THE INTER-RELATIONSHIPS AND CLINICAL SIGNIFICANCE OF TRANSIENT ISCHAEMIC DILATION AND STUNNING OF THE LEFT VENTRICLE ON NUCLEAR MYOCARDIAL PERFUSION IMAGING.

DOCTOR LOUISE EMMETT BhB, MBChB (Auckland)

FRACP (Nuclear Medicine)

A thesis submitted in fulfillment of the requirements for the degree of Doctor of Medicine, The University of Auckland, 2014.

THESIS ABSTRACT

Background. Transient ischaemic dilation (TID) and left ventricular (LV) stunning on nuclear myocardial perfusion imaging (MPI) are important findings that convey a high risk of subsequent cardiac events. However, the mechanisms leading to TID or stunning on MPI, are not well elucidated. Further, detailed analysis of the clinical factors that may influence the present of TID, apart from severe coronary artery disease, have not been studied. The aim of this thesis was (1) explore the clinical significance of LV stunning on MPI, (2) to determine the likely pathophysiology of both TID and stunning on MPI using concurrent multimodality imaging, and (3) to undertake a careful multivariate analysis of likely clinical risks. *Methods*. The four published research papers that comprise the body of this research were prospective (3/4) and retrospective (1/4) and used database analysis of multiple clinical and imaging variables. They relied on assessment of both MPI functional data, on concurrent echocardiographic assessment of LV mass index and volumes, and on quantitative coronary analysis of angiographic correlative data (see METHODS section in each chapter). *Results and Conclusions*; (1) The presence of regional wall motion abnormalities on MPI are highly specific for high grade coronary angiographic stenoses. The sensitivity of a wall motion abnormality is higher than the presence of a perfusion defect (in stenoses >80%), which has important clinical relevance in reducing the false negative results in MPI, particularly in patients with significant left main disease. (2) All patients with TID had diabetes, LVH or both, suggesting the pathophysiology of these disease processes may play an integral role in the manifestation of TID on MPI. (3) The significant drop in both LVEF and increase in LV volumes measured in patients with TID on Adenosine MPI were not measurable on concurrent echocardiography. This suggests that TID on Adenosine MPI is not related to true myocardial stunning, but is a reflection of the severity of the underlying coronary flow reserve abnormality. This also explains the increased incidence of TID in patients with diseases affecting coronary microvascular function such as LVH and diabetes.

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INTRODUCTION TO THESIS AND REVIEW OF THE RELEVANT LITERATURE.

Myocardial perfusion imaging (MPI) is a powerful diagnostic and prognostic tool in patients with coronary artery disease. It is unique among cardiac imaging techniques in that it measures physiological not anatomical changes, and provides important complimentary information to anatomical imaging techniques. MPI measures perfusion to the myocardial muscle cells, which is a complex aggregate of both microvascular and macrovascular arterial function, and not just a measure of epicardial stenotic severity as often thought. For this reason MPI provides important added prognostic information in patients with known epicardial coronary artery disease. Important adverse prognostic indicators on MPI include the severity of both fixed and reversible perfusion defects (myocardial infarction and ischaemia), reduced left ventricular function after stress, and dilation of the left ventricle following stress (TID). This introduction aims to provide a comprehensive overview of myocardial perfusion imaging and the previous literature surrounding TID and myocardial stunning on MPI, allowing an insight into the clinical considerations that have led to the instigation of the research in this thesis.

FUNDAMENTALS OF NUCLEAR MYOCARDIAL PERFUSION IMAGING

Myocardial perfusion imaging is a noninvasive procedure that plays an important role in the risk assessment of patients with known or suspected coronary artery disease. While it is an important tool for the diagnosis of coronary artery disease, its strength lies in its powerful prognostic abilities. A constantly moving field, significant improvements have been made in recent years in techniques designed to improve specificity, positive predictive value, and diagnostic yield. It now provides information not only

on myocardial perfusion, but also on resting and post stress left ventricular volume, in addition to both systolic and diastolic function.

MPI involves the use of radiolabelled tracers that are extracted by myocardial cells directly proportional to blood flow.

These include Tc 99m SESTAMIBI, Tc 99m TETROFOSMIN or Thallium. All of these agents bind to the myocardial cells approximately proportional to cell blood flow. As coronary flow rates increase, such as with exercise or pharmacologic stress, the uptake of the tracer by the myocardial cells also increases. In this manner, it is possible to see areas of reduced perfusion in regions where the flow rate has not been able to increase, either due to a haemodynamically significant epicardial lesion, or due to microvascular dysfunction.

Myocardial cell uptake of tracer is not directly proportional to blood flow with the clinically available radioiosotopes. A plateau 'roll off' phenomena occurs at higher rates of coronary flow, above 2.5ml/min/g. While uptake of tracer into the cell is proportional to blood flow at lower flow rates, and at flow rates expected with exercise (3 x normal flow), the increased coronary flow rates achieved with Adenosine stress (4 x baseline resting cardiac flow) is not reflected with increased relative concentration of Adenosine. This is one of the hypotheses that Adenosine stress is not more sensitive than exercise stress[2].

Because the cells must be metabolically active to bind the tracer agent, the uptake by the cell is a reflection of both cell viability and blood flow. As the relationship between coronary blood flow and the uptake of myocardial perfusion tracer agents into myocardial cells is essentially linear at low flow rates, there is increased uptake of tracer with increasing blood flow in normally perfused and functioning myocardial tissue.

-The resting images reflect resting myocardial blood flow as well as myocardial cell viability, giving information on extent of myocardial infarction, and myocardial viability.

-The post stress images reflect the ability of the coronary arterial tree to deliver increased blood flow. If there is a haemodynamically significant epicardial coronary stenosis, flow in that vascular territory will not increase, and neither will the uptake of tracer. This will be seen as an area of reduced perfusion on the images, relative to the resting images and to the other vascular territories.

Post Stress Myocardial Perfusion

Resting myocardial perfusion

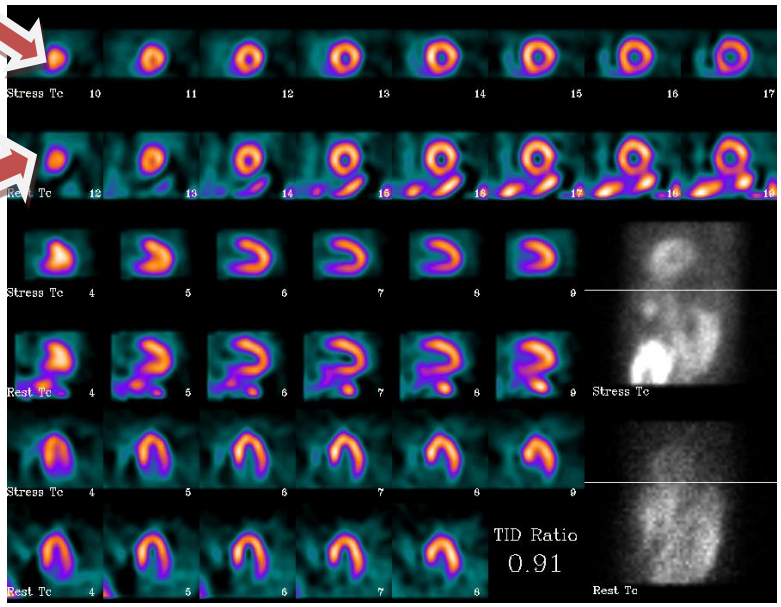


FIGURE 1.
A normal exercise myocardial perfusion study in a male patient.
The patient was injected with Tc-99m SESTAMIBI at rest and the resting images obtained 30 minutes later.

A further injection of Tc99m SESTAMIBI was then given when the patient was exercising maximally on the treadmill. Images were then acquired using a gamma camera 10 minutes post exercise.

A normal exercise myocardial perfusion study in a nondiabetic patient confers an excellent prognosis with a <0.5%/year risk of a coronary event for up to 6 years [1]

Comparison of resting perfusion to post stress perfusion images (reversible perfusion abnormalities) allows vascular territories at risk of myocardial infarction to be identified. The presence of significant coronary flow reserve abnormalities on MPI has important prognostic ramifications. The more severe the reversible perfusion abnormality, the higher the risk of a coronary event[3]. As shown by Brown et al; JNC 1996, there is almost a direct correlation between the severity of a reversible perfusion abnormality on MPI and the risk of a subsequent coronary event (Myocardial infarction or death). The prognostic value of both exercise and pharmacologic myocardial perfusion imaging is now well established with thousands of patients in multiple clinical trials[4].

Patients can undergo a variety of stress tests, depending on their exercise capacity. The optimum stress test remains a full exercise test with the patient achieving a minimum of 6 METS and a minimum of 85% of peak maximal heart rate for their age and sex. This provides incremental information of exercise capacity, the presence of angina and exercise ECG information for the patient. In this protocol, patients are injected with a flow radioisotope (either Thallium or Tc 99m SESTAMIBI) at peak exercise. The patient is then imaged under the gamma camera a short while later. The perfusion images obtained are a reflection of the perfusion of the perfusion at the time of stress. However, the functional information is a measure of volume and function at the time of imaging. For this reason, the time at which the post stress imaging is undertaken has been shortened, and is now recommended within 30 minutes post stress to identify patients who drop their LVEF post stress and have regional wall motion abnormalities that may identify them as patients at high risk of a coronary event.

Pharmacologic stress MPI is useful in patients who are unable to exercise adequately for a multitude of reasons. This can be undertaken using Adenosine, Dipyridamole or Dobutamine infusion. Both Adenosine and Dipyridamole increase coronary flow by 3 – 5 times baseline. Endogenous Adenosine induces vasodilation by its action on A2 receptors on cardiac arteriolar smooth muscle cells. There are a number of receptor subtypes, A2a in the coronary circulation and A2b in the systemic circulation. The A1 receptor is responsible for atrioventricular conduction delay and other receptors are responsible for the bronchospasm sometimes induced in patients with severe asthma or COPD.

Exogenous Adenosine is administered as a continuous infusion at a dose of 140mcg/kg/min for between 4-6 minutes. Using this protocol, Wilson et al; documented a 4.4 fold increase in coronary flow velocity using Doppler flow wires in normal coronary arteries [5]. In significantly stenosed arteries, the ability to augment flow with vasodilators is inversely related to the severity of the stenosis, in part due to the presence of dilation of microvasculature at baseline as a compensatory mechanism to maintain resting flow [6] MPI relies on the flow heterogeneity induced by coronary vasodilation to identify perfusion defects in patients with coronary artery disease [7]

Vasodilator flow agents rely on flow heterogeneity rather than inducing ischaemia directly. Severe myocardial ischaemia can occur rarely due to arterial steal in the presence of collateral circulation dependent vascular territories. This occurs when a vascular territory with a high grade stenosis is entirely reliant on blood flow from collaterals of another coronary artery. During maximal vasodilation coronary resistance decreases in the donor artery leading to increased flow in the normal area and reduced flow to the collaterals[8]. This makes vasodilator stress agents a safe method for stress testing patients with known coronary artery disease, except in the small subgroup of patients with critical triple vessel disease, or left main disease, in which large regions of myocardium are dependent on small caliber collateral vessels. With Adenosine, flow may also be redirected to the subepicardium away from the subendocardium in myocardium supplied by a stenosed vessel, resulting in subendocardial hypoperfusion [9] . The lack of significant ischaemia with vasodilator stress makes it less likely that findings associated with ischaemic myocardium seen on exercise or dobutamine stress echo, such as transient ischaemic myocardial stunning , would be frequently identified with vasodilator MPI.

The specificity of MPI has been a major limitation to the diagnostic value of the procedure. As the technique relies on radiation decay, specificity is limited largely due to attenuation artifact, with false positives occurring in LAD territory with breast shadow in women, and in RCA territory due to diaphragmatic fat in men. Use of Tc99m labeled tracer agents instead of thallium has significantly reduced the problem of attenuation. Simple procedures such as prone imaging (reimaging the patient lying on their front, not their back to allow the fat to settle in a different position), have significantly improved the specificity of the procedure with no significant change in sensitivity. Slomka et al; undertook both prone and supine imaging on 700 women undergoing routine MPI [10]. They found that use of both images to assess artifact improved specificity from 72% to 94%, with no significant change in sensitivity (86%).

The sensitivity of MPI for the detection of significant coronary artery stenoses is estimated at between 85% to 93% dependent on the techniques and isotopes used [11]. This has not increased significantly with improvements in the technique, and the lower sensitivity likely relates to variations in

the pathophysiology of individual stenoses, as much as to the resolution limitations of the technique. An 80% coronary artery stenosis may have good collateral supply, or well preserved endothelial function, allowing arterial dilation that will lead to normal perfusion in the vascular territory with the known stenosis. This may limit diagnostic sensitivity, but leads to excellent prognostic outcome information in patients with known significant stenosis, which is likely the tests long-term clinical role.

While sensitivity for the detection of any coronary artery disease of >50% stenosis is relatively high, the ability to accurately detect the second or third vascular stenosis in multivessel disease, is poorer [12]. Unlike PET flow tracer agents, the SPECT imaging technique is unable to measure absolute myocardial blood flow. Instead, the technique relies on relative changes in myocardial perfusion. The computer assumes that at least a small region of the post stress myocardium must have 'normal myocardial flow', and normalizes the area with the highest counts on the post stress images, to the resting images. For this reason, false negative results, or underestimation of the extent of ischaemia can occur, particularly when all coronary vascular territories have a similar burden of coronary artery stenoses. The computer will still pick the brightest area of the myocardium to be 'normal', even if, in reality, the perfusion in that area is reduced. This is referred to as 'balanced ischaemia'. This means that, in a small group of patients with severe triple vessel disease, the perfusion pattern may only look mildly abnormal, and in some instances, completely normal[12]. A recent study looking at patients with left main disease found that if a perfusion abnormality (> 5% of myocardium) was the only criteria for determining an abnormal scan, MPI missed 13% of patients and only 59% of patients were identified as 'high risk'. When other criteria such as transient ischaemic dilation, reduced post stress left ventricular function, abnormal ECG or blood pressure responses to stress were included, 87% of patients were properly identified as 'high risk' [13]This is one of the major limitations in the diagnostic value of MPI. To maximize sensitivity of MPI, it is important to look at other non perfusion signs that indicate a high risk of coronary events. These signs include the presence of transient ischaemic dilation, reduced post stress left ventricular function, stress induced regional wall motion abnormalities, and, occasionally, prominence of right ventricular wall perfusion on the post stress images [14].

Advances in the use of radionuclide tracers, the count rate capabilities of the new cameras and the memory and speed of computer systems have incrementally improved the non perfusion diagnostic information that can be gleaned from myocardial perfusion imaging for the benefit of the patients. The introduction and preferential use of the Technetium labeled flow agents such as Tc 99m Methoxyisobutylisonitrile (MIBI) rather than Thallium has enabled the additional detailed evaluation of both resting and post stress myocardial left ventricular function, regional wall motion abnormalities, myocardial volume assessment, and myocardial stunning. Technetium gives off a 140Kev gamma ray, which is excellent for medical imaging, and which allows reduced attenuation artifact and a higher count rate image than previously possible with Thallium. This has meant that the ECG gated imaging and assessments of LV volumes and function have become more reproducibly accurate, and allows the assessment of both rest and post stress left ventricular function and regional wall motion.

FIGURE 2.

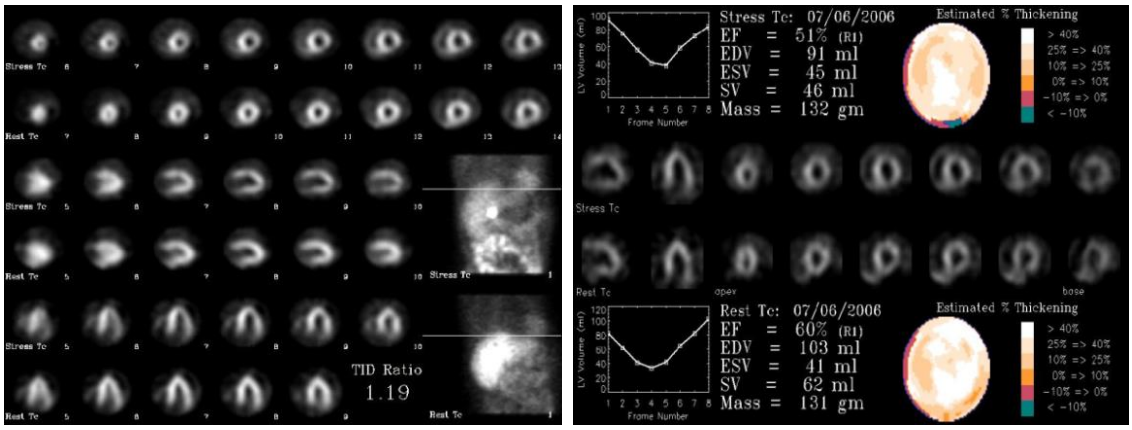


Figure 2: These are the single day Tc 99m SESTAMIBI myocardial perfusion images of a patient subsequently found to have high grade multivessel disease on coronary angiography. The myocardial perfusion images demonstrate both severe reversible perfusion abnormalities and dilation of the left ventricle post stress. There is a drop in LVEF of 9% between the resting and post stress images, consistent with a diagnosis of myocardial stunning. The ventricle dilatation visualized post stress is a finding described as 'Transient Ischemic Dilation'.

MYOCARDIAL STUNNING

Myocardial stunning is characterized by prolonged non-permanent post ischaemic systolic (and/ or diastolic) left ventricular dysfunction. It can occur due to an acute ischemic injury, or following significant stress-induced myocardial ischemia[5-7]. The ability of stress and rest ECG-gated Tc-99m SPECT myocardial perfusion imaging (MPI) to provide myocardial perfusion data as well as resting and post stress left ventricular function, affords the opportunity to further evaluate the frequency and clinical relevance of stress-induced reduction in LVEF and wall motion abnormalities on MPI.

The delayed return of contractile function following exercise in patients with coronary artery disease and in dogs with known coronary stenoses has been well documented [15, 16]. By definition, myocardial *stunning* is present if left ventricular dysfunction is reversible and persists when myocardial perfusion has returned to normal [17]. That myocardial stunning occurs post exercise in patients with coronary artery disease was elegantly demonstrated by Ambrosio *et al* who studied 30 patients with known coronary artery disease to determine the period of time that stunning of the myocardial wall persisted following cessation of exercise [18]. They found that in previously ischemic regions, the regional ejection fraction remained at only 82% of baseline and systolic thickening was impaired for up to 45 min post-exercise. They showed that less severe angiographic lesions were associated with more prompt resolution of regional contractile abnormalities.

Good correlation has been demonstrated between the severity of myocardial perfusion defects and a drop in post stress left ventricular ejection fraction (LVEF) on MPI [19, 20]. An association has also been demonstrated between stress induced regional wall motion abnormalities and severe perfusion defects [21]**.** However, to date there is little information available as to the significance of an exercise-stress induced stress induced regional wall motion abnormality on nuclear myocardial perfusion imaging with respect to the angiographic findings. It is one of the aims of this thesis to determine the angiographic and prognostic significance of both reversible wall motion abnormalities (regional stunning) and

reduction in left ventricular function (global myocardial stunning) present on MPI post exercise stress (see Chapter 1).

Myocardial stunning has been shown to occur relatively frequently with both exercise and Adenosine MPI, being found in up to 32% of those with ischaemia on vasodilator MPI in one study [19, 20, 22]. Barnes et al[23]; showed a similar drop in LVEF post stress in patients with ischaemia undergoing exercise and dobutamine stress, using echocardiographic techniques. However, MPI tends to use vasodilator agents rather than Dobutamine as pharmacologic stress agents. Vasodilator agents (Dipyridamole or Adenosine) act to increase myocardial blood flow, and use techniques that assess the relative increase in blood flow in different vascular territories, rather than inducing myocardial ischaemia directly (except in rare instances of a collateral dependent coronary circulation). Explaining a high incidence of myocardial stunning post vasodilator stress on the basis of myocardial ischaemia, is theoretically difficult. As MPI is a physiological rather than an anatomical imaging technique, it is possible that the measured changes in LVEF and left ventricular volumes with pharmacologic stress are not real, but due to a shift in the measured endocardial perfusion edge. To date, there have been no studies undertaken that assess either the clinical implication of global or regional myocardial stunning on myocardial perfusion imaging, or the underlying pathophysiological process that is occurring. One of the aims of this thesis is to explore the functional changes occurring in the left ventricle during vasodilator stress, to determine if the dilation and reduced LVEF post stress evident in patients with significant ischaemia is a real phenomena related to reduced myocardial contractility, or if the dilation on MPI is more a physiologic phenomena related to underperfused subendocardium post stress.

Because the perfusion agents (SESTAMIBI and Thallium) used in MPI are taken up proportional to blood flow at a myocardial cell level, the results of MPI reflect not only haemodynamic function of the epicardial coronary arteries, but also the vascular function of the smaller vessels. It is now well recognized that a myocardial perfusion image may be abnormal even in the presence of normal coronaries on angiography. This is seen in patients with significant microvascular or endothelial dysfunction such as in patients with hypertrophic obstructive cardiomyopathy[24, 25], diabetes[26], or with systemic

inflammatory disorders such as systemic lupus erythematosis[27]. This can sometimes also explain a 'false positive' finding, when a patient with an abnormal MPI has a normal coronary angiogram[25].

Marcelo Di Carli et al, in a series of studies assessing myocardial blood flow using PET tracer agents on asymptomatic patients with diabetes, found that diabetics have impaired arterial endothelial function compared to healthy controls[26, 28, 29]. Further, diabetics with significant sympathetic nerve dysfunction demonstrate more marked coronary flow reserve abnormalities than diabetics with intact sympathetic nerve function, even in the presence of normal coronary arteries on coronary angiography. [26, 28, 29] This helps to explain, at least in part, the poorer prognosis in diabetic patients, particularly women, with abnormal myocardial perfusion, even in the presence of a similar CAD burden to nondiabetics [30].

The diabetic population is one which benefits from MPI, the pathology of diabetes making traditional symptoms less reliable. The DIAD (The Detection of Ischemia in Asymptomatic Diabetics) trial assessed the incidence of ischaemia in 1123 asymptomatic type II diabetics using Adenosine MPI. The study found that 22% had an abnormal Adenosine MPI, and that abnormal perfusion and 'silent ischaemia' was more prevalent in those diabetic patients with poor glycaemic control and evidence of autonomic dysfunction. While the sensitivity and specificity of MPI for diabetics is similar to the general population, prognostic outcome is markedly different. MPI effectively stratifies diabetic patients into low and high risk groups, although, diabetic patients are at higher risk of a cardiac event than non-diabetics at every level, particularly diabetic women [30, 31]. Additionally, the good prognosis conferred with a normal MPI study is more short-lived in diabetics, rising sharply after one year [1]. While it has been shown that both diabetes, and other disease processes that affect microvascular function such as hypertrophic cardiomyopathy can cause impaired coronary flow reserve and reversible perfusion abnormalities on MPI even in the absence of significant coronary artery disease, the effect of these disease processes on the prevalence and prognostic value of Transient ischaemic dilation or myocardial stunning on MPI has not been thoroughly evaluated.

FIGURE 2.

Image A. Image B.

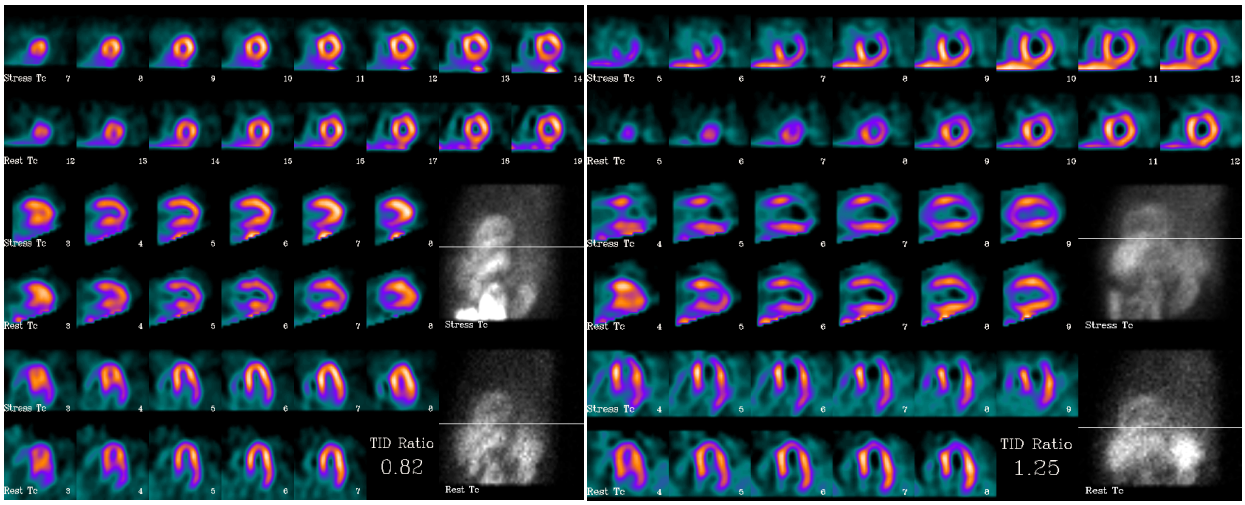


Figure 3. Image A: demonstrates an Adenosine MPI with minimal reversible perfusion abnormalities in an asymptomatic diabetic patient with known low grade triple vessel disease (60% stenosis in each vascular territory).

Image B: is the same patient 18 months later. Now the image shows TID and multiple severe reversible perfusion defects. A high risk scan that has change markedly in a short period of time.

TRANSIENT ISCHEMIC DILATION

Transient ischaemic dilation (TID) is an important adverse prognostic indicator on myocardial perfusion imaging. TID is an infrequent finding on both exercise and pharmacologic stress MPI occurring in 14% of scans, and is an estimation of the physical dilation of the left ventricle between the fused rest and post stress perfusion images on myocardial perfusion imaging[32]. This dilation can be assessed both visually and quantitatively, with a number of quantitative cutoffs validated based on the type of MPI protocol undertaken[3]. Dilation of the left ventricle post stress (TID) is a powerful predictor of poor

outcome, and has been shown in a number of studies to be highly specific for haemodynamically significant left main coronary artery disease, high grade LAD disease and triple vessel disease [32-39]. Transient ischaemic dilation of the left ventricle was first described by Stoltzenburg et al in 1981 [40]. It has subsequently been identified with all myocardial perfusion agents and protocols, including dual isotope protocols, thallium and Technetium labeled perfusion agents, although the quantitative cutoffs that indicate a significant TID ratio vary, dependent on the protocol used[36, 41-43].

TID is a poor prognostic sign carrying an 11-60%/year cardiac event rate, based on multiple studies, and is highly specific for high grade epicardial stenoses of the LAD, left main, or multivessel disease[32, 34, 36, 44]. The literature is divided as to whether TID is a real phenomena, related to absolute dilation of the LV cavity due to myocardial stunning, or whether the phenomena is physiological, and due to reduced perfusion of the subendocardium with stress, leading to apparent dilation of the ventricular cavity [33, 45, 46]. No multimodality imaging studies have been undertaken to properly assess this.

A recent large study assessing the prognosis of patients with TID and normal perfusion on myocardial perfusion SPECT imaging, found that TID was an independent predictor of cardiac events. Even in those patients with normal myocardial perfusion, those with TID demonstrated a 2.4%/year cardiac event rate compared with a < 1%/ year event rate for patients with no TID. However, this is far lower than the 11.4%/year cardiac event rate previously reported in a broader group of patients with TID[47]. Were all TID in patients with normal perfusion due to 'balanced ischaemia' and multivessel CAD, the cardiac event rate would be expected to be higher. This discrepancy suggests that the pathology leading to the presence of TID is unlikely to be related to macrovascular CAD alone.

TID has been documented in the HOCM population in the absence of significant coronary artery disease[24], and also in a patient with left ventricular hypertrophy, normal coronary arteries on angiography and normal perfusion on MPI[27]. However, the underlying pathophysiology, and the clinical risk factors apart from coronary artery disease that predispose a patient to manifest TID on myocardial perfusion scan has not been well evaluated. Further, there has been no good multivariate

analysis of other clinical factors that may influence the incidence of TID, especially those factors that have an effect on coronary microvascular function, such as diabetes, smoking or left ventricular hypertrophy.

CONCLUSION:

The aim of this thesis is to explore the clinical significance of left ventricular stunning on myocardial perfusion imaging, to determine the likely pathophysiology of both TID and stunning on MPI using concurrent multimodality imaging, and to undertake a careful multivariate analysis of likely clinical risks for TID and stunning. The impact of this thesis will be to better guide clinical outcomes based on the findings of this research, and to gain a better understanding of the reasons behind these adverse prognostic signs, that are not infrequently seen on myocardial perfusion imaging.

CHAPTER ONE

Reversible regional wall motion abnormalities on exercise Tc-99m gated cardiac SPECT predict high-grade angiographic stenoses.

AUTHORS' NAMES:

Louise **Emmett**^, MBChB; Robert M. **Iwanochko**^, MD; Michael R. **Freeman**[$], MD, FACC; Alan **Barolet**[&], MD; Douglas S. **Lee**, MD^; Mansoor **Husain**^*, MD

INSTITUTIONS:

^Robert J. Burns Nuclear Cardiology Laboratory, Toronto Western Hospital

[$]Terrence Donnelly Heart Centre, St. Michael's Hospital, Toronto

[&]Division of Cardiology, Mt. Sinai Hospital, Toronto

^[$&]Department of Medicine, University of Toronto

INTRODUCTION:

Myocardial stunning can occur due to an acute ischemic injury, or following significant stress-induced myocardial ischemia[15, 16, 18]. The ability of stress and rest ECG-gated Tc-99m SPECT myocardial perfusion imaging (MPI) to provide myocardial perfusion data as well as left ventricular function, affords the opportunity to further evaluate the frequency and clinical relevance of stress-induced myocardial stunning.

The value of ECG-gated SPECT MPI of the higher dose post stress-images has been demonstrated for left ventricular function[48, 49] , myocardial viability [50] and the assessment of perfusion artifacts due to tissue attenuation[51, 52]. With newer cameras and software, gating of both the rest and stress Tc-99m Sestamibi SPECT perfusion data in single day protocols is possible and a good correlation has been demonstrated between the severity of myocardial perfusion defects and a drop in post stress left ventricular ejection fraction (LVEF)[20, 21]. An association has also been demonstrated between regional wall motion abnormalities (RWMA) and severe perfusion defects [19]**.** However, to date there is little information available as to the significance of an exercise-stress induced RWMA with respect to the angiographic findings [53]. Indeed, this relationship has not previously been studied in patients with resting perfusion defects nor has it involved gating of rest images.

The purpose of this study was to determine the severity and extent of angiographic stenoses at which *reversible* RWMA are present on exercise stress gated Tc-99m SPECT MPI, and whether assessments of stress and rest RWMA add incremental information to the treadmill exercise ECG and MPI data.

METHODS:

***Study Population*:** The study included consecutive patients referred for routine single day Tc-99m Sestamibi rest and exercise ECG-gated SPECT myocardial perfusion imaging (MPI) between January 1999 and June 2000 (2330 patients) who also underwent coronary angiography within 6 months of their perfusion imaging (132 patients), and had no cardiac event (myocardial infarct) or a revascularization procedure in the interval between the MPI and angiogram (112 patients). A further 12 patients were excluded for incomplete exercise, MPI or coronary angiographic data leaving a total of 100 patients to form the study group.

Exercise Protocol: Exercise stress was performed in all patients using a Bruce protocol treadmill test. Nitrates and β-blockers are not routinely stopped prior to MPI in our laboratory. In our study population, 13% were taking long acting nitrates and 40% were taking β-blockers at the time of exercise. Accepted endpoints for exercise stress included achievement of 85% of target heart rate, > 2mm ST segment depression on the exercise ECG, or typical ischemic chest pain. A total of 70 patients reached a minimum 85% of target heart rate. Of the 30 who did not achieve target heart rate, 21 had a positive exercise ECG and 6 had typical exercise-induced angina, with only 3 not achieving a target endpoint.

Radionuclide Protocol: A same-day rest-exercise gated Tc-99m Sestamibi SPECT myocardial perfusion protocol (n=67) or exercise-rest gated SPECT MPI (n=33) was performed. The initial study was performed with 300 MBq Tc-99m Sestamibi, followed by the second portion of the exam using 900 MBq at least 4 hours following the first injection. Rest images were obtained 1

hour following the injection of Tc-99m Sestamibi. In all patients, post-exercise image acquisition was commenced within 15-30 minutes following the end of exercise stress.

SPECT Imaging Protocol: Images were obtained over a 180 degree orbit from right anterior oblique 45^{o} to left posterior oblique 45^{o} using a dual head-variable angle gamma camera equipped with ultra high resolution collimators. For image acquisition, a 20% acceptance window around the 140KeV photopeak was used. Sixty-four projections were acquired at 25-seconds/ projection for 300MBq studies versus 21-seconds/ projection for 900MBq studies. A 64 x 64 x 16 matrix was utilized for all studies. Both rest and stress acquisitions were gated at 8 frames/cycle, with 100% beat acceptance. The projection data sets were pre-filtered using a Butterworth filter (order 5, cut-off 0.66 for high dose acquisitions, order 10, cut-off 0.50 for low dose acquisitions) and reconstructed using filtered backprojection. When necessary, images were motion corrected manually.

Scan Interpretation*:* All images were visually interpreted using a semi-quantitative method by the consensus agreement of at least 2 experienced observers blinded to the clinical or angiographic findings of the patient. Scoring of perfusion images was performed on non-gated images. However, gated images were made available at this session for the exclusion of attenuation defects. Actual *scoring* of wall motion segments was performed with gated images only, and carried out several weeks removed from the session at which perfusion scores were assigned. Neither the non-gated perfusion images, nor the segmental perfusion scores, were available at the time of wall motion scoring. The rest and post stress images were interpreted for the presence, extent, severity and reversibility of perfusion and wall motion defects. A 20

segment model of the left ventricle was used for scoring perfusion defects, with a 5 point scoring system for defect severity (0 = normal perfusion, 1 = equivocal or mildly reduced, 2 = moderate reduction, 3 = severe reduction, 4 = absent perfusion) (13). A Summed Stress Score (SSS) was calculated as the sum of all scores on the stress scan, a Summed Rest Score (SRS) as the sum of all scores on the rest scan, and a Summed Difference (i.e. reversibility) Score (SDS) was calculated as the difference between the summed stress and rest scores. For interpretation of the wall motion component of the study, both rest and stress gated images were assessed simultaneously by 2 experienced observers blinded to the results of the myocardial perfusion, clinical or angiographic findings of the patients. Gated images were displayed as 3 short axis slices with wall contours removed. Rest and stress gated images were displayed adjacently to allow for assessment of a change in regional wall motion. The left ventricle was again divided into the same 20-segment model for scoring. A composite severity score was utilized which accounted for both wall motion and wall thickening within each segment. A severity scoring system of 0 - 4 was used for each segment (0 = normal wall motion and thickening, 1 = mild hypokinesis/reduced thickening, 2 = moderate hypokinesis/reduced thickening, 3 = severe hypokinesis/reduced thickening, 4 = akinesis/absent thickening. A Summed Stress Score for Wall Motion (SSSWM) was determined from the sum of the scores on the stress-gated image, which reflects the degree and extent of post-stress Regional Wall Motion Abnormality (RWMA). The Summed Rest Score for Wall Motion (SRSWM) is the sum of the scores on the rest-gated images, which thus reflects the degree and extent of fixed RWMA. The Summed Difference (i.e. reversibility) Score for Wall Motion (SDSWM) is the difference between SSSWM and SRSWM, and reflects the degree and extent of *reversible* RWMA. Left ventricular ejection fraction (LVEF) and end systolic volume (ESV) were also recorded for both the rest and stress images

using a previously validated automated algorithm and this estimation was confirmed visually (14). Johnson *et al* (12) determined the serial reproducibility of LVEF estimation to be ± 5% (2 SD from the mean). We considered a drop in LVEF of ≥5% to be significant for the purposes of statistical analysis. The presence or absence of transient ischemic dilation (TID) was determined by the visual consensus of the two experienced observers. No attempt to record the severity of TID was made in this study. To allow for statistical correlation with angiographic findings, the 20 perfusion segments for both perfusion and wall motion were divided into *anterior*, *inferior* and *lateral* vascular territories.[54].

Angiographic Analysis: All coronary angiographic studies were read with the consensus of two experienced observers blinded to the clinical and perfusion findings of the patients. The site (distal or proximal) of angiographic stenoses were identified visually, however, severity of angiographic stenoses was assessed by a validated quantitative coronary stenosis analysis (QCA)[55]. In patients with previous coronary artery bypass surgery (7/100), both the site and severity of disease in native vessels and bypass grafts was documented. Dominance of the right versus the circumflex artery was determined. A coronary artery jeopardy score was calculated according to the method described by Califf *et al[56]*. Briefly, this method assigns a score of 2 for a coronary angiographic stenosis of >75% in the left anterior descending artery, major septal perforator, left circumflex artery, obtuse marginal branch and the posterior descending artery. In patients with a left dominant system, the right coronary artery is assigned no points. Each vessel distal to a 75% or greater stenosis is also given a score of 2 points (to a maximum of 12 points). For the purposes of statistical analysis and comparison to perfusion imaging, angiographic findings were divided into *anterior*, *lateral* and *inferior* vascular territories. The *anterior*

territory included stenoses within the left main, the left anterior descending, the diagonal and the septal perforator arteries. The *lateral* territory included the circumflex and obtuse marginal arteries and the *inferior* territory included the right coronary and posterior descending arteries.

Statistical analysis: Continuous data are expressed as mean ± SD. Comparisons were made using Student's t-test for normally distributed variables and Wilcoxon rank sum test for nonparametric analysis. Categorical data were assessed using the chi-square or Fisher's exact test where appropriate. For multivariate analysis, a backward stepwise elimination method was employed in a least squares linear regression model. Variables with a level of significance $p<0.10$ on univariate analysis were entered into the multivariate regression model employing a multivariate significance level of $p<0.05$ (two-sided). The model was also re-evaluated with a stepwise multivariate regression approach, by adding univariate predictors into the model and assessing for the incremental change in residual variance of the model. We were cautious to avoid highly collinear covariates and variables resulting in high variance inflation in the modeling strategy. Residual plots were constructed to test the validity of the statistical assumptions of the linear regression model. A Pearson correlation coefficient was used to evaluate associations between the predefined perfusion variables and RWMA scores if the variables assessed satisfied the assumptions of normality. Comparison of sample correlation coefficients was performed via Fisher's z transformation of sample R estimates (two-sided). Sensitivity, specificity, positive and negative predictive value were determined for the summed stress (SSS) and summed defect reversibility (SDS) perfusion scores, as well as the summed stress (SSSWM) and summed defect reversibility (SDSWM) wall motion scores, for predicting

angiographic stenoses of both >50% and >80%. Statistical analyses were performed using SYSTAT ® 9.0 (SPSS Science, Chicago, IL) and SAS v8.0 (SAS Institute, Cary, NC)

RESULTS:

Patient Characteristics: The study population consisted of 23 females and 77 males with a mean age of 60 ± 9 years. The most common reason for referral was for the diagnosis of chest pain (55%), which divided equally between patients with typical (27%) and atypical (28%) angina. Another 29% of patients had a documented history of prior myocardial infarction, and these patients were referred for risk-stratification. Clinical characteristics stratified by the presence or absence of a reversible RWMA are shown in Table 1.

Patients with reversible RWMA were older (64±8 years, n=37) and more likely to be male (92% or 34/37) than patients that did not show a reversible RWMA (Age: 58±10 years, n=63, p=0.003; Male: 68% or 43/63, p=0.007). Significantly more patients with a reversible RWMA had a post-stress or resting perfusion defect than those that did not have a reversible RWMA (post-stress perfusion defect: 97% or 36/37 vs. 59% or 37/63, p=0.001; resting perfusion defect: 73% or 27/37 vs. 46% or 29/63, p=0.009).

Table 1. Patient Characteristics in the Presence or Absence of a Reversible Regional Wall Motion Abnormality.

Variable	Reversible RWMA* (n=**37**)	No Reversible RWMA* (n=**63**)	P value
Age (years)	64±8	58±10	0.003
Female Gender	8% (3)	32% (20)	0.007
History of Prior MI	38% (14)	24% (15)	NS
History of CABG	11% (4)	5% (3)	NS
Stress-Rest Protocol	43% (16)	27% (17)	NS
Duke Treadmill Score	-2.8□7.7	-0.8□7.0	NS
Stress Perfusion Defect **	97% (36)	59% (37)	0.001
Resting Perfusion Defect ***	73% (27)	46% (29)	0.009

Summed Defect Reversibility Wall Motion Score (SDSWM) ≥ 2

** Summed Stress Perfusion Score (SSS) ≥ 4

***Summed Rest Perfusion Score (SRS) ≥ 4

Table 1. Patient Characteristics in the Presence or Absence of a Reversible Regional Wall Motion Abnormality. Mean ± SD of continuous variables and percentages of patients with dichotomous variables are shown for those with (n=37) and without (n=63) a reversible regional wall motion abnormality (RWMA). *Patients classified as having a RWMA are those with a summed defect reversibility wall motion score (SDSWM) ≥2; **Patients classified as having a post-stress perfusion defect are those with a summed stress perfusion score (SSS) ≥4; ***Patients classified as having a resting (fixed) perfusion defect are those with a summed rest perfusion score (SRS) ≥4; MI: myocardial infarction; CABG: coronary artery bypass graft; NS: not statistically significant as defined by p>0.05.

Coronary Angiography: All patients in our study had undergone coronary angiography within 6 months (58±50 days) of their MPI study and only those with no interval cardiac event or revascularization procedure were included. In 88% of cases, patients underwent coronary angiography *following* MPI. In our population, 26% of patients demonstrated no hemodynamically significant lesions on coronary angiography, 25% had single vessel disease (>50% stenosis), 19% double vessel disease and 30% triple vessel disease.

Myocardial Perfusion: Perfusion imaging revealed 9% of patients to have only *fixed* perfusion defects (SRS≥4, SDS≤2), 47% to have *fixed and reversible* perfusion defects (SRS≥4 and SDS≥2), and 24% with only *reversible* perfusion defects (SRS≤4 and SDS≥2). A standard cut off of SSS<4 was used to define *normal* perfusion (17,18), and 20% of the study population were so categorized. The sensitivity and specificity for the perfusion component of the study is demonstrated in Figure 1. In our study population, perfusion imaging alone achieved a high sensitivity (88%) and reasonable specificity (63%) for the diagnosis of angiographic stenosis >70%.

Regional Wall Motion: Thirty seven percent (37/100) of patients in the study demonstrated a reversible regional wall motion abnormality (SDSWM≥2). The presence or absence of a *reversible* (SDSWM≥2), *post-stress* (SSSWM≥2) and *fixed* (SRSWM≥2 and SDSWM<2) RWMA were compared to the grade of angiographic stenoses within the anterior, inferior and lateral vascular territories. No *reversible* RWMA (SDSWM≥2) were detected with an angiographic stenosis <70%. Thus, the specificity of a reversible RWMA for detecting angiographic stenoses of ≥70% is 100% (Figure 1).

FIGURE 1.

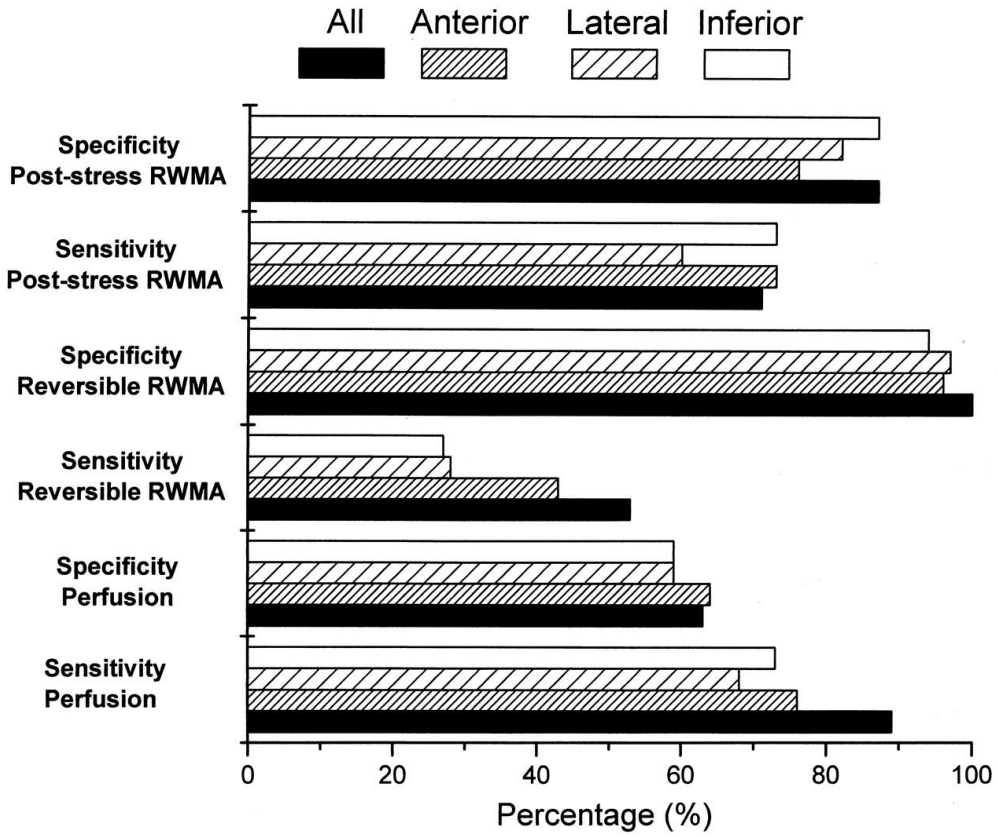


Figure 1 . Sensitivity and Specificity of Perfusion, Reversible RWMA, and Post-Stress RWMA for Angiographic Stenoses of >70% by Vascular Territory. The overall and vascular territory-specific ability of Tc-99m Sestamibi myocardial perfusion SPECT to detect (sensitivity) and exclude (specificity) angiographic stenoses >70% on the basis of a post-stress perfusion defect (SSS□4), reversible RWMA (SDSWM□2) and post-stress RWMA (SSSWM□4) are shown. Vascular territories are defined as myocardial segments supplied by the following coronary arteries: Anterior = left anterior descending, septal, and diagonal; Inferior = right and posterior descending; Lateral = circumflex and obtuse marginal.

Using the *post-stress* RWMA score (SSSWM≥2), the sensitivity of a RWMA for detecting an angiographic stenosis >70% was 73%, 60% and 73% for the anterior, lateral and inferior vascular territories respectively (Figure 1).

When complete occlusions were excluded and patients were stratified by the severity of their angiographic stenoses (50-79% and 80-99%), the presence of a *reversible* RWMA distinguished higher angiographic severity with a positive predictive value of 77%, 86% and 88% for the anterior, inferior and lateral coronary vascular territories respectively. Figure 2 compares the prevalence of reversible RWMA and reversible perfusion defects in patients with angiographic stenoses of 50-79% (mean and median ~70%) and 80-99% (mean and median ~90%). For all vascular territories, reversible RWMA were more often detected than reversible perfusion defects in the presence of high-grade (>80%) angiographic stenoses (Figure 2).

Protocol: Both rest–stress (n=67) and stress–rest (n=33) imaging protocols were used in this study. The stress-rest protocol was significantly less sensitive for the detection of angiographic stenoses >70% for both perfusion imaging (*77% (20/26) for the stress-rest vs. 95% (42/44) for the rest-stress protocol*) and the post-stress RWMA (*65%(17/26) for the stress-rest and 75% (33/44) for the rest-stress protocol ($p<0.004$*)). The sensitivity of reversible RWMA for >70% angiographic stenoses was higher in the stress-rest group than the rest-stress group *(61% (16/26) vs. 47% (21/44)).*

FIGURE 2

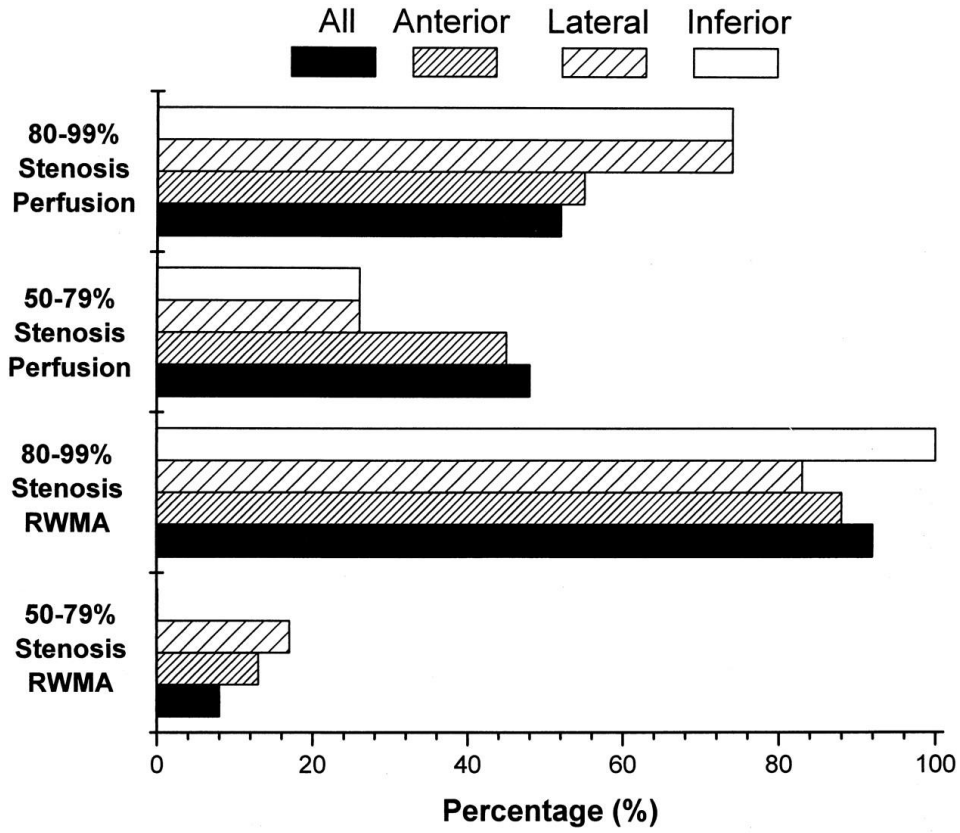


Figure 2. Prevalence of Reversible Regional Wall Motion Abnormalities and Reversible Perfusion Defects with Varying Degrees of Angiographic Coronary Stenosis by Vascular Territory. The percentage of patients with angiographic stenoses of 50-79% (mean and median ~70%) and 80-99% (mean and median ~90%) that show reversible regional wall motion abnormalities (SDSWM□2) as compared to those that show reversible perfusion defects (SDS□2) are shown for specific coronary artery territories (Anterior = left anterior descending, septal, and diagonal; Lateral = circumflex and obtuse marginal; Inferior = right and posterior descending).

Gender: Perfusion imaging was more specific for the detection of significant CAD in women in this study than in men *(91%(10/11) vs. 61%(8/13)*), while reversible RWMA was less sensitive in men than women (3/12-25% vs. 34/64-53%). The Post-stress RWMA was less sensitive and more specific in women than in men (*4/12-33% vs. 47/64-73% and 11/11-100% vs. 6/13-46% respectively*). In this study, women had a higher incidence of normal coronary angiography than men (11/23 vs. 15/77, $p<0.001$), and a lower incidence of multivessel disease (4/23 vs. 46/67, $p<0.008$).

Correlation between Perfusion & Wall Motion: Figure 3 reveals the correlation between the severity of *reversible* RWMA (SDSWM) and reversible perfusion defects (SDS).. While a significant correlation between the severity of reversible perfusion defects and reversible RWMA is observed in all patients this relationship tended to be stronger when patients with significant fixed perfusion defects (SRS≥4, n=55) were excluded from the analysis (Figure 3: $R=0.61$, $p<0.0001$, n=100 vs. $R=0.76$, $p<0.0001$, n=45; $p=0.09$). Correlation between the severity of reversible perfusion defects and reversible RWMA tended to be stronger in the anterior vascular territory ($R= 0.59$ for the anterior wall vs. $R = 0.46$ and $R=0.46$ for the inferior and lateral wall respectively).

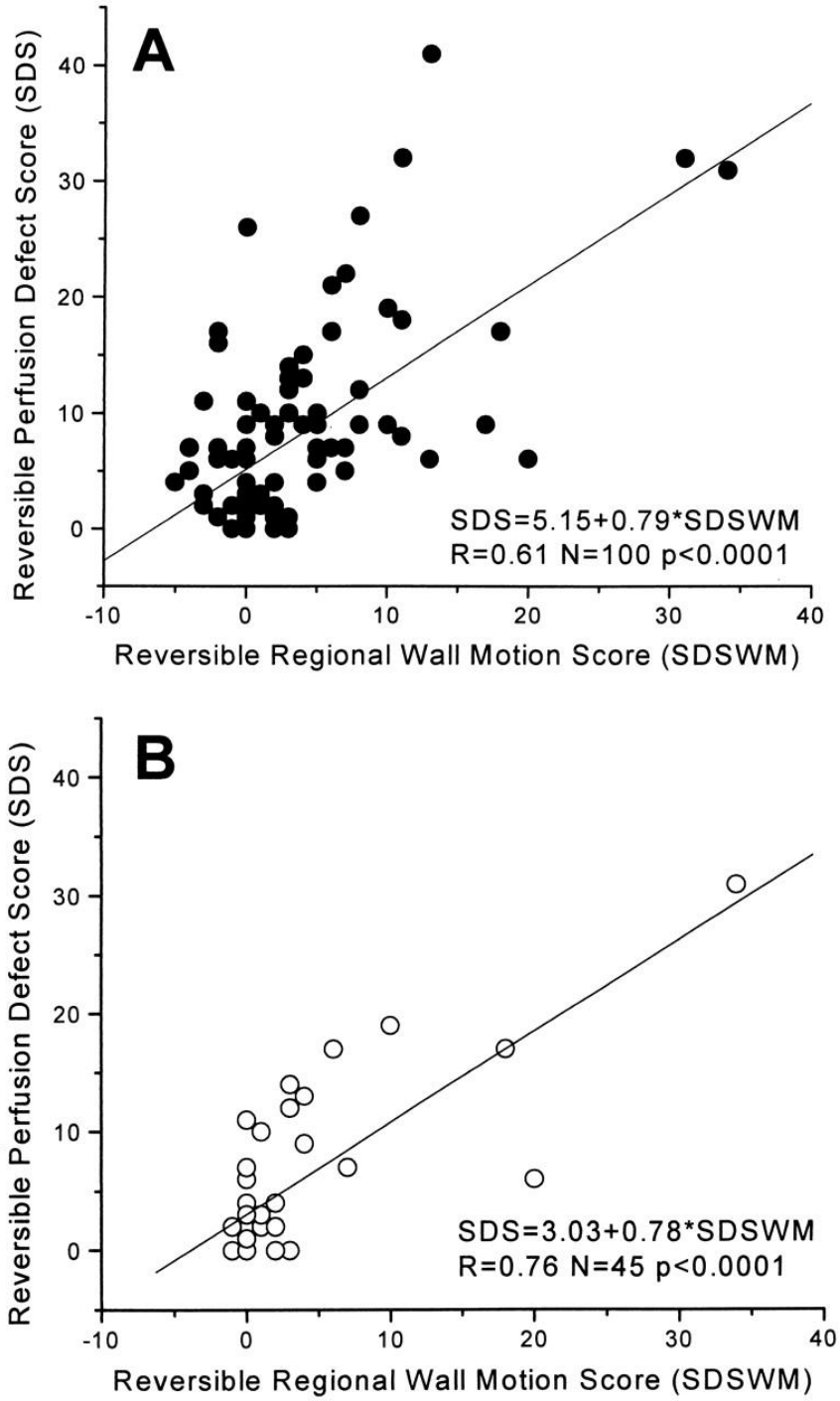


Figure 3. Correlation of Reversible Perfusion Defects and Reversible Regional Wall Motion Abnormalities. Scatter-plots and correlation coefficients between reversible perfusion (SDS) and reversible regional wall motion (SDSWM) defect scores are shown. Panel A includes all patients (closed circles; n=100). Panel B is an analysis excluding patients with significant fixed perfusion defects (SRS<4; open circles; n=45).

Transient Ischemic Dilation: As with reversible RWMA, no transient ischemic dilation (TID) was present with an angiographic stenosis of <70%. When assessed by the extent of angiographic stenoses, TID was most strongly associated with triple vessel disease and single vessel disease involving the anterior wall (data not shown). The presence of TID correlated well with the severity of reversible perfusion defects (SDS) ($R=0.70$, $p<0.0001$) and also with the severity of reversible RWMA ($R=0.70$, $p<0001$). However, reversible RWMA (SDSWM) correlates at least as well and probably better than does TID with both the angiographic jeopardy score ($R=0.60$, $p<0.0001$ vs. $R=0.46$, $p<0.0001$, $p=0.17$), and the presence of triple vessel disease ($R=0.41$, $p<0.0001$ vs. $R=0.29$, $p<0.004$, $p=0.34$).

Multivariate Regression: Of all clinical, ECG, exercise, perfusion, wall motion and LV function parameters recorded (see Methods), only the (i) stress wall motion (SSSWM), (ii) difference wall motion (SDSWM), (iii) stress perfusion (SSS), and (iv) Duke treadmill scores, (v) the presence of transient ischemic dilatation (TID), and (vi) a greater than 5% reduction from the rest to the post-stress LVEF, correlated with the angiographic jeopardy score on univariate analysis ($p<0.05$). Of these, only the SSSWM, SDSWM and Duke treadmill scores emerged as independent incremental predictors of the angiographic jeopardy score on stepwise multivariate regression ($p < 0.0001$, $p< 0.02$, $p < 0.0001$ respectively). Thus, after adjusting for reversible and post-stress RWMA, and Duke treadmill scores, the effect of TID or a >5% drop in LVEF were no longer significant in predicting the angiographic jeopardy score.

Table 5: **Incremental prognostic value of MPI and exercise variables correlated to the Angiographic Jeopardy Score using stepwise multivariate logistic regression analysis**

MPI Variables	**F- Ratio**	p- value
Summed stress wall motion score	23.2	0.0001
Summed difference wall motion score	9.6	0.02
Transient ischemic dilation	3.5	0.63
Summed stress perfusion score	1.3	0.26
Dukes Treadmill Score	17.0	0.0001
>5% reduction in post stress LVEF	0.9	0.771

Multiple R (correlation coefficient) = 0.69

DISCUSSION:

The major finding of this study is that a stress-induced (i.e. reversible) RWMA on a single-day exercise Tc-99m Sestamibi gated cardiac SPECT is highly specific for a severe angiographic stenosis. Moreover, the presence or absence of reversible RWMA correlated well with the coronary anatomy as measured by the number of vessels diseased or a coronary artery jeopardy score. Therefore, the presence of a reversible RWMA on a single-day MPI protocol may indicate a patient at high risk of future cardiac events [56]. While RWMA present on both the rest and the stress images were more sensitive for the presence of angiographic stenoses >70%, they were less specific than reversible RWMA. Both reversible and post-stress RWMA, and high Duke treadmill scores were significant *independent* predictors of the severity of the angiographic jeopardy score.

Only one previous study compared RWMA on MPI to the severity and extent of angiographic stenoses [53]. While this study showed that post-exercise RWMA predicted coronary artery disease, it did not evaluate the incremental value of comparing post-stress to resting LV function. Moreover, this study excluded patients with fixed perfusion defects, thus limiting its application from a large number of patients in whom gated cardiac SPECT is frequently performed. By contrast, the current study includes patients with a broad range of perfusion defects, and has assessed the value of gating both rest and stress MPI. We have examined both the level of angiographic stenosis required to induce a *reversible* RWMA, and the independent incremental information that an assessment of RWMA adds to the perfusion and ECG data.

By definition, myocardial *stunning* is present if left ventricular dysfunction is reversible and persists when myocardial perfusion has returned to normal [17]. Ambrosio *et al* studied 30 patients with known coronary artery disease to determine the period of time that stunning of the myocardial wall persisted following cessation of exercise[18]. Consistent with our findings, they showed that less severe angiographic lesions were associated with more prompt resolution of regional contractile abnormalities. We demonstrate the absence of reversible RWMA with angiographic stenoses <70%. In fact, the presence of a reversible RWMA was able to differentiate well between angiographic stenoses of between 50-79% and 80-99%.

Johnson *et al* used a method of chordal shortening to quantify RWMA on post-stress images in patients with reversible perfusion defects[19]. They showed a significant reduction in post-stress regional wall motion in ischemic vs. non-ischemic segments. We also detected a strong correlation between ischemia, as demonstrated by reversible perfusion defects, and the presence of a reversible RWMA. This association was particularly strong when patients with purely reversible perfusion defects were examined, suggesting that the presence of a myocardial infarct and fixed wall motion abnormality may make it more difficult to identify regions of reversible RWMA in adjacent ischemic regions.

The presence of a reversible RWMA was relatively insensitive for the detection of high grade angiographic stenoses. This may be for a number of reasons. Hibernating myocardium with persistent RWMA due to severe ischemia would be classified in our study as a fixed RWMA rather than a reversible one. It is possible that the visual scoring technique and inherent resolution of SPECT is insensitive for the detection of mild stunning.

Our study population included a broad range of patients with up to 55% demonstrating partially or completely fixed perfusion defects. Regions of infarction likely have fixed rather

than reversible RWMA. Reflecting this, the sensitivity of post-stress RWMA for angiographic lesions >70% was higher (71%, Figure 1) than that of reversible RWMA (51%, Figure 1), as both fixed and reversible RWMA are encompassed in the former.

Gender Differences. The higher observed prevalence of RWMA in men vs. women reflects a difference in the burden of coronary artery disease. While women represented 23% of our study population they had a higher incidence of normal coronary angiography, a lower incidence of multivessel disease and a correspondingly lower coronary artery jeopardy score. This difference most likely reflects selection bias based on angiographic gender referral patterns. Accordingly, the lower incidence of RWMA in females is more likely to reflect a true paucity of stunning in this group, rather than a gender-dependent difference in diagnostic accuracy.

The presence of TID and reversible RWMA predicted equally well a high-grade angiographic stenosis, multivessel disease and angiographic stenoses involving the anterior wall. These findings have important implications in how patients with reversible RWMA are managed. As in those patients in whom TID or perfusion defects in multiple vascular territories are identified , patients with reversible RWMA may be at higher risk of future cardiac events. Further prognostic studies are indicated to determine if the finding of a reversible RWMA on MPI increases the risk of cardiac events and warrants early intervention.

The angiographic jeopardy score was developed and validated by Califf *et al* as a method of determining prognosis on the basis of angiographic findings (16). Five year survival was 97% in patients with a score ≤2, and only 56% in patients with a maximal score of 12 (16). We used the jeopardy score to indirectly explore the possible prognostic implications of perfusion defects, RWMA, TID, a >5% reduction from rest to post-stress LVEF, and the Duke treadmill score. Multivariate regression analysis demonstrated that both reversible and post-stress RWMA and

the Duke treadmill score added incremental information to the perfusion data in predicting the severity of angiographic disease.

Limitations:, While the validity of gating low dose Tc-99m-based perfusion protocols has been confirmed by a number of studies demonstrating a high correlation between the rest and stress LVEF calculations[20, 21, 57], it is possible that the evaluation of reversible RWMA may have been compromised by using low dose rest gated studies, and that a similar study performed using a 2 day protocol may yield more accurate results.

The angiographic jeopardy score presented some problems in its correlation with perfusion. The right coronary artery is considered relatively unimportant in the jeopardy score, as evidenced by an occlusion of the right coronary artery scoring only 2 points out of a maximal 12. However, the right coronary artery territory involves 6 segments in a 20-segment perfusion model and may result in a relatively higher summed stress or summed difference perfusion score. The fact that high-grade lesions of the right coronary artery were common in our patient population may have contributed to the weaker correlation between the perfusion imaging and jeopardy scores.

It is possible that an adequate collateral circulation in some territories with a high grade angiographic stenosis may have influenced both the perfusion and the RWMA results. It was not felt that enough angiographic information was available to adequately address this question in this study.

Both a rest-stress and stress-rest MPI protocol was utilized in this study in accordance with our laboratories routine clinical practice. The rest-stress protocol demonstrated better accuracy for the detection of significant coronary artery disease both with post-stress RWMA and perfusion data.. Interestingly, the sensitivity of a reversible RWMA for a high grade

angiographic stenosis was higher in the stress-rest than the rest-stress protocol group. This may simply be a reflection of the higher prevalence of high grade (>70%) anterior vascular territory stenoses in the stress-rest group vs. the rest-stress group (64%(21/33) vs. 47%(32/67) respectively)**.** However, the major finding of this study, that a reversible RWMA was highly specific for a high grade angiographic stenosis, was demonstrated with both protocols.

A potential limitation of this method is that in patients with severe perfusion defects and few counts, wall motion may be erroneously underestimated in those regions. This issue was not specifically addressed in this study in which a semi-quantitative assessment of wall motion was made.

All patients in this study received an angiogram within 6 months of the myocardial perfusion study. As the majority of the patients were referred to angiography as a result of an abnormal myocardial perfusion scan, an inherent selection bias may affect our results. However, the sensitivity and specificity of our perfusion data are comparable to that of the published literature, and given that the study population was composed of patients with and without significant coronary artery disease, we believe that meaningful extrapolation of our results may be possible.

CONCLUSION:

A reversible RWMA on Tc-99m gated cardiac SPECT is highly specific for a high-grade angiographic stenosis. Incremental information from assessment of RWMA, including post-exercise and reversible RWMA, added to the clinical and perfusion data to improve the evaluation of coronary artery disease. More widespread implementation of gated rest and stress MPI may be warranted. The prognostic significance of these findings requires prospective evaluation.

CHAPTER 2.

Comparative assessment of rest and post stress left ventricular volumes and left ventricular ejection fraction on gated myocardial perfusion imaging (MPI) and Echocardiography in patients with Transient ischemic dilation on Adenosine MPI: Myocardial stunning or subendocardial hypoperfusion?

AUTHORS' NAMES:

Louise Emmett, MBChB*, Austin Ng MBBS*, Leo Ha, MBBS, *Michael Magee, MBBS*, Robert Russo, MBBS* Robert Mansberg MBBS*, Wei Zhao, MD PhD[§], S. Vincent Chow, MBBS[§], Leonard Kritharides, MBBS, PhD[§].

INSTITUTIONS:

[*]Nuclear medicine department, Concord Hospital, Sydney, Australia

[§]Cardiology department, Concord Hospital, University of Sydney, Sydney, Australia

INTRODUCTION

Transient ischaemic dilation (TID) of the left ventricle is an important adverse prognostic indicator on myocardial perfusion imaging (MPI). Patients who manifest TID of the left ventricle on MPI have a higher incidence of coronary events, and it has been shown to be highly specific for severe coronary artery disease[32, 34, 36, 37, 39].There has been some debate in the literature as to whether TID is due to true dilation and stunning of the left ventricle post stress, or whether it is an apparent phenomenon related to subendocardial hypoperfusion [33, 45]. The fact that TID is more common in patients with concurrent diseases that predispose to microvascular dysfunction such as HOCM, left ventricular hypertrophy and diabetes[24, 58-60], and is more prevalent in patients undergoing Adenosine rather than exercise stress protocols (such that higher TID ratios are required to be predictive of events) supports a possible role for subendocardial hypoperfusion rather than true stunning. However, to date, no study has performed a comparative multimodality assessment of the physical changes in the left ventricle occurring in patients with TID on vasodilator MPI. The aim of this study was to determine if the apparent dilation of the left ventricle post stress evident on MPI in patients with TID was also evident on concurrent echocardiographic imaging, or if the dilation on MPI is more a physiologic phenomena related to underperfused subendocardium post stress.

METHODS

STUDY GROUP

Following approval by the ethics committee at Concord Hospital, 37 patients consented to undergo concurrent echocardiography in addition to the routine clinically indicated single day Adenosine Tc99m myocardial perfusion scan (MPI). Patients were preferentially selected on the basis of having a high clinical likelihood for TID, such as typical anginal symptoms, diabetes, or significant coronary artery disease on recent angiography. 5 patients were excluded due to poor echocardiography windows, and 1 patient declined echocardiography following the rest image. 31 patients were included in the final analysis, of whom, 30/31 had both early (immediate) and delayed MPI (2 hour post stress) imaging. A single patient (1/31) did not have the 2 hour delayed post stress imaging. Exclusion criteria included atrial fibrillation at the time of imaging, evidence of myocardial infarction on the resting MIBI images, or significant valvular disease on the resting echocardiogram.

ADENOSINE PROTOCOL All patients underwent a clinically indicated standard 4 minute Adenosine infusion protocol (140ug/kg/min) with injection of Tc99m SESTAMIBI at 2 minutes from the start of the infusion. Single day rest- stress myocardial perfusion imaging protocols were undertaken in all patients with 300MBq Tc-99m SESTAMIBI injected for the resting images and between 1000 and 1200 MBq Tc 99m SESTAMIBI injected for the stress images based on patient weight. Cardiovascular risk factors and medications were recorded at the time of stress.

SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY IMAGING PROTOCOL

ECG gated myocardial SPECT images were acquired at rest, immediately following cessation of Adenosine infusion, and 2 hours post Adenosine infusion. Images were reconstructed with QGS® software. Images were obtained over a 180 degree orbit from RAO 45^{o} to LPO 45^{o} using a Phillips Forte® gamma camera equipped with high resolution collimators. For image acquisition, a 20% acceptance window around the 140KeV photopeak was used. A 64 x 64 matrix was utilized for all studies. All raw data was re-analysed for the study. The projection data sets were pre- filtered using a Butterworth filter and reconstructed using filtered backprojection. All scans (both resting and post stress) were 8 and 16 bin gated for assessment of post stress LVEF, left ventricular volumes, and wall motion. The 8 bin gated information was utilized in the analysis for this study. A quantitative TID ratio was derived using QGS® software.

SCAN INTERPRETATION

A TID ratio derived from an automated QGS® cardiac software program was used for the assessment of both early and delayed TID ratios. As there is no published validated cutoff for significant TID with Adenosine single day Tc99m Sestamibi protocols, the patient population was divided into quartiles of TID, with the top quartile identified as TID positive (TID+) (9/31 patients) The remaining 22 patients were classified as TID negative (TID -) (Table 1). The rest and post-stress (early and delayed) images were semi-quantitatively interpreted for the presence, extent, severity and reversibility of perfusion defects by two experienced physicians blinded to the clinical and angiographic findings of the patient. A 17 segment model of the left ventricle

was used for scoring perfusion defects, with a 5 point scoring system for defect severity (0 = normal perfusion, 1 = equivocal or mildly reduced, 2 = moderate reduction, 3 = severe reduction, 4 = absent perfusion) [61]. Based on this scoring system, a summed stress score (SSS), a summed difference score (SDS) and a summed rest score (SRS) was determined for each subject.

ECHOCARDIOGRAPHY

Standard 2-dimensional and Doppler echocardiography (Vivid.7, GE, Horten, Norway) was performed by an experienced cardiologist blinded to the patient's clinical information. Echocardiograms were recorded and stored in a digital database and then analysed offline using commercially available software (GE EchoPac 7.0.1, Horten, Norway). Echocardiogram was performed with patients in the left lateral decubitus position. Each patient had a resting echocardiogram, followed by a second study immediately upon completion of the Adenosine stress test (performed prior to the initial post stress MPI), and a final echocardiogram 2 hours after the Adenosine stress test. Left ventricular end-diastolic volume and end-systolic volume were calculated using Simpson's biplane method of discs [62]. The LVEF was calculated and expressed as a percentage. All measurements were calculated from the average of 3 cardiac cycles.

STATISTICAL ANALYSIS

All continuous variables are expressed as mean ± SD (standard deviation). Comparisons of continuous variables between two groups used unpaired *t* test, while χ^2 or Fisher's exact test was performed for non-continuous variables. One-way ANOVA test was used for continuous

variables comparing across the TID quartiles, and post hoc analysis for significant results were performed using Bonferroni correction. Analysis was performed using SPSS version 11.0 (SPSS Inc., Chicago, Illinois). A two-tailed probability value < .05 was considered statistically significant.

FINDINGS

The study population of 31 patients is shown in Table 1.

Table 1. Patient Characteristics.

	TID + (n = 9)	TID – (n= 22)	p value
Female	0/9	9/22	0.025
Diabetes mellitus	5/9	11/22	0.54
Hypertension	8/9	16/22	0.76
Smoker	1/9	2/22	0.65
History of AMI	4/9	15/22	0.47
CABG	2/9	3/22	0.47
PTCA	3/9	6/22	0.55
Ischaemia score (SDS)	6.78 ± 4.4	1.45 ± 1.7	0.001
Composite score (SSS)	9.9 ± 6.1	3.27 ± 4.8	0.004
TID ratio	1.30 ± 0.09	0.88 ± 0.09	0.0001
Severe CAD on angio	3/5	4/17	0.272
CAD on angiography	5/5	11/13	0.510

The group studied was a high risk population given that 51% (16/31) of the patients enrolled had diabetes, and 61% (19/31) had a history of coronary artery disease. In this group of patients, only male gender and the presence of a high SSS, and SDS, were significantly associated with TID (Table 1). The mean TID ratio for the highest quartile was 1.30 ± 0.09 vs. 0.88 ± 0.09 for the lowest quartile ($p < 0.0001$). Patients in the higher TID quartile had a higher ischaemia score ($p < 0.001$) than all other quartiles (Table 2.).

In the TID positive group, there was a statistically significant reduction between the resting and early post stress LVEF, and an increase in both LVEDV and LVESV on the MPI images, compared to all other TID quartiles (Table 2).

Table 2. Comparison of left ventricular volumes, LVEF and ischaemia scores when divided by quartiles of TID severity on MPI.

Quartiles for TID	**Q1 (TID +)**	**Q2 (TID -)**	**Q3 (TID -)**	**Q4 (TID -)**	**P value**
TID ratio	1.31 ± 0.09	1.14 ± 0.04	1.03 ± 0.01	0.88 ± 0.09	0.001
SDS (early)	6.8 ± 4.4	1.5 ± 1.9	1.75 ± 1.7	1.13 ± 1.6	0.0001
Change in LVEF *	-9.7 ± 6.3	-4.0 ± 3.8	+1.25 ± 5.4	+1.5 ± 3.9	0.0001
Change in LVEDV*	14.4 ± 7.1	8.8 ± 9.7	-0.38 ± 16	-4.6 ± 10.8	0.01
Cha.nge in LVESV*	16.9 ± 8.8	10 ± 8.7	-1.6 ± 10	-3.8 ± 3.9	0.0001

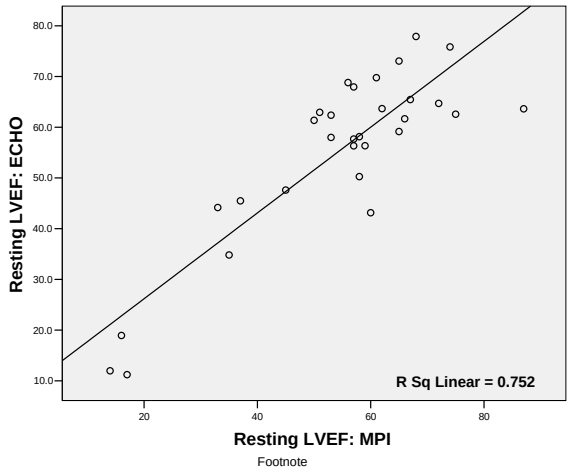
* Rest – early post stress

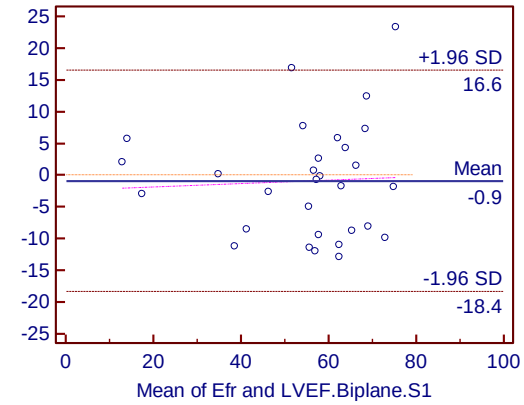
A progressive trend was evident with increasing TID ratio, whereby good correlation exists between TID and the change in LVEF, LVEDV and LVESV between rest and early stress on MPI ($r = -0.61$, 0.56 and 0.64 (all $p < 0.0001$) respectively) (Figure 1). There was also a significant relationship between ischaemia (SDS) and a change in LVEF between rest and early stress on MPI ($r = -0.44$ ($p < 0.01$) for change in LVEF, $r = 0.37$ ($p< 0.04$) for change in LVESV, and $r = 0.32$ ($p< 0.07$) for change in LVEDV), although this was not as strong the relationship observed between TID and change in LVEF and LV volumes on MPI. Those in the lowest TID quartile, instead, had an increase in LVEF following stress, and a drop in both LVESV and LVEDV post stress, on MPI (Table 2).

Generally there was a good correlation between the resting MPI and resting echocardiographic measures of LVEF ($r^2 = 0.79$), LVESV ($r^2 = 0.9$) and LVEDV ($r^2 = 0.75$) (Figure 1).

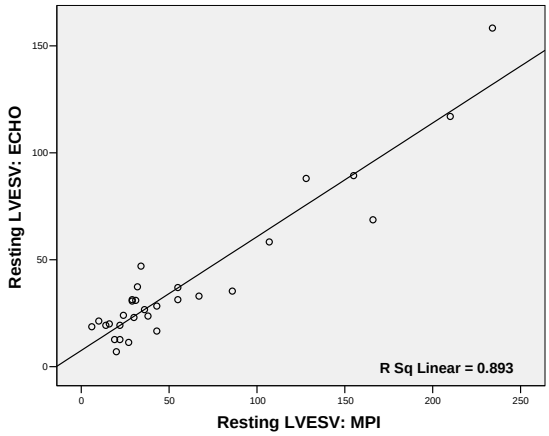
FIGURE 1: Comparison of resting LVEF (A), LVESV (B) and LVEDV (C) on transthoracic echocardiography and ECG gated MPI. Bland Altman Plots on the Right

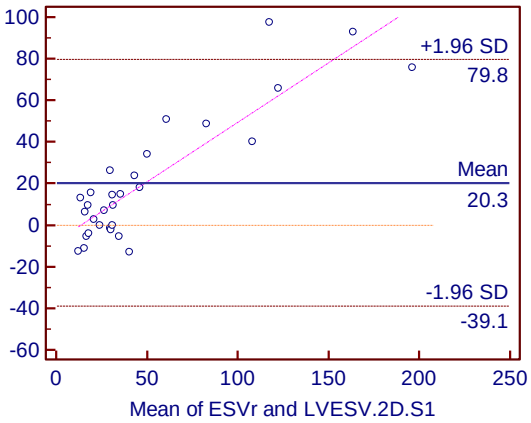
A



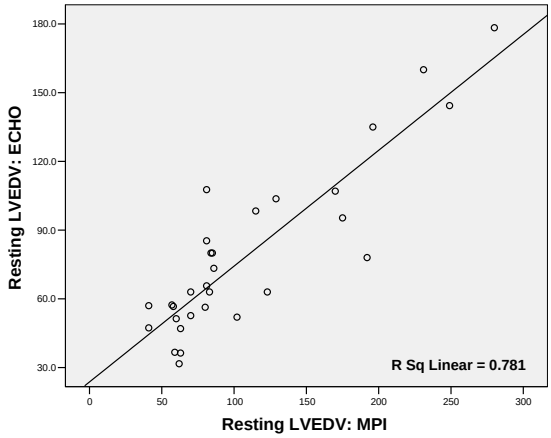


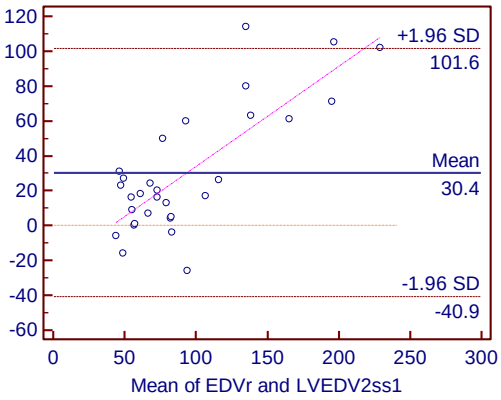
B





C





However, the findings of a reduced post stress LVEF on MPI in the TID + group was not found on the concurrent echocardiographic study. On echocardiography, there was no statistically significant difference measured in the LVEF, LVEDV or LVESV between the rest, and either the early, or delayed, post Adenosine stress images when comparing the TID positive and TID negative population (Table 3). Further there was no trend to reduced LVEF or increased LV volumes on Echo, with the TID ratio as a continuous variable, as was seen with MPI (Figure 2).

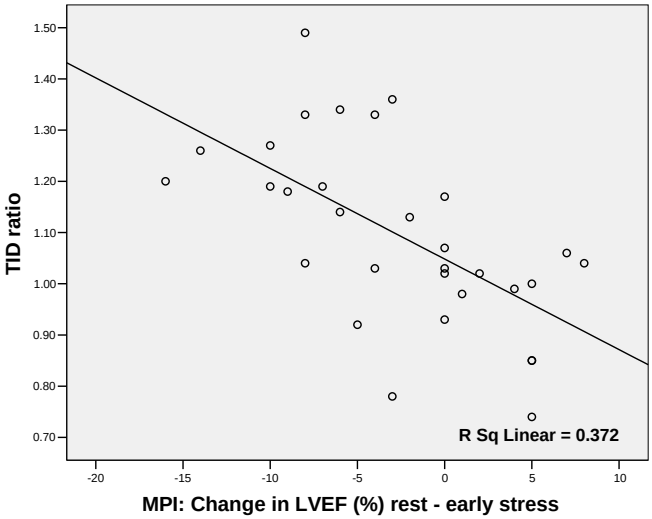
Table 3. Comparison of resting and early post stress left ventricular volumes and LVEF on both Echocardiography and MPI in patients with (TID+) and without TID (TID -).

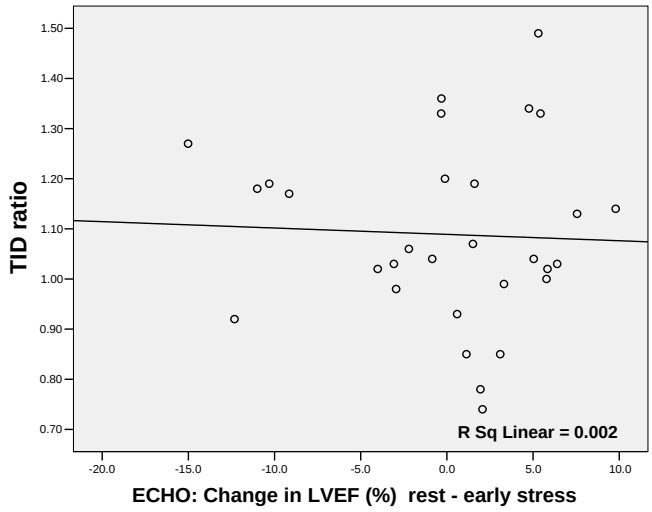
		TID +			**TID -**		
		Resting	**Early post stress**	**p value**	**Resting**	**Early post stress**	**p value***
ECHO	**LVEF (%)**	57 ± 23	56 ± 22	0.662	54 ± 14	55 ± 13	0.71
	LVESV (mls)	46 ± 51	54 ± 68	0.262	37 ± 25	38 ± 30	0.75
	LVEDV(mls)	87 ± 49	98 ± 70	0.299	76 ± 32	79 ± 43	0.31
MIBI	**LVEF (%)**	**56.6 ± 18**	**46.5 ± 17**	**0.002**	53 ± 17	53.5 ± 16	0.97
	LVESV (mls)	**62 ± 73**	**79 ± 78**	**0.0001**	57 ± 55	58 ± 57	0.76
	LVEDV (mls)	**113 ± 74**	**130.6 ±77**	**0.0001**	105 ± 59	106 ± 62	0.69

*p values determined using paired T test statistics.

Figure 2: Comparison of the correlation between the TID ratio and change in LVEF (%) between rest and early stress on ECG gated MPI (A) and .transthoracic echocardiogaphy (B).

A





B

Comparison of the left ventricular volumes, left ventricular ejection fraction and ischaemia scores on MPI between the scans undertaken early post Adenosine stress, and 2 hours post Adenosine stress, reveal no statistically significant difference between the early, and the 2 hour post stress measurements, either in the TID positive, or the TID negative group. There was a non- statistically significant trend for an increase in LVEF, and a reduction in both LVESV and LVEDV, and the TID ratio, on the 2 hour versus the early post stress image in all patient groups (Table 4). Similarly, with echo, there was no statistically significant difference identified between the early post stress and the delayed 2 hour post stress left ventricular volumes and LVEF.

Table 4: Assessment of left ventricular volumes, function and ischaemia scores: Comparison between the early post -stress (<10 mins) and delayed post-stress (2 hour) MPI measurements.

- 8/9 patients in the TID+ group underwent delayed 2 hour imaging and 22/22 patients in the TID - group underwent delayed 2 hour imaging.

	TID+			**TID-**		
	Early MPI	**Delayed MPI**	**p value**	**Early MPI**	**delayed MPI**	**p value**
LVEF	51.2 ± 12	53.8 ±14	0.11	53 ±16	56 ±19	0.09
LVESV	57.5 ± 45	57.7 ± 53	0.94	58 ± 56	56 ± 54	0.14
LVEDV	110 ± 51	112 ± 59	0.66	108 ± 62	105 ± 58	0.22
SDS	6.8 ± 4.7	6.1 ± 4.3	0.05	1.48 ± 1.7	1.33 ± 1.6	0.37
SSS	8.8 ± 6.0	7.5 ± 5.0	0.04	3.4 ± 4.9	3.2 ± 4.2	0.76
TID ratio	1.30 ± 0.09	1.26 ± 0.07	0.23	0.99 ± 0.12	0.96 ± 0.11	0.28

DISCUSSION:

In this study, we compared resting and post stress left ventricular volumes and ejection fraction on concurrently undertaken echocardiography and Tc-99m single day Adenosine Tc99m MPI, with a particular focus on those who were TID positive on MPI, in order to understand the underlying mechanisms of this finding. This study demonstrates that the post stress left ventricular dilation and reduction in LVEF post stress evident in patients with TID on Adenosine MPI, are not measurable on concurrent echocardiography. Furthermore, there is no significant change in either the LVEF or the left ventricular volumes on MPI up to 2 hours post Adenosine stress. These findings suggest that the volume changes measured on post stress MPI in patients with TID are a function of the change in the detected edge of the subendocardium post Adenosine stress MPI. TID on Adenosine MPI is therefore not related to true myocardial stunning, measurable on multiple imaging modalities, but is more likely a reflection of the severity of the underlying coronary flow reserve abnormality.

Manrique et al (2007)[63], used computerized phantom simulations of cardiac perfusion abnormalities on MPI to assess the impact of the severity of perfusion abnormalities on measures of left ventricular volumes and function. They found that by manipulating the severity of reversible perfusion abnormalities on the phantom, they also altered the measured LVESV, LVEDV and LVEF on gated MPI, even though the phantom had a set LVEF of 62%, and preset LV volumes [63]. They concluded that the severity of perfusion defects had a significant effect on the evaluation of myocardial stunning using MPI. Similarly, a study by Ward et al (2006)[64] assessed the presence of post stress regional wall motion abnormalities using both Echo and MPI post exercise stress. They found a poor correlation between post stress LVEF on Echo, and post

stress LVEF on MPI, in patients with moderate to severe ischaemia. In their study, those with ischaemia on the MPI demonstrated a significantly lower post stress LVEF on MPI, than seen on Echocardiography. In this current study, we also found a correlation between a drop in LVEF post stress, and the severity of the coronary flow reserve abnormality (SDS) on Adenosine MPI. However, this correlation was not as strong as that shown between the TID ratio and reduction in LVEF post stress. It is likely that this is because TID is due to a concentric reduction in subendocardial perfusion, that would have a greater impact on where the software detects the ventricular edge to mathematically determine LVEF, than would regional myocardial perfusion abnormalities.

Stunning, the presence of prolonged, but reversible impairment of myocardial function after an episode of ischaemia, has been a well documented phenomena in the cardiac and nuclear cardiology literature [18]. A number of previous studies have investigated the relationship between TID, ischaemia and post stress stunning on myocardial perfusion imaging without concurrent echo assessment[20, 46, 57, 65, 66]. A study using pharmacologic stress dual isotope MPI by Hung et al [46], found a significant drop in LVEF and increases in both LVEDV and LVESV in patients with TID on MPI, while the LVEDV and LVESV did not increase in those without TID. They concluded that enlargement of the ESV on MPI as a result of ischemic stunning was an important factor resulting in TID. Our study found very similar results, in that patients with TID on MPI had enlargement in both ESV and EDV post stress, as opposed to the TID negative group, which showed no significant change in left ventricular volumes. However, in this current study, the increase in EDV and ESV on MPI in the TID positive group was not present on the concurrent echo measurements, which found no significant change in LV volumes in patients with TID. Hence it is likely that, instead of as previously understood, it is not

ischaemic stunning that is responsible for TID, but more likely, the global reduction in perfusion at the endocardial border, leading to an apparent increase in ESV volumes.

Gated SPECT imaging on MPI relies on detection of perfusion at the endocardial edge for measurements of left ventricular volume, and hence, the mathematical determination of LVEF and the TID ratio. Most previous studies assessing whether the dilation of the left ventricle post stress with TID is real or apparent have relied on measurements from MPI alone without using concurrent multimodality imaging. Van Tosh et al [67] used both exercise thallium and echocardiography to assess 24 patients, of whom 8 were deemed to have TID. They used echocardiographic volume measurements to assess change in LV cavity with TID, but did not undertake concurrent gated thallium estimations of rest and post stress LVEF and volumes. They found no dilation in LV cavity parameters on echo in those with TID, finding only a reduced LVESV post stress in the TID negative group. Although we found no significant reduction in LVESV in the TID negative group, either on MPI or echocardiography, the finding by Van Tosh et al, of no dilation of the LV cavity on echocardiography in those with TID, supports the findings on our current study.

Adenosine does cause significant haemodynamic changes at the time of administration. Perfusion abnormalities on Adenosine MPI are thought to reflect impairment of coronary flow reserve rather than true myocardial ischaemia, although it has been shown to induce subendocardial hypoperfusion by redirecting flow to the subepicardium away from the subendocardium in myocardium supplied by stenosed vessels [68]. Severe ischaemia can occur rarely, due to coronary steal in collateral dependent vascular territories [68]However, post stress stunning on vasodilator MPI has been estimated to occur in up to 33% of patients with severe ischaemia on MPI [22]. It has been difficult to explain how the incidence of true myocardial

stunning on Adenosine MPI could be so common on the basis of the physiological changes occurring with Adenosine stress. The findings from this study, that there is no physical change in ventricular volumes post Adenosine stress on echocardiography, helps explain the previous paradox. The measured increase in LV volumes, TID, and reduced LVEF in patients with ischaemia on Adenosine MPI is a marker of impaired subendocardial coronary flow reserve rather than true myocardial stunning. This also helps explain the increased incidence of TID in patients with diseases affecting coronary microvascular function such as left ventricular hypertrophy, diabetes[58, 59] and hypertrophic cardiomyopathy [24, 27].

In this study, the significant reduction in LVEF and dilation of the left ventricle evident in those with TID on MPI persisted on the 2 hour post Adenosine stress images, as did the severity of the reversible perfusion abnormalities. Using echocardiography, myocardial stunning has been demonstrated to occur for up to 45 minutes following both exercise and Dobutamine stress in patients with significant coronary artery disease [23, 69, 70], with resolution of myocardial stunning demonstrated in all those studied by 1 hour post stress. By contrast, myocardial stunning has been documented to occur for up to 24 hours post Tc99m exercise MPI protocols, in those with severe ischaemia [20]. When Thallium is used as the isotope for perfusion imaging, this myocardial stunning resolves progressively over 4 hours [66]. The prolonged reduction in measured left ventricular function following both Adenosine and exercise stress Tc 99m- MPI, beyond that able to be measured on either echocardiography or thallium MPI is almost certainly due to subendocardial hypoperfusion. The reduced post stress left ventricular function persists on Tc MPI protocols as, in contrast to Thallium, there is little redistribution of the Tc labeled perfusion agents over time.

Study Limitations:

The study relies on Echocardiography to have the sensitivity to reliably detect relatively small changes in LV volumes and LVEF. That echocardiography can reliably detect changes of this magnitude post exercise and Dobutamine stress has been well demonstrated in the stress echocardiography literature. Barnes et al; were able to detect a statistically significant drop in LVEF of 10% for up to 30 mins post Dobutamine stress using stress echocardiography[23]. In our study, MPI detected a similar drop of 10% in LVEF between rest and stress imaging in those who were TID positive, and an increase in LVEF in those in the highest TID ratio quartile. To maximise the sensitivity of the Echo findings, Echo was undertaken first following the Adenosine stress, with the MPI immediately following. However, in this study, Adenosine, not Dobutamine, was the pharmacologic stress agent. No measured changes in volume, or LVEF were identified on Echo in patients with TID on MPI in this study, as it is likely they were functional, not anatomical.

A relatively small number of patients were enrolled into the study, of whom only 9/31 patients had TID on MPI. The study results convincingly showed that there was no statistically significant change in LV volumes or LVEF on echocardiography in patients with TID on MPI. However, a single patient with TID on MPI showed a concurrent increase in LVESV and LVEDV on both echo and MPI post Adenosine stress (with no change in LVEF post stress on echocardiography to suggest stunning). It may be that there is a small subgroup of patients with TID following Adenosine MPI that do demonstrate functional dilation of the left ventricular cavity due to left ventricular stunning, that was not measurable in this study due to small cohort size.

The study patients enrolled came from a high risk population in a tertiary referral centre, preferentially selected for a high likelihood of coronary artery disease, and a high incidence of diabetes. Many of these patients had severe CAD on angiography. For this reason, a relatively higher proportion of these patients had high TID ratios compared to the standard referrals for MPI at a community centre. This may well have influenced the results, with the patients in the TID negative group having relatively higher mean TID ratios than generally expected. This would, if anything, reduce the chance of the study finding statistically significant differences between the TID + and TID – groups in terms of change in LV volumes and LVEF on either Echo or MPI. The fact that strong statistical differences were found between the 2 groups on MPI highlights the strength of the findings.

CONCLUSION:

The significant drop in both LVEF and increase in left ventricular volumes measured in patients with TID on Adenosine MPI are not measurable on concurrent echocardiography, and persist for a prolonged period post Adenosine stress. This suggests that the volume changes measured on post stress MPI in patients with TID are a function of subendocardial hypoperfusion. TID on Adenosine MPI is therefore not related to true myocardial stunning as measured by independent imaging modalities, but is more likely a reflection of the severity of the underlying coronary flow reserve abnormality.

CHAPTER THREE

THE ROLE OF LEFT VENTRICULAR HYPERTROPHY AND DIABETES IN TRANSIENT ISCHAEMIC DILATION OF THE LEFT VENTRICLE ON MYOCARDIAL PERFUSION SPECT IMAGING

Louise Emmett, MBChB[1]; Michael Magee, MBBS[1]; S. Ben Freedman, MBBS, PhD[2]; Hans Van der Wall MBBS PhD[1]; Vivienne Bush MHA[1], ; Joseph Trieu, MBBS[1]; William Van Gaal, MBBS[1]; Kevin C Allman, MBBS[1] and Leonard Kritharides, MBBS, PhD[2].

[1] Department of Nuclear Medicine, Concord Hospital, Sydney, Australia; [2] Department of Cardiology, Concord Hospital, Sydney, Australia

INTRODUCTION

Myocardial perfusion imaging is a powerful diagnostic and prognostic tool for evaluating coronary artery disease. Prognostic indicators on myocardial perfusion imaging include the severity of both fixed and reversible perfusion defects (myocardial infarction and ischaemia)[71], reduced post stress left ventricular function[19, 65], and dilation of the left ventricle post stress[32, 37, 72].

The presence of transient ischaemic dilation (TID) of the left ventricle on myocardial perfusion imaging is considered to be a marker of severe and extensive coronary artery disease (CAD), and has been demonstrated following both pharmacologic and exercise stress [34-39, 67, 72-75]. Until recently [72], the significance of TID in the absence of apparent focal ischaemia on the myocardial perfusion image has not been addressed. It is unclear if this signifies the presence of balanced ischaemia and triple vessel disease, as previously assumed, or whether other physiological factors are at play in the development of TID on myocardial perfusion SPECT. The aim of this study was to investigate clinical factors that may influence the incidence of TID, particularly those factors that may independently affect subendocardial perfusion, such as left ventricular hypertrophy and diabetes.

METHODS

STUDY POPULATION

Medical records and investigations of consecutive patients who had undergone routine single day Tc99m sestamibi myocardial SPECT between January 2000 and December 2001 were reviewed. Patients were included in the study if they had undergone coronary angiography within 6 months of their perfusion imaging with no intervening cardiac event (myocardial infarct or revascularisation procedure), and transthoracic echocardiography within 1 year. A total of 103 patients fulfilled entry criteria, and were included in the study. A diagnosis of diabetes was determined on the basis of a patient history of diabetes, and current oral diabetic medication and/or insulin requirement.

STRESS PROTOCOL

Exercise stress was performed in 24 patients using a Bruce protocol treadmill test. Endpoints for exercise stress included achievement of 85% of target heart rate, > 2mm ST segment depression on the exercise electrocardiogram, or typical ischemic chest pain. A further 48 patients underwent a combined protocol, comprising a 4 minute adenosine infusion with low grade supplemental treadmill stress. The remaining 31 patients received a 4 minute adenosine infusion without supplemental exercise.

All patients underwent a rest – stress MPI protocol with 300 Mbq Tc-99 Sestamibi injected for the rest image, and an injection of between 1200-1400 Mbq (dependent on subject weight)Tc-99m Sestamibi for the stress image.

SPECT IMAGING PROTOCOL

Images were obtained over a 180 degree orbit from RAO 45^{o} to LPO 45^{o} using a Siemens© triple head gamma camera equipped with high resolution collimators. For image acquisition, a 20% acceptance window around the 140KeV photopeak was used. A 64 x 64 matrix was utilized for all studies. All raw data was reanalysed for the study. The projection data sets were pre-filtered using a Butterworth filter and reconstructed using filtered backprojection. The post stress images were gated for assessment of post stress LVEF and wall motion.

Standard 8 bin gating was used for all patients using Siemens software (Chicago, USA). Reconstruction from the raw data was performed for all studies by a technologist experienced in nuclear cardiology.

SCAN INTERPRETATION

A TID ratio derived from an automated Emory cardiac toolbox software program was used for the assessment of TID, with the previously validated cutoff of ≥1.22 used as evidence of TID. Images were also interpreted visually for the presence or absence of TID with the consensus agreement of 2 experienced observers blinded to the clinical and angiographic findings of the patient. The rest and post-stress images were semi-quantitatively interpreted for the presence, extent, severity and reversibility of perfusion defects by two experienced physicians blinded to the clinical and angiographic findings of the patient. A 17 segment model of the left ventricle was used for scoring perfusion defects, with a 5 point scoring system for defect severity (0 = normal perfusion, 1 = equivocal or mildly reduced, 2 = moderate reduction, 3 = severe reduction, 4 = absent perfusion) [76]. Based on this scoring system, a summed stress score (SSS), and a summed difference score (SDS) was determined for each subject.

ECHOCARDIOGRAPHY

Transthoracic echocardiography was performed in all patients (Vingmed Vivid 5, GE, Milwaukee USA). Left ventricular hypertrophy was defined as a measurement of >11mm wall thickness of either the posterior or the septal wall on M-mode echocardiography in the parasternal long axis view as previously described[77].

ANGIOGRAPHIC ANALYSIS

The coronary angiographic findings were retrospectively analysed visually. Significant coronary artery disease was identified as absent if there were no stenoses of major coronary arteries ≥ 50% lumen diameter reduction. Severe CAD was defined as ≥ 90% stenosis of either the left anterior descending coronary artery, or 2 or more major coronary vessels, a definition well validated in the assessment of TID[36, 72]. For patients with previous coronary artery bypass surgery, both the site and severity of disease in native vessels and bypass grafts was documented. For each grafted vascular

territory, stenosis of the bypass graft was used to define disease severity, unless the graft was occluded, in which case, the percentage stenosis of the native vessel was used.

STATISTICAL ANALYSIS

Continuous variables are reported as mean ± standard deviation. Comparison of categorical variables was performed using a chi-square statistic. Multivariate stepwise logistic binary regression analysis was performed using variables that were significant by univariate analysis. All statistical analyses were performed using SPSS release 11.0 (Chicago, USA). A p-value < 0.05 was considered statistically significant.

RESULTS

PATIENT CHARACTERISTICS

The characteristics of 103 patients enrolled in the study are described in Table 1. Patients had undergone coronary angiography within a mean of 2.6 ± 2.4 months of their MPI study. Forty five percent (46/103) of subjects had severe CAD, while 55% (57/103) had either less severe CAD (30/103), or non haemodynamically significant CAD (26/103). Using a quantitative TID ratio cutoff of ≥ 1.22, 19/103 (18%) of subjects had TID. A total of 19/103 (18%) of patients had LVH on echocardiography (mean wall thickness 13.5mm ± 2.5mm). The diagnosis of diabetes, determined on the basis of a history of oral diabetic medication, or insulin requirement, was made in 23/103 (22%) of subjects.

TABLE 1. Patient Characteristics.

Variables	Overall	TID	No TID	p value
AGE (mean ± SD)	68 ± 12	72 ± 8	68 ± 12	p = ns
SEX				
-female	29/103 (28%)	10/19 (52%)	19/84 (23%)	p<0.001*
-male	74/103 (72%)	9/19 (47%)	65/84 (77%)	
STRESS PROTOCOL				
-exercise	24/103 (23%)	4/19 (21%)	20/84 (23%)	
-Adenosine/exercise	31/103 (30%)	4/19 (21%)	27/84 (32%)	p = ns[§]
-Adenosine	48/103 (46%)	11/19 (57%)	37/84 (44%)	
CAD				
- Non Severe	57/103 (55%)	4/19 (21%)	53/84 (63%)	p<0.0001[€]
- Severe	46/103 (45%)	15/19 (79%)	31/84 (36%)	
LVH	19/103 (18%)	8/19 (42%)	11/84 (13%)	p< 0.0001
SDS (mean ± SD)	5.0 ± 5.9	8 ± 7.0	3 ± 3.7	p< 0.0001
SSS (mean ± SD)	16 ± 13	24 ± 16	12 ± 10	p<0.0001
Diabetes	23/103 (22%)	11/19 (58%)	12/84 (14%)	p< 0.0001
Coronary artery surgery	23/103 (22%)	4/19 (21%)	19/ 84 (22%)	p = ns

* p value relates to the difference in the incidence of TID between males and females.

[§] p value relates to the difference in the incidence of TID between the different stress protocols.

[€] p value refers to the difference in the incidence of TID between severe and non severe CAD.

Other p values refer to comparison of TID and no TID values.

TRANSIENT ISCHAEMIC DILATION

Severe CAD, LVH, severity of ischaemia (SDS), female sex and diabetes all demonstrated a statistically significant association with the presence of TID on chi square analysis (Table 1). Diabetes, Left ventricular hypertrophy, severe CAD and the ischaemia score (SDS) were all independent predictors of TID by multivariate logistic regression (Table 2).

TABLE 2: Multivariate binary logistic regression analysis for the prediction of TID.

VARIABLE	**F VALUE**	**MEAN SQUARE**	**P VALUE**
Diabetes	18	8.0	0.0001
Severe CAD	12	8.0	0.001
LVH	9.2	6.2	0.003
IschaemiaScore (SDS)	5.3	1.0	0.023

SEVERE CAD

Both the extent of ischaemia and the presence of severe and extensive CAD on angiography were independent predictors of TID (Table 2). As in previous studies[32, 35, 36, 38, 39], TID was highly predictive of severe CAD on angiographic criteria, with an overall specificity of 93% (53/57) and a sensitivity of 32% (15/46). However, in the presence of either LVH or diabetes, the specificity of TID for severe CAD fell, with a rise in sensitivity (Table 3).

TABLE 3: Changes in the sensitivity and specificity of TID for severe and extensive CAD with or without LVH or diabetes.

	SENSITIVITY	SPECIFICITY
Overall	32% (14/46)	93% (54/57)
LVH	75% (6/8)	80% (9/11)
No LVH	23% (9/38)	95% (44/46)
Diabetics	61% (8/13)	70% (7/10)
Non diabetics	21% (7/33)	98% (46/47)

LEFT VENTRICULAR HYPERTROPHY

The majority 14/19 (74%) of subjects with LVH had a history of hypertension, 2/19 (10%) with LVH had diabetes, and 3/19 (15%) of patients with LVH gave neither a history of diabetes nor hypertension. No patients in the study had significant valvular disease or hypertrophic obstructive cardiomyopathy on echocardiography. LVH was an independent predictor of TID on multivariate logistic regression (Table 2). There was a strong additive relationship demonstrated between the presence of LVH and severe CAD, and the incidence of TID (Fig. 1). In patients with severe CAD, the incidence of TID increased from 21% (8/38) without LVH to 75% (6/8) with LVH ($p < 0.01$) (Fig. 1). Additionally, there was a reduction in the specificity of TID for the diagnosis of severe CAD from 95% in subjects without LVH, to 80% in patients with LVH (Table 3).

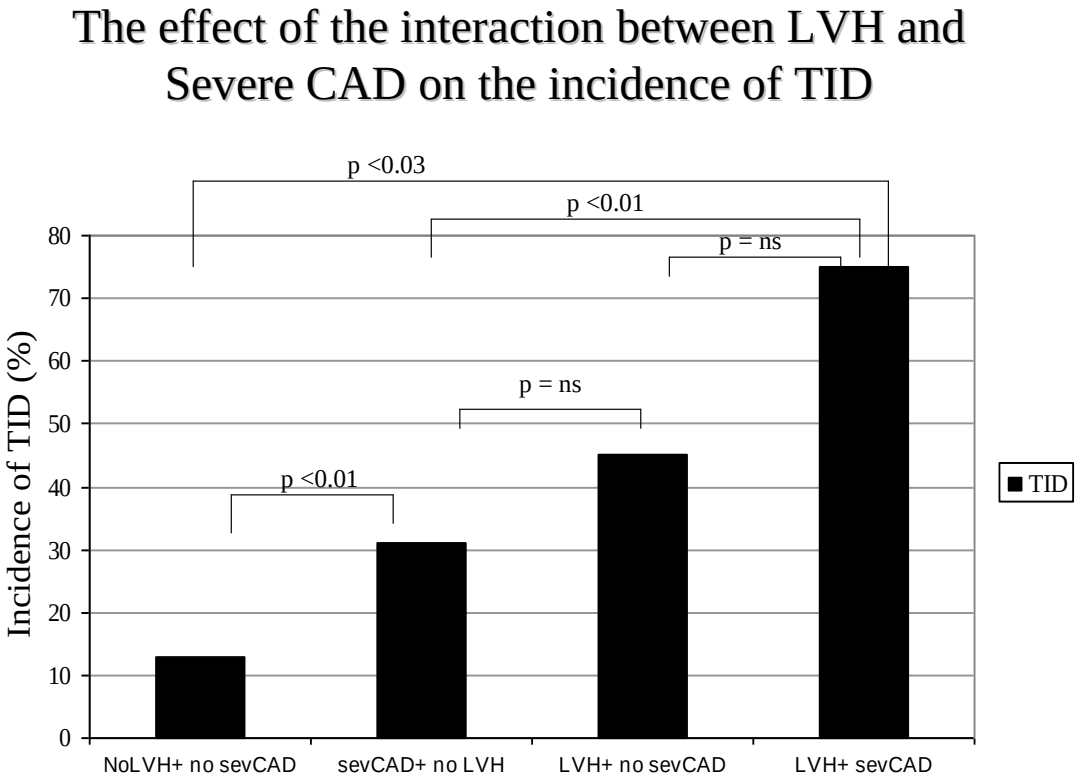


FIGURE 1. Interaction between LVH and severe CAD on the incidence of TID.

The incidence of TID was higher in patients with both LVH and severe CAD than severe CAD alone ($p < 0.006$).There was a statistically significant difference in the incidence of TID in patients with or without severe CAD in the absence and the presence of LVH ($p = 0.02$.)

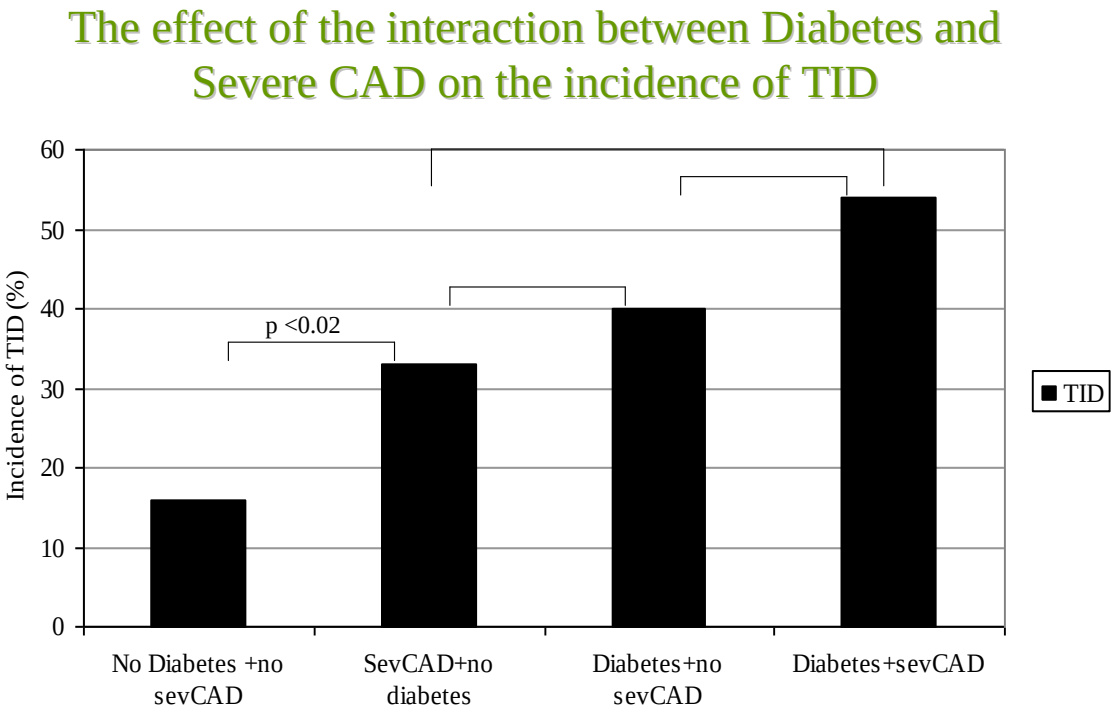


FIGURE 2: In patients with severe CAD the incidence of TID was significantly higher in the subgroup with diabetes ($p < 0.04$). There was a statistically significant difference in incidence of TID between severe CAD and less severe CAD in the absence ($p < 0.007$), but not the presence, of diabetes ($p = ns$).

DIABETES

Diabetes was the strongest independent predictor of TID on multivariate logistic regression ($p<0.0001$) (Table 2). As with LVH, an incremental relationship was observed between diabetes, severe CAD and the incidence of TID (Fig. 2). In the presence of severe CAD, the incidence of TID increased from 21% (7/33) without diabetes, to 53% (7/13) with diabetes ($p<0.04$) (Fig. 2). In the absence of severe CAD the incidence of TID rose from 2% (1/47) without diabetes, to 30% (3/10) with diabetes ($p<0.015$) (Fig 2). Accordingly, the specificity of TID for severe CAD fell from 98% (47/48) in the absence of diabetes, to 70% (7/10) in patients with diabetes (Table 3). Of the patients with both diabetes and LVH, all with severe CAD (4/4 (100%)) had TID, while those without severe CAD had a 50% (2/4) incidence of TID.

GENDER

Female patients demonstrated an increased incidence of TID relative to male subjects [10/29 (34%) vs. 9/74 (12%) $p < 0.01$]. Further analysis of this revealed an increased prevalence of both diabetes and LVH amongst females relative to males in the population. (9/29 (31%) of women and 14/74 (19%) of males were diabetic, and 7/29 (24%) of women, and 12/74 (16%) of males had LVH.). Consequently, multivariate analysis, accounting for the effect of LVH and diabetes, did not find female sex to be an independent predictor of TID.

CORONARY ARTERY BYPASS GRAFTING

A high proportion of the group had prior bypass surgery (23/103). The association between LVH, diabetes, ischaemia and TID was unaffected when these patients were excluded from the analysis.

VISUAL ASSESSMENT OF TRANSIENT ISCHAEMIC DILATION

Using the visual consensus method to determine the presence or absence of TID, 27/103 (26%) of patients were classified as having TID. Severity of ischaemia (SDS), left ventricular hypertrophy, severe CAD and diabetes all remained independent predictors of TID by multivariate binary logistic regression using this method. However, the burden of ischaemia (SDS) on myocardial SPECT imaging was the strongest predictor of TID rather than diabetes on multivariate logistic regression. TID remained highly predictive of severe CAD on angiographic criteria, with an overall specificity of 81% (46/57) and a sensitivity of 39% (18/46).

DISCUSSION

TID is an apparent increase in left ventricular cavity size in the immediate post-stress image compared with the resting image on myocardial perfusion imaging. This phenomenon was first described by Stolzenberg et al. in 1980 on planar 201-Thallium imaging in a small group of patients[78]. Subsequently, a considerable literature has accumulated on the subject, covering exercise and pharmacologic stress, single photon emission computed tomography (SPECT) and 99m-Tc sestamibi

myocardial perfusion imaging. Regardless of the agent utilized in myocardial perfusion imaging (MPI) or the type of stress, TID of the left ventricle on myocardial SPECT imaging has become an accepted marker of severe and extensive CAD, and poor prognosis [35-39, 44, 72, 75]. This study confirms that TID is an important finding that can identify severe and extensive CAD, and correlates well with the extent of ischaemia demonstrated on myocardial SPECT imaging. However, we found that both LVH and diabetes increase the incidence of TID independent of the presence of angiographically severe CAD. This raises important questions regarding the pathophysiology of TID on myocardial SPECT imaging, and the predictive value of TID for severe CAD in the presence of either LVH or diabetes.

McClellan et al.[37] provided data for the important prognostic role of TID in patients undergoing dipyridamole stress-testing with 99m-Tc SESTAMIBI SPECT imaging. They followed 512 consecutive patients for a period of 13±7 months. In the 14% with TID they found a cardiac event rate of 11% compared with 2% in a group without TID or fixed left ventricular dilatation. In contrast, a recent large study by Abidov and colleagues[72] assessing the prognosis of patients with TID and normal perfusion on myocardial perfusion SPECT imaging, found that those with TID demonstrated a 2.4% per year cardiac event rate compared with an event rate of less than 1% per year for patients with no TID. This is far lower than the 11 % per year cardiac event rate reported in patients with TID by McClellan et al.[37] The difference almost certainly reflects the higher prevalence of ischemia in the population in the McClellan study. In the past, the commonly accepted explanation for TID in the presence of ‘normal perfusion’ was thought to be ‘balanced ischaemia’ and multivessel

CAD, in which case the cardiac event rate in those subjects with TID and normal perfusion in the Abidov study would be expected to be higher. This discrepancy suggests that the pathology leading to the presence of TID is not always related to macrovascular CAD alone.

The mechanism of TID remains controversial, and may in fact be due to more than one pathological process. Although there is some evidence that physical left ventricular dilatation can occur with ischemia[39, 74], it is generally accepted that TID is most likely an 'apparent' phenomenon due to subendocardial ischemia[34, 38, 43] and systolic dysfunction of the left ventricle[67] Evidence for this comes from both the scintigraphic and echocardiographic measurement of the ventricular parameters immediately post-stress or during stress respectively. Iskandrian et al.[34] demonstrated a 30% increase in cavity area of the endocardial border, compared with only a 6% increase in cavity area of the epicardial border. Van Tosh et al.[67] examined patients with and without TID on scintigraphic imaging with echocardiography. They found that the rest and stress echocardiographic end-diastolic area did not change in patients with TID, suggesting that the scintigraphic manifestations were due to systolic dysfunction of the left ventricle. Takeishi et al.[38] showed that stress and rest end-diastolic left ventricular volume and ejection fraction were unchanged amongst patients with TID, also supporting the concept of subendocardial hypoperfusion. The loss of tracer uptake in the hypoperfused inner endocardial border on the post stress images may produce an effect of apparent "thinning", and therefore the impression of cavity enlargement.

There is limited data implicating LVH in the etiology of TID. Sugihara et al.[79] studied 50 patients with hypertrophic cardiomyopathy and compared them to 20 normal controls using 201-Thallium SPECT imaging. They found a high prevalence of TID in patients with hypertrophic cardiomyopathy, and theorized that this was on the basis of diffuse subendocardial hypoperfusion. Robinson et al.[27] also found TID in patients with hypertensive heart disease and LVH on thallium or ECG criteria. We found that 18% of our patient cohort had LVH by echocardiographic criteria. These patients demonstrated a higher incidence of TID in the presence or absence of severe CAD. This supports the argument that other pathophysiological factors play a role in the development of TID, over and above the presence of angiographically severe CAD. More likely, hypertrophied myocardium develops a greater reduction in subendocardial perfusion, than transmural perfusion, generating apparent dilatation at lower levels of quantifiable ischaemia.

This is the first time that diabetes mellitus has been shown to be an independent predictor of TID. Furthermore, in this study diabetes was a stronger independent predictor of TID than either the presence of severe CAD, or ischaemia. This may be due to the presence of undetected diffuse atherosclerosis, or possibly from coronary flow reserve abnormalities related to microvascular disease [80, 81].

Both LVH and diabetes may affect coronary flow reserve in the absence of macrovascular CAD [81, 82]. In LVH, there is a relative decrease in capillary density within the hypertrophied muscle leading to coronary flow reserve abnormalities that can cause myocardial ischaemia even in the absence of large vessel CAD. In the presence of CAD, coronary flow reserve abnormalities may exacerbate the severity of

ischaemia[73, 82]. We hypothesize that, in subjects with LVH or diabetes, the relatively compromised resting subendocardial perfusion, with or without severe CAD, may lead to a greater reduction in endocardial radiotracer uptake during stress, and a greater apparent increase in LV cavity size on the post-stress images.

This study demonstrates that the presence of either LVH or diabetes alters both the specificity and the sensitivity of TID for severe CAD. This may have important implications for the clinical interpretation of TID in patients with known LVH or diabetes.

One of the limitations of this study, is that assessment of the angiographic data was based on visual assessment alone, with no QCA of the data undertaken. This may have affected the number of patients classified as 'severe' CAD' and should be taken into account in the interpretation of the data.

As this was a retrospective analysis, selection bias of patients undergoing coronary angiography is possible. However the confirmation of our results by scintigraphic ischaemia as well as angiographic stenoses supports an independent role of LVH and diabetes mellitus in TID. Although an interval of up to 6 months occurred between MPI, angiography and echocardiography, this would be expected to diminish the strength of association between LVH, angiographic stenosis and TID, and is therefore unlikely to affect the conclusions. Although we show a strong correlation between diabetes and TID, the retrospective nature of this study prohibited further investigation of diabetic subgroups, and disease severity or duration. We are currently conducting a prospective study specifically examining these issues.

CONCLUSION

The presence of diabetes, and to a lesser extent LVH, modifies the relationship between TID and severe CAD. The threshold of CAD at which TID is identified on myocardial SPECT perfusion imaging is reduced. This may have important implications for the clinical interpretation of TID in patients with known LVH or diabetes, and requires prospective investigation with a larger patient cohort.

CHAPTER FOUR

PROSPECTIVE EVALUATION OF THE IMPACT OF DIABETES AND LEFT VENTRICULAR HYPERTROPHY ON THE RELATIONSHIP BETWEEN ISCHEMIA AND TRANSIENT ISCHEMIC DILATION OF THE LEFT VENTRICLE ON MYOCARDIAL PERFUSION IMAGING.

AUTHORS' NAMES:

Louise Emmett, MBChB*, William J.Van Gaal, MBBS*, Michael Magee, MBBS*, Sarah Bass, BAppSc*, Onn Ali, MBBS[§], S. Ben Freedman, MBBS, PhD[§], Hans Van der Wall, MBBS, PhD*, Leonard Kritharides, MBBS, PhD[§].

INSTITUTIONS:

[*]Nuclear medicine department, Concord Hospital, Sydney, Australia

[§]Cardiology department, Concord Hospital, University of Sydney, Sydney, Australia

INTRODUCTION

Transient ischemic dilation (TID) of the left ventricle has been associated with a poor prognosis and the presence of severe epicardial coronary stenoses (particularly the left anterior descending artery), and multi vessel disease[32, 34, 36-40, 44, 83]. We have retrospectively shown that both left ventricular hypertrophy (LVH) and diabetes alter the threshold of coronary artery disease (CAD) at which TID is evident on myocardial perfusion imaging (MPI)[59]. Both LVH and diabetes are known to cause coronary flow reserve abnormalities in the absence of major epicardial coronary stenoses [26, 28, 29, 84]. Prior research has demonstrated that while TID is highly specific for the presence of severe coronary artery disease, it is relatively insensitive, with studies reporting a sensitivity of just 32-34% [59, 65]. What determines which patient with ischemia, or severe CAD on angiography will develop TID on MPI? Is this related to ventricular stunning, or does microvascular function play a role?

The aim of this study was to prospectively assess the impact of such factors as diabetic disease severity, and the presence of LVH, on TID in both the presence, and the absence of demonstrable ischemia on MPI, or severe coronary artery disease on angiography.

METHODS

Following ethics approval from the Institutional ethics committee at Concord Repatriation Hospital, all consecutive patients presenting to our department for routine MPI were prospectively recruited to the study after informed consent was obtained. A total 200 patients were enrolled in the study. Routine single day rest-stress Tc-99m Sestamibi MPI was performed in all patients, in addition to transthoracic echocardiography for assessment of left ventricular wall thickness. Blood samples were drawn from all diabetic patients for HbA1c. The type of diabetes, duration of disease, and a history of retinopathy or nephropathy was documented.

STRESS PROTOCOL

A maximal Bruce protocol treadmill test was performed in 21% (43/200) of patients. The remaining 79% (157/200) underwent a 4 minute Adenosine infusion (140mcg/kg/min) protocol. All patients underwent a single day rest – stress MPI protocol with 300 Mbq Tc-99 Sestamibi injected for the rest image, and an injection of between 1200-1400 Mbq (dependent on subject weight) Tc-99m Sestamibi for the stress image.

SPECT IMAGING PROTOCOL

Imaging was performed within 10 minutes following cessation of the stress test in those patients who underwent an exercise stress test. Imaging was delayed for up to half an hour post stress in those who underwent Adenosine stress alone. Images were obtained over a 180 degree orbit from RAO 45^{o} to LPO

45^{o} using a Siemens© (Chicago, USA) triple head gamma camera equipped with high resolution collimators. For image acquisition, a 20% acceptance window around the 140KeV photopeak was used. A 64 x 64 matrix was utilized for all studies. All raw data was re-analysed for the study. The projection data sets were pre- filtered using a Butterworth filter and reconstructed using filtered backprojection. The post stress images were gated for assessment of post stress LVEF, left ventricular volumes, and wall motion. Standard 8 bin gating was used for all patients using Siemens software (Chicago, USA). A quantitative TID ratio was derived using Emory toolbox software® (Atlanta, USA).

SCAN INTERPRETATION

A TID ratio derived from an automated Emory cardiac toolbox software program was used for the assessment of TID, with a cutoff of ≥1.18 for males and ≥ 1.36 for females used as evidence of TID based on validated cutoffs for single day Tc99m MPI protocols[85]. The rest and post-stress images were semi-quantitatively interpreted for the presence, extent, severity and reversibility of perfusion defects by two experienced physicians blinded to the clinical and angiographic findings of the patient. A 17 segment model of the left ventricle was used for scoring perfusion defects, with a 5 point scoring system for defect severity (0 = normal perfusion, 1 = equivocal or mildly reduced, 2 = moderate reduction, 3 = severe reduction, 4 = absent perfusion) [61]. Based on this scoring system, a summed stress score (SSS), a summed difference score (SDS) and a summed rest score (SRS) was determined for each subject.

ECHOCARDIOGRAPHY

Transthoracic echocardiography was performed before stress in all patients (Vingmed Vivid 5, GE, Milwaukee USA) for the assessment of left ventricular wall thickness, and to exclude significant valvular disease. LVH was defined as a measurement of >11mm wall thickness of both the posterior and the septal wall on M-mode echocardiography in the parasternal long axis views.

ANGIOGRAPHIC ANALYSIS

Coronary angiography was performed at the discretion of the treating physician in 62/200 (31%) of patients. The coronary angiographic findings were analysed both visually and using quantitative coronary assessment (QCA). Significant CAD was identified as absent if there were no stenoses of major coronary arteries ≥ 50% lumen diameter reduction. Severe CAD was defined as ≥ 90% stenosis of either the left anterior descending coronary artery, or 2 or more major coronary vessels, a definition previously validated in the assessment of TID[36, 72]. For patients with previous coronary artery bypass surgery, both the site and severity of disease in native vessels and bypass grafts was documented. For each grafted vascular territory, stenosis of the bypass graft was used to define disease severity, unless the graft was occluded, in which case, the percentage stenosis of the native vessel was used.

STATISTICAL ANALYSIS

Continuous variables are reported as mean ± standard deviation. Comparison of categorical variables was performed using Fisher's exact test. Multivariate stepwise logistic binary regression analysis was performed using variables that were significant by univariate analysis, with sequential entry of variables to test for colinearity at each step. Comparison of mean values was done using a 2 tailed unpaired t test. All statistical analyses were performed using SPSS release 11.0 (Chicago, USA). A p-value < 0.05 was considered statistically significant.

RESULTS

The characteristics of the 200 patients are shown in Table 1.

TABLE 1: PATIENT CHARACTERISTICS

VARIABLE	**MEAN ± 1SD, OR N (%)**
Age	66.0 ±11.3 years
Gender	78/200 (39%) female
Documented CAD	83/200 (41%)
Prior myocardial infarct	52/200 (26%)
Diabetes	65/200 (32%)
Hypertension	128/200 (64%)
Coronary artery bypass grafts	30/200 (15%)
Protocol Exercise MPI Adenosine MPI	43/200 (21%) 157/200 (79%)
TID	23/200 (11.5%)
LVH	48/200 (24%)
Left ventricular ejection fraction post stress	57 % ± 13.7 %
Anteroseptal wall thickness on echocardiography	1.08 ± 0.53cm
Posterior wall thickness on echocardiography	1.09 ± 0.42cm
HbA1c	7.6 ± 1.4
Summed stress score on MPI	6.7 ± 10
Summed difference score on MPI	2.0 ± 3.5
Summed rest score on MPI	4.7 ± 8.4

A third of the population had diabetes (65/200), and 24% (48/200) were considered to have LVH on echocardiography. TID was present on MPI in 11.5% (23/200) of patients. Univariate analysis of those who developed TID showed a greater prevalence of ischemia and severe CAD on angiography, and that they were more likely to be diabetic, have LVH, or both (Table 2).

TABLE 2: CLINICAL AND SCAN CHARACTERISTICS STRATIFIED BY TID ON MPI

VARIABLE	**TID +**	**TID -**	**P VALUE**
Age (years)	68+/-10	65+/-11	p = 0.46
Gender (female)	8/23 (35%)	70/177 (39%)	p = 0.82
Hypertension	19/23 (83%)	109/177 (61%)	p = 0.06
LVH	15/23 (65%)	33/177 (19%)	p < 0.0001
Diabetes	19/23 (83%)	46/177 (26%)	p < 0.0001
Both Diabetes and LVH	11/23 (48%)	9/177 (5%)	p < 0.0001
Severe CAD (on coronary angiography)	8/12 (67%)	17/50 (34%)	p < 0.04
PROTOCOL **- Exercise** **- Adenosine**	 1/43 (2%) 22/157 (14%)	 42/43 (98%) 135/157 (86%)	 p <0.027*
SSS	9.8 +/- 12	6.2 +/- 9.6	p = 0.07
SDS	4.4 +/-4.8	1.6 +/- 3.1	p < 0.0001
Ischemia (SDS > 2)	14/23 (61%)	34/177 (19%)	p < 0.0001

* p value relates to the difference in the incidence of TID between exercise and Adenosine MPI protocols

TABLE 3: INDEPENDENT PREDICTIVE VALUE OF CLINICAL AND SCAN VARIABLES FOR TID ON MULTIVARIATE LOGISTIC REGRESSION

VARIABLE	SE	ODDS RATIO	95% CONFIDENCE INTERVALS	P VALUE
LVH*	0.557	9.57	3.1 - 29.0	0.0001
Diabetes	0.642	12.5	3.5 - 44.0	0.0001
Ischemia on MPI	0.575	4.26	1.4 – 12.7	0.009

LVH was analysed as a binary cutoff based on LV mass: Mean value for LVH negative patients was 246+/- 80 gms and for LVH positive patients was 341=/- 100gms

Multivariate logistic regression of the clinical, echocardiographic and scintigraphic parameters revealed that diabetes, LVH and ischemia (SDS >2) remained independently associated with TID (Table 3). All patients with TID had either diabetes (35% (8/23)), LVH (17% (4/23)), or both (48% (11/23)

Patients with diabetes had a higher incidence of TID compared to the non diabetic population (28% (19/65) vs. 3% (4/135) ($p < 0.0001$)).This association was even more marked in the presence of ischemia on the MPI. Among patients with diabetes and ischemia, 48% (13/27) demonstrated TID, whilst only 4.7% (1/21) of non-diabetics with ischemia, had TID ($p < 0.014$). Degree of diabetic control assessed clinically by HBA1c, duration of diabetes and a history of nephropathy or retinopathy were not predictive of TID (Table 4).

TABLE 4: ASSOCIATION BETWEEN MEASURES OF DIABETIC SEVERITY, AND TID.

VARIABLES	TID	NO TID	P VALUE
HbAIc	7.96 ± 1.66	7.65 ± 1.29	0.475
Duration of diabetes (years)	10 ± 9.3	10 ± 9.0	0.972
Retinopathy	2/19 (10%)	3/46 (6.5%)	0.459
Hypertension	16/19	35/46	0.357
Insulin dependent (IDDM)	6/19	25/46	0.527

LVH was strongly associated with TID on multivariate analysis (Table 3). In those with LVH, 34% (15/48) had TID compared to 7% (8/149) of those without LVH. This association between TID and LVH was more marked in the presence of ischemia (59% (10/17) vs. 13% (4/31), $p < 0.001$). There was an apparent synergistic effect between diabetes, LVH and ischemia on MPI. All patients (9/9) with LVH, diabetes and ischemia had TID, whereas no patients (0/12) with ischemia on MPI, but with neither diabetes nor LVH, had TID ($p < 0.0001$) (Figure 1).

Of 200 patients enrolled in the study, 62 (31%) had coronary angiography performed within 6 months of their MPI. By angiographic criteria, 24/62 (39%) were classified as having severe CAD. In those who had angiography, 12/62 (21%) had TID. The majority of these (8/12 (67%)) had severe CAD. Of the four patients with TID that were not classified as severe CAD, 3/4 (75%) had either proximal 2 vessel non LAD disease (>70%) or high grade (>90%) single vessel non LAD disease. All of these patients (4/4) had either diabetes, LVH or both.

Multivariate analysis on the population who underwent coronary angiography showed that both diabetes and LVH were predictive of TID independent of the presence of severe CAD on angiography (Odds Ratio 17.6, $p < 0.007$, and Odds Ratio 9.9, $p < 0.013$ respectively). The incidence of TID in patients with severe CAD on angiography, diabetes and LVH was 75% (6/8), versus 0% (0/8) ($p < 0.007$) in those with severe CAD on angiography, but neither diabetes nor LVH (Figure 1).

Figure 1: Impact of Diabetes on the interaction between TID and Ischemia on MPI

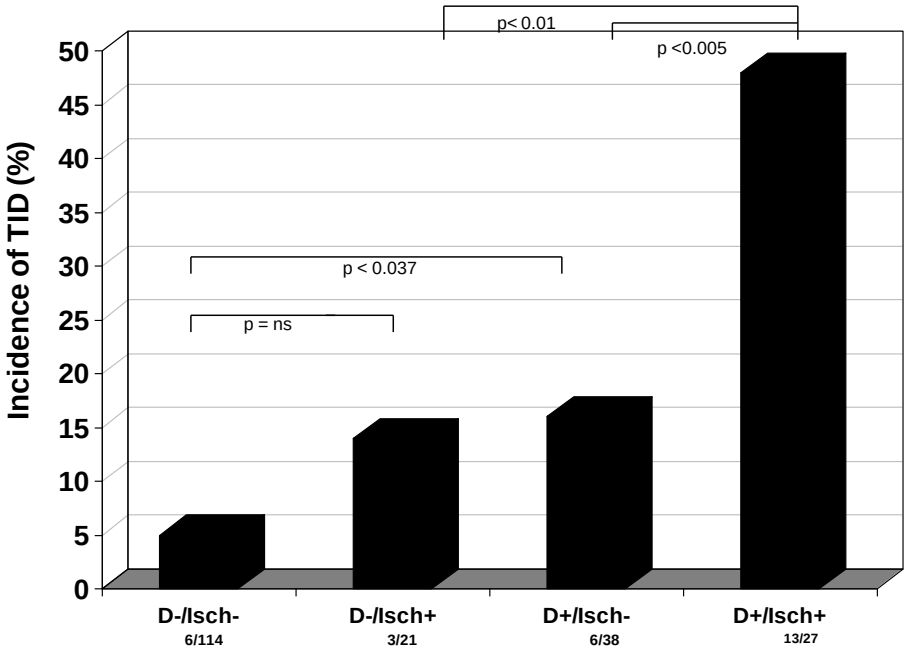
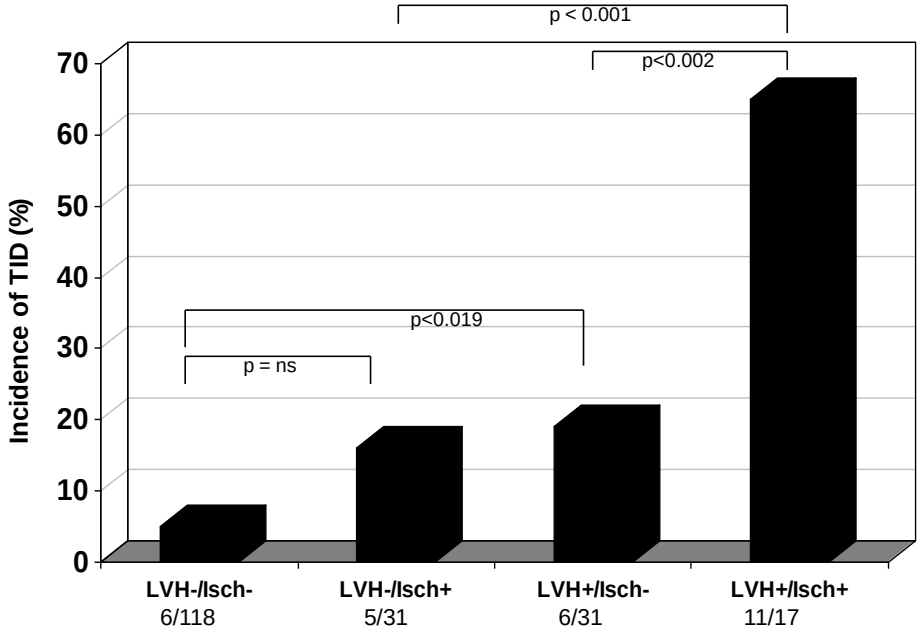


Figure 2: Impact of LVH on the interaction between TID and Ischemia on MPI



The post stress LVEF correlated far more strongly with the presence or absence of ischaemia (59% ± 7% vs. 50% ± 12% $p < 0.0001$), than with the presence or absence of TID (54.5% ± 12% vs. 57% ± 14% $p < 0.37$) (Table 5)

TABLE 5: RELATIONSHIP BETWEEN FUNCTIONAL PARAMETERS ON MPI, TID, AND ISCHEMIA

VARIABLES	NO ISCHEMIA	ISCHEMIA	P VALUE	NO TID	TID	P VALUE
End diastolic volume (mls)	109 ± 53	142 ± 56	0.0001	114 ± 52.8	140 ± 66	0.10
End systolic volume (mls)	50 ± 42	76 ± 47	0.0001	54 ± 43.8	70 ± 52	0.037
Post stress LVEF (%)	59% ± 13%	50% ± 13%	0.0001	57% ± 12%	54% ± 13%	0.37

DISCUSSION

First described by Stolzenberg et al in 1980[40], transient ischemic dilation of the left ventricle is an important prognostic sign on myocardial perfusion imaging. Several studies have subsequently confirmed its high specificity for multivessel and LAD disease, as well as the poor prognostic outcome in patients with TID on MPI, who have cardiac event rates ranging from 11-60% [32, 35-40, 44, 83]. This study confirms the strong association of TID with ischemia and severe CAD on angiography. It also confirms the strong association of diabetes and LVH to TID on MPI, independent of the presence of ischemia. In fact, all patients with TID had either diabetes, LVH, or, most commonly, both diabetes and LVH. This suggests that epicardial CAD is not the sole pathophysiological process involved in the etiology of TID, and that coronary microvascular disease may be intrinsic to the process.

The mechanism of TID remains controversial, and is likely due to more than one pathological process. One theory is that TID may be an 'apparent' phenomenon due to subendocardial ischemia [32, 34]. Tracer uptake in the hypoperfused subendocardium is compromised, producing the effect of apparent "thinning" of the ventricular wall on the post stress

images, and thereby, the impression of cavity enlargement[32]. A number of studies support this concept [34, 67, 75]. Another theory is that TID is due to absolute left ventricular cavity dilation and myocardial stunning secondary to ischemia. To support this, a recent study found a statistically significant reduction in LVEF post stress in the group of patients in the highest quartile for TID (TID ratio > 1.19) on a dual isotope MPI protocol [46]. In the present study the post stress LVEF was (not significantly) lower in those patients with TID, than those without TID. Furthermore, the presence of ischemia on MPI was much more strongly associated with a low post stress LVEF than was TID itself. The findings of this study suggest that while TID is strongly associated with ischemia on MPI, and hence with impaired post stress LV function, the association is indirect, and stunning may not be a requirement for the manifestation of TID on MPI.

We found that LVH and diabetes were most strongly associated with TID, independent of the level of ischemia on MPI, or severe CAD on angiography. The subgroup of patients with both diabetes and LVH comprised nearly half (48%) of those with TID on MPI, in spite of the fact that this group made up a relatively small proportion of the total population (10%). Both diabetes and left ventricular hypertrophy can cause coronary flow reserve abnormalities in the absence of significant epicardial coronary stenoses [26, 28, 29, 84]. Endothelium dependent (response to cold pressor testing) and independent coronary vasdodilator function is impaired in young diabetics with no known CAD [26]. Similarly, using trans-oesophageal doppler echocardiography, an impaired coronary blood flow response to low dose dipyridamole infusion has been documented in patients with hypertension and LVH[84]. The strong association of LVH and diabetes to TID, and their effect on coronary flow reserve gives credence to the hypothesis that subendocardial hypoperfusion plays a role in the pathophysiology of TID on MPI.

In spite of the strong association with diabetes and LVH, little TID was seen in the absence of severe CAD on angiography. In the four patients with TID without severe CAD on coronary angiography, 75% had high grade non LAD disease. Thus, it does not appear that diseases affecting coronary microvascular function are solely responsible for TID on MPI, but that they exert a synergistic effect in conjunction with epicardial coronary artery disease. Additionally, our finding that patients without diabetes or LVH did not manifest TID on MPI in spite of severe CAD on angiography may also help explain the relatively low sensitivity (32-34%) of TID for severe CAD documented in previous studies [59, 65].

The high incidence of diabetes in patients with TID has been demonstrated in a number of previous studies [35, 37, 72]. We assessed the severity of diabetes by type (Insulin dependent or non insulin dependent), duration (years), and the presence of retinopathy and renal impairment, with HbA1C as a measure of short/medium term control. No significant association was found between the presence of TID, and measures of diabetic control or microvascular disease. In an assessment of the effect of autonomic neuropathy on coronary blood flow in diabetics, Di Carli et al [28] found only duration of diabetes and abnormal cardiac sympathetic innervation (measured using positron emission tomography tracers) to be associated with abnormalities in coronary blood flow. It may be that more complex measures of microvascular disease, and larger patient numbers are needed to adequately assess the relationship between TID and diabetic disease severity. In any case, our data suggest that the contribution of diabetes to TID must be seriously considered, regardless of diabetic disease severity or duration.

The majority of patients who demonstrated TID in this study underwent pharmacologic stress. This preponderance of TID in pharmacologically stressed patients is not unusual and was highlighted in a review of TID [33]. There are a number of possible explanations for this. Firstly,

patients undergoing pharmacologic stress tend to be sicker, and have more severe CAD than those who undergo exercise stress. Secondly, pharmacologic stress is generally an assessment of coronary flow reserve rather than a direct measure of ischemia. Myocardial blood flow response is impaired during Adenosine induced hyperemia in diabetics compared to age matched controls [29]. Similarly, using trans-esophageal doppler echocardiography, an impaired coronary blood flow response to low dose dipyridamole infusion has been documented in patients with hypertension and LVH[84]. Thus, underlying coronary flow reserve abnormalities may predispose a patient to TID on MPI, particularly when vasodilator stress is undertaken.

STUDY LIMITATIONS

TID is a relatively uncommon finding on MPI, only present in 32% of patients with severe CAD [59], and less commonly in a broader patient population. This study had only 11.5% (23/200) of patients with TID on MPI. In spite of this, the small standard of error of our multivariate analysis confirms the strength of our findings, and particularly the independent association between LVH, diabetes and TID.

The small numbers of diabetic patients with microvascular complications on clinical history made meaningful assessment of the cause of the higher incidence of TID in diabetics impossible. It may be that more direct measures of cardiac autonomic dysfunction such as autonomic reflex testing or assessment of cardiac sympathetic innervation would be more valuable.

CONCLUSION

TID was strongly associated with both ischemia and severe CAD. However, all patients with TID had diabetes, LVH or both, suggesting that the pathophysiology of these disease processes may play an integral role in the manifestation of TID on MPI.

THESIS CONCLUSION

The four papers that form the body of this thesis are a linked theme of research that has attempted to elucidate both the clinical significance and biomechanical cause of a number of adverse prognostic signs observed in myocardial perfusion imaging. From a personal point of view, the findings from this research has better informed the clinical reporting of the author, allowing insight into the pathophysiology present behind the adverse prognostic features on myocardial perfusion images, and in improving the diagnostic value of the report to referrer and patient. This conclusion will overview the major findings of the four papers, and place the results in context with the current literature in the field, and its clinical relevance.

The ability to measure both resting and post stress left ventricular function and left ventricular volumes on myocardial perfusion imaging is a relatively recent occurrence (post 1997) , and is due to the more widespread use of Technetium based perfusion agents that have physical imaging characteristics more suited to higher resolution imaging, and higher count rate capabilities that improve the resolution and reduce the statistical error in the measured volumes and ejection fractions both at rest and following stress. Computer capacity has also improved in recent years, allowing more complex analysis of the detected images. The findings of the first 2 papers in this thesis have contributed to establishing the clinical significance of regional and global myocardial stunning identified on myocardial perfusion imaging, and also in determining the likely aetiology of myocardial stunning on vasodilator MPI.

Research undertaken initially by Johnson et al (1997) [19] determined that a drop of > 5% in LVEF between the rest and stress MPI images was significant based on serial

reproducibility of LVEF values in patients who had repeated Gated SPECT MPI imaging. They found that in patients with ischaemia on MPI, up to 36% demonstrated a drop in LVEF > 5% on the post stress images relative to the resting images and that this drop was associated with chordal shortening that was more severe in regions of more marked ischaemia (suggestive of regional wall motion abnormalities). A further study by Bacher Stier et al;[86] confirmed the strong correlation between reversible wall motion abnormalities on MPI, and the severity of the reversible perfusion defects identified (ischaemia). They found that up to 47% of those with severe reversible ischaemia on MPI had visually and quantitatively apparent regional wall motion abnormalities. The research that forms the 1st chapter of this thesis aimed to determine both the prevalence and the clinical significance of the reversible regional wall motion abnormalities evident on rest and stress gated MPI. The study was able to confirm the strong correlation previously identified between the severity of ischaemia on MPI, and the extent of reversible wall motion abnormalities identified. It was also able to determine that the presence of a reversible wall motion abnormality on MPI is highly specific for a high grade angiographic stenosis, with no reversible wall motion abnormalities identified in the study with angiographic stenoses of < 70%. This finding has important clinical ramifications. If a reversible wall motion abnormality is identified on MPI, independent of the severity of the perfusion abnormality, the underlying epicardial stenosis responsible is haemodynamically significant, and angiography is warranted, if not previously undertaken. This is important particularly in patients with 'balanced ischaemia' on MPI. Berman et al[13]; undertook a study of patients with known significant left main coronary artery disease on angiography and assessed the sensitivity of MPI for identifying patients at high risk. They found that only 60% of patients with significant left main disease were identified by reversible perfusion abnormalities alone, and that up to 13% were still missed if

other criteria such as transient ischaemic dilation and reduced LVEF were not taken into account. The study did not assess reversible wall motion abnormalities or a change in LVEF post stress. We found that the specificity of a reversible perfusion abnormality on MPI for a stenosis > 70% on angiography was 100%, with a sensitivity of just 53%. That reversible wall motion abnormalities are so highly specific for significant angiographic stenoses, and so strongly correlative with the angiographic jeopardy score, allows the clinician a further tool by which to identify patients at high risk of a significant coronary event, even when other features on the MPI scan are more equivocal. Further, the study also found that at higher grade angiographic stenoses (80-99%), the presence of a reversible wall motion abnormality had a higher sensitivity than the presence of a reversible perfusion defect (ischaemia) on the MPI scan. This was not the case in less severe angiographic stenoses. This finding fits nicely with that of Berman et al;, who found that perfusion abnormalities alone missed up to 40% of haemodynamically significant left main stenoses, and concluded that assessment of perfusion abnormalities alone was not a sufficiently sensitive approach. The initial study undertaken in this thesis also analysed both the presence of TID and a drop in LVEF of >5% between the resting and post stress images. We found both the presence of TID, and a drop in LVEF to correlate strongly with the angiographic jeopardy score. Although, while they were significant univariate predictors of the angiographic jeopardy score, when placed in a multivariate analysis, they did not remain independently predictive, with only the severity of ischaemia (perfusion score) and the severity of a reversible wall motion abnormality remaining predictive of a high angiographic jeopardy score. This is not surprising as TID and perfusion are measuring similar phenomena, and it is likely (as shown later) that TID is also influenced by other pathophyisological factors, such as endothelial function, and not just the severity of the epicardial arterial stenosis.

Subsequent to the publication of our findings regarding the clinical relevance of reversible wall motion abnormalities on MPI a number of further papers have been published which have helped shed light on the relationship between myocardial stunning, regional wall motion abnormalities and ischaemia on MPI [22, 46, 57, 63, 64, 66]. Heiba et al; found a strong correlation between ischaemia on MPI and the magnitude of the drop in LVEF post stress in patients undergoing exercise or dobutamine stress MPI[66]. A large prospective study by Usui et al; [87]followed 4000 patients for 3 years to assess the prognostic significance of functional parameters measured with both exercise and vasodilator stress MPI. They used pre-designated cutoffs to define myocardial stunning (change in LVEF >= 5%) and also defined LV dilation as a change of > 5mls in LVESV. This large study found only a dilation in LVESV to be predictive of coronary events, with the drop in LVEF post stress not predictive of outcome. However, change in LVEF between rest and stress was not analysed as a continuous variable, and the study is flawed for this reason. A change of 5% is the minimum reproducible measure for LVEF on MPI, with many people only accepting a change of 10% in LVEF between rest and stress on MPI as definitely significant. Unfortunately, no other study has directly assessed the prognostic strength of measures of change in functional parameters on MPI, except by using proxy measures such as the coronary artery jeopardy score.

Myocardial stunning has been well documented following both transient and prolonged arterial occlusion in animal experiments[15, 18]. However, with vasodilator stress imaging, the explanation cannot be so simple. Adenosine and Dipyridamole infusions do cause significant haemodynamic changes at the time of administration, increasing coronary arterial flow 3-5 times above baseline and increasing cardiac output in the short – term (during Adenosine infusion) by 50% [5, 88]. However, perfusion abnormalities on vasodilator MPI are thought to reflect

impairment of coronary flow reserve rather than true myocardial ischaemia. Adenosine has been shown to induce subendocardial hypoperfusion by redirecting flow to the subepicardium away from the subendocardium in myocardium supplied by stenosed vessels[68, 89] . Severe ischaemia can occur due to coronary steal from collateral dependent vascular territories. The exact incidence of this, while thought to be rare, is not documented [68]However, post stress stunning on vasodilator MPI has been estimated to occur in up to 33% of patients with severe ischaemia on MPI [22, 46]. Studies by Druz et al and Lee et al;[22, 90] have both confirmed measurable drops in post stress LVEF, and post stress wall motion abnormalities following vasodilator myocardial perfusion imaging, the conclusion of both papers being that the wall motion abnormalities are due to true myocardial stunning following an ischaemic episode. A study using pharmacologic stress dual isotope MPI by Hung et al [46], found a significant drop in LVEF and increases in both LVEDV and LVESV in patients with TID on MPI, while the LVEDV and LVESV did not increase in those without TID. They concluded that enlargement of the ESV on MPI as a result of ischemic myocardial stunning was an important factor resulting in TID. However, it has been difficult to explain how the incidence of true myocardial stunning on Adenosine MPI could be so common on the basis of the known physiological changes occurring with Adenosine stress.

Manrique et al (2007)[63], used computerized phantom simulations of cardiac perfusion abnormalities on MPI to assess the impact of the severity of perfusion abnormalities on measures of left ventricular volumes and function. They found that by manipulating the severity of reversible perfusion abnormalities on the phantom, they also altered the measured LVESV, LVEDV and LVEF on gated MPI, even though the phantom had a set LVEF of 62%, and preset LV volumes [63]. They concluded that the severity of perfusion defects had a significant effect

on the evaluation of myocardial stunning using MPI. These results would suggest that the drop in LVEF and changes in LVESV and LVEDV measured post stress in those with severe ischaemia on MPI may not be true physical changes but may be related to the underlying physiological changes occurring.

The second paper of this thesis was designed to assess the physical changes occurring in the left ventricle both immediately, and 2 hours following Adenosine MPI stress testing. The aim of the study being to assess whether the dilation of the left ventricle and the reduction in post stress LVEF in patie nts with severe ischaemia or TID on Adenosine MPI, are due to true myocardial stunning, or due to subendocardial hypoperfusion. Gated SPECT imaging relies on detecting the physiological endocardial edge to determine LV volumes and LVEF. In the presence of subendocardial perfusion abnormalities, the software may be tracing an edge which is not truly reflective of the anatomical endocardial border, and give misleading volume assessments. To determine if this is the case, a multimodality approach was used with transthoracic echocardiography acquired in conjunction with Gated SPECT MPI both at rest, immediately following cessation of Adenosine infusion, and 2 hours following Adenosine infusion. The study found that, in patients with severe ischaemia on MPI, or with TID, there was a significant drop (mean 10%) in LVEF between rest and stress imaging, with an increase in the measured LV volumes post stress relative to the resting images. When the concurrent echo data was analysed, no statistically significant change in LVEF, or in LV volumes was identified between the resting or the post stress images. Furthermore, there was no significant change in either the LVEF or the left ventricular volumes on MPI up to 2 hours post Adenosine stress, compared to those measured immediately post Adenosine infusion. As previously demonstrated in the stress echo literature, ischaemic myocardial stunning has been demonstrated to occur for

up to 45 minutes following both exercise and Dobutamine stress in patients with significant coronary artery disease [23, 69, 70], with resolution of myocardial stunning demonstrated in all those studied by 1 hour post stress. These findings suggest that the volume changes measured on post stress MPI in patients with TID, or severe ischaemia, are a function of the change in the detected edge of the subendocardium post Adenosine stress MPI, rather than true anatomical dilation. This finding fits nicely with the results of a study by Ward et al (2006)[64] who assessed of post stress regional wall motion abnormalities and LV function using both Echo and MPI post exercise stress. They found a poor correlation between post stress LVEF on Echo, and post stress LVEF on MPI, in patients with moderate to severe ischaemia. In their study, those with ischaemia on the MPI demonstrated a significantly lower post stress LVEF on MPI, than seen on Echocardiography. Hence, from the findings of both these studies, it is likely that the measured increase in LV volumes, TID, and reduced LVEF in patients with ischaemia on Adenosine MPI is a marker of impaired subendocardial coronary flow reserve rather than true myocardial stunning and LV dilation. This helps explain the previous paradox. The high incidence of myocardial stunning identified in those with ischaemia on Adenosine MPI [22, 90] is not due to true myocardial dysfunction in collateral dependent ischaemic vascular territories, but is a reflection of subendocardial hypoperfusion.

A further aim of the 2nd paper in this thesis was to more fully evaluate the pathophysiology of TID on MPI with the use of multimodality imaging. Gated SPECT imaging on MPI relies on detection of perfusion at the endocardial edge for measurements of left ventricular volume, and hence, the mathematical determination of the TID ratio. Most previous studies assessing whether the dilation of the left ventricle post stress with TID is real or apparent have relied on measurements from MPI alone without using other imaging modalities to confirm

the findings. Van Tosh et al [67] used both exercise thallium and echocardiography to assess 24 patients, of whom 8 were deemed to have TID. They used echocardiographic volume measurements to assess change in LV cavity with TID, but did not undertake concurrent gated thallium estimations of rest and post stress LVEF and volumes. They found no dilation in LV cavity parameters on echo post stress in those with TID, finding only a reduced LVESV post stress in the TID negative group. In our research, the increase in LVEDV and LVESV on MPI in the TID positive group was not present on the concurrent echo measurements, which found no significant change in LV volumes or LVEF in patients with TID. Hence it is likely that, instead of as previously understood, it is not ischaemic stunning that is responsible for TID, but more likely, the global reduction in perfusion at the endocardial border, leading to an apparent increase in LVESV volumes. This helps explain the increased incidence of TID in patients with diseases affecting coronary microvascular function such as left ventricular hypertrophy, diabetes[58, 59] and hypertrophic cardiomyopathy [24, 27].

The final 2 papers of this thesis were designed to assess the clinical factors that are associated with TID on MPI, independent of high grade coronary artery disease. Both LVH and diabetes have been shown to affect coronary flow reserve in the absence of macrovascular CAD [81, 82]. In LVH, there is a relative decrease in capillary density within the hypertrophied muscle leading to coronary flow reserve abnormalities that can cause myocardial ischaemia even in the absence of large vessel CAD. In the presence of CAD, coronary flow reserve abnormalities may exacerbate the severity of ischaemia[73, 82]. Endothelium dependent (response to cold pressor testing) and independent coronary vasdodilator function is impaired in young diabetics with no known CAD [26]. Similarly, using trans-oesophageal doppler echocardiography, an impaired

coronary blood flow response to low dose dipyridamole infusion has been documented in patients with hypertension and LVH[84].

The 2 studies were undertaken sequentially. The initial study was retrospective in nature, and aimed to determine clinical associations with TID using a database of 100 patients who had undergone echocardiography, coronary angiography and stress MPI within a short space of time. Due to its retrospective nature, there was a high proportion of patients with severe CAD in the population. A number of variables were studied, including gender, stress type (vasodilator or exercise), smoking, diabetes, hypertension, LVH and medications. The study confirmed the known strong association between TID and severe CAD, but also found that diabetes and left ventricular hypertrophy were strong independent predictors of TID. In fact, the predictive strength of these 2 variables for TID was at least as strong as the presence of severe CAD. Further, the presence of either diabetes or LVH significantly altered the sensitivity and specificity of TID for severe CAD, such that less severe grades of angiographic stenosis were required for TID to be present when the patient had either diabetes or left ventricular hypertrophy.

This was the first study in the published literature to establish a link between TID on MPI and clinical variables other than severe coronary artery disease, or ischaemia. However, the study was not of sufficient size to properly assess parameters of diabetic severity, or to assess the interaction between clinical variables on TID. Also, significant biases may have influenced the results due to the retrospective nature of the study. For these reasons, a further study examining the same clinical questions, but of larger size, and prospective in nature was then developed.

The aim of the final study of this thesis was to prospectively confirm the initial findings that diabetes and left ventricular hypertrophy were strongly linked to TID. It also attempted to

determine if parameters of diabetic severity influenced the incidence of TID, and if TID could be present in patients with microvascular disease, in the absence of significant coronary artery disease. In all, 200 patients underwent echocardiographic assessment of left ventricular mass index at the time of their clinically indicated MPI. The findings of the prospective study confirmed those of the smaller retrospective analysis. In the larger study, all patients with TID had either diabetes, LVH, or both. The subgroup of patients with both diabetes and LVH comprised nearly half (48%) of those with TID on MPI, in spite of the fact that this group made up a relatively small proportion of the total population (10%). Among patients with both diabetes and ischemia on MPI, 48% demonstrated TID, whilst only 4.7% of non-diabetics with ischemia, had TID. While the study confirmed the known strong correlation between severe CAD on angiography and TID, it appears that this is selective. The incidence of TID in patients with severe CAD on angiography, diabetes and LVH was 75%, while none of the group with severe CAD on angiography, but neither diabetes nor LVH had TID on MPI. These strong results suggest that epicardial CAD is not the sole pathophysiological process involved in the etiology of TID, and that coronary microvascular disease may be intrinsic to the process.

The study was unable to determine that LVH or diabetes resulted in TID on MPI in the absence of significant epicardial coronary stenoses on angiography. As the study was prospective, with MPI as the initial procedure, only 33% of all patients included in the study subsequently underwent coronary angiography (12/23 of those with TID). In spite of the strong association with diabetes and LVH, little TID was seen in the absence of severe CAD on angiography. In the four patients identified with TID without severe CAD on coronary angiography, 75% had high grade non LAD disease. Thus, it does not appear from this research that diseases affecting coronary microvascular function are solely responsible for TID on MPI, but that they exert a synergistic

effect in conjunction with epicardial coronary artery disease. Additionally, the finding that patients without diabetes or LVH did not manifest TID on MPI in spite of severe CAD on angiography may also help explain the relatively low sensitivity (32-34%) of TID for severe CAD documented in previous studies [59, 65].

The high incidence of diabetes in patients with TID has been demonstrated in a number of previous studies [35, 37, 72]. We assessed the severity of diabetes by type (Insulin dependent or non insulin dependent), duration (years), and the presence of retinopathy and renal impairment, with HbA1C as a measure of short/medium term control. No significant association was found between the presence of TID, and measures of diabetic control or microvascular disease. In an assessment of the effect of autonomic neuropathy on coronary blood flow in diabetics, Di Carli et al [28] found only duration of diabetes and abnormal cardiac sympathetic innervation (measured using positron emission tomography tracers) to be associated with abnormalities in coronary blood flow. It may be that more complex measures of microvascular disease, and larger patient numbers are needed to adequately assess the relationship between TID and diabetic disease severity. In any case, our data suggest that the contribution of diabetes to TID must be seriously considered, regardless of diabetic disease severity or duration.

The majority of patients who demonstrated TID in the prospective study underwent pharmacologic stress. This preponderance of TID in pharmacologically stressed patients is not unusual and was highlighted in a review of TID [33]. There are a number of possible explanations for this. Firstly, patients undergoing pharmacologic stress tend to be sicker, and have more severe CAD than those who undergo exercise stress. Secondly, pharmacologic stress is generally an assessment of coronary flow reserve rather than a direct measure of ischemia. Myocardial blood flow response is impaired during Adenosine induced hyperemia in diabetics compared to age

matched controls [29]. Similarly, using trans-esophageal doppler echocardiography, an impaired coronary blood flow response to low dose dipyridamole infusion has been documented in patients with hypertension and LVH[84]. Thus, underlying coronary flow reserve impairment may predispose a patient to TID on MPI, particularly when vasodilator stress is undertaken**.**

TID was strongly associated with both ischemia and severe CAD. However, all patients with TID had diabetes, LVH or both, suggesting that the pathophysiology of these disease processes may play an integral role in the manifestation of TID on MPI. Thus, it does not appear from this research that diseases affecting coronary microvascular function are solely responsible for TID on MPI, but that they exert a synergistic effect in conjunction with epicardial coronary artery disease.

SUMMARY:

The clinical research that forms the basis of this thesis has furthered the understanding of a number of facets of myocardial perfusion imaging. It has found that the presence of regional wall motion abnormalities on MPI are highly specific for high grade angiographic stenoses. In the case of high grade stenoses on angiography (80-99%), the sensitivity of a wall motion abnormality is higher than the presence of a perfusion defect, which has important clinical relevance in reducing the false negative results in MPI, particularly in patients with significant left main disease. It has found that the term 'myocardial stunning' is misleading when a drop in LVEF is present on MPI, as the drop in LVEF is more a reflection of global subendocardial ischaemia than a true change in LVEF. Similarly the term TID or Transient ischaemic dilation is also misleading as the ventricular dilation measured is also not anatomical, but more a physiological phenomena related to a change in the detected subendocardial perfusion edge. The presence of both diabetes and left ventricular

hypertrophy are instrumental in the manifestation of TID on MPI, likely due to their negative effect on microvascular function, and endocardial perfusion. Such disease processes have a synergistic effect in conjunction with severe coronary artery disease, leading to both 'TID' and 'myocardial stunning' on MPI.

The research has also raised further questions that are the subject of ongoing investigation. If the reduced LVEF and transient ischaemic dilation present in high risk patients on MPI is due to subendocardial hypoperfusion and impaired coronary flow reserve, then can MPI be viewed as a surrogate measure of microvascular function? Does increasing LVEF and reduced LV cavity size on vasodilator MPI indicate normal microvascular function, and hence, good prognosis in patients with diabetes or known multivessel disease?

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