" NON INVASIVE ASSESSMENT OF CORONARY FLOW VELOCITY RESERVE WITH TRANSTHORACIC COLOUR DOPPLER ECHOCARDIOGRAPHY TO PREDICT SIGNIFICANT LEFT ANTERIOR DESCENDING CORONARY ARTERY STENOSIS ".

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CERTIFICATE

This is to certify that the dissertation entitled " **NON INVASIVE ASSESSMENT OF CORONARY FLOW VELOCITY RESERVE WITH TRANSTHORACIC COLOUR DOPPLER ECHOCARDIOGRAPHY TO PREDICT SIGNIFICANT LEFT ANTERIOR DESCENDING CORONARY ARTERY STENOSIS** " is the bonafide original work of **Dr.K.TAMILSELVAN**, in partial fulfillment of the requirements for D. M. Branch-II (CARDIOLOGY) Examination of the Tamilnadu Dr.M.G.R. Medical University to be held in August 2007.

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DECLARATION

I, **DR.K.TAMILSELVAN**, solemnly declare that the dissertation titled ""**NON INVASIVE ASSESSMENT OF CORONARY FLOW VELOCITY RESERVE WITH TRANSTHORACIC COLOUR DOPPLER ECHOCARDIOGRAPHY TO PREDICT SIGNIFICANT LEFT ANTERIOR DESCENDING CORONARY ARTERY STENOSIS "** the bonafide original work done by me at Government Stanley Medical College and Hospital during May 2006 to May 2007 under the guidance and supervision of **PROF.R.SUBRAMANIAN, MD, DM.** Professor and Head Of the Department.

This dissertation is submitted to The Tamilnadu DR.M.G.R. Medical University, towards partial fulfillment of the requirements for **D. M. Branch-II (CARDIOLOGY)** Examination to be held in August 2007

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CONTENTS

INTRODUCTION

Definite diagnosis of coronary occlusion can be made by coronary angiography (CAG). However, it is an invasive technique and only available in the catheterization laboratory. Patients without anginal symptoms, left ventricular dysfunction or electrocardiographic changes may not be diagnosed until cardiac events occur. If noninvasive detection of total coronary occlusion before CAG becomes possible, it could help in the consideration of further invasive procedures and in the estimation of the results of various interventions.

Coronary flow velocity measurements have provided useful clinical and physiologic information. They have been assessed by several Doppler techniques with a Doppler catheter, a Doppler guidewire , an epicardial probe and a transesophageal probe . Doppler catheter and a Doppler guidewire are already have been validated for the measurement of Coronary flow velocity and established as useful techniques in the clinical setting. However, they are invasive.. Transesophageal Doppler echocardiography is semiinvasive,. Thus, it has been difficult to apply assessment of CFV to patients in routine clinical practice.

Transthoracic Doppler echocardiography is noninvasive, relatively inexpensive and widely used in the clinical setting, and can be used for serial studies in echocardiographic laboratories. Several studies have reported that CFV can be measured by visualizing LAD using transthoracic two-dimensional and Doppler echocardiography with a high-frequency transducer . It has been also shown that CFV in the distal LAD can be measured at high success rate by TTDE under the guidance of color Doppler flow mapping, and assessment of CFVR in the LAD by this noninvasive technique is useful in the diagnosis of significant LAD stenosis .

AIM

- To determine whether the coronary flow velocity pattern assessed by Transthoracic Colour Doppler Echocardiography serves as a predictor of significant Left Anterior Descending coronary artery stenosis.

- To evaluate the value of coronary flow velocity reserve determined by Transthoracic Colour Doppler Echocardiography for the assessment the degree of severity of Left Anterior Descending coronary artery stenosis.

- To compare coronary flow velocity pattern assessed by Transthoracic Colour Doppler Echocardiography and Exercise stress testing with Treadmill to predict significant Left Anterior Descending coronary artery stenosis.

REVIEW OF LITERATURE

Atherosclerotic coronary stenosis is the most common cause of myocardial ischemia. Based on data from the Framingham Heart Study, the lifetime risk of developing symptomatic CAD after age 40 is 49 percent for men and 32 percent for women. Ischemic heart disease is now the leading cause of death worldwide. The World Health Organization estimates that by 2020 the global number of deaths from CAD will have risen from 7.1 in 2002 to 11.1 million [1.]

Different clinical ischemic syndromes result from fixed obstruction to coronary blood flow by atherosclerotic plaques or thrombosis,or by abnormal epicardial coronary vasomotion,or by microvascular dysfunction. These events can occur together or separately. Understanding the coronary circulatory physiology aids physicians to diagnose and treat these events effectively.

DIAGNOSIS OF CORONARY ARTERY DISEASE

Definite diagnosis of coronary stenosis can be made by coronary angiography (CAG). However, it is an invasive technique and only available in the catheterization laboratory. Patients without anginal symptoms, left ventricular dysfunction or electrocardiographic changes may not be diagnosed until cardiac events occur. If noninvasive detection of coronary stenosis before CAG becomes possible, it could help in the consideration of further invasive procedures and in the estimation of the results of various interventions.

Many noninvasive methods like Exercise stress testing, Stress Echocardiography, Nuclear imaging and CT angiography can aid in prediction of coronary stenosis.Each has different sensitivity and specificity to predict coronary stenosis in relation to stenosis diagnosed by coronary angiogram as a gold standard investigation.

ANGIOGRAPHIC ASSESSMENT OF CORONARY ARTERY NARROWINGS:

An angiographic lumen narrowing is commonly referred to as a stenosis which may be due to atherosclerosis, vasospasm, or angiographic artifact.

To quantify the coronary stenosis accurately it must be seen in profile, free from artifact related to foreshortening or obfuscation by a crossing vessel. Multiple views are important, because many lesions have a markedly eccentric lumen. When seen across its major axis, the width of the lumen may appear to be normal, but a clue to the presence of a severe degree of narrowing in the other axis may be marked lucency caused by thinning of the contrast column.

The normal caliber of major coronary arteries, Left main 4.5±0.5mm,LAD 3.7±0.4mm, LCX 3.4±0.5mm for non dominant and dominant LCX 4.2 ±0.6mm; RCA 3.9 ± 0.6 for dominant and 2.8 ± 0.5 for non dominant.

By comparing the diameter of a presumably disease free segment of coronary artery to the size of the diagnostic catheter (6F equals 2mm), the operator can identify vessels that fall below these normal size ranges and may thus be diffusely diseased. The evaluation stenosis relates to the percentage of reduction in the diameter of narrowed vessel site to the adjacent unobstructed vessel. The diameter stenosis is calculated in the projection where the greatest narrowing is seen. It should be noted that the stenotic lumen is compared to near by unobstructed lumen, which indeed may have diffuse atherosclerotic disease and thus is angiographically normal but still may be diseased. The area of stenosis is always greater than diameter stenosis and assumes the lumen is circular when in reality most of the time the lumen is eccentric.

A 50 % of reduction in diameter is equivalent to a 75% reduction in Cross Sectional area, and a 75% reduction diameter is equal to a 90 % reduction in cross sectional area. Stenosis that reduces the lumen diameter by 50% (and hence cross sectional area by 75%) is hemodynamically significant, in that it reduces the normal three fold to four fold flow reserve of coronary bed.

Whereas a diameter stenosis of 70% (90% cross sectional area) eliminates virtually any ability to

increase flow above it's resting level. Stenosis that reduced the lumen diameter by 90%, however, rarely exists without reducing antegrade flow. Because of the subjective nature of a visual lesion assessment, there is a ± 20% variation between readings of two or more experienced angiographers especially for lesions 40 – 70% narrowed.

The simplest way to resolve this problem is, project the coronary image on a wall mounted viewing screen, and use inexpensive digital calipers to measure the relative diameters of the stenotic and reference segment. Percent stenosis can be calculated as 100 × (1 – stenosis diameter/reference diameter) to provide a more accurate estimate of stenosis.

TIMI FRAME COUNT

Myocardial blood flow has been assessed angiographically using Thrombolysis in Myocardial infarction (TIMI) score for qualitative grading of coronary flow. TIMI flow grades 0 – 3 have become a standard description of angiographic coronary blood flow in clinical trails. Quantitative method of TIMI uses cine angiography with 6F catheters and filming at 30 frames per second .The number of cine frames from the introduction of dye in the coronary artery to predetermined distal landmark is counted.

The first frame used for TIMI frame counting is that in which the dye fully opacifies the artery origin and in which the dye extends across the width of the artery touching both borders with anterograde motion of the dye. The last frame counted is when the dye enters the first landmark branch. Full opacification of distal branch not required. The distal landmark commonly used in analyses are,

(1) for LAD -the distal bifurcation of LAD.

(2) for the circumflex system ,the distal bifurcation of branch segments with the longest total distance.

(3) for the RCA the first branch of posterolateral artery.

The TIMI frame count can further be quantified for the length of the LAD for comparison to the two other major arteries. This is called corrected TIMI frame count (CTFC). The average LAD coronary artery is 14.7cm long, RCA 9.8cm, LCX 9.3cm. CTFC accounts for the distance the dye has to travel in

the LAD relative to the other arteries. CTFC divides the absolute frame count in LAD by 1.7 to standardise the distance of dye travel in all the three arteries. Normal TFC for LAD is 36±3 and CTFC 21±2, for LCX TFC is 22±4, for RCA TFC is 20±3. TIMI flow grades do not correspond to measured Doppler flow velocity or CTFC. High TFC may be associated with microvascular dysfunction despite an open artery. CTFC of <20 frames were associated with low risk for adverse events in patients following myocardial infarction. A contrast injection rate of >1ml/sec by hand injection can decrease the TIMI frame count by 2 frames. The TIMI frame count method provides valuable information relative to clinical responses after coronary intervention.

COLLATERAL CIRCULATION

The reopacification of a totally or subtotally (99%)occluded vessel from antegrade or retrograde filling is defined as collateral filling... Angiographically visible collateral channels are not usually seen until the coronary obstruction is greater than 90%, at which point coronary perfusion pressure falls substantially and the blood flow through the collaterals increases.The collateral circulation may provide upto 50% of anterograde coronary flow in chronic total occlusions.

PHYSIOLOGY OF CORONARY CIRCULATION:

The flow through the coronary arteries is pulsatile, with characteristic phasic systolic and diastolic flow components. Systolic compression of the intramural coronary vessels causes mean systolic arterial flow to be reduced relative to diastolic flow, despite having a higher systolic driving pressure.

The systolic flow wave has rapid, brief retrograde responses corresponding to phasic myocardial compliance over the cardiac cycle. Diastolic flow occurs during the relaxation phase after myocardial contraction with an abrupt increase above systolic levels and a gradual decline parallel with that of aortic diastolic pressure.The coronary blood flow not only is phasic but also varies with the type of vessel and location in the myocardium.

A system of multiple functional "valves" permits fine control of the coronary circulation. The smallest arterioles dilate during metabolic stress, resulting in reduced microvascular resistance and increased myocardial perfusion. As the upstream arteriolar pressure decreases owing to a fall in distending pressure across a stenosis, myogenic dilation of slightly larger arterioles upstream occurs and causes an additional decrease in resistance. Increased flow in the largest arterioles augments shear stress and triggers flow-mediated dilation, further reducing the resistance of this network. Thus, coronary arterioles appear to have specialized regulatory elements along their length that operate "in series" in an integrated manner.

INFLUENCE OF A STENOSIS ON CORONARY BLOOD FLOW

Resistance to flow changes exponentially with lumen cross-sectional area and linearly with lesion length. Additional factors contributing to resistance include the shape of the entrance and exit orifices, vessel stiffness, and distensibility of the diseased segment (permitting active or passive vasomotion) and the variable lumen obstruction that may be superimposed by platelet aggregation and thrombosis compromising lumen area, a process active in acute coronary syndromes.

The physiological effect of a coronary stenosis also depends on the degree to which the resistance to flow can be compensated by dilation of the microcirculation distal to the stenosis. Resting coronary flow is not impeded by mild or moderate stenoses and is maintained by normal vasodilatory regulation of the microcirculation.

Resting coronary blood flow remains constant up to the point where an epicardial coronary constriction exceeds 85 to 90 percent of the normal segment diameter.However, unlike resting flow, maximal hyperemic coronary blood flow begins to decline when diameter stenosis exceeds 45 to 60 percent.

The capacity to increase coronary blood flow in response to a hyperemic stimulus, called

coronary flow reserve (CFR), is abolished when diameter stenosis exceeds 90 percent.

CORONARY PRESSURE AND FLOW FOR THE PHYSIOLOGICAL ASSESSMENT OF A CORONARY STENOSIS

The hemodynamic significance of a given stenosis in humans can be measured by the pressure-flow relationship using sensor angioplasty guidewires.

Three types of stimuli have been used to elicit maximal coronary blood flow in humans: (1) transient coronary occlusion during angioplasty (reactive hyperemia); (2) pharmacological vasodilators; and (3) metabolic stress Reactive hyperemia follows an occlusion as short as 200 milliseconds. Maximal reactive hyperemia follows coronary occlusion of 20 seconds. Longer occlusion increases the duration but not the amplitude of the hyperemic response. At maximal hyperemia, autoregulation is also abolished and coronary blood flow is directly related to the driving pressure.

Adenosine, dipyridamole, and papaverine are the principal pharmacological vasodilators used to elicit coronary hyperemia.

CORONARY FLOW RESERVE (CFR)

CFR is defined as a ratio of maximal to baseline (resting) coronary blood flow.. CFR measurement is used both to assess epicardial coronary stenoses and to examine the integrity of micro vascular circulation.. In the absence of stenosis in epicardial coronary artery,the CFR may be decreased when coronary micro vascular circulation is compromised by arterial hypertension with or without left ventricular hypertrophy, diabetes mellitus, hypercholesterolemia, syndrome X, hypertrophic cardiomyopathy or other diseases[1].

METHODS TO ASSESS CFR

CFR measures the ability of the two components of myocardial perfusion, namely the epicardial stenosis resistance and the microvascular resistance, to achieve maximal blood flow.

There are two invasive methods available to measure coronary blood flow in the catheterization laboratory: intracoronary Doppler flow velocity and coronary thermodilution. Volumetric flow is the product of vessel area (square centimeters) and flow velocity (centimeters per second) yielding a value in cubic centimeter per second. The coronary thermodilution technique uses thermistors on a pressure-sensor angioplasty guidewire and measures the arrival time of room temperature saline bolus indicator injections through the guiding catheter into the coronary artery. When combined with poststenotic pressure measurements, CFR measurements can provide a complete description of the pressure-flow relationship and the response of the microcirculation.

Normal CFR in young patients with normal arteries by intravascular ultrasound commonly exceeds 3.0. In patients with chest pain undergoing cardiac catheterization with angiographically normal vessels, the CFR averages 2.7 ± 0.6. Tachycardia increases basal flow, reducing CFR. Increasing mean arterial pressure reduces maximal vasodilation, reducing hyperemic flow more than basal flow. CFR may be reduced in patients with normal coronary arteries who have essential hypertension or aortic stenosis. Diabetes mellitus also reduces CFR, especially in patients with diabetic retinopathy

Several methods have been established for measuring CFR . However, these methods are either invasive (intracoronary Doppler flow wire), highly expensive and scarcely available (Positron Emission Tomography) or semiinvasive and scarcely feasible (transesophagealDoppler), thus their clinical use is limited. In addition, PET and intracoronary Doppler flow wire involve radiation exposure, with inherent risk, environmental impact and biohazard connected with use of ionizing testing.

NONINVASIVE ASSESSMENT OF CORONARY FLOW VELOCITY RESERVE WITH TRANSTHORACIC COLOR DOPPLER ECHOCARDIOGRAPHY

Transthoracic coronary Doppler ultrasound turns our attention from surrogate markers of atherosclerosis, such as brachial/ankle index, left ventricular mass, and carotid intima/media thickness to a direct screening modality of coronary flow

THE WINDOW

Coronary blood flow velocity should be measured from an apical window by pulsed Doppler ultrasound under colour-coding guide. The best long axis view in colour flow imaging should be obtained to maintain a <30 degree angle between flow and the Doppler beam. Correction for the theta angle may be used,5–7 but it is a redundant operation, since CFVR is not an absolute, but a derived value (ratio between hyperaemic and baseline coronary blood flow velocity).

METHODOLGY.

The TTDE examinations were performed with color Doppler flow mapping, the velocity range was set at ±9.6 to 28.8 cm/s. The color gain was adjusted to provide the optimal images.

The transducer was placed at the fourth or fifth intercostal space the cardiac apex and the parasternal area the anterior interventricular groove was visualized in the short-axis view.,. In the short-axis images of the left ventricle, the mid-portion of the LAD can be identified as a cross section of the tubular structure containing the color Doppler flow signal, positioned in the anterior interventricular sulcus.. After confirming its position, the transducer was rotated counterclockwise to visualize the LAD, which runs along the interventricular sulcus, in the long-axis section while color Doppler flow with a Nyquist limit of ±19 to ±24 cm/s was applied to visualize the LAD flow with relatively low velocity; After positioning a sample volume (1.5 to 2.5 mm wide) on the color signal in the LAD, Doppler spectral tracings of flow velocity were recorded by the pulsed Doppler method. Transducer position and direction were adjusted to make the Doppler beam as parallel as possible to LAD flow, and an angle

correction was performed Angle correction was needed in each examination (incident angle 41 ± 11°). All studies were recorded on s-VHS videotape. Using the computer analysis system incorporated in the ultrasound system, off-line measurements of mean diastolic velocities and peak diastolic velocities were performed by tracing the contour of the spectral Doppler signal.

Flow velocity recordings were performed in a stable transducer position at rest and during maximal hyperemia, which was induced by intravenous administration of adenosine (140µg/kg/min). Systolic-diastolic average peak velocities at rest and during maximal hyperemia (mean peak velocity) were used for off-line analysis of spectral Doppler tracings to calculate CFR. The values of three consecutive beats were averaged to calculate the flow velocity at rest and during hyperaemia . When the distal LAD flow was retrograde by color Doppler or was not visualized within 5 minutes, antegrade LAD flow was considered to be absent, and the TTDE coronary study was discontinued

The sampling site is critical for correct coronary flow measurements because the results may be very different when CFVR is measured proximal to the stenosis, at the level of the stenosis or distal to it.

Proximal to the stenosis, CFVR may be perfectly normal, as it reflects perfusion in normal territories . It may be altered only in the rare case there are no side branches between the sampling site and the stenosis.

This is one of the reasons why transoesophageal echocardiography, which allows imaging of the left main and the very initial tract of the LAD, has been abandoned for the study of CFVR in CAD.

At the level of the stenosis, baseline coronary flow accelerates to 40–50 cm/s or more to compensate for lumen loss and maintain the coronary output constant.

This accelerated baseline flow prevents reliable calculation of CFVR.

Coronary flow should therefore be measured at the distal tract of the coronary artery for three reasons, (1) The effect of flow acceleration from a proximal

or mid coronary stenosis is minimal (2) The cumulative effect of sequential stenoses can be assessed,

because all end in alteration of distal flow; (3) Compared to the proximal and middle tract of the coronary artery, the capacitance of the distal tract is minimal, and changes in velocity best reflect changes in vital, intramural flow.24

BASELINE FLOW VELOCITY

Myocardium can incur only a small oxygen debt, and myocardial oxygen consumption is strictly flow-dependent. For this reason, baseline coronary blood flow may be readjusted on a beat-by-beat basis, and baseline coronary flow velocity may change from one beat to the other of even 5–10 cm/s.

It is therefore important, in case of significant variability of baseline flow velocities, to average values obtained from at least three beats, in order to prevent misinterpretations.

Elevated resting flow velocities may occur in several cardiac and non-cardiac conditions increasing oxygen consumption at rest, including tachycardia, anaemia,hyperthyroidism, severe left ventricular hypertrophy, valvular diseases, etc.

On the other hand, coronary vasodilators such as nitrates or calcium antagonists increase the diameter of the epicardial artery and reduce baseline flow velocity. B-Blockers may also reduce baseline coronary flow velocity, mainly by decreasing heart rate and blood pressure, and hence oxygen consumption.

Adenosine and Doppler Hyperaemic flow is obtained by venous infusion of adenosine (140 lcg/kg/min), a pure and strong dilator of the coronary microcirculation, having little or no effect on the epicardial artery.

ADENOSINE

Adenosine, the most commonly used agent in the catheterization laboratory, can be administered by the intravenous or intracoronary route.

RF Wilson et al investigated in humans the effects of adenosine, administered by intracoronary bolus (2-16 micrograms), intracoronary infusion (10-240 micrograms/min), or

intravenous infusion (35-140 micrograms/kg/min) on coronary and systemic hemodynamics and the electrocardiogram. Coronary blood flow velocity (CBFV) was measured with a 3F coronary Doppler catheter.

Intracoronary infusions of 80 micrograms/min or more into the left coronary artery also caused maximal hyperemia, and doses up to 240 micrograms/min caused a minimal decrease in arterial pressure (-6 +/- 2 mm Hg) and no significant change in heart rate or in electrocardiographic variables.

Intravenous infusions in normal patients at 140 micrograms/kg/min caused coronary vasodilation similar to that caused by papaverine. At submaximal infusion rates, however, CBFV often fluctuated widely. During the 140-micrograms/kg/min infusion, arterial pressure decreased 6 +/- 7 mm Hg, and heart rate increased 24 +/- 14 beats/min..

MJ Kern et al showed that coronary blood flow velocity were measured at rest and during peak hyperemic responses to continuous intravenous adenosine infusion (50, 100 and 150 micrograms/kg per min for 3 min) and intracoronary papaverine (10 mg) and after low dose (2.5 mg) intravenous bolus injection of adenosine. The maximal adenosine dose did not change mean arterial pressure but increased the heart rate. ... Intracoronary boluses caused a small, brief decrease in arterial pressure (similar to that caused by papaverine) and no changes in heart rate or in the electrocardiogram. The duration of hyperemia was much shorter after adenosine than after papaverine administration.. Low dose bolus injection of adenosine increased mean velocity equivalently to that after continuous infusion of 100 micrograms/kg, but less than after papaverine. There was a strong correlation between adenosine infusion and papaverine for both mean coronary flow velocity and coronary vasodilator reserve ratio. No patient had significant arrhythmias or prolongation of the corrected QT (QTc) interval with adenosine, but papaverine increased the QT (QTc) interval .

Adenosine is benign in the appropriate dosages (20 to 30 µg in the right coronary artery or 30 to 50 µg in the left coronary artery or infused intravenously at 140 µg/kg/min) . Intravenous dobutamine (10 to 40 µg/kg/min) can also produce maximal hyperemia without modifying the angiographic area of

the epicardial stenosis.

Coronary flow is the product of velocity and the cross-sectional area of the vessel. Because the diameter of the epicardial artery does not change significantly during adenosine infusion , velocity can be used as an acceptable surrogate of flow. This is an important prerequisite for any drug used to study CFVR, because according to the Poiseuille's law, even small variations in calliper may cause large variations in velocities and hence in flow. Compared to dipyridamole, adenosine is more potent and more versatile, as it can be repeatedly infused just after coronary flow velocity returns to baseline.

SAFETY

It is better to infuse adenosine for no more than 90 s, for three main reasons: (1) the maximal hyperaemic effect is already reached at 30–60 s; (2) short infusion times prevent the development of myocardial ischaemia, which may occur for more prolonged infusion; (3) the costs are significantly reduced. Small bolus injection is safe and effective.

The adenosine dose may actually be reduced to a minimum of 2.5 mg bolus injection, which produces an increase in CFVR similar to that obtained by 3 min venous infusion, and has no significant side-effects,40 with important practical and economical implications.

According to **Voci** et al, in his series of more than 1000 patients studied with either short infusion or bolus injection, including those with acute coronary syndromes, there was only one episode of transient atrial fibrillation in a patient with poor left ventricular function and recurrent episodes of paroxysmal atrial fibrillation. Nevertheless, some authors still use infusion times of up to 5–6min, which may cause significant side-effects, and may result in myocardial ischaemia in critical patients[5–7.]

IS THERE A ROLE FOR SYSTOLE?

It may be difficult to record both diastolic and systolic flow in the same cardiac cycle in all patients, because rotational and translational movements of the heart displace the coronary artery from the ultrasound beam in systole. However, compared to the diastolic, systolic flow is a less important and

less stable measure.

Diastolic flow is anterograde in both epicardial and intramural vessels, whereas systolic flow is anterograde in epicardial but retrograde in intramural vessels, where blood is squeezed backwards by myocardial contraction. As a result of the two opposite forces, the magnitude of systolic flow velocity may change along the coronary tree and close to the origin of a perforator there might be a watershed area with stagnation of systolic flow.[16] Therefore, the epicardial anterograde systolic flow is mainly a capacitance, rather than a nutrient flow, and does not reflect myocardial perfusion.

DIAGNOSIS OF SIGNIFICANT CORONARY STENOSIS:

CFVR reflects the impact on total coronary resistances of: (1) The patency of the epicardial coronary artery, and (2) The vasodilator capacity of the microcirculation.

In normal coronary arteries, CFVR entirely describes the resistances of the microcirculation. A flow-limiting stenosis introduces a strong proximal resistance that is higher than that opposed by the microcirculation, as demonstrated by the early normalization of CFVR after the mechanical relief of the stenosis by coronary stenting.11 Therefore, the impact of microcirculation on CFVR is of secondary importance, compared to that of a significant epicardial stenosis.

Lance Gould established in his seminal experimental work that a CFVR of 2 discriminates significant (P70%) from non-significant (<70%) coronary stenoses.[28,29].

Human studies using single photon emission computed tomography [30] and intracoronary[45] and transthoracic coronary Doppler ultrasound [3–8], have confirmed these findings, and a cut-off value of 2 has been widely adopted as the ‘‘magic number’’ discriminating significant impairment of coronary flow that should be treated invasively by mechanical removal of the stenosis.

Translated into clinical practice, transthoracic coronary Doppler ultrasound helps deferring revascularization in patients with CFVR above 2, with important economical, ethical and

social implications.

In keeping with the experimental findings,[28 29] transthoracic coronary Doppler ultrasound correlates well with the angiographic degree of the stenosis.[3–8,] This is true for non-significant (<50%) and significant (P70%) coronary lesions, but data on intermediate (50–69%) lesions[10] are more dispersed.

This is not surprising, since intermediate lesions are difficult to quantify even with quantitative coronary angiography, which in fact cannot reliably predict the physiological impact of these stenoses. In intermediate stenoses, coronary Doppler ultrasound may guide our clinical decision making, reserving percutaneous coronary interventions only to patients with reduced CFVR.[47.]

Transthoracic coronary Doppler ultrasound has several advantages over other stress tests:

(1) It is accurate in detecting single vessel disease,[17,19] However, with the currently available technology, transthoracic coronary Doppler ultrasound cannot detect branch stenosis;

(2) It is less time consuming, because theoretically only few baseline and hyperaemic diastoles are needed to measure CFVR;

(3) It provides a quantitative measure of coronary blood flow, which is particularly useful for follow-up evaluation;[13]

(4) It is independent of baseline ST alterations and bundle branch block;

(5) Drugs such as b-blockers may not be discontinued.[35]

INTERMEDIATE STENOSIS

Understanding the functional impact of stenosis is important for clinical decision making. One example is whether to refer or defer patients with intermediate stenosis for percutaneous transluminal coronary angioplasty (PTCA).CFR measured distal to the stenosis precisely defines the hemodynamic significance of stenosis. In studies using transthoracic Doppler echocardiography, CFR <2 is associated with stress-induced ischemia and reduced CFR is considered as a manifestation of

functionally important stenosis even if coronary angiography reveals intermediate severity[5 6 11]. In contrast, patients with intermediate stenosis but with adequate CFR value, PTCA can be safely deferred.

The measurement of CFR by transthoracic Doppler echocardiography provides data equivalent to those obtained by thallium-201 scintigraphy for physiologic estimation of the severity of LAD stenosis.

CRITICAL LAD STENOSIS:

The **C**oronary **A**rtery **S**urgery **S**tudy registry states that patients with >90% stenosis have a 3–7.5 times higher probability to develop acute myocardial infarction than those with less severe lesions. Unfortunately, neither the clinical presentation, nor the currently available non-invasive tests can reliably discriminate severe from non-severe stenosis. Using transthoracic Doppler echocardiography, it is possible to detect severe LAD stenosis >90%. The CFR <1, which suggests coronary steal may be a predictor of critical coronary stenosis[23]. Coronary steal is defined as a decrease of CFR to a certain vascular region in favor of another area during maximal coronary vasodilatation, that is, CFR <1.

Lance Gould showed that the hyperaemic response disappears at 90% vessel stenosis.[37,38] a damped CFVR during adenosine infusion is consistently found in patients with severe LAD stenosis.[39] Three main mechanisms may be proposed to explain, isolated or in combination, why coronary flow cannot increase or may actually drop during adenosine infusion in severe stenoses:

(1) In extremely tight stenoses, the microvascular reserve may already be exhausted at rest, because of maximal peripheral vasodilation, and cannot increase any further under stress;

(2) An incompletely calcified coronary stenosis may maintain some degree of elasticity and may collapse during adenosine infusion[37,38] for a drop in intraluminal distending pressure induced by flow acceleration at the stenosis site (Venturi effect);

(3) Pre-stenotic collaterals may open at stress, stealing blood from the ischaemic territory to perfuse other less jeopardized segments.[58]

Other authors have postulated that a relative increase in systolic velocity at rest is a marker of severe stenosis.[40]Further studies are needed to confirm the diagnostic value of this parameter, which has the limits described above for systolic flow, but the advantage of being obtained with a simple resting exam.

CHRONIC TOTAL OCCLUSION

Reverse diastolic flow at rest, reflecting retrograde filling of the artery by collaterals, is a very specific marker of coronary occlusion[41] but it unfortunately has a low sensitivity, since collaterals may perfuse the vessel either retrogradely or anterogradely.

The collateral flow is routinely evaluated at rest with coronary angiography[42] but the predictive role of this method is uncertain. Conversely, the response of collateral flow to stress, which can be measured by intracoronary and transthoracic Doppler ultrasound, may add useful prognostic information.

In his experience, according to **Voci** et al, it is feasible to measure CFVR in the PD in around 50% of the patients regardless of its origin from the right or circumflex coronary artery,12 but others have reported higher figures.[15]

The lower success rate of imaging the PD compared to the LAD (feasibility 98%) depends on two factors: (1) The PD runs deep into the chest (7–8 cm) while the LAD is more superficial (<2 cm); (2) The PD runs close to the right ventricular inflow tract and to the mid-cardiac vein, which generate strong and disturbing diastolic and systolic flow signals.

Adenosine-induced hyperventilation dedicated transducer has been designed for the LAD, whereas the PD is studied with a conventional imaging of the PD can be improved in several ways: (1) The use of ultrasound contrast agents improving the signal-to-noise ratio; (2) The use of specific A2A adenosine receptor agonists reducing side effects as hyperventilation; (3) The design of specific probes and software; (4) Reducing the heart rate to minimize wall motion artifacts on Doppler sampling.

Additional piece of information in the Doppler spectrum: the intensity of the reflected signal. Doppler intensity can be used to detect coronary vasomotion: it may decrease during handgrip in patients with coronary artery disease whereas it may increase or remain unchanged in normals.

ROLE FOR THE MICROCIRCULATION

Transthoracic coronary Doppler ultrasound has been used to study the impact on microvascular flow in a number of settings known to, or suspected of, altering microvascular flow, such as coronary stenting,[44] remote coronary artery disease, sex hormones, cigarette smoking,20 left ventricular hypertrophy,22 diabetes and ageing[52 53.] With regard to remote microvascular alteration in focal CAD, we have found that CFVR in the angiographically normal coronary artery is never affected by remote coronary stenosis, AMI, or stenting.[55] These findings confirm that focal factors in each territory are the major determinants for CFVR, and impaired CFVR one region is not a general phenomenon of the coronary circulation.

MONITORING THE CHANGES OF CFR IN THE EARLY, POST-PTCA PERIOD TO DETECT ARTERY OCCLUSION.

Microvascular stunning due to microembolization,thrombogenicity (by thrombin release) and vasoconstriction (by endothelin release),and temporary reactive hyperemia, a state with high post-ischemic baseline flow velocity, masks normal reserve. Invasive CFR is obtained after multiple balloon inflations, injection of contrast agent and administration of vasoactive drugs that may produce immediatepost-procedural vasomotion instability.. Early reoclussionof the coronary artery is another complication after PTCA detectable by transthoracic Doppler echocardiography.

SERIAL CFR EXAMINATION AFTER PTCA TO PREDICT RESTENOSIS

Pierre Legalery et al showed that , One-year clinical follow-up demonstrated that patients left with medical treatment alone had a similar outcome to those submitted to revascularization and

concluded that subset of patients in whom the decision to revascularize contradicted the FFR results had less favourable event-free survival.

Detection restenosis is feasible in mid- and long-term follow-up to monitor restenosis [37,38]. The decrease of CFR <2 during follow-up was proposed as a sensitive and specific predictor of restenosis [25]. This method may be complementary to exercise test, or may be its substitute if patients are unable to perform adequate exercise test. Besides CFR measurements distally to the stenosis, other methods have been been developed to detect restenosis after PTCA..

CORONARY STENTING AND CFR:

CFR may normalize in 80 percent of patients after stenting, corresponding to improved lumen area as the mechanism responsible for improved coronary blood flow. The remaining 20 percent of patients with widely patent stents had impaired CFR (<2.0) attributed to microvascular disease and/or transient emboli from PCI. A low postprocedural CFR has been associated with a worse periprocedural outcome.

FFR after stenting also predicts adverse cardiac events at follow-up. FFR immediately after stenting was an independent variable related to all adverse cardiac events. The event rate was 5 percent in patients in whom FFR normalized, 6 percent in patients with poststent FFR between 0.90 and 0.95, and 20 percent in those with FFR less than 0.90. In patients with FFR less than 0.80, the event rate was 30 percent

POSTINFARCTION CFR ASSESSMENT

Ueno et al. showed that the decreased CFR <1.5 was identified to predict an increase in left ventricular volume (remodeling) after myocardial infarct reperfusion. A significant negative correlation was found between CFR and progression of left ventricular dilatation at 6-month follow-up.

Colonna et al has shown that preconditioning due to pre infarction angina had a protective role on microvascular function as demonstrated by CFR preservation (>2.5) after myocardial infarction.

CORONARY GRAFTS

It is very easy to measure flow in the left and right internal mammary arteries both at the origin [46] and at the level of the suture over the LAD 1,2,with important perioperative and follow-up information on the functional status of the graft. For saphenous vein grafts it is possible to measure flow at the level of the suture over the LAD.

ASSESSMENT OF CORONARY GRAFT PATENCY

Chirillo F, et al showed the identification rate for mammary artery grafts was 100%, for saphenous vein grafts to LAD coronary artery 91%, for the vein grafts to the right coronary artery 96% and for the vein grafts to circumflex artery 90%43. CFR <1,9 had 100% sensitivity, 98% specificity for mammary artery graft stenosis. CFR <1,6 had 91% sensitivity, 87% specificity for significant vein graft stenosis.

ABSOLUTE VOLUMETRIC FLOW VERSUS FLOW VELOCITY MEASUREMENT OF CFR

Only **Hozumi e**t al.[19] achieved a very high feasibility of coronary flow imaging in their first study, i.e. 94%. Limitation may be minimized by using echo-contrast agents enhancing Doppler signal intensity, which are however expensive. With regard to cost-effectiveness balance, it was calculated that using 90-s noncontrast/adenosine vasodilator approach, the cost of the test was 14 times less expense than the 7-min contrast-enhanced approach.

DIFFUSE ATHEROSCLEROSIS.

Coronary arteries without focal stenosis are generally considered non-flow limiting. A diffusely diseased atherosclerotic coronary artery can be viewed as a series of branching units diverting and gradually distributing flow and reducing pressure longitudinally along the conduit. In such a vessel, a reduced CFR is not associated with any single location of stenotic pressure loss..

PITFALLS AND TROUBLE-SHOOTING

CFR must be measured distally to stenosis, because erroneous CFR assessment at stenosis site is underestimated due to increased baseline flow velocity. In addition, the flow in the LAD branches

could be erroneously interpreted as flow in LAD main trunk.

PIONEER WORKS OF NON INVASIVE ASSESSMENT OF CFR TO PREDICT LAD STENOSIS BY TTCDE WITH ANGIOGRAPHIC COORELATION:

In chronological order, **Lance Gould** first established coronary blood flow velocity reserve can be measured by transthoracic ultrasound in his experimental works on effects of coronary stenoses on coronary flow reserve and resistance, and in hi s seminal work of 'physiologic basis for assessing severe coronary stenosis: instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve'.

Later**, Fusejima** reported that it was possible to measure coronary flow velocity in the midportion of the LAD with two-dimensional Doppler echocardiography, in the earlier studies with 65% success rates.

Subsequent works by **Voci** in more than 1000 patients he established safety of adenosine induced vasodilation.

Hozumi revealed that transthoracic CFR evaluation is useful in predicting restenosis after PCI. .

Matsumura suggested Cut-off value of coronary flow velocity reserve by transthoracic Doppler echocardiography for diagnosis of significant left anterior descending artery stenosis in patients with coronary risk factors

Transthoracic Doppler echocardiography is noninvasive, relatively inexpensive and widely used in the clinical setting, and can be used for serial studies in echocardiographic laboratories.

Several studies have reported that CFV can be measured by visualizing LAD using transthoracic two-dimensional and Doppler echocardiography with a high-frequency transducer . It has been also shown that CFV in the distal LAD can be measured at high success rate by TTDE under the guidance of color Doppler flow mapping, and assessment of CFVR in the LAD by this noninvasive technique is useful in the diagnosis of significant LAD stenosis .

MATERIALS AND METHODS

STUDY PATIENTS

We have selected 59 patients who underwent coronary angiography for the evaluation of coronary artery disease, for chronic stable angina. They were included in this study after strictly adhering to study protocol.

EXCLUSION CRITERIA

Unstable angina

Congestive heart failure

Atrial fibrillation

Previous coronary bypass graft surgery

Diabetes mellitus

Severe chronic obstructive pulmonary disease, or bronchospasm

II–III degree atrioventricular block

Patients with short PR intervals

Clinical history or ECG signs of a previous myocardial infarction,

Evidence of primary myocardial or valvular heart disease.

Uncontrolled hypertension.

As the microvascular dysfunction in many of situations listed above, especially diabetic retinopathy and unstable angina, may cause alteration in CFVR independent of coronary stenosis, we carefully excluded those patients from the study.

The entire patients who were included in the study were evaluated on the basis of proforma. Detailed history with special focus on cardiovascular risk factors were obtained.. Their treatment history was noted. All were submitted to thorough physical examination, routine

biochemical and hematological tests , resting ECG and Treadmill Exercise stress testing with bruce protocol.

TWO DIMENSIONAL ECHOCARDIOGRAPHIC MEASUREMENTS OF LV FUNCTION AT BASELINE

Before CFVR measurements by TTDE, we measured septal and LV posterior wall thickness at end diastole by two-dimensional echocardiography. LV volume measurements were performed according to the recommendation of the American Society of Echocardiography. Apical two- and four-chamber views were obtained at baseline. End-diastolic and end-systolic LV volumes and Ejection fraction were computed by use of modified Simpson's method.. Furthermore, we assessed regional wall motion at rest on the basis of 16 segments of the LV as recommended by the American Society of Echocardiography. No patient had evidence of LV hypertrophy (septal or posterior wall thickness at diastole >12 mm) on echocardiographic examination, as LVH itself becomes an exclusion criteria for the study.

Then TTCDE for measuring CFR was carried out for all patients before coronary angiography .Those who had lesions in the LAD were included in this study.

COLOUR DOPPLER ECHOCARDIOGRAPHIC STUDIES

TWO –dimensional and M-mode measurements were obtained with patients in left lateral position using an **ALOKA SSD4000** phased array system equipped with tissue Doppler and harmonic imaging technology with Doppler frequency of 2.5 to 3.8 mhz. Later it was switched over to 5mhz to 7.5mhz , When optimal images not obtained in individual patients.

The acoustic window was around the midclavicular line in the fourth and fifth intercostal spaces in the left lateral decubitus position. First, the left ventricle was imaged in the long-axis cross section, and then the ultrasound beam was inclined laterally. The color gain was adjusted to provide optimal images. Next, coronary blood flow in the distal portion of the LAD was searched under the guidance of color Doppler flow mapping. With a sample volume (1.5 or 2.0 mm wide) positioned on the color

signal in the LAD, Doppler spectral tracings of flow velocity in the LAD were recorded by pulsed doppler.

The spectral Doppler of the LAD flow showed a characteristic biphasic flow pattern with a larger diastolic component and a small systolic one. All studies were continuously recorded on 1/2 inch super-VHS videotape for off-line analysis.

CFVR MEASUREMENTS BY TTCDE

We first recorded baseline spectral Doppler signals in the distal portion of the LAD. Adenosine was administered (140 µg · kg-1 · min-1 IV) for 2 minutes to record spectral Doppler signals during hyperemic conditions. All patients had continuous heart rate and ECG monitoring. Blood pressure was recorded at baseline, every minute during adenosine infusion, and at recovery.

Measurements were performed off-line by tracing the contour of the spectral Doppler signal using the computer incorporated in the ultrasound system.

MDV and PDV were measured at baseline and peak hyperemic conditions. PSV was also measured at baseline and peak hyperemic conditions. An average of the measurements was obtained in three cardiac cycles. Density of Doppler spectrum was also noted in all patients both at baseline and after adenosine.

CFR was defined as the ratio of hyperemic to basal peak diastolic coronary flow velocity (CFR PDV) and the ratio of hyperemic to basal mean diastolic coronary flow velocity (CFR MDV). Normal CFR was defined as >2.0 on the basis of previous studies that evaluated flow velocities in the distal LAD.[11-13]

CORONARY ANGIOGRAPHY

Reason for coronary angiography was evaluation for coronary artery disease, for chronic stable angina. Coronary angiogram done in the Siemens mobile unit cath lab in our hospital, and Philips mounted lab at GH. Coronary angiograms were done through right femoral approach using modified seldinger technique. Low osmolar nonionic contrast agent (omnipaque) was used. Coronary angiography was

performed with the Judkins catheters, after injection of 2500 IU IV heparin. Coronary stenosis was evaluated by use of multiple projections Quantitative analysis was done with a Medical Imaging Systems CMS analysis software. A stenosis was considered significant if there was >70% lumen diameter narrowing in at least one projection. Those patients with significant lesions in LAD were grouped as **GROUP A**. Those without significant lesions in LAD were grouped as **GROUP B**. Those with significant lesions in other coronary artries were excluded. Those with severe lesions in LAD when lumen diameter narrowing, was more than 90%. In all the study patients, there was no significant stenosis (diameter stenosis >70%) in the other coronary arteries besides the LAD.

RESULTS AND DATA ANALYSIS :

Based on the study protocol, study patients were divided as, those patients with significant lesions, >70% luminal narrowing in proximl LAD were grouped as GROUP A and those without significant lesions in proximal LAD were grouped as GROUP B for statistical analysis. History obtained and physical findings in both groups did not show much difference. There was no difference in the distribution of some of the variables like, hypertension, smoking , history of drug intake like asprin,enalapril,atenolol, and isosorbide dinitrate, and dyslipidemia in both groups. Routine laboratory , both biochemical and hematological findings had similar range in both groups .

Resting ECG showed T wave changes in both groups ,but statistically not significant. Average time taken to perform TTDE study was 21.4 minutes. Average time taken to perform coronary angiogram after TTDE study, was 2.5days. Average time taken to achieve maximal coronary flow velocity was 44 seconds.

STATISTICAL METHODS:

Mean and SD are expressed for the baseline parametric data. The differences between the two groups for the parametric data were tested by use of an student independent t test.

Differences between baseline and hyperemic data within the two groups were tested by use of chi square test.

Sensitivity, specificity, positive predictive value, and negative predictive value for CFR as a predictor of significant LAD stenosis were calculated in the traditional manner.

CLINICAL AND ECHO PARAMETERS IN STUDY PATIENTS:

When baseline parameters were analysed between the two groups , no significant relationship existed for variables like age, sex ,SBP,DBP,pulse rate.

Mean peak diastolic CFVR values for males were 1.363, 2.242 and for females 1.431, 2.306 in group A and group B respectively. Mean mean diastolic CFVR values for males were 1.3685, 2.3219 and for females 1.4591 ,2.4400 in group A and group B respectively.

When we analysed gender influence upon presence of LAD stenosis , distribution in Group A and Group B for males 76.2% and 71.1% and for females 23.8% 28.9% respectively.Critical LAD stenosis more than 90% luminal narrowing was presnt in 18.9 % in females and 20.1% in males.

Analysis of gender influence shows that it is not statistically significant, though study population mainly consists of males(73%).

When comparing patients between the groups, the mean age of patient population in group A was 54.92 years while that of group B was, 51.43 years, not statistically significant.

Mean systolic BP was 132.37mmHg group A as against 132.10mmHg in Group B. While Diastolic Blood pressure in group A was 85.95mmHg as against 89.33mmHg in Group B, although Diastolic BP was slightly higher in group B patients than in group A, statistically it was not significant.

We found that LV dimension in diastole and systole were normal in all study patients, while mean LVDd was 4.76cms as against 4.88cms in Group A and Group B respectively while that of mean LVDs was 3.32cms as against 3.33cms in Group A and Group B respectively. Similarly the difference in EDV and ESV between the two groups was not statistically significant.

Mean Ejection Fraction in Group A and in Group B, was 54.11 and 55.76. Similarly Fractional shortening(FS) was also similar in both groups, while it was 30.40 versus 31.25in Group A and Group B respectively.

No patient noted AV block, chest pain, flushing, or palpitations during the vasodilator infusion in the TTDE studies.

HEMODYNAMICS

During adenosine administration, heart rate increased from 81.05 to 88.12 bpm in the study patients. Systolic arterial pressure decreased from 132.37mm Hg to 124 mmHg, and diastolic arterial pressure decreased from 85.95 mm Hg to 76.6 mm Hg, in Group A, and in Group B the variations in pulse rate , systoloic blood pressure and diastolic blood pressure are similar without statistical significance .An increase in coronary flow velocity was obtained within 50 seconds of the start of the vasodilator infusion(average: 44 sec).

Flow velocity remained stable throughout the infusion period and returned to baseline within 30 seconds of discontinuation of the drug.

Average PDV and MDV at baseline did not differ between groups A and B (23.42versus 23.18cm/s and 32.92 cm/s 52.39versus cm/s, respectively.

However, average PDV and MDV during hyperemia in group A were significantly smaller than those in group B, $p<0.001$.

There were significant differences in CFVR PDV and CFVR MDV measured in groups A and B (versus and versus, respectively; $P<.001$).

A CFVR (PDV) < 2.0 had a sensitivity of 95%, a specificity of 86%, positive predictive value of 92%, and a negative predictive value of 90% for the presence of significant LAD stenosis.

A CFVR MDV <2.0 had a sensitivity of 90%, a specificity of 91%, positive predictive value of 89%, and a negative predictive value of 95% for the presence of significant LAD stenosis .

When we analyzed the relationship of TMT results to predict presence of significant LAD stenosis, in our study TMT has had a sensitivity of 82%, a specificity of 67%, positive predictive value of 79%, and a negative predictive value of 65% for the presence of significant LAD stenosis.

A cut off value 1 has very good sensitivity(96%) to predict LAD stenosis, but it has low specificity to

predict the same(75%).

Peak systolic velocity as such did not have much statistical significance in our study. .Average PSV was 5.62 cm/s and 5.362 cm/srespectively. A cut off value >5cm/s was tried to predict LAD stenosis without success. It was not significant.

The ratio between restng PDV and PSV was calculated and its mean value was 4.34 and 4.59 in patients with and without LAD stenosis. Instead hyperemic ratio between PDV and PSV was 3.88 and 5.17, which was statistically significant , p value< 0.001.

ANGIOGRAPHIC FINDINGS :

Coronary angiogram in 59 patients were reviewed with two different persons to quantify the lesion severity. Of 59 patients 38 persons showed significant stenosis, luminal diameter narrowing > 70%. Of these 27 were males and 11 were females.

Out of the 21 patients who did not have significant LAD lesions in any of its segments ,especially proximal, 10 patients had <40% lesions. Of these ten patients, 4 patients had entirely normal LAD and rest of them had luminal irregularities.

Among the 38 patients who had significant LAD lesions, 27 patients had lesion severity less than 90%. Most of them had TIMI grade 2 flow.

Rest of the 11 patients had more than 90% luminal diameter narrowing severe flow limiting lesions. Among these, 5 patients had very severe flow limiting lesions with extensive collateral supply and retrofrade filling of distal and mid LAD.

All patients who had significant stenosis, had proximal LAD lesion, while many had coexisting mid LAD involvement of lesser degree of involvement.

None of the patients had significant lesion in LCX, RCA or in Ramus (which was present in 2 of our patients), though nonsignificant lesions of varying degree was evident in most of the cases.

Resting TIMI frame count was calculated for each patient, though no statistical analysis was

attempted because of differential reporting, since hyperemic TIMI frame count was not done in our study to compare with CFR.

TABLE :1 BASELINE PARAMETRIC DATA

VARIABLES	GROUPS				Student independent t-test
	With Stenosis		Without Stenosis		
	Mean	SD	Mean	SD	
age	54.92	7.93	51.43	7.65	t=1.64 P=0.11
SBP	132.37	25.07	132.10	21.94	t=0.04 P=0.97
DBP	85.95	12.78	89.33	13.07	t=0.96 P=0.34
PR	81.05	11.98	77.48	15.81	t=0.98 P=0.33
LVDd	4.76	.39	4.88	.39	t=1.07 P=0.29
LVDs	3.32	.36	3.35	.34	t=0.33 P=0.74
EF%	54.11	5.24	55.76	4.74	t=1.20 P=0.23
FS	30.40	3.72	31.25	4.58	t=0.77 P=0.44
PSV	5.62	1.30	5.36	1.68	t=0.66 P=0.58
PDV_B	23.42	1.06	23.18	.75	t=0.91 P=0.36
MDV_B	16.19	.65	15.31	1.30	t=2.90 P=0.01
PSV_M	8.82	1.77	10.23	1.17	t=3.28 P=0.01
PDV_M	32.93	7.11	52.39	6.55	t=10.34 P=0.001
MDV_M	22.55	5.16	35.81	4.21	t=10.06 P=0.001
P_CFR	1.38	.31	2.26	.27	t=10.76 P=0.001
M_CFR	1.39	.30	2.35	.31	t=11.61 P=0.001
PDV_PSV-P	4.34	.83	4.59	.92	t=1.07 P=0.26

PDV_PSV -M	3.88	1.05	5.17	.84	t=4.82 P=0.001

FIG:1. GENDER DIFFERENCES IN GROUP A & B

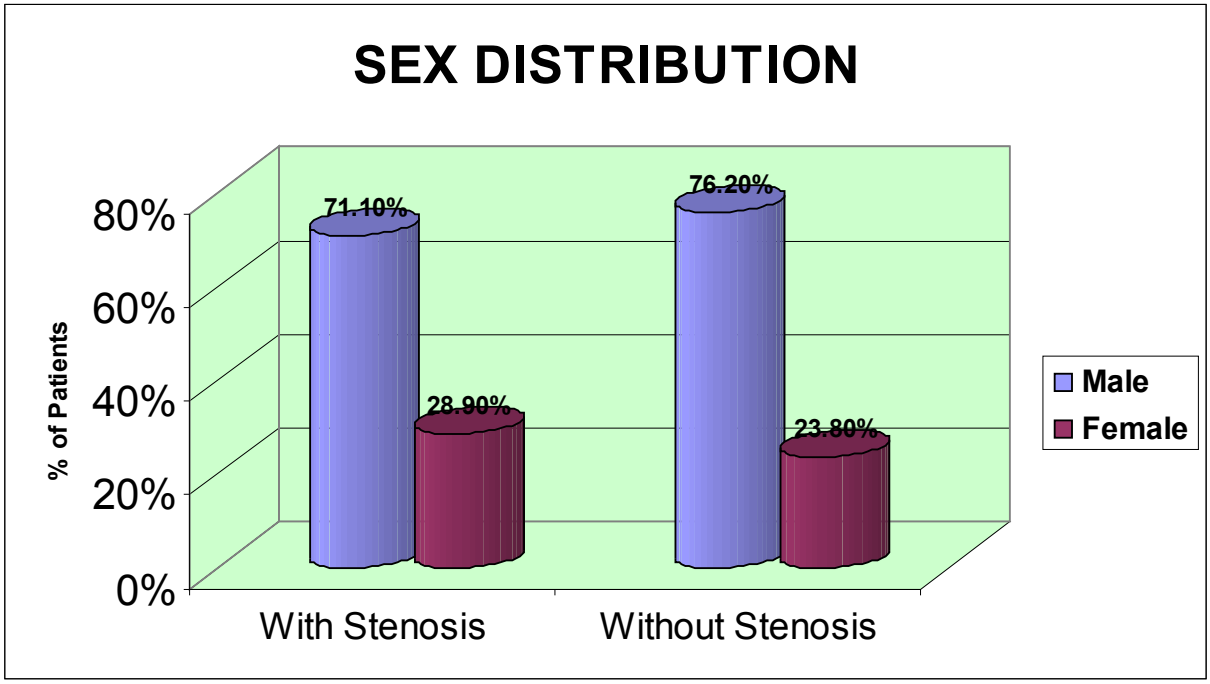

FIG:2. CORONARY ANGIOGRAPHIC LESION REPRESENTATION (ALL PATIENTS N = 59)

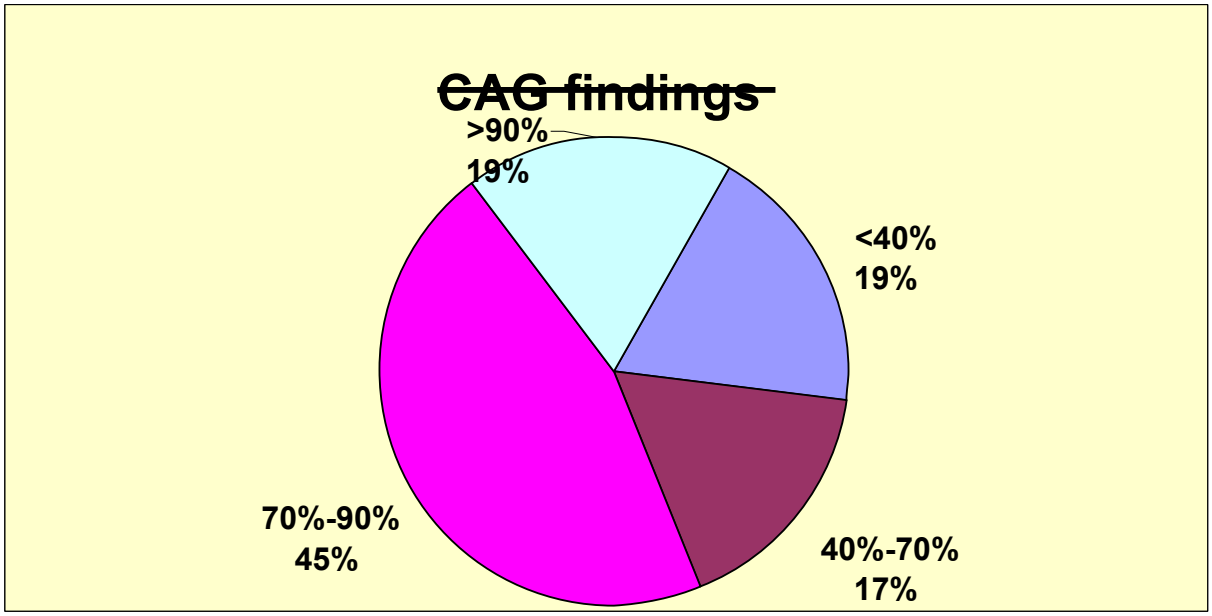

FIG:3.EFFICACY TO PREDICT LAD STENOSIS: COMPARISON BETWEEN TMT AND CFR<2

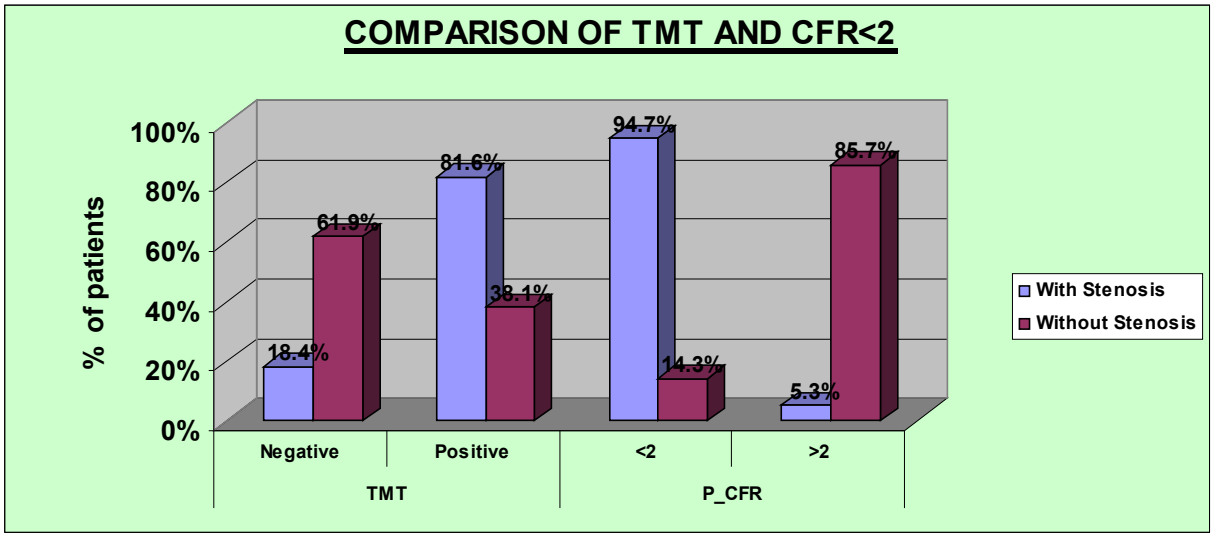

TABLE:2. . GENDER DIFFERENCES IN GROUP A & B

	group				
	With Stenosis		Without Stenosis		
	n	%	n	%	Chi-square test
sex Male	27	71.1%	16	76.2%	$\chi 2=0.18$
Female	11	28.9%	5	23.8%	P=0.67
Group Total	38	100.0%	21	100.0%	Not significant

TABLE:3. CFR<2 AS A PREDICTOR OF LAD STENOSIS

	group				
	With Stenosis		Without Stenosis		
	n	%	n	%	Chi-square test
P_CFR <2	36	94.7%	3	14.3%	$\chi 2=39.07$
>2	2	5.3%	18	85.7%	P=0.001
Group Total	38	100.0%	21	100.0%	significant
M_CFR <2	36	94.7%	3	14.3%	$\chi 2=39.07$
>2	2	5.3%	18	85.7%	P=0.001
Group Total	38	100.0%	21	100.0%	significant

TABLE:4. CFR<1 AS A PREDICTOR OF CRITICL STENOSIS

	group				
	With Stenosis		Without Stenosis		
	n	%	n	%	Chi-square test
P_CFR <1	10	26.3%	1		$\chi 2=6.65$
>1	28	73.7%	21	100.0%	P=0.01
Group Total	38	100.0%	21	100.0%	significant
M_CFR <1	9	23.7%	1		$\chi 2=5.86$
>1	29	76.3%	21	100.0%	P=0.01
Group Total	38	100.0%	21	100.0%	significant

TABLE:5. TMT AND LAD STENOSIS

		group				
		With Stenosis		Without Stenosis		
		n	%	n	%	Chi-square test
TMT	Negative	7	18.4%	13	61.9%	$\chi 2=11.41$
	Positive	31	81.6%	8	38.1%	P=0.001
Group Total		38	100.0%	21	100.0%	significant

FIG 5:. DISTRIBUTION OF CFR AND NUMBER OF PATIENTS

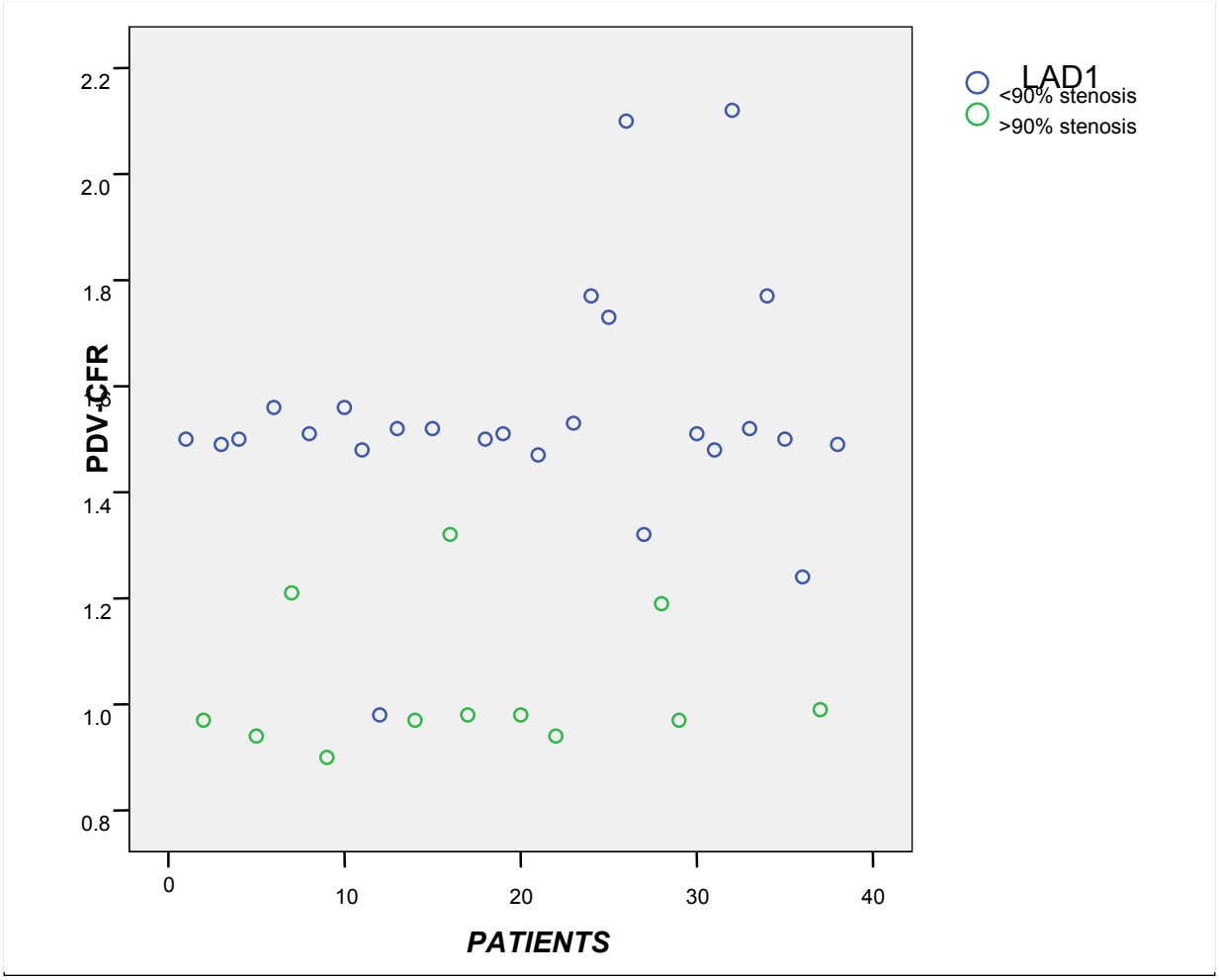

TABLE:6. PEAK AND MEAN DIASTOLIC CFR AND PREDICTION OF LAD STENOSIS: GENDER INFLUENCE

group		sex	N	Mean	Std. Deviation	Student independent t-test
With Stenosis	P_CFR	Male	27	1.363	.3437	t=0.60 P=0.55 notsignificant
		Female	11	1.431	.2319	
	M_CFR	Male	27	1.3685	.32705	t=0.84 P=0.40 notsignificant
		Female	11	1.4591	.21305	
Without Stenosis	P_CFR	Male	16	2.242	.3071	t=0.45 P=0.63 notsignificant
		Female	5	2.306	.0493	
	M_CFR	Male	16	2.3219	.34322	t=0.73 P=0.47 notsignificant
		Female	5	2.4400	.15556	

DISCUSSION

It has been reported that assessment of coronary flow reserve by administration of coronary vasodilators provides an important diagnostic index of the functional significant coronary artery stenosis.[1 2 3 4 5 6]

With Doppler technique, coronary flow reserve has been alternatively assessed as the ratio of hyperemic to basal coronary flow velocity after drug-induced coronary vasodilation by invasive techniques with a Doppler catheter[5 6 7 8 9] or a Doppler guide wire[8 9 10 11 12 13 14] because changes in coronary flow velocities induced by coronary vasodilation closely reflect changes in coronary blood flow.[7]

Although these invasive methods have already been established as useful techniques, they are available only in the catheterization laboratories and limit the clinical application of CFVR in the assessment of coronary artery disease.

Positron emission tomography has been used to measure coronary flow reserve noninvasively.[33 34 35] However, this method is expensive and not generally available.

Several studies have reported that transesophageal Doppler echocardiography is useful in the assessment of significant LAD stenosis by measuring hyperemic to basal coronary flow velocity in the proximal LAD.[21 22 23] However, strictly speaking, the transesophageal approach is not noninvasive, but semi-invasive.

TTDE is noninvasive, relatively inexpensive, and widely used in the clinical setting and can be used for serial studies in echocardiographic laboratories. In the present study, we evaluated the value of CFVR determined by TTDE for the assessment of significant LAD stenosis after drug-induced coronary vasodilation. TTDE was shown to be a feasible method for the noninvasive measurement of CFVR and detection of significant LAD stenosis

Fusejima[24] reported that it was possible to measure coronary flow velocity in the midportion of the LAD with two-dimensional Doppler echocardiography, in the earlier studies with 65% success rates. Subsequent works by **Voci, Hozumi, Illicito** and many others, the success rate was vastly improved manyfold and many innovations lead to even 100% success rate to visusalise LAD by myocardial contrast enhancement.

In the present study, the success rate of the measurement of coronary flow velocity in the distal LAD for the assessment of CFVR was 79%, though it was lower than the values reported bymany workers. The moderate success rate in this study was due to the following reasons: reduction of the velocity range in color Doppler flow mapping and modified method to position the sample volume in the distal LAD under the guidance of color Doppler flow mapping.

First, the reduction in the velocity range enhanced the visualization of the low-velocity signal in the distal LAD by lowering the cutoff limit of the wall motion filter.

The velocity range in conventional color Doppler flow mapping is usually set in the range of 60 to 70 cm/s in routine echocardiographic examinations. It is possible that use of conventional ultrasound systems that incorporate color Doppler flow mapping set only in the high velocity range leads to difficulty in visualization of the low-velocity signals usually seen in the LAD flow.

In our present study, we lowered the setting of the velocity range in color Doppler flow mapping. Application of this newly modified velocity range in color Doppler flow mapping provided improved visualization of coronary flow signal in the distal LAD.

Second, our method combined color Doppler flow mapping and the conventional pulsed Doppler technique. This modification facilitated the positioning of the sample volume in the distal LAD flow.

Our study demonstrated that color Doppler flow mapping enables a more efficient guidance of the sample volume in the distal LAD compared with previous studies that used only two-dimensional imaging.

Under the guidance of color Doppler flow mapping, adequate spectral Doppler recordings of coronary

flow in the distal portion of the LAD for the assessment of CFVR were obtained 59 of 75 patients who were submitted for TTCDE to estmate CFR and those patientsfor whom LAD could not be visualized, were excluded for statistical analysis. Only 59 patients were included for further statistical analysis. Of the 59 patients, 38 had a significant stenotic lesion in the proximal or middle portion of the LAD (group A; diameter stenosis >70%; 27 men, 11women; mean age, 54.92 years; the remainder did not have a significant stenotic lesion in the LAD (group B; 16 men, 5 women; mean age, 51.43 years). In our study out of 43 males 22 were smokers, While none had Diabetes, 4 had Hypertension, 11 had combination of risk factors such as HT and dyslipidemia, without statistical significance in distribution between the groups.

Baseline echo parameters were vital for interpretation of CFR since LVH, wall motion abnormalities and dilated LV with reduced EF can cause alterations in CFR values. In our study,for the measurement of LV wall thickness (septal and posterior wall), there were no significant differences between groups A and B (9.7±1.2 versus 9.8±1.4 mm and 10.0±1.0 versus 9.9±1.1 mm, respectively). None of the patients had LVH by Echocardiographic criteria. Both end-diastolic and end-systolic LV dimensions did not differ between groups A and B (4.76cms versus 4.88cms and 3.32cms versus 3.35, respectively) at baseline. There was no significant difference in ejection fraction measurement between groups A and B (54.11% versus 55.76%).

In each case in both groups, segmental wall motion abnormality was not found by two-dimensional echocardiography at baseline.

As the coronary physiology experimental studies reveal that every 10% increase in pulse rate ,ther is proportionate 15% decrease in CFR. So when we tried to analyse the influence of pulse rate upon the results, We found it that mean pulse rate was, 81.05 and 77.48 in group A and group B respectively, statistically not significant.

None of our patients had developed any untoward incidents to administration of adenosine. 2 patients complained transient chest tightness which disappeared immediately. None

developed bronchopasm, atrial fibrillation and myocardial ischemia. Entire study was under the control of continous ECG monitoring and any eventuality was anticipated and was well prepared to meet the same.

DETECTION OF LAD STENOSIS BY CFR

When we analyzed CFR, it is shown that most of the patients with significant LAD stenosis, both peak and mean diastolic CFVR values were hovering around 1.5 cut off value.

We found that though CFR > 2 effectively ruled out significant LAD stenosis,two patients had value more than 2. similarly, though patients with LAD stenosis had CFR value<2 most of the times, it is not always we could predict lAD stenosis when the CFR value was less than 2, because in 3 patients without angiographic evidence of significant LAD stenosis, the CFR value was less than 2..

While the mean diastolic CFR had slightly better specificity to predict LAD stenosis , when compared to peak diastolic CFR has better sensitivity for the same.

A cut off value 1 has very good sensitivity(96%) to predict LAD stenosis, but it has low sensitivity to predict the same(75%).

Peak systolic velocity as such did not have much statistical significance in our study. .Average PSV was 5.62 and 5.362 respectively. A cut off value >5 was tried to predict LAD stenosis without success. It was not significant.

The ratio between restng PDV and PSV was calculated and its mean value was 4.34 and 4.59 in patients with and without LAD stenosis. So the resting value was not powerful to predict LAD lesions. Instead hyperemic ratio between PDV and PSV was able to predict Lad lesion with success, p value< 0.001.

Very severe lesions , like chronic total occlusion usually have collaterals to supply the mid and diastal LAD. When collaterals feed the obstructed LAD, retrograde blood flow in mid and distal LAD produces diastolic flow reversal. We had recorded such diastolic flow reversal in few patients (5), and we tried to analyse to predict the value of presence of diastolic flow reversal, it did not appear to

predict the very severe lesions, though it was specific for retrograde collateral filling in as many cases it was present.

When we compared the Treadmill test and CFVR to predict significant LAD stenosis, CFVR has more beneficial results in both sensitivity and specificity.

There were significant differences in CFVR PDV and CFVR MDV measured in groups A and B (versus and versus, respectively; P<.001).

A CFVR (PDV) < 2.0 had a sensitivity of 95%, a specificity of 86%, positive predictive value of 92%, and a negative predictive value of 90% for the presence of significant LAD stenosis.

A CFVR MDV <2.0 had a sensitivity of 90%, a specificity of 91%, positive predictive value of 89%, and a negative predictive value of 95% for the presence of significant LAD stenosis .

The transthoracic approach is completely noninvasive. The higher success rate in the assessment of CFR and the fact that it is a noninvasive procedure should be important advantages in the present transthoracic method.

LIMITATIONS

CFVR is defined as a flow velocity ratio, regardless of the concomitant pressure gradient or of the absolute values of flow. Its value inherently depends on frequently independent variations in baseline or maximal flow that may be caused by factors unrelated to stenosis severity. Hence, the limitation to only 1 of 2 interdependent signals, pressure or flow velocity, may be a source for potential inaccuracies in the assessment of functional stenosis severity for diagnostic purposes by CFVR. Furthermore, determination of both CFVR and FFR critically depends on the achievement of maximal vasodilation

However, with the currently available technology, transthoracic coronary Doppler ultrasound cannot detect branch stenosis;

We measured changes in coronary flow velocity, not changes in coronary blood flow. However, it has been reported that changes in coronary flow velocities induced by coronary vasodilation closely reflect changes in coronary blood flow.[5]

Previous studies with Doppler catheter, Doppler guide wire, and transesophageal Doppler echocardiography have shown that these techniques are useful in the prediction of significant coronary artery stenosis by the assessment of coronary flow velocity.[11] [12] [13] [14] [15] [16] [17] [18].

Second, we measured CFVR from only diastolic mean velocities, not mean velocities throughout the entire cardiac cycle. It was difficult to obtain complete Doppler spectral envelopes throughout the entire cardiac cycle because of cyclic cardiac motion.. However, diastolic component of the spectral Doppler signal of the LAD flow could be clearly obtained by positioning the sample volume in the LAD during the diastolic phase under the guidance of color Doppler flow mapping.

Third, in the present study, there was only a small number of patients with significant coronary stenosis in the LAD. In future investigations, more patients should be studied by the present method.

In the present study, we excluded several factors influencing CFR measurement such as LV hypertrophy and myocardial infarction. However, other potential determinants of CFR that were not measured and were not excluded in this study may affect the sensitivity and specificity for the presence of significant LAD stenosis in the present method.

CONCLUSIONS

. In the present study, the success rate of the measurement of coronary flow velocity in the LAD for the assessment of CFVR was over **79%** of patients.

2. Both Peak and Mean diastolic velocity based **CFVR <2** correlated well with angiographic evidence of significant stenosis in LAD.

3. A **CFVR (PDV) < 2.0** had a sensitivity of **95%,** a specificity of **86%,** positive predictive value of **92%**, and a negative predictive value of 90% for the presence of significant LAD stenosis in this study.

4. **CFVR<2** has statistically significant better correlation with angiographic evidence of significant stenosis in LAD in comparison with TMT positivity.

5. This study shows that **CFVR** correlates well with the angiographic degree of the stenosis. **CFVR** <1 has significant correlation to predict very severe LAD stenosis.

6. It is shown in our study that Peak SystolicVelocity >5 cm did not correlate with the presence of critical LAD Stenosis. .The hyperemic PDV/PSV ratio has statistical significance to predict LAD lesion in our study, while basal ratio did not.

8.TTCDE assessment of CFVR is safe. No complications observed in our study.

9. Reverse diastolic flow at rest, reflecting retrograde filling of the artery by collaterals, is a very specific marker of coronary occlusion but it unfortunately has a low sensitivity

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PROFORMA

NON INVASIVE ASSESSMENT OF CORONARY FLOW VELOCITY RESERVE WITH TRANSTHORACIC COLOUR DOPPLER ECHOCARDIOGRAPHY TO PREDICT SIGNIFICANT LEFT ANTERIOR DESCENDING CORONARY ARTERY STENOSIS NAME :

AGE : SEX :

OCCUPATION : C.D. NO. : ADDRESS :

RISK FACTOR PROFILE :

HYPERTENSION SMOKING OBESITY (BMI)

HYPERLIPIDEMIA PREVIOUS CAD DM/ RETINOPATHY

CLINICAL PROFILE :

CHEST PAIN CCS CLASS VITAL PARA METERS : P R : BP

CVS RS OTHER SYSTEMS

DRUGS USED

ASPRIN ISDN ACEI B.BLOCKER

INVESTIGATION :

BLOOD SUGAR : CARDIAC ENZYMES : CHEST X RAY PA :

ECG : LVH PR INTERVAL AF DELTA WAVES

ECHOCARDIOGRAPHY : SYSTOLIC FUNCTION : LV DIMENSION : LVIDd : LVIDs:

EDV : ESV : EF : FS : RWMA : WALL THICKNESS

DIASTOLIC FUNCTION : TRANS MITRAL FLOW PATTERN : E A

TTCDE EXAMINATION OF MID AND DISTAL LAD

COLOUR FLOW STUDY

1.LAD VISUALISED 2. TURBULENT COLOUR FLOW IN LAD

3.VISIBLE PERFORATORS 4.DIASTOLIC FLOW REVERSAL

DOPPLER STUDY: BASAL HYPEREMIC

1. PEAK SYSTOLIC VELOCITY

2. PEAK DIASTOLIC VELOCITY

3. MEAN DIASTOLIC VELOCITY

4.DOPPLER DENSITY CHANGE

5.DIASTOLIC FLOW REVERSAL.

HEMODYNAMIC CHANGES

1.PULSE RATE

2.SYSTOLIC BP

3.DIASTOLIC BP

COMPLICATIONS

1.PALPITATIONS 2.CHEST TIGHTNESS 3.MYOCARDIAL ISCHEMIA

4.ATRIAL FIBRILLATION 5.WHEEZE 6.AV BLOCK

CORONARY ANGIOGRAM :

LMCA LCX : RCA : RAMUS

LAD :

COLLATERELS WITH RETROGRADE FILLING OF LAD .

GLOSSARY

TTCDE : TRANSTHORACIC COLOUR DOPPLER ECHOCARDIOGRAPHY.

CFVR: CORONARY FLOW VELOCITY RESERVE

PDV: PEAK DIASTOLIC VELOCITY

MDV : MEAN DIASTOLIC VELOCITY

LVDd : LEFT VENTRICULAR INTERNAL DIMENSION IN DIASTOLE

LVDs : LEFT VENTRICULAR INTERNAL DIMENSION IN SYSTOLE

CHD : CORONARY HEART DISEASE

DM : DIABETES MELLITUS

LVH : LEFT VENTRICULAR HYPERTROPHY

MI : MYOCARDIAL INFARCTION

EF : EJECTION FRACTION

EDV : END-DIASTOLIC VOLUME

ESV : END-SYSTOLIC VOLUME

LVEF : LEFT VENTRICULAR EJECTION FRACTION

CCS : CANADIAN CARDIAC SOCIETY

AMI : ACUTE MYOCARDIAL INFARCTION

LAD : LEFT ANTERIOR DESCENDING ARTERY

LCX : LEFT CIRCUMFLEX ARTERY

RCA : RIGHT CORONARY ARTERY

LMCA: LEFT MAIN CORONARY ARTERY