A DISSERTATION ON

"A STUDY ON USEFULNESS OF FLOW MEDIATED VASODILATATION OF BRACHIAL ARTERY IN ASSESSING THE SEVERITY OF CORONARY ARTERY DISEASE AND ITS CORRELATION WITH CORONARY ANGIOGRAM"

Submitted to

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In partial fulfilment of the Regulations
for the Award of the Degree of

M.D. BRANCH - I

GENERAL MEDICINE

DEPARTMENT OF GENERAL MEDICINE
STANLEY MEDICAL COLLEGE
CHENNAI – 600 001.
APRIL 2015

CERTIFICATE BY INSTITUTION

This is to certify that **Dr. NARENDRAN .A,** Post - Graduate Student (MAY 2012 TO APRIL 2015) in the Department of General Medicine STANLEY MEDICAL COLLEGE, Chennai- 600 001, has done this dissertation on **"A STUDY ON USEFULNESS OF FLOW MEDIATED VASODILATATION OF BRACHIAL ARTERY IN ASSESSING THE SEVERITY OF CORONARY ARTERY DISEASE AND ITS CORRELATION WITH CORONARY ANGIOGRAM"** under my guidance and supervision in partial fulfilment of the regulations laiddown by the Tamilnadu Dr. M.G.R. Medical University, Chennai, for M.D. (General Medicine), Degree Examination to be held in April 2015.

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CERTIFICATE BY THE GUIDE

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DECLARATION

I **Dr. NARENDRAN .A** solemnly declare that I carried out this work on "A **STUDY ON USEFULNESS OF FLOW MEDIATED VASODILATATION OF BRACHIAL ARTERY IN ASSESSING THE SEVERITY OF CORONARY ARTERY DISEASE AND ITS CORRELATION WITH CORONARY ANGIOGRAM**" in the Intensive Medical care Unit of Government Stanley Hospital during the period February 2014 to September 2014. I also declare that, this bonafide work or a part of this was not submitted by me or any other for any award, degree, or diploma to any other university, board either in India or abroad.

This is submitted to The TamilnaduDr.M.G.R. Medical University, Chennai in partial fulfilment of the rules and regulation for the M.D. Branch I, General MedicineDegree examination

DR . NARENDRAN .A

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INTRODUCTION

FLOW MEDIATED VASODILATATION

There is a lot of research study dedicated to observe vascular biology in humans. The vascular endothelium is in a unparallel position to function as a marker of risk of atherosclerosis.

The endothelium is a special tissue that releases numerous substance that moderates tone of the vascular bed, growth of cells , platelet and WBC interactions . The endothelium responds to various internal and

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- BIBILIOGRAPHY
- PROFORMA
- CONSENT FORM
- ETHICAL COMMITTEE APPROVAL LETTER
- MASTER CHART

LIST OF ABBREVIATIONS

CAD	CORONARY ARTERY DISEASE
FMD	FLOW MEDIATED VASODILATATION
CIMT	CAROTID MEDIA INTIMA THICKNESS
NO	NITRIC OXIDE
BP	BLOOD PRESSURE
WBC	WHITE BLOOD CELLS
eNOS	ENDOTHELIAL NITRIC OXIDE
USG	ULTRASONOGRAM
ACS	ACUTE CORONARY SYNDROME
ECG	ELECTRO CARDIO GRAM
T2DM	TYPE 2 DIABETES MELLITUS
HTN	HYPERTENSION
ACE	ANGIOTENSIN CONVERTING ENZYME
CA	CALCIUM
CAG	CORONARY ANGIOGRAM
MHZ	MEGA HERTZ
MI	MYOCARDIAL INFARCTION
SVD	SINGLE VESSEL DISEASE
DVD	DOUBLE VESSSEL DISESASE
TVD	TRIPLE VESSEL DISEASE
UA	UNSTABLE ANGINA

A STUDY ON USEFULNESS OF FLOW MEDIATED VASODILATATION OF BRACHIAL ARTERY IN ASSESSING THE SEVERITY OF CORONARY ARTERY DISEASE AND ITS CORRELATION WITH CORONARY ANGIOGRAM

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KEY WORDS : FLOW MEDIATED VASODILATATION, CORONARY ARTERY DISEASE, CORONARY ANGIOGRAM.

SECONDARY OBJECTIVES

1. TO ASSESS THE CORRELATION BETWEEN OTHER WELL ESTABLISHED CARDIOVASCULAR RISK FACTORS LIKE SMOKING, WAIST HIP RATIO, LIPID ABNORMALITIES AND CAROTID INTIMA MEDIA THICKNESS.

2. TO ASSESS THE RELATIONSHIP BETWEEN PER-CAPITA INCOME AND CAG CHANGES

3. TO ASSESS THE RELATIONSHIP BETWEEN DIET PREFERRENCE AND CAG CHANGES

MATERIALS AND METHODS

PLACE OF STUDY:

DEPARTMENT OF CARDIOLOGY, CARDIOLOGY OPD, MEDICAL WARDS AND IMCU AT STANLEY MEDICAL COLLEGE AND HOSPITAL, CHENNAI.

DURATION:JAN 2014 TO SEP 2014.

STUDY DESIGN:RETROSPECTIVE OBSERVATIONAL STUDY

SAMPLE SIZE: 75

METHODOLOGY-

Patients diagnosed with coronary artery disease within 1 month and have undergone coronary angiogram ;from the period January 2014 to September 2014 in ICCU/ cardiology wards are included in the study. Patients will be subjected to symptom analysis, clinical examination, laboratory investigations and flow mediated vasodilation studies of brachial artery. The final analysis will be made at the end of the study to achieve the fore mentioned goals using appropriate statistical methods.

PATIENT SELECTION:

INCLUSION CRITERIA

1. All patients who have been diagnosed having coronary artery disease which includes chronic stable angina, ST elevation MI, non ST elevation MI , unstable angina

within the last 1month and have undergone CAG.
2. All patients who have undergone primary/ facilitated PCI within the above mentioned time.
3. Patients between 20 and 60 years of age.

EXCLUSION CRITERIA

1. Patients with any form of connective tissue disorder, chronic kidney disease, Chronic liver disease
2. Any patient < 20 and > 60 yrs of age.

CONCLUSION OF THIS STUDY

Our aim of this study was to determine if there is any correlation between severity of CAD and FMD of the brachial artery , as well as to observe the relationship with various other cardiovascular risk factors .

A total of 75 patients were included in the study and following are conclusions from the statistical analysis. The subjects were divided into 4 four study groups as described above and subsequently analysed.

- The association between the study group and factors like age , gender , diet ,alcohol intake ,duration of hypertension was found to have no correlation
- There is a positive correlation between duration of smoking and severity of CAD
- Presence of diabetes had an meaningful correlation with the study groups and there is a increase in severity of CAD with increase in duration of diabetes
- BMI was found to have a positive correlation with the study groups and as the BMI of the patient increased more severe was the CAD observed in them
- Non HDL (LDL) was found to be the better marker for assessing the cardiovascular risk as there was a significant increase in CAD severity with increasing levels of LDL ,however no such positive correlation existed between study groups and HDL
- Left ventricular ejection fraction measured at the time of admission was significantly lower as the severity of CAD increased
- There was no positive correlation between brachial artery resting diameter and post occlusive diameter among the various CAD groups
- Interestingly percentage of increase in flow mediated vasodilatation correlated well with the severity of CAD , in which the more severe CAD patients had significantly lower percentage increase in FMD

- There is also a meaningful correlation between % increase in FMD and modified GENSINI SCORE.As the severity of CAD as assessed by modified GENISINI score increased significantly lower was the % increase in FMD.

Hence we conclude that apart from assessing the traditional cardiovascular risk factors , it is also important to assess the endothelial function of the patient by methods like FMD. It is very clear the physiological alteration(endothelial dysfunction) in the body due to atherosclerosis, diabetes and other risk factors occur much before the structurally evident changes like plaques. FMD could be used as a tool to determine the endothelial function of the patients very early in the course natural history of CAD . Its use could be widely employed as it is non invasive and very simple procedure . Interestingly even unstable angina patients with normal /non obstructive CAG had endothelial dysfunction and whether this could be the reason for angina is still debatable. Since it a direct reflection of the health status of coronary vessels this could be utilised in screening of even young healthy individuals with family history of CAD . This technique has great scope in the near future mainly because of its non invasive technique in assessing the severity of CAD. It however requires large sample studies to substantiate this and though not yet recommended for routine clinical use, non invasive endothelial function testing has provided valuable insights into vascular changes associated with early atherosclerosis and the potential reversibility of arterial disease.

INTRODUCTION

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There is a lot of research study dedicated to observe vascular biology inhumans. The vascular endothelium is in a unparallel position to function as a marker of risk of atherosclerosis .

The endothelium is a special tissue that releases numerous substance that moderates tone of the vascular bed, growth of cells , platelet and WBC interactions . The endothelium responds to variousinternal and external stimuli via complicated receptors in cell membrane and mechanisms of signal transduction , leading to the formation and discharge of various vascular active hormones and factors. The ability of blood vessels to react to physical and biochemical stimuli in the blood flow and circulation in response to changes in the local surroundings . Various blood vessels react to an amplification in flow or more accurately stress , by dilation. This process is defined as flow mediated vasodilatation.A primary mediator of FMD is nitric oxide derived

from endothelium . This property of endothelium could be used for risk evaluation .

The finding of nitric oxide (NO) as a vital molecule forvascular relaxation and the detection of the endothelium as more than a passive inert medium between blood and the vessel wall gave way to a significant breakthrough in vascular research. Endothelial dysfunction is a pathologicalprocess in which there is an imbalance between factors with vasodilating, antimitogenic properties and substances with vaso-constrictive, prothrombotic properties . Among the most vital vasodilating factors , chiefly in muscular arteries(is NO) whichalso slows down other key events inthe progress of atherosclerosis such as platelet adhesion and aggregation, WBC adhesion and migration, and proliferation of smooth muscle cells.Importantly in the microcirculation, prostacyclin and other endothelium-derived growth factors also execute an vital role.

Usually , loss of NO bio function denotes a widely dysfunctional phenotype across endothelial properties . Hence, the evaluation of its vasodilating property as a result of NO and various other molecules could offer knowledge on the reliability and utility of the endothelium.Surprisingly, cardiovascular risk factors are related with dysfunction of endotheliumand risk factor alteration leads to enhancement in vascularfunction. Endothelial dysfunction has been found out in the coronary epicardialand resistance vessels and in the arteries of periphery , so endothelial dysfunction could be considered as a systemic condition. Significantly, the evolution of atherosclerosis occurs much early in life, and endothelialdysfunction accelerates atherosclerosis and occurs much before the development of morphological changes in the vascular bed.The aim of our study is to give a short overview of the most commonly usedtechnique to assess endothelial function in human beings, predominantly noninvasive methods, and to sum up the clinicalimportanceofendothelialdysfunction in the inhabitants and in person . The potentialoutlookof endothelial function quantification for personalised medicine is alsoadvised.

Brachial artery flow-mediated dilation (FMD) has emerged as the most common assessment tool of endothelial function. This response is

1) nitric oxide dependent

2)abnormal early in the course of the disease

3)dysfunctional in response to various cardiovascular risk factors

4)correlated with abnormalities of coronary endothelium-dependent vasodilatation

5)improved with interventions known to improve cardiovascular outcomes such as STATIN therapy

6)relatively inexpensive

7)noninvasive

8)reproducible

A disturbance of endothelial function is considered as akey event in the development of atherosclerosis, hypertension and heart failure. Thus reliable assessment of endothelial function in humans is fairly important. This can be achieved by different approaches.

1) measurement of morphological and mechanical characteristics of the vascular wall (intima media thickness, distensibility , compliance , remodelling indexes .

2)determination of soluble endothelial markers (Von-Willebrand factor , plasminogen activator) .

3)measurement of the endothelial dependant regulation of the vascular tone at focal sites of the circulation by flow mediated vasodilatation techniques (FMD) .

METHODS TO ASSESS VASCULAR FUNCTION

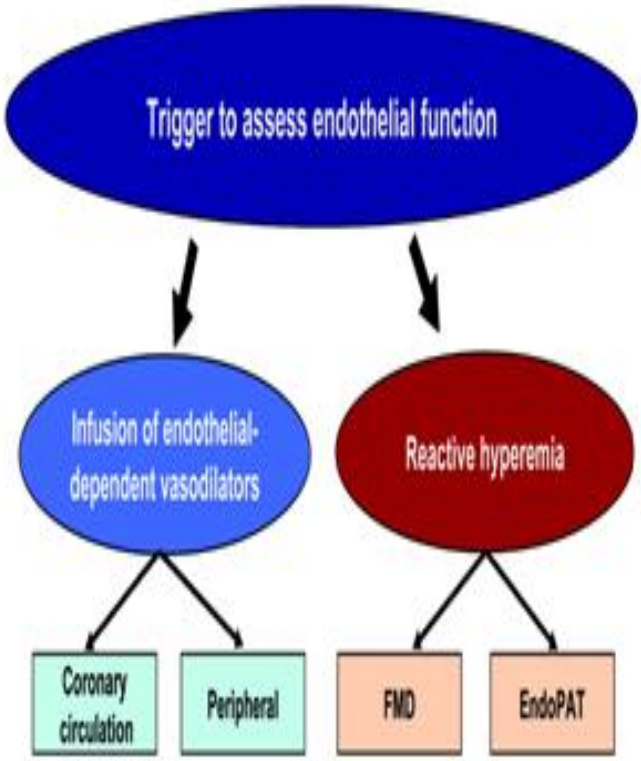
The first exhibition of endothelial dysfunction in atherosclerosed coronary arteries using the technique of intracoronary infusion of the drug acetylcholine and its subsequent quantification of coronary angiography was done by doctor Ludmer and his associates in 1986. Theirinfluentialstudy marked an significant shift of hypothesis in the perceptive ofatherosclerosis, which was formerly been considered as a solely structural disease.This research drew interest to the functional features of atherosclerosis such as increased vasoconstriction as a result of improperly functioning endothelium. Then , non invasive methods were designed using the forearm circulation as a replacement for assessing coronary arteries. All techniques had their plus and minuses , most essentially different vascular beds were examined

The basic rule however was similar , Healthy arteries such as the brachial and coronary arteries expand in reaction to reflex hyperaemia (which is nothing but flow-mediated vasodilatation) or following pharmacological stimuli ,which

includes infusion of intra arterial endothelium-dependent vasodilators such asbradykinin or acetylcholine, through discharge of NO and other vasoactive substances. In disease condition , this endothelium-dependent vasodilatation is either reduced or absent. However, regardless of whichever method is applied, vascular responses are governed not only by the functional status of the vascular bed at the measurement positionbut also by theresistance arteriesstructural condition in the micro vascular bed .

In addition, to distinguish response which are endothelium-dependent from endothelium-independent ones , exogenous donators of NO such as glycerol-trinitrate or direct non–NO donators like adenosine can be used. Improper endothelial-independent function is however related more with structural vascular modifications and changes in smooth muscles cells rather than alteration in the endothelium.

The principles of the most commonly used methods to assess endothelial function.



Non-Invasive	-	-	+	+
Predictive	++	++	++	+
Reversible	+	+	+	+
Control vessel	+ (control segments)	+	-	++
Not expensive	-	+	+	+/-
Low-risk	+/-	+	++	++
Operator independent	+/-	+/-	-	++
Easy to use	-	-	-	+

CORONARY EPICARDIAL AND MICROVASCULAR FUNCTION

To measurethe function of coronary endothelium, a functionalanalysis is done to assess the endothelial function of epicardial and resistance vessels. Even though these techniques are restricted by its invasive nature, their benefit is to quantify endothelial function directly in this vascular bed which is clinically important.

EPICARDIAL ENDOTHELIAL FUNCTION

To illustrate vasomotor reactiveness of epicardial coronary arteries, quantitative CAG or intravascular high frequency ultrasound is performed, and alteration in vessel thickness and cross-sectional areas in reaction to endothelium-dependent interventions are recorded . Following infusion of acetylcholine , vessels with integralendothelium vasodilate,but vessels with non intact endothelium will react with vasoconstriction as a consequence of direct enhancement of muscarinic receptors which are present on the smooth

musclevasculature . Comparable induced functional alterations in vascular reactivity have been established with salbutamol and other substances. Physical variables like exercise or pacing-induced tachycardia as a equivalent forexercise can be considered endothelium derived response which cause an amplification in coronary blood flow and also increase the stress on the coronary circulation, ultimately leading to flow-mediated endothelium-dependent vasodilatation of the vessels in the epicardium. Identical changes can also be observed in reaction to mental stress. This study of flow-mediated vasodilatation in the coronary vessels and its dysfunction inatherosclerosis gave away the idea to study identical responses in the peripheral vascular bed . By using cold pressor test which is a “physiological” test to gauge epicardial vessels vasoreactivityin which the patient puts her or his hand into ice cold water and this leads to sympathetic nervous system amplification which cause NO release and endothelium-derived hyperpolarizing substances and consequently vasodilation in healthy vessels.But , in case of endothelial dysfunction , vasoconstriction of smooth muscle cells will govern, identical to responses to acetylcholine.

Figure 18.4b Gross anatomy of the heart.

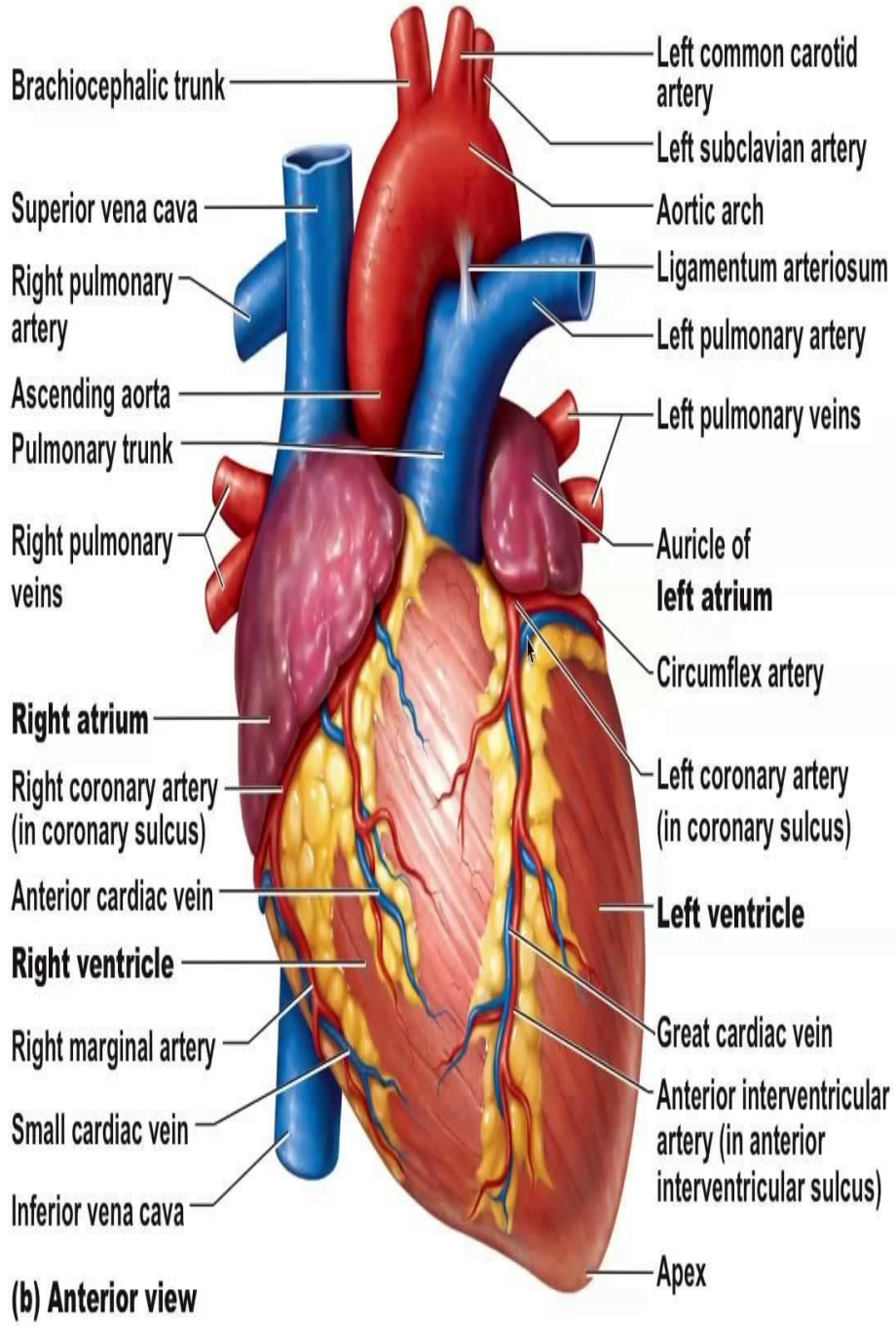


Table 2.

Pharmacological Triggers for the Assessment of Coronary Vascular Function

	Epicardial Vessels	Microcirculation
Endothelium-dependent vascular function	Acetylcholine	Acetylcholine
	Salbutamol	Salbutamol
	Serotonin	Bradykinin
	Substance P	
	Calcitonin gene-related peptide	
Endothelium-independent vascular function	Nitroglycerin	Adenosine
	Nitroprusside	Dipyridamole
	Papaverine	Nitroprusside
		Papaverine

CORONARY MICROVASCULAR FUNCTION

Variations in myocardial blood flow could be utilised as a stand-infactor for micro vascularutility. Coronary blood flow reserve is calculated by using the numerator as maximal coronary blood flow during maximal coronary hyperaemia divided by the resting coronary blood flow. This optimal flow response process is both endothelium- and non–endothelium-dependent, and a coronary blood flow reserve capacity ration <2.0 is taken as not normal.The quantification of microvascular function which is dependent on endothelium, the percentage rise in coronary blood flow in reaction to vasodilators (acetylcholine) administered at rising titre is monitored.Numerous ways to quantify microvascular function have been used , examplewith proximal injection of contrast the amount of cineangiographic frames that will take to fill a distal most vessel is measured . The corrected Thrombolysis in Myocardial Infarction frame count provides a semiquantitative assessment of epicardial coronary blood flow. Taking the main disadvantage—the invasive nature of the above-mentioned tests—into account, noninvasive functional tests to assess the

coronary microvasculature have been developed, among them positron emission tomography, myocardial perfusion imaging, blood oxygen level–dependent magnetic resonance imaging, and echocardiography; however, a detailed discussion of these tests is beyond the scope of this review.

FLOW-MEDIATED VASODILATION OF BRACHIAL ARTERY

As a result of its noninvasive approach, flow-mediated vasodilatation of the arm arteries (FMD) has become the most widely used technique to measure endothelial function. The technique measures the ability of the arteries to respond with endothelial NO release during reactive hyperaemia (flow mediated) after a 5-minute occlusion of the brachial artery with a blood pressure cuff. Celermajer and colleagueswere the first to measure this response in vivo by measuring the respective diameter changes of the brachial or radial artery by ultrasound, a response later demonstrated to be mainly NO dependent, although other vasodilator pathways also may contribute. Importantly, peripheral endothelial function as assessed by FMD correlates with coronary artery

endothelial function.However, although the principle of this technique seems simple, its application is technically challenging and requires extensive training and standardization . Study preparation, image acquisition and site selection, sphygmomanometer probe position, cuff occlusion time, accurate use of edge-detection software, and correct characterization of the FMD response are crucial, as recently outlined in detail in guidelines by Charakida et al, Harris et al, and Thijssen et al. These publications are useful in that they draw attention to the need to standardize the different protocols; indeed, if efforts to standardize the technology are followed, reproducibility of FMD can be considerably improved.

An vital determinant in the path physiology of systemic hypertension , atherosclerosis, and cardiac failure was linked to endothelial dysfunction. High-frequency USG image attainment of the brachial artery vessel to gauge endothelium-dependent flow-mediated vasodilatation (FMD) was established in the early 1990. The vasodilatation observed is because of liberation of NO that is stimulated in this technique and that could be measured as a marker of vasomotor function. It is a very useful technique to swot up the efficiency of

various interventions that could influence the vascular endothelial function , as it is non invasive and further allows repetitive measurements over time . There are other technical and interpretive restrictions of this technique in spite of its widespread use. With new guidelines for its application in the field of research to study vascular endothelial physiology and latest technologies which provide information , insights which strengths its application and reduce its limitations to make it effective in using high -resolution ultrasonography of the brachial artery to evaluate vascular endothelial function .The endothelium is a special tissue that releases numerous substance that moderates tone of the vascular bed, growth of cells , platelet and WBC interactions . The endothelium responds to variousinternal and external stimuli via complicated receptors in cell membrane and mechanisms of signal transduction , leading to the formation and discharge of various vasoactive hormones and factors. Dysfunction of the endothelium plays a vital role in the progress of atherosclerosis, hypertension, and cardiac failure. In the last few years, a noninsidious method has been developed to appraise FMD which is a process dependant on the endothelium , in the brachial artery . This spur activates the

cells of endothelium to dischargeof NO with consequentdilation which can be pictured and used as a marker of vascular bed function. Theprocedure is up-coming as it is non-insidious and makes way forrepetitive measuring options . Inspite of its prevalent usage , it has procedural and practical restrictions. Our study will focus on analysing and developing this striking and buddingmethod.

PHYSIOLOGY OF FMD

The ability of blood vessels to react to physical and biochemical stimuli in the lumen enables the capability to self-regulate tone and to modify blood flow and circulation in response to changes in the local surroundings . Various blood vessels react to an amplification in flow or more accurately stress , by dilation. This process is defined as flow mediated flow mediated vasodilation. A primary mediator of FMD is nitric oxide derived from endothelium .

The exactphysiology for the immediate recognition of stress effects and its consequentimpulse transmission to alter the tenor of vessels is not totally explained . Specific ion channels that are present in the endothelial cell membrane like potassiumchannels that calcium dependant ,thatopeninresponse to shear stress forces . Hyperpolarisation of the endothelial cell caused by

opening of the potassium channel , increases the dynamic force for calcium entry into the cells as there are no voltage- gated CA channels in endothelial cell membrane . This activates an enzyme, endothelial nitric oxide synthase (eNOS), andtheconsequentproductionofNOseems to be responsible for FMD . FMD can be impaired in a range of arterial vessels when there is administration of inhibitor of the enzyme nitric oxide synthase (NOS)

MEASURING FMD IN HUMAN BEINGS: ANALYTICAL AND CURATIVE FEATURES

Dysfunction of the endothelium is indicated by an improper response in the FMD . In the vascular bed of human beings , forearm and coronary circulation are the ideal location to study FMD. Predominantly, a vasodilatation stimuli is given to the vessels in downstream there by picking up a flow-mediated vasodilation of the vessel in upstream . Doctor Celermajer and his associates designed a distinctive method to observe FMD non-insidiously and consistently in forearm vessels of human beings . Aenhancement in blood flow into the brachial artery is achieved by postischemicvasodilatation in the vasculature of the distal forearm. This can be caused by inflating a B.P cuff

positioned over proximal part of forearm to pressure above systolic blood pressure inducing a ischemia in the vessels distal to the cuff . When the pressure of the cuff is liberated , a swiftaugmentation of blood flow through the vessels that were dilated . The succeedingamplification in stress forces acting in upstream vessels induce vasodilatation of brachial artery, which can be evaluated using an USG device . As the amount of cardiovascular risk associations rise , more demonstrable is the endothelial dysfunction . This has to be well thought-out while we studysubjects with atherosclerosis of coronary or systemic vessels . Various stimulus intensely control FMD: such as fatty meal and post-meal hyperlipidemia , stress, increased levels of catecholamine , high quantities of oestrogen and progesterone , smoking , blood sugar changes and alterations in electrolytes .Sudden elevation in stress levels that occur in dialysis have been noticed , which could be linked to impair FMD in brachial vessels .However this the response of FMD seems to be non dependent from the viscosity of blood . Also , circadian rhythm alteration brings about changes in tone of vascular bed is well documented. Therefore FMD is a very reliable technique that allows clinicians to accurately

note the endothelial function alteration in human beings . In further studies deciding curative interventions based on functioning of endothelium , subjects should be cross-matched and standardized protocol must be developed for demonstrating impact of various factors on FMD. The prerequisites about subject choice and settingof study in assessment of brachial vessel response holds good to coronary circulation also. Vasodilatation of cardiac resistance arteries to bring about raise in stress forces in the epicardial vessels can be fulfilled by metabolic stimulus like physical exercise or stimulation of pacemaker . Instead, this can also be achieved by selectively infusing drugs like adenosine into the mid part of epicardial vessels and concurrent measurement of FMD in the proximal most part of the vessel under examination. It is fully not understood whether the dysfunction of the endothelium in the cardiac circulation is a local or a systemic disorder of the vascular bed that happens concurrently in other areas of the circulation. Assessing FMD in the epicardial vessels is a to a great extent more invasive method as compared with FMD assessment in the brachial vessels. Hence , numerous studies stress on the issue that assessing FMD in brachial artery

could signify as a marker for analytical evaluation of cardiac circulation in subjects with apparent coronary artery disease (CAD) or those patients who are at danger for developing CAD. In these studies conducted the endothelium-dependent vasodilatationaswellasthe endothelium- independent vasodilatation in the brachial circulation was observed in subjects with CAD . Some studies have demonstrated a intriguing association of endothelium function in coronary and peripheral vascular bed . It has been revealed that large proportion of subjects with acute coronary syndromes had concomitant endothelium dysfunction of the brachial vessels in the USG scan. However , this endothelial function impairment was correctable after management of ACS . Nevertheless, the specificity and sensitivity of FMD of brachial artery to foretell relation between endothelial dysfunction CAD is questionable as the subject sample involved in the study so far are too less to confirm it as statistically significant. In patients with high cholesterol levels , systemic hypertension and diabetes mellitus all of which regarded as main cardiovascular riskfactors FMD measurement accurately senses endothelium dysfunction in them and there is adequate evidence for this.

FMD of the brachial artery is altered more by increased total cholesterol values , as triglycerides levels do not alter it and total cholesterol levels correlates with extent of endothelial dysfunction .Distortedbioactivityof nitric oxide causes dysfunction of endothelium of coronary and peripheral vessels in patients with arterial hypertension. Rigorousness and extent of arterial hypertension as reflected by the extent of left ventricle hypertensioninfluences the amount of endothelial dysfunction in coronary arteries. Diabetes also causes endothelial dysfunction in the coronary and peripheral vessels. Endothelium-dependent vasodilatation is impaired in conduit and resistance vessels of patients having diabetes mellitus . FMD in humans is very useful not only to measure the extent of dysfunction in endothelium in relation to the dyslipidemia, systemic hypertension, and diabetes mellitus but also useful to make reliable diagnosis of endothelial dysfunction in association with cardiovascular risk factors .

Table 3.

Technical Considerations in Flow-Mediated Dilation Measurements

Subject preparation
Fasting state (>6 h)
No smoking or any tobacco consumption at least 6 h before study
No exercise or food/beverages that contain alcohol or caffeine or are rich in polyphenols (cocoa, tea, fruit juices) for >12 h
No vitamins for at least 72 h
Vasoactive medications withheld on the morning of the study if possible with careful noting of the use and timing of any drugs
No exercise >12 h before test
Quiet, temperature-controlled room
In female patients, repetitive studies should be made at the same time of the menstrual cycle (ideally on days 1-7 of the menstrual cycle)
Rest for at least 10 min before measurements
Supine position
Arm resting comfortable with cradle support with the imaged artery at the heart level
Test should be performed at the same time of the day (especially if multiple tests are performed)
Sphygmomanometer probe position and cuff occlusion time
Placement of the cuff 1-2 cm distal to the elbow crease

Other sites are discouraged because proximal cuff positioning affects the magnitude of the peak vasodilatory response
Occlusion time, 5 min (shorter inflation attenuates FMD response)
Cuff inflation to at least 50 mm Hg above systolic pressure
Site selection
Brachial artery with a minimum diameter (usually >2 mm); small arteries are difficult to measure, and changes in absolute diameter correspond to big relative changes
If repetitive measurements are planned, site has to been replicated; anatomic landmarks should be used
Image acquisition
Longitudinal images obtained by high-resolution ultrasound (7.5-12 MHz)
A clear **interface** between the near and far arterial wall should be achieved
Diameter measurements are obtained in end diastole or averaged over the heart cycle
Stereotactic adjustable prop holding is essential to ensure image quality
Recording of the baseline diameter for at least 1 min
Simultaneous acquisition of pulse-wave Doppler velocity signals for quantification of shear stress (stimulus) if feasible; insonation angle should be <60°

Measurement
Automated edge detection should be used
Reported as maximal percentage change from baseline diameter (most reproducible)
Baseline diameter and absolute change reported also
Characterization of the hyperemic stimulus (ideally the flow-velocity time integral)

CLINICAL IMPLICATIONS OF ENDOTHELIAL DYSFUNCTION IN POPULATIONS AND IN THE INDIVIDUAL

In the coronary arteries, impairment of endothelial function occurs early in the course of atherosclerosis in relation to systemic risk factors and abnormal hemodynamic shear stresses. The more systemic cardiovascular risk factors are present, the worse epicardial vascular function is. Extensive literature documents that endothelial dysfunction is associated with almost every condition predisposing to atherosclerosis and cardiovascular disease. There are many studies correlating endothelial dysfunction (conduit artery and microvasculature likewise) with cardiovascular risk. For example, endothelial dysfunction has been observed in patients with arterial hypertension, normotensive subjects with a family history of hypertension, smokers,passive smokers,patients with dyslipidemia, ageing patients, those with diabetes mellitus, obese individualpatients with hyperhomocysteinemia,individuals with low intracellular magnesium level and patients with inflammatory or infectious diseases. Importantly, the effects of cardiovascular risk on the endothelium can be seen in children as early as 8

years of age. Thus, endothelial dysfunction may represent the effect of these risk factors on vascular health.

The fact that endothelial dysfunction is a systemic condition may explain why peripheral endothelial function (microvascular and macrovascular) correlates with endothelial function in the coronary arteries. The path physiology behind the functional changes in impaired endothelial function also leads to structural changes of the vessel over time. In a cross-sectional study in healthy middle-aged men, there is no evident correlation between brachial FMD and the carotid intima-media thickness (IMT); however, in a similar population free of cardiovascular disease, FMD correlated with IMT progression over a 6-year follow-up. Interestingly, in this study, in contrast to FMD, Framingham risk was not correlated with IMT progression. Similarly, FMD also predicted IMT progression in less healthy patients as demonstrated after 1 year in hypertensive, postmenopausal women.

Taken together, there is good evidence that endothelial dysfunction is significantly associated with the burden of cardiovascular risk and can be considered a barometer of the total risk burden (the risk of the risk factors).

However, transient endothelial function impairment, example, by intercurrent acute illnesses, after strenuous exercise, or with certain foods, has to be taken into account, posing a potential limitation for interpretation. Thus, it may be that endothelial function measurements should not rely on a single test but rather on the average of several tests.

Technique of FMD

How to prepare the subjects for the study

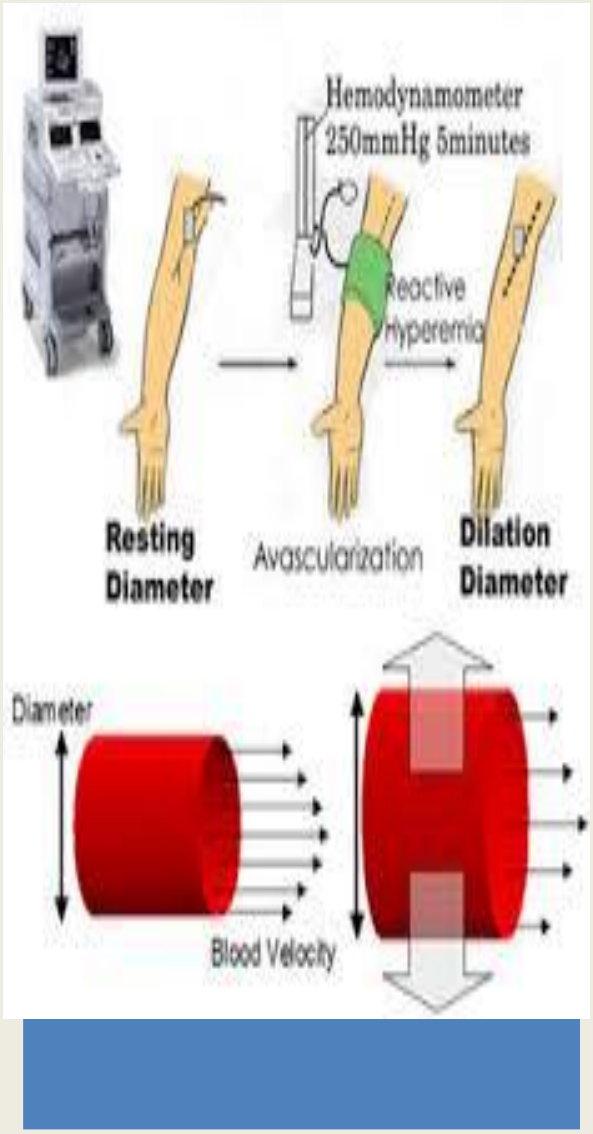
Various modalities affect FMD response which includes food, body temperature, medication and other sympathetic stimuli . Hence, patients should be made to fast for at least eight to twelve hours before the start of study, and it should be performed in a silentroom and at room temperature . Any drugs affecting vasodilator response must be stopped for at least 1 day before study , must avoid exercise, no consumption of caffeine containing diet , fatty food, smoking etc . All of these perplexing factors should be well thought-outwhile getting a patient ready for the study to deter any of these factors intervening with the study. While performing observational cohortstudies, information must be recorded based on those factors which can influence the measurement of FMD and subsequently must attend to its impact .

EQUIPMENT.

USG machines should be provided with software for 2D imaging, spectral and colour Doppler system, an internal monitor to record ECG and avascular transducer with high-frequency. To attain images with adequate resolution for successiveexamination needs a linear range transducer with a seven MHZ frequency , connected to a high- performance USG system . The quality of images can be greatly improved with a system that has numerous linear range transducers that can pick up a wide range of frequency ranging from seven to twelve MHZ. Every image frame is timed with correlation to the events of cardiac cycle and is observed with concurrent Electrocardiograph video recording on the USG scan system.

IMAGE ATTAINMENT

The patient must be placed in a supine position with the forearm in a relaxingarrangement forbrachial artery imaging .The antecubitalfossa is focussed in a longitudinal plane to image the brachial artery. For constant 2D imaging a section with patent anterior and posterior interfaces between the vessel wall and lumen is chosen . To find out the maximum area of the lumen , brachial artery cross- sectional images should not be used because of insufficient imaging of the lateral walls and there is a problem of skew artefacts in this view which alter the accuracy of diameter determination. Both M mode and A mode scan could be used to assess the diametercontinuously and yet these techniques may be issue to error due to drift in tracking. However there is no direct comparison between diametermeasurements from recording using wall tracking versus grayscale images.Anatomical landmarks such as veins and fascias planes should be noted at the time of image capture to ensure the identical image of the artery is captured right through the study.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250mmHg 5minutes
Reactive
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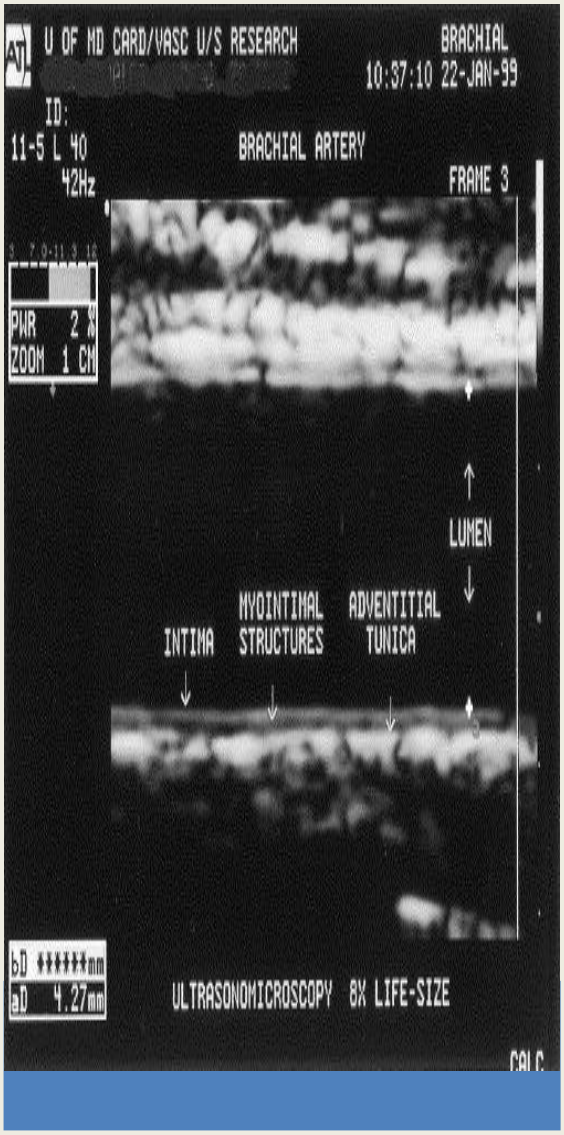
Diameter
Avascularization
Dilation
Diameter
Diameter
Blood Velocity


U OF MD CARD/VASC U/S RESEARCH
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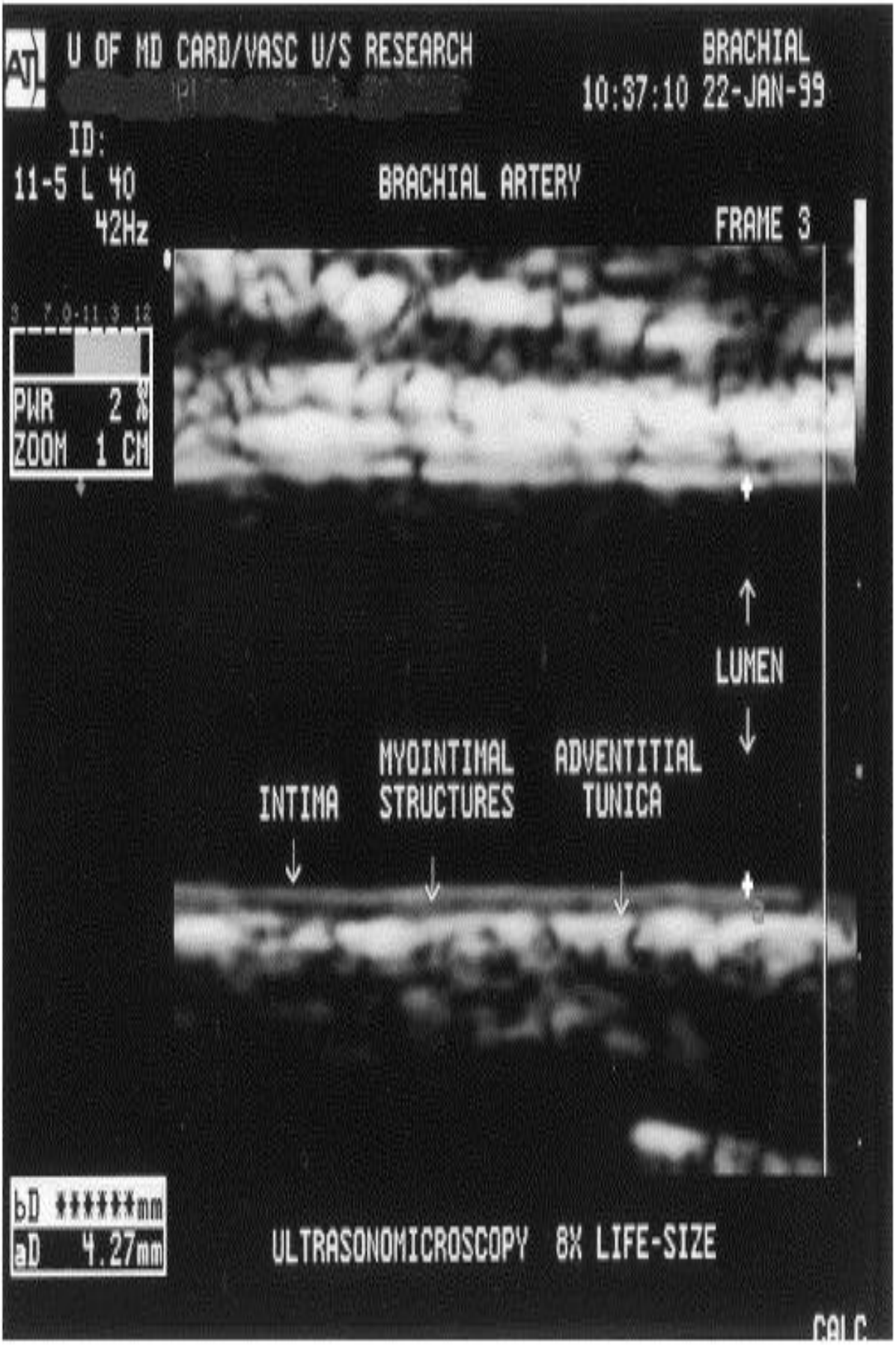
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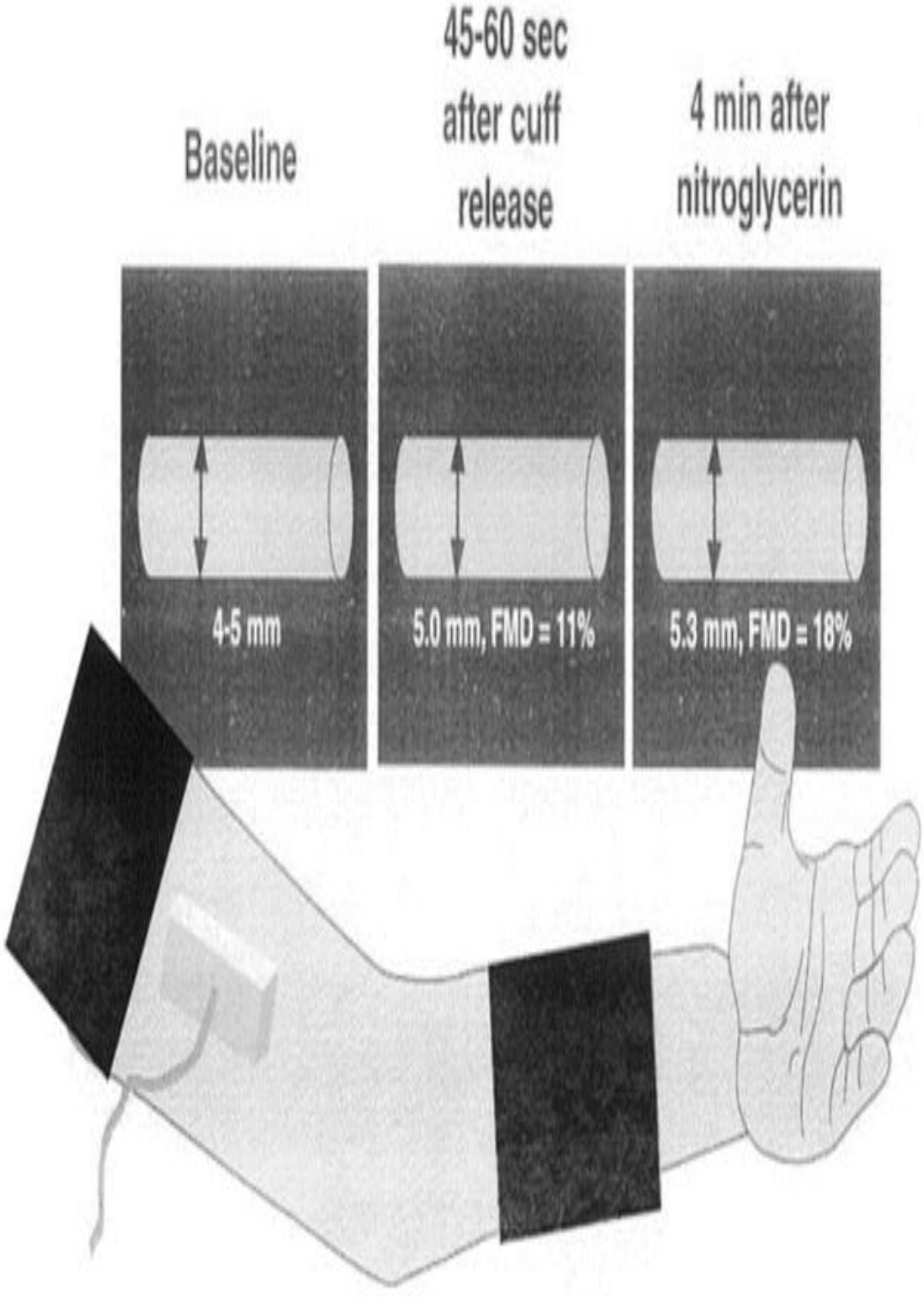
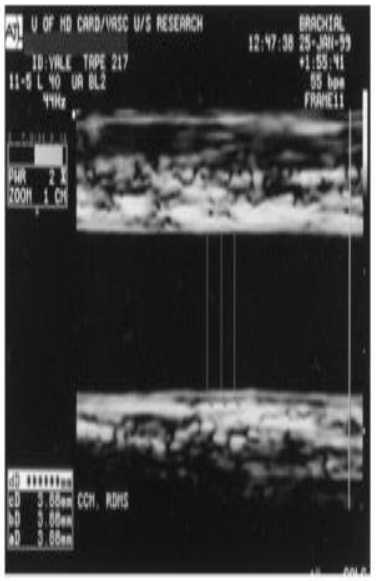
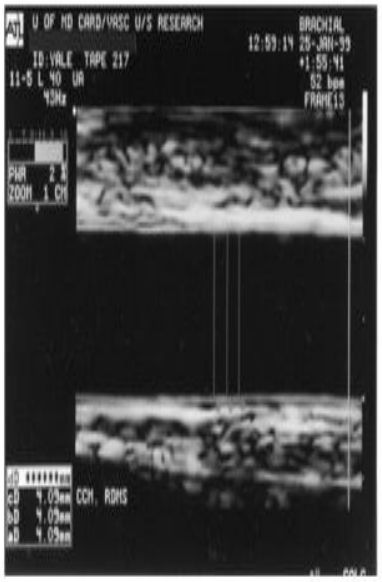

Baseline
45-60 sec after cuff release
4 min after nitroglycerin
4-5 mm
5.0 mm, FMD = 11%
5.3 mm, FMD = 18%



A



B

Figure Legend:

Ultrasound image of the brachial artery at (A) baseline and (B) 1 min after hyperemic stimulus.

ENDOTHELIUM-DEPENDENTFMD.

In order togeneratea flowmediated stimuli in the brachial artery, blood pressure cuff is initially positioned preferably on the forearm. A baseline resting brachial artery image is obtained , and flow of blood is also calculated using the velocity signal got from a midartery sample volumeby time-averaging the pulsed Doppler. Cuff inflation to at least 50 mmhg above systolic pressure to cause occlusion of the arterial inflow for at least 5 minutes of standard time is required . arterial occlusion is created by cuff inflation to suprasystolic pressure. As a result there is ischemia and subsequent vasodilation of downstream resistance vascular bed through various auto-regulatory mechanisms already described . Immediately following deflation of the cuff causes a short-lived high-flow state through the brachial vessel to put up for the dilated downstream resistancevessels.The net resultant accumulation of stress forces leads to brachial artery dilation .

After cuff deflation the longitudinal section of the artery is imaged and recorded constantly from thirty seconds before to two minutes . Experts have widely used both cuff occlusion of upper arm or forearm techniques , and there is no great detail to support as to which method gives us the best results. FMD generally induces a greater % alteration in diameter when we place the cuff on the upper part of arm compared with that induced by positioning of the cuff on the forearm . Conscription of more number of resistance vessels or may

be due to direct effects of ischemia on the brachial vessel causes this greater amount of flow stimulus.However ,precise data attainment is very challenging in this technique as the image is misshapen by brachial artery collapse and soft tissue alteration . As theperiod ofcuffinflation increasesfromthirty seconds tofive minutes , proportional increase in brachial artery diameter also happens. No change is noted after five and ten minutes of occlusion; hence , the more comfortably tolerated five minute occlusion is generally used. Other site for FMD measurement include the radial, axillaries and superficial femoral arteries. Importantly arteries less than2.5mmindiameteraredifficult to measureand vasodilatation is very hard to perceive in arteries bigger than five mm in diameter.

ANALYSIS

Eminence of ultrasound images greatly influences the precise analysis of brachial artery reactivity .Longitudinal images in which the lumen-intima interface is visualized on the near (anterior) and far (posterior) walls is the ideal way to measure the diameter of the brachial artery. When the angle of insonation is perpendicularly placed the boundaries are best visualised. For theimagingplane to bisect the artery wall in the longitudinal direction it needs perfect revelation of both the near and far wall lumen tunica intima boundaries, and diameters calculated from these images mostly give away the true diameter. The boundaries for measurements of brachial artery diameter is made

automatically using edge- detection software , once the image for analysis is chosen. The diameter measurement variability is most minimal when there is an average obtained from a sum of multiple measurements of diameter taken along the vessel segment and maximum when there is a single measured value. When a single point in the length of vessel is utilised to find out the maximum diameter , cross-sectional images are not dependable . The alignment of the image decides the measurements of vessel diameter along the longitudinal plane . When the plane of the ultrasound beam is not completely bisecting the artery skewing occurs.

TIMING OF FMD

The relaxationof a stream artery when exposed to amplifiedstress forces causes flow mediated vasodilatation which in turn is a endothelium-dependant process. During postocclusive reactive hyperaemia there is an large amount of stress forces and flow through the artery. Maximumraise in diameter occurs around sixty seconds after release of the cuff occlusion or forty-five to sixty seconds after peak reactive hyperaemic blood flow and this has been recommended by many studies Period to maximum reactivity , vasodilator response time duration and the region under the dilation curve are the various other modalities predicting vasodilator response . Effectively using automated electrocardiograph gating during image attainment imaging of the brachial artery should be calculated at the same time in cardiac cycle . End diastole is

denoted by the onset of R-wave, and end systole is denoted by the peak of T-wave . Peak systolic diameter is largerthanendsystolicdiameter,As theartery expands more during systole to have room for the rise in both volume and pressure generated by left ventricular contraction. Various factors like old age , systemic hypertensionand T2DM significantly alter the vessel compliance and in turn affect the magnitude of systolic expansion of vessel. Hence if the measurementof vessel diameter isdone at the end systole; functional properties of the brachial artery may complicate the measurements,however this has not been proved in a meticulous trial.

CHARACTERIZING FMD

FMD is classically expressed as a alteration in post-occlusive diameter as a percentage from the baseline diameter . This percentage change is influenced by the Baseline diameter in two ways. First, for any specified absolute change in the post occlusive stimulus diameter, a larger baseline diameter gives a smaller amount of change in percentage. In order to reduce this error calculating the absolute change in diameter is the best method . Second, larger arteries seem to dilate relativelyless thanthe smaller arteries . Percentchange seems to be the best method to use if baseline diameter stays constant over time for studies which involve comparisons in the same individual before and after an intervention.

IS THERE ANY ROLE OF ENDOTHELIAL FUNCTION FOR PROGNOSIS IN PATIENTS WITH ALREADY ESTABLISHED CORONARY ARTERY DISEASE OR EVENTS?

Because endothelial dysfunction plays an important role in the pathogenesis of atherothrombotic disease, it is not surprising that many studies have demonstrated a potential prognostic role of endothelial function in the coronary and peripheral circulation in secondary prevention. First evidence came from patients with nonobstructive coronary artery disease in whom significantly higher incidences of cardiovascular and cerebrovascular events in those with impaired coronary vascular function were found. Similarly, peripheral endothelial dysfunction assessed with FMDand venous occlusion plethysmography predicted cardiovascular events in patients with coronary artery disease and in patients after acute coronary syndromes. In the setting of established coronary artery disease, patients with endothelial dysfunction have higher rates of adverse cardiovascular events compared with those with normal endothelial function, and impaired FMD has been shown to be an independent predictor of in-stent stenosis after single-vessel coronary interventions.In

patients with advanced ischemic heart failure, endothelial function is a strong and independent predictor of 1-year mortality, and in patients with graft vasculopathy (atherosclerosis associated with cardiac transplantation), normal endothelial function is associated with lower progression of coronary intimal thickening; epicardial endothelial dysfunction independently predicts outcome in these patients.

In acute myocardial infarction, microvascular endothelial dysfunction has especially been documented to be indicative of a poorer prognosis. For example, no reflow on angiography strongly predicts 5-year mortality independently of infarct size in patients with acute ST-segment–elevation myocardial infarction. Interestingly, no reflow might be reversible in some cases, which is associated with a better prognosis.

ENDOTHELIAL FUNCTION AS A CONTRIBUTOR TO DISEASE PROGRESSION?

Endothelial dysfunction in the periphery and in the coronary arteries is not only a marker for cardiovascular risk but also a contributor to the progression of

atherosclerosisand cardiovascular events. Interestingly, the atherosclerotic epicardial segments that show the most endothelial dysfunction are those with characteristics of vulnerable atherosclerotic plaques. These segments are characterized by the loss of NO activity and increase in endothelin-1 activity,the same segments more likely to progress to obstructive coronary artery disease.

Importantly, microvascular dysfunction may contribute to the impaired regulation of myocardial perfusion by reducing the capacity to increase perfusion in response to exercise or mental stress, a circumstance that may lead to myocardial ischemia. In the context of myocardial infarction, endothelial microvascular dysfunction is an important mediator of the event rather than just a consequence, likely via reducing coronary blood flow by altering shear stress on the epicardial level, lowering endothelial function, and aggravating thrombus formation. Diabetes mellitus and the accumulation of risk factors in the metabolic syndrome, for example, have significant deleterious effects on myocardial perfusion and infarct size in patients with an acute infarction.Moreover, patients with preprocedural impairment of microvascular function are more likely to have postprocedural microvascular impairment,

procedure-related injury, and a worse outcome.Thus, preexisting microvascular endothelial dysfunction leads to a greater vulnerability to myocardial injury, highlighting the potentially clinically relevant role of a dysfunctional microcirculation and damage.

DOES ENDOTHELIAL FUNCTION IDENTIFY RESPONDERS AND NON RESPONDERS TO THERAPY?

Many medical or lifestyle interventions can improve endothelial function and reduce cardiovascular events. For example, Statin treatment significantly improves peripheral and coronary vascular function, although not all studies were able to prove such an effect within a 6-month treatment period. Of note, the impact on risk reduction despite this successful intervention is limited and is in the range of ≈20% to 45% in clinical trials. Even with the combination of all therapies proven to lower risk in secondary prevention (or primary prevention), some patients may develop later events and therefore are obviously not completely protected by their therapy.

Therefore, it is the ultimate goal to identify those patients who will develop future events despite therapy (to potentially escalate and intensify current treatment). One concept could be to measure the individual impact of therapy on endothelial function as a parameter of cardiovascular disease, targeting those with no improvement in vascular function. Important studies in this respect have recently been performed.

IS IMPROVEMENT IN ENDOTHELIAL FUNCTION AN INDICATOR OF SUCCESSFUL TREATMENT?

It is probably a good sign when endothelial dysfunction is (partly) reversed with treatments. The first proof of this principle came from 2 controlled studies in 1995 in which cholesterol-lowering therapy (statins) improved endothelial function. Statins now have convincing evidence for their beneficial effect on coronary and peripheral endothelial function, likely because of their antiinflammatory and antioxidant properties and because of the restoration of the vascular NO bioavailability. Since the first evidence in humans with statins, numerous interventions in a broad range of patients have demonstrated a

beneficial effect on endothelial function. Most pharmacological intervention studies with an effect on cardiovascular risk factors also show improved endothelial function. For example, antihypertensive therapy in generalsuch as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and certain β-blockers, particular the NO group containing the molecule nebivolol, might reverse endothelial dysfunction; however, angiotensin-converting enzyme inhibitors seem to be particularly important. Calcium channel blockers reduce calcium entry though L-type voltage-dependent channels of the vascular muscle cells, thus dilating coronary and other arteries. Additionally, some calcium channel blockers activate endothelial NO synthase or have antioxidative properties, thus increasing NO bioavailability. The Evaluation of Nifedipine and Cerivastatin on Recovery of Coronary Endothelial Function-1 and -2 (ENCORE-1 and -2) trials showed that long-acting nifedipine consistently improved coronary endothelial function in patients with stable coronary artery disease and that the improvement persisted even after cessation of the drug. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are also preferred medications in diabetes

mellitus. Diabetes-modulating drugs like metformin or glitazones may also improve vascular function in patients with type 2 diabetes mellitus; however, the latter may have negative effects on cardiovascular risk, thus limiting its use.

Not only pharmacological agents but also lifestyle factors and medications that increase the release of or prevent the degradation of endothelium-derived relaxing factors, NO in particular, and those that decrease the production of endothelium-derived constricting factors such as endothelin, among others, can improve endothelial function. Many interventions such as physical exercise, weight reduction (including bariatric surgery),and enhanced external counterpulsation and dietary interventions with foods rich in polyphenols, especially fruits, tea, and cocoa, have been demonstrated to be beneficial for microvascular or macrovascular endothelial function by increasing NO bioavailability. An important lifestyle modification with an impact on endothelial function is smoking cessation. Smoking cessation clearly demonstrates a favourable effect on epicardial coronary endothelial function that was not observed in the microvasculature. This finding

demonstrates the differences in macrovascular function and microvasculature function and their complex, incompletely understood interactions.

Although therapies with a proven benefit on morbidity and mortality in cardiovascular patients concordantly improve endothelial function, it is not certain whether the opposite is always true. For example, vitamin C or E and folic acid supplementation, praised for their antioxidative capacity and associated with significant acute improvement in endothelial function, failed to show any benefit in the long term or in cardiovascular disease prevention so far. On the other end, the path physiological information derived from studies on endothelial function is not correctly applied in clinical trials. Available evidence demonstrates that vitamin C can improve endothelial function but also that this effect is obtained with concentrations much higher than those reached after oral administration. Many studies evaluating path physiological aspects were performed in the setting of acute intravenous or intraatrial interventions. Moreover, the response to vitamins may be dependent on the presence of increased endogenous oxidative stress. This kind of information should be evaluated carefully during the design of intervention studies. The abundant

current trials with any kind of positive effects on the endothelium are path physiologically interesting, but care should be taken to extrapolate the findings to cardiovascular morbidity and mortality. Finally, it is of concern that the drug effects on endothelial function may be different according to which vascular bed is considered. Additionally, many lifestyle interventions, foods, and drugs have been shown to improve endothelial dysfunction in a population as a whole, but not necessarily in the individual patient, a fact which should be addressed in further studies.

ARE MICROVASCULAR FUNCTION AND CONDUIT VESSEL ENDOTHELIAL FUNCTION COMPARABLE?

Although cardiovascular risk factors are associated with endothelial dysfunction in virtually every arterial bed, because of the different physiological role of conduit and resistance arteries, important differences should be considered. Whereas reduced NO release in response to stimuli plays a central role in the pathophysiology of endothelial dysfunction in the conduit arteries, NO in the microcirculation may primarily modulate tissue metabolism. Furthermore, metabolic and other factors are becoming increasingly important in the

regulation of microvascular function. Therefore, pharmacological tests inducing NO release might not reflect the physiological adaption of endothelial function in the microvasculature in response to exercise or ischemia.

The aforementioned differential effect of smoking on microvasculature and epicardial vasculature as outlined above might be only 1 example.Furthermore, FMD is particularly sensitive to being impaired by traditional risk factors (eg, age, hypertension), whereas the peripheral arterial tonometry reactive hyperaemia index (microvasculature) is more sensitive to metabolic risk factors, especially body mass index and diabetes mellitus(and interestingly shows a paradoxical association with age in the Framingham cohort). Microvascular and macrovascular dysfunction could also reflect different stages of vascular disease in that conduit artery endothelial dysfunction may be more important in patients with existing atherosclerosis and microvascular dysfunction may be an earlier indicator of risk. The fact that microvascular endothelial function and macrovascular endothelial function only show a weak (if any) correlation with each othershould caution against the extrapolation of findings in 1 circulation level to the other.

Given that macrovascular and microvascular endothelium is susceptible to different risk factors, both should be evaluated whenever possible.

IS THERE A ROLE OF ENDOTHELIAL FUNCTION IN DRUG-DEVELOPMENT PROGRAMS?

For new drugs, the requirement by drug regulation authorities is to prove the principle by *primum non nocere* (first, do no harm); however, testing the effect of a certain drug on morbidity and mortality requires large sample sizes. Sometimes, such as for drugs with relatively small effects on the cardiovascular system or in children, such outcome trials are not feasible at all. Clinical endothelial function evaluation is of potential value in reassessing the risk of drug-development programs, especially as it becomes more challenging to choose novel agents for clinical use. With endothelial function as a mechanistic surrogate integrating various types of cardiovascular risks, the sample size can be significantly smaller compared with clinical end-point trials. Furthermore, endothelial function may respond rapidly to therapies (within hours, days, or weeks), long before the effects on clinical outcomes are seen. Thus, the impact on endothelial function may give important signals of efficacy or, more

important, may warn of potential harm. Therefore, endothelial function not only is a valuable measure to assess drug efficacy on surrogate end points but also may play an important potential role in the evaluation of drug safety, as exemplified in the recently completed Dalcetrapib's effects on vascular function study (DAL-VESSEL) study, notably the first multicenter study to use FMD as outcome measure. For certain studies, a multimodality approach, which includes peripheral endothelial function measurements, may be of particular value.

WHAT KIND OF STUDIES DO WE NEED IN THE FUTURE?

As outlined above, endothelial function measurement may differentiate responders from nonresponders to therapy. In secondary prevention, studies demonstrate that patients who do not respond to interventions with improved endothelial function are at a considerable risk for further events. These early data suggest that therapy guided by individual endothelial function measurements might be feasible in these settings, but larger studies in this respect are needed to answer the question of whether endothelial function–guided therapies help to improve outcomes.

In primary prevention, it is still unknown whether endothelial function should be assessed in apparently healthy individuals at low risk from traditional risk factors. To address this issue, endothelial dysfunction, which depicts mechanisms at the core of atherosclerosis and its complications, could be chosen for future similar studies, with different medical and lifestyle interventions to be tested. Designing such a trial would require very careful consideration of which noninvasive test or combination of tests of endothelial function should be included. If such results prove positive, there would be a good rationale to implement endothelial function testing in everyday clinical practice.

Currently, clinical guidelines and risk management for prevention are based on the risk factors established in the Framingham study and certain cardiovascular surrogates such as carotid IMT and coronary calcium. However, the Framingham score and other scores provide inconsistent results when applied to different populations, and adjustment based on different populations might be needed. Additionally, the Framingham score is limited to the fact that risk factors were collected years ago, when, for example, no statin therapy was

available and most people smoked or were exposed to secondhand smoke. The effect of a changing environment might be better depicted by endothelial function assessments. With the assumption that endothelial function provides an integrated functional risk assessment, the question of whether endothelial function might be a better predictor for cardiovascular events than the actual scoring systems is intriguing and should be tested with larger-scale studies.

When using the Framingham Risk Score, we are aware how to deal with patients in the high- or low-risk category. However, many patients end up having intermediate risk; for these patients, the recommendation are less clear. As demonstrated by the studies discussed above, reclassification of patients with intermediate risk according to their endothelial function seems to be feasible and reasonable, although further studies in this area are required.

FMD MEASUREMENTS IN HUMANS: GENETIC AND PROGNOSTIC ASPECTS

To explore the aspects of genetic influence on early vasculature physiology which could be significant to a afterwards clinical disease reactivity of brachial

artery has been used effectively. Brachial artery FMD seems to be influenced by intrauterine and childhood factors. Latest studies have illustrated that FMD definitely and appreciably correlates with birth weight. Long-term alterations in vascular function which are apparent by the 1st decade of life may be associated with growth in-utero and other unidentified growth determinants . As a important contributor in the pathogenesis of atherosclerosis in adults endothelial dysfunction has been highlighted . FMD is impaired with progressive atherosclerosis (14, 71). Furthermore, there is some evidence that a Impaired FMD in coronary arteries predicts cardiovascular incident rates and is significantly . Measuring FMD of brachial artery is a non invasive analytical procedureand therefore it permits feasible evaluation of endothelial function in offspring or in 1ST -degree relatives of subjects with apparent atherosclerosis. Even if there islack of other risk factors , young healthy adults with a family history of early onset CAD have endothelial dysfunction as predicted by an impaired FMD. In offspring of patients with premature CAD brachial artery FMD impairment coincides and correlates with a increased carotid artery intima thickness , demonstrating a early structural and functional changes of the

vascular endothelium . Even in first-degree relatives of subjects with T2DM identical results were observed . To potentially recognize subjects at risk for atherosclerotic complications , measurement of FMD is very useful. FMD is useful in prognostic predictions of endothelial dysfunction and also in risk stratification of high risk individuals.Even environmental factors could affect vascular function. After assessing brachial artery FMD, it has been established that passive smoking alters endothelial function in human beings . The combined determination of FMD and By using single nucleotide polymorphisms of target genes concerned in atherosclerosis and along with it combined determination of brachial artery FMD in studies involving very large patient populations could surely endow with new information and new insights into the pathogenesis of early atherosclerosis.

FMD MEASUREMENTS IN HUMANS: OUTLOOK AND FUTURE PERSPECTIVES

Numerous experimental models have been studied extensively to understand the underlying physiological mechanism of FMD. To explore endothelial function one of the most commonly used method is by assessing FMD .

Alterations in FMD have been documented Inpatients with major cardiovascular risk factorsconsidered .Considering studies in huge subject populations and while comparing data from various labs , proper standardization of FMD measurement is required. In FMD measurement there is a absolute need for an international consensus for normal(baseline) , borderline and pathological indication values . For accurate detection of boundaries of the brachial artery wall a latest automated analysis system was developed , which khelped indecreasing variability and study time of FMD measurement . To prove that there is a causal relation between endothelial dysfunction and the clinical predictors of cardiovascular morbidity and mortality , FMD measurements must be carried out in large scale trials and this definitely k8requires much superior methods of FMD measurement . In clinical routine FMD serves as a valuable stand-in of endothelial dysfunction and also as a biomarker . For a better understanding of various phases in the pathogenesis of atherosclerosis, new breakthrough in the field of DNA array technologies will aid us in recognizing the target genes responsible . Categorization of differential gene expression will allow us to obtain

clinicaldiagnosisofvasculardiseases which remain subclinical and this could be made more effective along with a combined measurement of FMD and IMT .FMD assessment provides a more functional and genomic approach to study CAD apart from merely coronary angiographic changes with the perspective to lay down various new strategies in risk stratification and deciding on goals of treatment

APPLICATION IN CLINICAL TRIALS

In view ease to use, high efficacy and noninvasive nature assessment of brachial artery FMD in clinical trials has drastically improved . Several factors must be well thought-out while preparation of a clinical trial in which FMD is the end aim of interest due to the technical and biological variability of the measurement that consist of study design, sample size and uniform technique. Latest studies that include both acute and long term intervention trials have demonstrated the outcome of pharmacologic or physiologic interventions on brachial artery FMD . The major proportion of studies up till now have been from single centre institutions, but multicenter trails are also being undertaken ,

with both crossover and parallel-group design being effectively used .In a crossover design study minimum of twenty to thirty patients may be required for a significant improvement in FMD and forty to sixty patients in a parallel-group design study. An absolute change in FMD of 1.5 percent to 2 percent needs to be observed following a intervention , which could be shown as statistically significant improvement in our study.

FUTURE DIRECTIONS

In spite of various new approaches and indigenous scientific advances that have emerged, USG measurement of brachial artery FMD has provide us the most vital and accurate inputs about endothelial function in healthy and diseased individuals.To obtain vital data about microvasculature endothelial function spectral Doppler is very useful to reproducibly quantify the changes in flow in the brachial artery during FMD procedure . In establishing the clinical efficacy of brachial artery FMD there is a huge amount of interest that is developing among clinicians. Studies have hypothesized that endothelial dysfunction could prove to be a preclinical indicator of cardiovascular disease

burden and also serves as an predictive bridging index of genetic susceptibility and risk factor burden . Endothelial dysfunction of the coronary arteries is an self-determining predictor of cardiovascular disease events and this has been well established by various studies.

Upcoming several large population trials that includes the Framingham Heart Study and the Cardiovascular Health Study, should be able to decide whether endothelial dysfunction in the brachial artery will recognize patients at risk for developing CAD , CVA and peripheral vascular disease .Forswot upof the initial stages of atherosclerosis in children and young adults this technique is very helpful , thus giving us adequate chance for prevention and early intervention. As there is an attempt to modify the risk factors and early intervention with drugs well known to decrease cardiovascular risk , consequently brachial artery vascular reactivity improves drastically and this has been proved by numerous studies . Whether this enhancement in vascular endothelial function directly brings about an overall improved outcome of the patient remains questionable. FMD may be used to assess the response to drug therapy and to prioritize individual patient risk factor modification programs in

the near future by clinicians. In order to make FMD a clinically effective tool to measure or quantify cardiovascular risk in an individual or involving a large group ,further supportive studies are required to decide whether this technique is constantly reproducible and whether there is sufficiently low bio variability amongst subjects . To that day, thistechnique will need time to mature, with officialtraining opportunities for , certification and continuing medical education, as currently exist for other cardiovascular testing modalities

AIMS AND OBJECTIVES

PRIMARY OBJECTIVE

TO STUDY THE CORRELATION BETWEEN FLOW MEDIATED VASODILATATION OF BRACHIAL ARTERY AND CORONARY ANGIOGRAPHIC CHANGES

SECONDARY OBJECTIVES

1. TO ASSESS THE CORRELATION BETWEEN OTHER WELL ESTABLISHED CARDIOVASCULAR RISK FACTORS LIKE SMOKING, WAIST HIP RATIO, LIPID ABNORMALITIES AND CAROTID INTIMA MEDIA THICKNESS.

2. TO ASSESS THE RELATIONSHIP BETWEEN PER-CAPITA INCOME AND CAG CHANGES

3. TO ASSESS THE RELATIONSHIP BETWEEN DIET PREFERRENCE AND CAG CHANGES

MATERIALS AND METHODS

PLACE OF STUDY:

DEPARTMENT OF CARDIOLOGY, CARDIOLOGY OPD, MEDICAL WARDS AND IMCU AT STANLEY MEDICAL COLLEGE AND HOSPITAL, CHENNAI.

DURATION:JAN 2014 TO SEP 2014.

STUDY DESIGN:RETROSPECTIVE OBSERVATIONAL STUDY

SAMPLE SIZE: 75

METHODOLOGY-

Patients diagnosed with coronary artery disease within 1 month and have undergone coronary angiogram ;from the period January 2014 to September 2014 in ICCU/ cardiology wards are included in the study. Patients will be subjected to symptom analysis, clinical examination, laboratory investigations and flow mediated vasodilation studies of brachial artery. The final analysis will be made at the end of the study to achieve the fore mentioned goals using appropriate statistical methods.

PATIENT SELECTION:

INCLUSION CRITERIA

1. All patients who have been diagnosed having coronary artery disease which includes chronic stable angina, ST elevation MI, non ST elevation MI , unstable angina within the last 1month and have undergone CAG.

2. All patients who have undergone primary/ facilitated PCI within the above mentioned time.

3. Patients between 20 and 60 years of age.

EXCLUSION CRITERIA

1. Patients with any form of connective tissue disorder, chronic kidney disease, Chronic liver disease

2. Any patient < 20 and > 60 yrs of age.

Study Groups

Treatment Groups	Name of Group	Number of Subjects
Group A	Non Critical CAD	18
Group B	SVD	33
Group C	DVD	8
Group D	TVD	16

Statistics

Descriptive statistics was done for all data and suitable statistical tests of comparison were done. Continuous variables were analysed with ANOVA and categorical variables were analysed with the Chi-Square Test and Fisher Exact Test. Statistical significance was taken as $P < 0.05$. The data was analysed using Epi Info software (7.1.0.6 version; Centre for disease control, USA) and Microsoft Excel 2010.

SAMPLE SIZE CALCULATION

Sample size was determined on the basis of a pilot study in which the presence increased percentage of FMD was measured at 4%. We calculated a minimum sample size of 59 patients was required, assuming a type 1 error (two-tailed) of 0.05 and a margin of error of 10%. Therefore, the final sample selected was n=75.

$$n = \frac{t^2 \times p(1-p)}{m^2}$$

Description:

n = required sample size

t = confidence level at 95% (standard value of 1.96)

p = estimated prevalence of malnutrition in the project area

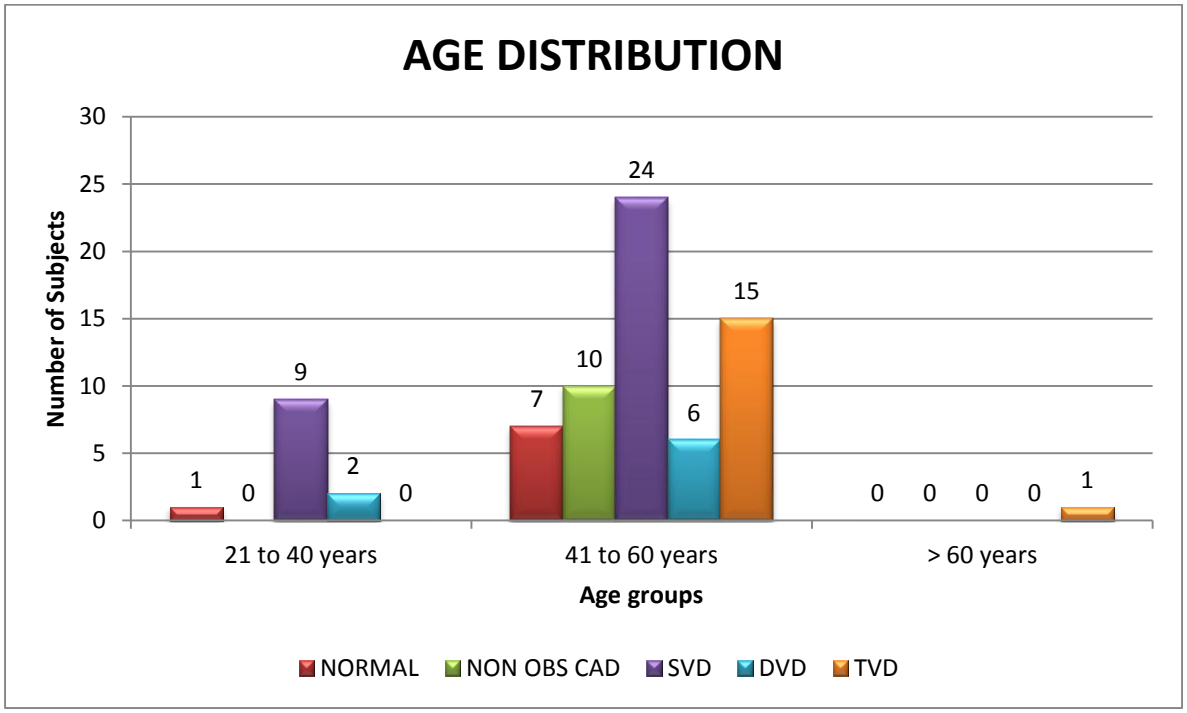
m = margin of error at 10% (standard value of 0.05)

$$n = \frac{(1.96)^2 \times 0.04(1-0.96)}{(0.05)^2}$$

$$n = \frac{3.8146 \times 0.0384}{0.0025}$$

= 59

Age

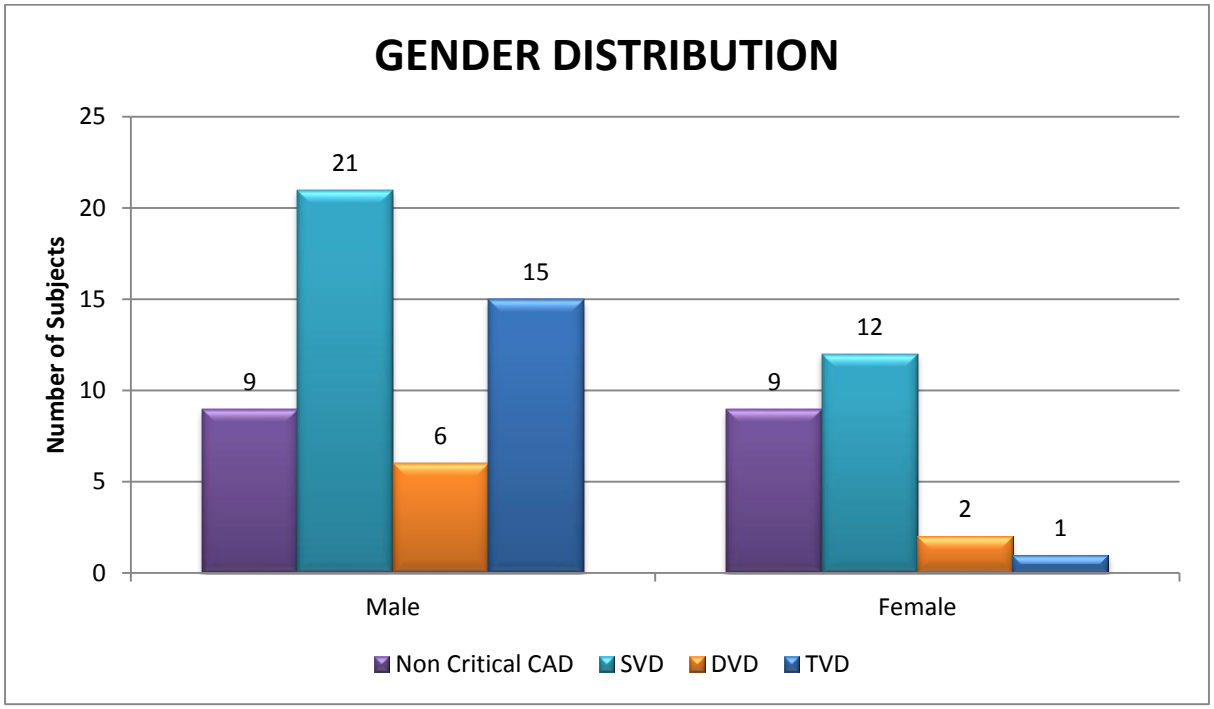


AGE DISTRIBUTION	Non Critical CAD	SVD	DVD	TVD
N	18	33	8	16
MEAN	53.11	47.85	50.88	54.69
SD	5.87	7.72	10.87	4.63

AGE DISTRIBUTION	Non Critical CAD	%	SVD	%	DVD	%	TVD	%
≤ 20 years	0	0	0	0	0	0	0	0
21 to 40 years	1	6	9	27	2	25	0	0
41 to 60 years	17	94	24	73	6	75	15	94
> 60 years	0	0	0	0	0	0	1	6
Total	18	100	33	100	8	100	16	100
P value ANOVA	0.1376							

By conventional criteria the association between the study groups and age is considered to be not statistically significant since $p > 0.05$

Gender

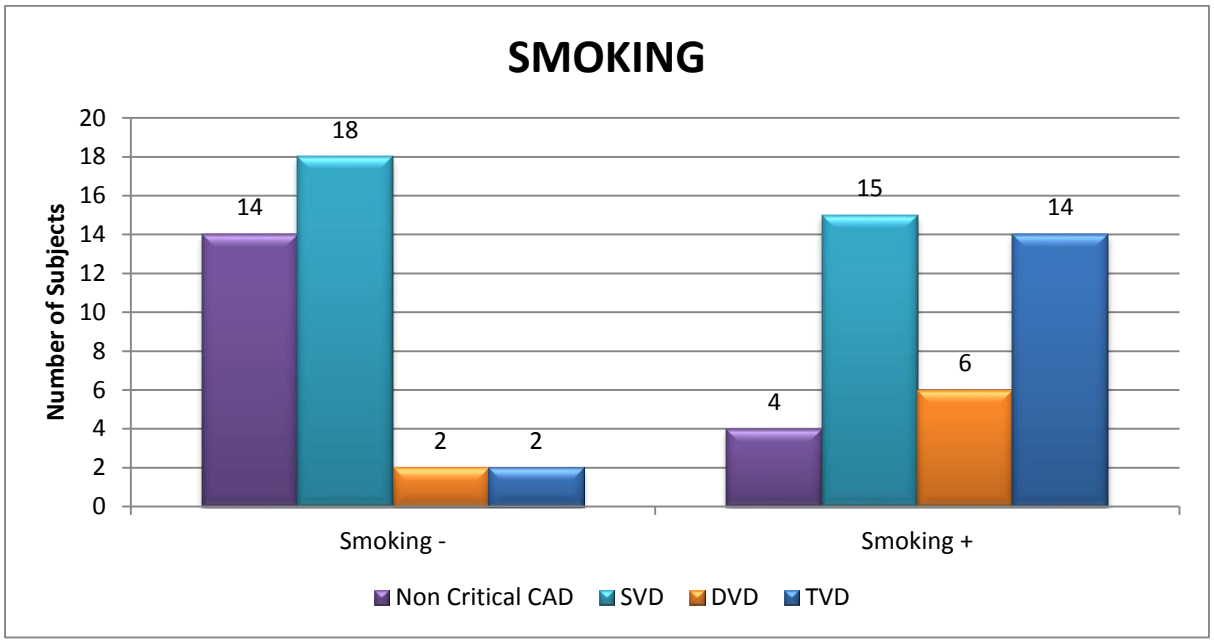


GENDER DISTRIBUTION	Non Critical CAD	%	SVD	%	DVD	%	TVD	%
Male	9	50.00	21	63.64	6	75.00	15	93.75
Female	9	50.00	12	36.36	2	25.00	1	6.25
Total	18	100	33	100	8	100	16	100
chi-square statistic	9.06							
degrees of freedom	3							
P value Chi Squared Test	0.6000							

By conventional criteria the association between the study groups and gender is considered to be not statistically significant since $p > 0.05$.

Since age and gender is not statistically significant, it means that there is no difference between the groups. In other words the groups contain subjects with the same basic demographic characteristics.

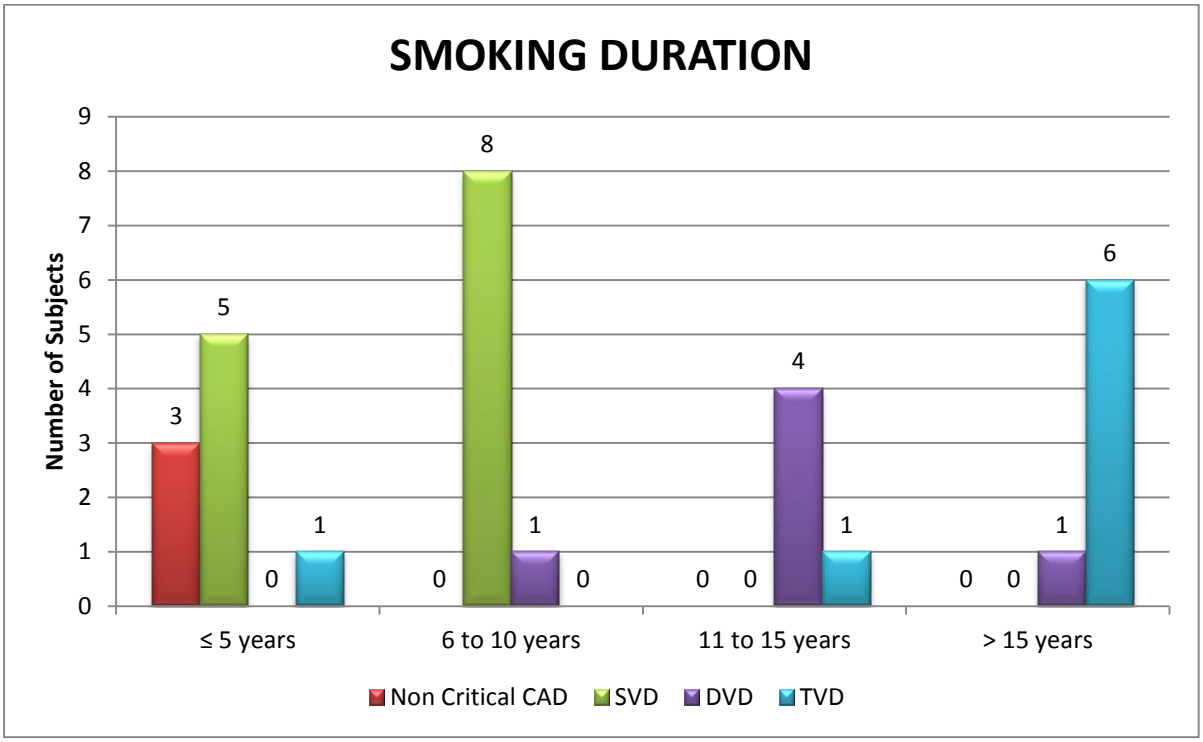
Smoking



SMOKING	Non Critical CAD	%	SVD	%	DVD	%	TVD	%
Smoking -	14	77.78	18	54.55	2	25.00	2	12.50
Smoking +	4	22.22	15	45.45	6	75.00	14	87.50
Total	18	100	33	100	8	100	16	100
chi-square statistic	6.89							
degrees of freedom	3							
P value Chi Squared Test	0.142							

By conventional criteria the association between the study groups and smoking is considered to be not statistically significant since $p > 0.05$.

Smoking Duration



SMOKING DURATION	Non Critical CAD	SVD	DVD	TVD
N	3	13	6	8
MEAN	2.00	3.85	4.33	23.50
SD	0.00	3.69	5.43	10.41

SMOKING DURATION	Non Critical CAD	%	SVD	%	DVD	%	TVD	%
≤ 5 years	3	100	5	38	0	0	1	13
6 to 10 years	0	0	8	62	1	17	0	0
11 to 15 years	0	0	0	0	4	67	1	13
> 15 years	0	0	0	0	1	17	6	75
Total	3	100	13	100	6	100	8	100
P value ANOVA	0.0000043							

By conventional criteria the association between the study groups and duration of smoking levels among study subjects is considered to be statistically significant since $p < 0.05$.

Statistical Significance

This indicates that there is a true difference among groups and the difference is significant. . In simple terms, when studying the association between flow mediated vasodilatation and coronary angiographic changes, the duration of smoking in non-critical CAD group is predominantly less(2 years) when compared to SVD group(3.85 years), DVD group(4.33) and TVD group(23.50 years). It is statistically significant with a p-value of 0.0000 according to ANOVA.

Clinical Significance

The average duration of smoking in non-critical CAD group is meaningfully less than SVD group by 1.92 times with a mean difference of 1.85 years.

The average duration of smoking in non-critical CAD group is meaningfully less than DVD group by 2.16 times with a mean difference of 2.33 years.

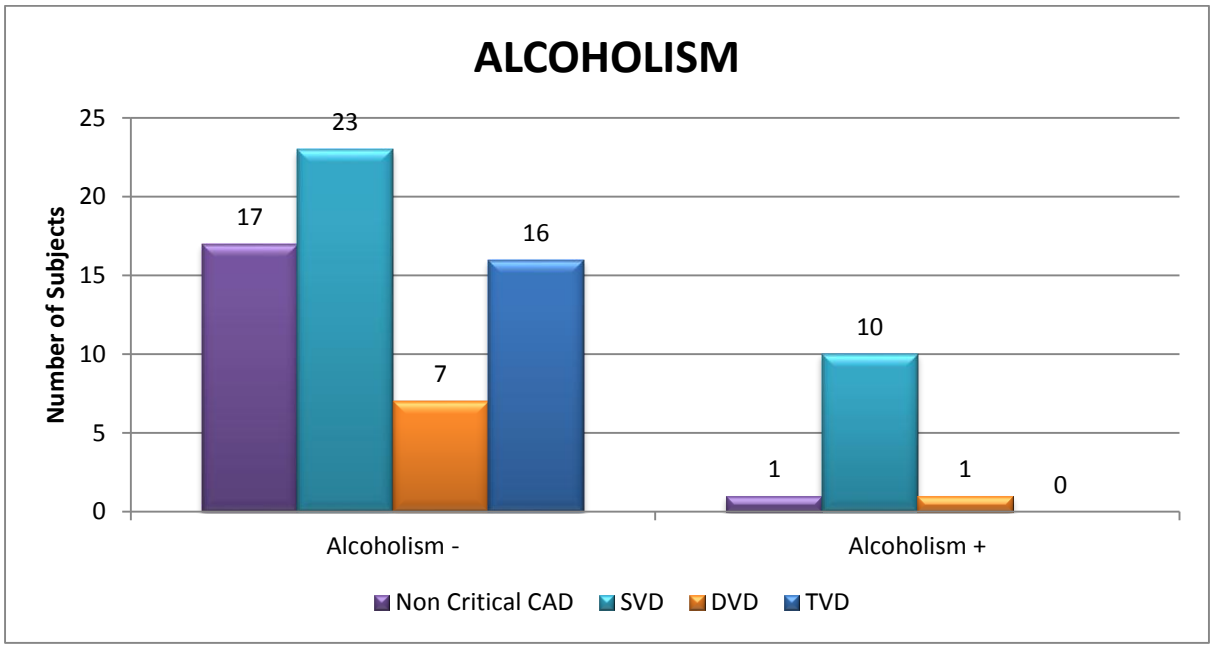
The average duration of smoking in non-critical CAD group is meaningfully less than TVD group by 11.75 times with a mean difference of 21.50 years.

This difference is true and significant and has not occurred by chance.

Conclusion

We conclude that there is meaningfully real increase in severity of CAD as duration of smoking increases in our study subjects.

Alcoholism

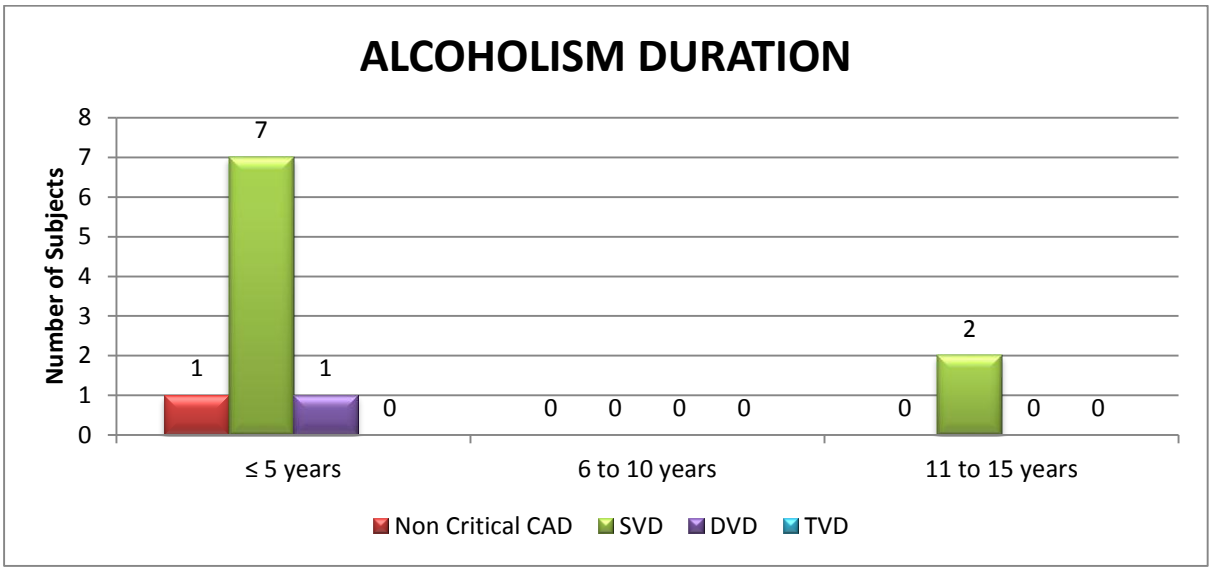


ALCOHOLISM	Non Critical CAD	SVD	DVD	TVD
N	18	33	8	16
MEAN	0.06	0.30	0.13	0.00
SD	0.24	0.47	0.35	0.00

ALCOHOLISM	Non Critical CAD	%	SVD	%	DVD	%	TVD	%
Alcoholism -	17	94	23	70	7	88	16	100
Alcoholism +	1	6	10	30	1	13	0	0
Total	18	100	33	100	8	100	16	100
chi-square statistic	10.1							
degrees of freedom	3							
P value Chi Squared Test	0.308							

By conventional criteria the association between the study groups and alcoholism is considered to be not statistically significant since $p > 0.05$.

Alcoholism Duration

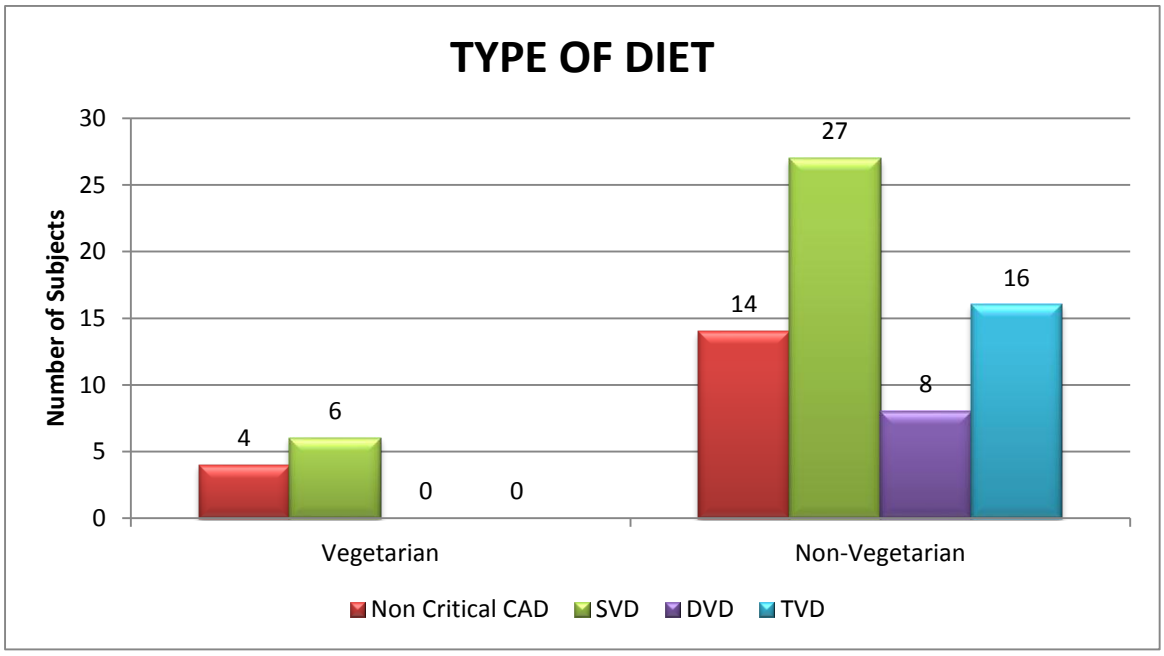


ALCOHOLISM DURATION	Non Critical CAD	SVD	DVD	TVD
N	1	9	1	0
MEAN	5.00	4.67	5.00	0
SD	0	6.18	0	0

ALCOHOLISM DURATION	Non Critical CAD	%	SVD	%	DVD	%	TVD	%
≤ 5 years	1	100	7	78	1	100	0	0
6 to 10 years	0	0	0	0	0	0	0	0
11 to 15 years	0	0	2	22	0	0	0	0
> 15 years	0	0	0	0	0	0	0	0
Total	1	100	9	100	1	100	0	0
P value ANOVA	0.999997886							

By conventional criteria the association between the study groups and duration of alcohol intake is considered to be not statistically significant since $p > 0.05$.

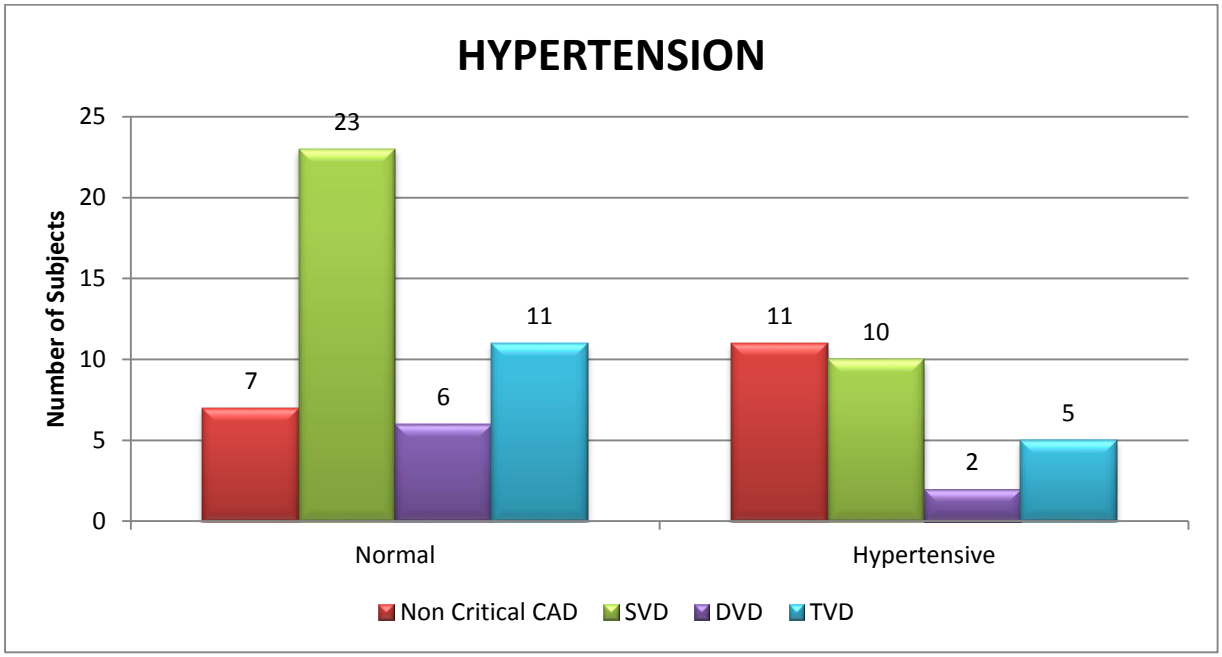
Diet



TYPE OF DIET	Non Critical CAD	%	SVD	%	DVD	%	TVD	%
Vegetarian	4	22	6	18	0	0	0	0
Non-Vegetarian	14	78	27	82	8	100	16	100
Total	18	100	33	100	8	100	16	100
chi-square statistic	5.69							
degrees of freedom	3							
P value Chi Squared Test	0.223							

By conventional criteria the association between the study groups and type of diet intake is considered to be not statistically significant since $p > 0.05$.

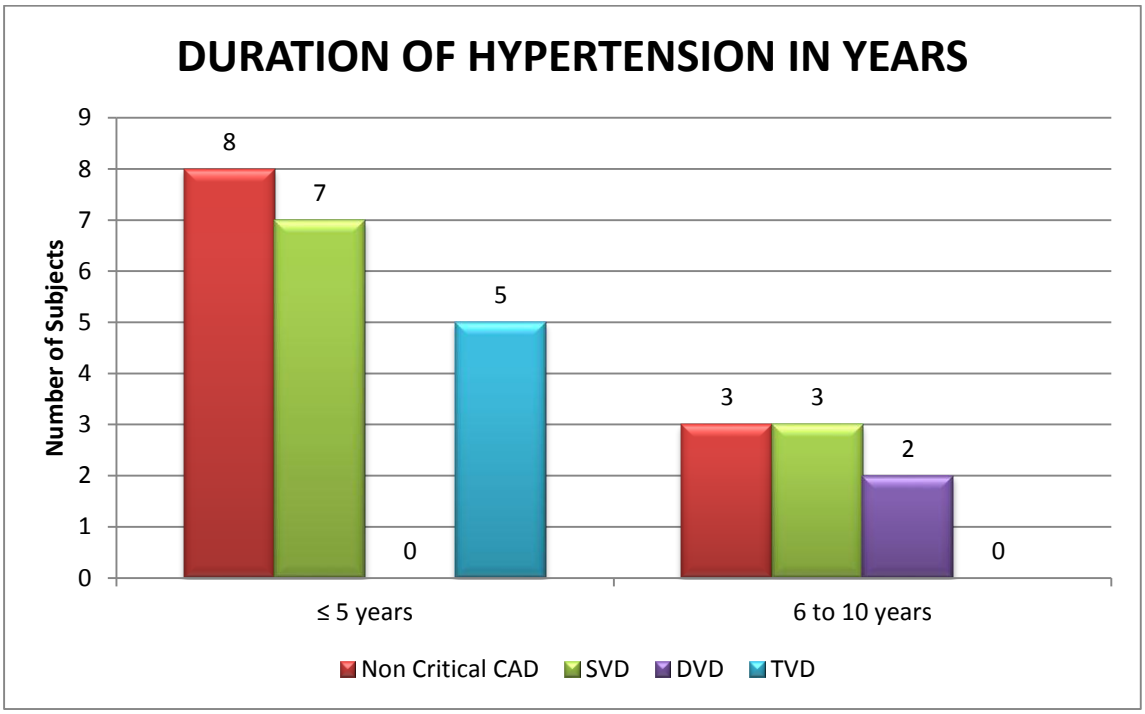
Hypertension



HYPERTENSION	Non Critical CAD	%	SVD	%	DVD	%	TVD	%
Normal	7	39	23	70	6	75	11	69
Hypertensive	11	61	10	30	2	25	5	31
Total	18	100	33	100	8	100	16	100
chi-square statistic	9.25							
degrees of freedom	3							
P value Chi Squared Test	0.055							

By conventional criteria the association between the study groups and hypertension status is considered to be not statistically significant since p > 0.05.

Duration of Hypertension

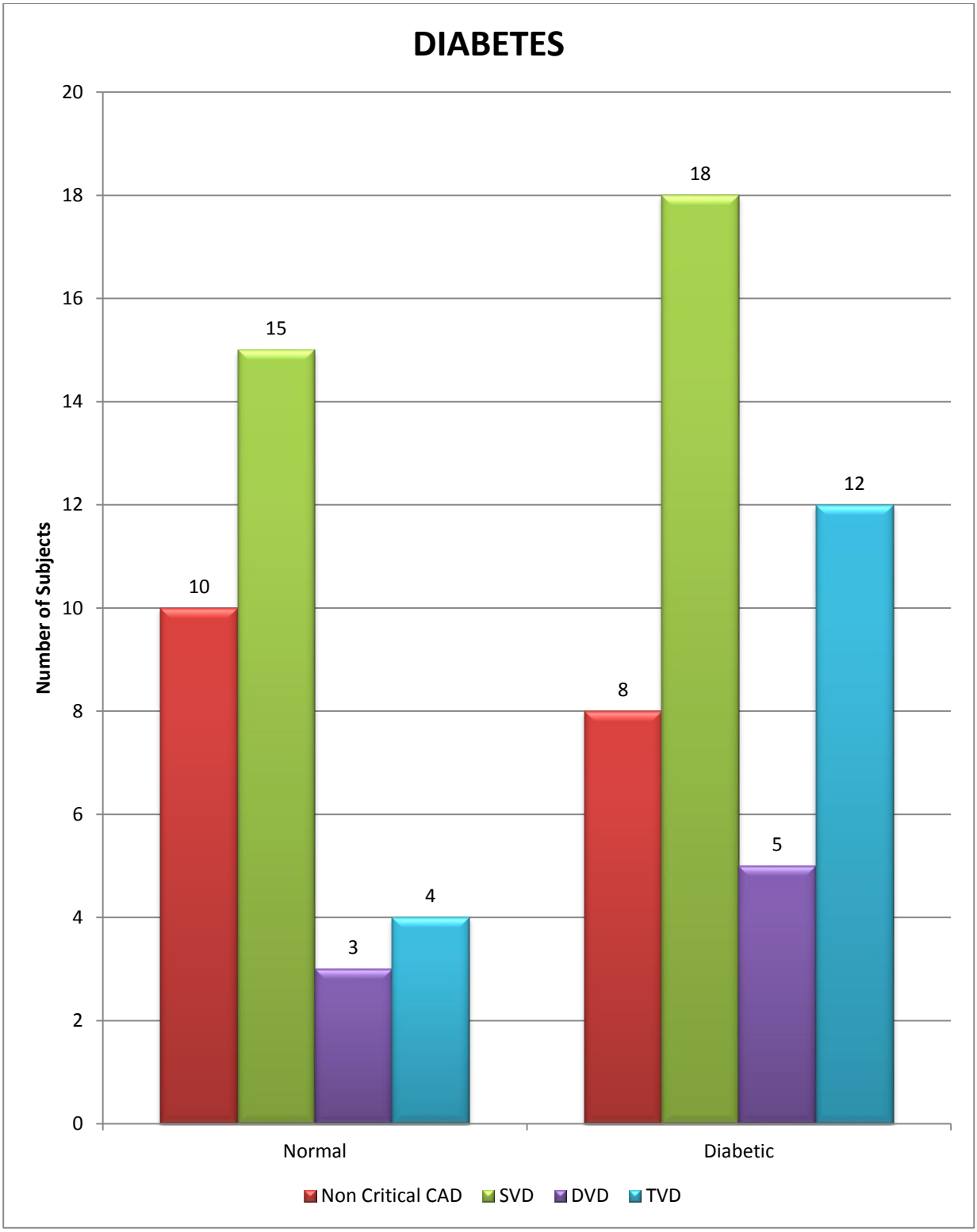


DURATION OF HYPERTENSION IN YEARS	Non Critical CAD	SVD	DVD	TVD
N	11	10	2	5
MEAN	4.45	3.00	10.00	4.40
SD	3.08	2.30	0.00	1.34

DURATION OF HYPERTENSION IN YEARS	Non Critical CAD	%	SVD	%	DVD	%	TVD	%
≤ 5 years	8	73	7	70	0	0	5	100
6 to 10 years	3	27	3	30	2	100	0	0
11 to 15 years	0	0	0	0	0	0	0	0
> 15 years	0	0	0	0	0	0	0	0
Total	11	100	10	100	2	100	5	100
P value ANOVA	0.111981261							

By conventional criteria the association between the study groups and duration of hypertension is considered to be not statistically significant since $p > 0.05$.

Diabetes



DIABETES	Non Critical CAD	%	SVD	%	DVD	%	TVD	%
Normal	10	56	15	45	3	38	4	25
Diabetic	8	44	18	55	5	63	12	75
Total	18	100	33	100	8	100	16	100
chi-square statistic	14.5							
degrees of freedom	3							
P value	0.006							

By conventional criteria the association between the study groups and diabetes status levels among study subjects is considered to be statistically significant since $p < 0.05$.

Statistical Significance

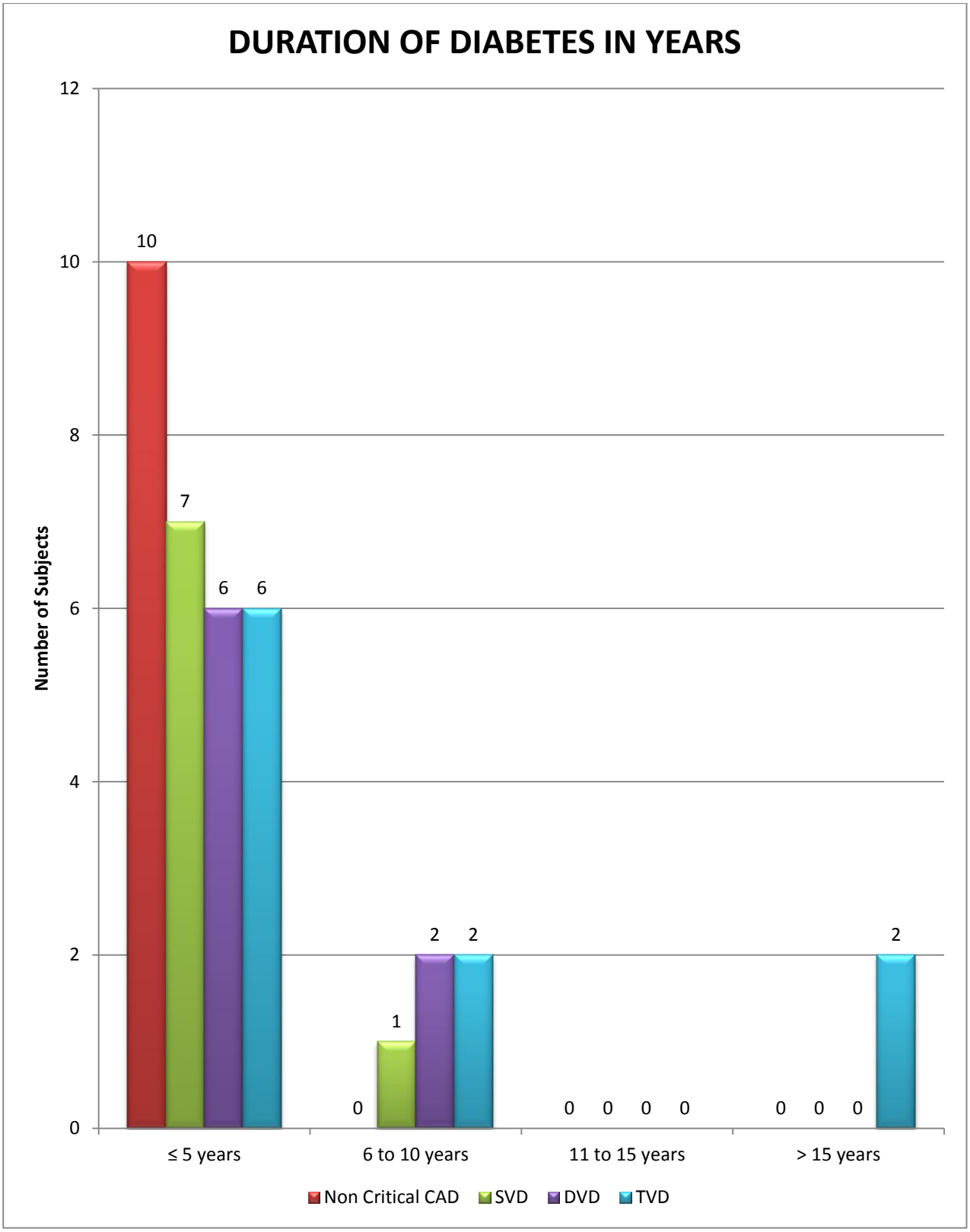
This indicates that there is a true difference among groups and the difference is significant. . In simple terms, when studying the association between flow mediated vasodilatation and coronary angiographic changes, the diabetes status in non-critical CAD group(44%) is predominantly less when compared to SVD(55%), DVD(63%) and TVD(75%) groups. It is statistically significant with a p-value of 0.006 according to chi squared test.

Clinical Significance

The diabetic status in non-critical CAD group is meaningfully less than SVD group by 1.22 times with a mean difference of 10 percentage points.

The diabetic status in non-critical CAD group is meaningfully less than DVD group by 1.15 times with a mean difference of 8 percentage points.
The diabetic status in non-critical CAD group is meaningfully less than TVD group by 1.2 times with a mean difference of 13 percentage points .This difference is true and significant and has not occurred by chance.

Conclusion We conclude that there is meaningfully real increase in severity of CAD in relation to diabetic status in our study subjects.


DURATION OF DIABETES IN YEARS
Number of Subjects
12
10
8
6
4
2
0
10
7
6
6
0
1
2
2
0
0
0
0
0
0
0
2
≤ 5 years
6 to 10 years
11 to 15 years
> 15 years
Non Critical CAD
SVD
DVD
TVD

DURATION OF DIABETES IN YEARS	Non Critical CAD	SVD	DVD	TVD
N	10	8	8	10
MEAN	2.90	4.25	5.25	7.30
SD	2.01	2.49	2.25	6.41

DURATION OF DIABETES IN YEARS	Non Critical CAD	%	SVD	%	DVD	%	TVD	%
≤ 5 years	10	100	7	88	6	75	6	60
6 to 10 years	0	0	1	13	2	25	2	20
11 to 15 years	0	0	0	0	0	0	0	0
> 15 years	0	0	0	0	0	0	2	20
Total	10	100	8	100	8	100	10	100
P value ANOVA	0.0111981261							

By conventional criteria the association between the study groups and duration of diabetes among study subjects is considered to be statistically significant since $p < 0.05$.

Statistical Significance

This indicates that there is a true difference among groups and the difference is significant. . In simple terms, when studying the association between flow mediated vasodilatation and coronary angiographic changes, the duration of diabetes in non-critical CAD group is predominantly less(2.9 years) when compared to SVD group(4.25years), DVD group(5.25) and TVD group(7.30 years). It is statistically significant with a p-value of 0.0112 according to ANOVA.

Clinical Significance

The average duration of diabetes in non-critical CAD group is meaningfully less than SVD group by 1.47 times with a mean difference of 1.35 years.

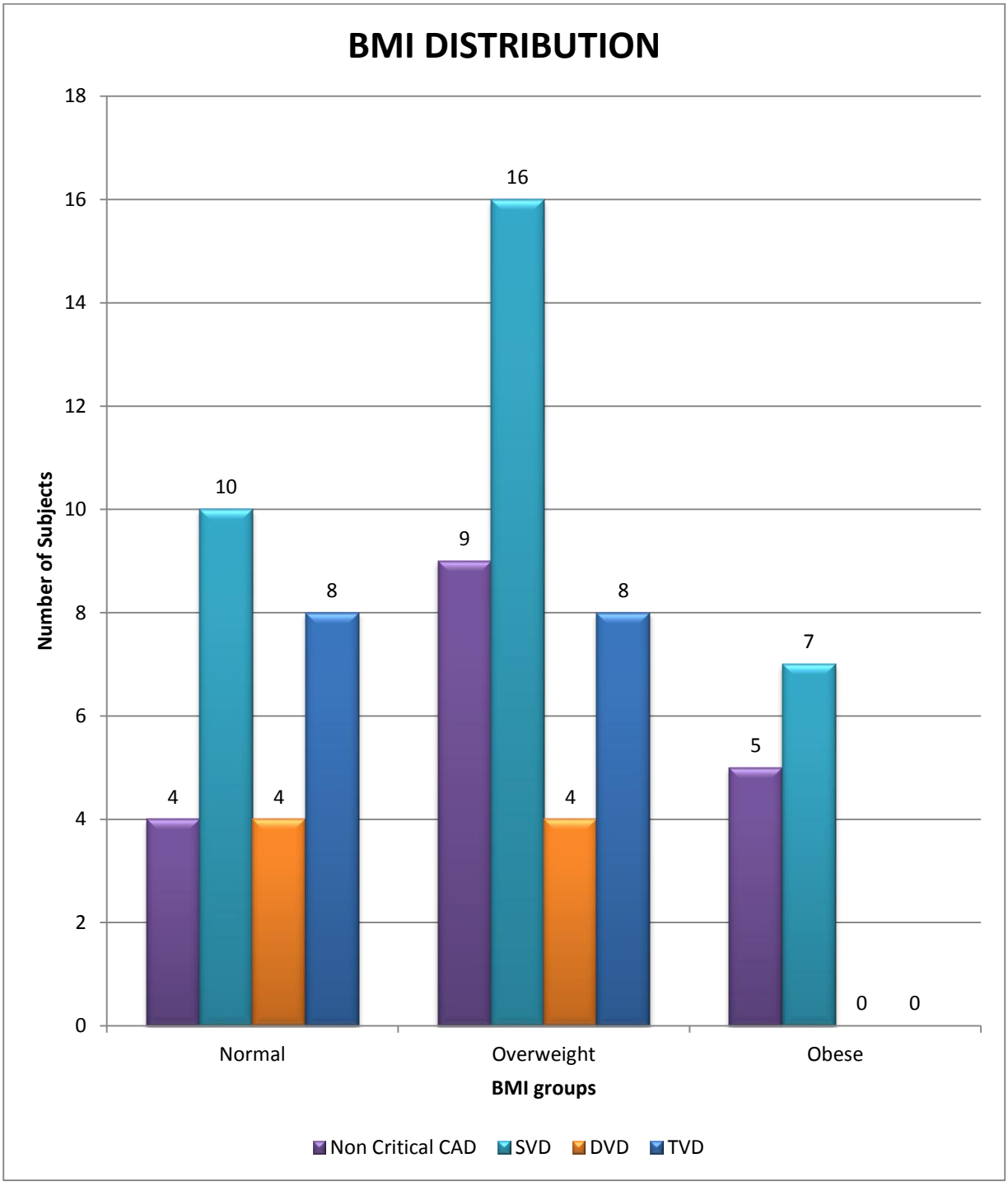
The average duration of diabetes in non-critical CAD group is meaningfully less than DVD group by 1.24 times with a mean difference of 1.00 years.

The average duration of diabetes in non-critical CAD group is meaningfully less than TVD group by 1,39 times with a mean difference of 2.05 years.

This difference is true and significant and has not occurred by chance.

Conclusion We conclude that there is meaningfully real increase in severity of CAD as duration of diabetes increases in our study subjects.

BMI


BMI DISTRIBUTION
Number of Subjects
18
16
14
12
10
8
6
4
2
0
4
10
8
9
16
8
5
7
0
0
Normal
Overweight
Obese
BMI groups
Non Critical CAD
SVD
DVD
TVD

BMI	NORMAL	Non Obstructive CAD	SVD	DVD	TVD
N	8	18	33	8	16
MEAN	24.34	27.38	29.15	30.15	31.34
SD	2.89	3.40	4.64	2.59	1.95

BMI	Non Critical CAD	%	SVD	%	DVD	%	TVD	%
Normal	4	22	10	30	4	50	8	50
Overweight	9	50	16	48	4	50	8	50
Obese	5	28	7	21	0	0	0	0
Total	18	100	33	100	8	100	16	100
P value ANOVA	0.02694							

By conventional criteria the association between the study groups and BMI among study subjects is considered to be statistically significant since $p < 0.05$.

Statistical Significance

This indicates that there is a true difference among groups and the difference is significant. . In simple terms, when studying the association between flow mediated vasodilatation and coronary angiographic changes, the BMI in non-critical CAD group is predominantly less(24.34) when compared to non-obstructive CAD(27.38), SVD group(29.15), DVD group(30.15) and TVD group(31.34). It is statistically significant with a p-value of 0.0112 according to ANOVA.

Clinical Significance

The average duration of diabetes in non-critical CAD group is meaningfully less than SVD group by 1.20 times with a mean difference of 4.81 points..

The average duration of diabetes in non-critical CAD group is meaningfully less than DVD group by 1,24 times with a mean difference of 5.81 points.

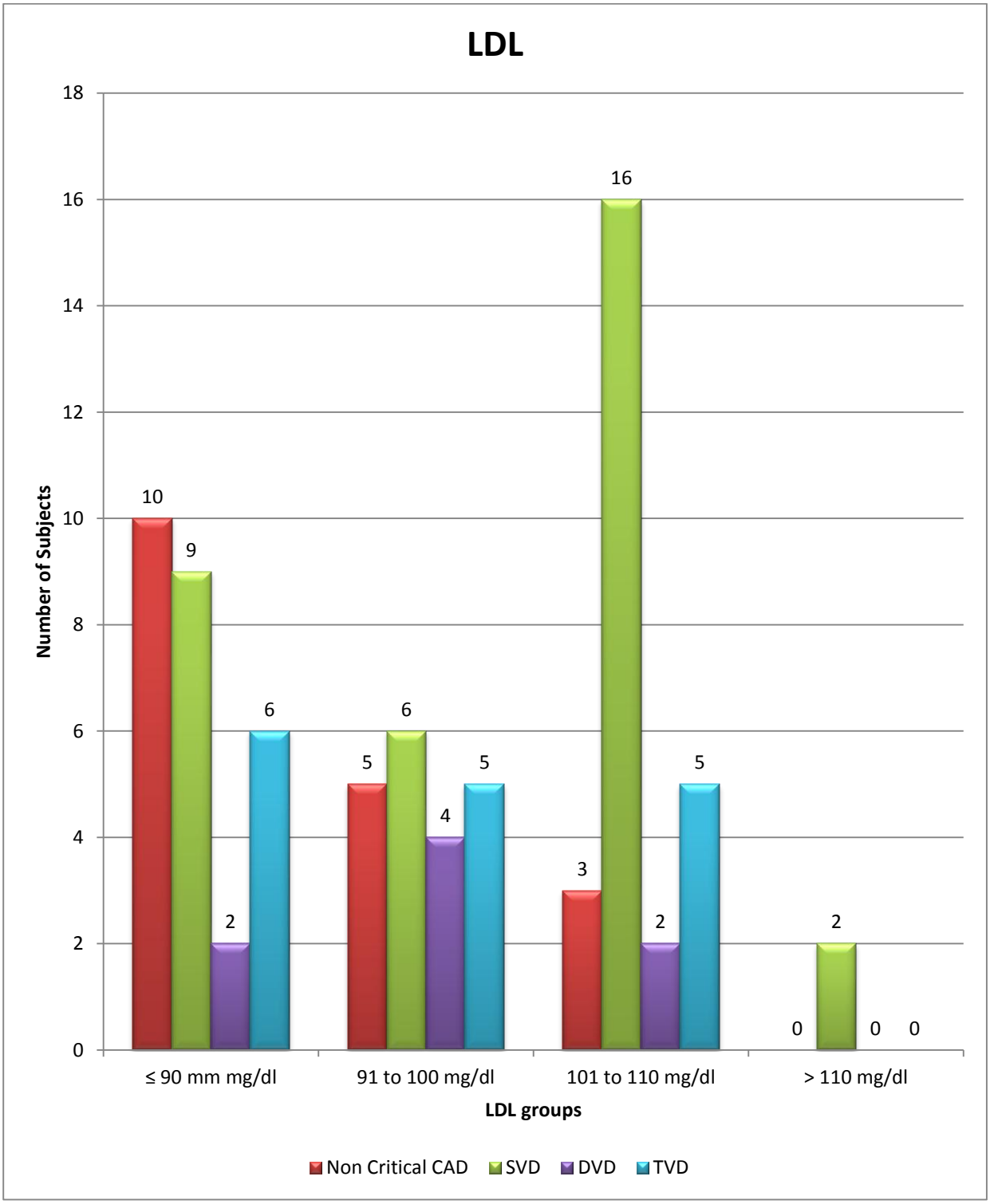
The average duration of diabetes in non-critical CAD group is meaningfully less than TVD group by 1,29 times with a mean difference of 7.00 points.

This difference is true and significant and has not occurred by chance.

Conclusion

We conclude that there is meaningfully real increase in severity of CAD as BMI increases in our study subjects.

LDL


LDL
Number of Subjects
18
16
14
12
10
8
6
4
2
0
10
9
2
6
5
6
4
5
3
16
2
5
0
2
0
0
≤ 90 mm mg/dl
91 to 100 mg/dl
101 to 110 mg/dl
> 110 mg/dl
LDL groups
Non Critical CAD
SVD
DVD
TVD

LDL	Non Critical CAD	SVD	DVD	TVD
N	18	33	8	16
MEAN	93.00	95.63	99.39	103.81
SD	8.29	10.13	6.43	9.45

LDL	Non Critical CAD	%	SVD	%	DVD	%	TVD	%
≤ 90 mm mg/dl	10	56	9	27	2	25	6	38
91 to 100 mg/dl	5	28	6	18	4	50	5	31
101 to 110 mg/dl	3	17	16	48	2	25	5	31
> 110 mg/dl	0	0	2	6	0	0	0	0
Total	18	100	33	100	8	100	16	100
P value ANOVA	0.02561195							

By conventional criteria the association between the study groups and LDL levels among study subjects is considered to be statistically significant since $p < 0.05$.

Statistical Significance

This indicates that there is a true difference among groups and the difference is significant. . In simple terms, when studying the association between flow mediated vasodilatation and coronary angiographic changes, the LDL levels in non-critical CAD group is predominantly less(93.00 mg/dl) when compared SVD group(95.63 mg/dl), DVD group(99.39 mg/dl) and TVD group(103.81 mg/dl). It is statistically significant with a p-value of 0.0256 according to ANOVA.

Clinical Significance

The average duration of diabetes in non-critical CAD group is meaningfully less than SVD group by 1.02 times with a mean difference of 2.63 mg/dl.

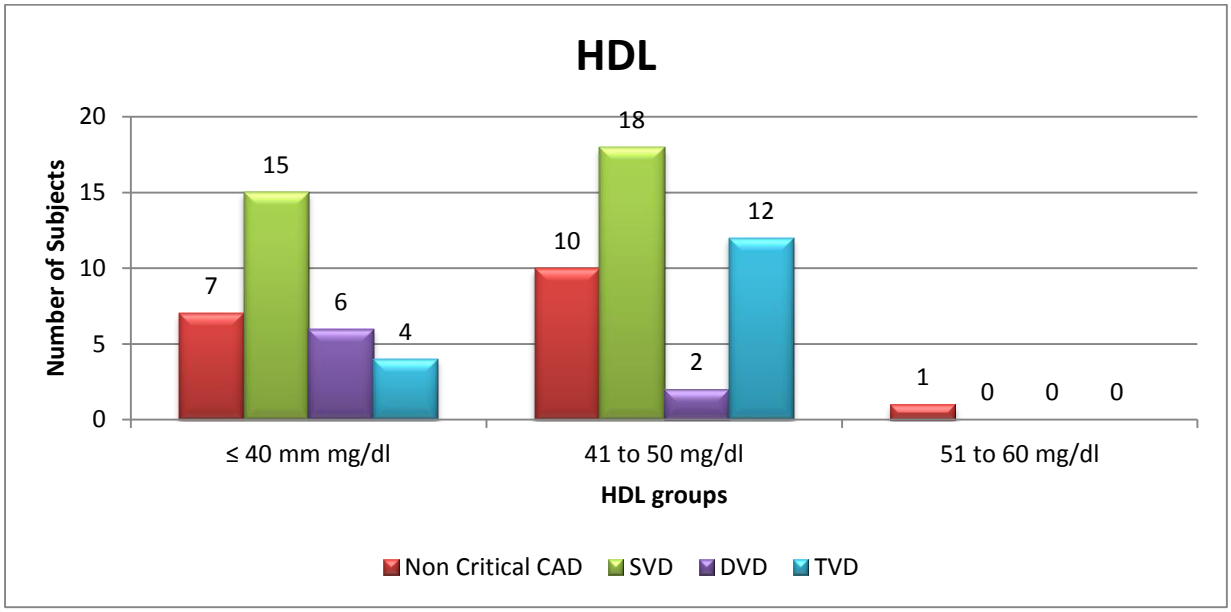
The average duration of diabetes in non-critical CAD group is meaningfully less than DVD group by 1,06 times with a mean difference of 6.39 mg/dl.

The average duration of diabetes in non-critical CAD group is meaningfully less than TVD group by 1,12 times with a mean difference of 10.81 mg/dl.

This difference is true and significant and has not occurred by chance.

Conclusion We conclude that there is meaningfully real increase in severity of CAD as LDL increases in our study subjects.

HDL

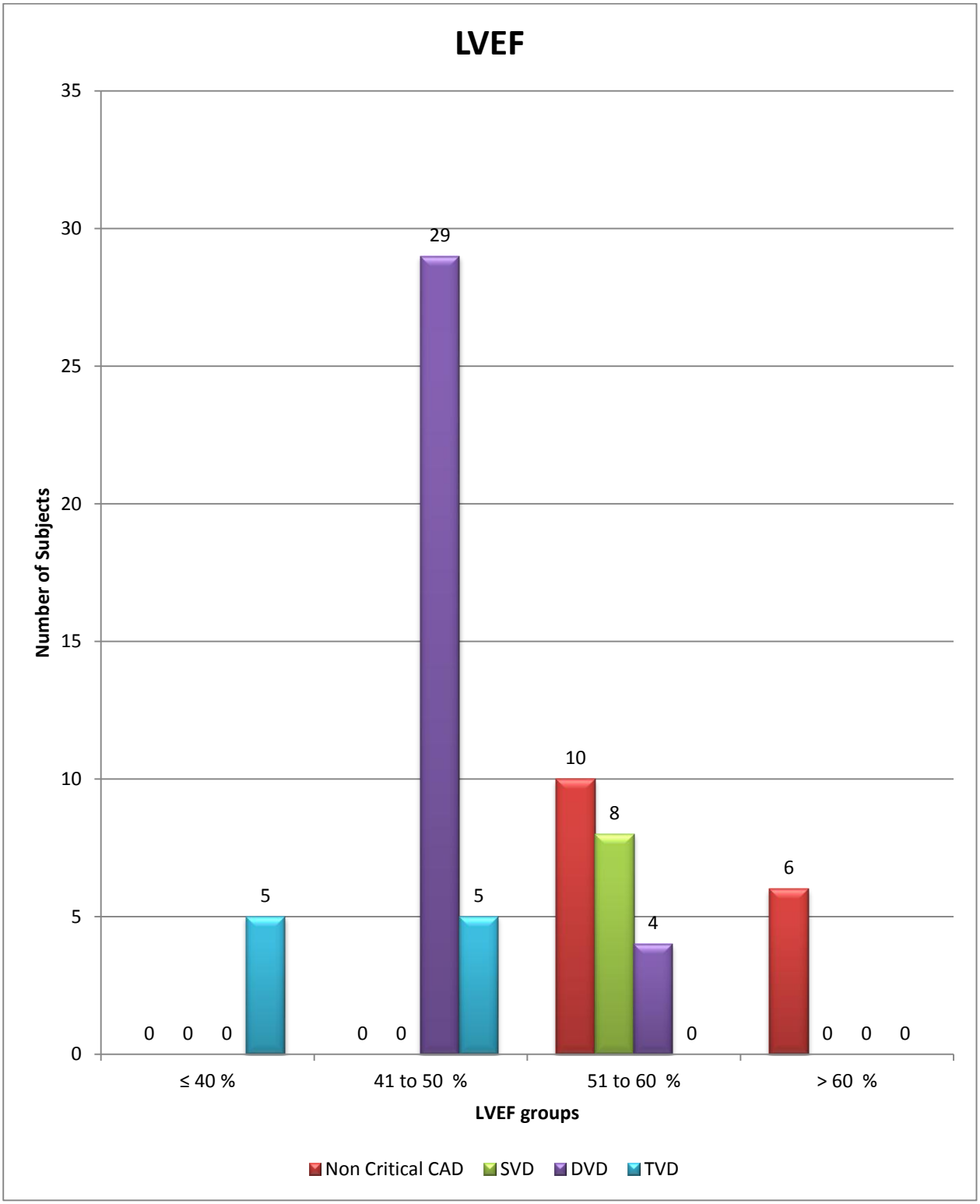


HDL	Non Critical CAD	SVD	DVD	TVD
N	18	33	8	16
MEAN	41.94	41.67	38.50	42.69
SD	4.71	5.54	7.54	5.84

HDL	Non Critical CAD	%	SVD	%	DVD	%	TVD	%
≤ 40 mm mg/dl	7	39	15	45	6	75	4	25
41 to 50 mg/dl	10	56	18	55	2	25	12	75
51 to 60 mg/dl	1	6	0	0	0	0	0	0
> 110 mg/dl	0	0	0	0	0	0	0	0
Total	18	100	33	100	8	100	16	100
P value ANOVA	0.554489079							

By conventional criteria the association between the study groups and HDL status is considered to be not statistically significant since $p > 0.05$.

LVEF


LVEF
35
30
25
20
15
10
5
0
Number of Subjects
0 0 0 5
0 0 29 5
10 8 4 0
6 0 0 0
≤ 40 %
41 to 50 %
51 to 60 %
> 60 %
LVEF groups
Non Critical CAD
SVD
DVD
TVD

LVEF(%)	Non Critical CAD	SVD	DVD	TVD
N	16	8	33	10
MEAN	61.00	56.75	46.45	39.22
SD	2.73	3.63	2.05	1.46

LVEF(%)	Non Critical CAD	%	SVD	%	DVD	%	TVD	%
≤ 40 %	0	0	0	0	0	0	5	50
41 to 50 %	0	0	0	0	29	88	5	50
51 to 60 %	10	63	8	100	4	12	0	0
> 60 %	6	38	0	0	0	0	0	0
Total	16	100	8	100	33	100	10	100
P value ANOVA	0.0000							

By conventional criteria the association between the study groups and LVEF% among study subjects is considered to be statistically significant since $p < 0.05$.

Statistical Significance

This indicates that there is a true difference among groups and the difference is significant. . In simple terms, when studying the association between flow mediated vasodilatation and coronary angiographic changes, the LVEF% in non-critical CAD group is predominantly more(61%) when compared to SVD group(56,75%), DVD group(46.45) and TVD group(39,22). It is statistically significant with a p-value of 0.0000 according to ANOVA.

Clinical Significance

The average LVEF% in non-critical CAD group is meaningfully less than SVD group by 0.93 times with a mean difference of 4.25 percentage points.

The average LVEF% in non-critical CAD group is meaningfully less than DVD group by 0.76 times with a mean difference of 14.55 percentage points.

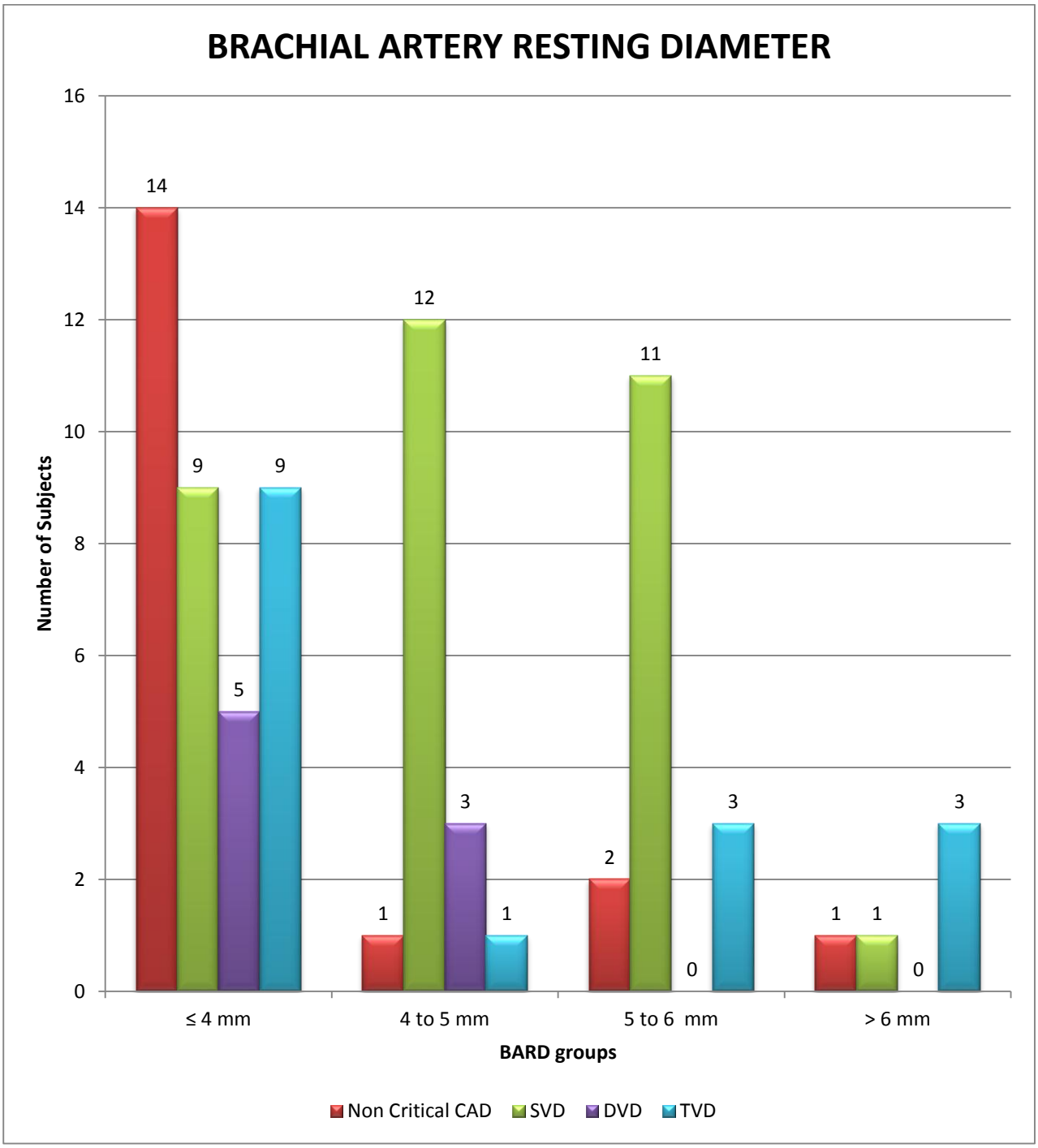
The average LVEF% in non-critical CAD group is meaningfully less than TVD group by 0.64 times with a mean difference of 21.78percentage points.

This difference is true and significant and has not occurred by chance.

Conclusion

We conclude that there is meaningfully real increase in severity of CAD as LVEF% decreases in our study subjects.

BARD

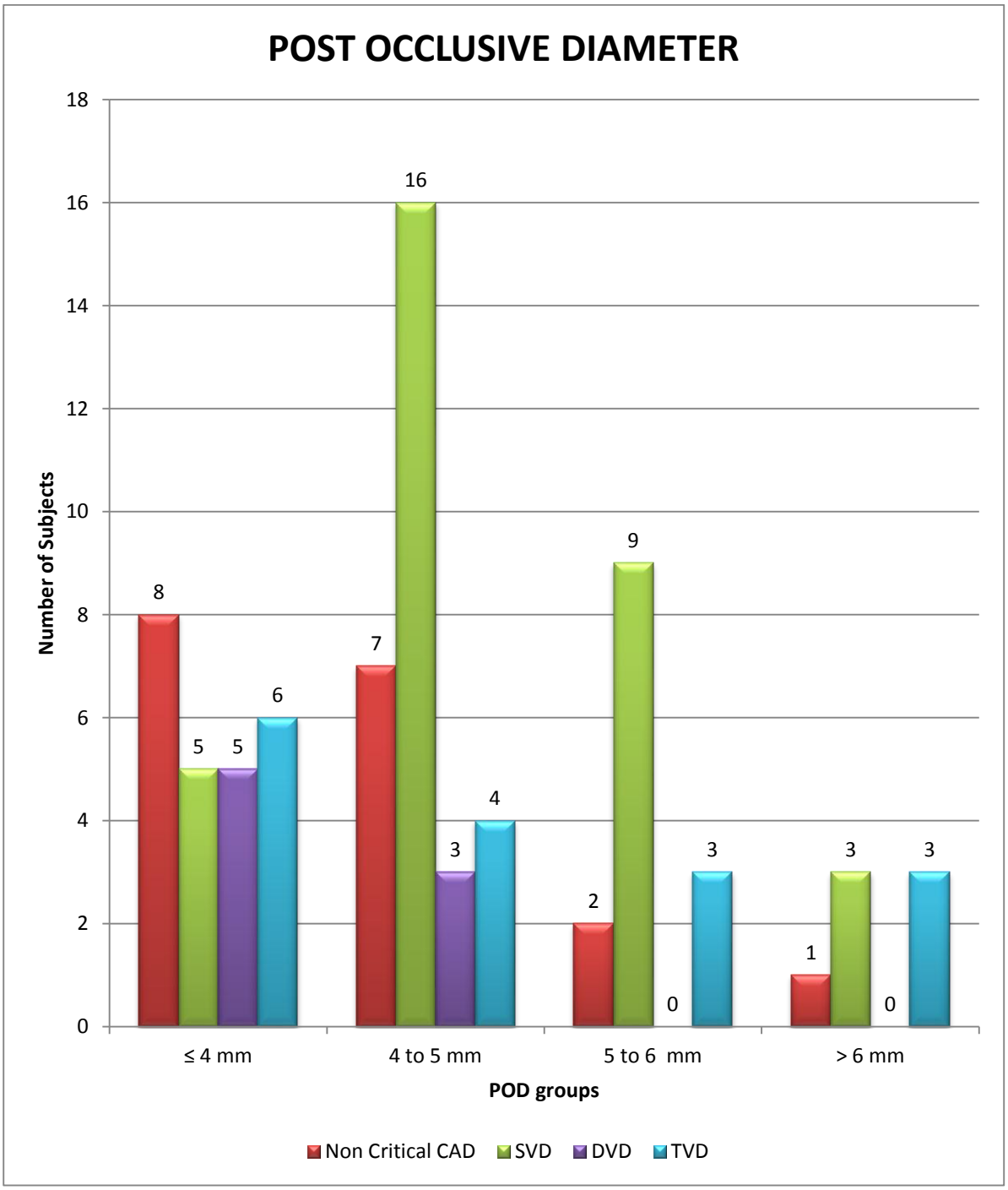

BRACHIAL ARTERY RESTING DIAMETER
Number of Subjects
16
14
12
10
8
6
4
2
0
14
9
5
9
1
12
3
1
2
11
0
3
1
1
0
3
≤ 4 mm
4 to 5 mm
5 to 6 mm
> 6 mm
BARD groups
Non Critical CAD
SVD
DVD
TVD

BRACHIAL ARTERY RESTING DIAMETER	NORMAL	Non Critical CAD	SVD	DVD	TVD
N	8	18	33	8	16
MEAN	3.89	3.93	4.51	3.75	4.59
SD	1.12	1.00	0.87	0.59	1.20

BRACHIAL ARTERY RESTING DIAMETER	Non Critical CAD	%	SVD	%	DVD	%	TVD	%
≤ 4 mm	14	78	9	27	5	63	9	56
4 to 5 mm	1	6	12	36	3	38	1	6
5 to 6 mm	2	11	11	33	0	0	3	19
> 6 mm	1	6	1	3	0	0	3	19
Total	18	100	33	100	8	100	16	100
P value ANOVA	0.092547156							

By conventional criteria the association between the study groups and brachial artery resting diameter status is considered to be not statistically significant since $p > 0.05$.

POD

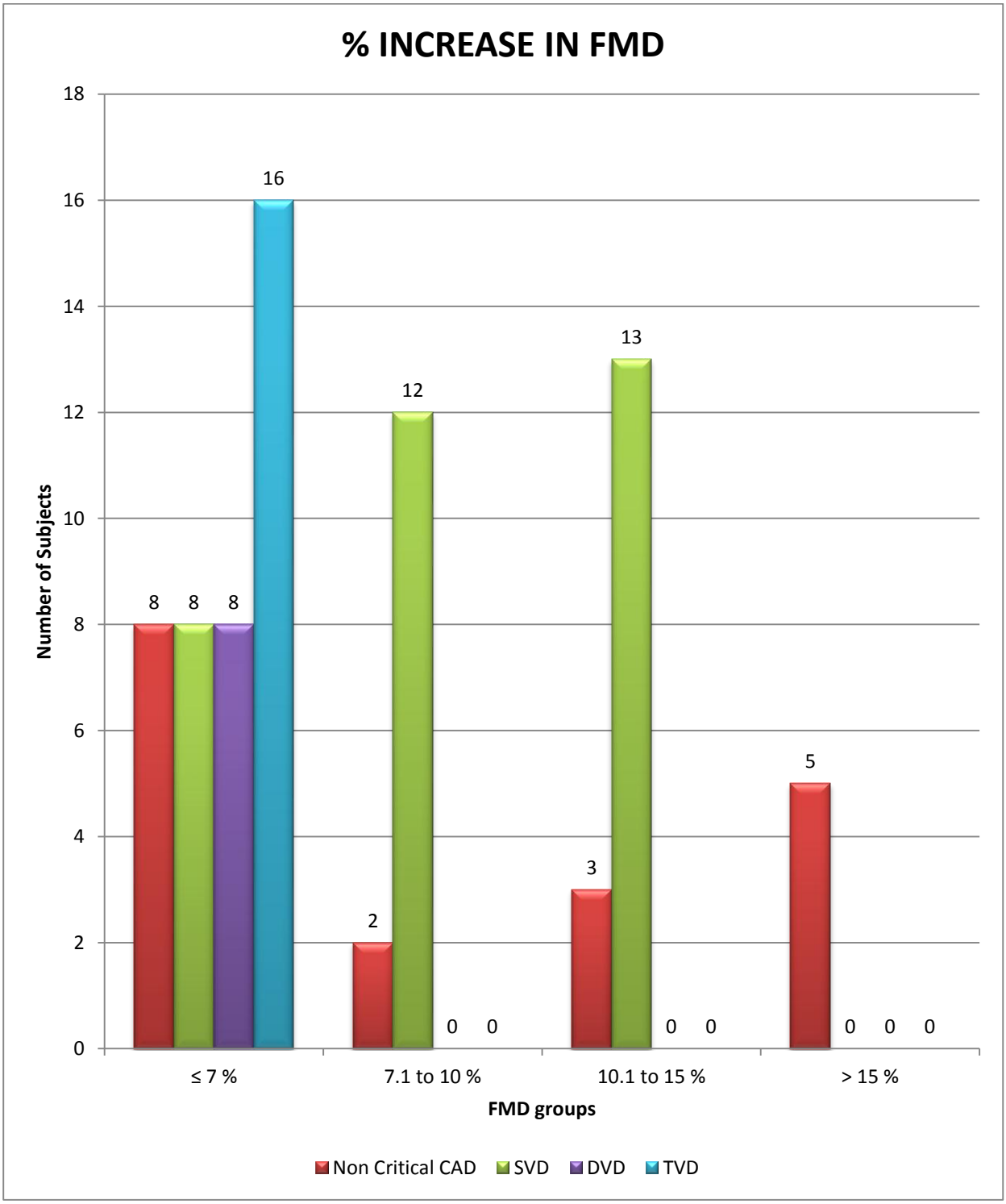

POST OCCLUSIVE DIAMETER
Number of Subjects
18
16
14
12
10
8
6
4
2
0
8
5
5
6
7
16
3
4
2
9
0
3
1
3
0
3
≤ 4 mm
4 to 5 mm
5 to 6 mm
> 6 mm
POD groups
Non Critical CAD
SVD
DVD
TVD

POST OCCLUSIVE DIAMETER	Non Critical CAD	SVD	DVD	TVD
N	18	33	8	16
MEAN	4.29	4.92	3.93	4.71
SD	1.03	0.95	0.63	1.19

POST OCCLUSIVE DIAMETER	Non Critical CAD	%	SVD	%	DVD	%	TVD	%
≤ 4 mm	8	44	5	15	5	63	6	38
4 to 5 mm	7	39	16	48	3	38	4	25
5 to 6 mm	2	11	9	27	0	0	3	19
> 6 mm	1	6	3	9	0	0	3	19
Total	18	100	33	100	8	100	16	100
P value ANOVA	0.54579025							

By conventional criteria the association between the study groups and post occlusive diameter status is considered to be not statistically significant since p > 0.05.

FMD


% INCREASE IN FMD
Number of Subjects
18
16
14
12
10
8
6
4
2
0
8 8 8
16
2
12
0 0
3
13
0 0
5
0 0 0
≤ 7 %
7.1 to 10 %
10.1 to 15 %
> 15 %
FMD groups
Non Critical CAD
SVD
DVD
TVD

% INCREASE IN FMD	Non Critical CAD	SVD	DVD	TVD
N	18	33	8	16
MEAN	9.50	9.35	4.64	3.10
SD	6.39	2.64	1.60	1.12

% INCREASE IN FMD	Non Critical CAD	%	SVD	%	DVD	%	TVD	%
≤ 7 %	8	44	8	24	8	100	16	100
7.1 to 10 %	2	11	12	36	0	0	0	0
10.1 to 15 %	3	17	13	39	0	0	0	0
> 15 %	5	28	0	0	0	0	0	0
Total	18	100	33	100	8	100	16	100
P value ANOVA	0.0000							

By conventional criteria the association between the study groups and increase in FMD among study subjects is considered to be statistically significant since $p < 0.05$.

Statistical Significance

This indicates that there is a true difference among groups and the difference is significant. . In simple terms, when studying the association between flow mediated vasodilatation and coronary angiographic changes, the increase in FMD in non-critical CAD group is predominantly more (9.50%) when compared to SVD group(9.35%), DVD group(4.64) and TVD group(3.10). It is statistically significant with a p-value of 0.0000 according to ANOVA.

Clinical Significance

The average increase in FMD in non-critical CAD group is meaningfully less than SVD group by 1.02 times with a mean difference of 0.15 percentage points.

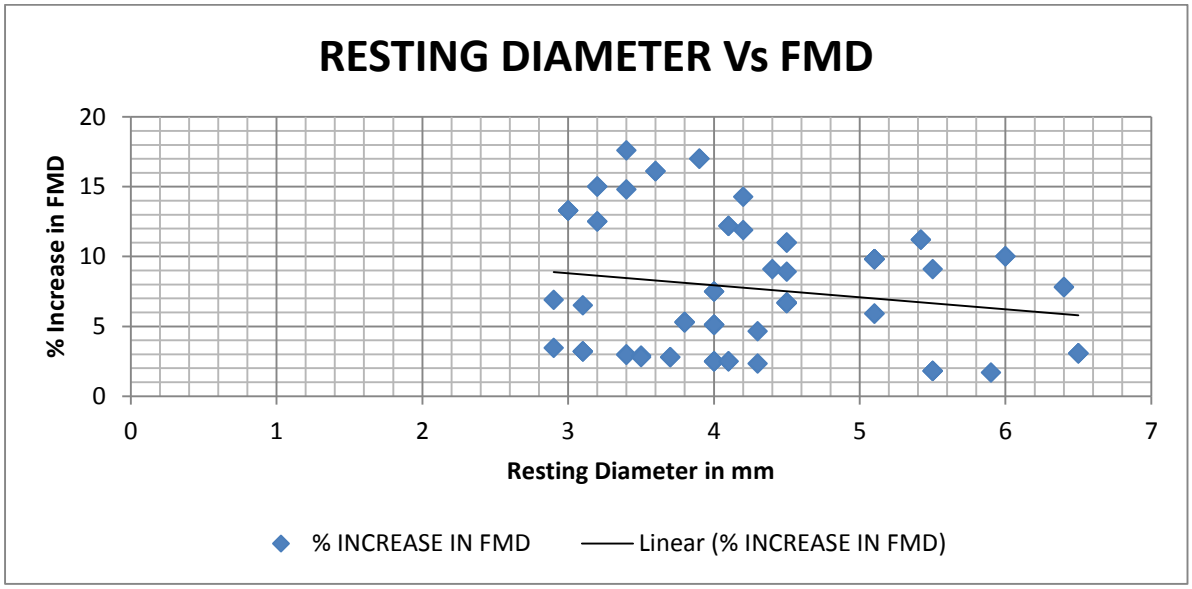
The average increase in FMD in non-critical CAD group is meaningfully less than DVD group by 0.49 times with a mean difference of 4.86 percentage points.

The average increase in FMD in non-critical CAD group is meaningfully less than TVD group by 0.33 times with a mean difference of 6,40 percentage points.
This difference is true and significant and has not occurred by chance.

Conclusion

We conclude that there is meaningfully real increase in severity of CAD as the percentage increase in FMD decreases in our study subjects.

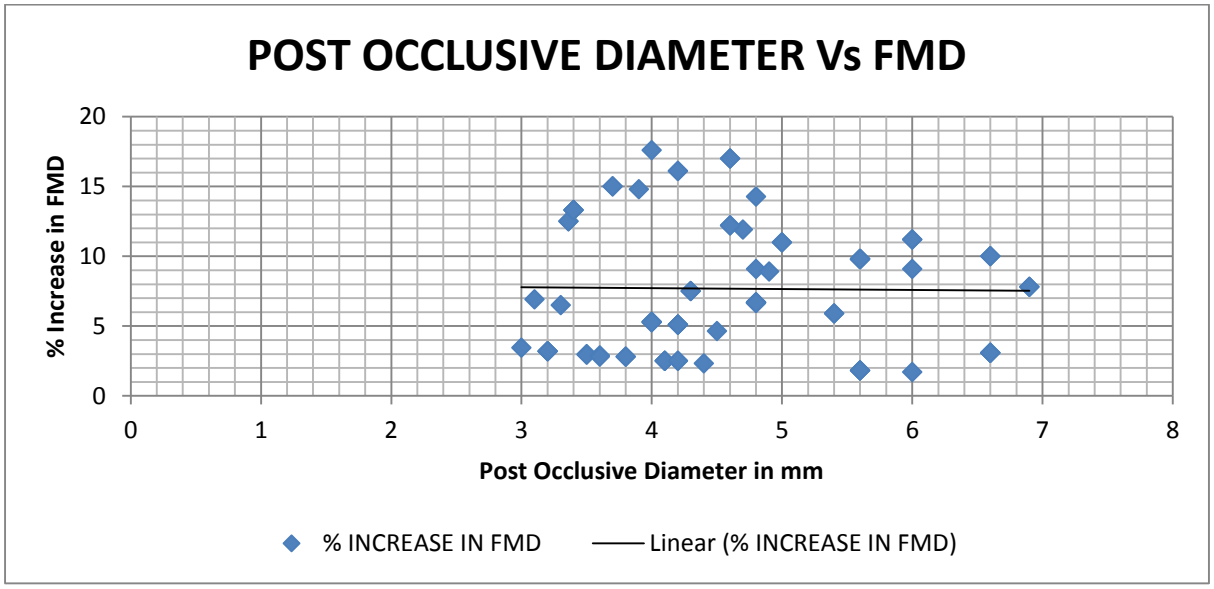
RESTING DIAMETER Vs FMD



Pearson's Correlation(r)	-0.1869
P Value	0.0000

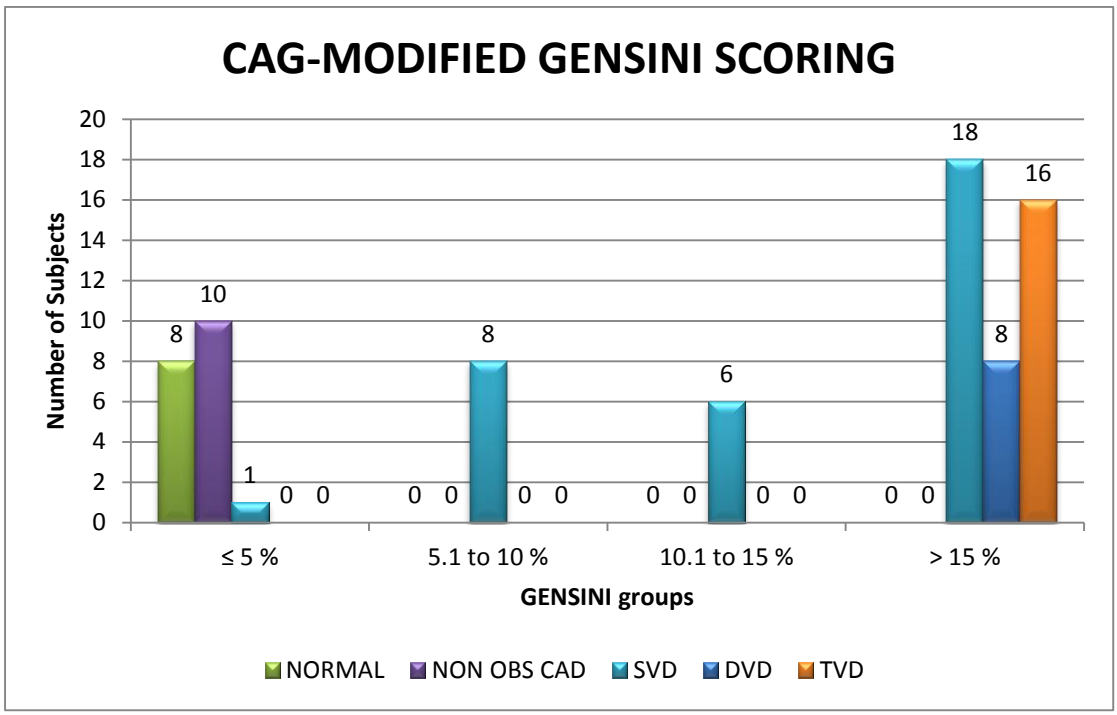
There is a negative correlation between resting diameter and FMD. This is indicated by the Pearson's R Correlation value of -0.1869with a p-value of 0.0000.
This means as resting diameter increases the percentage increase in FMD decreases in our study subjects.

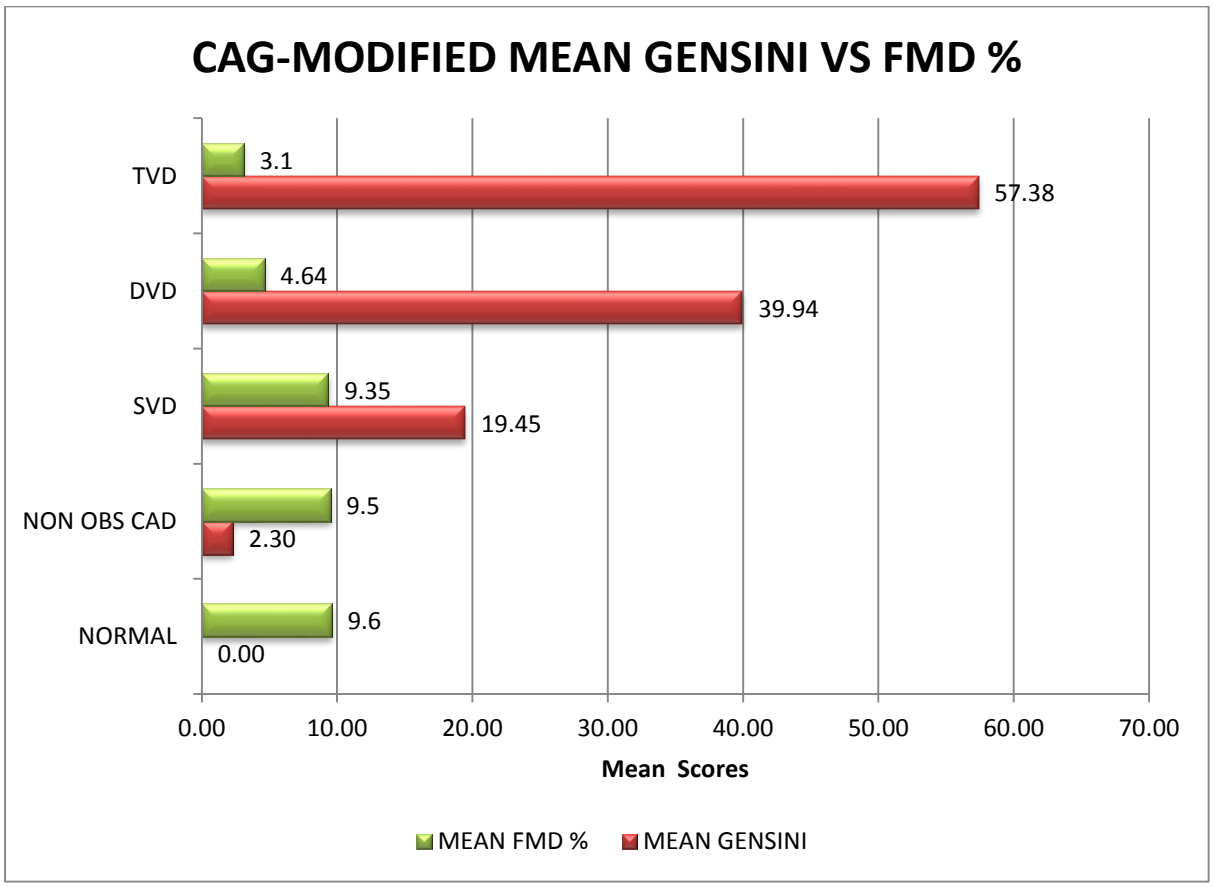
POST OCCLUSIVE DIAMETER Vs FMD



Pearson's Correlation(r)	-0.0148
P Value	0.0000

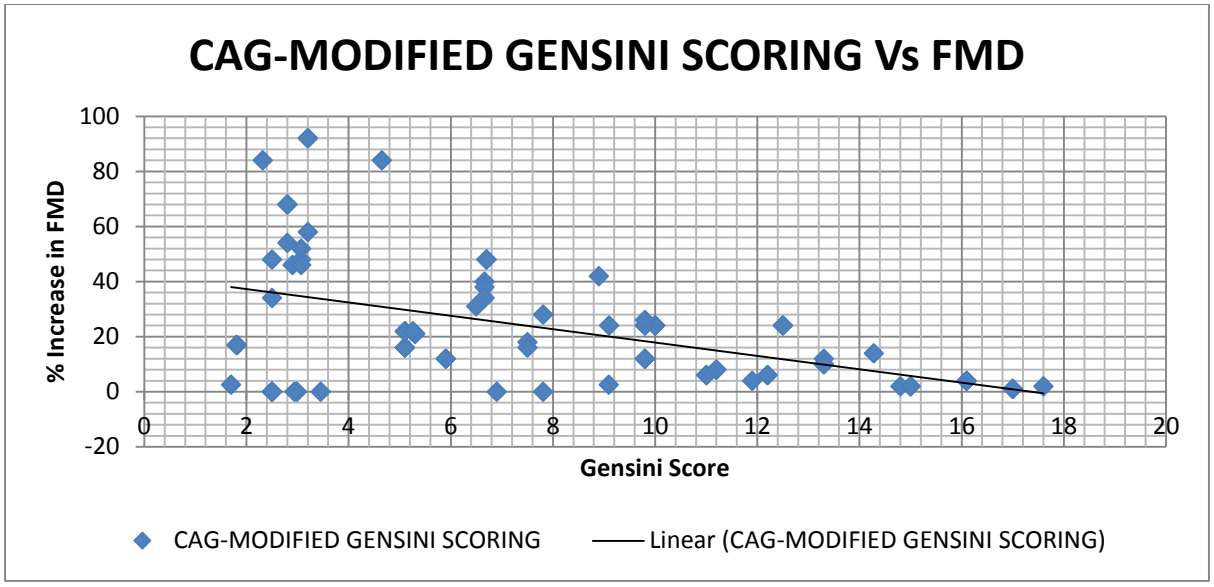
There is a positive correlation between post occlusion diameter and FMD. This is indicated by the Pearson's R Correlation value of -0.0148with a p-value of 0.0000.
This means as post occlusion diameter increases the percentage increase in FMD increases in our study subjects.


CAG-MODIFIED GENSINI SCORING
Number of Subjects
20
18
16
14
12
10
8
6
4
2
0
8
10
1
0 0
0 0
8
0 0
0 0
6
0 0
0 0
18
8
16
0 0
≤ 5 %
5.1 to 10 %
10.1 to 15 %
> 15 %
GENSINI groups
NORMAL
NON OBS CAD
SVD
DVD
TVD


CAG-MODIFIED MEAN GENSINI VS FMD %
TVD
3.1
57.38
DVD
4.64
39.94
SVD
9.35
19.45
NON OBS CAD
9.5
2.30
NORMAL
9.6
0.00
0.00
10.00
20.00
30.00
40.00
50.00
60.00
70.00
Mean Scores
MEAN FMD %
MEAN GENSINI

CAG-MODIFIED GENSINI SCORING	NORMAL	%	NON OBS CAD	%	SVD	%	DVD	%	TVD	%
≤ 5 %	8	100	10	100	1	3	0	0	0	0
5.1 to 10 %	0	0	0	0	8	24	0	0	0	0
10.1 to 15 %	0	0	0	0	6	18	0	0	0	0
> 15 %	0	0	0	0	18	55	8	100	16	100
Total	8	100	10	100	33	100	8	100	16	100

CAG-MODIFIED GENSINI SCORING	NORMAL	NON OBS CAD	SVD	DVD	TVD
N	8	10	33	8	16
MEAN GENSINI SCORES	0.00	2.30	19.45	39.94	57.38
MEAN FMD %	9.6	**9.5**	**9.35**	**4.64**	**3.1**
P value ANOVA		0.0000			



PEARSON'S CORRELATION	*% INCREASE IN FMD*	*CAG-MODIFIED GENSINI SCORING*
% INCREASE IN FMD	1	
CAG-MODIFIED GENSINI SCORING	-0.474204513	1

By conventional criteria the association between the study groups and Gensini scores among study subjects is considered to be statistically significant since $p < 0.05$.

Statistical Significance

This indicates that there is a true difference among groups and the difference is significant. . In simple terms, when studying the **carotid intima media thickness in assessing the severity of coronary artery disease**, the Gensini scores in normal group (0) and non-obstructive CAD(2.3) group is predominantly less when compared to SVD group(19.45), DVD group(39.94) and TVD group(57.38). It is statistically significant with a p-value of 0.0000 according to ANOVA.

There is a strong negative correlation between increase in FMD % and Gensini scores. This is indicated by the Pearson's R Correlation value of -0.474204513. This means as increase in FMD % decreases the Gensini scores increases.

Clinical Significance

The average Gensini scores in non-obstructive CAD group is meaningfully less than SVD group by 8.45 times with a mean difference of 17.15 scoring points.

The average Gensini scores in non-critical CAD group is meaningfully less than DVD group by 17.36 times with a mean difference of 37.64 scoring points.

The average Gensini scores in non-critical CAD group is meaningfully less than TVD group by 24.94 times with a mean difference of 55.08 scoring points

The increase in increase in FMD % correlates negatively, directly and strongly with the Gensini scores. This means that the times of increase in average Gensini scores in comparision to CAD groupsis true 47.42 % of times

This difference is true and significant and has not occurred by chance.

Conclusion

We conclude that there is meaningfully real increase in severity of CAD as Increase in FMD % decreases in our study subjects.

CITATIONS

- MANGANARO et al studied the endothelial dysfunction in patients with coronary artery disease in which 89 patients who underwent CAG were subjected to FMD and the severity of CAD was correlated with it . This study confirmed that FMD is reduced in patients with CAD and that such reduction in FMD is related to the extent of the disease. Therefore, FMD at the brachial artery is likely to represent a reliable indicator of CAD burden.

- SHECHTER et al studied the usefulness of brachial artery flow - mediated vasodilatation to predict the long -term cardiovascular events in subjects without cardiac disease . In conclusion, brachial artery median FMD independently predicts long-term adverse CV events in healthy subjects with no apparent heart disease in addition to those derived from traditional risk factor assessment.

- CARERI G et al studied the clicinal correlation and prognostic value of FMD in patients with ACS. In conclusion, endothelial function is markedly impaired in the acute phase of (NSTEMI)ACS but improves significantly at 3-month follow-up. In patients with (NSTEMI)ACS, FMD at 3 months after the acute event is a significant independent predictor of cardiac outcomes.

- KOYOSHI et al compared the clinical significance of FMD and CIMT in patients with and without coronary artery disease .The study concluded that FMD was a better predictor of severity of CAD than CIMT

- MUTLU B et al studied the usefulness of FMD and CIMT in predicting occult CAD . FMD and CIMT might predict patients with occult CAD and be helpful in selecting patients for Multidetector row computed tomography (MDCT)

- LUO C studied the association of FMD and highly sensitive C reactive protein with DUKE treadmill score(DTS) in patients with micro vascular angina. The results showed that FMD and C reactive protein correlate with DTS and useful in screening micro vascular angina

- BAMPI AB et al studied the comparisons between various non invasive methods for the detection of coronary artery disease .The results showed that it is possible to approximately determine the presence and extent of CAD by non-invasive methods, especially by FMD ,calcium score, HDL-c and TG/HDL-c ratio assays

- OZDEMIR AO studied the relation between FMD and coronary collateral circulation in a large cross sectional study . Results showed no significant association was found between the extent of angiographically visible coronary collaterals and systemic endothelial function assessed by FMD of the brachial artery.

- VASILIEVA E et al studied the correlation of FMD with total occlusion of infarct related coronary artery in patients with STEMI. The conclusions were that spontaneous coronary thrombolysis in patients with acute STEMI is associated with a preserved endothelium-dependent vasodilator response in the brachial artery. It can depend on the levels of hs-CRP, of fasting glucose, and of ACE-inhibitors from previous treatment.

CONCLUSION OF THIS STUDY

Our aim of this study was to determine if there is any correlation between severity of CAD and FMD of the brachial artery , as well as to observe the relationship with various other cardiovascular risk factors .

A total of 75 patients were included in the study and following are conclusions from the statistical analysis. The subjects were divided into 4 four study groups as described above and subsequently analysed.

- The association between the study group and factors like age , gender , diet ,alcohol intake ,duration of hypertension was found to have no correlation
- There is a positive correlation between duration of smoking and severity of CAD
- Presence of diabetes had an meaningful correlation with the study groups and there is a increase in severity of CAD with increase in duration of diabetes
- BMI was found to have a positive correlation with the study groups and as the BMI of the patient increased more severe was the CAD observed in them
- Non HDL (LDL) was found to be the better marker for assessing the cardiovascular risk as there was a significant increase in CAD severity with increasing levels of LDL ,however no such positive correlation existed between study groups and HDL
- Left ventricular ejection fraction measured at the time of admission was significantly lower as the severity of CAD increased
- There was no positive correlation between brachial artery resting diameter and post occlusive diameter among the various CAD groups

- Interestingly percentage of increase in flow mediated vasodilatation correlated well with the severity of CAD , in which the more severe CAD patients had significantly lower percentage increase in FMD
- There is also a meaningful correlation between % increase in FMD and modified GENSINI SCORE.As the severity of CAD as assessed by modified GENISINI score increased significantly lower was the % increase in FMD.

Hence we conclude that apart from assessing the traditional cardiovascular risk factors , it is also important to assess the endothelial function of the patient by methods like FMD. It is very clear the physiological alteration(endothelial dysfunction) in the body due to atherosclerosis, diabetes and other risk factors occur much before the structurally evident changes like plaques. FMD could be used as a tool to determine the endothelial function of the patients very early in the course natural history of CAD . Its use could be widely employed as it is non invasive and very simple procedure . Interestingly even unstable angina patients with normal /non obstructive CAG had endothelial dysfunction and whether this could be the reason for angina is still debatable. Since it a direct reflection of the health status of coronary vessels this could be utilised in screening of even young healthy individuals with family history of CAD . This technique has great scope in the near future mainly because of its non invasive technique in assessing the severity of CAD. It however requires large sample studies to substantiate this and though not yet recommended for routine clinical use, non invasive endothelial function testing has provided valuable insights into vascular changes associated with early atherosclerosis and the potential reversibility of arterial disease.

ANNEXURES

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PROFORMA

PRELIMINARY DATA OF THE PATIENT :

NAME :

AGE

SEX

OP NO IP NO

PER CAPITA INCOME

PHONE NUMBER

CHIEF COMPLAINTS.

CHEST PAIN

SITE

CHARACTER

RADIATION

INTENSITY

GRADE

PALPITATION

SYNCOPE

GIDDINESS

BLACKOUTS

PAST HISTORY

CAD :

TIA :

CVA :

PVD :

DM : TREATMENT : OHA : INSULIN :

SHT : TREATMENT : ON : OFF :

DYSLIPIDIMIA :

PCOD :

PERSONAL HISTORY :

VEGETARIAN : NON VEGETARIAN :

SMOKING : YES : NUMBERS/ DAY NO
DURATION

< 5 5 – 10 > 10

BEDI :

CIGARETTE :

ALCOHOLIC YES : NO :ML / DAY

ILLICIT DRUG USE YES NO :

FAMILY HISTORY :

MENSTRUAL HISTORY :

TREATMENT HISTORY :

HEPARINISED OR NOT

THROMBOLYSED OR NOT :

ANTI DYSLIPIDIMICS :

GENERAL EXAMINATIONS

CONSIOUS/ ORIENTED/ COMFORTABLE

DYSPNEA

JVP

PALLOR/ CYANOSIS/ CLUBBING/ PEDAL EDEMA

YES : NO :

ARCUS SENILIS

TENDON XANTHOMA

ERRUPTIVE XANTHOMA

TUBO ERRUPTIVE XANTHOMA

HEIGHT

WEIGHT

BMI

WAIST HIP RATIO

SYSTEMIC EXAMINATION

CVS

RS

P/ A

CNS

INVESTIGATIONS

FBS < 110 111 – 126 >126

PPBS <140 141 – 200 > 200

FLP

TFT

SERUM FIBRINOGEN

SERUM CALCIUM

CRP

ECG

CARDIAC MARKERS

ECHO - AV SCLEROSIS

TMT

USG ABDOMEN

CIMT

CAG

GOVT.STANLEY MEDICAL COLLEGE, CHENNAI- 600 001

INFORMED CONSENT

DISSERTATION TOPIC: "A STUDY ON USEFULNESS OF FLOW MEDIATED VASODILATATION OF BRACHIAL ARTERY IN ASSESSING THE SEVERITY OF CORONARY ARTERY DISEASE AND ITS CORRELATION WITH CORONARY ANGIOGRAM"

PLACE OF STUDY: GOVT. STANLEY MEDICAL COLLEGE, CHENNAI

NAME AND ADDRESS OF PATIENT:

I, _____ have been informed about the details of the study in my own language.

I have completely understood the details of the study.

I am aware of the possible risks and benefits, while taking part in the study.

I understand that I can withdraw from the study at any point of time and even then, I will continue to receive the medical treatment as usual.

I understand that I will not get any payment for taking part in this study.

I will not object if the results of this study are getting published in any medical journal, provided my personal identity is not revealed.

I know what I am supposed to do by taking part in this study and I assure that I would extend my full co-operation for this study.

Name and Address of the Volunteer:

Signature/Thumb impression of the Volunteer

Date:

Witnesses: (Signature, Name & Address)

Date:

Name and signature of investigator:

Date:

ப்ரக்கியல் தமனியின் விரிவு தன்மையை அளப்பதின் முலம் கரோனரி தமனி இதயநோய் தீவீரத்தையும்மற்றும் கரோனரி ஆஞ்சியோகிராம் உடன் ஒப்பிட்டுபார்க்கும் ஒரு ஆய்வு

ஆய்வாளர்:**மரு. .நரேந்திரன்.அ,**

துநிலைபட்டமேற்படிப்புமாணவர்,

பொதுமருத்துவபட்டபடிப்பு.

வழிகாட்டி:**பேராசிரியர்மரு.க தமிழ்செல்வன்**

பொதுமருத்துவபேராசிரியர்,

அரசுஸ்டான்லிமருத்துவமனை.

<u>சுயஒப்புதல்படிவம்</u>

பெயர்: வயது: உள்ளிருப்புஎண்:

இந்தமருத்துவஆய்வின்விவரங்கள்எனக்குவிளக்கப்பட்டது.என்னுடையசந்தேகங்களைக்கேட்கவும்,அதற்கானதகுந்தவிளக்கங்களைப்பெறவும்வாய்ப்பளிக்கப்பட்டது.

நான்இவ்வாய்வில்தன்னிச்சையாகத்தான்பங்கேற்கிறேன்.எந்தகாரணத்தினாலும்,எந்தகட்டத்திலும்,எந்தசட்டசிக்கலும்இன்றிஇந்தஆய்விலிருந்துவிலகிக்கொள்ளலாம்என்றும்அறிந்துகொண்டேன்.

நான்ஆய்விலிருந்துவிலகிக்கொண்டாலும்ஆய்வாளர்என்னுடையமருத்துவஅறிக்கைகளைப்பார்ப்பதற்கோ அல்லதுஉபயோகிக்கவோஎன்அனுமதிதேவையில்லை எனவும் அறிந்துகொண்டேன்.என்னைப்பற்றியதகவல்கள்இரகசியமாகப்பாதுகாக்கப்படும்என்பதையும்அறிவேன்.

இந்தஆய்வின்மூலம்கிடைக்கும்தகவல்களையும்பரிசோதனைமுடிவுகளையும்.ஆய்வாளர்அவர்விருப்பத்திற்கேற்பஎவ்விதமாகப்பயன்படுத்திக்கொள்ளவும்,அதனைபிரசுரிக்கவும்முழுமனதுடன்சம்மதிக்கிறேன்.

இந்தஆய்வில்பங்குகொள்ளஒப்புக்கொள்கிறேன்.எனக்குகொடுக்கப்பட்டஅறிவுரைகளின்படிநடந்துகொள்வதுடன்,
ஆய்வாளருக்குஉண்மையுடன்இருப்பேன்என்றும்உறுதியளிக்கிறேன்.என்உடல்நலம்பாதிக்கப்பட்டாலோஅல்லதுவழக்கத்திற்குமாறானநோய்க்குறிதென்பட்டாலோஉடனேஅதைதெரிவிப்பேன் என உறுதிகூறுகிறேன்.

இந்தஆய்வில்எனக்கு எவ்விதமான
பரிசோதனைகளையும்,சிகிச்சைகளையும்மேற்கொள்ளநான்முழுமனதுடன்சம்மதிக்கிறேன்.

இப்படிக்கு

நோயளியின்கையொப்பம் ஆய்வாளர்கையொப்பம்/பெயர்

(பெயர்:) (மரு..) **நரேந்திரன்.அ,**

ப்ரக்கியல்தமனியின்விரிவுதன்மையைஅளப்பதின்முலம்கரோனரிதமனி இதயநோய்தீவீரத்தையும்மற்றும்கரோனரிஆஞ்சியோகிராம்உடன்ஒப்பிட் டுபார்க்கும்ஒருஆய்வு

ஆய்வாளர்:**மரு.நரேந்திரன்அ,**

முதுநிலைபட்டமேற்படிப்புமாணவர்,

பொதுமருத்துவபட்டபடிப்பு.

வழிகாட்டி:**பேராசிரியர்மரு.கதமிழ்செல்வன்**

பொதுமருத்துவபேராசிரியர்,

அரசுஸ்டான்லிமருத்துவமனை.

<u>பங்கேற்பாளரின்தகவல்படிவம்</u>

நீங்கள்இந்தஆய்வில்பங்கேற்க அழைக்கப்படுகிறீர்கள். இந்தஆய்வில்பங்கேற்கும்முன், இதன்நோக்கத்தையும்,முறைகளையும்,இதனால்ஏற்படும்பின்விளைவுகளையும்நீங்கள்அறிந்துகொள்ளஆ ய்வாளர்அளிக்கும்தகவல்:

உங்கள்நோயின்வரலாறும்,உங்களின்முழுஉடல்பரிசோதனையும்தெளிவாகவும்விரிவாகவும்பதிவுசெய்யப் படும்.

இந்தஆய்வின்முடிவுகள்மருத்துவகாரணங்களுக்காகவும்,மருத்துவகல்விக்காகவும்பயன்படுத்தப்படும்.இந் தஆய்வுபற்றியசந்தேகங்களுக்குஉரியமுறையில்விளக்கமளிக்கப்படும்.தங்களைப்பற்றியதகவல்கள்இரகசி யமாகபாதுகாக்கப்படும்.

இந்தஆய்வில்இருந்துஎப்போதுவேண்டுமானாலும்தாங்கள்எவ்விதமுன்னறிவிப்பின்றியும், எவ்விதசட்டசிக்கலும்இன்றிவிலகிக்கொள்ளலாம்.

இந்தஆய்வில்பங்கேற்குமாறுகேட்டுக்கொள்கிறேன்.

நன்றி,

ஆய்வாளர் கையொப்பம் நோயாளியின் கையொப்பம்

(மரு.) **நரேந்திரன்அ**(பெயர்:)

MASTER KEY CHART

AGE	SEX	SMO	NV	HT	DM	BMI	SBP	DBP	LDL	HDL	LVEF(%)	DIAG	BAD1	BAD2	%BAD	CAG	GEN
55	M	YES,10 YRS	YES	NO	NO	23.712	140	110	95	36	40	AWMI	4.4	4.8	9.1	SVD	24
55	M	NO	YES	NO	NO	20.449	130	80	90	35	53	IW+PW+RVMI	3.5	3.6	2.9	TVD	46
60	M	YES,20 YRS	YES	NO	NO	21.193	100	60	92	30	42	AWMI	3.1	3.3	6.5	DVD	31
48	M	YES,40 YRS	YES	NO	NO	24.442	130	80	89	39	45	ASMI	4.2	4.7	11.9	SVD	4
45	M	YES,15 YRS	YES	NO	NO	29.017	120	80	120	32	45	AWMI	4.5	4.8	6.7	SVD	48
35	M	YES,10YRS	YES	NO	NO	21.517	140	90	105	34	42	EXT AWMI	3.1	3.2	3.2	DVD	92
46	M	YES,20YRS	YES	NO	NO	24.539	140	80	110	32	55	UA	4.1	4.2	2.5	NORMAL	0
58	F	NO	YES	YES,3YRS	YES,6 MON	30.252	110	70	98	42	60	NSTEMI	3.2	3.7	15	NON OBS CAD	2
48	F	NO	YES	NO	NO	26.896	120	80	85	45	60	NSTEMI	3.4	3.5	2.99	NORMAL	0
39	F	NO	YES	YES,6YRS	YES,6YRS	32.895	110	80	105	33	60	EA-CLASS 3	3.2	3.36	12.5	SVD	24
50	M	NO	YES	NO	YES,3YRS	27.435	120	90	80	41	33	AWMI	3.7	3.8	2.8	TVD	68
54	F	NO	NO	NO	YES,3YRS	30.252	120	80	86	40	62	UA	2.9	3	3.45	NORMAL	0
58	F	NO	YES	YES,10YRS	NO	27.111	150	70	89	50	60	NSTEMI	3.8	4	5.3	DVD	21
55	F	NO	YES	YES,10YRS	YES,5YRS	29.728	150	100	90	40	60	NSTEMI	3.6	4.2	16.1	NON OBS CAD	4
56	F	NO	YES	YES,3YRS	YES,5YRS	31.626	120	80	92	37	64	EA-CLASS 3	3.4	3.9	14.8	NON OBS CAD	2
59	M	yes,3YRS	YES	YES,1YR	YES,1YR	25.217	130	80	89	52	60	UA	5.9	6	1.7	NON OBS CAD	2.5
55	M	NO	NO	NO	NO	22	130	80	87	43	50	UA	3.9	4.6	17	NON OBS CAD	1
59	M	YES,50YRS	YES	NO	NO	26.026	120	70	99	38	54	IW+PWMI	4.3	4.4	2.32	DVD	84
36	M	YES,20YRS	YES	NO	NO	27.64	120	70	99	45	45	ASMI	5.1	5.6	9.8	SVD	12
38	M	YES,10YRS	YES	NO	NO	20.957	110	70	87	42	50	ASMI	6.4	6.9	7.81	NORMAL	0
35	M	NO	NO	NO	NO	23.111	120	80	95	39	45	IW+PWMI	4.5	5	11	SVD	6
50	M	YES,30YRS	YES	NO	NO	24.977	120	80	110	46	45	ASMI	6	6.6	10	SVD	24
40	F	NO	YES	NO	YES,3YRS	37.195	190	110	104	40	41	ASMI	4.5	4.8	6.66	SVD	40
50	M	NO	YES	YES,1YR	NO	28.134	100	70	83	46	45	IWMI	5.42	6	11.2	SVD	8
57	M	NO	YES	YES,6MONTHS	YES,18YRS	27.734	140	90	88	48	40	AWMI	5.1	5.4	5.9	SVD	12
60	M	YES,10YRS	YES	NO	YES,2YRS	30.405	140	90	108	50	48	NSTEMI	4.1	4.6	12.2	SVD	6
58	M	YES,25YRS	YES	NO	YES,10YRS	22.862	150	80	91	46	42	UA	6.5	6.6	3.07	TVD	48
59	M	NO	YES	YES,5YRS	NO	25.217	120	80	87	43	40	AWMI	5.5	5.6	1.81	TVD	17
52	M	YES,5YRS	YES	NO	NO	19.607	140	80	105	48	40	AWMI	3	3.4	13.3	SVD	10
50	M	YES,32YRS	YES	NO	YES,2YRS	22.719	130	80	104	50	48	IW+PWMI	4	4.2	5.1	TVD	22
55	M	NO	YES	YES,5YRS	NO	26.037	120	60	108	47	62	AWMI	4	4.1	2.5	TVD	34
57	F	NO	NO	NO	YES,5YRS	25.3	136	70	104	43	56	UA	4	4.2	5.1	SVD	16
47	F	NO	YES	YES,3YRS	YES,4YRS	26.3	124	86	85	37	43	AWMI	5.1	5.6	9.8	SVD	24
45	M	yes 20 yrs	YES	NO	NO	24.5	130	90	96	34	38	AWMI	4.5	4.8	6.66	DVD	34
56	F	NO	YES	YES 2YRS	YES 5YRS	25.5	120	80	95	34	53	AWMI	3.5	3.6	2.8	TVD	54

65	M	YES 15 YRS	YES	NO	YES 10YRS	25.6	110	70	92	36	42	IW+PW+RVMI	3.1	3.2	3.2	TVD	58
53	M	YES,40 YRS	YES	YES 6 YRS	NO	25.6	130	80	95	33	45	ASMI	4.2	4.8	14.28	SVD	14
45	M	YES,15 YRS	YES	NO	NO	29.017	120	80	120	32	45	AWMI	4.5	4.8	6.7	SVD	48
35	M	YES,10YRS	YES	NO	NO	21.517	140	90	105	34	42	EXT AWMI	3.1	3.2	3.2	DVD	92
46	M	YES,20YRS	YES	NO	NO	24.539	140	80	110	32	55	EXT AWMI	4.1	4.2	2.5	TVD	48
58	F	NO	YES	YES,3YRS	YES,6 MON	30.252	110	70	98	42	60	NSTEMI	3.2	3.7	15	NON OBS CAD	2
48	F	NO	YES	NO	NO	26.896	120	80	85	45	60	NSTEMI	3.4	3.5	2.94	NORMAL	0
60	F	NO	YES	YES,6YRS	YES,6YRS	32.895	110	80	105	33	60	EA-CLASS 3	3.2	3.36	12.5	SVD	24
50	M	NO	YES	NO	YES,3YRS	27.435	120	90	80	41	33	AWMI	3.7	3.8	2.8	TVD	68
44	M	NO	NO	YES 5YRS	YES,3YRS	29.5	160	90	96	36	35	UA	2.9	3.1	6.9	NORMAL	0
58	F	NO	YES	YES,10YRS	NO	27.111	150	70	89	50	60	NSTEMI	3.8	4	5.3	DVD	21
55	F	NO	YES	YES,10YRS	YES,5YRS	29.728	150	100	90	40	60	NSTEMI	3.6	4.2	16.1	NON OBS CAD	4
58	F	NO	YES	YES,3YRS	YES,5YRS	31.626	120	80	92	37	64	EA-CLASS 3	3.4	4	17.6	NON OBS CAD	2
59	M	yes,3YRS	YES	YES,1YR	YES,1YR	25.217	126	84	86	45	60	UA	5.5	6	9.09	NON OBS CAD	2.5
55	M	NO	NO	NO	NO	22	130	80	87	43	50	UA	3.9	4.6	17	NON OBS CAD	1
57	M	YES,50YRS	YES	NO	NO	26.026	120	70	99	38	54	IW+PWMI	4.3	4.5	4.65	DVD	84
36	M	YES,20YRS	YES	NO	NO	27.64	120	70	99	45	45	ASMI	5.1	5.6	9.8	SVD	12
38	M	YES,10YRS	YES	NO	NO	20.957	110	70	87	42	50	ASMI	6.4	6.9	7.81	SVD	28
35	M	NO	NO	NO	NO	23.111	120	80	95	39	45	IW+PWMI	4.5	5	11	SVD	6
50	M	YES,30YRS	YES	NO	NO	24.977	120	80	110	46	45	ASMI	6	6.6	10	SVD	24
40	F	NO	YES	NO	YES,3YRS	37.195	190	110	104	40	41	ASMI	4.5	4.8	6.66	SVD	38
50	M	NO	YES	YES,1YR	NO	28.134	100	70	83	46	45	IWMI	5.42	6	11.2	SVD	8
45	M	NO	YES	YES,6MONTHS	YES,18YRS	27.734	140	90	88	48	40	AWMI	5.1	5.4	5.9	SVD	12
59	M	YES,10YRS	YES	NO	YES,2YRS	30.405	140	90	108	50	48	NSTEMI	4.1	4.6	12.2	SVD	6
58	M	YES,25YRS	YES	NO	YES,10YRS	22.862	150	80	91	46	42	UA	6.5	6.6	3.07	TVD	46
59	M	NO	YES	YES,5YRS	NO	25.217	120	80	87	43	40	AWMI	5.5	5.6	1.81	TVD	17
52	M	YES,5YRS	YES	NO	NO	19.607	140	80	105	48	40	AWMI	3	3.4	13.3	SVD	12
50	M	YES,32YRS	YES	NO	YES,2YRS	22.719	130	80	104	50	48	IW+PWMI	4	4.2	5.1	TVD	22
55	M	NO	YES	YES,5YRS	NO	26.037	120	60	108	47	62	UA	4	4.1	2.5	NORMAL	0
57	F	NO	NO	NO	YES,5YRS	25.3	136	70	104	43	56	UA	4	4.2	5.1	SVD	16
47	F	NO	YES	YES,3YRS	YES,4YRS	26.3	124	86	85	37	43	AWMI	5.1	5.6	9.8	SVD	24
60	M	YES,25YRS	YES	NO	YES,10YRS	22.862	150	80	91	46	42	UA	6.5	6.6	3.07	TVD	52
59	M	NO	YES	YES,5YRS	NO	25.217	120	80	87	43	40	AWMI	5.5	5.6	1.81	TVD	17
52	M	YES,5YRS	YES	NO	NO	19.607	140	80	105	48	40	AWMI	3	3.4	13.3	SVD	10
50	M	YES,32YRS	YES	NO	YES,2YRS	22.719	130	80	104	50	48	IW+PWMI	3.8	4	5.26	TVD	22
55	M	NO	YES	YES,5YRS	NO	26.037	120	60	108	47	62	UA	4	4.1	2.5	NORMAL	0
57	F	NO	NO	NO	YES,5YRS	25.3	136	70	104	43	56	UA	4	4.3	7.5	SVD	18
47	F	NO	YES	YES,3YRS	YES,4YRS	26.3	124	86	85	37	43	AWMI	5.1	5.6	9.8	SVD	26
40	F	NO	YES	NO	YES,3YRS	37.195	190	110	104	40	41	ASMI	4.5	4.9	8.9	SVD	42
45	F	NO	NO	NO	YES,5YRS	25.3	136	70	104	43	56	UA	4	4.3	7.5	SVD	16

KEY TO MASTERCHART

NV – NON VET DIET

HT – HYPERTENSION

DM – DIABETES

BMI – BODY MASS INDEX

SBP – SYSTOLIC BLOOD PRESSURE

DBP – DIASTOLIC BLOOD PRESSURE

LDL – LOW DENSITY LIPOPROTEIN

HDL – HIGH DENSITY LIPOPROTEIN

CAG – CORONARY ANGIOGRAM

LVEF – LEFT VENTRICULAR EJECTION FRACTION

BAD1 – BRACHIAL ARTERY DIAMETER PRE DILATATION

BAD2 – BRACHIAL ARTERY DIAMETER POST DILATATION

%BAD – PERCENTAGE INCREASE IN BRACHIAL ARTERY DIAMETER

GEN - MODIFIED GENSINI SCORE

SVD – SINGLE VESSEL DISEASE

DVD – DOUBLE VESSEL DISEASE

TVD – TRIBLE VESSEL DISEASE

NON OBS – NON OBSTRUCTIVE CAD

UA – UNSTABLE ANGINA