ROLE OF NON INVASIVE STUDY OF BRACHIAL ARTERY FLOW MEDIATED VASODILATATION WITH CORRELATION TO ENDOTHELIAL DYSFUNCTION IN HYPERTENSIVE PATIENTS

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ABSTRACT

BACKGROUND

The endothelium is an early target of cardiovascular diseases like hypertension and Diabetes mellitus (DM). In hypertension, endothelial dysfunction has been shown at the level of both resistance and conduit arteries. The fact that Forearm's Brachial artery endothelial dysfunction is a marker of future cardiovascular events in patients with hypertension stresses the importance of the clinical evaluation of endothelial function.

MATERIALS AND METHODS

This is a prospective study of hypertensive patients admitted in King George Hospital of Andhra Medical College, Visakhapatnam, India during May 2015 to August 2016 and diagnosed as per the criteria laid down by JNC 7 Classification. Patients of Diabetes Mellitus, Hyperthyroidism, Heart Failure, Coronary Artery Disease, Smokers and Peripheral Vascular Disease which are known to affect endothelial dysfunction were excluded from the study.

RESULTS

The study group comprised of 50 subjects and the control group had 30 subjects. There are 18 males (59.4%) and 12 females (39.6%) among Controls and 31 males (62%) and 19 females (38%) in the Cases group. In this study, the mean age among the controls is (55.6±13.63) and among the cases is (56.4±15.24). Mean FMD (Flow-mediated dilation) among Cases is 8.15 and mean FMD among controls is 19.3. Mean Hyperemic Flow among Cases is 70.1 and among Controls is 121. 26% of the males have Endothelial Dysfunction and 9% of the females among cases have Endothelial Dysfunction.

CONCLUSION

FMD% is a diagnostic aid for evaluation of endothelial function. It is an experimental tool to measure endothelial dysfunction which is a fundamental basis for atherogenesis and CAD. It is a user friendly, non- invasive, cheap, reliable, reproducible technique for risk stratification of CAD.

KEYWORDS

FMD (Flow Mediated Dilatation), Endothelial Dysfunction, Non - Invasive Study, Ultrasonographic measurement.

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INTRODUCTION: Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths in India[1]. This fact is important because hypertension is a controllable disease and a 2 mmHg population-wide decrease in BP can prevent 151,000 stroke and 153,000 coronary heart disease deaths in India[2]. Systolic BP 140 mmHg and/or diastolic BP 90 mmHg is the currently accepted dividing line based on epidemiological and intervention studies[3].

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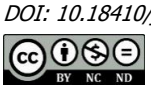


The endothelium is an early target of cardiovascular diseases like hypertension and Diabetes mellitus (DM). This key role not only results from its capacity to respond to numerous autocrine and paracrine stimuli and to mechanical factors like shear stress but also from the pathophysiological consequences of endothelial dysfunction on vasomotor tone, arterial stiffness, arterial remodeling, and inflammation. In hypertension, endothelial dysfunction has been shown at the level of both resistance and conduit arteries and mainly results from an increase in nitric oxide (NO) degradation by interaction between NO and superoxide anions. Development of non-invasive methods of endothelial function assessment by brachial artery flow mediated vasodilatation (FMD), as described by Celermajer, provided an extremely useful tool for cardiovascular research and for clinical application. This test can be performed easily and has proven reproducibility. The International Task Force on brachial artery reactivity has recently laid guidelines for performance of FMD, thus standardizing the test for wider application[4,1,5].

Flow mediated dilatation is designated as an endothelium dependent process, that reflects the relaxation of artery, when exposed to increased flow and thereby increased shear stress. This physiologic process was first described by Schetzenmayer. This non-invasive technique for testing endothelial function by Ultrasonographic measurement of FMD has recently generated considerable interest as a marker of atherosclerosis, played important role in prediction of clinical hypertensive and coronary events and is found to be a useful access for endothelial dysfunction. In humans with abnormal endothelium dependent vasodilatation has been observed in the brachial artery. Since, endothelial function has been defined as an excellent barometer of vascular health and disease process; it can be optimally utilized to gauze the severity of disease process like atherosclerosis and related pathophysiology. Hence, present study has been designed to measure flow mediated vasodilatation of brachial artery by high resolution ultrasonographic imaging and pulse Doppler study [6,7].

AIMS AND OBJECTIVES:

1. To study endothelial dysfunction in patients of Hypertension and to compare with age and sex matched control subjects.
2. To correlate the severity of Hypertension with endothelial dysfunction.

Flow Mediated Dilatation: The brachial artery FMD assessment was performed once in all subjects using 7.5 MHz transducer attached to Philips ultrasound machine. The test is done after overnight fasting. After tying the sphygmomanometer cuff to the right arm with the patients in supine position, the brachial artery is imaged in the antecubital fossa and its diameter measured from intima media manually at end-systole. The systole and diastolic VTIs (Velocity Time Integrals) are also recorded using pulsed wave Doppler. The arm was then occluded with the sphygmomanometer cuff inflated to at least 50 mm Hg above systole blood pressure for five minutes. The same measurements are repeated immediately within 15 seconds after release of the cuff. The brachial artery diameter is measured again at 1 minute to assess FMD. The ultrasound of the brachial artery is continuously recorded on the videotape before, during and up to two minutes after release of occlusion.[4]

The Flow in the Brachial Artery Calculated as:

Baseline flow = $\pi\ d_1^2/4$. HR1. (VTIS1 + VTID1); where d1 is brachial artery diameter, HR1 is heart rate, VTI S1 is systolic VTI and VTID1 is diastolic VTI at baseline.

Reactive hyperemia flow = $\pi\ d_2^2/4$.HR2 (VTIS2 + VTID2); where d2 is brachial artery diameter, HR2 is heart rate, VTIS2 is systolic VTI and VTID2 is diastolic VTI measured immediately after release of cuff. Percentage increase in brachial artery flow was calculated as-% Reactive hyperemia = (Reactive Hyperemia flow- Baseline flow) × 100/Baseline flow. FMD was calculated as- FMD = (d3- d1) × 100/ d1; where d3 is brachial artery diameter at 1 minute cuff release.

Clinical Assessment of Endothelial Function: Endothelial function can be assessed by both invasive and non-invasive methods. Non-invasive method is to measure brachial artery dilatation in response to shear stress due to release of nitric oxide from endothelium has been correlated.

METHODOLOGY: AIM OF THE STUDY:

1. To study endothelial dysfunction in patients with Hypertension and to compare with age and sex matched control subjects.
2. To correlate the severity of Hypertension with endothelial dysfunction.

MATERIAL AND METHODS:

Study Design: Prospective Study:

Selection of Cases: Cases of Hypertension treated in OPD or admitted to different Wards, King George Hospital of Andhra medical College, Visakhapatnam, Andhra Pradesh, India, during May 2015 to August 2016 and diagnosed as per the criteria laid down by JNC 7 Classification constituted the material for the present study.

Inclusion Criteria: JNC 7 Classification of Hypertension.

Category	Systolic Pressure (mm Hg)	Diastolic Pressure (mm Hg)
Normal	<120	<80
Pre-Hypertension	120-139	80-89
Stage 1 HTN	140-159	90-99
Stage 2	>160	>100

Patients are included according to the above criteria irrespective of their drug intake.

Exclusion Criteria: Patients of Diabetes Mellitus, Hyperthyroidism, Heart Failure, Coronary Artery Disease, Smokers and Peripheral Vascular Disease which are known to affect endothelial dysfunction were excluded from the present study.

Study Protocol:

1. Cases were selected as per the Inclusion and Exclusion criteria described above.
2. The patients were subjected to thorough history taking; clinical examination and relevant biochemical investigations as described below and the findings were recorded in Case Record Form.
3. Brachial artery FMD shall be performed in all the included subjects after taking informed consent for the study.

Assessment of brachial artery Flow Mediated Dilatation (FMD), as described by Celermajor provided an extremely useful tool for cardiovascular research and for clinical application. The Brachial artery FMD assessment to be performed in all included subjects using high resolution ultrasonography of the brachial artery.

Smoking will be prohibited for at least 4 hrs. before the test and all the vasoactive drugs will be withheld for 48 hrs preceding the test. Brachial artery is imaged in the antecubital fossa and its diameter is measured in End Systole. Systolic and diastolic VTI of brachial artery were recorded with Hewlett- Packard Image Point Machine using 7.5 to 10 MHz linear transducer probe. After Baseline images along with measurements were obtained, cuff compression was done for 5 min and imaging started 15 sec prior to release of cuff and observed for 3 min and then images and measurements were obtained at 3rd min.

Statistical Analysis: In the present study the data collected is analyzed statistically by computing the standard quantities namely mean, Standard deviation, Standard error of mean and percentages. The differences between different parameters based on quantitative variables are compared using student's t test for independent samples and the difference is considered statistically significant whenever p value <0.05.

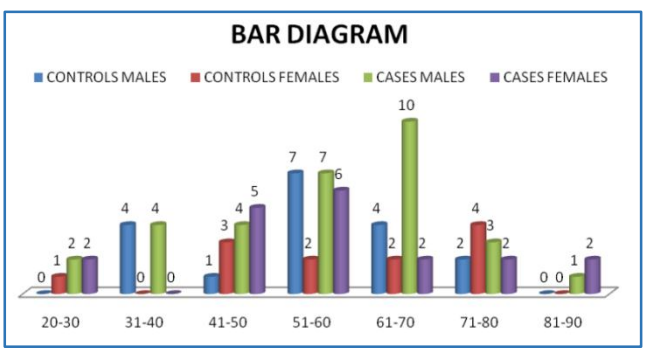
Ethical Clearance: This study was approved by ethical committee of Andhra Medical College, Visakhapatnam, Andhra Pradesh state.

RESULTS: The study group comprised of 50 subjects and the control group had 30 subjects as shown. There are 18 males (59.4%) and 12 females (39.6%) among Controls and 31 males (62%) and 19 females (38%) in the Cases group. In this study, the mean age among the controls is (55.6±13.63) and among the cases is (56.4±15.24). p value is <0.8 which is not considered to be statistically significant. Height among the controls is (168.56±8.36) and among the controls is (167.48±7.0). p value is <0.55 which is not statistically significant. Weight among the controls is (69.1±8.77) and among the cases is (70.3±7.66). p value is <0.5 which is not significant. BMI mean among the controls is (24.3±2.10) and among the cases is (25.1±2.32). The cases are slightly overweight but as the p value is <0.13, it is not statistically significant. Waist mean among the controls is (83.1±5.38) and among the cases is (82.8±4.72). p value is <0.79 and hence, it is not statistically significant. Hip mean among the controls is (97.5±5.54) and among the cases is (95.8±5.92). p value is < 0.2 and hence, this is also statistically not significant. Waist/Hip ratio mean is 0.85 among controls and 0.86 among cases. P value is <0.34 and hence, not statistically significant. In this study, when different parameters for FMD are assessed, hyperemic flow % for Hypertensive patients is (70.1±81.2, p value < 0.004) and is significantly lower than Hyperemic flow % in non-hypertensive subjects (121±62.3). FMD in Hypertensive patients is (8.15±12.4, p value <0.0001) and is very significantly lower to FMD in non-hypertensive subjects (19.3±10.3). Mean FMD among Cases is 8.15 and mean FMD among controls is 19.3.

Mean Hyperemic Flow among Cases is 70.1 and among Controls is 121. 26% of the males have Endothelial Dysfunction and 9% of the females among cases have Endothelial Dysfunction. Mean FMD% is highest (20.62%) in Controls having SBP 121-130 mm of Hg. Highest FMD% (26.71%) is present in Controls having DBP 86-90 mm of Hg. Mean FMD% (12.37%) is highest in cases having SBP 120-139 mm of hg and lowest (1.75%) in Cases having SBP >160 mm of Hg. Mean FMD% is highest (10.75%) in Cases having DBP 90-99 mm of hg and lowest (1.41%) in Cases having DBP >100 mm of Hg.

Age	Cases	Controls	Total
20-30	4(8%)	1(3.3%)	5(6.25%)
31-40	4(8%)	4(13.2%)	8(10%)
41-50	9(18%)	4(13.2%)	13(16.25%)
51-60	13(26%)	9(29.7%)	22(27.5%)
61-70	12(24%)	6(19.8%)	18(22.5%)
71-80	5(10%)	6(19.8%)	11(13.75%)
81-90	3(6%)	-	3(3.75%)
Total	**50(100%)**	**30(100%)**	**80(100%)**

Table 1: Age Distribution of Cases and Controls



Graph 1: Bar Diagram Showing Sex Distribution of Cases and Controls

There are 31 males and 19 females among cases and 18 males and 12 females in the control group.

Duration Of HTN	No. of Subjects
<1YR	7*(14%)
1-5 YRS	16(32%)
6-10 YRS	14(28%)
11-15 YRS	7(14%)
16-20 YRS	6(12%)

Table 2: Distribution of Cases by Duration of HTN

*Newly Diagnosed HTN or Less Than 1 YR.

The patients in study group are classified as per duration of hypertension. Most of the subjects (32%) have their duration of hypertension between 1 to 5 yrs.

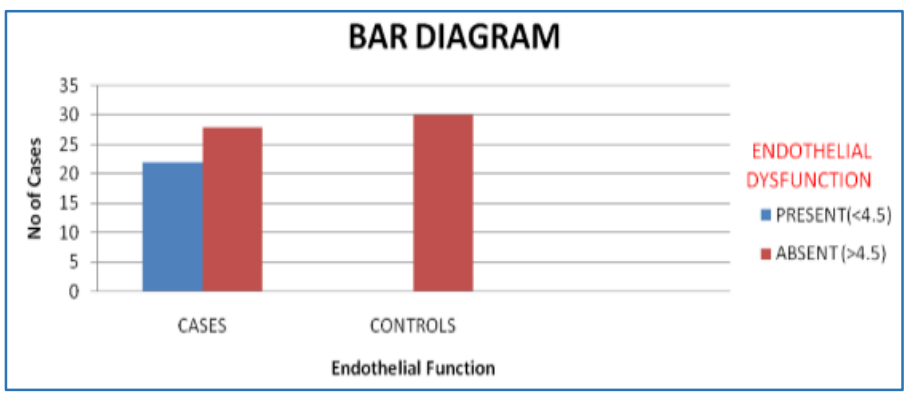
BMI	Cases	Control	Total
Underweight (<18.5)	0(0%)	0(0%)	0(0%)
Normal (18.5-24.9)	28(56%)	18 (59.4%)	46 (57.5%)
Overweight (25=29.9)	20(40%)	12 (39.6%)	32 (40%)
Obese (30-34.9)	2(4%)	0(0%)	2(2.5%)
Total	50 (100%)	30 (100%)	80 (100%)

Table 3: Table Showing Distribution of Subjects Based on BMI

Endothelial Dysfunction (FMD%)	Study Group		Total
	Cases	Controls	
Present (<4.5%)	22(44%)	-	22(27.5%)
Absent (>4.5%)	28(56%)	30(100%)	58(72.5%)
Total	**50 (100%)**	**30(100%)**	**80 (100%)**

Table 4: Distribution of Subjects Based on Endothelial Dysfunction

This table shows that 44% of the cases have Endothelial Dysfunction while no controls have Endothelial Dysfunction.



Graph 2: Bar Diagram Showing Distribution of Subjects Based On Endothelial Dysfunction

Endothelial Dysfunction is present in 22 cases which represent 44% of the cases but no control presented with Endothelial Dysfunction.

Study Variable	Study group	No of subjects	Mean	Std deviation	Std Error	T-value	P value	Degrees of Freedom
Age	Cases	50	56.42	15.24	2.15	0.252	<0.8	78
	Controls	30	55.6	13.63	2.48			
Height	Cases	50	167.48	7.66	1.08	0.59	<0.55	78
	Controls	30	168.56	8.36	1.52			
Weight	Cases	50	70.3	7.0	0.99	0.674	<0.5	78
	Controls	30	69.1	8.77	1.60			
BMI	Cases	50	25.1	2.32	0.32	1.35	<0.13	78
	Controls	30	24.3	2.109	0.38			
Waist (cm)	Cases	50	82.82	4.72	0.66	0.272	<0.79	78
	Controls	30	83.13	5.38	0.98			
Hip (cm)	Cases	50	95.8	5.92	0.83	1.30	<0.20	78
	Controls	30	97.5	5.54	1.01			
Waist/Hip	Cases	50	0.86	0.034	0.004	0.955	<0.34	78
	Controls	30	0.85	0.044	0.008			

Table 5: Statistical Inference Based on Student T-Test for Independent

P value considered to be statistically significant if <0.05.

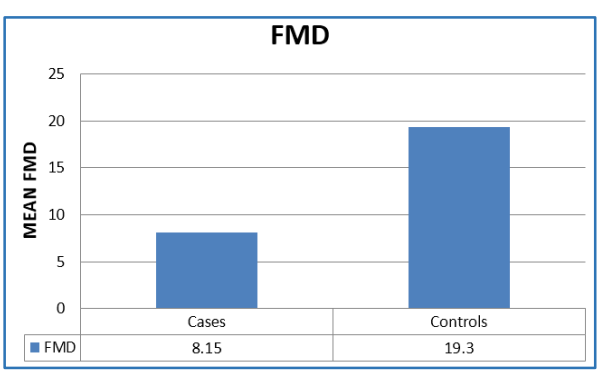
In this study, the mean age among the controls is (55.6±13.63) and among the cases is (56.4±15.24). p value is <0.8 which is not considered to be statistically significant. Height among the controls is (168.56±8.36) and among the controls is (167.48±7.0). p value is <0.55 which is not statistically significant. Weight among the controls is (69.1±8.77) and among the cases is (70.3±7.66). p value is <0.5 which is not significant. BMI mean among the controls is (24.3±2.10) and among the cases is (25.1±2.32). The cases are slightly overweight but as the p value is <0.13, it is not statistically significant. Waist mean among the controls is (83.1±5.38) and among the cases is (82.8±4.72). p value is <0.79 and hence, it is not statistically significant. Hip mean among the controls is (97.5±5.54) and among the cases is (95.8±5.92). p value is < 0.2 and hence, this is also statistically not significant. Waist/Hip ratio mean is 0.85 among controls and 0.86 among cases. P value is <0.34 and hence, not statistically significant.

Study Variable	Study Group	No. of Subjects	Mean	Std Deviation	Std Error	T-value	P Value	Degrees of Freedom
Baseline Diameter	Cases	50	3.85	0.624	0.088	1.84	<0.07	78
	Ctrls	30	3.60	0.531	0.096			
Baseline Flow	Cases	50	661	280	39.59	0.725	<0.47	78
	Ctrls	30	619	191	34.87			
Reactive Hyperemia	Cases	50	878	472	66.75	0.250	<0.80	78
	Ctrls	30	906	471	85.99			
Hyperemic Flow %	Cases	50	70.1	81.2	11.438	2.96	<0.004*	78
	Ctrls	30	121	62.3	11.374			
FMD %	Cases	50	8.15	12.4	1.753	4.13	<0.0001*	78
	Ctrls	30	19.3	10.3	1.880			

Table 6: Statistical Inference Based On Student T-Test for FMD in all Subjects

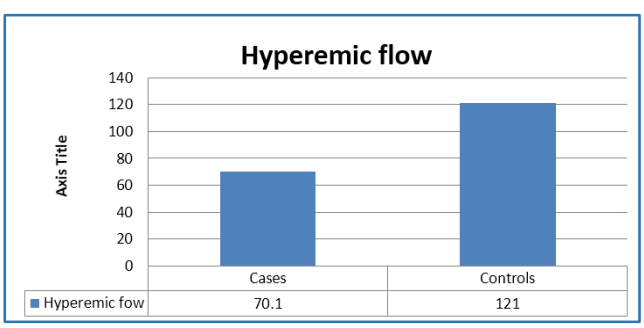
P value considered to statistically significant if <0.05, *Statistically significant.

In this study, when different parameters for FMD are assessed, hyperemic flow % for Hypertensive patients is (70.1±81.2, p value < 0.004) and is significantly lower than Hyperemic flow% in non-hypertensive subjects (121±62.3). FMD in Hypertensive patients is (8.15±12.4, p value <0.0001) and is very significantly lower to FMD in non-hypertensive subjects (19.3±10.3).



Graph 3: Bar Diagram Showing Mean FMD among Cases and Controls

This Bar Diagram is showing that mean FMD among Cases is 8.15 and mean FMD among controls is 19.3.



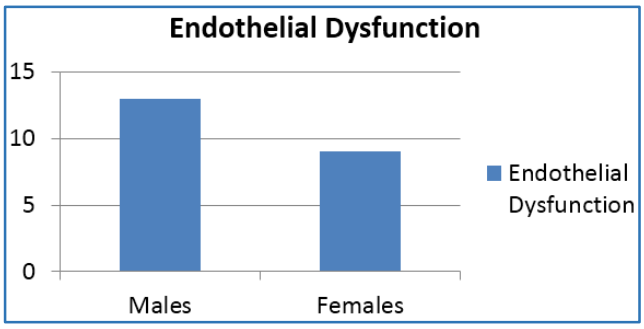
Graph 4: Bar Diagram Showing Distribution of Cases and Controls Based on Mean Hyperemic Flow

This Bar Diagram is showing that mean Hyperemic Flow among Cases is 70.1 and among Controls is 121.

Endothelial Dysfunction	
Males	Females
13(26%)	19(18%)

Table 7: Endothelial Dysfunction in Males and Females

This table is showing that 26% of the males have Endothelial Dysfunction and 9% of the females among cases have Endothelial Dysfunction.



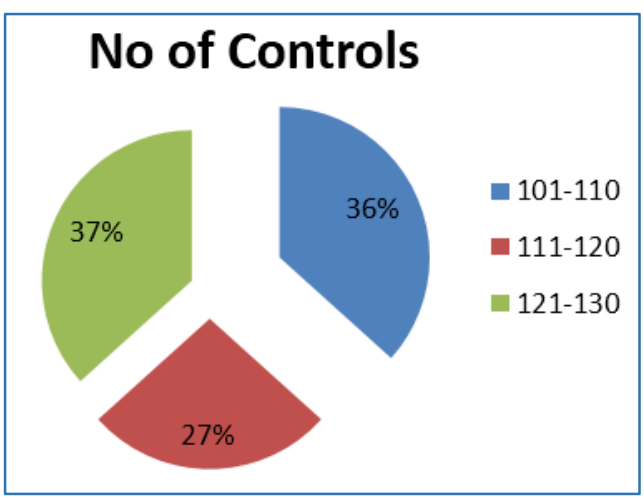
Graph 5: Bar Diagram Showing Endothelial Dysfunction in Males and Females

This Bar Diagram is showing that 26% of the males have Endothelial Dysfunction and 9% of the females among cases have Endothelial Dysfunction.

SBP Range	No. of Controls	FMD% Mean
101-110	11	17.97
111-120	8	19.14
121-130	11	20.62

Table 8: Mean FMD% in Controls According to Systolic Blood Pressure (SBP) Range

This table is showing that mean FMD% is highest (20.62%) in Controls having SBP 121-130 mm of hg.



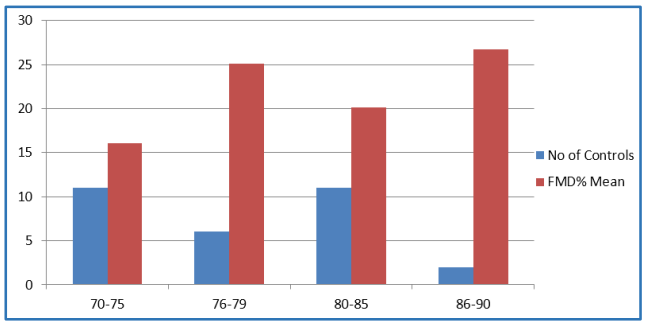
Graph 6: Pie Diagram Showing Distribution of Controls by Mean FMD% According to SBP

This Pie Diagram is showing that mean FMD% is highest (20.62%) in Controls having SBP 121-130 mm of Hg.

DBP Range	No. of Controls	FMD% Mean
70-75	11	16.05
76-79	6	25.12
80-85	11	20.16
86-90	2	26.71

Table 9: Mean FMD% in Controls According to Diastolic Blood Pressure (DBP) Range

This Table shows that the highest FMD% (26.71%) is present in Controls having DBP 86-90 mm of Hg.

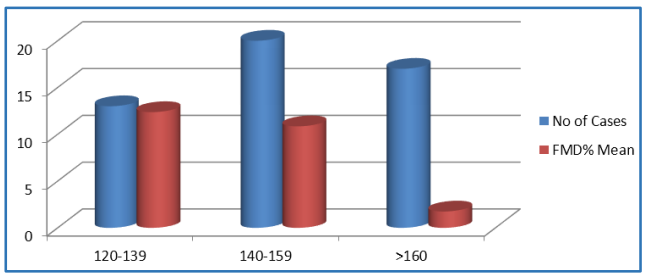


Graph 7: Bar Diagram Showing Distribution of Controls by Mean FMD% According to DBP

SBP Range	No of Cases	FMD% Mean
120-139	13	12.37
140-159	20	10.85
>160	17	1.75

Table 10: Mean FMD% in Cases According to Systolic Blood Pressure (SBP) Range

This Table shows that mean FMD% (12.37%) is highest in cases having SBP 120-139 mm of hg and lowest (1.75%) in Cases having SBP >160 mm of Hg.

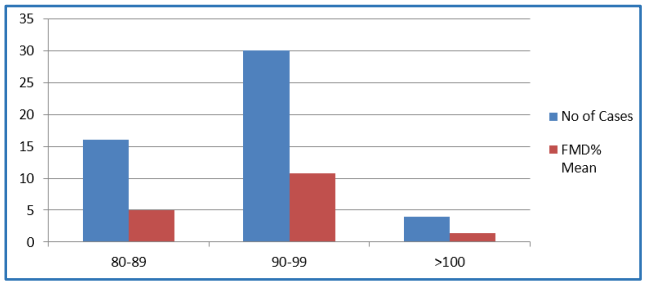


Graph 8: Bar Diagram Showing Distribution of Cases by Mean FMD% According to SBP

This Bar Diagram shows that mean FMD% (12.37%) is highest in cases having SBP 120-139 mm of hg and lowest (1.75%) in Cases having SBP >160 mm of Hg.

DBP Range	No. of Cases	FMD% Mean
80-89	16	4.95
90-99	30	10.75
>100	4	1.41

Table 11: Mean FMD% in Cases According to Diastolic Blood Pressure (DBP) Range



Graph 9: Bar Diagram Showing Distribution of Cases by Mean FMD% According to DBP

This Bar Diagram shows that mean FMD% is highest (10.75%) in Cases having DBP 90-99 mm of hg and lowest (1.41%) in Cases having DBP >100 mm of hg.

DISCUSSION: Assessment of endothelial function can provide valuable insight into pre-intrusive phase of atherosclerotic disease. In this study, 50 cases of Hypertension have been studied and compared with 30 normal subjects. It is noticed that majority, [13(26%)] of the cases are in the age group of 51-60 years, followed by [9(18%)] in between 41-50 years. The mean is (56.4±15.24) years for cases and (55.6±13.63) years for control. Observation in hypertensive patients over a wide range showed that there is a gradual decline in mean FMD% as SBP increases. The mean FMD% in Pre-hypertensive patients is 12.37% and it decreased to 10.85% in patients with Stage 1 Hypertension. It further decreased to 1.75% in patients with Stage 2 Hypertension thereby showing that there is more endothelial dysfunction with Stage 2 Hypertension. Similar results are seen with increasing DBP as the mean FMD% is 1.41% in Stage 2 Hypertension. Prolonged sustained hypertension results in persistent shear stress and hence, leading to decreased FMD% which in turn results in endothelial dysfunction.

The mean baseline diameter among cases is (3.85±0.624) and among the controls is (3.6±0.531) showing that there is not much of difference in baseline diameter in both cases and controls. P value <0.07 and is not statistically significant. The mean baseline flow for cases is (661±280) and among the controls, it is (619±191). This is also not statistically significant as p value is <0.47. The mean Hyperemic flow in cases is (70.1±81.2) and among controls is (121±62.3). This is statistically very significant as the p value is <0.004. This clarifies that though, there is not much of a difference between Baseline flows of both cases and controls, and there is a significant difference in Hyperemic flows of both cases and controls. These variations are dependent on a complex cascade controlling endothelial function like endothelin-1, Nitric oxide, shear stress and hyperaemia. The mean FMD% among cases is (8.15±12.4), which is very low when compared to mean FMD% among controls (19.3±10.3). p value is also very significant statistically as it is <0.0001. This shows that endothelial dysfunction is present in Hypertensive patients. 1. Comparison with other studies: Bogomir Zizek et al[8] had FMD 12.1±2.4 in Hypertensive patients and 15.3±2.6 in Controls. Gokce N, Holbrook M et al[9] had FMD 8.5±3.8 in Hypertensive patients and 18.4±6.4 in Controls.

CONCLUSION: FMD% is a diagnostic aid for evaluation of endothelial function. It is an experimental tool to measure endothelial dysfunction which is a fundamental basis for atherogenesis and CAD. It is a user friendly, non-invasive, cheap, reliable, reproducible technique for risk stratification of CAD. It may be used as a screening test before coronary angiography. It is safe in pregnancy and for children. Most of the Indian Studies are performed on Diabetic Patients and not on Hypertensive patients. This study is done to characterize Flow Mediated Dilatation in Hypertensive patients.

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