEROL* 2013, Volume 2013.
2. Flammer AJ, Anderson T, Celermajer DS, Creager MA, Deanfield J, Ganz P, Hamburg NM, Luscher TF, Shechter M, Taddei S, Vita JA, Lerman A. The assessment of endothelial function: from research into clinical practice. *Circulation*, 2012 Aug 7; 126(6):753-67 (www.IVSL.com).
3. Boo YC, Sorescu G, Boyd N, et al. Shear Stress Stimulates Phosphorylation of Endothelial Nitric-oxide Synthase at Ser1179 by Akt-independent Mechanisms. *J Biol Chem* ,2002; 277:3388–96.
4. Deanfield J, Donald A, Ferri C, Giannattasio C, Halcox J, Halligan S, Lerman A, Mancina G, Oliver JJ, Pessina AC, Rizzoni D, Rossi GP, Salvetti A, Schiffrin EL, Taddei S, Webb DJ. Endothelial function and dysfunction. Part I: Methodological issues for assessment in the different vascular beds: a statement by the Working Group on Endothelin and Endothelial Factors of the European Society of Hypertension. *Journal of hypertension* ,2005; 23:7–17. (www.IVSL.com).
5. Sessa WC. Endothelial NO synthase at a glance. *J Cell Sci*, 2004; 117:2427–2429 (www.IVSL.com).
6. Alam TA, Seifalian AM, Baker D. A Review of Methods Currently Used for Assessment of In vivo Endothelial Function. *Eur J Vasc Endovasc Surg*, 2005; 29:269–76.
7. Carretero O.A: Essential hypertension part I: definition and etiology. *Circulation*, 2000; 101:329-335.
8. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, Deanfield J, Drexler H, Gehard-Herman M, Herrington D, Vallance P, Vita J, Vogel R. Guidelines for the Ultrasound Assessment of Endothelial-Dependent Flow-Mediated Vasodilation of the Brachial Artery. *J Am Coll Cardiol*, 2002; 39:257–265.
9. Corretti, M.C., et al., Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol*, 2002; 39(2): p. 257-
10. Black MA, Cable NT, Thijssen DH, Green DJ. Importance of measuring the time course of flow-mediated dilatation in humans. *Hypertension*, 2008; 51:203–210.
11. Ryan A. Harris, I, Steven K. Nishiyama, Walter Wrayand Russell S. Richardson3. Ultrasound Assessment of Flow-Mediated Dilatation. *Hypertension*, 2010; 55:1075-1085.
12. Decramer I, Vanhoenacker PK, Sarno G, Van Hoe L, Bladt O, Wijns W. Effects of sublingual nitroglycerin on coronary lumen diameter and number of visualized septal branches on 64-MDCT angiography. *AJR Am J Roentgenol*, Jan 2008; 190(1):219-25.
13. Min J.K., Feignoux J., Treutenaere J., Laperche T., Sablayrolles J.; The prognostic value of multidetector coronary CT angiography for the prediction of major adverse cardiovascular events: a multicenter observational cohort study. *Int J Cardiovasc Imaging*, 2010:721-728.
14. Mulukutla SR, Venkitachalam L, Bambs C, Kip KE, Aiyer A, Marroquin OC, Reis SE. Black race is associated with digital artery endothelial dysfunction: results from the Heart SCORE study. *Eur Heart J.*, 2010 Nov; 31(22):2808-15.
15. Schnabel RB, Wild PS, Schulz A, Zeller T, Sinning CR, Wilde S, Kunde J, Lubos E, Lackner KJ, Warnholtz A, Gori T, Blankenberg S, Munzel T; Gutenberg Health Study Investigators. Multiple endothelial biomarkers and noninvasive vascular function in the general population: the Gutenberg Health Study. *Hypertension*, 2012 Aug; 60(2):288-95.
16. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. *Atheroscler Thromb Vasc Biol.*, 2003 Feb; 23(2):168-75.
17. Yeboah, A. R. Folsom, G. L. Burke et al., "Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study: the multi-ethnic study of atherosclerosis," *Circulation*, 2009, vol. 120, no. 6, pp. 502–509.