Original Research Article

A study of brachial artery flow mediated dilatation and carotid intima media thickness in subjects having risk factors for coronary artery disease

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ABSTRACT

Background: Endothelial dysfunction (ED) is an early phenomenon in atherosclerosis and often progresses to structural changes and clinical manifestations. Brachial artery flow mediated dilatation (BAFMD) has recently emerged as a reliable tool for assessment of ED. Carotid artery intima media thickness (CCAIMT) is an established tool for the detection of early structural atherosclerosis. This study was done to assess the reliability of BAFMD as a surrogate marker of atherosclerosis by comparing it to CCAIMT.
Methods: Seventy-one subjects were divided in to Group I (n = 42, patients with overt cardiovascular disease; abnormal resting ECG or history of myocardial infarction/angina or an abnormal coronary angiogram), Group II (n = 17, apparently healthy individuals, with risk factors, but no overt cardiovascular disease) and Group III (n = 12, control, healthy individuals without risk factors). Ischemia induced BAFMD and CCAIMT were studied using ultrasound imaging along with presence of metabolic abnormalities.
Results: Age ranged from 18-70 years with male predominance [42 (49.4%)]. Mean BAFMD in Group I, Group II and Group III was 6.68±3.52%, 7.39±3.62 and 11.65±4.32% respectively. Impaired BAFMD was highest in Group I [31 (73.80%)] compared to other two groups (p = 0.0002). Abnormal CCA-IMT was significantly higher in group I [33 (78.57%)] than in group II [9 (52.94%)] and Group III (3 (25%)] (p = 0.0018).
Conclusions: Both BAFMD and CCAIMT can be used interchangeably as surrogate markers for endothelial dysfunction and atherosclerosis. BAFMD is a reliable tool for prediction of early atherosclerosis.

Keywords: Atherosclerosis, BAFMD, CCAIMT, Coronary artery disease, Endothelial dysfunction

INTRODUCTION

Coronary artery disease (CAD) is emerging as a major killer throughout the world. The chief underlying cause of CAD is atherosclerosis. Endothelial dysfunction (ED) is an early phenomenon in atherosclerosis and often progresses to structural changes and clinical manifestations.[1]

ED is characterized by a reduced bioavailability of endothelium-derived nitric oxide (NO).[2] It is an important precursor in the development of atherosclerosis. A number of risk factors for cardiovascular disease, including age, hypertension, obesity, hypercholesterolemia, diabetes mellitus and smoking are associated with systemic ED.

ED can be assessed invasively using agonists that stimulates the release of endothelial NO and noninvasively by performing occlusion of brachial artery flow with a blood pressure cuff, after which, the cuff is deflated and the change in brachial artery diameter is measured ultrasonographically.[2]

A noninvasive ultrasound technique to evaluate endothelial dysfunction; brachial artery flow-mediated dilatation (BAFMD) has recently been much used in the study of arterial physiology.[3,4] Typically, the change in vessel diameter detected by these invasive and noninvasive approaches is 10%. It is said to be impaired if the change is less than 7.5%. Impaired BAFMD has been proved to be correlated with the extent and severity of CAD.[5] An early detection of ED by BAFMD would lead to instituting preventive measures, thereby reducing CAD and stroke significantly.

The present study was undertaken to examine the incidence of impaired BAFMD and increased CCAIMT (accepted marker for atherosclerosis) in subjects having risk factors for cardiovascular disease and to find out whether their predictive values are similar.[6]

METHODS

This study was conducted on 71 patients admitted in the wards or attending the outpatient department at G.R. Medical College and J. A. Group of Hospitals, Gwalior between June 2010 to November 2011.

Institute Ethics Committee approval and written informed consent was obtained from all the patients before commencement of the study.

Cases were divided in to, Group I (n = 42, patients with overt cardiovascular disease; abnormal resting ECG or history of myocardial infarction/angina or an abnormal coronary angiogram), Group II (n = 17, apparently healthy individuals, with risk factors, but no overt cardiovascular disease) and Group III (n = 12, control, healthy individuals without risk factors).

BAFMD was used to assess the endothelial mediated vasodilator response of the artery to increased blood flow. CCA-IMT was assessed in all cases to ascertain early atherosclerosis. Resting ECG was performed on all subjects.

BAFMD test was performed in the fasting state; smoking and caffeinated beverages were prohibited on the morning of the study, and all vasoactive medications including nitrates, ACE inhibitors and beta blockers were withheld for 24 hours before the study. BAFMD was performed with the patient lying in supine position. After the patient, had been lying at rest for at least 5 minutes, the brachial artery was imaged above the elbow using a linear array transducer with a minimum frequency of 7 MHz attached to a high quality ultrasound system.

Baseline brachial artery diameter and blood flow velocities were recorded. The artery was then occluded completely using the sphygmomanometer cuff, tied around the arm and inflated to at least 50 mmHg above systolic pressure. The cuff was deflated after 5 minutes. The flow velocities were recorded again immediately after cuff deflation (and no later than 15 sec) and brachial artery diameter was recorded after 1 min of cuff deflation. Magnitude of FMD was expressed as percentage increase in diameter during hyperemic phase compared to baseline. After the cuff was deflated ischemia-induced distal hyperemia produced a transient increase of artery diameter. The relative change in mean arterial diameter was calculated as: % Dilation = (Maximum diameter - Baseline diameter) × 100 / Baseline diameter, where the maximum diameter was the maximum mean diameter observed at 45 – 60 seconds after cuff release. Endothelial dysfunction was defined at a cut off value of 7.5%.

Subjects voluntarily completed a questionnaire for identification of CV risk factors, which comprised: personal data (age, gender), hypertension or diabetes history, and cigarette smoking. An objective examination assessed systolic arterial blood pressure and body mass index.

Venous blood samples were withdrawn in the morning, after an overnight fast. Serums total cholesterol (TC), triglyceride (TG), high density lipoprotein - cholesterol (HDL - C) and fasting glucose concentrations were measured using standard enzymatic methods.

CCA-IMT: For carotid ultrasound study, the image was focused on the posterior (far) of the left carotid artery. A minimum of 4 measurements of the common carotid far wall were taken 10 mm proximal to the bifurcation to derive mean carotid IMT. Ultrasound analysis was done with high resolution echo Doppler machine (Toshiba Ecocee) with a 7.5 MHz high frequency linear vascular probe. A reading of more than 0.9mm was taken as abnormal.

Statistical analysis was done using IBM SPSS ver. 20 software. Chi square test was used for categorical variables. A 'p' value of less than 0.05 was taken as significant.

RESULTS

The age of study subjects ranged from 18-70 years. Out of 71 subjects, 42 (49.4%) were male and 29 (41.6%) were female.

Mean BAFMD in Group I, Group II and Group III was 6.68±3.52%, 7.39±3.62 and 11.65±4.32% respectively.

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respectively. Impaired BAFMD was highest in Group I [31 (73.80%)] compared to other two groups (p = 0.0002). Abnormal CCA-IMT was significantly higher in group I [33 (78.57%)] than in group II [9 (52.94%)] and Group III [3 (25%)] (p = 0.0018). Impaired BAFMD was recorded in 63.15%, 70.45%, 64.10%,71.42%, 100% and 68% patients with increased TG (p = 0.011), increased body mass index (p = 0.0001), increased WC (p = 0.012), smoking (p = 0.0013), impaired glucose tolerance (p = 0.0005) and diabetes mellitus (DM) (p = 0.01) respectively. Increased CCAIMT was recorded in 65.11%, 70.27%, 60.52%, 78.12%, 77.27%, 67.85%, 68.57% and 64% patients with raised BP (p = 0.002), increased total cholesterol (p = 0.0002), increased TG (p = 0.032), increased LDL (p = 0.0001), increased BMI (p = 0.0001), smoking (p = 0.0075), impaired fasting glucose (p = 0.001) and DM (p = 0.0477) respectively. Predictive value of both tests were comparable (p = 0.1349).
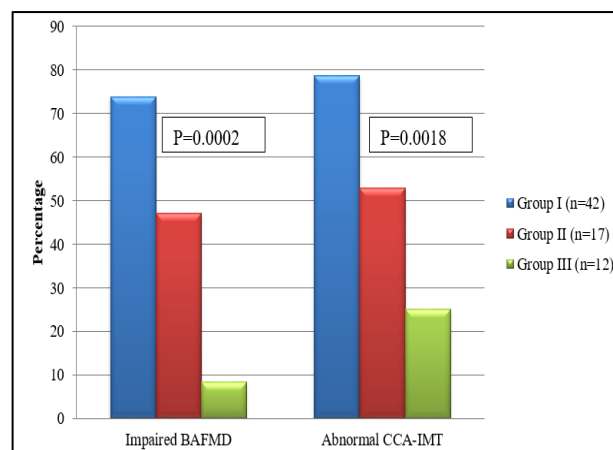

Figure 1: Impaired BAFMD and abnormal CCA-IMT among different groups.

Table 1: Comparison of BAFMD and CCAIMT with different risk factors (in group I and II).

Risk factor	BAFMD (<7.5%)	BAFMD (>7.5%)	P	CCAIMT (<0.9 mm)	CCAIMT (>0.9 mm)	P
Raised BP (n = 43)	26 (60.4)	17 (39.60)	NS	15 (34.88)	28 (65.11)	0.002
Increased TC (n = 37)	22 (59.45)	15 (40.54)	NS	11 (29.72)	26 (70.27)	0.0002
Raised TG (n = 38)	24 (63.15)	14 (36.84)	0.011	15 (39.47)	23 (60.52)	0.032
Reduced HDL (n = 32)	24 (75)	8 (25)	NS	8 (25)	24 (75)	NS
Raised LDL (n = 32)	24 (75)	08 (25)	NS	9 (28.12)	25 (78.12)	0.0001
Increased BMI (n = 44)	31 (70.45)	13 (29.54)	0.0001	10 (22.72)	34 (77.27)	0.0001
Increased WC (n = 39)	25 (64.10)	14 (35.89)	0.012	17 (43.58)	22 (56.41)	NS
Smoking (n = 28)	20 (71.42)	8 (28.57)	0.0013	9 (32.14)	19 (67.85)	0.0075
IFG (n = 35)	21 (60)	14 (40)	NS	11 (31.42)	24 (68.57)	0.001
IGT (n = 6)	6 (100)	0 (0)	0.0005	2 (33.33)	4 (66.66)	NS
DM (n = 25)	17 (68)	8 (32)	0.010	9 (36)	16 (64)	0.0477

Data is expressed as no of patients (%), BP; blood pressure, TC; total cholesterol, TG; triglyceride, HDL; high density lipoprotein, LDL; low density lipoprotein, BMI; body mass indexed, WC; waist circumference, IFG; impaired fasting glucose, IGT; impaired glucose tolerance, DM; diabetes mellitus, BAFMD; brachial artery flow mediated vasodilatation, CCA-IMT; common carotid artery intima media thickness, NS; not significant, p value <0.05 is considered as significant.

Table 2: The impact of increasing number of risk factors on BAFMD and CCA-IMT (Group II).

Risk factors	N	BAFMD (%)	CCA-IMT (mm)
Subjects with no risk factors	12	10.4	0.65
Dyslipidemia	19	8.9	0.66
HTN	15	8.7	0.68
DM	16	8.4	0.70
Smoking	27	8.8	0.71
Obesity	22	9.2	0.74
HTN + obesity	10	8.6	0.79
HTN + DM+ obesity	6	7.8	0.81
DM + Obesity+ HTN+ smoking	5	7.7	0.81
DM + Dyslipidemia+ HTN + obesity	5	7.5	0.87
DM + HTN + Smoking + Dyslipidemia	5	7.4	0.85
DM + Dyslipidemia + obesity + HTN + smoking	4	7.1	0.91
DM + Dyslipidemia + obesity + HTN+ smoking + CAD	3	6.9	1.007
DM+Dyslipidemia + obesity + HTN+ CAD	3	6.7	1.003

DM; diabetes mellitus; HTN; hypertension, CAD; coronary artery disease, BAFMD; brachial artery flow mediated vasodilatation, CCA-IMT; common carotid artery intima media thickness, p value <0.05 is considered as significant.

No significant difference was obtained between the predictive value of both BAFMD and CCAIMT tests (p = 0.1349).

DISCUSSION

ED is believed to be the earliest functional abnormality in blood vessels in the process of atherogenesis. It serves as a very important predictive factor for atherosclerosis, which may lead to CAD or stroke.[1]

Development of a noninvasive method of endothelial function assessment by BAFMD as described by Celermajer provided an extremely useful tool for cardiovascular research and for clinical application.[3] International task force on Brachial artery reactivity has recently laid guidelines for performance of FMD, thus standardizing the test for wider application.[4]

In present study BAFMD was reduced significantly in group I and II subjects compared to group III. Schnell et al studied endothelial functions in patients with hyperlipidaemia without any other risk factors. They found that in patients having modest elevations of TG or LDL do not have significantly impaired BAFMD.[7] In present study, similarly, raised TC was not correlated with impaired BAFMD. However, raised TG was correlated with both impaired BAFMD and raised CCAIMT.

Kasliwal studied CCAIMT and BAFMD in patients with or without metabolic syndrome. They found that metabolic syndrome per se was not associated with greater extent of subclinical atherosclerosis compared to individual cardiovascular risk factors. The presence of diabetes mellitus, however, resulted in significant endothelial dysfunction and evidence of subclinical atherosclerosis; similar to that seen in patients with already established coronary artery disease, thus, concluding that DM is a CAD equivalent.[7] In our study also, we had a good correlation of DM II with both impaired BAFMD and raised CCAIMT.

Celermajer did a similar study in smokers and compared the results with controls. BAFMD was observed to be normal in all the control subjects.[8] In the present study, amongst the 28 smokers, impaired BAFMD and raised CCAIMT was seen in significantly higher numbers.

The values of CCAIMT were significantly higher in groups I and II compared to group III. In a study by Dharmalingam et al fasting triglyceride was found to be significantly correlated with CCA-IMT.[9] We also found a significant difference between raised TG and increased CCAIMT.

In the study by Agarwal et al, mean CCA-IMT was significantly higher in DM patients with CAD and even those without overt CAD.[10] Mohan et al found significantly higher values of IMT in Diabetic subjects.[11]

In our study also, there was a strong correlation between DM and abnormal CCAIMT.

The present study 57.69% subjects had normal CCA-IMT and BAFMD. Hence, it appears that the predictive value of both the tests is comparable (p = 0.1349). R Ravikumar et al in the CUPS study, found a good correlation between BAFMD and CCAIMT in diabetic subjects.[12] However, Raymond et al performed a similar study in middle-aged subjects with low cardiovascular risk, concluded that, in relatively healthy middle-aged subjects, there is no significant correlation between CCAIMT and BAFMD. This observation suggested that these two tests have different and distinct predictive values. This finding may be related to a temporal dissociation between functional and structural vascular abnormalities in a low risk population.[13] However, in our study, the correlation between the predictive value of BAFMD and CCAIMT was good. No significant difference was found between their predictive values.

This suggests that BAFMD, a marker of endothelial dysfunction would also be a good predictor for atherosclerosis. Vice versa, CCAIMT, an accepted marker for atherosclerosis, would also function as a predictor of endothelial dysfunction. These two tests may therefore be used interchangeably for prediction of future CAD.

CONCLUSION

BAFMD and CCAIMT measurement by colour doppler ultrasound are very simple, cheap, non-invasive, easily available and convenient tests. So, both tests can be used as surrogate markers for endothelial function and atherosclerosis respectively and hence as early markers for CAD. They cannot replace coronary angiography to detect CAD. But by serial measurement the clinician can easily predict outcome of the subjects with cardiovascular risk factors about future development of overt disease and can start early intervention. Both these tests have similar predictive value and maybe used interchangeably. This study establishes that both FMD and IMT can serve as excellent screening tools for subjects having risk factors for cardiovascular disease to predict the development of coronary artery disease in the future.

REFERENCES

1. Furchgott RF, Zawadski JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature. 1980;288:373-6.
2. Palmer RM, Ferrige AG, Monacada S. Nitric oxide release accounts for the biological activity of

endothelium - derived relaxing factor. Nature. 1987;327:524-6.

3. Celermajer DS. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet. 1992; 340:1111-5.

4. Coretti MC, Anderson TJ, Benjamin EJ. Guidelines for the ultrasound assessment of endothelium dependent flow mediated vasodilatation of the brachial artery. A report of the international brachial artery reactivity task force. J Am Coll Cardiol. 2002;39:257-65.

5. Neunteufl T, Katzenschlager R, Hassan A. Systemic endothelial dysfunction is related to the extent and severity of coronary artery disease. Atherosclerosis.1997;129(1):111-8.

6. Haskote SS, Joshi SR. Carotid intimomedial thickness - a non - invasive index of vascular health. JAPI. 2008;56.

7. Scnell GB, Robertson A, Houston D, Malley L, Anderson TJ. Impaired brachial artery endothelial function is not predicted by elevated triglycerides. J Am Coll Cardiol. 1999:33(7):2038-43.

8. Celermajer DS, Sorensan KE, Georgakopoulos D. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium- dependent dilation in healthy young adults. Circulation. 1993;88:2149-55.

9. Dharmalingam M, Deshpande NR, Vidyasagar S. Triglyceride levels and its correlation with Carotid Intima-Media Thickness. Int J Diab Dev Countries. 2004;24:19-22.

10. Agarwal AK, Gupta PK, Singla S, Garg U, Prasad A, Yadav R. Carotid intimomedial thickness in type 2 diabetic patients and its correlation with coronary risk factors. JAPI. 2008;56:581-6.

11. Mohan V, Ravikumar R, Shanthi Rani S, Deepa R. Intima medial thickness of the carotid artery in South Indian diabetic and non-diabetic subjects: the Chennai Urban Population Study (CUPS). Diabetologia. 2000;43:494-9.

12. Ravikumar R, Deepa R, Shanthirani C, Mohan V. Comparison of carotid intima-media thickness, arterial stiffness, and brachial artery flow mediated dilatation in diabetic and non-diabetic subjects (the chennai urban population study cups-9. Am J Cardiol. 2002;90:702-7.

13. Raymond TY, Todd JA, Francois C. Relationship between carotid artery intima-media thickness and brachial artery flow- mediated dilatation in middle - aged healthy men. J Am Coll Cardiol. 2005;45:1980-6.