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Original Research Article

To study the endothelial dysfunction by brachial artery flow mediated dilatation in coronary artery disease patients

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ABSTRACT

Background: Brachial artery flow mediated dilatation (BAFMD), assessed by high resolution ultrasonography, reflects endothelium dependent vasodilator function. BAFMD is diminished in patients with atherosclerosis and with coronary risk factors and improves with risk reduction therapy.
Methods: Study was conducted on 50 patients of coronary artery disease from In-patients who were admitted in the Department of Medicine and 25 healthy control without cardiovascular disease risk factors. All patients having established CAD i.e. Acute coronary syndrome and past history of CABG/angioplasty were included in study. Those morbidly ill and patients with evidence of chronic inflammatory or malignant disease were excluded. Doppler ultrasound of brachial artery was performed in all of them to assess baseline lumen diameter and flow mediated dilatation (i.e. percent change in brachial artery diameter after occlusion cuff release). Patients were divided into two groups; first group was classified as those having BAFMD less than 7.5% and the second group consisted patients having BAFMD less than 10%.
Results: Flow mediated dilatation in cases was 6.87±5.48% as compared to the control group in which it was 13.08±3.40% and was statistically significant (P value 0.000002). Brachial artery flow mediated dilatation was abnormal in 80% cases at a cut off value <10% significant abnormalities; i.e. BAFMD <7.5% was found in 66% patients.
Conclusions: Endothelial function as assessed by FMD is significantly impaired in patient of coronary artery disease. Hence it may be used as an important screening tool in people having cardiovascular disease risk factors and may play as a crucial role in preventive cardiology.

Keywords: BAFMD, CAD

INTRODUCTION

Coronary artery disease is the cause of 25-30 per cent of deaths in most industrialized countries. The WHO has drawn attention to the fact that CAD is our epidemic, i.e. a disease that affects populations, not an unavoidable attribute of ageing. When the coronary artery disease emerged as the modern epidemic, it was the disease of the higher social classes in the most affluent societies. Fifty years later the situation is changing; there is a strong inverse relation between social class and coronary artery disease in developed countries.[1] Coronary artery disease is assuming serious dimension in developing countries. It is expected to be the single most import cause of death in India by the year 2015.

The risk of CAD in Indians is 3-4 times higher than white Americans, 6 times higher than Chinese, and 20 times higher than Japanese.[2,3] Indians are prone as a community to CAD at a much younger age.[4,5] CAD is affecting Indians 5-10 years earlier than other communities. Indians also show higher incidence of hospitalization,

morbidity, and mortality than other ethnic groups.[6] This global phenomenon of prematurity and severity suggests that the disease starts at an early age and has a malignant course.[7]

Brachial arterial flow-mediated dilation (BAFMD), assessed by high-resolution ultrasonography, reflects endothelium-dependent vasodilator function. BAFMD is diminished in patients with atherosclerosis and with coronary risk factors, and improves with risk-reduction therapy. Therefore, the measurement of BAFMD can be a good prognostic instrument in preventive cardiology, is useful to predict short-term postoperative cardiovascular events in a high-risk population and to assess long-term cardiovascular risk in a lower risk population, and is an excellent experimental tool to detect changes in endothelial function after new therapeutic interventions.[8]

METHODS

Study was done in Department of Medicine G.R.M.C., Gwalior. Study included 50 patients of coronary artery disease and 25 healthy control without cardiovascular disease risk factor. All patients having established CAD a) Acute coronary syndrome b) Past history of CABG/ angioplasty were included in the study.

Those morbidly ill patients and patients with evidence of chronic inflammatory or malignant disease were excluded. Subjects fasted for at least 8 to 12 hours before the study and they were studied in a quiet, temperature controlled room.

In addition, subjects did not exercise, didn't ingest substances that might affect flow mediated dilatation such as caffeine high fat food, and vitamin C or use tobacco for at least 4 to 6 hours before the study. High resolution echo-Doppler (Toshiba Ecocee) with a 7.5 MHz high frequency linear vascular probe that has an axial resolution of 0.1 mm was used for small parts (Brachial artery) to measure arterial diameter in right brachial artery at affixed distance.

The subject is positioned with the arm in a comfortable position for imaging the brachial artery. The brachial artery was imaged above the antecubital fossa in the longitudinal plane (approximately 4 cm above birfucation). A segment with clear anterior and posterior intimal interfaces between the lumen and vessel wall is selected for 2-D gray-scale imaging.

A sphygmomanometric cuff is first placed on the forearm. A baseline rest image is acquired, and diameter measurement were taken from one media-adventitia interface to other. Thereafter, arterial occlusion is created by cuff inflated to suprasystolic pressure. Typically, cuff is inflated to at least 50 mm Hg above systolic pressure for 5 minutes. Lumen diameter was then measured a second time 45-60 seconds after deflation. Percentage increase in lumen diameter during post ischaemic hyperemia as compared to basal lumen diameter was labeled as flow mediated dilatation (FMD%), a marker of endothelium dependent dilatation.

RESULTS

Indians are prone as a community to CAD at a much younger age. In present study, the mean age was 53.46±12.82 and ranged from 28-82 years. In the present study, 30% cases were ≤45 years. 42% of our patients were under the age of 50 years. The mean age of cases having impaired BAFMD (<10%) in present was 53.67±13.79 years. In present study 83.33% patients from the age group >60 years are having impaired FMD. In present study 8 (16%) patients were having diabetes mellitus. 7 (16.3%) of the males were diabetic and 1 (14.3%) of the females was diabetic. 87.5% of diabetic patients showed impaired BAFMD.

Central obesity as described by increased waist circumference was found in 52% of cases of CAD .47.5% of males was obese and 85.7% of females were obese.

Dyslipidemia is strongly related both to atherosclerotic plaque formation and to endothelial dysfunction. In present study 37 (84%) patients were having dyslipidemia. Total 24% patients had hypercholesterolemia, 91.66% hypercholesterolemia patients showed impaired BAFMD.

In the present study 42% of population was having hypertriglyceridemia, 85.7% of hypertriglyceridemic patients showed impaired BAFMD. Most of them (71.42%) had significant impairment (BAFMD < 7.5 %).

Total 58% patients had low HDL, Mean LDL cholesterol in present study was 109.14+40.34 mg/dl, present study showed 26% had increased serum LDL cholesterol. In present study, 85.7% patients with high LDL showed impaired BAFMD.

In present study 36 (83.7%) of the males were smokers, none of the females were smokers. 83.33% of smokers had impaired BAFMD.

In present study mean base-line lumen diameter was 4.22±0.58mm in cases and in the control group it was 3.61±0.55 mm. the difference was statistically significant (p value-0.00004).

In the present study mean diameter after occlusion cuff release was 4.53±0.60 mm and in the control group it was 4.09±0.56 mm and was statistically significant (p value-0.0031). Flow mediated dilatation in percentage was 6.87±5.48 as compared to the control group in which it was 13.08±3.40 and was statistically significant (p value-0.000002).

Present study was conducted on patients of established coronary artery disease, it can be presumed that majority

of our cases would have endothelial dysfunction. In the present study 80% of patients had abnormal BAFMD (<10%). Significant abnormal BAFMD i.e. less than 7.5%, was seen in 66% of our cases.

DISCUSSION

The present study involved subjects of Coronary Artery Disease (CAD) and conversely can be presumed to already have endothelial dysfunction. Hence the present study was designed to establish an association between the endothelial dysfunction detected by BAFMD and patients of CAD which is an outcome primarily of endothelial dysfunction.

Indians are prone as a community to CAD at a much younger age. In present study, the mean age was 53.46±12.82 and ranged from 28-82 years. In the present study, 30% cases were ≤45 years. In some studies, from India the percentage of patients below the age of 45 years suffering from acute myocardial infarction, is reported to be as high as 25 to 40%.[20,21]

Table 1: Age and sex distribution of patients of CAD.

Age	Male (n=43)	Female (n=07)	Total (n=50)
20-29	1 (2.32%)	0 (0%)	1 (2%)
30-39	7 (16.27%)	0 (0%)	7 (14%)
40-49	10 (23.25%)	3 (42.85%)	13 (26%)
50-59	9 (20.93%)	1 (14.29%)	10 (20%)
60-69	10 (23.25%)	2 (28.57%)	12 (24%)
70-79	4 (9.30%)	1 (14.29%)	5 (10%)
≥80	2 (4.65%)	0 (0%)	2 (4%)

42% of our patients were under the age of 50 years; this observation is consistent with Enas et al.[9] He observed that among Asian Indian men, about half of all MI occur under the age of 50.

The mean age of cases having impaired BAFMD (<10%) in present was 53.67±13.79 years. In Kuvin et al study mean age amongst study population (n=94) was 56±2 year which is consistent with present study.[10] In Sondegaard E et al, study on patients with established ischemic disease (n=119) mean age group was 62±9.9 year.[11] Wu et al, who studied patients with chest pain, mean age in patients with abnormal endothelial dysfunction was 65.9±1.28 years.[12] This shows that Indians are likely to have earlier onset of epithelial dysfunction.

In present study 83.33% patients from the age group >60 years are having impaired FMD. Yavuz et al, in 2008 studied on 30 elderly (mean age 71.3±5.80 and 36 younger age (mean age 26.5±7.2) subjects free from major cardiovascular risk factors and concluded that endothelial function detected by FMD declines with increasing age in healthy human subjects.[13] Advanced age is a predictor of impaired endothelial function. FMD of the elderly group was significantly lower than the younger group (7.9±3.1) in the elderly, 10.8±1.9 in the younger group, p<0.001).

In present study 43 (86%) were male and 7 (14%) were female which was consistent with Sondegaard E et al study in which 85 (71%) were males.[11] In present study, 6 (85%) of the females (n=7) showed impaired BAFMD, whereas 34 (68%) of the males (n=43) showed impaired BAFMD. In Wu et al study 97.4% were males in CAD patients with endothelial dysfunction in abnormal thallium tests group (n=40) and 93.3% in patients with normal thallium tests group (n=15).[12]

Table 2: Habit of smoking of patients of CAD.

Habit of smoking	Male (n=43)	Females (n=7)	Total (n=50)
Smoker	36 (83.7%)	0 (0%)	36 (72%)
Non-smoker	7 (16.3%)	7 (100%)	7 (14%)

The mean BMI in the present study is 22.89±3.15kg/m^2, our 30% study population was obese and 42% were having BMI within normal limit whereas 8% were underweight. 60% of obese CAD patients were having impaired FMD.

Table 3: Distribution of cases according to BMI of patients of CAD.

BMI	Male (n=43)	Females (n=7)	Total (n=50)
Underweight (< 18.5)	4 (9.3%)	0 (0%)	4 (8%)
Normal (18.5-22.9)	20 (46.5%)	1 (14.3%)	21 (42%)
Overweight (23-24.9)	8 (18.6%)	2 (28.6%)	10 (20%)
Obese 1 (25-29.9)	11 (25.6%)	4 (57.1%)	15 (30%)
Obese 2 (≥30)	0	0	0

Mean BMI in Sondegaard Eva study was 26.6±4.1 kg/m^2.[13]

In Lewis et al, study on subjects having hypertriglyceridemia but with normal LDL mean BMI in subjects with high triglycerides was 30.10±1.03 kg/m^2 and in patients with high cholesterol was 27.96±2.03 kg/m^2 while in control group mean BMI was 25.02±0.30 kg /m^2.[22]

In Kuvin et al study in, the mean BMI amongst study population (n=94) was 29±1 kg /m^2. Amongst men, mean BMI was 28±1 kg/m^2, and amongst female, it was 29±1 kg/m^2.[10]

In present study 26 (52%) of the patients having increased waist circumference. Out of them, 20 (47%) of

the males are having increased waist circumference, whereas 6 (85.7%) of the females are having increased waist circumference.

19 (73.07%) of the patients having increased waist circumference showed impaired BAFMD. In present study 8 (16%) patients were having diabetes mellitus. 7 (16.3%) of the males were diabetic and 1 (14.3%) of the females was diabetic. 87.5% of diabetic patients showed impaired BAFMD.

Table 4: Distribution of cases according to blood sugar level of patients of CAD.

	Male (n=43)	Females (n=7)	Total (n=50)
Euglycemic	36 (83.7%)	6 (85.7%)	42 (84%)
Diabetic	7 (16.3%)	1 (14.3%)	8 (16%)

Table 5: Triglycerides in cases of patients of CAD.

Serum triglycerides	Male (n=43)	Females (n=7)	Total (n=50)
Normal	24 (55.8%)	5 (71.4%)	29 (58%)
Hyper-triglyceridemia ≥150mg/dl	19 (44.2%)	2 (28.6%)	21 (42%)

This is consistent with a study conducted by Kuvin et al, 9 (9.57%) patients were diabetic amongst study population (n=94), amongst men 6 (12%) were diabetic and 3 (7%) of the women were diabetic.[10]

In Wu et al study, 27.5% patients were diabetic in patients of CAD with abnormal thallium tests group and 20% in CAD patients with normal thallium tests group.[12]

In Sondegaard E et al, study 33 (28%) of the established ischemic heart disease patients (n=119) were having hypertension which is comparable to present study.[11]

In present study mean systolic BP is 127.92±18.95 mm Hg. 14 (28%) of the patients were hypertensive. Out of them, 10 (71.42%) of the hypertensive patients showed impaired FMD. Most of the patients (42.5%) with impaired BAFMD had pre-hypertension.

In Wu et al study 42.5% patients were hypertensive in patients with abnormal thallium tests group and 53.3% in patients with normal thallium tests group.[12] In Bhargava K et al study, 46.6% patients were hypertensive in group 3 i.e. patients with CAD but no DM and 65.7% in group 4 i.e. patients with both CAD and DM.[15] Perticone Froncesco et al, for the first time showed that forearm endothelial dysfunction is a marker for future cardiovascular morbid event in initially untreated and uncomplicated subjects with essential hypertension.[23]

Dyslipidemia is strongly related both to atherosclerotic plaque formation and to endothelial dysfunction.

In present study 37 (84%) patients were having dyslipidemia. 31 (72.09%) of the males were having dyslipidemia while 6 (85.71%) of the females were having dyslipidemia which was similar to the study conducted by Sondegaard E et al, 83 (70%) patients were having dyslipidemia.[11] In Bhargava K et al, study 31 (53.4%) patients in group 3 (n=58) and 18 (51.4%) patients in group 4 were having dyslipidemia.[15]

In present study mean serum cholesterol observed was 176.07+4.72 mg/dl.

Table 6: Relation of BAFMD with serum LDL cholesterol of patients of CAD.

LDL Cholesterol	BAFMD			
	Abnormal response			Normal response
	FMD < 7.5%	FMD 7.5%-<10	Total (<10%)	(FMD ≥ 10%)
Normal (n=36)	23 (63.88%)	5 (13.8%)	28 (77.77%)	8 (22.2%)
High ≥ 130 (n=14)	0 (71.4%)	2 (14.28%)	12 (85.77%)	2 (14.28%)

Total 24% patients had hypercholesterolemia, 91.66% hypercholesterolemia patients showed impaired BAFMD. In Kuvin et al, study, mean total cholesterol amongst study population was 207±5 mg/dl which is higher compared to present study.[11]

In Wu et al, study on chest pain syndrome patients, hypercholesterolemia was observed in 35% of patient with abnormal thallium tests group (n=40) and in 26.7% in patients with normal thallium tests group (n=15).[12] 42% of present study population was having hypertriglyceridemia, 44.2% of the males were having increased triglycerides whereas in female it was 28.6%. 85.7% of hypertriglyceridemic patients showed impaired BAFMD. Most of them (71.42%) had significant impairment (BAFMD < 7.5 %). Mean HDL in present study was 40.08±6.88 mg/dl. Total 58% patients had low HDL, 51.2% of the males had low HDL while all of the females showed low HDL. However other studies have shown higher values of HDL.

In Kuvin et al, study, mean HDL cholesterol amongst study population (n=94) was 51±2 mg/dl, amongst male it was 47±2 mg/dl and in female mean HDL cholesterol

was 56± 3 mg/dl.[10] Kitta et al in his prospective study on 251 patients with newly diagnosed CAD observed mean HDL-C 48±13 mg/dl in patients with persistently impaired BAFMD and 46±11 mg/dl in patients with improved BAFMD.[17]

Mean LDL cholesterol in the present study was 109.14±40.34 mg/dl, present study showed 26% had increased serum LDL cholesterol, 25.6% of the males had increased cholesterol while in female it was 28.6%. In present study, 85.7% patients with high LDL showed impaired BAFMD. In Kuvin et al, study mean LDL cholesterol amongst study population was 122±6 mg/dl, amongst male it was 125±7 mg/dl and amongst female it was 117±9 mg/dl. Kitta et al, in his study observed mean LDL-C 130±36 mg/dl in patients with impaired and 128±35 mg/dl in patients with improved BAFMD.[10,17]

In present study 36 (83.7%) of the males were smokers, none of the females were smokers.

Table 7: Relation of BAFMD with habit of smoking of patients of CAD.

Habit of smoking	BAFMD			
	Abnormal response			Normal response (FMD ≥ 10%)
	FMD < 7.5%	FMD 7.5%-<10	Total (<10%)	
Non-smoker (n=14)	6 (42.85%)	4 (28.57%)	10 (71.4%)	4 (28.57%)
Smoker (n=36)	27 (75%)	3 (8.34%)	30 (83.34%)	6 (16.67%)

Table 8: Relation of BAFMD with risk factors of patients of CAD.

Risk factors	BAFMD			
	Abnormal response			Normal response (FMD ≥ 10%)
	FMD < 7.5%	FMD 7.5%-<10	Total (<10%)	
Hypertension (n=14)	8 (57.14%)	2 (14.29%)	10 (71.43%)	4 (28.57%)
DM (n=8)	5 (62.5%)	2 (25%)	7 (87.5%)	1 (12.5%)
Smoking (n=36)	27 (75%)	3 (8.33%)	30 (83.33%)	6 (16.67%)
Dyslipidemia (n=37)	23 (62.16%)	7 (18.92%)	30 (81.08%)	7 (18.92%)
Obesity (n=15)	6 (40%)	3 (20%)	8 (60%)	6 (40%)

Table 9: Relation of BAFMD with prevalence of risk factors of patients of CAD.

Risk factors	BAFMD			
	Abnormal response			Normal response (FMD ≥ 10%)
	FMD < 7.5%	FMD 7.5%-<10	Total (<10%)	
Smoking + DM (n=4)	4 (100%)	0 (0%)	4 (100%)	0 (0%)
Smoking + HTN (n=9)	6 (66.67%)	0 (0%)	6 (100%)	3 (33.33%)
Smoking + Obesity (n=8)	4 (50%)	0 (0%)	4 (50%)	4 (50%)
Smoking + Dyslipidemia (n=24)	17 (70.83%)	3 (12.5%)	20 (83.83.33%)	4 (16.67%)
Dyslipidemia + Obesity(n=11)	5 (45.46%)	3 (27.27%)	8 (72.73%)	3 (27.27%)
DM + HTN(n=2)	1 (50%)	1 (50%)	2 (100%)	0 (0%)
DM + Obesity(n=2)	0 (0%)	2 (100%)	2 (100%)	0 (0%)
Obesity + HTN(n=7)	3 (42.86%)	1 (14.28%)	4 (57.14%)	3 (42.86%)
Smoking + DM + HTN(n=1)	1 (100%)	0 (0%)	1 (100%)	0 (0%)
DM + HTN + Obesity(n=1)	0 (0%)	1 (100%)	1 (100%)	0 (0%)
Dyslipidemia + Obesity +HTN (n=2)	1 (50%)	1 (50%)	2 (100%)	0 (0%)
Smkoing + DM + HTN+ Obesity(n=0)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Smoking + DM + HTN + Dyslipidemia + Obesity(n=0)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

In present study mean base-line lumen diameter was 4.22±0.58mm in cases and in the control group it was 3.61±0.55 mm. The difference was statistically significant (p value-0.00004) and this was consistent with Bhargava K et al, study in which mean base-line diameter was 3.800±0.434 mm in patients with CAD but no DM group and 3.797±0.670 mm in patients with both DM and CAD group.[15] Similar observation were made by

Sondegaard Eva et al study base line lumen diameter was 3.97±0.68 mm.[11] In the present study mean diameter after occlusion cuff release was 4.53±0.60 mm and in the control group it was 4.09±0.56 mm and was statistically significant (p value-0.0031).

Flow mediated dilatation in percentage was 6.87±5.48 as compared to the control group in which it was 13.08±3.40 and was statistically significant (p value-0.000002). In a study conducted by Wu et al healthy control subjects had significantly higher FMD values (18.88%±2.31%) than patients overall; patients with risk factors but no CAD had slightly higher FMD measurements (7.85%±1.66%) then those with CAD (5.91%±1.07%). This was similar to the results achieved by us.[12]

Table 10: Summary of clinical and biochemical profile of all cases of patients of CAD.

Clinical and biochemical profile	Cases Mean ±SD
Age	53.46±12.82
Sex	Male: 43 (86%) Female: 7 (14%)
SBP	127.92±18.95
DBP	79.2±9.86
BMI	22.95±3.15
Waist circumference	88.90±8.08
Blood sugar	106.02±32.52
Lipid profile	
TC	176.07±4.72
TG	150.72±62.58
HDL	40.08±6.88
LDL	109.14±40.34
Baseline lumen diameter	4.22±0.58
Lumen diameter after occlusion - cuff release	4.53±0.60
FMD (%)	6.87±5.48

In another study by Robert A. et al, flow mediated dilatation was significantly greater (p<0.01) in the normal subjects (n=10) than in the subjects with coronary artery disease risk factor (13.4±5.3% versus 7.9±3.6%) using the upper arm occlusion technique. Invasive studies on adult coronaries show that flow mediated dilatation is 10-12% for vessels of about 3 mm diameter. Celermajer et al also reported flow mediated vasodilatation in their subjects ranging from -1to 17%.[18,19]

In Sondegaard Eva et al study on 119 patients with established ischemic heart disease, ambulatory holter monitoring for a mean time of 48±11 hours were done.[11] They recorded 181 episodes of ischemic ST segments distributed amongst 31 patients (26%). Fifteen episodes (8%) were symptomatic and distributed among 10 patients; the remaining 166 episodes were asymptomatic. FMD in all patients was 4.38±5.66, in patients with ischemic episode was 2.09±4.935 and in patients with no ischemic episode was 5.20±5.71%. This is similar to observations made in the present study.

In present study 80% of patients had abnormal BAFMD (<10%). Significant abnormal BAFMD i.e. less than 7.5%, was seen in 66% of our cases. Wu et al, described the sensitivity of 72.5% and specificity of 73.1% to detect CAD at a FMD cut off value of 7.5%.[12]

Brachial artery flow mediated dilatation as assessed by using high frequency Doppler ultrasound provides a non-invasive and convenient method for detection of endothelial dysfunction. This may be used for early detection of endothelial dysfunction and in prognosis of clinical events such as coronary artery disease. Hence it could be used as a screening tool in those who are having risk factors for coronary artery disease.

CONCLUSION

In this study, brachial artery flow mediated dilatation was abnormal in 80% of cases at a cut off value <10%. Significant abnormality, that is, BAFMD <7.5% was found in 66% patients.

As present study was conducted in patients of established coronary artery disease and significant abnormality was detected in majority of cases. Hence it may be used as an important screening tool in people having cardiovascular disease risk factors and may play a crucial role in preventive cardiology.

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