CLINICAL AND ANGIOGRAPHIC PROFILE OF PATIENTS WITH ANGINA AND NORMAL EPICARDIAL CORONARIES

A Study Using Clinical, Biochemical, Electrocardiographic, Echocardio graphic and Angiographic variables

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR DM BRANCH II CARDIOLOGYEXAMINATION OF THE TAMIL NADU DR.M.G.R MEDICAL UNIVERSITY TO BE HELD IN JULY/AUGUST 2013

BONAFIDE CERTIFICATE

This is to certify that the work presented in this dissertation titled **" Clinical and angiographic profile of patients with angina and normal epicardial coronaries: A study using clinical, biochemical, electrocardiographic, echocardiographic and angiographic variables"** done towards fulfillment of the requirements of the Tamil Nadu Dr. M.G.R Medical University, Chennai for the DM (Branch II – Cardiology) examination to be conducted in July/August 2013 is a bonafide work of the candidate Dr.Gireesh G.K, post graduate student at the Department of Cardiology, Christian Medical College, Vellore, performed under my guidance and supervision. This dissertation has not submitted, fully or in part to any other board or university.

Dr. Sunil Thomas Chandy, M.D.,D.M.,M.Phil.,F.C.S.I,
Professor and Head of Cardiology,
Christian Medical College Hospital,
Vellore - 632004

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Dr. Paul V. George M.D.,D.M.,
The Professor and Head,
Department of Cardiology,
Christian Medical College,
Vellore - 632004

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CONTENTS

ABSTRACT

Background: Angina with normal epicardial coronaries occurs in upto 20% of patients who underwent coronary angiogram for angina. Coronary slow flow comprises a separate group among this population designed Syndrome Y and accounts for upto 7% of patients undergoing CAG for angina. Coronary slow flow is characterized by the delayed passage of contrast injected into the epicardial coronaries. Conventionally, coronary slow flow is determined by the coronary filling time. We tried to determine whether coronary emptying time is a significant predictor of coronary slow flow

Methods: We selected consecutive patients, who underwent angiogram for angina and found to have normal epicardial coronaries, randomly between the study period November 2011 and November 2012. We assessed the coronary filling and emptying times at prespecified standard vascular landmarks on the basis of TIMI frame counts

Results: We analysed the angiograms of 37 patients. 27 patients had LAD slow flow and 17 patients had RCA slow flow (10 had normal flow in LAD and 12 had normal flow in RCA). 8 had non dominant small RCA and was excluded from the study. We observed positive correlation of coronary filling times and emptying times, both in LAD and RCA, in slow flow patients unlike those with normal flow. We found the filling times and emptying times are significantly prolonged in slow flow patients (p value <0.05) in LAD and RCA. Capillary and venous transit time is prolonged in both LAD and RCA slow flow groups, but was significantly prolonged in RCA slow flow patients. (Pvalue <0.05, LAD slow flow group, P value 0.43). We observed slow flow significantly more in male population and significantly associated with high LDL/HDL ratios and high triglycerides.

Conclusion: Coronary emptying time is an independent and significant predictor of Coronary Slow Flow Phenomenon.

INTRODUCTION

The coronary slow flow phenomenon is a coronary microvascular disorder characterized by the delayed passage of contrast, injected into the epicardial coronaries, in the absence of obstructive epicardial coronary artery disease. It is well recognized by coronary angiographers but largely has been considered an angiographic curiosity and received little attention despite previous studies demonstrating coronary microvascular dysfunction.

The presentation of coronary slow flow phenomenon differs from other coronary microvascular disorders, with most patients undergoing angiography after admission with an acute coronary syndrome accounting for 4% of unstable angina admissions. The clinical course is debilitating, with over 80% of patients experiencing recurrent chestpain necessitating readmission to the coronary care unit in almost 20%*(5)*.

In the previous studies CSFP was defined on the basis of angiographically normal or near normal epicardial coronary arteries and TIMI 2 flow. Conventionally, the dye injected to the coronaries will opacify the distal vascular bed within 3 cardiac cycles(as evidenced by 3 cardiac contractions). If the duration is more than that is designated slow flow. TIMI (Thrombolysis In Myocardial Infarction) frame count was developed as a simple objective quantitative reproducible method to assess coronary blood flow. This method counts the number of cine angiographic frames required for radioopaque contrast to reach specified distal landmarks in each coronary artery.

Cineangiography is performed with 5rF catheters and filming at 30 frames per second. The TIMI frame count can further be corrected (CTFC) by normalizing for the length of the LAD for comparison with the 2 major arteries. Distal landmarks used in analysis are as follows 1. For the LAD, the distal bifurcation of the LAD 2. For the circumflex system distal bifurcation of the branch segment with the longest total

distance 3. For the right coronary artery, the first branch of the posterolateral artery. Normal TFC for LAD is 36+/- 3; for LCx 22+/-4, for RCA 20+/-3. Each has CTFC of 21+/-2.

High CTFC may be associated with microvascular dysfunction despite and open artery where as CTFC < 20 frames per second are associated with normal microvascular function, low risk for adverse events in patients following myocardial infarction. Coronary slow flow is defined by elevated TFC observed in the epicardial coronaries. Coronary slow flow is defined by the coronary filling time that is the number of frame counts that the contrast takes to travel from the ostium of a coronary artery to the specified distal landmark.

The emptying time of the coronaries are not studied previously though it indirectly determines the flow of blood through the coronary microvasculature. Hence we postulated that coronary emptying time is a better predictor of coronary slow flow as compared to the coronary filling time. Coronary filling time is more operator dependant but emptying time is an independent variable that determines the ease with which the dye flows through the coronary microvasculature.

AIMS AND OBJECTIVES OF THE STUDY

Aims

The primary aim of the study is to determine the epicardial coronary arterial filling time and emptying time at prespecified vascular landmarks in patients with chestpain and normal epicardial coronaries and to determine whether coronary artery emptying time is a predictor of coronary slow flow phenomenon (CSFP).

Objectives

1. To determine the coronary artery filling time and emptying time at prespecified vascular landmarks in patients with chestpain and normal epicardial coronaries.
2. To determine the association of coronary arterial filling time and emptying time in patients with coronary slow flow phenomenon.
3. To determine the association of various conventional coronary artery disease risk factors in patients with coronary slow flow phenomenon.
4. To determine the association of coronary artery risk factors with the coronary filling and emptying times.
5. To determine the clinical profile of patients with coronary slow flow phenomenon
6. To determine the association of various clinical parameters with coronary filling and emptying times.

Hypothesis

The hypothesis we made is that coronary artery emptying time is a significant predictor of coronary slow flow phenomenon.

REVIEW OF LITERATURE

The Coronary Slow Flow Phenomenon (CSFP) is an angiographic observation characterised by delayed passage of contrast in the epicardial vessels during selective coronary arteriography*(2)*. This is thought to represent dysfunction of the coronary microcirculation. Coronary slow flow phenomenon is designated Syndrome Y*(6)*. Patients with angina or angina like chest pain and normal coronaries is termed Syndrome X. They may represent 10 to 20% of those who undergo coronary angiogram for clinical suspicion of angina*(1)*. Syndrome Y is a different clinical entity compared to syndrome X as evidenced by

1. Mechanistic difference between syndrome X and CSFP.
2. CSFP has typical clinical features as compared to syndrome X.
3. The prognosis of patients with CSFP is not benign as those with syndrome X.

CSFP is a known clinical entity for the interventional cardiologists for the past 4 to 5 decades. However the pathogenetic mechanisms is not clearly understood yet. CSFP is not just a clinical curiosity. It has significant clinical implications. It has been associated to clinical manifestations of myocardial ischaemia, life threatening arrhythmias, sudden cardiac death and recurrent acute coronary syndromes*(7)*.

This should be differentiated from the delay contrast progression in the context of coronary reperfusion therapy like angioplasty or coronary stenting or other secondary causes of coronary slow flow.

Conditions associated with secondary coronary slow flow*(10-12)*

Conditions	Mechanism of slow flow
Coronary ectasia	Reduced coronary flow velocity
Coronary spasm	Increased epicardial resistances
Coronary stenosis	Increased epicardial resistances
Embolism	Microvascular plugging
Heart failure	Increased intracavitary pressure
Angioplasty and stenting of acute myocardial infarction	Reperfusion injury, impaired rheology
Valvular heart disease	Increased left ventricular end diastolic pressure
Connective tissue disorders	Impaired rheology

ASSESSMENT OF THE CORONARY MICROCIRCULATION

The study of human coronary microvasculature function is complicated by two fundamental problems. Firstly, there is no currently feasible means to directly visualise the coronary microcirculation in vivo. Secondly, obtaining coronary microvessels for ex-vivo or in-vitro analysis is methodologically challenging and difficult to sustain on ethical grounds. Thus any dynamic study of the human coronary microcirculation usually involves a combination of indirect measures of microvessel function and/or the use of surrogate vessels, either from other human vascular beds or animal models.

IN VITRO TECHNIQUES

In vitro experimental techniques permit individual vasoactive agents and their receptors to be studied within the vessel type in question free from neurohumoral influences. Unfortunately, while these techniques maximise the analysis of drug- receptor interactions the results obtained are difficult to extrapolate to the intact organism. This is circumvented to a degree by the preservation of the endothelium in the isolated vessel preparations and the local vascular environment in the perfused heart preparation. Despite these caveats the following techniques provide relatively simple and robust methods of evaluating microvascular reactivity.

1. Wire Myograph
2. Pressure Myograph
3. Isolated perfused heart models

IN VIVO TECHNIQUES

The more an experimental model approaches 'real world' physiology the less the number of parameters that can be measured and the greater the variation in the measurements. This is due to progressively more feedback, feed forward and counter regulatory systems that are present within the model. Hence, the quality and detail of experimental data must be balanced against clinical relevance. A combined approach is usually adopted whereby individual parameters are analysed in vitro and their contribution to overall vascular physiology examined in vivo. Where possible confounding variables are anticipated and minimised.

Direct Visualisation – Intravital Microscopy

Needle-probe videomicroscopy can be used to directly visualize epicardial, endocardial and intramyocardial coronary microvessels in open chested, beating heart, animal preparations. The technique was pioneered by Chilian et al*(16)* and involves positioning the microscope within the relevant myocardial territory and recording vessel calibre in much the same way as the pressure

myograph. Pacing and cardiac-cycle synchronised ventilation are required to reduce movement artefact and perturbations in myocardial demand. Vessel diameter can be recorded continuously to determine systolic to diastolic ratios or strobascopically at end diastole to minimise temporal resolution artefact. Cannulation of the epicardial coronary vessels allows the infusion of vasoactive agents. Changes in small vessel resistance can be verified by recording flow within the large feeding vessels concurrently with small vessel diameter*(17)*.

Indirect Assessment – Coronary Blood Flow

The determination of coronary flow remains the cornerstone of human coronary microvascular reactivity assessment. Coronary flow is a good surrogate for microvascular tone as the coronary microvessels are the vascular segments that exert the greatest influence on coronary vascular resistance (in the absence of obstructive large vessel disease). Coronary flow can either be measured indirectly in the epicardial vessels or directly within regions of perfused myocardium. Large vessel flow will always represent the net result of individual vessel tone within the microvasculature. Substantial changes of tone within regions of the microvessel network may not be appreciated if they move in opposite directions (e.g. subendocardial shunting of flow to subepicardium). Direct measurement of microvascular flow can overcome this problem but only if it has sufficient resolution.

Flow assessment techniques either provide an index of flow or measure absolute flow. Absolute total coronary flow provides little meaningful information because of the large variation in resting myocardial demand between individuals. Absolute flow within each coronary vessel is even less useful due to the extreme individual variability in perfusion territory subtended by each coronary artery. Absolute coronary flow must therefore be normalised to myocardial mass for it to be a useful measure of resting microvessel tone*(18)*.

In terms of the in vivo assessment of vasomotor-stimulus induced changes in coronary flow a number of flow-modifying factors may operate concurrently and confound the results. These include; (a) transcoronary pressure gradient shifts, due to aortic or right atrial pressure changes, (b) transmyocardial pressure gradient shifts, caused by changes in intraventricular pressure, (c) variation in myocardial demand caused by changes in peripheral resistance, neurohormones and heart rate (d) variation in heart rate causing changes in diastolic perfusion time.

Coronary Sinus Thermodilution Technique

Coronary blood flow can be estimated by determining flow in the coronary sinus (CS). The anatomy of the coronary venous system is such that the coronary sinus drains 75% of total coronary flow and 85% of left main coronary flow. The rest returns to the heart via the anterior cardiac vein and the thespian veins. If the great cardiac vein is selectively cannulated its flow is closely correlated to that of the left anterior descending coronary artery.

The technique of coronary sinus thermodilution was introduced in 1971. The relatively demanding technique is less frequently utilized today given its measurement limitations (see below) and inability to continuously assess blood flow. Thermodilution uses the same principles as other indicator dilution techniques; the greater the dilution of the indicator, in this case – saline temperature, the greater the blood flow, because greater blood flow transfers more heat to the perfusate. From a practical viewpoint this involves injecting room temperature saline into the CS at a constant rate and temperature via a catheter and accurately recording the increase in downstream temperature with a thermistor attached to the same catheter. Absolute flow is calculated using empirical data derived from an in vitro model. Subsequent in vivo validation studies have shown it to be poorly correlated with coronary flow. For example, it has been demonstrated that a 1cm movement of the catheter within the sinus can cause a threefold change in flow readings and that significant catheter movement occurs even with normal respiration*(19,20)*. This can be exacerbated by increased right atrial pressures and CS reflux. Furthermore the technique can be insensitive for even moderate changes (< 30%) in flow; under reporting flow reserve by up to 90% compared with doppler flow wire. Its main advantage lies in the ability to perform coronary sinus blood sampling (for substrate metabolism) while recording blood flow from the same territory.

Coronary Sinus - Oxygen Saturation

Coronary sinus blood flow can be measured by the Fick principle as well as the thermodilution technique. The Fick principle states that; flow through tissue has an inverse linear relationship to the amount of oxygen extracted from its arterial blood (provided that tissue oxygen consumption remains constant). Stated another way; reduced perfusion allows longer for oxygen extraction, increased perfusion reduces oxygen extraction. As long as myocardial demand remains stable an index

of coronary sinus flow can be calculated by determining the arteriovenous difference in oxygen content. As arterial oxygen content is constant, changes in coronary flow will be reflected in changes in CS venous oxygen content which is measured by oxygen saturation.

The technique can be performed either by CS catheter insertion and intermittent blood sampling, or the use of catheter tipped oxymeters. The technique is more robust than CS thermodilution but suffers similar constraints imposed by measuring the venous outflow*(21)*. CS oxygen saturation is often combined with thermodilution to determine the true stimulus causing changes in blood flow. For example, a pure vasodilator will increase absolute flow, as calculated by thermodilution, without increasing myocardial oxygen consumption – resulting in a rise in CS oxygen saturation. In the case of vasodilatation caused by a pure metabolic stimulus, a flow increase will still be recorded by thermodilution but because myocardial consumption is elevated there will be no corresponding increase in CS saturations.

Coronary Artery Thermodilution

The determination of a flow index for individual coronary vessels using a thermodilution technique has only recently been introduced although the videodensometric principle it is based upon was first described in 1967. It has been validated in animal and humans by electromagnetic flow probe and doppler flow wire data. Early results indicate that it has the potential to be the most accurate method of invasively calculating relative changes in epicardial coronary flow*(22,23)*. The technique uses a thermistor/pressure transducer tipped guide wire inserted a minimum of 6cm into the coronary vessel. A bolus of room temperature saline is rapidly injected via the guiding catheter and the mean transit time (T_{mn}) for the saline bolus (and hence coronary blood) to reach the thermistor can be derived from the thermodilution curve. The inverse of T_{mn}, is an index of coronary flow velocity which has a strong linear correlation with absolute coronary blood flow.

Invasive Intracoronary Doppler Flowire

Intravascular doppler-tip devices can analyse the shift in piezoelectric-generated ultrasound frequency produced by the movement of red blood cell in the blood stream. The magnitude of the Doppler effect is proportional to blood velocity, and the continuous acquisition of doppler-shifted

ultrasound frequencies allows phasic and average blood flow velocity to be measured. This is one of the few techniques that can measure systolic and diastolic phases of coronary blood flow and the most extensively validated. In common with coronary thermodilution it can measure regional coronary flow of each coronary vessel. The piezoelectric guidewire is the only intracoronary doppler device currently in use and as it does not need to be deployed a set distance from the guide catheter, can interrogate each coronary artery irrespective of length. A 12MHz crystal creates a fixed pulse-wave sampling volume which records blood velocity 5mm distal to the wire end to avoid wire-generated turbulence*(25,26)*. The doppler signal is plotted as a continuous spectral trace concurrently with the electrocardiogram. As with coronary-thermodilution determined T_{mn}, flow-wire determined velocity can be used as an index to measure relative changes in coronary flow provided that changes in vessel crossectional area do not occur. Absolute flow can be calculated by multiplying the integral of the spectral velocity trace by quantitative coronary angiography / intravascular ultrasound derived vessel area. Furthermore the deceleration slope of the diastolic flow signal can provide further information regarding flow in the microcirculation. In patients with ischemic impairment of coronary microvascular flow the deceleration half time (DHT) is substantially and significantly reduced compared to normals.

The practicalities of achieving a stable epicardial diameter usually mean pre- treatment with nitrates which have the potential to alter the microvascular response to the studied vasoactive agent. Conversely, substances active on the coronary microvasculature, also can act on large epicardial segments even if only by flow mediated vasodilatation. This means that correct estimation of vessel lumen is essential for most study protocols, and care must be taken to exclude the effects of contrast medium on coronary blood flow if angiography is employed. The other drawback of the technique is achieving a stable, transaxial position of the flow wire. The doppler signal is critically dependent on the angle between the crystal and the direction of coronary flow. This angle can change with vessel movement through the cardiac cycle or during intracoronary injections*(27)*.

Non-invasive Transthoracic Coronary Doppler Techniques

It has been possible to measure coronary artery velocity with transthoracic doppler since 1987. However it has only become feasible, in most patients, following recent technical advances in ultrasound technology (high-resolution 2-dimensional and colour flow doppler transducers with harmonic imaging). It is currently possible to get doppler data from the LAD in 90% of transthoracic

echocardiogram studies as it lies only a few centimetres from the chest wall. The RCA is a deeper structure and can only be visualised in 75% of cases. The circumflex is not amenable to interrogation. It is a non invasive technique, which is inexpensive and repeatable. The benefits are tempered by a number of important drawbacks; (a) limited access to all myocardial territories (b) velocity data only (not able to assess epicardial disease or epicardial dimensions) (c) moderately high inter- and intra-observer variability. As a result it can only realistically provide an index of coronary flow within the LAD and the confounding effect of changes in LAD diameter cannot be excluded*(30-32)*.

TIMI Flow Grade / Corrected TIMI Frame Count

The corrected TIMI frame count technique (CTFC) is variation on the theme of indicator-derived coronary transit time (the same principle used by coronary thermodilution). It involves calculating the number of cine frames (as a measure of time) for angiographic contrast to reach a predefined landmark (distance) to derive an index of coronary velocity and hence flow. Angiographic contrast has been validated as an accurate flow tracer and a correction factor has been determined to normalise the longer of the left anterior descending artery length to that of the circumflex and right coronary arteries. CTFC is a more quantitative adaptation of the categorical TIMI flow grade scheme which was first introduced to assess flow post myocardial infarction in 1985. TIMI grading utilises cardiac cycles to measure contrast transit as follows; (a) Grade 0, no contrast progression (b) Grade 1, contrast progression insufficient to opacify vessel (b) Grade 2, ≥ 3 cardiac cycles for full coronary opacification (c) Grade 3, < 3 cardiac cycles for coronary opacification. This grading scheme, although normalising flow for heart rate, suffers from poor inter-observer agreement, can only determine gross differences in flow and does not correct for vessel length. Furthermore, no significant differences in flow exists between grades 1 and 2 as determined by doppler flow wire, and a large overlap in velocities exists between grade 2 and 3.The CTFC was introduced by Gibson to provide a simple, continuous angiographic measure of coronary flow without the need for excessive intracoronary instrumentation. It has been validated with doppler-determined coronary flow over a range of flow states (r^2=0.5-0.6) and discrepancies appear to be due to cTFC measuring average flow velocity as opposed to doppler which measures point velocity. It is not affected by injection variables (speed, volume or timing). It is however, predictably altered by changes in epicardial diameter produced by nitrates. 1-2 minutes must be left between injections to allow the brief, contrast- induced vasodilatation of coronary resistance vessels to

subside*(33-40)*

Videodensitometry/Myocardial Blush

The assessment of angiographic contrast appearance in the myocardium provides a direct, semi-quantitative measure of microvascular flow. Videodensitometry is an offline technique whereby contrast time-density curves are derived in myocardial regions of interest after the epicardial injection of radio-opaque contrast. Time from the beginning of ECG triggered contrast injection to the peak of the myocardial time- intensity curve is measured usually in cardiac cycles. The myocardial blush grade (MBG) is a simplification of the videodensometric technique and involves subjective grading of myocardial contrast appearance (blush) according to the following scale; 0, no myocardial blush; 1, minimal myocardial blush; 2, moderate myocardial blush but less than that obtained during angiography of a contralateral or ipsilateral coronary artery; and 3, normal myocardial blush or contrast density. Given its qualitative nature MBG, can only provide information of gross regional differences in microvascular coronary flow and has relatively poor inter- and intra-observer agreement*(42-43)*. Both methods have shown that discrepancies exist between epicardial flow and myocardial flow, with myocardial perfusion often being impaired in the presence of normal large coronary flow.

Echocardiography – Myocardial Contrast

Myocardial contrast echocardiography (MCE) offers substantial improvements over the videodensitometry techniques as it can measure the regional myocardial blood volume as well as microvascular blood velocity and has sufficient resolution to assess differences in transmural perfusion. It is one of only two techniques able to perform frequent, longitudinal assessment of coronary flow reserve. MCE utilises gas filled microbubbles that are inert, remain entirely within the vascular space, possess an intravascular rheology similar to that of red blood cells and, with a mean diameter of ~4μm, cross the pulmonary capillary bed unrestricted. During intravenous infusion and following the attainment of a steady state, the microbubbles are destroyed with a burst of high energy ultrasound within the scan plane. The rate of myocardial microbubble replenishment is measured, which represents mean red blood cell velocity (β). In the normal resting state the scan plane refills within 4 to 5 seconds and at maximal hyperaemia (~ 4 times baseline coronary flow) normal replenishment occurs within one second. At plateau replenishment myocardial contrast intensity represents relative blood volume within the scan plane which can be normalised to the LV

cavity signal to give myocardial blood volume fraction (A). This is multiplied by the rate of replenishment (velocity or β) to derive an accurate index of myocardial flow - Aβ. The MCE flow index is closely correlated with absolute coronary flow and can accurately measure relative changes in flow in response to vasoactive agents. Because the capillaries constitute 90% of the myocardial vessels and do not respond to vasoactive stimuli, myocardial blood volume does not change between high and low flow states *unless there is an epicardial stenosis*. In this scenario endocardial arterioles beyond the stenosis are maximally dilated at rest. Epicardial arterioles however, remain partially constricted, thereby maintaining pressure within the system and preventing transmyocardial steal. With a vasodilatory stimulus the epicardial arterioles open and effectively depressurise the system resulting in capillary collapse (de-recruitment) beginning in the endocardial layers. This results in a regional loss of myocardial blood volume and hence ultrasound signal. A reduced contrast signal is also seen when imaging infracted / non perfused tissue. Hence, when imaging myocardium subtended by normal large coronary vessels A is not required. The main drawback with MCE derived myocardial flow is movement artefact. The technique is critically dependent on destroying and then recording contrast replenishment within the same myocardial scan plane. This is no thicker than 5mm and often less than 1mm at the focus. Cardiac translation caused by base to apex shortening and rotation results in areas of the myocardium being imaged at different times during the cardiac cycle. Respiratory translation compounds the problem. Both can be avoided by ECG triggering and breath hold. ECG triggering however reduces the number of data points used for calculating the replenishment-time curve, requiring replicate imaging for each area of interest. As a consequence the technique is time consuming and lacks sensitivity in difficult to image subjects*(44-48)*.

Positron Emission Tomography

PET scanning remains the gold standard for the non-invasive assessment of coronary microvascular flow, because flow can be measured absolutely and adjusted for tissue mass, allowing valid comparisons between individuals' resting coronary microvessel tone as well as reactivity. Positron emitters are formed when neutrons are added to the nucleus of normal elements resulting in nuclear instability and decay. When positrons are released they annihilate on contact with nearby electrons to form 2 photons of identical energy that are released in exactly opposite directions and can be detected by a coincidence circuit within a scanner. By building up positron counts in a tomographic fashion, 2 dimensional planes through the ventricle can be reconstructed. Intraventricular blood pool counts can also be measured. By determining the amount of myocardial uptake relative to

the arterial tracer concentration and using a validated kinetic model, tracer counts can be converted to absolute units of flow per minute per gram of tissue. The resolution of the technique is sufficient for the assessment of flow within 480 individual myocardial segments allowing quantitative assessment of microvascular flow heterogeneity. The technique is critically dependent on a positron emitting agent that is completely extracted by the myocardium in direct proportion to the local blood flow, and is not influenced by myocardial metabolism. In this regard oxygen-15 labelled water is regarded as ideal as it is metabolically inert and freely diffusible. However it produces images of less impressive resolution than nitrogen-13 labelled ammonia which is almost as good. Both agents have a limited half life which allows multiple studies over a short period. PET is particularly useful in instances of diffuse microvascular impairment*(52-53)*.

MRI-Myocardial Perfusion

An index of myocardial perfusion by MRI has been validated for the quantification of changes in transmural blood flow. Early studies suggest that this modality has the greatest resolution of any technique yet available. A standardised bolus of gadopentetate dimeglumine is given intravenously by power injection followed by rapid image acquisition. Regions of interest are drawn on the Epicardial and endocardial short axis images and propagated automatically throughout the perfusion series. Curves showing signal intensity plotted against time are constructed for each region of interest. Curve fitting is used to obtain the slope of the first-pass contrast enhancement which when normalised to the slope within the left ventricular cavity can be used as and index of myocardial blood velocity and hence flow. The technique has been validated for large and small coronary disease.

Electron beam CT has encouraging data for assessing myocardial blood flow in animal models. EBCT derived coronary flow reserve, in particular shows a strong correlation with doppler derived flow data and may even be able to differentiate arteriole from capillary flow*(54,55)*.

ASSESSMENT OF MICROVASCULAR FUNCTION / REACTIVITY

The assessment of the cardiac microvasculature is usually performed as an adjunct to large vessel assessment, be this for the indirect diagnosis of epicardial stenosis or for determination of the downstream effects of epicardial plaque rupture. Consequently the microvascular vasoactive

stimuli used and validated are predominantly vasodilators (either to provoke regional differences in myocardial flow or to reverse impaired microvascular flow). With the emergence of cardiac syndrome x as a clinical entity the direct assessment of the coronary microvascular response to endothelium specific agents and putative vasoconstrictors as well as the above mentioned vasodilators, has been conducted but published data remains limited.

Coronary Flow Reserve

Coronary flow reserve (CFR) is a widely applied method for assessing the human coronary microcirculation. It is used primarily in the context of epicardial disease to determine functional stenosis severity. It can be performed utilising any technique that can quantitate coronary or myocardial blood flow or velocity. Validated techniques include; CS thermodilution, CA thermodilution, CA doppler (intracoronary and transthoracic), myocardial contrast echo, TIMI frame count and PET. Intracoronary doppler is currently the gold standard, however PET provides the best resolution. When large vessel stenosis is absent CFR can be used for 'pure' assessment of the vasodilator response of the coronary microcirculation. In simple terms, CFR measures the relative capacity of the coronary microvasculature to maximally dilate from a resting level of vasomotor tone. In reality a number of factors other than vasorelaxation determine CFR and include; (a) the level of resting vascular tone (b) the perfusion pressure and total crossectional area of the resistance vessels at peak vasodilatation (c) the blood viscosity*(56,57)*

Determinants and Limitations of CFR

As previously stated CFR is designed to assess the vasodilatory capacity of the microvasculature. Unfortunately it cannot determine the underlying mechanism of reduced capacity. A number of confounding factors can cause false positive and negative results by either increasing resting blood flow or reducing maximal flow.

A. Resting flow is set by auto regulatory mechanisms as described by Mosher in 1964 and is largely determined by myocardial oxygen demand. Any condition that increases myocardial metabolism above normal will artefactually reduce CFR;
   - Heart rate: thyrotoxicosis, fever, anaemia

- Wall stress: hypertension, heart failure, valvular disease
- Pre/afterload: hypertension, heart failure, renal failure

B. Reduced maximal flow: maximal flow follows a steep, linear flow-pressure relationship. Any condition, other than an intrinsic microvascular disorder, that reduces the maximal flow for a given perfusion pressure (i.e. reduces the slope of the flow-pressure relationship) will artefactually reduce CFR.
   - extrinsic compression, (phasic and/or continuous): tachycardia, left ventricular hypertrophy, elevated end diastolic pressure.
   - Reduced microvascular crossectional area: infarction, left ventricular hypertrophy (LVH)
   - Increased viscosity: polycythemia.

In reality the main confounders are very rapid tachycardia, elevated ventricular filling pressures and LVH (which can be corrected for if ventricular mass is known). The other significant drawback is the limited resolution of the flow measuring modalities.Flow is spatially and temporally heterogeneous within the myocardium, particularly between the sub and epicardium*(58-60).*

Endothelial Function

Most studies dealing with the endothelial control of vascular tone have examined large conduit arteries. Coronary microvascular endothelial vasomotor function has also been evaluated, in a limited number of studies, with: (a) acetylcholine, L- arginine, (b) serotonin, (c) atrial natriuretic peptide and (d) substance P. These substances can induce vasodilatation only in the presence of an intact endothelium, while their effects may be reduced or even reversed in the presence of endothelial impairment. Pacing has also been used to examine endothelium derived, flow mediated vasodilatation. Zeiher *et al*., found that intracoronary injection of acetylcholine increased myocardial blood up to 140% in normals. In patients with non flow-limiting coronary atherosclerosis, however, the increase was limited to 12% (in the presence of preserved adenosine-derived coronary reserve). These findings document the possibility of selective alteration of endothelial control of microvascular tone.

Golino et al., using a similar patient population and techniques, documented absolute constriction of the microvasculature to serotonin, rather than reduced vasodilatation. A significant correlation in patients with cardiac syndrome x, between the threshold for exercise-induced ECG changes and reduced acetylcholine-induced intracoronary flow has also been demonstrated. Although these studies demonstrate the endothelium may be important for the regulation of coronary microvascular tone in certain disease states, the data should be interpreted with caution. For example, it is generally accepted that acetylcholine produces endothelial mediated vasodilatation as well as a direct vasoconstrictor effect on the coronary smooth muscle. However, the net response depends as much on the applied dose as endothelial integrity. This is highlighted by vasoconstriction to acetylcholine in the presence of vasodilatation to pure endothelial agonists in large vessels. Whether these differences are also present in the coronary microvasculature and the role endothelial impairment plays in coronary microvascular disease remains largely unknown*(61-66)*.

CLINICAL ASSESSMENT OF MICROVASCULAR DYSFUNCTION

Direct visualisation of the coronary microvessels in the clinical setting is not possible. Nevertheless, by simultaneously assessing epicardial vessel diameter and myocardial blood flow/perfusion (directly or indirectly) vasoconstriction of coronary microvessels can be assumed when alterations in blood flow cannot be explained by changes in large artery calibre. The measurement of alterations in cardiomyocyte homeostasis caused by ischaemia is thought to be the most clinically relevant assessment of impaired microvascular function (in the presence of normal epicardial vessels). A number of research and clinical techniques are available to measure these alterations.

Indirect Visualisation

Coronary Angiography

Direct evaluation of changes in vessel diameter can be obtained in man by quantitative angiography or intracoronary echo, however these techniques can only explore epicardial vessels no smaller than 0·5–2 mm in diameter. Investigators have inferred that constriction of vessels at the lower limit of angiographic resolution may also extend to smaller vessels. In the study of vasoactive drugs,

McFadden and co-workers analysed coronary angiograms in patients before and after the intracoronary injection of serotonin. These authors noted that vasoconstriction, in response to serotonin, was more marked in distal segments of the arterial tree. Accordingly, they speculated that this constriction might also affect the coronary microvasculature. Similar results have been also obtained with intracoronary acetylcholine. A further example is the study by Pupita et al., who evaluated patients with proximal epicardial vessel occlusions supplied distally by collateral circulation. In these patients, episodes of resting myocardial ischaemia were associated with angiographic disappearance of the collateral vessels*(67)*.

Thus, angiographic studies have been used as indirect evidence of the participation of coronary microcirculatory disturbances in the genesis of myocardial ischaemia. However, this technique does not provide any insight into the microvascular segment involved or the mechanism of the disorder. To obtain this data, the use of angiography with methods able to evaluate regional myocardial perfusion is necessary.

MCE and MRI

MCE is a sensitive technique for qualitatively assessing impaired microvascular flow. Using techniques to completely suppress the tissue signal, relative differences in the amount of contrast (and hence perfusion) present within transmural regions and between coronary territories can be assessed. Flash destruction of contrast by a high intensity pulse, followed by observation of its relative time to reperfuse increases the sensitivity of the technique. MRI uses a similar principle whereby relative differences in contrast accumulation between and within myocardial segments, following intravenous administration of contrast are recorded*(68)*.

Evaluation of Microvascular Ischaemia

In the assessment of coronary microvascular reactivity, ischaemia is seen as a gold standard end-point because, on face value, it provides a clinically meaningful measure of abnormalities in vasomotor response. Myocardial ischaemia develops whenever the flow of arterial blood through constricted or obstructed vessels is inadequate to meet the metabolic needs of the myocardium. There is a characteristic sequence of events that occurs following interruption to the supply of arterial

blood. Tissue oxygen tension diminishes due to consumption of oxygen in its freely diffusible form as well as from stores of oxymyoglobin. Intracellular respiration shifts from its aerobic (free fatty acids) to its anaerobic form (glucose). Adenosine triphosphate (ATP) stores are rapidly depleted, causing adenosine diphosphate (ADP), adenosine monophosphate (AMP) and adenosine to accumulate(69). Shortly thereafter, the ischemic region of the myocardium loses its ability to maintain the negative resting membrane potential. Depleted supplies of ATP and the competition of H^+ for Ca^{+2} cause the cessation of cardiac contraction. Characteristic metabolic changes occur in the ischemic tissue, including an accumulation of tissue lactate, H^+ ions, phosphate, and potassium. There is also a rise in tissue tension of carbon dioxide (P_{CO2}). Mitochondrial calcium increases as well, which may contribute to ischemic akinesis. If myocardial reperfusion is rapidly re-established, however, cellular function can return to near baseline levels. Irreversible damage to mitochondria and cell membranes causes the release into blood of numerous plasma markers, which can be used to quantify the degree of myocardial necrosis. Markers of cardiac myocyte death appear in the plasma as plasma membrane integrity is compromised; these include enzymes such as lactate dehydrogenase (LDH), creatine phosphokinase (CK), serum glutamic oxaloacetic transaminase (sGOT), and other intracellular proteins, such as myoglobin and troponin T and I. Ischemic perturbations in myocyte homeostasis can be detected by the ECG, myocardial scintigraphy, echocardiography and sampling for ischemic metabolites. Reduced perfusion can be detected by the techniques already described.

ECG

The ECG is the most frequently used technique to detect ischaemia. Reuptake of potassium is reduced and the formation of lactic acid increased during ischaemia resulting in reduction in amplitude and duration of the action potential and a reduction in the resting membrane potential. This produces potential difference between normal and ischemic myocardium following repolarisation resulting in a 'current of injury' and depression of the ST segment. ST segmental shifts are however not specific for ischaemia and regional impairment of potassium handling in the absence of ischaemia has been demonstrated to produce false positive results particularly during exercise*(70-73)*.

Echocardiography

Impaired wall motion is a relatively late manifestation of myocardial ischaemia and is caused by homogeneous ischaemia of large regional myocardial segments. Hence echocardiographic assessment

of wall motion is specific but not sensitive particularly if there is patchy ischaemia in multiple coronary territories*(74)*.

Myocardial Scintigraphy

Scintigraphic assessment of ischaemia involves imaging the distribution of radionuclide tracer within the myocardium following metabolic uptake. Thallium (^{201}Tl) is a gamma emitting potassium analogue which is both passively and actively (via the sodium/potassium ATPase pump) taken up by myocytes. It has high first pass metabolism and there is a linear relationship between blood flow and ^{201}Tl accumulation. The agent demonstrates washout from normal tissue and wash in to ischemic tissue over time.

^{99m}Technetium labelled Sestamibi and Tetrofosmin are the most frequently used gamma emitting agents. After administration they are trapped within the mitochondria during first pass circulation. Mitochondrial uptake is a function of myocardial perfusion to viable tissue. Although these gamma emitting scintigraphic agents require non-ischemic tissue for uptake their strength resides in their ability to detect regional differences in myocardial blood flow. Perfusion defects however commonly occur in the absence of ischaemia. False positive results may also occur due to soft tissue attenuation.

Positron emitting agents overcome this lack of specificity for ischaemia by tracing differences in metabolite utilisation. During ischaemia oxidative phosphorylation of fatty acids ceases and anaerobic metabolism of glucose occurs. Using positron emitting analogues of glucose and free fatty acids, areas of ischaemia can be specifically imaged.

MRI Spectroscopy

Is a sensitive method of identifying ischaemia pioneered by Bottomley et al*(75)* It involves defining the intrathoracic volume containing the heart and then acquiring the radiofrequency signal particular to 31-phosphorous from within the volume. Phosphorous contained within different molecules produces different peaks along the spectral trace. Ischaemia causes a fall in phosphocreatine relative to ATP which has been validated in patients with large and small vessel coronary disease. The main problem with the technique is its inability to localise the site of ischaemia within the myocardium and

not being able to include the posterior wall in the sample volume in all patients*(75,76)*.

Biomarkers of Myocardial Ischaemia

Metabolic markers for ischaemia can be divided into those that occur as a direct result of ischaemia and those that occur as a consequence of ischaemia-induced infarction. Myocardial lactate production has traditionally been the gold standard for the detection of ischaemia. Lactate production is the result of anaerobic metabolism of glucose. Lactate, when present in arterial plasma, is used by the non-ischemic myocardium as an energy substrate. Hence in the normal situation there is net transmyocardial lactate extraction. However, reduced lactate extraction can be due to inhibition of lactate uptake by free fatty acids as well as ischaemia. Hence, this test, although specific, has poor sensitivity due to heterogeneous lactate production and consumption both within and between myocardial regions in addition to the regional limitations imposed by CS sampling. pH measurement from the CS, is a simple technique to indirectly measure lactate and is able to provide continuous data, however it does not overcome the above limitations and is less specific for ischaemia. Ischaemia-modified albumin (IMA) is a new biomarker that is highly sensitive for ischaemia in preliminary studies. The discovery that albumin, in the serum of patients with myocardial ischaemia, exhibited lower metal-binding capacity for cobalt than the albumin in serum of normal subjects was made by Bar-Or et al. In sera from patients with ischaemia, less cobalt is bound by the IMA, leaving more free cobalt to react with an indicator. Significant changes in albumin-cobalt binding occur minutes after transient ischaemia and return to baseline within 12 h. IMA is the result of reactive oxygen species (ROS) modifying albumin within the coronary circulation. ROS are produced when ischaemia activates the oxidative mitochondrial respiratory chain and endothelial xanthine oxidase. IMA has a high negative predictive power for ischaemia in the clinical setting, but is not specific for cardiac ischaemia or cardiac region of ischaemia. Furthermore, whether this test is sufficiently sensitive to detect small zones of ischaemia associated with small vessel disease is unknown. Lipid peroxidation products are also generated by the actions of reactive oxygen species which occur as a result of myocardial ischaemia. Current data would suggest that they are the most accurate ischemic markers yet found. Rapid and sustained elevations occur following brief large vessel occlusion and they are also elevated in active coronary microvascular disease. However CS sampling is required as well as sophisticated and prolonged chromographic analysis which limits the use of the technique*(77,78)*.

Biomarkers of infarction are released following loss in membrane integrity. Troponin and creatine kinase are the most thoroughly validated. Troponin has largely replaced CK due to its higher sensitivity to smaller myocardial injury and its virtually total specificity for cardiac damage. Despite the ability to detect quantitatively smaller degrees of myocardial necrosis, cardiac troponins need 4–10 h after symptom onset to appear in serum, and remain elevated for prolonged periods, making the determination of ongoing myocardial damage difficult. The main drawback of both markers is their complete lack of specificity for the aetiology of myocardial injury.

THE CORONARY SLOW FLOW PHENOMENON

The coronary slow flow phenomenon (CSFP) has been defined as a coronary microvascular disorder characterised by the delayed passage of angiographic contrast in the absence of obstructive epicardial coronary disease. It is observed in 1% to 7% of unselected patients undergoing angiography, 40% *(3,4)* in the subgroup of patients with angiographically normal arteries and in 16% of those meeting the diagnosis for Coronary Syndrome X. In those having angiography for rapid assessment of unstable angina (UAP) it is evident in 4% of patients (30% of UAP patients without obstructive epicardial disease)*(79,80).* It is a separate entity from no-reflow (even though the angiographic appearance may be similar) which is predominantly observed in the setting of primary angioplasty following prolonged thrombotic occlusion of an epicardial vessel. It has variably been labelled as 'slow coronary flow', 'slow flow velocity', slow coronary run off' and 'slow dye progression' since its first description in 1972 by Tambe et al. In Thrombolysis In Myocardial Infarction III A (TIMI IIIA) study, among patients presenting with unstable angina, 4% had normal coronaries with impaired coronary filling suggestive of CSFP. Mangieri et al reported 7% incidence of the phenomenon in patients suspected to have CAD.

Method of Assessment

In a similar manner to blood pressure measurement, coronary flow velocity appears to exist along a bell shaped continuum. The cut-off velocity for categorical definitions of CSFP is entirely arbitrary, and includes:- (a) TIMI grade 2 or less flow (b) Corrected TIMI frame count (CTFC) above normal mean value (21 frames) (c) cTFC of 1 or more, or 2 or more standard deviations above normal (24, 27 frames respectively)(2). CSFP was initially assessed subjectively by visual

judgement. TIMI flow grade classification is a semiquantitative assessment of coronary blood flow. This grading system reflects the speed and completeness of passage of the contrast through the coronary tree. This is a widely used method of grading of coronary flow. It has been a valuable tool for comparison of flow data in clinical trials. But variability in the visual assessments limits its broad clinical applicability. This is a qualitative method of assessing coronary flow. It is limited by significant inter observer variability. Conventionally, the contrast injected to the coronary arteries opacifies the distal vascular bed within 3 cardiac cycles (evidenced objectively by 3 cardiac contractions). This is prolonged in coronary slow flow phenomenon*(2)*.

TIMI FLOW GRADES
TIMI 3 – Normal distal run off – Contrast flows briskly into the distal distal segment and clears rapidly.
TIMI 2 – Good distal run off – Contrast material opacifies the distal bed but slowly. Contrast clears slowly from the distal bed as compared with a comparable segment of another vessel.
TIMI 1 – Poor distal run off – Portion of contrast material reaches the distal bed but distal bed is not opacified fully.
TIMI 0 – Absence if distal run off – No contrast material reaches the distal bed.

In contrast CTFC (corrected TIMI frame count) provides an objective and quantitative index of coronary fow. It facilitates the standardization of TIMI flow grades and flow assessment. It represents the number of cine frames the contrast injected into the coronaries takes to travel from the proximal to distal vascular bed. CSFP is defined as CTFC greater than 2 standard deviations from the normal published range for that particular vessel. CTFC is a more quantitative and reproducible index of coronary artery flow.

Distal landmarks used commonly in the analysis are as follows

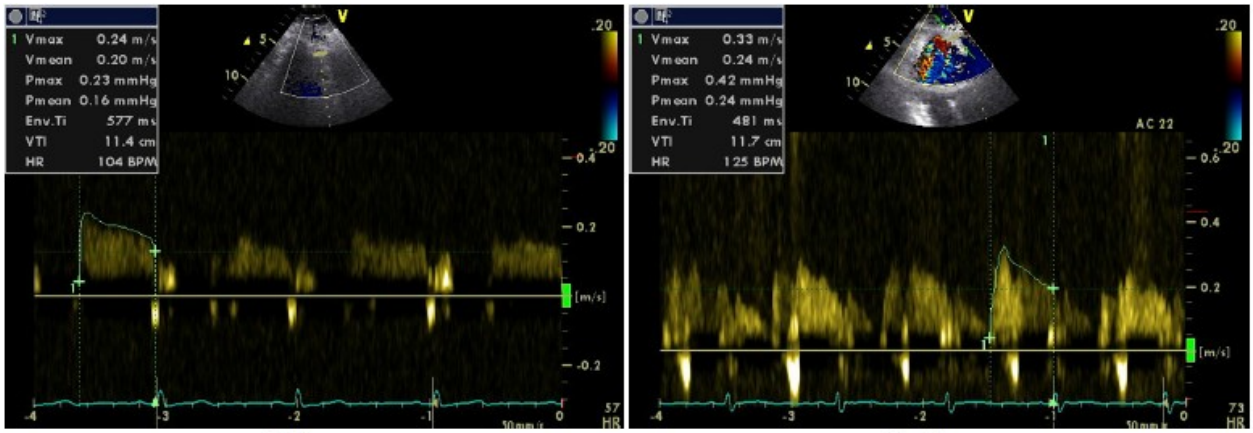
1. The distal bifurcation for the left anterior descending artery(LAD).
2. Distal bifurcation of the branch segments with the longest distance for the left circumflex artery(LCx).
3. The first branch of posterolateral artery for the right coronary artery.

The corrected TIMI frame count is obtained by normalizing for the length of the LAD as compared with the other 2 arteries. CTFC accounts for the distance the dye has to travel in the LAD relative to the arteries. The length of LAD, LCx and RCA on an average are 14.7, 9.3 and 9.8 respectively. CTFC divides the absolute frame count in LAD by 1.7. TFC(TIMI frame cont) for LAD, LCx and RCA are 36+/-3, 22+/-4 and 20+/-3 respectively. Each has CTFC of 21+/-2. High CTFC is associated with microvascular dysfunction. CTFCs of <20 frames are associated with normal microvascular function. Gibson et al and Kern et al suggested visual estimates of TIMI flow bear little relationship to the quantitative TIMI frame count. Injection techniques can also impact on the CTFC. Using 7F diagnostic catheters, mean increase of 1mL/s of hand injection can induce a reduction of 2 frames in the CTFC.

As can be seen, the TIMI flow grade definitions of coronary slow flow are set at a substantially higher flow velocity threshold than the TIMI frame count definitions. Using published data, approximately 43% of CTFC defined slow flow patients would not meet the TIMI grade 2 slow flow definition and would also be unlikely to meet the original qualitative definition of slow flow as described by Tambe(83). It should be appreciated that a very wide range exists for normal resting volumetric flow and that this is even greater for flow velocity due to the added variable of vessel calibre. Hence to achieve adequate specificity for those with 'truly' reduced coronary flow, a flow velocity threshold must be set well below the accepted normal value.

The TIMI 2 definition meets these criteria and is supported by validated outcome data albeit from reperfusion trials. Limited data suggests an inverse correlation between flow velocity and chest pain symptoms. Consequently patients defined by lower velocity thresholds may be quite different to those selected by a higher cut-off. By using CTFC as a quantitative index of coronary flow, coronary angiography is the only tool for the diagnosis and assessment of CSFP. This method does not permit long-term clinical follow-up and dynamic treatment evaluation of CSFP due to the invasiveness of coronary angiography. Transthoracic Doppler echocardiography (TTDE) have enabled the non-invasive

demonstration of coronary flow patterns in the left anterior descending (LAD) coronary artery. Measurement of coronary flow in the distal LAD using TTDE technique with a high success rate (92.3%). Patients with CSFP exhibited lower coronary diastolic velocities of LAD, which was negatively correlated with CTFC. TTDE may provide a useful tool for the monitoring of treatment effect and long-term follow-up for CSFP. However, there is a lack of confirmation in clinical trials, and there is need for further evaluation of TTDE in the diagnosis of CSFP*(84-90)*.



CSFP group Control group

CLINICAL FEATURES

Demographics

Tambe et al first described the CSFP when he reported the clinical and haemodynamic features of 6 cases in 1972. Most had chest pain that was consistent with stable or unstable angina, but no history of other cardiac disease or cardiovascular risk factors. A number of case series have subsequently been published and have consistently shown the phenomenon to occur in a unique demographic group. Patients with the CSFP are characterised by:-

- Preponderance of middle aged males. In the largest series, 79% of the study population was male with a mean age of 52 years. In other trials the proportion of males range from 47 to 88% with average ages between 48 and 57.

- Most have mixed pattern angina with many (30 – 94%) experiencing symptoms indistinguishable from unstable angina. Only a small proportion primarily exhibit symptoms of stable angina.

- Ongoing chest pain symptoms despite treatment with many undergoing repeat invasive and non invasive investigations.

Only one large case control series has been published comparing the CSFP group to patients also lacking obstructive coronary disease but with *normal* flow velocity. The results were consistent with the above data but new findings emerged:-

- Patients with the CSFP were younger, more likely to be male, frequently had multiple coronary risk factors and were often active cigarette smokers.
- Typically, patients with the CSFP were more likely to present with acute onset rest/mixed pattern angina and an abnormal ECG, prompting emergency admission and rapid angiographic assessment. This is consistent with the findings from the TIMI IIIA trial which demonstrated the CSFP in a high proportion of patients with non obstructive coronary disease presenting with unstable angina.
- The control group, in contrast, usually presented with chronic exertional chest pain, a positive stress test and underwent angiography on an elective basis. Half met the criteria for CSFP*(91-97).*

Clinical Manifestations

Coronary slow flow phenomenon is a frequent angiographic observation with a reported incidence of 1% to 7% in patients undergoing diagnostic coronary angiography for angina. CSFP occurs commonly in young men and smokers. CSFP may present at times with features suggestive of acute coronary syndrome. Clinical course is variable. Upto 80% of patients experience recurrence of chest pain; may be occurring at rest. Upto 20% of patients necessitates admission to coronary care units. CSFP has been described to be associated with life threatening arrhythmias and sudden cardiac death. Arrhythmic potential of CSFP is probably contributed to by the increased QTc dispersion in these patients. Yilmaz et al delineated clinical and laboratory features of CSFP. Metabolic syndrome was more frequent in CSFP in the presence of high total cholesterol, high low density cholesterol, high fasting blood glucose levels and high body mass index. These data are in line with the observations that insulin resistance states and impaired glucose tolerance correlate with CSFP occurrence. These data suggest a common pathogenic

mechanism for CSFP and metabolic syndrome. The underlying pathology in both is probably endothelial dysfunction.

Non Invasive Investigations

ECG/Exercise Stress Findings

Controlled data suggests that those with the CSFP are significantly more likely to have resting non-diagnostic ST/T wave changes (49 vs. 21%). Other studies have reported a wide range in both the type and prevalence of ECG changes at rest, including episodes of non sustained ventricular tachycardia and increased QT Dispersion which may indicate low grade myocardial ischaemia. During spontaneous episodes of chest pain, ECG changes consistent with ischaemia are found in approximately 30% CSFP patients and are present in all those who subsequently have evidence of infarction. In terms of inducible ECG changes with exercise stress, reports vary widely form none to all. In the larger series, half or less of

CSFP patients tested had an ECG positive for ischaemia. When compared to a control group there was a trend for CSFP patients to have less exercise induced ECG changes (20 vs.39%, p=0.07) in a study by Beltrame et al.

SPECT Scintigraphy

Two studies have specifically examined CSFP patients with myocardial SPECT scintigraphy. Ciavolella et al performed exercise radionuclide ventriculography and perfusion studies in 21 patients with the CSFP. The ^{99m}Tc-sestamibi scintigraphic studies showed abnormalities in regional wall motion in 81% patients and perfusion defects in 86% patients with 76% patients having abnormalities in both parameters. 70% of these defects occurred in area supplied by vessels affected by the CSFP. Ceasar et al studied 17 slow flow patients and revealed thallium defects in 76% with a 92% concordance between perfusion defects and coronary slow flow territories. Other studies that have looked at scintigraphic perfusion report reversible changes in between 26 to 84% of patients.

Echocardiography

Most studies report normal findings. Beltrame et al found no evidence of left ventricular disease in over 90% of a 64 patient CSFP cohort. Small numbers of slow flow patients do, however, show evidence of LVH, dilated cardiomyopathy, diastolic impairment of left ventricular filling and resting regional wall motion abnormalities consistent with previous infarction (despite normal coronary vessels). Stress echocardiography has not been studied in this group.

Infarction Biomarkers

Little data exists regarding release of myocardial biomarkers associated with the CSFP. Beltrame et al. have reported CK rise consistent with infarction in 6% of CSFP patients compared to no rise in the control population. In observational series an infarction rate of 8 to 9% has been reported.

Coronary Angiography

Early investigators systematically excluded artefact induced by the contrast injection process as a potential cause of the phenomenon. No appreciable difference in the phenomenon was observed despite changing the operator, the catheters and the injection amount, velocity and timing. Perturbations in perfusion pressure at the time of the phenomenon were also excluded. Subsequent research on healthy normal subjects, has shown that contrast progression is independent of catheter size, injection velocity/amount and shows <5% increase in transit time if injected in systole compared to diastole. In most studies, the left anterior descending and circumflex arteries are the most and least affected vessels, respectively, despite their common origin from the left main coronary artery, which provides further evidence against the condition being an angiographic artefact. The strongest evidence against the phenomenon being an artifact or a haemodynamic aberration is provided by a controlled angiographic study by Beltrame et al. Using a standardised technique, performed by the same operator they were unable to demonstrate differences in left ventricular function, large vessel diameter, heart rate or blood pressure between the CSFP and control groups*(3)*.

Depending on the definition between 60 to 100% of coronary vessels demonstrate slow flow in any given CSFP patient. Most studies exclude coronary ectasia as it has been shown to reduce coronary velocity in the presence of normal coronary flow. Even if all vessels with slow flow are included,

angiographically smooth contoured vessels are found in 74% of patients, suggesting that the phenomenon is not a condition of excess large vessel capacitance or deformity in the majority.

Beltrame et al. have studied the persistence of the phenomenon over time and its relationship to anginal symptoms. In 12 CSFP patients, angiography was initially conducted during or immediately after periods of significant chest pain. Angiography was then repeated when the patients were asymptomatic and revealed that only 30% of patients continued to meet criteria for slow flow, implying an association between flow rate and symptomatic status. However, compared to controls, angiographic flow velocity in the non-TIMI 2 vessels was still significantly reduced, suggestive of chronically abnormal coronary flow with a dynamic component. Persistence of the phenomenon at time points up to 10 years apart has been demonstrated indicating a chronic process.

IVUS

Cin et al. have published unblinded but controlled data regarding the intravascular ultrasound characteristics of the epicardial vessels in patients with the CSFP. They demonstrated that intima media thickness of patients with the CSFP was twice that of the control group ($p< 0.001$), even though both groups were well matched in terms of cardiovascular risk factors. This observation was diffusely present and was frequently associated with confluent or discrete calcification. There was a strong inverse correlation between intima media thickness and coronary flow velocity.

Prognosis

The long term clinical course of these patients was first examined by Ciavolella et al who asked 21 CSFP patients to complete questionnaires after a mean follow-up period of 91±44 months. During this period, no patient had experienced a major cardiac event but over 50% described their symptoms as unchanged or deteriorating. Although this study portends a good prognosis from a cardiac event perspective, at least one case report describes a patient presenting with an anterolateral myocardial infarct.

Beltrame et al followed 64 patients for a median period of 21 months. During this period 84% continued to experience chest pain with a third presenting to the emergency department because of severe pain and 29% required admission to the coronary care unit. Although there were no

myocardial infarctions, two deaths occurred in the follow up period. One patient died in hospital of non-cardiac causes but a second died suddenly from an apparent coronary event. Voelker et al followed angiographically normal patients with chest pain, both with and without the CSFP, for 9 years and showed that 81% of slow flow patients (compared with 46% of normal flow patients) continued to experience angina.

HISTOPATHOLOGY

Mosseri et al undertook right ventricular endomyocardial biopsies in 6 patients with documented CSFP. These demonstrated histologically abnormal small coronary arteries with fibromuscular hyperplasia, medial hypertrophy, myointimal proliferation and endothelial degeneration. Electron microscopy of these specimens showed degenerative foci in most myofibrils with lipofuscin deposits. The most consistent finding in the specimens was endothelial swelling and degeneration resulting in luminal narrowing. Further histopathology data was produced by Mangieri et al who performed left ventricular endomyocardial biopsies on 10 patients with CSFP. These investigators also found histological evidence of small vessel wall thickening with associated luminal narrowing, dilated interstitial spaces filled with granular fibrillar material. Of note, the disease involvement appeared to be patchy with specimens showing co- existing normal and pathological zones. Likewise, electron microscopy showed patchy involvement, myofibrillar disarray being present to some extent in most specimens. Other findings included reduced cellular glycogen content, swollen mitochondria with disrupted cristae, and endothelial cell disruption and thickening. In summary, these two studies both suggest evidence of non-specific 'fixed' small vessel pathology. Whether these morphological abnormalities are a consequence or a cause of the CSFP and how much they represent sampling artefact requires further clarification.

PATHOPHYSIOLOGY

Investigation of pathophysiology of the phenomenon has proceeded along similar lines to that of CSX and variant angina. CSFP patients have reduced coronary flow velocity, predominantly in the absence of large vessel abnormality, systemic haemodynamic impairment or myocardial disease. This combination of features is an accepted surrogate for increased microvessel resistance. The episodic nature of ischemic manifestations (often at rest) in the CSFP group combined with the lack of exercise ischaemia, suggests a disorder of vasomotor hyper-reactivity as also seen in variant angina.

Initial pathophysiology investigations were designed to (a) confirm the presence of increased coronary microvascular resistance (b) calculate the vasodilator reserve (c) assess the action of vasomotor stimuli in this patient group.

H aemodynamics

Evaluation of microvascular dysfunction was first performed by Mangieri et al who observed normalisation of contrast opacification rate in 6 patients with the CSFP following intravenous dipyridamole. In contrast, intracoronary GTN administered to all 10 study patents had no impact on opacification rate. A similar finding was made by Kurtoglu et al following 30 days of oral dipyridamole treatment (normalisation of angiographic flow in 70 of 75 CSFP vessels). These findings of CSFP resolution with a small coronary vasodilator are entirely consistent with the presumed microvascular site of the disorder. A controlled haemodynamic trial was subsequently performed with 12 subjects in each group. All participants underwent coronary sinus catheterisation. Parameters of coronary flow where measured in the resting state and during vasomotor stimuli (rapid atrial pacing, cold pressor testing and intracoronary acetylcholine infusion).

Resting haemodynamics

Resting coronary sinus flows were lower and a coronary resistance higher in the CSFP group than the control group despite similar myocardial demand as determined by the rate pressure product. This was supported by significantly lower coronary oxygen saturations in the CSFP patients, also a marker of reduced coronary flow.

Coronary Flow Reserve

CFR to a pacing stimulus revealed no difference between CSFP patients and controls in terms of peak coronary sinus flow or coronary resistance despite both groups achieving similar peak haemodynamic measures. This would suggest normal vasodilator reserve in the CSFP group, albeit from a lower baseline.

Vasomotor Stimuli

(a)Cold pressor testing; resulted in variable responses in coronary resistance between subjects with no consistent outcomes for the group. Several patients did, however, experienced chest pain and a substantial increase in coronary resistance to this sympathetic stimulus.

(b)Acetylcholine infusion; using a similar protocol for the assessment of large coronary spasm, produced no overall changes in haemodynamic parameters for the group but there was a large degree of individual variability, suggesting that a subgroup of the CSFP population may be susceptible to this form of provocation. Of interest ACh infusion did not induce large vessel spasm in any patient effectively excluding dynamic epicardial disease as a potential contributing factor in the disease.

Transmyocardial Biomarkers

As part of the above study transmyocardial lactate gradients were measured. Rapid atrial pacing produced chest pain in 50% of CSFP patients but only 2 showed ECG changes and none exhibited lactate production. Maximal coronary blood flow was similar to controls. Hence there was no metabolic evidence of significant ischaemia, which was consistent with their normal vasodilatory response and normal maximal blood flow to metabolic stimuli. Yaymaci et al also studied pacing induced changes in transmyocardial lactate gradients in 34 CSFP patients. Net lactate production was observed in 17% of their group and was always accompanied by chest pain and ischemic ECG changes. However without a control group in this study it is difficult to determine how specific for the CSFP these findings were and whether they were an artefact of the testing process.

Endothelial Function

Coronary endothelial function has never been studied directly. Sezgin et al have measured flow-mediated brachial artery dilation in a controlled trial of 27 CSFP subjects. They were careful to exclude cardiovascular risk factors in both groups and were able to demonstrate brachial vasodilatation in the CSFP patients was 3 times lower than the control group ($p<0.001$). There was a weak linear correlation between coronary flow velocity and brachial artery dilation.

PATHOGENESIS

Small vessel disease

The coronary circulation is traditionally considered as a two compartment model. The first compartment consists of epicardial vessels are also referred to as "conductance vessels", because they do not pose any resistance to blood flow. The second compartment consists of "small vessels" of <400 μm known as resistive vessels which primarily regulate myocardial blood flow in the absence of any significant obstructive epicardial stenosis . Small vessel dysfunction has been typically involved in the pathogenesis of CSFP since its first description. Confirming this hypothesis, investigators reported fibromuscular hyperplasia, medial hypertrophy, myointimal proliferation, as well as endothelial edema, thickening and degeneration in the coronary microvessels. Mangieri et al. found thickening of vessel walls with luminal size reduction, mitochondrial abnormalities, and glycogen content reduction in left ventricular endomyocardial biopsies in CSFP patients. Subsequently, Beltrame et al. indicated that CSFP was associated with a chronically elevated resting coronary microvascular tone characterized by low coronary sinus oxygen saturation as well as blunted responses to endothelial stimuli such as cold pressor or acetylcholine testing. Based on these data, it can be suggested that a combination of structural and functional abnormalities coexists in the coronary microcirculation.

Endothelial dysfunction

A growing body of evidence has suggested that the endothelium plays an integral role in the regulation of vascular tone, platelet activity, leukocyte adhesion, vascular smooth muscle proliferation, and is intimately involved in the development of atherosclerosis. It has been reported that reduced endothelium dependent flow-mediated dilatation (FMD) of the brachial artery was detected in patients with CSFP, suggesting that endothelial dysfunction is implicated in etiology of CSFP. Noteworthy is the recent finding demonstrating that baseline and peak exercise endothelin-1 plasma concentrations were higher and nitric oxide plasma concentrations were lower in slow coronary flow patients. In addition, patients with slow coronary flow had raised level of plasma homocysteine and asymmetric dimethylarginine , a nitric oxide synthase inhibitor, both of which have a detrimental effect on endothelial function. More recently, decreased adiponectin concentrations and paraoxonase activity, two significant markers of endothelial dysfunction have also been shown to be responsible for the etiopathogenesis of CSFP.

Subclinical atherosclerosis

Utilizing IVUS technique and flow rate measurements, Cin et al. demonstrated that patients with CSFP have diffuse intimal thickening, widespread calcification along the coronary vessel wall, and non-obstructive atheromatous coronary changes. In line with these results, Pekdemir et al. showed that most patients with CSFP have longitudinally extended massive calcification throughout the epicardial coronary arteries. These data are evidence that CSFP may reflect diffuse, non-obstructive atherosclerotic disease of epicardial vessels together with microvascular disease. These findings are supported by previous IVUS study indicating that diffuse atherosclerosis is often present in angiographically normal coronary arteries.

Inflammation

Inflammation is a contributing factor to several cardiovascular conditions and inflammatory mechanisms have also been observed in the context of CSFP. Li et al. showed that the plasma concentration of high-sensitivity C-reactive protein and interleukin-6 was increased in CSFP patients. Similarly, coronary slow flow was associated with higher levels of plasma soluble adhesion molecules, including intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and E-selectin .

Other inflammatory markers, such as red cell distribution width and serum uric acid levels, were also shown to be correlated with CSFP occurrence . Collectively, abnormalities in inflammatory parameters might be an indicator of endothelial dysfunction, both of which contribute to coronary slow flow.

Anatomic factors

Blood flow patterns in epicardial coronary arteries depend on the geometry and motion of these vessels . Disturbed laminar blood flow occurs in arterial segments with geometric irregularities such as curvatures, branches, and bifurcations . It is in these complex regions that low blood velocity rates tend to occur. Confirming this theory, recent observation with multidetector CT coronary angiography demonstrated that in patients with CSFP, the angulations of the main coronary arteries from the aorta were smaller determined. Based on this theory, we recently performed a case-control study to explore the correlation between anatomic properties of coronary arteries and CSFP occurrence.

The results showed that the presence of CSFP was associated with higher tortuosity and more distal branches in coronary arteries. Accordingly, it is reasonable to assume that certain anatomic properties of coronary arteries could be predisposing to disturbed coronary flow and endothelial damage, ultimately leading to CSFP occurrence*(97-99).*

MANAGEMENT

Despite good prognosis of CSFP patients, the subsequent progress is frequently characterized by remitting, relapsing anginal episodes resulting in considerable impairment in quality of life. Unfortunately, currently available anti-anginal agents are of limited clinical value. To date, no large trial testing pharmacological approaches has been conducted, and the evidence available derives from small studies with inhomogeneous inclusion criteria. It was shown that dipyridamole and mibefradil, which both influence functional obstruction in arteries <200 μm, normalized CTFC but nitroglycerine, which dilates arteries with diameters >200 μm, did not. Importantly, statins appear beneficial for patients with CSFP, likely in part due to their anti-inflammatory properties. More recently, several studies demonstrated that nebivolol can both improve endothelial function and markedly ameliorate symptoms, thereby improving quality of life in patients with CSFP. Besides its beta-receptor blocking activity, nebivolol can cause endothelium-dependent vasodilatation through increased nitric oxide release. On June 8, 1998, Roche announced the voluntary withdrawal of the drug from the market, due to the potential for drug interactions, some of them serious, which may occur when it is taken together with some other medications*(3,98))*.

CONCLUSION

CSFP is an important, angiographic finding typically observed in patients presenting with
acute coronary syndrome, in particular unstable angina. This phenomenon should be considered a separate clinical entity with peculiar characteristics, pathogenic mechanisms, and defined diagnostic criteria. Previous studies have shown that small vessel disease, endothelial dysfunction, subclinical atherosclerosis, inflammation, and anatomic properties of coronary arteries are are related to the occurrence of CSFP.

Current findings support the hypothesis that CSFP may be part of systemic vascular disturbance.
Despite relatively few publications the picture of a unique coronary microvascular disease process is beginning to emerge, identifiable by its characteristic angiographic appearance – the coronary slow flow phenomenon.The disorder has a number of distinctive features; it predominately affects middle aged male smokers and causes episodes anginal pain frequently at rest and frequently severe enough to prompt emergency treatment. Ischemic ECG and scintigraphic evidence of ischaemia is variably present and appears to depend on symptomatic status. Inducible ischaemia in the absence of resting symptoms is often difficult to demonstrate despite frequent non-specific ECG

abnormalities, and increased QT dispersion. Although infarction, left ventricular impairment (ischemic or otherwise) and sudden death are uncommon, the morbidity resulting from recurrent chest pain is high, partly because conventional antianginal treatment is ineffective.

At angiography the CSFP is present in 10% of patients with normal epicardial vessels. It is most commonly seen in two or more coronaries, with the left anterior descending coronary artery most commonly affected even when corrected for length. Non obstructive coronary disease or ectasia are infrequent associated features. Artefact as a cause of the phenomenon has been investigated and excluded. The phenomenon is most frequently seen during assessment of unstable angina and resolves in most patients when asymptomatic. The phenomenon is caused by increased coronary resistance at the level of the microvasculature which is present even when asymptomatic. In a proportion of patients, coronary resistance can increase further with the use of vasomotor stimuli. Small vessel vasodilators can abolish the phenomenon. Coronary vasodilator reserve is intact to pacing stimulus in asymptomatic individuals. The overall clinical picture is consistent with a disorder of coronary microvascular tone resulting in episodes of microvessel constriction sufficient to cause ischaemia.

When quiescent the vasodilator response is intact implying the periodic occurrence of an unidentified vasoconstrictor stimulus. The pathophysiology of the CSFP has received little attention. Although histopathology studies imply an element of fixed microvascular structural disease, this seems to be a minor component given the results of vasodilator and angiographic follow up studies which have shown a predominantly dynamic disturbance of coronary resistance. Vasomotor reactivity studies, although positive in a small number of patients (predominantly to sympathetic stimulation), show no consistent response across the group. More recently impairment of endothelial function has been indirectly implicated. Early and extensive intima and media disease of the epicardial vessels appears to be a feature of the disease, although its significance remains unclear. Our current understanding is incomplete, but clinicians should be aware of this condition and its clinical significance. Further experimental investigations are needed to reveal the pathogenesis involved in CSFP. In addition, large-scale clinical studies are warranted to better characterize these phenomenon, and most importantly, investigate potential therapeutic approaches.

CHEST PAIN AND THE NORMAL CORONARY ANGIOGRAM

SYNDROME X AND MICROVASCULAR ANGINA

Patients with unexplained anginal symptoms are not uncommon. Of those with symptoms suggestive of typical angina 10 to 30% will have normal coronary angiography. The early investigation and characterisation of patients with chest pain and angiographically normal coronary arteries was conducted independently by Kemp and Cannon, each working form a different perspective of the condition.

Definition

Kemp coined the term Cardiac Syndrome X (CSX) in 1973*(126)* after defining a patient group using predominantly clinical criteria;

1. exertional chest pain with an objectively positive stress test
2. absence of functional or structural epicardial disease
3. absence of valve disease and conditions known to impair microvascular structure/function.

Cannon took a more mechanistic approach and used the term 'microvascular angina' to describe patients with undifferentiated angina and normal angiography who demonstrated an abnormal coronary flow reserve to pacing which could be exaggerated with the use of ergonovine. The definitions however do not describe the same patient population as only 41% of CSX patients have reduced coronary flow reserve and only 10% of microvascular angina patients have a positive exercise ECG. In addition the microvascular angina definition includes a pre cardiomyopathic group particularly if combined with left bundle branch block .

Unfortunately there are no uniform definitions for patients with chest pain and normal angiography; hence there is considerable heterogeneity between studies. At present the terms 'cardiac syndrome X' and 'chest pain with normal coronary angiogram' are the most common terms for this group

and are used interchangeably. The term microvascular angina is used less frequently and is currently a short hand way of referring to impaired vasodilator reserve*(127,128).*

Clinical Features

Those with CSX share similar characteristics across a number of studies;

- Higher prevalence of women who are often peri or postmenopausal
- More episodes of painful ST segment depression on ambulatory monitoring compared to those with epicardial disease.
- Prolonged episodes of chest pain without evidence of LV impairment.
- Rapid increase in rate pressure product early in stress testing with angina experienced at a greater cardiac workload that those with large vessel disease.
- Half have a poor response to nitrates with some experiencing a paradoxical exacerbation of chest pain to nitrate therapy.
- Ongoing symptoms in the majority resulting in chronic disability, repeated investigations and prolonged, often ineffective, medical therapy.

Mechanisms

CSX appears to be the end result of two abnormalities, usually with both contributing variably to the chest pain syndrome within the same patient: (a) coronary microvascular dysfunction (b) increased pain sensitivity.

Microvascular Dysfunction and Ischaemia

Abnormal vasodilator reserve is a common finding in CSX and is present to endothelium dependent and independent stimuli, irrespective of how coronary flow is measured. Abnormal coronary hyper-reactivity to vasoconstrictor stimuli (cold pressor, hyperventilation, neuropeptide

Y, ergonovine and acetylcholine) has also been demonstrated in subgroups of these patients. Consistent with this, scintigraphic perfusion defects and PET derived flow heterogeneity are present in the majority of patients.

The documentation of ischaemia using coronary sinus sampling, however, has been difficult to demonstrate consistently until the recent introduction of sensitive markers. Early studies of transmyocardial lactate, pH and oxygen saturations were negative in the majority of patients despite pacing induced chest pain and ECG changes. This was congruent with the absence of wall motion abnormalities during ECG and chest pain positive stress echocardiography*(129,130)*.

The more recent investigation of these patients with phosphorous-31 MR spectroscopy, a highly sensitive metabolic marker of ischaemia, again demonstrated ischemic changes in only 20% of patients. In this study, however, handgrip exertion did not invoke ECG changes. In a study involving adenosine and MRI assessment of myocardial perfusion reserve, syndrome x patients were shown to have significantly reduced subendocardial blood flow during stress compared with normal controls. More recently the use of transmyocardial lipid peroxidation product sampling combined with pacing was able to demonstrate evidence of ischaemia in all CSX patients but was absent in all controls. This is the first study to unequivocally demonstrate ischaemia in this patient population.

The presence of abnormal coronary vasomotion combined with significant chest pain symptoms and a small ischemic burden (insufficient to cause significant metabolic/functional impairment or excess mortality) is best explained by a patchy transmural distribution of inappropriate pre-arteriolar constriction or reduced vasodilation. In this hypothesis, impaired arteriolar vasodilatation during pharmacologic or physiologic stress results in*(131)*:

(a) heterogeneous myocardial blood flow distribution with an overall reduction in CFR

(b) transmyocardial and intramyocardial steal and capillary de-recruitment at the end of

the most constricted vessels causing small areas of ischaemia and sustained increase in adenosine liberation to limit ischaemia.

(c) Normal or increased flow through unaffected vessels diluting ischemic metabolites and preventing ischemic impairment of myocardial function

(d) ST segment changes and anginal chest pain in the absence of ischaemia caused by excess adenosine acting on A1 receptors. These receptors are present in perivascular afferent nerves and ventricular myocytes. Excess stimulation results in nocioception as well as ECG changes (caused by shortening of the action potential).

The aetiology of microvascular dysfunction in CSX has not been fully elucidated. The reduced vasodilatory response that characterises the syndrome appears to be a common endpoint of a number of pathological processes:-

1. Structural abnormalities; mainly consisting of medial hypertrophy and/or fibrosis of arteriolar vessels, frequentlyassociated with systemic hypertension, have been described in small series of patients.
2. Endothelial dysfunction; is suggested by a decreased coronary flow response to endothelium mediated vasodilator stimuli and could be caused by impaired nitric oxide (NO) release and/or activity. Decreased NO generation, as determined by lower nitrate/nitrite systemic concentrations may be present, although a normal coronary cGMP release profile is present in CSX patients. An increased synthesis of asymmetric dimethyl arginine, (known to reduce the bioavailability of L-arginine for NO synthesis in endothelial cells), may contribute to impaired NO activity in CSX.
3. Primary smooth muscle cell abnormality; also may be present, as shown by impairment of coronary microvascular dilation in response to endothelium independent stimuli (adenosine, dipyridamole, and papaverine*)(132-134).*

4. Altered potassium handling; as demonstrated by increased exercise induced hyperkalemia in some CSX patients may account for the increased vasoreactivity (as well as ST segment changes and chest pain in the absence of ischaemia).
5. Oestrogen deficiency: oestrogen has vasodilatory properties, its deficiency is a recognised cause of endothelial impairment and the majority of female patients with CSX are post menopausal. Replacement therapy reduces symptoms and improves exercise tolerance in these patients which suggest that oestrogen deficiency may contribute to the microvascular dysfunction in CSX.
6. Elevated sympathetic tone; resulting in increased microvascular resistance is suggested by higher stress induced and ambulatory heart rates, hyperdynamic LV response to stress and a response in some patients to α adrenoceptor antagonism.
7. Inappropriate vasoconstriction; increased plasma concentrations of endothelin-1 (ET-1) have been found in peripheral blood of CSX patients and correlate with coronary microvascular dysfunction. ET-1 increases in the coronary circulation of CSX patients in response to atrial pacing. CSX patients may be more susceptible to the vasoconstricting effects of the sympathetic cotransmitter neuropeptide y.
8. Enhanced sodium–hydrogen exchanger activity; is consistently observed in CSX and represents a potential cause of microvascular dysfunction by inducing cellular alkalinisation and hence, increased susceptibility to smooth muscle constrictor stimuli. Furthermore, enhanced Na^{+}–H^{+} exchanger activity might be involved in several other typical features of CSX, including increased insulin resistance (associated with endothelial dysfunction), altered adrenergic activity and enhanced pain perception.
9. Increased rho-kinase activity; may enhance vasoconstriction in

microvascular smooth muscle cells by facilitating calcium overload, in a similar manner to large vessel constriction in variant angina.

10. Low grade inflammation; Recent studies have shown increased markers of inflammation in CSX patients, compared to matched healthy controls. A correlation between C reactive protein values, clinical and electrocardiographic indices of disease activity has been found in patients with angina and normal coronary arteries*(135-139)*.

Pain Sensitivity

Several studies have consistently shown that patients with angina and normal coronary arteries exhibit enhanced pain perception to both cardiac and other stimuli. These patients are more likely to have severe prolonged anginal pain, reduced tolerance to forearm ischaemia, develop pain with (usually innocuous) right sided catheter manipulation and respond to imipramine (an antidepressant with visceral pain relieving properties).

The high level of psychological morbidity sustained by CSX patients, particularly anxiety disorders, almost certainly contributes to the enhanced perception of symptoms. There is debate regarding whether psychological distress is a primary or secondary manifestation of the disorder*(140,141)*.

The reasons for enhanced pain perception remain elusive. Adenosine and potassium may be important, as already mentioned. More recently enhanced cortical activation during pain, compared to controls, has been observed. This may be due to transmission of afferent signals to the cortical pain area which are usually blocked at subcortical level. In addition there appears to be a failure for syndrome x patients to habituate to painful stimuli. Abnormality in afferent nerve conduction associated with abnormal autonomic function or elevated ET-1 seen in

syndrome x patients may play a role.

Integration of Pathologic Mechanisms

The interplay between microvascular dysfunction and enhanced pain perception will determine the individual patient's clinical presentation. A patient with greatly increased pain sensitivity may develop symptoms purely in response to algogenic cardiac (and/or non cardiac) stimuli. Patients with highly dysfunctional microvascular function may develop chest pain on the basis of ischaemia alone, in the presence of normal pain perception. Those patients with both elements are likely to be highly symptomatic and represent the subgroup in which ischemic indices are usually positive. The elements may also interact such that frequent low grade ischaemia may sensitise afferent pathways to clinically insignificant painful stimuli or abnormal neural function could contribute to abnormal microvascular function.

Overall the condition primarily represents a chronic pain syndrome, and as there is no excess mortality, management strategies are directed at symptoms rather than surrogate markers of ischaemia.

Management

Due to the multitude of pathophysiologic mechanisms responsible for CSX there is no one treatment strategy that suits all patients. Most approaches are based on identifying the most likely mechanism and tailoring therapy accordingly:

1. Beta Blockers and Calcium Channel Antagonists: Useful when ischaemia can be documented and where sympathetic overactivity is present
2. Hormone Replacement: is a proven therapy in post menopausal CSX patients but must be balanced against the small risk of major cardiovascular events
3. Analgesics: Imipramine, electrical nerve and cord stimulation all offer benefit particularly in

those with debilitating symptoms

4. Lifestyle Modifications: physical training, cardiovascular risk facor modification and cognitive behavioural therapy all have intuitive appeal but lack objective data

THE NO-REFLOW PHENOMENON

Definition

The no-reflow phenomenon was first described in an animal model of coronary occlusion followed by reperfusion by Kloner et al in 1974(100). Despite an open epicardial vessel flow within the infarcted regions of myocardium remained impeded. Myocardial flow was traced anatomically using dye entrapment. The phenomenon has become increasingly recognised in human hearts with the advent of routine percutaneous coronary intervention (PCI) for the treatment of myocardial infarction and elective revascularisation. It is currently clinically diagnosed by TIMI grade 0-2 flow within a coronary vessel or reduced MCE microbubble enhancement of a coronary territory, in the context reperfusion.

Pathophysiology

In the original animal model description, no reflow zones were confined to the irretrievably damaged myocardium and the area of no reflow approximated the infarct size. Loss of perfusion was due to progressive microvascular occlusion caused by cellular plugging, tissue oedema and ischemic contracture. It was not the result of microvessel destruction or loss of the microvascular network, which remained largely intact. No-reflow only became apparent after 90minutes of occlusion. It started in the endocardium, where blood flow is the most tenuous and spread to the epicardium in a time-dependent wavefront.

In the clinical setting reperfusion primarily occurs following ruptured atheroma and occlusive thrombus. Plaque contents and thrombus may embolise to the coronary microvasculature. Hence,

the eventual no reflow zone is usually a combination of ischemic necrosis, reperfusion injury and distal embolisation which are unable to be differentiated antemortem.

In the setting of elective PCI, no-reflow primarily occurs in vessels with a large atherothrombotic burden and is thought to be the result of distal embolisation, possibly combined with an element of reperfusion injury.

The no reflow zone can only be fully appreciated by imaging myocardial perfusion at the tissue level. Angiographic dye progression (TIMI flow grade) is used as a surrogate for no-reflow and although specific is insensitive and cannot determine the extent of the no-reflow zone. Consequently the phenomenon remains under reported(101-103).

Reperfusion injury

Reperfusion of coronary flow post acute myocardial infarction (AMI) is necessary to resuscitate ischemic and hypoxic myocardium. This may however result in paradoxical myocardial impairment or death, called reperfusion injury and contributes to the no-reflow phenomenon. The myocardium is tolerant of ischaemia for up to 15 minutes without death or functional impairment. This situation occurs frequently during stable angina, epicardial vasospasm and elective coronary angioplasty. With increasing periods of ischaemia subsequent reperfusion results in progressive myocyte dysfunction which takes time to resolve. The zones most affected also contain cells that are irreversibly damaged.

Myocardial stunning is the most studied manifestation of reperfusion injury. Global or regional myocardial tissue which is subject to prolonged ischaemia will often remain hypocontractile for long periods despite adequate blood supply. This is thought to be caused by ongoing anaerobic metabolism as a result of prolonged inhibition of mitochondrial pyruvate dehydrogenase, as well

as repair of non lethal cell injury. Blood flow, although restored remains low due to reduced cellular requirements acting via autoregulation mechanisms(104-107).

The microvascular endothelium is the cellular component most likely to be impaired by the restoration of normal epicardial flow and the tissue layer most likely to cause no-reflow following reperfusion. Reperfusion results in substantial endothelial dysfunction, largely due to ischaemia-induced changes in mitochondrial function and the build up of xanthine oxidase. With the reintroduction of oxygen these respiratory chain enzyme systems begin to produce large amounts of reactive oxygen species which overwhelm the innate tissue antioxidant capacity, in particular NO. As a result the usual antithrombotic, anti inflammatory, vasorelaxant properties of the endothelium are lost and platelet and neutrophil adhesion molecules are expressed on the endothelial cell surface. The subsequent cellular infiltrate results in the release of vasoconstrictors, more ROS and proteolytic enzymes. Combined with the physical plugging effects of cell adhesion, the increased expression of endothelin, and positive feedback caused by release of platelet activating factor, the end result is impaired tissue perfusion which contributes to ongoing or even worsening tissue ischaemia. If the endothelium is already functionally impaired, even brief periods of ischaemia are thought capable of causing no-reflow. The physical plugging effects may be overstated as the application of vasodilators is often effective at reversing the phenomenon. At the extreme end of reperfusion injury is contraction band necrosis. This is caused by reperfusion induced calcium reentry resulting in massive myofibril contraction and death. This is due to increased myofibril calcium sensitivity, increased calcium channel transit and impaired sarcoplasmic calcium cycling, coupled with calcium dependent protease activation(108-112).

Microembolisation

The latter stages of large vessel atherosclerotic plaque development are characterised by the formation of a positive-remodelled lipid core with a thin fibrous cap and a tendency to ulcerate, haemorrhage or rupture when inflamed by monocyte infiltration or subject to percutaneous intervention. These plaques cycle through periodic rupture and repair phases, often concurrently, and the development of an acute coronary syndrome or biomarker evidence of myocyte infarction is closely correlated with the overall atherothrombotic plaque burden. When rupture occurs or is induced, plaque and vessel wall constituents, including lipid, subendothelial matrix and platelet thrombus can embolise resulting in microvascular obstruction, loss of endothelial integrity, release of vasoactive amines and increased microvascular tone. If this of sufficient magnitude, no-reflow occurs and is usually accompanied by infarction(113-115).

There is increasing evidence that microvascular embolism plays an important role in the development of ischaemia, and cardiac related mortality in those with epicardial vessel disease. In the setting of rapidly reperfused infarction (and hence reduced likelihood of reperfusion injury), microvascular occlusion is not infrequent, thought to be secondary to microembolism and is an independent predictor of mortality. In those with delayed reperfusion 'classic' no-reflow may occur at the necrotic core while embolic no-reflow may occur in the surrounding tissue as emboli are preferentially shunted to the relatively well perfused penumbra and increase the zone of infarction. Microembolism is ubiquitous in the setting of elective PCI and results in microinfarction in 30 to 40% of cases. Periprocedural no-reflow and myocardial infarction is independently predicted by atheroma burden and invasiveness of revascularisation technique i.e. factors associated with distal embolisation(116-119).

Diagnosis

The diagnosis of no-reflow can be suspected when there is increased ST elevation and haemodynamic compromise post reperfusion. The original technique for the diagnosis of no-reflow was the TIMI flow grade. This however is an insensitive measure and misses up to 25% of instances post MI. Subsequently doppler flow wire characteristics of no-reflow were defined and include; rapid deceleration of diastolic blood flow and prominent systolic reversal. Scintigraphy and contrast enhanced MRI have also been used, predominantly in the research setting.

MCE appears to be the most clinically useful and accurate measure of no-reflow zones post MI. Unfortunately, due to post reperfusion hyperaemia, MCE will underestimate no-reflow if performed within the first 48 hrs of reperfusion. Thereafter it accurately determines the no-reflow area, the size of which predicts subsequent cardiac failure, arrhythmias and post MI mortality(120-122).

Management

The aims of management are twofold; (a) when 'classic' no-reflow predominates and microvessel occlusion is confined to the area of necrosis, re-establishment of microvascular flow encourages healing, reduces remodelling and promotes collateral circulation. (b) when micro embolisation causes no-reflow its amelioration may reduce the infarct zone and infarct expansion.
The strategies that have benefit include (a) primary preventive measures; early infarct reperfusion using primary angioplasty and glycoprotein IIb/IIIa inhibitors (b) secondary preventive measures; verapamil and adenosine both reduce vasospasm. Intra-aortic balloon pumping and inotropic support are effective particularly when there is evidence of haemodynamic compromise*(123,124).*

MATERIALS AND METHODS

Study design

This is an observational study of patients with normal epicardial coronary arteries who underwent coronary angiogram for angina. The coronary filling and emptying times at predetermined standard vascular landmarks were determined. The various coronary risk factors and clinical parameters were determined in the study population and their association with the coronary filling and emptying times were also determined.

Setting

The study was conducted in the Department of Cardiology, Christian Medical College Hospital, Vellore. The study was conducted during a 13 month period from November 2011 to November 2012. The patients with angina and normal epicardial coronaries in the coronary angiograms were consecutively enrolled for the study. Detailed history was obtained from each patient enrolled into the study. Detailed physical examination and coronary artery risk factor analysis performed for each patient. The coronary angiograms were cined at 30 frames per second. Informed consent was obtained from all enrolled patients.

Subjects

Inclusion Criteria

1. Patients with angina and normal epicardial coronary arteries.
2. Patients with structurally normal hearts
3. Patients with normal left ventricular systolic functions
4. Patients in sinus rhythm

Exclusion Criteria

1. Patients with occlusive coronary arterial disease
2. Patients with valvular heart diseases
3. Patients with left ventricular systolic dysfunction
4. Patients with cardiomyopathies
5. Patients with pericardial diseases
6. Patients with co-morbid conditions like renal failure, hepatic failure and significant pulmonary diseases
7. Patients in atrial fibrillation
8. Patients with unexplained left ventricular hypertrophy

Study Protocol

37 patients with angina and normal epicardial coronaries were enrolled for the study. Clinical and angiographic profile of the patients were studied in detail.

Clinical Profile

The clinical profile of all the patients were studied in detail. Detailed history was obtained from each patient. All of them had angina on presentation. The duration of angina was assessed for each patient and its significance in coronary slow patients was determined. Other important aspects of history that has been taken into consideration include

1. Associated symptoms like dyspnoea, palpitation and giddiness
2. Hospitalizations in the past including that for chest pain/acute coronary syndromes
3. History of allergy in the past
4. History of asthma and its duration
5. Past history of activity – athletic, body building, sedentary habits or yoga

The presence or absence of the conventional coronary artery disease risk factors and duration of each was assessed in each patient. The association of the risk factors in coronary slow flow phenomenon(CSFP) was also determined. The various risk factors considered include

1. Smoking
2. Essential hypertension
3. Diabetes mellitus

4. Dyslipidemia
5. Obesity
6. Sedantary activity

The personality type of each candidate was assessed (Type A personality, nervousness, prone to anxiety or cool and casual attitude) and its association with CSFP was also determined.

Baseline clinical characteristics like pulse rate, blood pressure, body mass index(BMI) were also assessed and their association with CSFP determined. Association of various biochemical parameters with CSFP was also determined. The biochemical parameters taken into consideration include hemoglobin, blood sugar, fasting cholesterol, LDL, HDL, LDL/HDL ratio, serum creatinine etc. ECG was obtained for each patient and looked for the presence of ST/T changes or voltage criteria for LVH. Echocardiography was done mandatory for all patients to rule out structural heart diseases, valvular heart diseases, cardiomyopathies and left ventricular systolic dysfunction. Each patient was assessed for presence of LVH by echocardiography. Association of the ECG and echocardiographic features with CSFP was determined.

Angiographic Profile

All patients enrolled into the study underwent coronary angiogram by transradial route. We used 5F radial sheaths for the procedure and 5F TIG catheter was used for the selective coronary angiography. Controlled hand injections were used for the selective coronary angiography. All procedures were performed by a single operator who was a cardiology trainee. Iohexol (omnipaque) was the contrast used in all patients.

Coronary angiography was performed by the transradial approach by the conventional techniques. Selective coronary angiography of the left and right coronary arteries were performed with the 5F TIG catheter. Angiographic images were cined at 30fps. Angiographic projections used for the analysis of LAD(Left anterior descending artery) were RAO cranial (RAO 10degrees and cranial 40 degrees) and LAO cranial (LAO 45degrees and cranial 20degrees) views. Angiographic projections for the analysis of RCA were RAO (30degrees) and LAO (45degrees) views. During acquisition, utmost care was taken for the proper visualization of the whole vascular territory. Long cineangiographic acquisitions were performed to visualize the contrast opacifying coronary artery ostium via distal standard vascular landmark to the coronary sinus ostium. Additional coronary acquisitions were acquired at the discretion

of the primary operator and consultant cardiologist. The additional acquisitions were cined at 15fps. The patient was hemodynamically monitored throughout the procedure. Assessment of the angiographic images was performed by the primary operator and consultant cardiologist. Coronary arterial filling and emptying times at prespecified landmarks were determined. Capillary and venous transit time and total transit time via the coronary vascular bed were also determined. The predictability of the above timings for CSFP was determined. The association of various clinical, physical and biochemical parameters with CSFP was also determined.

Assessment of coronary arterial filling and emptying times

Coronary flow is determined by the number of TIMI frame counts that the contrast takes to travel across the prespecified vascular landmarks. The landmarks for the TIMI frame count assessment of LAD are as follows

A. Contrast opacifying the LAD ostium
B. Contrast opacifying LAD at the origin of the major diagonal(D1 or D2 whichever is big)
C. Contrast opacifying LAD at distal bifurcation
D. Contrast opacifying the coronary sinus ostium
E. Contrast fading off from the point B
F. Contrast fading off from the point C

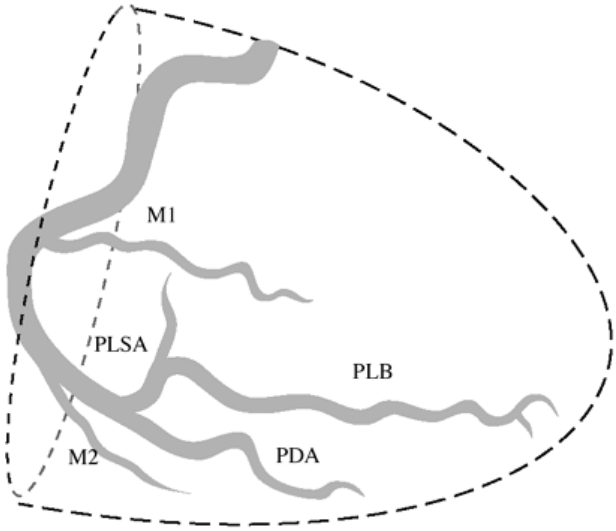
Similarly the angiographic landmarks for RCA are as follows

A. Contrast opacifying the RCA ostium
B. Contrast opacifying the RCA at the level of crux
C. Contrast opacifying RCA at the origin of first posterolateral branch
D. Contrast opacifying the coronary sinus ostium
E. Contrast fading off from the point B
F. Contrast fading off from the point C

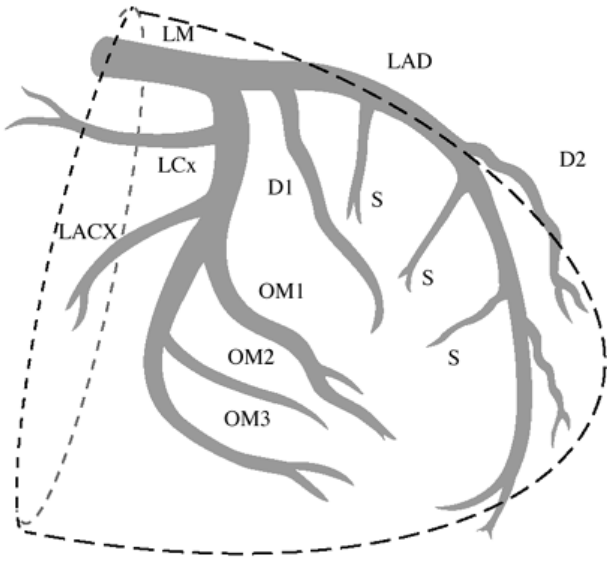
The coronary filling and emptying times were determined based on these above points. The filling time is determined as the time of first frame of opacification at a predetermined proximal point to the first frame of opacification at a set distal point. Similarly emptying time is determined as the time of first frame of opacification at a predetermined point to the frame at which the contrast disappears completely.

1. AB – Coronary filling time at point B. Time(Number of frame counts) taken for contrast to fill between points A and B.
2. BC – Coronary filling time from B to C. Time (Number of frame counts) taken for contrast to fill between points B and C.
3. AC – Coronary filling time at point C. Time(Number of frame counts) taken for contrast to fill between points A and B.
4. BB' – Coronary emptying time at point B. Time(Number of frame counts) that the contrast takes to totally fade off from point B from the moment it get opacified.
5. CC' - Coronary emptying time at point C. Time(Number of frame counts) that the contrast takes to totally fade off from point C from the moment it get opacified.
6. CD – Capillary and venous transit time. Time(Number of frame counts) taken for contrast to fill between points C and D.
7. AD – Total coronary transit time. Time(Number of frame counts) taken for contrast to fill between points A and D.

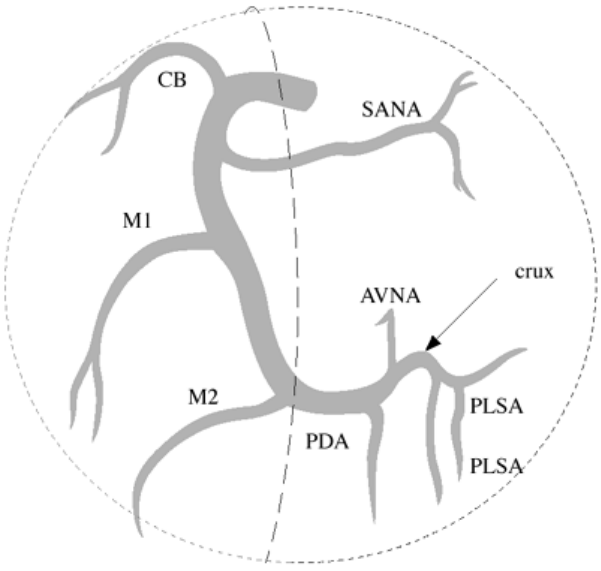
Angiographic Landmarks for LAD and RCA – Pictorial Representation



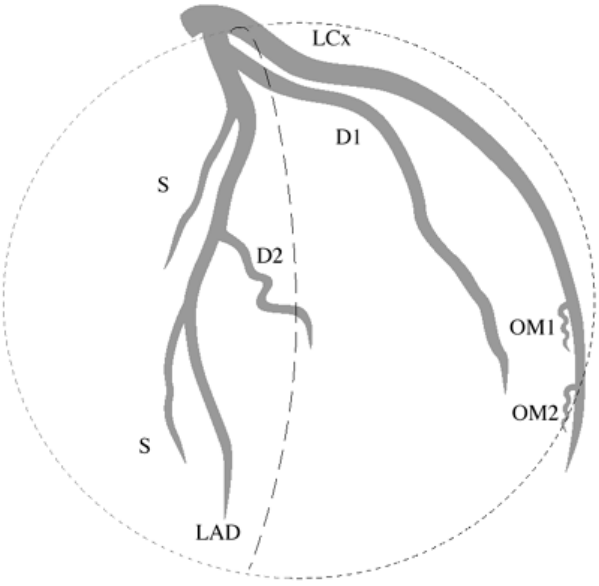
Right Coronary Artery in RAO View



Left Coronary Artery in RAO View



Right Coronary Artery in LAO View



Left Coronary Artery in LAO View

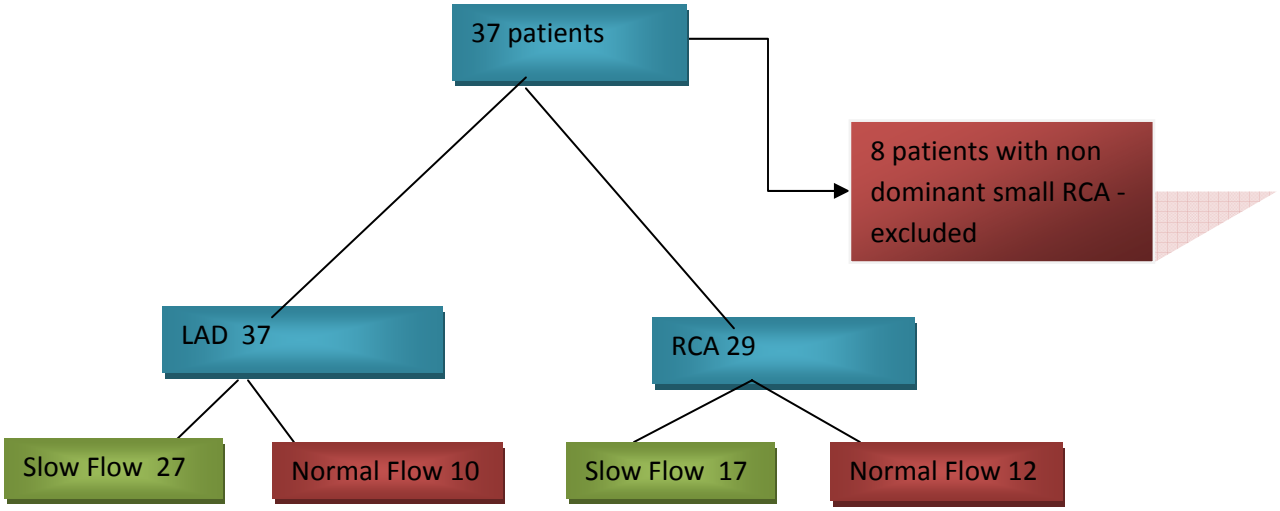
Statistical Analysis

Data was stored and and analyzed using SPSS version 17 (SPSS Inc. Chicago, IL, USA). Continuous variables are expressed as mean +/- standard deviation for normally distributed variables and median (inter-quartile range) for not normally distributed variables. Categorical variables expressed as number (percentage). Continuous variables were examined for normality of distribution using the Shapiro Wilk test. Differences in the frequency of the continuous variables were analysed using independent sample students t-test for normally distributed variables. For not normally distributed continuous variables a non-parametric Mann Whitney test was used. For discrete variables, Chi square statistics (or Fischers exact test if applicable for a cell count less than 5) was used. Binary logistic regression analysis was used to identify the potential predictors of coronary slow flow phenomenon namely the coronary arterial fillingtimes, coronary arterial emptying times and coronary capillary and venous emptying times. All parameters that showed a p value less than 0.1 during initial analysis were included in the binary logistic regression analysis. A p value of less than 0.05 was considered statistically significant.

RESULTS

Patients were enrolled into the study between November 2011 and November 2012. Among patients presenting with angina, who underwent coronary angiogram and found to have normal epicardial coronaries, 37 patients were selected consecutively based on inclusion and exclusion criteria. Among these patients flow in left anterior descending artery (LAD) and right coronary artery (RCA) were studied. Slow flow was ascertained on the basis of TIMI frame counts. TIMI frame counts more than 39 for the contrast to travel from LAD ostium to distal bifurcation for LAD and more than 24 for the contrast to travel from RCA ostium to first posterolateral branch was designed coronary slow flow in LAD and RCA respectively. On this basis we got 27 slow flow cases in LAD and 17 slow flow cases in RCA. Normal flow on the basis was seen in 10 cases in LAD and 12 cases in RCA. 8 patients had small dominant RCA and was excluded from the analysis.

Figure 1: Study design



Baseline Characteristics

Baseline clinical characteristics are given in Table 1 and 2. The continuous variables considered include age, pulse rate, body mass index, systolic and diastolic blood pressures, hemoglobin, blood sugars, HbA1c, serum creatinine, lipid profile, LDL/HDL ratio etc. These variables were analysed in LAD slow flow group versus normal flow group and RCA slow flow group versus normal flow group. There was no

significant difference between the 2 groups with respect to most of the variables. The mean blood sugar, HbA1c, total cholesterol, LDL and triglyceride levels were more for the slow flow group of LAD as compared to the normal flow group, on the other hand the mean HDL level was less in the slow flow group compared to the normal flow group, but were not statistically significant. On the other hand, the LDL/HDL ratio was observed to be more in the LAD slow flow group and was found to be statistically significant. The mean hemoglobin level was observed to be significantly higher in LAD slow flow group as compared to the normal flow group.

Table 1. Baseline characteristics of Left System (LAD).

Variable	LAD Slow Flow Mean (SD)	LAD Normal Flow Mean (SD)	P value 2 tailed
Age	51.4 (11.20)	54.5 (6.31)	0.378
Pulse rate	78.37 (12.80)	81.80 (7.08)	0.430
BMI	26.82 (3.22)	26.91 (5.05)	0.946
SBP	124.85 (18.09)	130.50 (22.45)	0.435
DBP	79.15 (9.66)	73.90 (14.79)	0.214
Hb	13.36 (1.51)	11.23 (1.91)	0.001
AC	123.44 (63.72)	113.22 (32.42)	0.649
PC	158.85 (75.72)	135.67 (59.20)	0.410
HbA1c	7.02 (1.92)	6.38 (1.08)	0.456
S.creatinine	1.10(0.19)	1.02(0.24)	0.293
S. Cholesterol	163.26(46.35)	144.30(37.37)	0.259
LDL	95.15(39.86)	85(36.40)	0.487
HDL	38.33(6.91)	49.9(17.72)	0.006
LDL/HDL	2.55(1.10)	1.58(0.64)	0.013
TG	164.93(78.03)	114.60(46.3)	0.065

LAD – Left anterior descending artery, SD – Standard Deviation, BMI – Body mass index, SBP and DBP – Systolic and diastolic blood pressure in mmHg, Hb – Hemoglobin in mg/dL, AC and PC – ante and post cibal blood sugars in mg/dL, TG – Triglycerides in mg/dL

The continuous variables behaved in a similar fashion with respect to the right coronary artery also with some differences. The mean blood sugars and HbA1c levels were lesser in the slow flow group. Total cholesterol, LDL, LDL/HDL ratio and triglycerides were higher in the slow flow group but HDL levels were lower. However they were not statistically significant.

Table 2.Baseline characteristics of RCA system.

Variable	RCA Slow Flow Mean (SD)	RCA Normal Flow Mean (SD)	P value 2 tailed
Age	53.53 (10.80)	48.67 (10.44)	0.236
Pulse rate	76.12 (13.26)	81.33 (8.11)	0.237
BMI	27.44 (3.73)	26.21 (4.42)	0.428
SBP	124.18 (19.71)	122.17 (16.77)	0.777
DBP	77.82 (10.22)	75.67 (12.21)	0.610
Hb	13.15 (1.71)	11.87 (1.89)	0.066
AC	116.88 (40.78)	140.64 (89.34)	0.346
PC	152.53(67.29)	167.64(99.77)	0.635
HbA1C	7.07(1.68)	7.32(2.26)	0.800
S.Creatinine	1.12(0.16)	1.05(0.24)	0.355
T. Cholesterol	166.47(48.05)	143.17(30.55)	0.151
LDL	96.47(41.76)	84.25(30.04)	0.394
HDL	39.76(5.49)	47.17(17.79)	0.117
LDL/HDL	2.45(1.08)	1.88(0.96)	0.146
TG	164.82(77.56)	129.17(58.63)	0.191

RCA – Right Coronary Artery

Baseline characteristics – categorical variables

Table 3. Sex distribution in the slow and normal flow group in LAD

		Coronary flow LAD		Total
		Slow flow	Normal flow	
Sex	Male	20	3	
	% (Coronary flow LAD)	74.1%	30.0%	
	Female	7	7	.023
	% (Coronary flow LAD)	25.9%	70.0%	
Total	Count	27	10	37
	% (Coronary flow LAD)	100.0%	100.0%	100.0%

P-value 0.023 (2 sided), 0.020 (1 sided)

Table 4. Sex distribution in slow and normal flow group in RCA

		Coronary Flow RCA		
		Slow Flow	Normal Flow	Total
Sex	Male	14	5	19
	% (Coronary Flow RCA)	82.4%	41.7%	65.5%
	Female	3	7	10
	% (Coronary Flow RCA)	17.6%	58.3%	34.5%
Total	Count	17	12	29
	% (Coronary Flow RCA)	100.0%	100.0%	100.0%

P value – 0.046 (2 sided), 0.030 (1 sided)

Among the patients with slow flow observed in LAD, 74.1% were males and 25.9% females versus 30% and 70% among males and females respectively in patients with normal coronary flow. Similarly in patients with slow flow in RCA 82.4% were males and 17.6% females versus 41.7% and 58.3% in the normal flow group. This observation that coronary slow flow in LAD and RCA is more among males was statistically significant.

Duration of angina was more than 1 month but less than 1 year in 63% of patients with slow flow in LAD and 58.8% of patients with slow flow in RCA (versus 30% in LAD normal flow and 50% RCA normal flow). The duration of angina more than one year, on the other hand, was observed in 33.3% of patients with LAD slow flow and 41.2% of patients with RCA slow flow (versus 70% in LAD normal flow and 50% in RCA normal flow). Duration of angina less than one month was quite uncommon in slow flow population. Only 1 patient (3.7%) in LAD slow flow group had angina less than 1 month.

Other significant cardiac manifestations like dyspnoea, palpitation, giddiness etc were not common in the slow flow group. Dyspnoea was observed in 18.5% and 23.5% in LAD slow flow and RCA slow flow groups. When history of activity was considered, slow flow was observed to be more in those with sedentary life style. Among those with LAD slow flow 59.3% (30% in LAD normal flow) had sedentary life style and those with RCA slow flow 41.2% (versus 50% in RCA normal flow group) had sedentary life style.

The distribution of the coronary artery risk factors in the slow flow group versus normal flow group is given in detail in the following tables separately for LAD and RCA.

Table 5. Categorical variables distribution in LAD group

Variable	LAD SF(present) Number(%)	LAD SF(absent) Number (%)	LADNF(present) Number (%)	LAD NF(absent) Number (%)
Sex	20(74.1)	7(25.9)	3(30)	7(70)
Smoking	6(22.2)	21(77.8)	0	10(100)
Hypertension	11(40.7)	16(59.3)	6(60)	4(40)
Diabetes mellitus	8(29.6)	19(70.4)	1(10)	9(90)
Dyslipidemia	4(14.8)	23(85.2)	1(10)	9(90)
Obesity	5(18.5)	22(81.5)	1(10)	9(90)
Sedentary life style	17(63)	10(37)	3(20)	7(20)

Table 6. Categorical variables distribution in RCA group

Variable	RCA SF(present) Number (%)	RCA SF(absent) Number (%)	RCA SF(present) Number (%)	RCA NF(absent) Number (%)
Sex	14(82.4)	3(17.6)	5(14.7)	7(58.3)
Smoking	4(23.5)	13(76.5)	0	12(100)
Hypertension	10(58.8)	7(41.2)	3(25)	9(75)
Diabetes Mellitus	5(29.4)	12(70.6)	4(33.3)	8(66.7)
Dyslipidemia	1(5.9)	16(94.1)	2(16.7)	10(83.3)
Obesity	4(23.5)	13(76.5)	1(8.3)	11(91.7)
Sedentary life style	7(41.2)	10(58.8)	7(58.3)	5(41.7)

ECG changes (ST/T changes) were seen in 8 patients (29.6%) in LAD slow flow group and 4 patients (23.5%) in RCA slow flow group versus 3 patients (30%) in LAD normal flow group and 3 patients (25%) in RCA normal flow group. Treadmill test was done in 18 patients enrolled to assess the LAD flow among which 15 had slow flow and 3 had normal flow. Treadmill test was positive for inducible ischaemia in 8 patients with slow flow and 2 patients with normal flow. On the other hand, treadmill test was done in 14 patients enrolled for RCA flow study of which 8 had slow flow and 6 had normal flow. Treadmill test was positive in 3 slow flow patients and 4 normal flow patients. However we didn't find any significant association of TMT positivity with slow flow phenomenon.

Angiographic Profile

The coronary filling and emptying times at points B (diagonal for LAD and crux for RCA) and C (distal bifurcation for LAD and first posterolateral branch for RCA) were determined promptly by counting the number of TIMI frames that the contrast takes to transit between the predetermined points. Capillary and venous transit time was determined by the number of TIMI frames the contrast takes to travel from C to D. Total transit time is determined by the TIMI frames the contrast takes to reach D from A.

In short, AB and BB' are the coronary filling and emptying times respectively at point B; AC and CC' filling and emptying times at point C; CD capillary and venous transit time and AD total coronary transit time. These timings of LAD and RCA were studied separately.

Angiographic Profile of LAD

The correlation between the filling and emptying times at point B and C in slow flow and normal flow were studied first. The significance of these timings in the coronary slow flow population were analysed. Logistic regression for the former and students t-test for the latter were done.

A positive correlation between AB and BB' was observed which was statistically significant. The coefficient of correlation considering BB' as the dependant variable to AB was 0.753. On the other hand there observed a negative correlation of BB' with AB in patients with normal flow which was not statistically significant.

A positive correlation between CC' and AC in LAD slow flow group with coefficient of correlation 0.082 for CC' with AC was observed, but was not statistically significant. But same as at the point B, CC' correlation with AC was negative and statistically insignificant for patients with LAD slow flow.

Table 7.Correlation of AB/BB' – LAD slow flow

LAD Slow Flow group

	Mean	Std. Deviation	N
BB'	84.370	23.7352	27
AB	21.72	15.660	27

Correlations

		BB'	AB
Pearson Correlation	BB'	1.000	.497
	AB	.497	1.000
Sig. (1-tailed)	BB'	.	.004
	AB	.004	.
N	BB'	27	27
	AB	27	27

LAD Slow Flow Group

Coefficients

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	68.020	7.001		9.716	.000
	AB	.753	.263	.497	2.861	.008

Dependant variable BB'

Table 8. Correlation of CC'/AC – LAD slow flow group

LAD Slow Flow group

	Mean	Std. Deviation	N
CC'	92.85	22.680	27
AC	77.944	32.6206	27

LAD – Slow Flow CC'/AC - Correlations

		CC'	AC
Pearson Correlation	CC'	1.000	.118
	AC	.118	1.000
Sig. (1-tailed)	CC'	.	.278
	AC	.278	.
N	CC'	27	27
	AC	27	27

Coefficients

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	86.434	11.634		7.429	.000
	AC_L	.082	.138	.118	.596	.556

Dependant Variable CC'

Figure 2. **Scatter plot showing the positive correlation of AB and BB' in LAD slow flow patients**

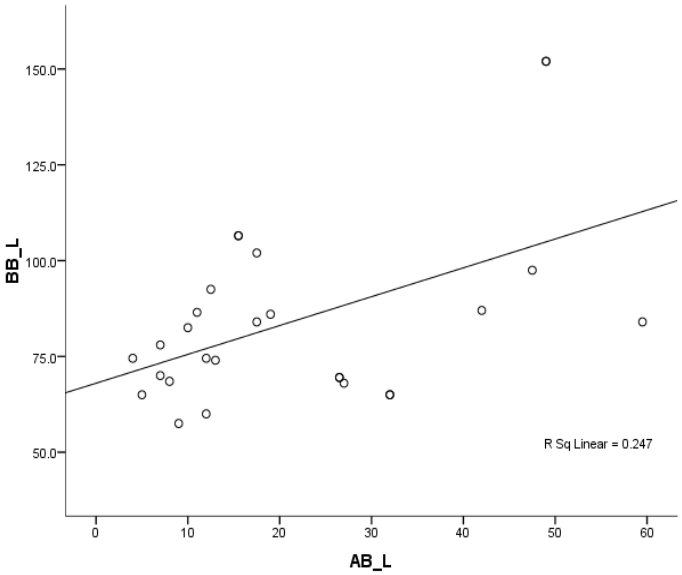


Figure 3. **Scatter plot showing non significant negative correlation of AB and BB' in LAD normal flow patients**

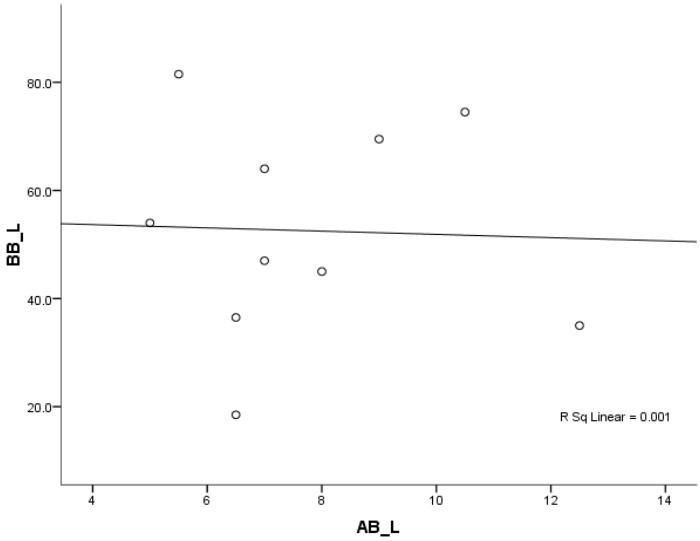
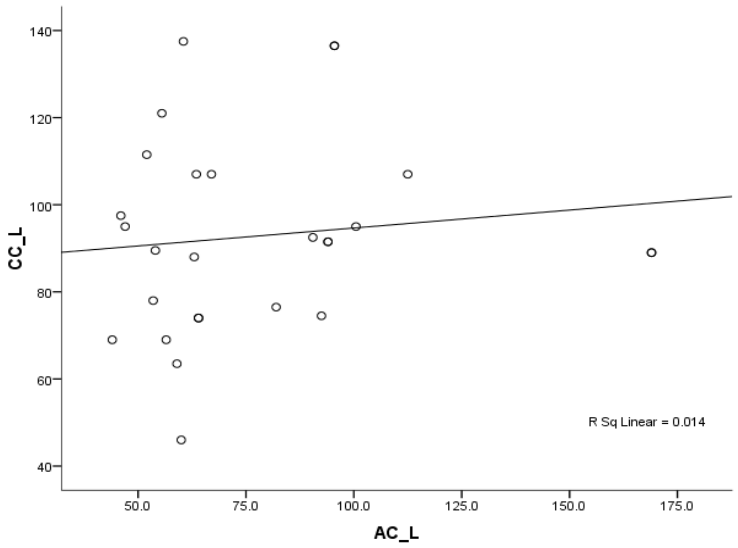


Figure 4. **Scatter plot showing the positive correlation between AC and CC' in LAD slow flow group**



The coronary arterial filling and emptying times at the origin of major diagonal and distal bifurcation are significantly prolonged in patients with coronary slow flow in LAD. The capillary and venous transit time on the other hand is found to be prolonged in slow flow patients but was not statistically significant. However the total transit time in LAD was significantly prolonged in slow flow patients.

The association of various clinical and biochemical parameters with the coronary flow (ie, association with respect to the coronary arterial filling and emptying times) was also analysed. Patients who presented to us with angina of duration one month to one year had prolonged filling times, emptying times, capillary and venous transit times and total transit times as compared with those who present with angina of more than one year duration. However this association was not statistically significant.

Males were found to have statistically significant prolonged coronary filling and emptying times and total transit times compared to females. The capillary and venous transit times were also prolonged but was not statistically significant. Smokers had prolonged filling times, emptying times and total transit times but the capillary and venous transit times were found to be less compared to non smokers, with no statistical significance. Hypertensives were found to have less filling times, emptying times, total transit time and capillary and venous emptying times compared to normotensives without statistical significance. Diabetics on the other hand were found to have prolonged timings without statistical significance. The

correlation of these timings with pulse rate, blood pressure, BMI and various biochemical parameters like Hb, blood sugars, total cholesterol, LDL and HDL were assessed. Variable association of the various timings with these parameters which was not significant statistically was observed. LDL/HDL ratio and triglycerides positively correlated to all the timings and was statistically significant.

Table 9. Association of the various LAD flow timings and its significance in CSFP

Association of various framecounts& significance in LAD slow flow

	Variable	N	Mean	Std. Deviation	Std. Error Mean	P Value – 2 tailed
AB	SF	27	21.72	15.660	3.014	0.009
	NF	10	7.75	2.324	.735	0.000
BB’	SF	27	84.370	23.7352	4.5678	0.001
	NF	10	52.550	19.8696	6.2833	0.001
AC	SF	27	77.944	32.6206	6.2778	0.000
	NF	10	34.900	5.2324	1.6546	0.000
CC’	SF	27	92.85	22.680	4.365	0.003
	NF	10	68.80	12.669	4.006	0.000
CD	SF	27	135.93	35.402	6.813	0.434
	NF	10	125.90	30.598	9.676	0.408
AD	SF	27	210.167	58.2097	11.2025	0.013
	NF	10	159.900	26.9730	8.5296	0.001

Angiographic Profile of RCA

Similar to the LAD system the correlation between the coronary arterial filling and emptying times at B (crux of RCA) and C (first posterolateral branch) of RCA was assessed. A positive correlation of coronary emptying times at both points, namely BB' and CC' with the filling times, namely AB and AC, was observed in slow flow patients but was not statistically significant. On the other hand in normal flow group the correlation was negative but without statistical significance.

In RCA the coronary arterial filling and emptying times at the level of crux and first posterolateral branch was observed to be significantly prolonged in coronary slow flow patients. Contrary to the LAD, RCA slow flow groups showed significant prolongation of the capillary and venous transit times also. The total transit time was also significantly prolonged in RCA slow flow patients. The association of the various timings with the clinical and biochemical parameters were variable and non significant in RCA slow flow patients.

Figure 5. **Scatter plot showing the correlation between AB and BB' in the RCA slow flow patients**

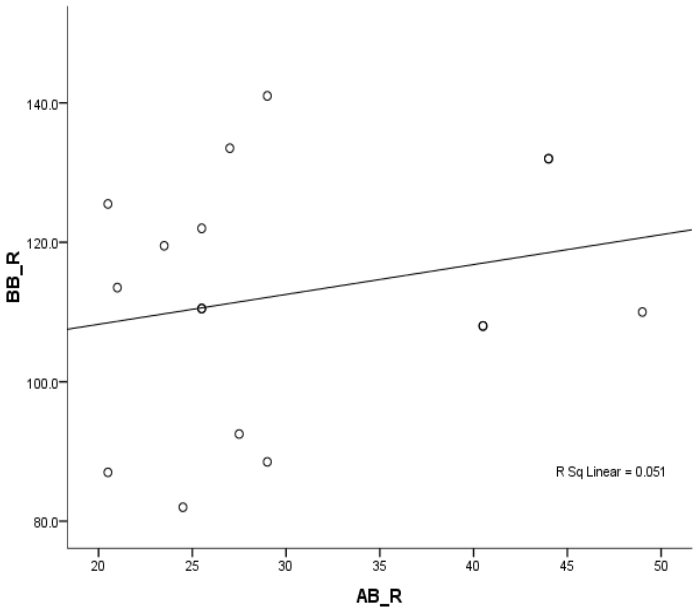


Figure 6. **Scatterplot showing correlation between AC and CC' in RCA slow flow patients**

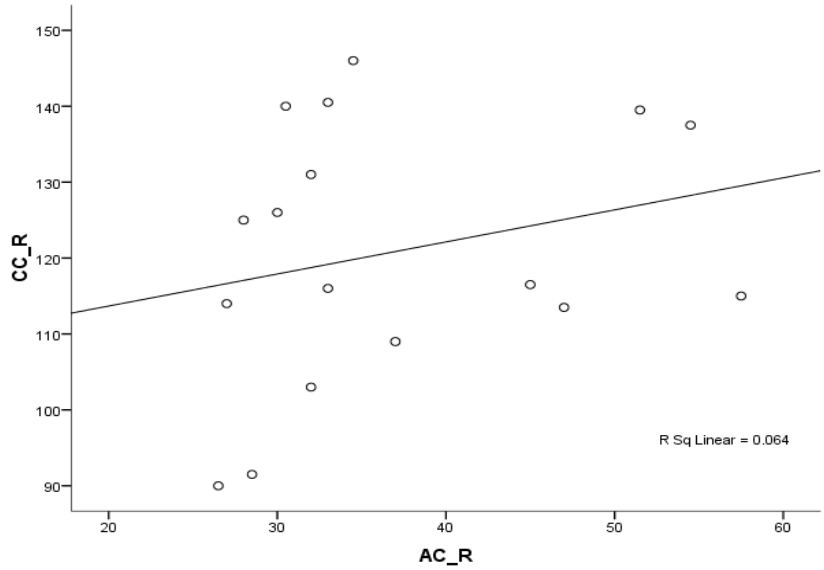


Table 10. **Association of the various RCA flow timings and its significance in CSFP**

Association of various framecounts& significance in RCA slow flow

	Variable	N	Mean	Std. Deviation	Std. Error Mean	P Value – 2 tailed
AB	SF	17	30.41	9.296	2.255	0.000
	NF	12	17.04	2.261	.653	0.000
BC	SF	17	6.50	2.411	.585	0.058
	NF	12	5.04	.940	.271	0.034
AC	SF	17	36.91	10.135	2.458	0.000
	NF	12	22.08	1.794	.518	0.000
CD	SF	17	228.765	62.3992	15.1340	0.044
	NF	12	188.125	27.4840	7.9339	0.026
BB’	SF	17	112.706	17.5598	4.2589	0.002
	NF	12	92.542	13.4628	3.8864	0.002
CC’	SF	17	120.82	16.969	4.116	0.045
	NF	12	107.58	16.232	4.686	0.044
AD	SF	17	265.676	68.3257	16.5714	0.013
	NF	12	210.333	27.5172	7.9435	0.006

DISCUSSION

Angina with normal epicardial coronaries occurs in upto 20% of patients who underwent coronary angiogram for angina. Coronary slow flow comprises a separate group among this population designed Syndrome Y and accounts for upto 7% of patients undergoing CAG for angina. Coronary slow flow phenomenon may manifest with unstable angina and acute coronary syndromes. It has been associated with clinical manifestations of myocardial ischaemia, life threatening arrhythmias and even sudden cardiac death.Coronary slow flow has already been defined as the delayed passage of the contrast through the coronary vascular bed. The delay however is not at the level of epicardial coronaries but mainly at the microvascular level.

John F Beltrame in many of his articles established the importance of microvascular tone in coronary slow flow patients. He suggested that the microvascular tone is elevated in patients with coronary slow flow even if the symptoms are quiescent. Coronary syndrome X is common in post menopausal women, on the other hand syndrome Y or coronary slow flow is commonly seen in young male smokers*(3)*. Saya et al *(7)* described the occurrence of life threatening arrhythmias and sudden cardiac death in these patients. All these observations point towards the non de novo nature of syndrome Y unlike syndrome X.

Conventionally slow flow is being determined by the delay in coronary filling. But the real pathology in coronary slow flow resides in the microvasculature. Hence we hypothesized that coronary arterial emptying time is a better predictor of slow flow phenomenon. We also aimed at capillary and venous emptying time and its association and significance in coronary slow flow patients. We also analysed the clinical and biochemical profile of these patients. Finally, the association of various clinical and biochemical parameters with the TIMI frame counts was also analysed.

Our study showed significant prolongation of coronary emptying times in LAD and RCA in coronary slow flow patients, though slow flow may not be present in both arteries simultaneously. The previous studies looked into the coronary arterial filling times mainly for the determination of coronary slow flow. The coronary filling time determination is biased by lots of confounding variables like speed of injection, heart rate, operator dependant variables etc. However coronary emptying time is non dependant on these

variables. Hence coronary emptying time may be considered to assess coronary slow flow in such circumstances.

The association of capillary and venous transit times in patients with CSFP was also analysed. We found the same to be significantly prolonged in patients with slow flow in RCA but prolonged in LAD but not statistically significant. The significance of the prolonged capillary and venous transit time may be related to the single arterial system on the right side. The non significance of the capillary and venous emptying time of LAD may be related to the

1. Confounding influence of the LCx flow.
2. Variable degrees of the capillary branchings
3. Non predictable venous diameters and tributaries

A positive correlation between the coronary filling and emptying times in coronary slow flow patients was observed, but there was a negative correlation in patients with normal flow. This may be due to the delayed passage of the blood through the coronary microvascular bed in coronary slow flow patients.

Coronary slow flow was observed to be significantly more in the males. Coronary flow as assessed by TIMI frame counts was observed to be significantly more in the male population. Coronary slow flow was observed to be more in smokers and the coronary flow filling and emptying times are prolonged in smokers, but there was no statistical significance. No significant association of hypertension or diabetes was observed with coronary slow flow. The coronary filling and emptying times were found to be prolonged in diabetics and shortened in hypertensives, however was not statistically significant. This may be a pointer towards the increased incidence of microvascular dysfunction in diabetic population.

No significant association of coronary slow with obesity was observed. Coronary slow flow was more in patients with sedentary lifestyle, also prolonged coronary filling and emptying times. No significant correlation was observed between total cholesterol, LDL cholesterol and HDL cholesterol in coronary slow flow patients. Significant association of CSFP in patients with high LDL/HDL ratio and triglycerides was observed . The coronary filling and emptying times were observed to be prolonged in

subjects with high LDL/HDL ratio and high triglycerides. The association was more in patients observed with LAD slow flow.

To conclude, Coronary Emptying Time was found to be an independent predictor of coronary slow flow. In circumstances where coronary filling is subjected to multiple confounding factors, as listed above, Coronary Emptying Time remains independant of them and can be utilized as a predictor of CSFP. Capillary and venous transit time is prolonged in LAD and RCA slow flow but was significantly prolonged in RCA slow flow group alone. CSFP is more in males and who were current smokers. CSFP as well as prolonged coronary filling and emptying times were more in patients with increased LDL/HDL ratio. CSFP was seen more in patients with sedentary life style. However, further studies with more sample size may be required to substantiate our observations.

LIMITATIONS

1. The vasodilatory response of various agents like calcium channel blockers, adenosine, NO, mibefradil has not been done . Ideally the coronary filling and emptying times to be reassessed after the vasodilators.

2. 27 slow flow and 10 normal flow patients in the LAD group and 17 slow flow and 12 normal flow in the RCA group were enrolled. The lesser number in the control arm might had confounding influences. Increased sample size would have provided better results

3. Controlled hand injections to fill up the coronary bed with the contrast was utilized that was likely to have confounding influences on the filling time assessment

4. Angiogram was performed by different operators and hence operator dependant factors might had a confounding influence

5. The vascular landmarks mainly the point B (diagonal origin for LAD and crux for RCA) was arbitrary and varies among the populations.

CONCLUSIONS

1. In addition to coronary artery filling times, Coronary artery emptying time is an independent and significant predictor of coronary slow flow phenomenon.

2. Capillary and venous transit time is significantly prolonged in patients with slow flow in RCA whereas in patients with LAD slow flow there is non significant prolongation of capillary and venous transit time.

3. There is a positive correlation of coronary emptying time with coronary filling time in Coronary Slow Flow . This correlation is not seen in patients with normal coronary flow.

4. Coronary slow flow is observed significantly more in male population.

5. Coronary slow flow is significantly associated with high LDL/HDL ratios and triglyceride levels

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STUDY PROFORMA

CLINICAL AND ANGIOGRAPHIC PROFILE OF PATIENTS WITH ANGINA AND NORMAL EPICARDIAL CORONARIES

Name:

Age:

Sex:

Hospital Number:

Occupation:

Address:

Phone number:

CLINICAL PROFILE

1)Chestpain – location – central/precordium/right side/whole chest

- type – heaviness/squeezing/pinpricking/burning

- radiation – left arm/right arm/jaw/throat/back

- associated sweating

- nature- continuous/intermittent

2)Duration – one month or less

one month to one year

more than one year

3)other symptoms –

Dyspnoea	yes	no
Palpitations	Yes	No
Giddiness	Yes	No

4)Any hospitalizations in the past – yes/no

For ACS	others

5)History of allergy in the past – yes/no

Allergen –

6)History of asthma – yes/no

- duration

7)Past history of activity – athletic past

- bodybuilding

- yoga

- sedantary

8)Risk Factors

Duration(years)

Smoking	Yes	No	
Essential Hypertension	Yes	No	
Diabetes mellitus	Yes	No	
Dyslipidaemia	Yes	No	
Obesity	Yes	No	
Sedentary life style	Yes	No	
Oral contracptive intake	Yes	No	
Hormone replacement	Yes	No	

9)Personality type – Type A personality

- prone to anxiety

- nervousness

- cool and casual attitude

10) ECG features –

ST/T changes	Yes	No
LVH SV1+RV6 >35	Yes	No

11)ECHO features –

LVPW :

IVS:

Mitral E/A:

LVEF:

LVH	Yes	No
RWMA	Present	Absent
Systolic dysfunction	Present	Absent
Diastolic dysfunction	Present	Absent

12)TMT features

Effort tolerance	Good	Moderate	Poor
Response	Positive	Negative	Equivocal
Positive (if)	Stage 1	Stage 2	Stage 3

13)Baseline clinical characteristics

Pulse Rate –

Blood Pressure –

Height -

Weight -

BMI –

Built – lean/muscular/athletic/obese

14)Blood Investigations

AC -

PC -

HbA1c –

S. Creatinine -

Fasting Lipid Profile :

Serum Cholesterol -

LDL -

HDL -

VLDL -

TG –

LDL/HDL ratio -

Extra Notes:

ANGIOGRAPHIC PROFILE

TIMI frame count in LAD

Parameters	LAD–LAO	LAD–RAO
AB		
BC		
AC		
CD		
BB’		
CC’		
AD		

TIMI frame count in RCA

Parameters	RCA–LAO	RCA–RAO
AB		
BC		
AC		
CD		
BB’		
CC’		
AD		

Angiographic landmarks for the TIMI frame count assessment of LAD

A. Dye filling to the ostium of LAD
B. Dye filling to the LAD at the origin of D2
C. Dye filling to the LAD at distal bifurcation
D. Dye filling to the ostium of coronary sinus
B'. Dye emptying totally from point B

C'. Dye emptying totally from point C

AB – Coronary filling time to D2

BC – Coronary filling time to LAD distal bifurcation

CD – Capillary and venous transit time

AC- Total filling time of LAD

AD – Total transit time AC+CD

BB' – Emptying time of LAD at D2 level

CC' - Emptying time at LAD distal bifurcation

Angiographic landmarks for the TIMI frame count assessment of RCA

A. Dye filling to the ostium of RCA
B. Dye filling to the crux of RCA
C. Dye filling to the first branch of posterolateral artery
D. Dye filling to the ostium of coronary sinus
B'. Dye emptying totally from point B

C'. Dye emptying totally from point C

AB – Coronary filling time to PDA

BC – Coronary filling time to distal bifurcation of RCA

CD – Venous and capillary transit time

AC- Total filling time of RCA

AD – Total transit time AC+CD

BB' – Emptying time of RCA at origin of PDA

CC' - Emptying time at distal bifurcation of RCA

CONSENT FORM

Study Title: Clinical and Angiographic profile of patients with angina and normal epicardial coronaries

Study Number:

Participant's name:

Date of Birth / Age (in years):

I_____

_____, son/daughter of _____

1. Declare that I have read the information sheet provide to me regarding this study and have clarified any doubts that I had. [ ]

2. I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights [ ]

3. I understand that I will receive free treatment for any study related injury or adverse event but I will not receive and other financial compensation [ ]

4. I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access [ ]

5. I understand that my identity will not be revealed in any information released to third parties or published [ ]

6. I voluntarily agree to take part in this study [ ]

Name:

Signature:

Date:

Name of witness:

Relation to participant: Date:

INFORMATION SHEET

CLINICAL AND ANGIOGRAPHIC PROFILE OF PATIENTS WITH ANGINA AND NORMAL EPICARDIAL CORONARIES

1. This study is for research purpose and to study the clinical and angiographic profile of patients with chestpain and normal coronaries
2. Expected duration : 1 year
3. Description of the procedures – This is an observational study. We are not doing any extra procedures. In patients with chestpain if coronary angiogram shows normal coronaries we are trying to study the flow in coronary arteries and look for any slow flow in the coronaries that can contribute to the chestpain
4. No foreseeable risks or discomforts to the subject
5. No direct benefit to the subject
6. No alternative procedures available to the subject
7. Complete confidentiality of records identifying the subject will be maintained by Principal Investigator
8. No compensation available to the subject in the event of a study – related injury
9. Contact person the principal investigator for queries
10. No anticipated prorated payment to the subject
11. No subjects responsibilities on participation
12. Subject's participation is voluntary, that the subject can withdraw from the study at any time and that refusal to participate will not involve any penalty or loss of benefits to which the subject is otherwise entitled
13. No apparent foreseeable circumstances under which the subject's participation may be terminated by the investigator without the subject's content.
14. No additional costs to the subject that may result from participation in the study
15. Subject can withdraw from the research and procedures at any time of study
16. There will be no consequences on subjects decision to withdraw from the research
17. Subject or subject's representative will be notified in a timely manner if significant new findings develop during the course of the research which may be affect the subject's willingness to continue participation will be provided
18. We are not involving pregnant women in our study
19. Approximate number of subjects enrolled in the study – 40 patients

GLOSSARY OF MASTER CHART

CLINICAL AND ANGIOGRAPHIC PROFILE OF PATIENTS WITH ANGINA AND NORMAL EPICARDIAL CORONARIES

Name:

Age:

Sex:

Hospital Number:

Occupation:

Address:

Phone number:

CLINICAL PROFILE

1)Chestpain – location – central/precordium/right side/whole chest

- type – heaviness/squeezing/pinpricking/burning

- radiation – left arm/right arm/jaw/throat/back

- associated sweating

- nature- continuous/intermittent

2)Duration – one month or less (1)

one month to one year (2)

more than one year (3)

3)other symptoms – 0- no symptoms

Dyspnoea	Yes(1)	no
Palpitations	Yes(2)	No
Giddiness	Yes(3)	No

4)Any hospitalizations in the past – yes(1)/no(0)

For ACS	others

5)History of allergy in the past – yes(1)/no(0)

Allergen –

6)History of asthma – yes(1)/no(0)

- duration

7)Past history of activity – athletic past(3)

- Normal(1)

- yoga(4)

- sedentary(2)

8)Risk Factors

Duration(years)

Smoking	Yes(1)	No(0)	
Essential Hypertension	Yes(1)	No(0)	
Diabetes mellitus	Yes(1)	No(0)	
Dyslipidaemia	Yes(1)	No(0)	
Obesity	Yes(1)	No(0)	
Sedentary life style	Yes(1)	No(0)	
Oral contracptive intake	Yes	No	
Hormone replacement	Yes	No	

9)Personality type – Type A personality(1)

- prone to anxiety(2)

- nervousness(2)

- cool and casual attitude(3)

10) ECG features –

ST/T changes	Yes(1)	No(0)
LVH SV1+RV6 >35	Yes(1)	No(0)

11)ECHO features –

LVPW :

IVS:

Mitral E/A:

LVEF:

LVH	Yes(1)	No(0)
RWMA	Present(1)	Absent(0)
Systolic dysfunction	Present(1)	Absent(0)
Diastolic dysfunction	Present(1)	Absent(0)

12)TMT features

Effort tolerance	Good	Moderate	Poor
Response	Positive	Negative	Equivocal
Positive (if)	Stage 1	Stage 2	Stage 3

0 – Not Done

1 – Positive

2 - Negative

13)Baseline clinical characteristics

Pulse Rate –

Blood Pressure –

Height -

Weight -

BMI –

Built – lean/muscular/athletic/obese

14)Blood Investigations

AC -

PC -

HbA1c –

S. Creatinine -

Fasting Lipid Profile :

Serum Cholesterol -

LDL -

HDL -

VLDL -

TG –

LDL/HDL ratio -

Extra Notes:

Angiographic Profile

NC_SF_L – Normal or slow flow LAD group

1- Slow flow group

2- Normal flow group

NC_SF_R – Normal or slow flow RCA group

1- Slow flow RCA

2- Normal flow RCA

3- Non Dominant small RCA

S.NO	Name	HospitalNc	Age	Sex	Durationof	Associated	Hospitaliza	Allergy	Asthma	Historyofa	Smoking	Hypertensi	DiabetesM	Dyslipidem	Obesity	Sedantaryl
1	Patan Dalu	026072f	66	1	3	0	0	0	0	3	0	1	1	0	0	0
2	Mathura m	071273f	69	1	2	0	0	0	0	3	0	0	1	0	0	0
3	Subhas Ch	071092f	60	1	3	0	0	0	0	4	0	1	0	0	0	0
4	Swapan Bi	072671f	44	1	2	1	0	0	0	2	0	0	0	0	1	1
5	Laxmi Kant	069252f	52	1	3	1	0	0	0	3	1	1	0	0	0	0
6	Dilwara Be	048796f	50	2	3	0	0	0	0	2	0	0	1	0	0	1
7	Gopal Pras	078649f	44	1	2	0	0	0	0	2	0	0	0	0	0	1
8	Nazeema	430104a	54	2	2	2	0	0	0	1	0	0	1	1	0	1
9	Bidwattan	078545f	48	1	3	1	0	0	0	2	1	1	0	1	1	1
10	krishna Ra	700956a	39	1	2	0	0	0	0	3	0	0	1	0	0	0
11	Anju Sinha	087212f	53	2	3	0	0	0	0	2	0	0	0	0	0	1
12	Ujjual Kum	087213f	55	1	2	0	0	1	1	4	0	1	1	0	0	0
13	Dr. Devwra	091803f	70	1	2	0	0	1	0	4	1	1	0	0	1	0
14	Manaf Ali	058726d	59	1	2	0	0	0	0	2	0	0	1	0	0	1
15	Balaram m	101936f	32	1	2	2	0	0	0	2	0	0	0	0	0	1
16	Satyabham	105673f	63	2	2	0	0	0	0	2	0	0	0	0	0	1
17	Zulaikha	124121c	39	2	2	2	0	0	0	2	0	0	1	1	0	1
18	Gopal V	098488f	43	1	2	0	0	0	0	2	0	0	0	0	0	1
19	Vivekanan	991552d	40	1	3	1	0	0	0	2	1	1	0	1	1	1
20	Narendra F	120471f	52	1	3	0	0	0	0	2	0	0	0	0	1	1
21	Rengaswar	127274f	65	1	1	0	0	0	0	2	0	0	0	0	0	1
22	Rajenthira	243485f	55	1	2	0	0	0	0	2	1	1	0	0	0	1
23	Ashok Kum	293018f	33	1	2	0	0	0	0	3	0	0	0	0	0	0
24	Suman Jais	307285f	52	2	2	0	0	0	0	2	0	1	0	0	0	1
25	Purnima Sa	324066f	47	2	2	1	0	0	0	2	0	1	0	0	0	1
26	Kajal Kanti	435563b	53	1	2	0	0	0	0	2	1	1	0	0	0	1
27	Biswajit Mi	260221f	29	1	2	0	0	0	0	3	0	0	0	0	0	0
28	Arati sarka	829535c	51	2	2	1	0	0	0	1	0	1	0	0	0	0
29	Sita Keriwa	335709f	60	2	3	1	0	0	0	2	0	0	0	0	1	1
30	Atindra Na	302775f	56	1	3	0	0	0	0	1	0	1	0	0	0	0
31	Umesh Cha	325535b	60	1	3	0	0	0	0	1	0	0	0	0	0	0
32	Lakshmi	295151c	44	2	2	3	0	0	0	1	0	0	0	0	0	0
33	Putul Mitra	335771f	49	2	3	1	0	0	0	1	0	0	0	0	0	0
34	Parul Bala	296392f	63	2	3	0	0	0	0	1	0	1	0	0	0	0
35	Mandira Sl	334140f	58	2	3	0	0	0	0	1	0	1	0	1	0	0
36	Sunaiana D	343199f	59	2	3	1	0	0	0	1	0	1	0	0	0	0
37	Jiban Chan	268080c	56	1	3	0	0	0	0	2	0	1	1	0	0	1

Durationo	Duratic	Personalitytype	ECGchange	ECG_LVH	ECHO_LVH	ECHO_Miti	TMT	PR	BP	SBP	DBP	BMI	Hb	AC
2	1	2	1	1			0	60	160/80			22.83	16.2	256
	1	2	0	0	0	0.84	2	60	110/80			24.24	12	98
10		2	0	0	0	1.4	0	80	140/80			27.12	12.9	131
		2	1	1	1	0.71	1	90	120/90			25.78	14.9	111
5		2	0	0	1	0.66	0	80	130/90			27.05	14.2	80
	14	2	1	0	0	0.64	0	90	110/80			26.31	11.8	386
		2	1	0	0	1.1	0	84	100/70			24.3	14.3	99
	0.5	2	0	0	0	1.2	1	70	140/90			27.63	12.6	100
8		2	1	0	1	0.48	2	108	148/86			28.23	15.2	122
	1	2	0	0	0	0.84	2	60	110/80			24.24	13	159
		2	0	0	0	0.64	2	90	110/80			26.31	10.4	100
15	2	2	0	0	0	0.68	2	70	110/80			29.76	14.3	115
1		1	0	0	0	0.49	0	70	104/60			31.93	11.9	109
	5	2	0	1	0	1.1	0	84	100/70			24.3	13.5	128
		2	0	0	0	0.96	2	80	120/80			23.23	13.4	104
		2	0	0	0	1.1	1	78	130/80			24.46	11.3	102
	2	2	0	0	0	1.2	0	76	140/90			27.63	12.9	182
		2	0	0	0	0.76	1	70	110/70			25.6	14.8	93
3		2	1	0	1	0.48	2	108	148/86			28.23	13.8	117
		2	0	0	0	1.5	1	82	130/80			37.13	12.6	98
		2	1	0	1	1.15	0	76	140/80			23.51	14.2	95
10		2	0	0	1	0.78	1	80	150/100			23.31	15.6	86
		2	0	0	0	1.86	0	62	92/55			27.03	14.7	92
2		2	0	0	1	1.3	0	82	130/80			31.99	10.5	101
2		2	1	1	1	1.2	0	88	154/96			30.56	12.9	102
3		2	0	0	0	0.78	1	78	120/68			28.23	13.8	89
		2	1	0	0	1.1	1	88	110/70			24.9	14.1	95
1		2	0	0	1	0.88	0	80	150/88			25.7	10.9	
		2	0	0	1	0.72	0	96	140/80			38.45	9.9	108
23		2	0	0	1	0.63	1	78	110/70			25.79	10	97
		2	0	0	0	1.2	0	70	98/50			19.68	8.7	98
		2	1	0	0	1.7	1	78	128/70			23.68	12.9	82
		2	1	0	0	0.83	0	78	108/64			28.3	12.1	105
4		2	0	0	0	1.1	2	84	148/92			23.53	9.3	119
4		2	0	0	1	0.81	0	86	159/69			28.15	10.8	113
12		2	0	0	1	1.4	0	60	149/82			28.8	11.7	85
1	4	2	0	0	1	0.63	0	80	110/60			25.3	14.8	195

PC	HBA1C	S_Creat	T_Ch	LDL	HDL	LDL_HDL	TG	NC_SF_L	NC_SF_L_1	AB_L	BC_L	AC_L	CD_L	BB_L
365	10.6	1.3	217	120	51	2.35	94	SF - 1	1	11	42.5	53.5	113	86.5
163	7.1	1.3	208	114	41	2.78	265	SF - 2	1	15.5	80	95.5	237	106.5
147		1.1	159	101	33	3.06	164	SF - 3	1	27	29.5	56.5	98	68
162		1.2	138	82	36	2.27	112	SF - 4	1	59.5	41	100.5	146	84
116		1.1	197	135	36	3.75	209	SF - 5	1	17.5	46	63.5	123	84
403	11.4	1	218	142	34	4.17	210	SF - 6	1	26.5	37.5	64	139	69.5
120		0.9	152	72	30	2.4	371	SF - 7	1	49	120	169	131	152
145	6	0.8	136	69	44	1.57	82	SF - 8	1	19	35	54	125.5	86
161	6.7	1.1	132	71	37	1.92	182	SF - 9	1	42	45	82	101	87
155	8.3	0.8	264	177	42	4.21	246	SF - 10	1	15.5	80	95.5	237	106.5
146	5.1	0.8	130	63	51	1.24	115	SF - 11	1	26.5	37.5	64	139	69.5
122	5.4	1.1	140	77	41	1.88	128	SF - 12	1	32	62	94	128	65
196		1.3	116	41	40	1	154	SF - 13	1	17.5	75	92.5	153.5	102
247	7.9	1.2	220	150	35	4.29	174	SF - 14	1	49	120	169	131	152
104		1.1	118	64	31	2.06	147	SF - 15	1	13	34	47	112	74
152		0.8	116	57	32	1.78	153	SF - 16	1	5	39	44	99.5	65
230	9.6	1	156	92	38	2.42	181	SF - 17	1	12.5	33.5	46	133.5	92.5
103		1.2	244	167	48	3.48	101	SF - 18	1	7	45	52	134	78
100	6.9	1.2	235	165	43	3.84	100	SF - 19	1	32	62	94	128	65
116		1.01	108	47	42	1.12	80	SF - 20	1	12	43.5	55.5	150	74.5
161	5.7	1.27	127	82	27	3.04	48	SF - 21	1	7	53.5	60.5	187.5	70
128	5.7	1.53	207	129	27	4.78	347	SF - 22	1	10	80.5	90.5	101	82.5
92		1.22	142	82	33	2.47	187	SF - 23	1	47.5	65	112.5	144	97.5
117	5.8	1.28	143	62	49	1.26	203	SF - 24	1	12	47	59	98	60
134	5.9	0.94	123	56	45	1.24	131	NC - 1	2	5.5	23.5	29	112	81.5
153	5.4	1.1	125	68	42	1.62	128	SF - 25	1	8	55	63	111.5	68.5
89	5.4	1.33	157	94	30	3.13	200	SF - 26	1	4	63	67	135	74.5
115		0.96	170	95	59	1.61	110	NC - 2	2	10.5	28.5	39	125.5	74.5
89	6.3	0.92	134	105	57	1.84	105	NC - 3	2	6.5	20	27.5	120.5	18.5
83		1.68	112	54	40	1.35	81	NC - 4	2	9	30	39	202.5	69.5
159	6.3	0.93	111	40	58	0.7	36	NC - 5	2	7	32	39	104.5	64
		1.05	121	68	32	1.12	76	NC - 6	2	7	32	39	153	47
127	5.7	0.83	232	152	34	2.81	149	NC - 7	2	5	34	39	111	54
126		1.06	163	101	40	2.52	115	NC - 8	2	12.5	15	27.5	101.5	35
107	5.6	0.89	122	54	42	1.28	136	NC - 9	2	6.5	25.5	32	109	36.5
96	6.3	0.8	103	46	42	1.09	72	SF - 27	1	9	51	60	134	57.5
281	8.5	0.97	155	125	92	1.36	207	NC - 10	2	8	30	38	119.5	45

CC_L	AD_L	NC_SF_R	NC_SF_R_1	AB_R	BC_R	AC_R	CD_R	BB_R	CC_R	AD_R
78	166.5	SF - 1	1	21	6	27	163.5	113.5	114	190.5
136.5	332.5	SF - 2	1	25.5	6.5	32	333	110.5	131	365
69	154.5	SF - 3	1	20.5	6	26.5	148.5	87	90	175
95	246.5	SF - 4	1	29	5.5	34.5	225.5	141	146	260
107	186.5	SF - 5	1	25.5	4.5	30	205.5	122	126	235.5
74	203	NC - 1	2	18	5	23	221	109.5	115.5	244
89	300	SF - 6	1	44	10.5	54.5	307.5	132	137.5	362
89.5	179.5	NC - 2	2	15.5	5	20.5	213	81.5	91	233.5
76.5	183									
136.5	332.5	SF - 7	1	25.5	7.5	33	332	110.5	116	365
74	203	NC - 3	2	18	4.5	22.5	221.5	109.5	117.5	244
91.5	222	SF - 8	1	40.5	6.5	47	228.5	108	113.5	275.5
74.5	246	SF - 9	1	49	8.5	57.5	273.5	110	115	331
89	300	SF - 10	1	44	7.5	51.5	310.5	132	139.5	362
95	159	NC - 4	2	14	6	20	170	104	109.5	190
69	143.5									
97.5	179.5	NC - 5	2	15.5	5	20.5	190	82.5	95	210.5
111.5	86									
91.5	222	SF - 11	1	40.5	4.5	45	230.5	108	116.5	275.5
121	205.5	SF - 12	1	27	3.5	30.5	226	133.5	140	256.5
137.5	248									
92.5	191.5									
107	256.5	SF - 13	1	24.5	4	28.5	157.5	82	91.5	186
63.5	157	SF - 14	1	23.5	4.5	28	225.5	119.5	125	253.5
85.5	141									
88	174.5	SF - 15	1	20.5	12.5	33	190.5	125.5	140.5	223.5
107	202	NC - 6	2	19	3.5	22.5	164.5	86	99	187
79	164.5	NC - 7	2	19	5	24	186.5	92	104.5	211
82.5	148	NC - 8	2	20	4	24	152	67	83.5	177
71.5	217	NC - 9	2	16.5	6.5	23	228	105.5	141	251
72.5	146.5	NC - 10	2	18.5	4	22.5	192.5	99	117.5	215
76	195.5	NC - 11	2	12.5	6	18.5	162.5	94	123	181
62	157									
54	129	SF - 16	1	27.5	4.5	32	159.5	92.5	103	191.5
51	141									
46	194	SF - 17	1	29	8	37	171.5	88.5	109	208.5
54	159.5	NC - 12	2	18	6	24	156	80	94	180


TNMGRMU APRIL 2013 EXAMINA...
Medical - DUE 31-Mar-2013
What's New
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BY GIREESH GOURIKUTTYKUNJURAYAN 16101752 D.M. CARDIOLOGY
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ABSTRACT
Background: Angina with normal epicardial coronaries occurs in upto 20% of patients who underwent coronary angiogram for angina. Coronary slow flow comprises a separate group among this population designed Syndrome Y and accounts for upto 7% of patients undergoing CAG for angina. Coronary slow flow is characterized by the delayed passage of contrast injected into the epicardial coronaries. Conventionally, coronary slow flow is determined by the coronary filling time. We tried to determine whether coronary emptying time is a significant predictor of coronary slow flow
Methods: We selected patients, who underwent angiogram for angina and found to have normal epicardial coronaries, randomly between the study period November 2011 and November 2012. We assessed the coronary filling and emptying times at prespecified standard vascular landmarks on the basis of TIMI frame counts
Results: We analysed the angiograms of 37 patients. 27 patients had LAD slow flow and 17 patients had RCA slow flow(10 had normal flow in LAD and 12 had normal flow in RCA). 8 had non dominant small RCA and was excluded from the study. We observed positive correlation of coronary filling times and emptying times, both in LAD and RCA, in slow flow patients unlike those with normal flow. We found the filling times and emptying times are significantly prolonged in slow flow patients (p value <0.05) in LAD and RCA. Capillary and venous emptying time is prolonged in both LAD and RCA slow flow groups, but was significantly prolonged in RCA slow flow patients.(Pvalue <0.05, LAD slow flow group, P value 0.43). We observed slow flow significantly more in male population and significantly associated with high LDL/HDL ratios and high triglycerides.
Conclusion: Coronary emptying time is an independent and significant predictor of coronary slow flow phenomenon.
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ABSTRACT Background: Angina with normal epicardial coronaries occurs in upto 20% of patients who underwent coronary angiogram for angina. Coronary slow flow comprises a separate group among this population designed Syndrome Y and accounts for upto 7% of patients undergoing CAG for angina. Coronary slow flow is characterized by the delayed passage of contrast injected into the epicardial coronaries. Conventionally, coronary slow flow is determined by the coronary filling time. We tried to determine whether coronary emptying time is a significant predictor of coronary slow flow Methods: We selected patients, who underwent angiogram for angina and found to have normal epicardial coronaries,...