



## ASSESSMENT OF FLOW MEDIATED DILATATION OF BRACHIAL ARTERY BY ANGIODEFENDER DEVICE IN PATIENTS WITH CONVENTIONAL RISK FACTOR WITH OR WITHOUT STABLE ISCHAEMIC HEART DISEASE

### Cardiology

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### ABSTRACT

**AIMS & OBJECTIVES:** The primary objective of this study was to assess percentage flow mediated dilatation (FMD) in patients with risk factors like smoking, diabetes, hypertension with or without stable ischaemic heart disease (SIHD) and compare it with the individuals without any risk factors.

**METHODS:** Study was conducted on 100 patients. Percentage FMD was measured by the Angio defender device and the results were compared.

**RESULTS:** Percentage FMD of Stable ischaemic heart disease with other conventional risk factor was  $6.65 \pm 1.17$  (p value < 0.001) whereas in patients without SIHD along with other conventional risk factor, percentage FMD was  $8.77 \pm 2.37$  (p value < 0.001) as compared to normal population ( $11.81 \pm 1.03$ ).

**CONCLUSION:** Patient with risk factors like smoking, diabetes, hypertension with or without SIHD showed significantly decreased percentage FMD as compared to individuals without any risk factors.

### KEYWORDS

Angio defender device, Flow mediated dilatation, Stable Ischaemic Heart Disease.

### INTRODUCTION:

Endothelium plays several important role in the systemic vasculature and is an important factor in the pathogenesis of atherosclerosis, hypertension and heart failure<sup>1,2,3</sup>. It is considered as an integration of risk factors affecting vascular function<sup>4</sup> and reflects the current vascular status as well as the risks associated to it<sup>5</sup>.

To assess endothelial function, various methods have been developed and are roughly divided into two types: tests assessing coronary endothelial function and tests assessing peripheral endothelial function<sup>2</sup>. Endothelial function of epicardial coronary arteries is assessed by the method of angiography, owing to its availability in clinical routine. More recently, non-invasive quantitative coronary angiography (QCA) has been developed by using computed tomography imaging or magnetic resonance imaging (MRI)<sup>6</sup>. Alterations in the coronary blood flow are assessed by the vessel diameter and Doppler flow velocities in the microvasculature<sup>7</sup>.

Coronary endothelial function correlated with brachial endothelial function in patients with angiographically normal coronary arteries, even when endothelial function is normal or impaired. These findings support the simultaneous presence of endothelial dysfunction in coronary and peripheral arteries<sup>2</sup>. The extent and severity of coronary artery disease can be predicted by FMD measured in forearm and can be correlated with the coronary endothelial function<sup>8</sup>.

Non-invasive endothelial function can be assessed by the method of arterial morphology, function of conductance arteries determined by FMD<sup>9</sup>. In the past decade, a non-invasive technique was evolved to evaluate FMD, an endothelium dependent function in the brachial artery is assessed by Brachial artery ultrasound imaging (BAUI)<sup>1,10,11</sup>. This technique stimulates the endothelium to release nitric oxide (NO) with subsequent vasodilation that can be imaged and quantitated as an index of vasomotor function<sup>1</sup>.

BAUI during reactive hyperemia is a widely used tool for quantifying endothelium dependent vasodilatation. Despite its reputation as the "gold standard" for measuring FMD, BAUI has not gained widespread clinical use in the general population and remains predominantly a research tool because this method is technically challenging, requires highly skilled operators using expensive equipment to capture the consistently high quality images needed for subsequent analysis<sup>1</sup>.

Angio defender device (Everist Genomics) which is CE certified and has been proven to be equivalent to gold standard BAUI for measuring percentage FMD<sup>8</sup> and does not require any expertise.

### MATERIALS & METHODS:

The present study was conducted in the Department Of Cardiology, RNT Medical College & MB Hospital from Aug 2015 to Nov 2016. A total of 100 cases were studied. All stable patients of either sex consecutively selected from the outdoor department of M B Hospital who were ready to participate, were included in this observational study. Written informed consent of each patient were obtained after explaining details of the study. Exclusion criteria were patients undergoing coronary catheterization for acute coronary syndrome or for other reasons like hypertensive crisis associated with troponin elevation, valvular heart disease, congenital heart disease, cardiomyopathy, patients with baseline ECG rhythm abnormalities. Percentage FMD was measured in the fasting state of the patient.

The Angio defender device uses a novel, proprietary software algorithm to analyse pulse wave amplitude data collected before and after brachial artery occlusion by a standard upper arm sphygmomanometric blood pressure cuff. The procedure is non-invasive and employs neither ultrasound nor Doppler flow analysis.

To measure %FMD, the device was run through a series of inflations and deflations in order to analyse the endothelial response to increased blood flow. %FMD was calculated using the following formula: %FMD = {(max P post-occlusion – mean P pre-occlusion) / mean P pre-occlusion} x 100

By combining the principles of blood pressure, pulse wave analysis, and a proprietary data analysis algorithm, the Angio defender device produces %FMD score.

Statistical analysis was done using the unpaired t-test.

### RESULTS:

Present study was conducted on a total of 100 patients out of which 90 were male and 10 female. Mean age was found to be 50.4 years. 90 out of 100 patients were less than 60 years of age and the remaining 10 patients were more than 60 years of age. Total no. of individuals free from all risk factor were 13. Mean age (in years) of population free

from all risk factor was  $42.46 \pm 4.52$ , in Diabetic Population  $45.75 \pm 3.96$ , in Hypertensive population  $57.34 \pm 5.37$ , in Smoker  $51.85 \pm 8.09$  and in SIHD  $54.54 \pm 9.22$ .

Percentage FMD measured in various subgroup based on age, sex and risk factors are shown in Table 1.

**Table 1- Percentage FMD in various subgroup**

Age group	% FMD
≤60 year(N=90)	7.68±2.44
>60 Years (N=10)	8.18±0.69
Female(N=10)	6.74±1.15
Male (N=90)	7.84±2.40
SIHD (N=44)	6.65±1.17
Diabetes (N=68)	7.03±1.26
Hypertension (N=44)	6.91±1.29
Smoker (N=68)	8.26±2.11

Percentage FMD of patients with conventional risk factor with or without SIHD were significantly lower compared to normal individual (p value < 0.001). Further, % FMD in patients with conventional risk factor with SIHD were significantly lower compared to patient with conventional risk factor without SIHD (p value < 0.001), (table 2).

**Table 2: Comparison of % FMD in SIHD, Non-IHD and Normal Individual**

	% FMD	
	Mean ±Sd	P Value
Normal (N=13)	11.81±1.03	
SIHD (N=44)	6.65 ± 1.17	<0.001
Non-IHD (N=43)	8.77 ± 2.37	<0.001
SIHD vs Non-IHD	--	<0.001

Percentage FMD in individuals having diabetes with SIHD and individuals with diabetes without SIHD along with other conventional risk factors were significantly lower compared to normal individuals (p value < 0.001). Percentage FMD in patients with diabetes and SIHD were significantly lower as compared to patient with diabetes without SIHD (p value < 0.001), (table 3).

**Table 3: Comparison of % FMD of Diabetes with SIHD, Diabetes without SIHD and Normal Individual**

	% FMD	
	Mean ±Sd	P Value
Normal (N=13)	11.81±1.03	
Diabetes with SIHD (with conventional risk factor) (N=44)	6.65 ± 1.17	<0.001
Diabetes without SIHD (with conventional risk factor) (N=24)	7.72 ± 1.13	<0.001
Diabetes with SIHD vs Diabetes without SIHD	--	<0.001

**DISCUSSION**

The primary objective of our study was to assess percentage FMD in patients with risk factors like smoking, diabetes, hypertension with or without SIHD and compare it with the individuals without any risk factors.

Percentage FMD in diabetics without SIHD were significantly lower as compared to normal individual which is similar to findings of Bots *et al.* who reviewed more than 200 papers from 1992 to 2001 and concluded that percentage FMD in diabetics were lower as compared to healthy subjects<sup>12</sup>.

In a study done by Neunteufl T *et al.*, CAD patients showed markedly impaired FMD as compared to the non-CAD group and to controls<sup>13</sup>. In our study also, patients with SIHD with any other conventional risk factors, percentage FMD was  $6.65 \pm 1.17$  which was significantly lower as compared to normal individual ( $11.81 \pm 1.03$ ). However, Corretti *et al.* reported that there was no significant difference in FMD between patients with known CAD and a control group of healthy individuals. Their study concluded that morphological but not functional parameters of the brachial artery were associated with the extent of coronary artery stenosis and atherosclerotic wall changes in the carotid arteries in patients with severe CAD<sup>14</sup>.

Early coronary atherosclerosis is associated with endothelial

dysfunction and it was demonstrated for the first time that severe endothelial dysfunction in patients with non-obstructive coronary artery disease is associated with increased cardiac events<sup>14</sup>. Endothelial dysfunction may be considered as a cardiovascular risk factor or at least as a cardiovascular risk marker<sup>5,16</sup> but impairment of vascular smooth muscle cell function has also been reported in diabetic patients and may be involved in altered FMD<sup>17</sup>.

Studies in patients with angiographically normal coronary arteries provide further evidence that endothelial dysfunction precedes and portends the development of atherosclerosis. Halcox *et al.* found both epicardial and microvascular endothelial dysfunction predicted future cardiovascular events independently of the angiographic presence of CAD at the time of enrollment<sup>18</sup>.

Study done by Shechter *et al.* also showed composite cardiovascular end points were significantly more common in subjects with below median %FMD of 10.7%<sup>19</sup>. Another confirmatory result is that a relation exists between the extent of the endothelial dysfunction, expressed by %FMD and the severity of CAD, as assessed by both the number of diseased vessel and the disease complexity, whenever angiographic lesion characteristics and location are considered in addition<sup>20</sup>.

Traditional methods of risk assessment for cardiovascular events use conventional risk factors to calculate risk and are often expressed as the 10-year Framingham Risk Score. However, these methods are not perfect in each individual. Although they identify high-risk groups, if followed up these high-risk groups contain at best only a fraction of the events that will occur in the subsequent 10 years. Aggressive risk factor modification can reduce morbidity and mortality from MI and stroke by 50%<sup>21</sup>. Despite weight gain, smoking cessation leads to prolonged improvements in endothelial function, which may mediate part of the reduced cardiovascular disease risk observed after smoking cessation<sup>22</sup>. The study by Modena *et al.* raises further possibility that persistent endothelial dysfunction during antihypertensive therapy identifies high-risk individuals and improvement in endothelial function obtained after six months of antihypertensive therapy was associated with a more favourable prognosis and hence endothelial function might be used to monitor the effectiveness of risk reduction therapy. Thus, evaluation of endothelial function could be advantageous in prevention of both primary and secondary events<sup>23</sup>.

Limitations of our study: We could not distinguish whether abnormal %FMD resulted from endothelium-dependent or endothelium-independent disorders as nitroglycerin induced vasodilation was not tested. Our study enrolled a small cohort of patients. Duration of risk factor was not taken into account, duration of risk factor may affect endothelial function. The possible confounding effect of cardiovascular medications and their interaction with risk factors also needs to be acknowledged.

**CONCLUSION**

In the present study %FMD was significantly lower in patients with risk factors like diabetes, smoking, hypertension with or without SIHD as compared to individuals without any risk factors. Further patients with SIHD has significantly decreased %FMD as compared to patient without SIHD therefore the clinical implication of our study is to monitor such patients as they are at a higher risk of cardiovascular morbidity and mortality so it can be used to predict future cardiovascular events. Life style modification and drug therapy may prevent both primary and secondary events in these group of patients.

**REFERENCES**

- Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, Deanfield J, Drexler H, Gerhard-Herman M, Herrington D, Vallance P. 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. *Journal of the American College of Cardiology*. 2002;Jan 16;39(2):257-65.
- Teragawa H, Ueda K, Matsuda K, Kimura M, Higashi Y, Oshima T, Yoshizumi M, Chayama K. Relationship between endothelial function in the coronary and brachial arteries. *Clinical Cardiology: An International Indexed and Peer-Reviewed Journal for Advances in the Treatment of Cardiovascular Disease*. 2005 Oct;28(10):460-6.
- Quyyumi AA: Endothelial function in health and disease: New insights into the genesis of cardiovascular disease. *Am J Med* 1998;105:32S-39S
- Schnabel RB, Schulz A, Wild PS, Siming CR, Wilde S, Eleftheriadis M, Herkenhoff S, Zeller T, Lubos E, Lackner KJ, Warmholtz A. Non-invasive vascular function measurement in the community: cross-sectional relations and comparison of methods. *Circulation: Cardiovascular Imaging*. 2011 Jan 1;CIRCIMAGING-110.
- Gokce N, Keaney JF Jr, Hunter LM, Watkins MT, Menzoian JO, Vita JA. Risk stratification for postoperative cardiovascular events via noninvasive assessment of endothelial function: a prospective study. *Circulation*. 2002;105:1567-1572.
- Husmann L, Gaemperli O, Schepis T, Scheffel H, Valenta I, Hoefflinghaus T, *et al.*

- Accuracy of quantitative coronary angiography with computed tomography and its dependency on plaque composition: plaque composition and accuracy of cardiac ct. *Int J Cardiovasc Imaging* 2008; 24(8): 895-904.
- 7 Di Mario C, Heyndrickx GR, Prati F, Pijls NH. Invasive imaging and haemodynamics. *The ESC textbook of cardiovascular medicine*, 2nd edn. Oxford University Press, New York. 2009 Aug 27:237-80.
- 8 Sancheti S, Shah P, Phalgune DS. Correlation of endothelial dysfunction measured by flow-mediated vasodilatation to severity of coronary artery disease. *Indian Heart Journal*. 2018 Jan 8.
- 9 Chowienczyk PJ, Kelly RP, MacCallum H, Millasseau SC, Andersson TL, Gosling RG, Ritter JM, Anggard EE. Photoplethysmographic assessment of pulse wave reflection: blunted response to endothelium-dependent beta2-adrenergic vasodilation in type II diabetes mellitus. *J Am Coll Cardiol*. 1999;34:2007-2014
- 10 Laurent ST, Lacolley PA, Brunel PA, Laloux BR, Pannier BR, Safar MI. Flow-dependent vasodilation of brachial artery in essential hypertension. *American Journal of Physiology-Heart and Circulatory Physiology*. 1990 Apr 1;258(4):H1004-11.
- 11 Anderson EA, Mark AL. Flow-mediated and reflex changes in large peripheral artery tone in humans. *Circulation*. 1989 Jan 1;79(1):93-100.
- 12 Bots ML, Westerink J, Rabelink TJ, de Koning EJ. Assessment of flow-mediated vasodilatation (FMD) of the brachial artery: effects of technical aspects of the FMD measurement on the FMD response. *Eur Heart J*. 2005, 26: 363-368. 10.1093/eurheartj/ehi017.
- 13 Neunteufl T, Katzenschlager R, Hassan A, et al. Systemic endothelial dysfunction is related to the extent and severity of coronary artery disease. *Atherosclerosis*. 1997;129:111-118.
- 14 Suwaidi JA, Hamasaki S, Higano ST, Nishimura RA, Holmes Jr DR, Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. *Circulation*. 2000 Mar 7;101(9):948-54.
- 15 Lind L, Berglund L, Larsson A, Sundström J. Endothelial function in resistance and conduit arteries and 5-year risk of cardiovascular disease. *Circulation*. 2011 Apr 12;123(14):1545-51.
- 16 Yeboah J, Folsom AR, Burke GL, Johnson C, Polak JF, Post W, Lima JA, Crouse JR, Herrington DM. Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study: the multi-ethnic study of atherosclerosis. *Circulation*. 2009;120:502-509. 10.1161/CIRCULATIONAHA.109.864801.
- 17 Lambert J, Aarsen M, Donker AJ, Stehouwer CD. Endothelium-dependent and -independent vasodilation of large arteries in normoalbuminuric insulin-dependent diabetes mellitus. *ArteriosclerThrombVasc Biol*. 1996, 16: 705-711. 10.1161/01.ATV.16.5.705.
- 18 J.P. Halcox, W.H. Schenke, G. Zalos, et al. Prognostic value of coronary vascular endothelial dysfunction *Circulation*, 106(2002), pp. 653-658
- 19 Shechter M, Issachar A, Marai I, Koren-Morag N, Freinark D, Shahar Y, Shechter A, Feinberg MS. Long-term association of brachial artery flow-mediated vasodilation and cardiovascular events in middle-aged subjects with no apparent heart disease. *International journal of cardiology*. 2009 May 1;134(1):52-8.
- 20 Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360(10): 961-972.
- 21 Nicolaides A. Screening for cardiovascular risk. *British Journal of Cardiology*. 2010;17(3):105.
- 22 Johnson HM, Gossett LK, Piper ME, Aeschlimann SE, Korcarz CE, Baker TB, Fiore MC, Stein JH. Effects of smoking and smoking cessation on endothelial function: 1-year outcomes from a randomized clinical trial. *Journal of the American College of Cardiology*. 2010 May 4;55(18):1988-95.
- 23 Modena MG, Bonetti L, Coppi F, Bursi F, Rossi R. Prognostic role of reversible endothelial dysfunction in hypertensive postmenopausal women. *Journal of the American College of Cardiology*. 2002 Aug 7;40(3):505-10.