Chapter 1: Introduction and review of literature

1.1 Background

Coronary artery disease (CAD) is a frequent cause of death in diabetes, and cerebrovascular diseases are significantly more common in diabetic individuals. Most studies that look at the genesis or prevention of cardiovascular disease, and the diagnostic criteria or risk factors for diabetes, have associated diabetes and cardiovascular disease.[1,2,3,4,5,6] However, diabetic individuals with CAD in their larger number are usually asymptomatic, and when they present with signs of disease, there is extensive and severe CAD.[7,8,9,10] It should be noted that while cerebrovascular disease is common amongst black South African, ischemic heart disease (IHD) remains rare, and there is little data liking diabetes mellitus with these conditions in the black population.

1.2 Diabetes and Cardiovascular disease (CVD) in Africa

There is enough evidence to show that diabetic patients are at high risk for CVD like CAD, stroke, peripheral arterial disease, cardiomyopathy, and congestive heart failure.[11]

The impact of diabetes on the cardiovascular system can be seen in the microvasculature, the larger arteries, the heart and kidneys. At present, the American Heart Association (AHA) has formally decided to designate diabetes as a major risk factor for CVS that is of equal status to cigarette smoking, hypertension and cholesterol disorders.

Contrary to early reports that have suggested a low prevalence of CAD in black population in Africa,[12-15] many studies have indicated a rapid change on the spectrum of CAD in numerous parts of the African continent.[16-20]

Despite these emerging reports, there are only a few data that directly link together CAD and diabetes in the continent. While data from a well structured study looking at risk factors that are associated with myocardial infarction (MI) in Africa have incriminated diabetes and hypertension, still hypertension was

the most important risk factor in terms of significance among individuals who suffered an acute MI.[21] The findings of this study included cases from 9 African countries and the major ethnic groups that are found within these countries. However, it is of an important note to stress that the majority of cases was from South Africa and the overall black population represented 36,3% of cases (table 1). One can conclude from the data of this study that the theory that black population was some how protected against acute MI could not continue to stand unchallenged, in view of changing patterns of CVD, particularly in the urban African areas. However, it is similarly important to state that diabetes was one of the 5 risk factors that accounted altogether for 89,2% of the risk for an initial MI. Of interest is also the fact that data from the study have shown a low number of acute MI cases in the black population, especially in countries other than South Africa. One could perhaps deduce that acute MI may be a relatively rare event in black population in these countries. In fact, Sliwa et al in their study that aimed to investigate the clinical range of disorders related to CVD in a tertiary medical institution have noted a high prevalence of risk factors for atherosclerotic disease and heart disease in black population[22]. The study was primarily an epidemiologic prospective registry that included an estimated 5000 patients who were seen in year 2006 at the cardiology unit of a 3500-bed public hospital that provides specialist cardiac care to the community. Data from the study have shown that 1593 (38%) of newly diagnosed patients and 2569 (62%) of patients with known CVD on treatment were seen during that period. The majority of patients were black and heart failure was the most common CVD in the studied population. This interesting epidemiologic study also found that black African suffered more from heart failure while CAD had shown to be a less likely diagnosis among those who entered the registry. Diabetes was noted in 165 (about 10%) of the newly diagnosed CVD patients but in 35 (21%) of patients diagnosed with CAD. The findings also concurred with the fact that diabetes as a comorbidity of hypertension and CAD is present in a broaden spectrum of CVD in African urban population. The later is also supported by findings of another epidemiologic study that had a major focus on the awareness and screening for risk factors to establish the presence of heart disease mainly in the black African population.[23] Using labeled of “Heart Awareness Days”, the

study utilized single full days of screening volunteers from the general population at four-weekly interval over a 12 month period. Participants were informed on the types and consequences of commonly known risk factors for heart disease. Analysis of data showed a total number of 1691 participants with the great majority (99%) being black African. One third of screened participants (476) have indicated a history of CVD or the presence of a common antecedent of heart disease. Hypertension dominated the number of participants (80%) while the remaining 20% have indicated to be told that they had diabetes (11%) or both diabetes and hypertension (9%). These last figures could be extrapolated to the general population of South Africa and thus enhancing the title of the study: "A time bomb of cardiovascular risk factors in South Africa…". In fact, epidemiological data have already suggested in the 1990s that approximately 1.5 million South African had diabetes and with the growing prevalence of the disease worldwide, particularly in developing countries, this figure is likely higher today.[24]

Similar figures should be expected in other regions of the continent. In a study conducted in the central African region, Longo-Mbenza and colleagues looking at the rates and predictors of stroke-associated case fatality in black population have indicated a 14.6% prevalence of diabetes mellitus among patients who had suffered stroke.[25] Another African study aiming in determining the prevalence of traditional cardiovascular risk factors among Nigerians with stroke has similar results.[26] The study has actually found 11.1% of patients who suffered stroke to have history of diabetes mellitus. Not only that these two studies enhance the fact that there is an association between diabetes and CVD they also indicate the prevalence of diabetes to be at around 10%-15% among patients with CVD.

1.3 Role of screening asymptomatic patients in Africa

The recognition that diabetes is an independent risk factor for CVD is of less doubt. One of the largest prospective studies, the Framingham Heart study, found a significant increase in the prevalence of diabetes mellitus in patients

suffering with CVD in the past 50 years.[27] The findings of the study have indicated the serious need to closely monitor patients with diabetes and aggressively control their CVD risk factors, thus the need for screening asymptomatic diabetic individuals.

Lutale and colleagues have looked at the prevalence of electrocardiography (ECG) left ventricular (LV) hypertrophy and its relation to other CVD risk factors in 237 asymptomatic diabetic patients seen at the university hospital in Tanzania.[28] They have considered patients from the study population to be asymptomatic if they did not have evidence of renal failure or cardiac and cerebral vascular disease. They have found ECG changes that were associated with LV hypertrophy but could also indicate the presence of myocardial injury. Furthermore, they have noted the presence of a clustering of risk factors for CVD among the type 2 diabetic patients that included hypertension, abdominal obesity, dyslipidaemia, albuminuria and advanced age.

Recently, abdominal obesity measured as waist circumference was indeed not only confirmed by Ntyintyane and colleagues to be a risk factor in urbanized black South African with established CAD[29] but also a risk factor among the rural South African community.[30]

There is also knowledge that cardiovascular risk factors clustering in diabetic patients were often associated with an increased risk for developing coronary heart disease.

Perhaps, of all the clustering risk factors in diabetic individuals, atherosclerosis is the most worry some.

Raal has indicated that about 70% of all mortality in diabetic patients is most likely due to atherosclerosis.[31] Furthermore, in those diabetic with known atherosclerosis, CAD would be the cause of mortality in them. Similarly, the majority of hospital admissions of diabetic individuals result from macrovascular disease. In fact, MI and stroke in diabetics are more extensive and rapidly fatal as compared to non-diabetic patients with MI or stroke.

All these findings undoubtedly indicate the need for systematic assessment of diabetic individuals. And this need is enhanced by actual facts like those noted in an audit by Steyn and coworkers who found a poor level of diabetes control among South African patients seen in the Cape region.[32] They noted

that at least 76% of patients with diabetes (N=455) had levels of glycosylated hemoglobin ($HbA1_c$) 1% above the upper limit of normal. There was also little understanding by diabetic participants on how to manage hyper-or-hypoglycemia, and also inadequate knowledge of the clinical impact of poor diabetes control. From poor diabetic control to development of CVD there is only a step to cross, hence the need to screen asymptomatic diabetic individuals for CVD risk factors.

1.4 Screening asymptomatic patients for CAD

The rapid advancement in technology has resulted in the assumption that clinical data are probably less accurate than methods used in laboratory and those using images. Usually a stress test is used and asymptomatic patients who are suspected to have CAD undergo same stress testing as individuals known to have the disease or who are presented with typical or atypical chest pain for evaluation.

1.4.1 Exercise testing

The predictive power of exercise stress testing makes it a focus of attention for assessing individuals with or suspected to have CAD. An abnormal ECG response in asymptomatic individuals who undergo exercise testing is an indicator of high risk for developing CAD. In fact, asymptomatic individuals with abnormal ECG response have worse outcome with regard to CAD as compared to individuals with normal ECG response.[33-36]

It was Bruce and coworkers who were the first to study large number of individuals without known CAD with exercise stress testing.[37-41] They have actually shown that ST-segment response on ECG together with other parameters that looked at the tolerance to the exercise were able to predict survival. The technique that they have used is known to us as the “Bruce protocol”. Using this protocol, a test is considered to be negative when a subject had achieved 85% of the maximum heart rate predicted and does not show evidence of ST-T changes on ECG. The predicted maximum heart rate

is simply determined by the subtraction of the individual age from 220. It is of interest to note that factors like pre-existing ST-T abnormalities, left bundle branch block (LBBB), beta blocking drugs, and the development of arrhythmias during exercise affect the exercise stress testing and often result in an indeterminate response rather a positive or negative ones. The prognostic value of exercise testing and also its sensitivity, specificity, and accuracy have been studied.[34,42] Actually, McNeer and colleagues studied 1472 patients with exercise testing to assess the presence of CAD.[42] Eight hundred seventy-six of these patients had proven significant artery disease on angiography and 596 had normal coronary anatomy or no significant disease. The ST-segment response and exercise duration were found to have the most predictive information, but ST-segment response was found to be superior to exercise duration for the prediction of significant coronary artery disease and its extent. They also found that 90% of patients with a positive exercise testing actually had angiographic evidence of CAD. However, not all patients with significant coronary disease on angiography could be identified by exercise test. Forty-three percent of the 793 patients with a negative but adequate treadmill test in the study were found to have significant disease on angiography. Furthermore, the level of exercise that one may achieve did not show a correlation with the presence or absence of coronary disease. They found that 47% of 421 patients who successfully completed the exercise test had demonstrated the presence of significant coronary disease on angiography. However, controversy regarding ST-segment response to exercise whenever an up sloping ST depression has been previously stated to question whether it should be considered abnormal or not[43].

The sensitivity and specificity of exercise test have shown variable results. Gianrossi and co-workers have done a meta-analysis of all reports published after 1967 on the diagnostic accuracy of the exercise ECG when compared with coronary angiography.[44] They found 325 publications and retained 147 for review. The weighted sensitivity was 68±16% and the weighted specificity was 77±17%.

The safety of the technique has also been reported and Rochmis and Blackburn were the most likely first authors to look at a very large number of individuals undergoing exercise test.[45] They have looked at the safety of the

procedure in about 170,000 patients and have noted a mortality rate of one death per 10,000 tests and the rate of 4 serious cardiac complications per 1,000 tests. Although an exercise test that is carried out by a qualified professional is considered to be a safe procedure, there is a belief that maximal exercise testing is dangerous and that many complications are possibly underreported.

Gibbons and his colleagues have looked at 26,471 men and 7,824 women, all volunteers who have given informed consent for a maximal exercise test.[46] they wanted to examine the frequency of major complication that were define as MI, ventricular fibrillation, ventricular tachycardia that requires treatment, atrial arrhythmia requiring treatment, stroke, and death. Only 3.7% of both groups of patients failed to reach the predicted 85% of their maximal heart rate. Their data have shown a risk complication rate associated with maximal exercise testing to be 0.8 per 10,000 tests. From their findings, on can state that exercise is a safe activity for individuals without coronary artery disease because cardiac events during or following vigorous exercise, including exercise that is performed in conjunction with ECG test , occur in individuals with heart disease rather than in healthy subjects. Therefore, individuals without heart disease can undergo maximal exercise testing to exhaustion with no fear to develop cardiovascular complication.

1.4.2. Myocardial perfusion imaging (MPI)

Myocardial perfusion imaging is based on radiopharmaceutical uptake by the myocardial cells. Products such as ^{201}Thallium (Tl-201), ^{99m}Tc-sestamibi (Tc-99m MIBI), ^{99m}Tc-tetrofosmin (Tc-99m Tetrofosmin) and others are used for MPI. It is performed at rest and stress, and provides semi-quantitative information on areas of myocardial infarction and ischemia. In the diagnosis and prognostic evaluation of CAD, MPI has higher sensitivity and specificity than clinical and historical data, and data from the non-imaging component of stress testing[47]. The sensitivity and specificity of MPI in detecting CAD range between 81% and 91%, and 82% and 91% respectively[48-51]. Single emission computed tomography (SPECT) is the routine technique in use for MPI.

1.4.2.1 Value of SPECT in MPI

SPECT-MPI is a widely utilized non-invasive imaging modality for the diagnosis and management of ischemic heart disease (IHD). The diagnostic value of SPECT is directly linked to several aspects of the radiotracer that is used in perfusion imaging. There are some well established aspects for an ideal tracer as described by Russell and Zaret[52]. The imaging agent should at first accurately reflect blood flow of the myocardium over a wide range of values. Secondly, the ideal tracer should not be affected by factors such as attenuation which is commonly related to the physical characteristics of the tracer. Because organs like the liver will also show uptake of the same tracer used for cardiac imaging, increased uptake in such organs should not impact on the quality of myocardial blood flow imaging. Thirdly, once in the myocardium after initial uptake, there should be no redistribution of the tracer with time. Lastly, the physical characteristics of the tracer should allow enough time for rapid serial imaging. Tracers that are most utilized for SPECT in clinical practice are Tl-201, Tc-99m MIBI, and Tc-99m Tetrofosmin.

A wide range of sensitivities and specificities for SPECT-MPI that derive from various protocols and tracer are summarized in table 2. Despite wide range of values from this table, a more recent and straightforward study by Kapur et al has shown similar sensitivities and specificities for all the three common radiotracers used in SPECT-MPI[53]. They assessed the sensitivities and specificities of these tracers in a subset of 137 patients who underwent subsequent angiography among 2560 individuals randomized to undergo SPECT-MPI and found an overall sensitivity of 91% with a specificity of 87% for the detection of coronary disease. They stated that there were no significant differences between the 3 tracers with regard to sensitivity and specificity.

It should also be noted that SPECT-MPI allows a three-dimensional assessment and quantification of myocardial perfusion, and functional assessment of the left ventricle through electro cardiogram (ECG) gating of the perfusion images[54].

1.4.2.2 Indication of SPECT perfusion imaging

Table 3 summarizes common clinical usage of SPECT perfusion imaging of the myocardium. There are in fact several indications for the use of SPECT-MPI in patients with known and unknown diagnosis of CAD.

In patients without the diagnosis of CAD, SPECT perfusion imaging is usually performed to exclude or diagnose CAD if they are suspected to have the disease. The imaging is done in these patients:

- As a screening test for individuals who are categorized to be at intermediate or high risk for CAD. There are usually individuals with family history of CAD, familial hyperlipidemia, type II diabetes mellitus or presenting with typical symptoms of IHD.
- After resting or post-stress ECG that is non-diagnostic. It should be noted that causes other than CAD that produce abnormal ECG exist and are listed in table 4.
- After risk of developing cardiovascular events in periods surrounding or following surgical operation. The elderly and those with peripheral vascular disease or aortic aneurism are the most common at risk for such events.
- In presence of acute chest to make the diagnosis of CAD.

If the diagnosis of CAD is known, SPECT-MPI is done:

- To assess the significance of a coronary stenosis, in other word to evaluate if the known coronary lesion is able to induce symptoms.
- To risk stratify patients with CAD and assess prognosis. In fact, MPI is known to be one of the most powerful non-invasive tools for risk stratification.
- To assess the extent and severity of perfusion defects after stress testing. Presence of multiple perfusion defects in different vascular territories of the myocardium is an indication for high risk in individuals with CAD.

1.4.2.3 Stress testing for MPI

Individuals who are referred for stress testing MPI usually undergo exercise on treadmill or bicycle. However, there is a significant portion of patients who are unable to exercise due to various reasons (table 5) and will rather benefit from pharmacologic testing as a substitute for exercise. However, it is claimed that the performance of MPI with exercise is preferable to assess full potential of exercise capacity[55,56], exercise induced chest pain[57], hypotension[58], and the ECG response to exercise[59-63], specifically the heart rate threshold[55,56,59,61] and the duration of ST-segment depression after stress testing. It is said that these variables cannot be assessed when pharmacologic instead of exercise testing is used. Although these variables are capable to provide prognostic information from the level of exercise that one may achieve during stress testing and the hemodynamic responses that follow such exercise, caution should be exercised here, because not all patients can exercise adequately and some patients may not provide same level of exercise in a repeat stress test. However, numerous studies have demonstrated that pharmacologic stress testing is capable of providing similar sensitivity and specificity as exercise MPI for the detection of CAD[64-71].

The common physical stress uses the standard Bruce protocol or the modified Bruce protocol with the patient connected to a 12-lead ECG. Periodic blood pressure and heart rate reading are required and the accepted target heart rate (THR) that one should achieve is 85% of maximum THR (calculated as 220 minus age of individual concerned). At 85% of THR, tracer is injected and the subject is allowed to exercise for a further one minute before stopping the test. In the event that the subject is unable to achieve the projected THR, she or he will be allowed to rest and the test will be converted to a pharmacologic stress if there is no contraindication.

1.4.2.3.1 Pharmacologic stress testing for MPI

Physical stress is not possible in many patients, especially the ones who cannot achieve at least 85% of their expected THR or simply due to contraindication to the test itself. Pharmacologic stress testing can be used as an appropriate alternative in this category of patients. The common indications for the test are listed in table 5.

Currently, agents that are available for pharmacologic stress testing with MPI include family of agents that cause vasodilatation through the adenosine receptor mediation (adenosine, adenosine triphosphate, and dipyridamole), and agents which, increase the contractility of the heart and increasing thereby myocardial oxygen demand and blood flow through stimulation of β-adrenergic receptor (dobutamine and arbutamine).

The pathophysiologic basis for the use of vasodilators is that in diseased coronary arteries that are narrowed, there is an inverse relationship between the capacity of vasodilators to increase the myocardial blood flow and the severity of the stenosis that results in a heterogeneous uptake of the tracer by the myocardium, and with reduced uptake in the areas supplied by the affected artery[18].

Adenosine and dipyridamole are both capable of increasing myocardial blood flow by three to five times of the resting level in regions of myocardium that are supplied by normal coronary arteries[72-74]. Adenosine is a direct coronary vasodilator and activates the adenosine A-2 receptors in the coronary arterial wall. This leads to an increase in the levels of adenosine cyclase and cyclic adenosine monophosphate (cAMP), and a decrease in uptake of transmembrane calcium, resulting in coronary vasodilatation. Dipyridamole on the other end acts by raising endogenous adenosine blood levels through block of the cell membrane transport and reuptake of endogenous adenosine. Dipyridamole has been shown to induce perfusion and regional wall motion abnormalities. While mechanism of heterogeneous uptake that is noted in diseased arteries may be multifactorial, there is a “proposed mechanism known as coronary steal” that affects blood flow in the compromised areas, whereby the normal vessels vasodilate, with as a direct result, an increase in

blood flow, leaving relatively reduced flow in areas with important coronary stenosis, therefore inducing ischemia, and regional wall motion abnormalities[75].

Infusion of dipyridamole or adenosine induces perfusion changes in the myocardium of individuals with CAD to similar extent that of perfusion changes that are induced by exercise testing. Action of dipyridamole and adenosine is directly blocked by xanthines. Therefore, preparation of patients referred for pharmacologic stress testing should bring caution for these agents. Patient should abstain from caffeine (coffee, tea, some soft drinks and medications) for at least 24 hours and stop slow release theophylline for 36-48 hours prior to pharmacologic stress testing with vasodilators as they are prototype adenosine receptor antagonists.

Dipyridamole is usually infused intravenously over a 4-minute period in a dose of 0.56 ng per kilogram. Tracer is injected 3-4 minutes after termination of the infusion at the time of maximum hyperemic effect[72-74]. Should patient develop severe ischemia evidence by chest pain or ST segment depression on ECG, intravenous administration of aminophylline (about 100 mg) is enough to quickly reverse dipyridamole effects. However, one should whenever possible delay such administration for at least 1 minute after tracer injection to maintain hyperemia in the myocardium and allow therefore substantial tracer uptake.

Adenosine is also given as an intravenous infusion, at the rate of 140 ng per kilogram per minute for 6 minutes. Its half life is very short (few seconds) and its peak effect is reached between 1-2 minutes after the start of infusion[76]. Tracer for MPI is injected 1-2 minutes after termination of adenosine infusion. The effects of adenosine disappear 1-2 minutes after infusion, rendering almost unnecessary any aminophylline intervention to stop the side effects.

Studies have suggested combining adenosine infusion with low-level exercise to increase patient tolerance of the test and at the same time to decrease extra cardiac tracer uptake that may complicate interpretation of the myocardial images[77-79].

Coronary vasodilators provide sufficient level of stress for MPI but are not without contraindications and side effects of their own (Tables 6&7)[80-89].

Activation of adenosine receptors that are different to adenosine 2A (A2A) receptors which, are found in the coronary vasculature, has been implicated in the induction of side effects noticed with the infusion of adenosine and dipyridamole. To minimize these side effects, several A2A receptors agonists have been developed and used in clinical trials to assess their usefulness. Early report suggests that the quality of MPI images using A2A receptor agonists is similar to image quality in adenosine MPI but with fewer symptoms and side effects[90,91]. The A2A receptor agonists have another advantage that is being agents with longer half-life than adenosine; they can therefore be given as a bolus rather than an infusion.

Dobutamine, the third used pharmacologic agent for MPI in clinical practice, is a synthetic catecholamine that has significant ionotropic but less chronotopic effect. It expresses primarily α1 activity with weak α2 activity. Dobutamine uses its α2 activity to increase the heat rate and contractility, and therefore the cardiac output[81,92-93]. In patients with heart failure or fall on systolic function, low-dose dobutamine (2.5-10 microgram per kilogram per minute) is often used for therapeutic purpose. The increase in heart rate and myocardial contractility noted during dobutamine infusion results in an increase in myocardial oxygen demand, with subsequent hyperemia. The direct result will be a dilatation of coronary arteries with an increased blood flow through normal coronaries[94]. Dobutamine is also administered intravenously using a special infusion pump or syringe. With its short half-life of about 2 minutes, it is given in stages, each one lasting 3-5 minute, and an incremental dosage is used from 5, 20, 15, 20, 30 and 40 microgram per kilogram per minute, not exceeding 40 microgram per kilogram per minute[86, 95-97]. Dobutamine has also side effect and contraindications like other previously mentioned pharmacologic agents (Table 6 &7).

Pharmacologic MPI using dobutamine has been shown to be associated with a high sensitivity and specificity similar to adenosine and dipyridamole[86, 98-100]. It also shows an agreement with exercise stress MPI[101-102].

Arbutamine, a β-adrenergic agonist, has also been used for MPI pharmacologic stress testing with similar outcome to adenosine and dobutamine, in terms of its sensitivity, specificity, and agreement for detecting ischemia[103-106].

The overall sensitivity and specificity of pharmacologic stress testing has been found to be quite similar among different agents that are used for MPI; dipyridamole 89% and 78%, adenosine 90% and 91%, and dobutamine 82% and 73%[68-69,71, 107-120].

1.4.2.3.2 Exercise versus pharmacologic stress testing

The level of exercise that an individual can achieve during stress testing undoubtedly provides significant clinical information but many patients undergo pharmacologic stress testing for reasons mentioned earlier (Table 5). Similar sensitivity and specificity have been found for exercise and pharmacologic stress testing for MPI but there are studies that have shown that only exercise capacity could offer important predictors of death[121,122]. This implies existence of differences in risk associated with MPI results between patients who are able to perform adequate exercise and those selected to undergo pharmacologic stress testing. Indeed, there is “a priori” clinical difference between these two categories of patients. Data from literature support the concept that suggest that sicker patients with numerous cormobidity, are also the ones who undergo pharmacologic stress testing MPI[123,124].

Due to lack of direct comparison between the two stress testing procedures, Navare et al[125] reviewed published literature as from year 1966 to 2001 and found 24 robust studies evaluating prognosis in 14918 patients undergoing either pharmacologic stress testing or exercise stress testing MPI. They actually found a higher number of cardiac event rates for both normal and abnormal pharmacologic stress testing MPI as compared to the normal and abnormal exercise stress testing MPI studies. They also looked at the demographics of the two groups to try understanding the reason for the difference in the rates of cardiac events. They have noticed that older patients with a higher prevalence of hypertension, diabetes, previous myocardial infarction (MI), and revascularization procedures were the ones who underwent pharmacologic stress testing MPI. When they applied a meta-regression analysis on all clinical variables, they have found that the inability

to exercise was the strongest predictor of cardiac event and, the male gender and history of hypertension, diabetes, and prior MI were also significant predictors of cardiac events. Their conclusion was that exercise stress testing MPI and pharmacologic stress testing MPI were comparable in their ability to risk-stratify patients. However, they emphasized the fact that patients who undergo pharmacologic stress testing were at a higher risk for subsequent cardiac events, even for those with normal perfusion imaging results.

1.4.2.4 Role of quantification

The main role of quantification is in bringing an element of objectivity as its approaches eliminate the subjectivity and the intra-and interobserver variability that affect the visual reading of images. It also helps training of inexperienced readers by providing a kind of “second opinion”. Quantification of SPECT MPI studies with Tl-201 have been utilized with a high degree of reproducibility in providing an accurate assessment of the size of perfusion defects and defect reversibility noticed on MPI, and in the same time has shown to have good correlation with the degree of stenosis that are caused by coronary lesions[126-131].

The introduction of SPECT quantification, based on Tc-99m MIBI, comparing the distribution of perfusion at rest and during stress brought a new dimension in the field of quantification. Improvement over the Tl-201 quantification approaches are notes in areas such as three-dimensional (3D) sampling, the degree of automation of processing, and the criteria employed for abnormality and the types of two-dimensional polar maps. In this 3D method, it is possible to extract in a 3D manner, the distribution of myocardial counts[132]. Spherical and cylindrical coordinates are utilized in this technique to sample the apical and the rest of myocardium. There is clear use of radial sampling that is essentially perpendicular to the myocardial wall to provide accurate representation of the perfusion distribution. Comparison of the count distributions that are extracted from this technique is done with normal limits from the database to ensure quantification of the presence, location and extent of myocardial perfusion defects. The 3D technique also has brought better automation of the choice of apical, mid-ventricular and basal slices; the

center of the left ventricle. The direct benefit of the technique is that it reduces the variability and incorporates the entire left ventricle, leading to a more accurate assessment of the extent of perfusion defects.

The use of Tc-99m MIBI also allows a long myocardial residence time with high count density and almost no significant redistribution. With such characteristics, gated SPECT imaging can easily be done. Programs to quantify 3D analysis and interpret gated studies information are available[133-135]. Gated SPECT acquisition is possible after resting or following stress injection to assess regional wall motion and ejection fraction (EF) with good correlation with contrast ventriculography and gated blood pool studies[136,137]. Method to accurately measure EF from gated SPECT have been developed and well validated[138,139]. The better role of the gated SPECT is undoubtedly its ability in differentiating between infarcts and attenuation artifacts that cause fixed perfusion defects[140].

There are currently a number of validated software packages that are commercially available for quantification of SPECT myocardial perfusion and function (CPS-QGS, Emory Toolbox, 4D-MSPECT, and Wackers-Liu CQ). They are all base on similar principles of SPECT quantification but with a different range of display of the processed data [polar plots or bull's-eye plots, circumferential count profiles, Summed stress score (SSS)].

Most centers including ours use CPS-QGS and Emory Toolbox to quantify MPI and assess the left ventricular function (EF and wall motion) [personal observation]. Watson and Smith from the University of Virginia have described in a more recent study and in simple terms the essence of quantitative imaging as being the measurement of image variables[141]. In the presentation of their non commercial package known as VQuant, they have listed the important clinical variables that one should consider whenever using quantitative methods for MPI. They have stressed the need to focus on measuring regional myocardial tracer uptake after stress testing, changes in regional uptake comparing stress and rest images, regional left ventricular thickening function, left ventricular diastolic volume index, systolic volume index, and global left ventricular EF (LVEF). Therefore, information concerning the extent and severity of perfusion and the wall motion abnormalities can then be extracted from these basic measurements. They

have also stated 3 objectives judged necessary to ensure meaningful results which should be independent of laboratory or system used to perform the test: (1) a good measurement must be related to a specific and recognizable physiologic variable, (2) it should uniquely characterize the physiologic variable, and (3) it must be reproducible and independent of system used. They have clarified the role of quantification as being intended to assist the reader by providing an objective means to characterize and communicate results of a study. Measurements help to reproduce perfusion severity and prognostic significance of the results than from subjective estimation. Measurements facilitate evaluation of serial studies to assess disease progression or response to therapy. The numeric values obtained from indicators of ventricular function such as ventricular volumes, EF, and regional thickening add to the ease of measurements needed for quantification.

The use of quantification should be promoted in each and every center performing MPI for standardizing the method. Reliable quantification of MPI regardless of the method used is extremely important and should be used routinely for the following reasons:

1. Readers derive greater confidence in interpretation due to the "objective" manner of data display.
2. The interobserver and intra-observer interpretive reproducibility is augmented.
3. Quantification provides a reproducible means of measuring the degree of abnormality

Despite the advancement in technology, there is room for improvement. In fact, quantification is not really new to nuclear cardiology or to MPI. A quick look to the rear mirror shows that the topic was already alive in the early 1980's. Indeed, Rigo et al in their quest to determine the value of Tl-201 MPI to identifying disease in the individual coronary arteries, they have performed segmental analysis of the rest and stress planar MPI in 133 patients with documented CAD on angiography[142]. They have found that segmental analysis of MPI was able to identify disease in the individual coronary arteries with high specificity and moderate sensitivity that was due to the tendency of the technique (planar imaging) to identify only the most severely ischemic area among several that may be present in a heart.

In early clinical application of SPECT technique for MPI, quantification continued to be subject of interest for better localization CAD on MPI.
De Pasquale et al have looked at a method developed in the infancy of SPECT to validate quantification of the uptake, redistribution and washout of Tl-201[143].
It was an interesting early study establishing normal limits for the distribution of Tl-201 in 36 patients with low (<5%) probability for CAD. They then applied the technique in 45 patients who had undergone coronary angiography as a pilot group to define criteria for identification and localization of defects seen on perfusion imaging. At the end, the have applied the defined criteria in a prospective study comparing visual, quantitative, and combined visual and quantitative analysis for the overall detection of disease and the detection of individual vessel involvement. The high sensitivity for detecting the disease from their data made the authors to conclude that quantitative analysis was a highly accurate technique for determining the presence and location of CAD.

To summarize, quantification should be regarded as a complementary to visual analysis. One should always start interpreting MPI images with a visual inspection. The visual inspection should be done for all acquired data, from the rotating planar images, reconstructed SPECT slices in their three orthogonal planes, to the quality and possible presence of artifacts. The quantitative display should come as to confirm the reader's impression on visual data. Quantitative analysis should not be expected to bring entirely new information.

1.4.2.5 Prognostic value of MPI

The prognostic value of MPI using SPECT technique has been extensively looked at in a wide range of patient population from many centers. The meta-analysis by Mowatt et al[144] for instance dissected reports on the prognostic power of SPECT-MPI from 21 studies that included 53762 patients with known or suspected CAD.
The meta-analysis has confirmed the fact that SPECT-MPI contributed in adding incremental prognostic value regarding mortality and MI to the

information already gained from the patient clinical variables, exercise treadmill testing, and angiographic findings. While most of the published data on the prognostic value o MPI was exclusively based on planar Tl-201 imaging, there is however abundant published data on SPECT-MPI since the early 1990s. Many studies have demonstrated that the extent and severity of perfusion defects correlated with the occurrence of cardiac events and also that the extent of MPI abnormalities in patients who had an acute infarction or suffered from chronic CAD, is a strong predictor of future hard cardiac events[145-147].

1.4.2.5.1 Meaning of normal stress MPI

One of the greatest strength of SPECT-MPI is the prognostic value of a normal study. A normal stress SPECT-MPI even in patients with documented CAD is associated with a very favorable prognosis[124,148-151]. In fact, several studies have stated that a negative SPECT-MPI has an excellent outcome with an annual cardiac event rate <1% for the general population[152-157]. Some authors even went to claim that it will take 9 years for the risk of a cardiac event to reach 1% if a low-risk patient has a normal SPECT-MPI[158]. The direct implication of this statement is that there may not be a need for a repeat MPI for about 3 to 5 years unless patients experiences new symptoms that are suspicious of CAD. For patients with normal stress SPECT-MPI, the warranty of long event free period is not a guarantee for all. Clinical factors like diabetes, CAD, increasing age, male gender and technical issues such as the need for pharmacologic stress testing, affect the warranty period by increasing annual cardiac even rate to as high as 1.8%, despite the presence of a normal study[158].

Because it was observed that the warranty for favorable prognosis in the presence of normal SPECT-MPI appeared to expire at about 2 years after the test, it would be prudent to consider repeating studies as frequent as possible in these high-risk patients with normal stress SPECT-MPI. In fact, this particular study by Hachamovitch et al[158] seems to be the best answer to the clinical setting question on how long should a normal stress MPI be considered as a warranty for cardiac event free. They have reviewed studies

performed on over 16 thousand consecutive patients who underwent SPECT.MPI between January1, 1991 and March 27, 1997. They excluded patients with valvular disease or any other cardiomyopathy. After the exclusion of patients with abnormal results and those who were lost to follow-up, they were left with 7,376 patients (48% of the follow up population). Within this group of patients with normal stress SPECT-MPI, there was a total of 78 cardiac events comprising 45 cardiac deaths and 33 non-fatal MI that have occurred during a mean follow up of 665 ± 200 days, and representing a cumulative cardiac event rate of 1.1%. When they have separated patients into those without (6,046) and those with (1,330) known CAD, the cardiac event rate were 0.7% and 1.3%, respectively. They have considered patients with previous MI or revascularization as to have known CAD. They have also analyzed the clinical characteristics of patients within the two groups to assess their impacts on risk for cardiac event after normal stress MPI and try to determine for how long these patients remain at low risk to define possible “warranty” period. For the group without CAD, they have found no impact of gender but most patients underwent exercise stress testing, and infrequently have had diabetes, or a history of smoking, hypertension, a family history of CAD, or elevated cholesterol, in quite significant number of them. Despite the presence of abnormal resting ECG in about half of these patients, only few were on anti-ischemic medications. In the group with known CAD, male gender dominated. About a third of patients in this group experienced some non-anginal chest discomfort. Typical and atypical angina or dyspnea was noted in smaller populations of these patients. The study has found a significant difference in cardiac events rate between patients with and without a history of CAD ($p<0.001$). Regarding the relationship between cardiac event and time, the authors have estimated the predicted cardiac event rate for 4 intervals of six months each for the first 2 years and have found the risk appeared to accelerate over time in patients with CAD. They concluded that the risk of cardiac even following a normal stress MPI and its change over time were a function of the clinical and historical factors that alter the time at which repeating stress MPI might become appropriate and therefore defining a warranty period for normal stress MPI.

A year later, Thomas et al[159], in their study that was set in the community out patient to evaluate the prognostic value of MPI, have found similar outcome. The annual cardiac event rate in their study was 0.4% in patients with normal stress MPI.

1.4.2.5.2 Stratification of a high-risk population

The severity and extent of perfusion defects on SPECTS-MPI are important prognostic factors in the stratification of a high-risk population. The association of an increasing annual cardiac event rate with increasing severity and extent of perfusion defects has been described in both patients with a history of prior MI and those without history of CAD[124,155,160-163].
There is a need to understand that patients who are referred for pharmacologic stress testing with MPI have higher clinical risks than those who are able to exercise. Furthermore, patients with mild perfusion defects, who have a low cardiac death rate that is almost similar to that of patients with completely normal studies, are still at higher risk than patients with normal studies regarding MI events[124]. Considering the SSS for example, a 1-unit increase was shown to be associated with a 5% increase in the risk of death or non fatal MI and provided independent prognostic information to angiography, in a study of high-risk patients who were referred for SPECT-MPI and cardiac catheterization[164]. The SSS is one of the most used quantitative methods to categorize myocardial perfusion abnormalities during stress testing with MPI as a marker of ischemia or infarct. A score of 4-8 is categorized as a small defect, 9-13 as a medium defect, greater than 13 as a large defect whereas a score lesser than 4 is considered normal.

Presence of either ischemia or infarction on SPECT-MPI is an indicator of bad outcome as patients who demonstrate these findings have twice the risk of developing heart failure as those with normal SPECT-MPI studies[165].
Prognostic information of the factors that are associated with the presence of high-risk features on SPECT-MI is listed in table 8. Usually, an elevated lung-heart ratio whether seen in Tl-201 or Tc-99m MIBI SPECT-MPI, indicates elevated left-sided filling pressures[166]. This pattern of increased lung-heart

ratio has also been found to be associated with poor prognosis SPECT-MPI outcome as a sensitive indicator of severe CAD[167-169]. Several studies have demonstrated that the increased pulmonary activity of Tl-201 was in fact related to left ventricular dysfunction during exercise[170-172]. However, caution should be exercised in the interpretation of pulmonary uptake of radiotracer as similar patterns may be caused by other factors than severe CAD. Mitral valve regurgitation, mitral stenosis, decreased left ventricular compliance, and non ischemic cardiomyopathy with LV dysfunction, can all cause increase in pulmonary uptake of Tl-201. It would be prudent not to look at increased pulmonary uptake of radiotracer in isolation as an index of severe CAD. The presence of transient ischemic dilatation (TID) of the left ventricle also correlates with severe CAD and poor prognosis whether perfusion defects on SPECT-MPI are present or not[173,174]. There is a claim that TID results from decreased subendocardial perfusion that makes the left ventricular cavity to appear larger. This dilation of the left ventricle lumen following exercise is considered to be a manifestation of severe induced ischemia. TID was shown to have a moderate sensitivity of 60% and a high specificity of 95% in identifying patients with multivessel stenosis and severe CAD[175]. The presence of TID should thus be interpreted as a strong evidence for multivessel or left main coronary stenosis, and this is true for both exercise and pharmacologic stress testing with SPECT-MPI[176]. However, on the pharmacological side of stress testing with MPI, one should be aware of scarcity for studies evaluating the prognostic value of Dobutamine SPECT-MPI. Calnon et al[177] have reviewed data from 308 consecutive patients who were referred for dobutamine MPI and have assessed their clinical outcome. They have found 15 cardiac deaths and 18 nonfatal MI within a follow-up period of 1.9±1.1 years, corresponding to 5.8% annual cardiac events rate. Their study has also noticed the presence of event-free survival among patients with normal stress MPI as opposed to patients with abnormal SPECT-MPI studies. They have concluded that dobutamine SPECT-MPI was able to offer cardiac risk stratification in high-risk patients who are unable to exercise and have contraindications to vasodilator stressors.

1.4.2.5.3 MPI as Predictor of cardiac death

MPI using SPECT technique can be used for the prediction of death. The basis in this application is to promptly identify those high-risk patients prior to their submission to certain interventions and thereby reducing their risk of dying from such interventions.

There are prospective studies which have shown in randomized clinical trials that several treatment modalities reduce cardiac mortality in a group of selected patients[178-180]. In fact, clinical trials of medical treatment have clearly demonstrated reductions in cardiac death[181-184].

Hachamovitch et al have used SPECT-MPI to assess if they could predict cardiac death[124]. They wanted to define the incremental prognostic value of MPI with SPECT for the prediction of death and the ability of nuclear testing to risk stratify patients. They have categorized patients in three different subgroups risk for cardiac death; a low risk for MI and cardiac death, an intermediate to high risk for MI but low risk for cardiac death, and an intermediate to high risk for both MI and cardiac death. They also wanted to determine from the study the impact on the cost of testing, if the initial therapy in patients at low risk for cardiac death but intermediate risk for nonfatal MI were medical as opposed to catheterization. They have identified 5183 suitable patients from this 2 year prospective study that included patients with either exercise or pharmacologic stress at Cedars-Sinai Medical center. They have used individuals without knowledge of patients' test results to conduct scripted telephone interview for follow-up. Cardiac death was defined as event noted and confirmed by review of the death certificate and hospital chart or records from treating physicians. Non fatal MI was evidenced by the appropriate clinical symptoms and signs on ECG and cardiac enzymes. The mean follow-up was 642±226 days with each patient being followed for at least 1 year. They have used clinical and historical information to determine the likelihood of CAD in patients undergoing pharmacological stress testing and for patients able to exercise, they have added the exercise information to clinical and historical ones. The analysis of their data has shown that there were 119 cardiac deaths or 3% event rate. Of these cardiac deaths, 13%

were observed in the group of patients with normal scans whereas the event rate in the group of patients with abnormal scans results was 10%, 15% and 62% for mild, moderate and severely abnormal scans results respectively. They also found that patients who benefited from early revascularization following MPI that demonstrated severely abnormal scans results showed lower number of cardiac death as compared to patients who underwent medical therapy for similar scans findings. They concluded that MPI yielded incremental prognostic information for the prediction of cardiac death and hard events. This study has also found that patients with mild changes on scans after exercise stress testing were at low risk for cardiac death and may thus be treated medically without invasive intervention.

1.4.2.5.4 MPI in revascularized patients

The use of MPI is not only limited to identifying patients with CAD and their risk stratification (Table 2). In the high risk patients with severe scans results, revascularization is usually done either by coronary bypass surgery or by percutaneous coronary interventions. SPECT-MPI then plays a strategic role in the follow-up of these patients in monitoring the effects of such revascularization.

1.4.2.5.4.1 After coronary artery bypass graft (CABG)

MPI is commonly done before revascularization but is not a routine test after CABG. It is indicated when symptoms reoccur to evaluate the possibility of postoperative graft blockage. The risk for closure of the graft a year after surgery is estimated to be around 12% to 20%[185]. However, occlusion rates from saphenous vein graft have been said to be as high as 41% to 50% 10 years post CABG[186,187]. It is actually during the time interval between 5 and 10 years post surgery that most symptoms manifest.

Studies have found a high correlation between MPI and angiographic findings for accurate assessment of graft patency regardless of the technique that was

used during CABG and also have shown superior sensitivity and accuracy for MPI to those of stress ECG findings[188-190].

In a study evaluating the prognostic efficacy of MPI with the use of exercise Tl-201 SPECT, Palmas and co-workers[191] studied 294 patients after at least 5 years post CABG. In that study, the ischemic index on MPI as measured by the summed reversibility score and the abnormal lung uptake of Tl-201 were found to add significant incremental information to the risk assessment of these patients. Similar findings were noted in own study in Johannesburg whereby we have evaluated 142 patients post CABG and have found 68% of these asymptomatic patients demonstrating presence of ischemia on MPI[166]. Follow-up of patients in post CABG can therefore be done with the use of MPI as normal stress scans results essentially exclude presence of significant graft stenosis. In an interesting study by Zellweger et al, 1765 consecutive CABG patients were evaluated with SPECT-MPI to assess timing point of stress testing following revascularization. They wanted to define the incremental prognostic value of MPI for the prediction of cardiac death following CABG, either before or 5 years after surgery, and define the ability of the test to risk stratify these patients and in the same time determine the impact of MPI on early referral for catheterization. They have used semi quantitative visual analysis employing a 20-segment model to define SSS, summed rest score (SRS), summed difference score (SDS) and the number of non reversible segments (NRS).

The results showed that ischemia (SDS) and infarct size (NRS) to be independent predictors of cardiac deaths (CD). They concluded that MPI was a strong predictor of subsequent CD in post CABG patients. Their data also suggested that symptomatic patients within 5 years of CABG and all those after 5 years post CABG may benefit from MPI.

1.4.2.5.4.2 Post percutaneous transluminal coronary angioplasty (PTCA)

Occlusion after PTCA is seen between 30%-40% of patients even if they remain asymptomatic[194-197]. The advent of new technique using intracoronary stenting has significantly reduced this rate however[198]. The main reason for using MPI rather than exercise ECG is the need for a highly sensitive modality to detect ischemia due to restenosis and also to assess the extent and severity of such ischemia to decide on possible repeat angioplasty.

Serial imaging with SPECT-MPI at 6 weeks, 3-6 month and then according to clinical presentation have been proposed as the necessary mean for optimal monitoring of patients following PTCA. In a study done in our center, we evaluated 122 patients at least 3 months post PTCA[199]. The MPI results showed 56% of asymptomatic patients to have ischemia. These findings were in keeping with those of Pfistere et al[200] showing silent restenosis in 60% of patients with ischemia on MPI. Furthermore, they also found that an abnormal MPI following PTCA was associated with increased risk for hospital admission or MI in both symptomatic and asymptomatic patients. While serial imaging is advised for monitoring patients who underwent PTCA, a normal MPI should be regarded as an indicator of successful procedure that is linked to a lower risk for recurrent cardiac events and late restenosis[201].

1.4.2.6 MPI in diabetes mellitus

There is worldwide increase in incidence of diabetes and cardiovascular disease is noted to be the leading cause of death in individuals who suffer from diabetes[6].

The risk of clinically obvious atherosclerosis responsible for cardiovascular disease is two to three times higher in both type 1 and type 2 diabetes compared to normal population[202-205]. The risk for major cardiovascular events is high in diabetic patients and the prognosis following these events is poor[206,207]. There is a direct relationship between the risk of atherosclerotic cardiovascular disease and the increase in plasma concentration of

glucose[208,209]. In fact, the prospective Diabetes Study done in the United Kingdom has shown that for each 1% increase in hemoglobin A_{1c} level (Hb A_{1c}), there was a 14% increase in the incidence of fatal and nonfatal myocardial infarction[208]. However, Gaede et al[210] have suggested that the strict control of glycemia together with reductions in blood pressure and plasma lipids will reduce macrovascular events in type 2 diabetes patients.

Awaad and Heller[5] have estimated the prevalence of CAD to be as high as 55% among individuals with diabetes, a significantly higher rate than the 4% estimation in the general population. Generally, the increased risk for diabetic individual includes a higher prevalence of CAD, a less favorable response to intervention, and short long-term survival[211]. While myocardial ischemia has a tendency of being silent in this group of patients, MPI has proved to be of a considerable role in the diagnosis and prognosis of diabetic individuals[212,213].

There are several studies supporting the use of stress testing SPECT-MPI in individuals with diabetes[212,214-216]. Retrospective analysis of data has shown a poorer prognosis in patients with diabetes and abnormal SPECT-MPI studies compared to non-diabetic patients with similar scans results[163].

The sensitivity, specificity and normalcy rates of SPECT-MPI in diabetic individuals are known to be similar to these obtained in SPECT-MPI studies of non-diabetic population[212]. Paillole and colleagues[214] have reported an 80% sensitivity and 87% specificity for Tl-201 SPECT-MPI using dipyridamole stress testing whereas Bell and coworkers, in a retrospective review, found a higher sensitivity of 97% with a high positive predictive value (PPV) of 88% in a group of individuals with diabetes that were sent to undergo SPECT-MPI and cardiac catheterization. For the detection of coronary artery occlusion that is 50% or greater, a relatively high sensitivity of 86% with a relatively low specificity of 56% were noted in the use of SPECT-MPI diabetic patients with suspicion of CAD, in the study by Kang and colleagues[212].

The ability of MPI to risk stratify patients with diabetes according to defect size and extent is well known, the larger the defect size, the greater the risk for a cardiac event.

Berman and colleagues looked at 2826 patients including 589 with diabetes who were referred for adenosine MPI with SPECT technique[217]. They have found that MPI studies results provided incremental prognostic value over clinical variables. They also found great risk for cardiac death in patients with abnormal perfusion scans who had insulin-dependent diabetes. The latter had a cardiac mortality estimated at 9% per year versus 4.6% per year for non diabetic patients ($p<0.05$).

Several studies also have focused on the use of SPECT-MPI to identifying diabetic patients who are asymptomatic but at increased risk for cardiac events.

A small study of patients with diabetes undergoing dipyridamole SPECT-MPI with Tl-201 before vascular surgery has found that 58% of patients with abnormal perfusion scans did not have evidence of clinical suspicion of CAD[218]. Another study has show 26% of abnormal SPECT-MPI studies in asymptomatic patients with diabetes and a 7 times higher rate of MI, CD, and late revascularization when compared to asymptomatic diabetes with normal perfusion scans results[219].

A larger study for the detection of ischemia in asymptomatic diabetics (DIAD) has found that 22% of patients with type 2 diabetes had abnormal adenosine SPECT-MPI using technetium-99m sestamibi[220]. Araz and colleagues associated poor control of glycemia, evidenced by elevation of HbA_{1c} and retinopathy, with the presence of silent ischemia in diabetic patients who show perfusion abnormality on SPECT-MPI[221].

When diabetic patients with symptoms of CAD were compared to asymptomatic counter parts, a higher rate of abnormal studies was found in both groups (51% Vs 39%)[222].

Kang and colleagues have looked at the incremental prognostic value of stress SPECT-MPI (exercise and adenosine), in a high number of patients with diabetes and compared the efficacy of stress testing MPI in these patients to that of non diabetic patients[223]. Their prospective study comprised of 1271 diabetic patients and 5862 non diabetic patients who were referred for

exercise or adenosine stress testing with SPECT-MPI between January 1991 and October 19994, an almost 4-year period of recruitment. However, the presence of diabetes in this study was identified by means of patient history that was taken only at the time of stress testing for SPECT-MPI. After the exclusion of patients with known non-ischemic cardiomyopathy and those with valvular heart disease, 684 patients and 490 patients with diabetes underwent exercise and adenosine stress testing SPECT-MPI, respectively. The diabetic patients were followed up for at least one year, with a mean FU period of 21.5±6.1 months. Cardiac death (evidenced by the review of death certificate and hospital chart or physician records) and nonfatal MI (documented by changes in ECG findings and cardiac enzymes levels) were considered as hard cardiac events. When both events occurred in a given patient, only CD was recorded. The results showed that patients with diabetes were significantly older, more frequently female, more frequently had prior MI, PTCA, CABG, hypertension, hypercholesterolemia, anginal symptoms, and had higher pre-scans likelihood for CAD. More perfusion defects on SPECT-MPI and multivessel ischemia were found in patients with diabetes. The event rates for diabetic patients were found to raise significantly as a function of scans abnormalities but there were more events noted among patients who underwent adenosine stress testing with SPECT-MPI than in the exercise group. They concluded that both exercise and adenosine stress testing for SPECT-MPI were able to add incremental prognostic value over clinical information in patients with diabetes, and the increasing risk of CAD was noted to function of abnormal perfusion scans on SPECT-MPI studies.

It should be noted that women with diabetes have a very high risk of CAD of about 7.5 times higher than that of a women without diabetes. Therefore, a different approach and special attention should be given to this population group in the management of diabetic individuals suspected with CAD. Furthermore, a normal SPECT-MPI study in a diabetic patient should not stop the possibility of early rescanning when compared with non diabetic individuals.

Chapter 2: Methods

2.1 Study objectives

The study was primarily directed to investigate asymptomatic diabetic black patients with the use of MPI and the objectives were to observe the following:

1. The changes in myocardial perfusion
2. Correlation of abnormal findings on images with coronary angiography in patients with severe ischemic changes and also with some conventional risk factors of cardiovascular disease
3. The presence of CAD in diabetic black patients
4. Differences in myocardial perfusion changes in asymptomatic diabetic black patients as compared to asymptomatic diabetic white and/or Indian patients

2.2 Ethical issues

2.2.1 Informed consent

Diabetic patients were solicited to contribute to this study and informed consent was obtained from them. Their right to withdraw their consent at any time without being penalized whatsoever; neither on their medical care nor on their follow up at the diabetic outpatient clinic was explained to them. Patients were also informed that declining participation wouldn't affect the management of their condition.
The study was submitted to the Human Ethics Committee (Medical) of the University of the Witwatersrand for review and ethical approval with success (Clearance number M990236).

2.2.2 Confidentiality

Reports on positive MPI were made available only to clinicians involved in the routine management of the concerned patients and also to cardiologists whenever required for coronary angiography.
Data from the study will be used for scientific meetings and publication without identifying participants.

2.3 Methods

2.3.1 Recruitment of patients

Participants were selected from the cohort of patients documented to have diabetes and who were attending the diabetic outpatient clinic at the Johannesburg hospital. Only asymptomatic patients (not know to have CAD) were solicited to voluntarily enter this study.

Data from symptomatic diabetic patients who were referred for MPI as part of their routine clinical management were also included for possible comparison.

2.3.2 Inclusion criteria

- Asymptomatic diabetic patients attending the outpatient clinic
- Patients aged 50 years and above were approached to participate in this study
- Blood for Hb_1ac, cholesterol and lipid profile levels were done on recruitment.

2.3.3 Exclusion criteria

- Patients known to suffer from CAD
- Patients with signs and/or symptoms of vascular complication of diabetes at the time of recruitment

- Patients with possible contraindication for stressing MPI
- Patients who were unable to complete MPI within the week of recruitment

2.3.4 Study visits

Patients were approached from the diabetic outpatient clinic on Wednesdays and referred to nuclear medicine for MPI on the following Mondays and Tuesdays for a 2 day protocol.

2.4 Protocol

2.4.1 Methods

A dual-head multipurpose gamma camera fitted with a large field- of- view was used for imaging purposes. Low-energy high-resolution parallel hole collimators were used to acquire SPECT images.

Technetium-99m methoxy-isobutyl-isonitrile (MIBI) was used as the myocardial perfusion radiopharmaceutical.

2.4.2 Techniques

A two-day protocol for SPECT MPI was used on all participants: on the first day the stress testing MPI, while the rest MPI was consistently done on the second day. Both exercise and pharmacologic stress testing were used. The standard Bruce protocol was used for exercise and dipyridamole was the stressing agent for pharmacologic testing. Patients were allowed to rest after the administration of the radiopharmaceutical using a dose of 740 MBq in each patient on the day of imaging testing, and imaging started 30 to 60 minutes later. SPECT images were acquired on a 64x64 matrix using a step-and shoot mode on an 180^0 acquisition arc for 20 seconds per image. This protocol forms part of the internationally accepted guidelines of the European Association of Nuclear Medicine and we did not deviate from the procedure guidelines[224]. Qualified nuclear medicine radiographers were responsible for acquiring images in all participants on the above described gamma camera.

2.4.3 Blood sampling

Results of the blood that was drawn on the day of recruitment for asymptomatic subjects and those for blood drawn within a week of MPI for those who were referred for MPI as part of their clinical management were recorded. Cholesterol and lipid profiles as well as Hb_1ac results were retrieved from the national health labs systems. I also registered the results on blood done to measure urea and creatinine.

2.5 Assessment of images and interpretation

The interpretation of all images was done by at least two experienced nuclear physicians. I personally interpreted the images of all the participants to this study and was at all the time joined by one or two other nuclear physicians.

Visual and semi quantitative assessments of MPI data were performed. The severity of perfusion abnormality was expressed with a scoring that categorized the perfusion patterns as follows: 0= normal; 1= mild decrease; 2= moderate decrease; 3= severe decrease; 4= absent perfusion. A software package for measuring the extent and severity of perfusion abnormality was used to calculate the summed stress score (SSS) on the stress MPI, summed rest score (SRS) on the rest MPI and the summed difference score (SDS) which was calculated by subtracting SRS from SSS. A SDS of more than four indicates the presence of myocardial ischaemia that can be graded as: mild for an SDS of 4-8, moderate for an SDS of 9-12 and severe for an SDS greater than 12.

Myocardial perfusion was assessed by means of a semi-quantitative scoring system to measure the extent and severity of perfusion abnormality. The above described SDS was used to assess the presence of ischaemia while the SRS was considered for the assessment of infarction. Xeleris multisync fitted with QPS/QGS software was used to quantify myocardial perfusion on an arbitrary scale. Visual inspection of the reconstructed SPECT- MPI images was carried out to assess perfusion deficit where there was doubt as to the extent and severity of perfusion abnormality. The QPS/QGS software also

allows obtaining resting and post stress left ventricular ejection fraction (LVEF).

2.6 Statistical analysis

The means and percentages of study variables were obtained. The Spearmen correlation coefficient was used to calculate correlations between variables. The Kruskal-Wallis test was used to assess differences between different groups in the study such as the asymptomatic black diabetics vs asymptomatic white and Indian diabetics. Wilcoxon scores (rank sum) two-sided were used to measure difference s within the groups such as the LVEF at rest or in post-stress with presence of ischaemia (SDS) or infarct (SRS) or SDS with the control of diabetes (Hb_1ac) and impact of dyslipideamia (LDL).

All variables were analyzed with the use of SAS software version 9.1 (SAS Institute Inc, Cary, NC, USA). A 2-tailed probability value <0.05 was considered to be significant.

Chapter 3: Results

3.1 Baseline information of the study population

One hundred black patients with a control group of 50 (28 whites and 22 Indians) entered this study (Table 9). Data from six black participants were excluded, four did not return for the second part of MPI and two refused to repeat the stress part that was of inadequate quality due to artifacts. Therefore analysis was done on data from 94 black participants.

Data from 90 subjects forming a group of symptomatic diabetic patients, 45 blacks and 45 whites and Indians referred for MPI as part of their clinical management were also analyzed (Table 9).

There were 123 females (52.6%) and 111 males (47.4%) in total. From the recruited participants, 53 (56.4%) asymptomatic females and 41 (43.6%) asymptomatic males were blacks whereas 24 (48%) asymptomatic females and 26 (52%) asymptomatic males were whites or Indians (Table 10). The symptomatic group comprised of 26 (57.8%) female and 19 (42.2%) male black patients and 20 (44.5%) female and 25 (55.5%) male white or Indian patients (Table 10).

For simplicity of contrasting data from the black population, the primary goal of this study, data from the other races were often combined to compare variables.

3.2 Changes in myocardial perfusion

3.2.1 Asymptomatic diabetic participants

Participants in this study were recruited from the diabetic outpatient clinic of the Johannesburg hospital. There were 94 asymptomatic diabetic black patients and 50 asymptomatic diabetic white and Indian patients.

Participants from the asymptomatic diabetic black group were younger than the participants from the asymptomatic diabetic white and Indian group with a mean age of 60 (SD±7.2) years vs 64 (SD±7.7) [p=0.003] {Table 11}.

No significant difference was noted in the ratio between female and male participants for both diabetic blacks (53:41) and diabetic whites and Indians (24:26) [x^2 =0.62, p=0.43] {Table 11}.

No improvement on perfusion was noted from the MPI at rest to the MPI in post-stress testing (reversibility) in 81 (86.2%) of the asymptomatic diabetic black participants (Fig 1, 2 & Table 12). In the same group of participants, the reversibility or improvement of perfusion that was consistent with mild stress testing induced ischaemia was noted in eleven (11.7%) participants, while in the remaining two participants- there was an improvement of perfusion consistent with moderate stress testing induced ischaemia in one (1.06%) and an improvement of perfusion that was consistent with severe stress testing induced ischaemia in the other (1.06%) [Fig 3, 4, 5 & Table12].

Thirty-six (72%) asymptomatic white and Indian participants did not show evidence of reversibility from rest to stress testing MPI. Reversibility of perfusion to suggest mild stress testing induced ischaemia was noted in twelve (24%) participants whereas two (4%) participants in this group showed evidence of perfusion reversibility that was consistent with stress testing induced moderate ischaemia (Fig 6).

The participant with changes on perfusion that was suggestive of severe ischaemia and two participants with changes suggesting moderate ischaemia underwent coronary angiography. One participant with moderate reversibility on MPI refused to undergo angiography. The decision to refer patients for angiography was based on clinical decision by the treating physician. All three participants who underwent coronary angiography did no show evidence of significant coronary artery disease on the test.

Besides improvement on the perfusion from rest to post stress testing MPIs, perfusion defects that did not change from rest to post stress testing MPI (fixed defect) were also noted (Fig 7).

In the asymptomatic diabetic black participants, two (2.12%) showed evidence of small fixed perfusion defects, ten (10.63%) showed evidence of medium fixed perfusion defects and seven (7.44%) showed evidence of large fixed perfusion defects (Table 13).

The fixed perfusion abnormality was also noted within the asymptomatic whites and Indians. A small fixed perfusion defect was noted in one (2%) participant, while a medium sized fixed perfusion defect and a large fixed perfusion defect were noted in five (10%) and seven (14%) of participants of this group respectively (Table 13).

These fixed perfusion defects are indicative of previous (small, medium or large volume) myocardial infarction and therefore suggestive of CAD though not necessarily of ischaemia. The prevalence of CAD as indicated by the presence of previous myocardial infarction was noted in 20% of the asymptomatic diabetic black and 26% of the asymptomatic diabetic white and Indian participants.

3.2.2 Symptomatic diabetic subjects

Data from the symptomatic subjects were obtained from MPIs done in the department of Nuclear medicine as part of their routine management. All were referred for atypical chest pain associated or not with exertional dyspnoea.

There were 45 subjects in the symptomatic diabetic black group as well as in the symptomatic white and Indian group.

Similar to the asymptomatic participants, the symptomatic diabetic black subjects were much younger than their white and Indian counterparts (p=0.006) [Table11].

Here too, there was no significant difference in the female/male ratio between the above mentioned two groups (x^2 =1.11, p=0.30) [Table11].

Thirty-six (80%) symptomatic diabetic black subjects had normal perfusion on MPIs. There were four (8.9%) subjects in this group who showed reversibility of perfusion to suggest stress testing induced mild ischaemia. Another four

(8.9%) also showed evidence of stress testing induced moderate ischaemia and one (2.2%) subject showed evidence of stress testing induced severe ischaemia on MPI (Table12).

Subjects in this group also had fixed perfusion defects that are suggestive of previous myocardial infarction and therefore CAD. Close to half of these subjects (42.2%) have shown perfusion abnormalities that are indicative of the presence of CAD (Table 13).

The symptomatic diabetic white and Indian subjects showed evidence of reversibility of perfusion on MPI as follows: eight (17.8%) with reversibility of perfusion that is in keeping with stress testing induced mild ischaemia and seven (15.6%) with reversibility of perfusion that is suggestive of stress testing induced moderate ischaemia (Table 12).

More than half (53.3%) of the subjects in this group have shown evidence of fixed perfusion defects on MPI that are in keeping with the presence of CAD (Table 13).

3.3 Biologic markers and MPI findings

The means of all biomarkers used in this study are given in table 14.
None of the asymptomatic participants showed typical evidence of dyslipidaemia. The asymptomatic diabetic black participants showed a mean above the control level for glucose (Hb_1ac >7.5%).
The symptomatic diabetic black subjects showed means that were higher than the limits of normal for Hb_1ac and TG, indicating poor glucose control but not necessarily the presence of dyslipidaemia.
A high mean for the control of glucose was also noted in the group of symptomatic diabetic whites and Indians.
Regardless of the race, symptomatic diabetics have shown means of LVEFs that were below the lower limits of normal at rest as well as in post-stress MPIs (Table 15).

3.3.1 Asymptomatic diabetic black participants

No association was found between changes on perfusion and the control of either glucose ($r=0.11$ $p=0.29$) or cholesterol ($r=-0.18$ $p=0.07$).
There was a strong association between perfusion abnormalities (SRS) and the resting left ventricular ejection fraction ($r=-0.54$ $p<0.0001$).
The severity of the perfusion changes between rest and post-stress MPI (SDS) showed a strong relation to the post-stress LVEF ($r=-0.48$ $p<0.0001$).

3.3.2 Asymptomatic diabetic white and Indian participants

There was a relation between LDL and the extent of perfusion abnormality (SRS) [$r=0.46$ $p<0.05$].

An association was noted between LDL and the LVEF at rest ($r=-0.45$ $p=0.001$) and in post stress ($r=-0.41$ $p=0.003$).

No relation was noted between perfusion abnormalities (SRS) and the control of glucose ($r=-0.08$ $p=0.57$).

There was no relation between reversibility of perfusion (SDS) with any of the variables.

3.3.3 Symptomatic diabetic black subjects

A relation between glucose control (Hb1ac) and the marker of dyslipidaemia (LDL) was noted in this group ($r=0.47$ $p<0.05$).

There was a strong relation between the changes on perfusion (SRS) and the resting LVEF ($r=-0.67$ $p<0.001$) and also between reversibility of perfusion from the rest to the post stress MPIs (SDS) with the resting and post stress LVEFs ($r=-0.74$ $p<0.0001$).

3.3.4 Symptomatic diabetic white and Indian subjects

The marker of dyslipidaemia (LDL) shows a relation to changes on the perfusion (SRS) [$r=-0.40$ $p<0.05$] and also with the LVEFs at rest ($r=-0.34$ $p<0.05$) and in post stress ($r=-0.33$ $p<0<0.05$). Similarly, cholesterol levels are also related to the resting and post-stress LVEFs ($p<0.05$).

A strong relation was noted between the changes on perfusion (SRS) and the resting LVEF ($r=-0.72$ $p<0.0001$).

3.4 Differences in myocardial perfusion

No significant difference was noted on the changes of perfusion at rest (SRS) between asymptomatic diabetic black participants and their white and Indian counterparts ($p=0.47$). The difference in the change of perfusion between the rest and the post-stress MPIs or reversibility of perfusion also did not show a significant difference between these two groups ($p=0.62$).

Considering the changes of perfusion within the asymptomatic and the symptomatic diabetic black participants and subjects, no significant difference was noted either in the extent of perfusion defect at rest (SRS) [$p=0.22$] or in the reversibility of perfusion from rest to post-stress MPIs (SDS) [$p=0.47$].

The only differences noted were also significant and seen between the asymptomatic and symptomatic whites and Indians both for the changes on perfusion at rest (SRS) [$p=0.0006$] and for the difference of perfusion from rest to post-stress MPIs (SDS) [$p=0.005$].

Chapter 4 Discussion

My research targeted primarily the asymptomatic diabetic black patients and contrasted the findings of their myocardial perfusion using MPI with the findings of the other racial groups. I have shown in this research a high prevalence of CAD within the target population group. I have also shown that asymptomatic diabetic black patients have similar prevalence of CAD to asymptomatic diabetics of other racial groups.

4.1 Relevance of methodology for detecting ischaemia in African Blacks

While MPI has been used in diabetic patients for the diagnosis of CAD and its prognosis,[212-216] we did not encounter a study solely using MPI in black diabetic patients. However, studies that link black diabetic patients with CAD alone or as part of clusters in CVD exist.[21-23,25,26,28-31]

Screening of asymptomatic diabetic black individuals for CVD in general and CAD in particular is growing.[28-32] The use of MPI as a screening test for CAD in asymptomatic individuals with risk factors is also well known (Table 3).

For completeness of this research, I also recruited asymptomatic diabetic individuals other than from the black population to enter this study for comparison. There were white and Indian asymptomatic diabetic patients who attend the same outpatient diabetic clinic and 50 participants were also d randomly selected. Here again, we were not able to find a direct comparison between asymptomatic diabetic black patients and asymptomatic whites and Indians as a separate group or altogether with the use of MPI technique.

Finally, we included data from symptomatic patients who were referred for MPI as part of the management of their condition if the indication was at least due to chest pain.

In my study, more asymptomatic diabetic black participants (57.4%) underwent exercise stress testing for MPI whereas a significant number of asymptomatic diabetic whites and Indians (77%) underwent dipyridamole pharmacologic stress testing for MPI. The reason for the difference can be speculated upon from the difference in age between the two groups noting that the asymptomatic diabetic black participants were younger than their white and Indian counterparts (p=0.003). Similar patterns were noted in the symptomatic diabetic individuals and the group of black subjects showed a younger age compared to the white and Indian population group (p=0.006).

It is worth noting that pharmacologic stress testing is known to be an effective tool for the diagnosis and risk stratification of individuals with CAD.[225] In fact, in a review of published literature on 24 robust studies that included 14 918 patients undergoing either pharmacologic stress testing MPI, Navare *et al* had similar findings to our study in that older diabetic patients were the ones who underwent pharmacologic stress testing MPI.[125] More interestingly, they also found that exercise and pharmacologic stress testing MPI were comparable in their ability to risk-stratify patients.

One of the objectives of this study was also to correlate findings on MPI with some conventional risk factors for CVD. Blood sampling for lipid profile, Hb1ac, urea and creatinine were done on the day of recruitment for MPI on asymptomatic participants. Results of the same biomarkers that were done within the week of referral for MPI were retrieved for the symptomatic group.

The association between diabetes and cholesterol disorder as a cause of CVD has been described.[11,21-23,27,28,30,31] In fact, Raal states that abnormalities of lipids in individuals with type 2 diabetes are seen in equal prevalence to the derangement of carbohydrate metabolism.[31] The concept is reinforced by views that about half of all individuals with diabetes are dyslipidaemic.[226]

One element well known to contribute to the occurrence of dyslipidaemia is poor metabolic control of diabetes. To assess diabetic control one should measure glucose levels either by fasting or in the postprandial period. The measurement of Hb1ac is also used to the same ends. We have used the

percentage of Hb1ac in all participants in this study for correlation with MPI findings and other variables.

As stated earlier, the relationship between the risk of atherosclerosis in CVD and the increase in plasma concentration of glucose is known.[208,209]

Furthermore, the association between the increase in the incidence of MI and an increase in Hb1ac has also been described.[208] Hence, the study by Araz *et al* has associated poor glucose control assessed by Hb1ac with silent ischaemia in diabetic individuals from the abnormal perfusion that was visualized on MPI.[221]

I utilized both visual and semi quantitative assessments for the abnormalities on the perfusion. The visual inspection was primarily used to help correct scores obtained from the semi quantitative assessment whenever doubt arose as to the extent of myocardial perfusion abnormality. The use of scoring and the quantification package provided me with SSS, SRS, SDS, EFs and ventricular volumes in all participants. The use of these methods allowed a more objective way of interpreting data, a more interobserver and intraobserver reproducibility and a simple means that is reproducible in measuring the degree of perfusion changes on MPI. My group has previously described these techniques[227] and many authors have also made use of them.[75,133-139,164,223,228]

4.2 Changes in myocardial perfusion in asymptomatic diabetic participants

There were 94 diabetic black and 50 white and Indian participants. The participants from the black population group were younger than the white and Indian participants (p=0.003).

The difference in age seems to explain the high number of white and Indian participants that underwent pharmacologic stress testing MPI in this study. The review of studies in the literature also suggests that older diabetic individuals tend to undergo pharmacologic stress testing MPI.[125]

There was no significant difference in the female/male ratio between the black population group and their white and Indian counterparts (p=0.43). However, the trend of having more female than male participants in the black population group seems to fit a published report that suggests that the diabetic patients who undergo MPI were more frequently female.[222] While this seems to be the case in the literature, one can note that male participants were rather dominant in our study in the white and Indian population group although by a small number only. It is therefore difficult to try to contrast this finding with a published report because of the small number of participants that would not support a strong conclusion.

Eighty-six percent of the participants from the black population group did not demonstrate a change in myocardial perfusion between the rest MPI and post-stress testing MPI, change that is described as reversibility. The remaining fourteen percent have shown different degrees of reversibility on the perfusion that was consistent with stress testing induced myocardial ischaemia on MPI. Eleven participants (11.7%) had myocardial perfusion changes that were consistent with mild stress testing induced ischaemia, one participant showed changes consistent with moderate reversibility and therefore suggestive of moderate stress testing induced ischaemia and the last one showed severe reversibility that is consistent with severe stress testing induced myocardial ischaemia on MPI. Although we were unable to identify a report on a study that was specifically directed towards asymptomatic diabetic black subjects with the use of MPI, our study has shown evidence of ischaemic changes on MPI. The overall findings showed evidence of perfusion abnormalities consistent with ischaemia in about 14% of the black population group and in 28% of the white and Indian participants (Fig 2). These findings echoed results of the large DIAD study that has found 22% of asymptomatic diabetic patients to have abnormal perfusion on their pharmacologic stress testing MPI.[220] My findings also fit the results of De Lorenzo and colleagues in their screening of asymptomatic diabetic individuals using MPI and finding that 15% had reversible defects that were consistent with ischaemia on MPI.[219]

The coronary angiography undertaken in three asymptomatic participants, two with moderate and one with severe reversibility of perfusion on MPI, has shown no evidence of significant coronary disease (stenosis ≥ 70%). Therefore, the findings on MPI could be due to changes at cellular level as a result of microvascular disease. However, most studies that use MPI exercise stress testing MPI for CAD in asymptomatic diabetic patients do not include coronary angiography because in most cases they often look at the predictive value of the test for the diagnosis of future coronary events.[229-235] Nonetheless in a study by Paillole and co-workers that used coronary angiography and stress testing MPI in 59 diabetic patients who were suspected to have CAD, normal coronary was documented in five of 39 patients with abnormal perfusion on MPI.[214] This outcome may be attributed to the specificity of the test which is not a hundred percent or simply due to CAD in diabetic patients with normal coronary angiography.[235]

However, perfusion defects that are not caused by ischaemia and therefore suggestive of previous infarction were commonly encountered in both population groups of the asymptomatic diabetic participants. Twenty percent of the black population group and 26 % of the white and Indian population group of asymptomatic diabetic participants showed fixed perfusion defects in both rest and post-stress testing MPIs that were consistent with previous infarction and thereby suggestive of silent CAD. Altogether, about 34 % of asymptomatic diabetic black participants demonstrated evidence of perfusion abnormality either fixed (infarct) or reversible (ischaemia) that suggested CAD. The asymptomatic diabetic white and Indian on their side also showed similar findings in 54 percent of participants. This incidence of CAD within asymptomatic diabetic black and white and Indian population groups is in keeping with current literature. Depending on patients' population studies have suggested incidence of occult CAD to range between 4% to 75%.[5,214, 218-222, 235] It is worthwhile to note the disparity between reported ranges of incidence which indicates the need for a standardized multicentre study.

4.3 Symptomatic diabetic subjects and changes in myocardial perfusion

Data for the symptomatic group came from patients referred to nuclear medicine as part of their routine management. There were 90 in total and each selected population group represented half of the subjects; 45 symptomatic diabetic black subjects and 45 symptomatic diabetic white and Indian subjects.

Similar to the asymptomatic diabetic participants, symptomatic diabetic black subjects were much younger than the symptomatic diabetic whites and Indians (p=0.006). The female to male ratio also showed a similar trend to the findings in the asymptomatic group between the two population groups (p=0.30).

Myocardial perfusion change on MPI that was consistent with ischaemia (reversibility) was noted in 20 % of the black subjects. Four had mild, four moderate and one severe stress testing induced ischaemia on MPI. Considering perfusion abnormalities as fixed defects without the presence of reversibility, about 42 % of the symptomatic diabetic black subjects showed features of small, medium and large perfusion defects indicating previous infarcts and therefore CAD. Similar to these findings, Cohen *et at* looking at long-term prognostic value of dipyridamole MPI in preoperative settings had found that 69% of diabetic patients undergoing peripheral vascular surgery had shown presence of reversible defects and 66% had shown the presence of fixed defects.[236]

In the symptomatic diabetic white and Indian subjects, reversibility of perfusion was noted in 33% of subjects and the fixed perfusion defects were noted in 53% of subjects. Again these findings are in keeping with current literature.

While my findings consolidate published reports, they also bring views to support that black Africans are at a similar risk for CAD as populations in the developed world and, more importantly, the diabetic population in our

geographic location does not differ from diabetic patients from other geographic locations concerning the risk for developing CAD.

4.4 Biomarkers and MPI findings

A study on factors that link asymptomatic diabetic individuals with perfusion defects seen on MPI has concluded that poor glycemic control was a significant predictor for the presence of silent ischaemia.[221] However, no significant relation between perfusion abnormalities and glycemic control assessed by Hb1ac was noted in both the asymptomatic diabetic black participants ($p=0.21$) and the white and Indian participants ($p=0.57$). Although a modest decrease in cardiovascular mortality has been noted when glycemic control was improved, there is no solid evidence to link glycemic control and the presence of macrovascular disease.[237]

The group of the symptomatic subjects did not show different patterns with regard to the relation between perfusion defects and glucose control.

The asymptomatic white and Indian subjects showed a relation between perfusion abnormalities and LDL. Although it is known that about half of all diabetic individuals have dyslipidaemia, such abnormalities usually affect the triglyceride and HDL.[226]

However, there is a tendency for LDL to be mildly increased and this could explain the finding in this one population group in this study as disturbances of lipids in diabetic individuals may contribute to the high incidence of vascular disease.

Although the mean of LVEFs measured in the asymptomatic diabetic black population was not below the normal limits, a strong relation was noted between the EFs and the abnormalities on perfusion, the more defects seen on perfusion the lower were the LVEFs ($p<0.0001$). This finding has been previously described and LV dysfunction has been cited as the cause of abnormal myocardial perfusion.[238]

4.5 Differences in myocardial perfusion

There was no significant difference in perfusion abnormalities noted in terms of fixed defects (p=0.47) or reversibility of perfusion defects (p=0.69) between the group of asymptomatic diabetic black participants and their white and Indian counterparts. This is most likely due to the fact that diabetic individuals submitted to MPI often show abnormalities on perfusion independent of their race. In fact, a large study of about 1500 asymptomatic diabetic patients by Rajagopalan *et al* that examined the association between high-risk findings on MPI and several variables did not mention race as a predictor of imaging abnormality.[239] Although the study may lack a number of multiracial participants, our study in its modest number did not find any influence of race on perfusion abnormalities. Our findings also imply that asymptomatic diabetic black individuals do not differ from other races in terms of risk for CAD. The study by Sliwa *et al* that looked at the spectrum of heart disease and risk factors in a black urban population corroborates well with our findings in that they have found a significantly high prevalence of cardiovascular risk factors among the black urban population.[22] Although their study did not directly target diabetic black individuals, CAD was noted in about 21% of the participants and 16% of them were diabetics.

A comparison of asymptomatic and symptomatic diabetic black groups did not demonstrate a significant difference for the presence of fixed perfusion defects (p=0.22) nor for reversible perfusion defects (p=0.47). This finding could be due to atypical chest pain commonly noted in a quite large number of black patients which may not be of cardiac origin (Personal communication with Prof Sliwa).

However, the difference in perfusion abnormalities on MPI between the asymptomatic and symptomatic white and Indian population group was significant both for fixed perfusion defects (p=0.0006) and reversible perfusion defects (p=0.005).

Similar findings were noted by Paillole *et at* in a study that was conducted to detect CAD in diabetic patients.[214]

Chap 5 Conclusion and the way forward

The association between diabetes and CAD has been recognized as a major public health problem in the developed world. There is also an increased prevalence of silent myocardial ischaemia among asymptomatic individuals with diabetes. Therefore, there is a dire need to strategize on the evaluation and management of asymptomatic diabetic individuals.

While a variation in the numbers of asymptomatic diabetic individuals with silent CVD in the published reports is real, data equally suggest that a significant prevalence of CAD goes undiagnosed and therefore screening of individuals with diabetes has become important.

MPI is a noninvasive method that has become essential in the screening of diabetic individuals who are at high risk of suffering from silent ischaemia. Both pharmacologic and exercise stress testing using gating techniques for MPI have shown high sensitivity and specificity in identifying balanced CAD even in the presence of normal coronary angiography. There is also enough evidence that CAD is no longer a rarity among the black population in Africa.

The following were noted in this study with the use of MPI:

1. The presence of CAD in asymptomatic diabetic black participants.
2. Similar findings in the asymptomatic diabetic white and Indians control group
3. No significant difference in the prevalence CAD between the two population groups (white and Indian forming one bloc as a population group)
4. Perfusion abnormalities on MPI showed a strong relation to LV dysfunction as measured by resting and post-stress testing MPIs

My research has demonstrated enough evidence to recommend screening of asymptomatic diabetic black individuals. Hence those with microvascular

disease or with evidence of peripheral arterial disease should be given particular attention.

The asymptomatic diabetic black individuals should be evaluated and managed in a similar manner as the other races for the detection of CAD.

Stress MPI should be routinely used as a noninvasive investigation in our environment and be utilized more actively in the management of all asymptomatic diabetic patients.

Limitations

Coronary angiography was not performed in all participants with evidence of previous infarction or stress induced mild ischaemia on MPI that were consistent with the imaging diagnosis of CAD.

The number of patients for the study was small, and therefore there is not sufficient power to provide a prognostic evaluation of silent ischaemia in this group.

All participants were from the mega city of Johannesburg where the diet is considered to be more westernized than the diet of African population who live in the rural areas.

The restricted availability of Nuclear medicine equipment outside the main teaching hospitals makes it almost impossible to study patients from rural areas who attend primary and secondary hospitals.

The way forward

It would be of great benefit to do further studies with the use of MPI techniques in the diabetic black population with the purpose of assessing the incremental prognostic value of MPI for future events with the knowledge that the risk factors for CVD are currently broadening among people who were previously thought to be protected from CAD.

Reproducing similar results in nuclear medicine centres in different provinces would provide a better picture of the prevalence of CAD in asymptomatic black diabetic individuals in the whole country.

Furthermore, extending collaboration with other African countries to conduct multicenter studies would provide a better understanding on the prevalence of CAD among African black diabetic individuals.

Because MPI studies do not look at the coronary anatomy, a normal study does not automatically exclude the presence of coronary disease in these patients. Newer modalities such as multiple slices CT together with the measurement of calcium score may be combine with the assessment of perfusion abnormality by MPI to predict cardiovascular risk at earlier stage. Furthermore, all the above may be combine with the use of biomarkers such as IL6, TNF and osteoprotegrin to assess the incidence of plaque inflammation and its association with obstructive coronary artery and perfusion abnormality in asymptomatic diabetic patients.

One of the problems we still face with would be how to manage those with evidence of silent ischaemia with the use of one or all these diagnostic tools that we mentioned above. Currently, there is no clear-cut evidence that revascularization would be beneficial to those patients. May be aggressive medical management would improve their prognosis and our study is an important will help in shaping future better trials in this field.

TABLE 1.

Overall African cases and control by Ethnicity and participating Country (The INTERHEART study)

	Controls		Cases	
	Women	Men	Women	Men
All participants	275	510	193	385
Major ethnic groups				
Black African	134	218	52	92
Colored African	120	212	115	192
European/other African	25	80	26	101
Countries				
Benin	…	8	…	4
Botswana	10	20	1	12
Cameroon	5	14	2	15
Kenya	34	14	17	10
Mozambique	5	15	3	13
Nigeria	…	7	1	6
Seychelles	…	2	…	1
South Africa	224	410	165	308
Zimbabwe	1	10	1	16

TABLE 2.

Reported sensitivity and specificity ranges of the different myocardial perfusion SPECT imaging protocols

Test type	Sensitivity (%)	Specificity (%)
Exercise treadmill test		
Thallium-201	60 – 82	65 – 82
Tc-99m sestamibi	82 – 97	36 – 90
Tc-99m tetrofosmin	60 – 95	77 – 89
Adenosine or dipyridamole		
Thallim-201	77 – 92	75 – 100
Tc-99m sestamibi	81 – 90	67 – 72
Tc-99m tetrofosmin	83 – 89	55 – 94
Dobutamine		
Thallium-201	86 – 100	36 – 100
Tc-99m sestamibi	76 – 100	64 – 100
Tc-99m tetrosfosmin	80 – 95	72 – 80

From Russell RR III, Zaret BL. Nuclear cardiology: present and future. *Curr Probl Cardio* 2006;**31**:557-629.

TABLE 3.

Use of myocardial perfusion SPECT in the clinical setting
Diagnosis of coronary artery disease
Identify the site and extent of ischemia
Quantification of the extent and severity of impaired coronary flow reserve
Acute ischemic syndromes
Pre-surgical evaluation
Prognostic assessment of CAD patients
Assessment of tissue viability

TABLE 4.

Non-coronary causes of ST-segment depression	
Severe aortic stenosis	Left ventricular hypertrophy
Severe hypertension	Hyperventilation
Cardiomyopathy	Mitral valve prolapse
Anemia	IV conduction distrurbances (RBBB, LBBB)
Hypokalemia	Preexcitation syndrome (i.e. WPW)
Severe hypoxia	Severe volume overload
Digitalis effect	Severe pressure overload
Sudden excessive exercise	Supraventricular arrhythmias
Glucose load	

TABLE 5.

Common indications for pharmacologic stress test
• Peripheral vascular disease
• Neurological/cerebrovascular disease
• Respiratory disease – bronchial asthma, chronic obstructive pulmonary disease *
• End stage renal disease on dialysis
• Musculoskeletal and joint diseases – poliomyelitis, arthritis
• Congestive heart failure
• Orthopaedic limitation – lower limb amputation or patients with artificial limbs
• Poor patient motivation to exercise
• Left bundle branch block
• Very soon after MI (< 3 days) and angioplasty/stent (<2 weeks)
• Electronically-paced ventricular rhythm
• Medications that blunt the heart response (beta blockers, calcium channel blockers)
• Chronic systemic illness
• General debility

*dobutamine only

TABLE 6.

Contraindication and patient instruction before pharmacological stress

Pharmacological Agents	Contraindications for pharmacological stress MPS	Patient instruction before stress
Adenosine Dipyridamole	Active wheezing 20 and 30 atrioventricular block Hypotension(systolic<90mHg) Sick sinus syndrome Severe bradycardia (Patients on dipyridamole should Discontinue the drug at least 24 hours prior to adenosine stress) Known hypersensitivity to adenosine	Theophylline and caffeine are prototype adenosine receptor antagonists. A 24-hours abstention from coffee, tea, some soft drinks and 36-48-hour abstention from slow release theophylline
Dobutamine Arbutamine (Dobutamine + Atropine)	Unstable angina (USA) Critical aortic stenosis Significant left ventricular out flow tract obstruction Ventricular tachycardia Supraventricular tachyarrhythmia Uncontrolled hypertension Patients with aortic dissections Patients with large aneurysms Hypertrophic obstructive cardiomyopathy (Atropine is contraindicated in patients with narrow-angle glaucoma, myasthenia gravis, obstructive uropathy, or obstructive gastrointenstinal disorders)	ß-blockers be withheld for at least 48 hours before the test, because ß-blockers reduce the ionotopic and chronotropic effects

From Gopinath G, Buscombe JR. Pharmacological stress agents in nuclear cardiology. *World J. Nucl Med* 2004;**3**:64-71

TABLE 7.

Common side effects of the Pharmacological agents

Pharmacological agents	Common side effects	Reversal of side effects
Adenosine	Flushing (33%) Dyspnoea (35%) Chest pain (35%) Gastrointestinal discomfort (15%) Headache (14%) Light-headedness (9%) THESE LAST LESS THAN 10 MINUTES	Side effects are spontaneous and disappear after stopping the infusion. The side effects can be reversed by the administration of theophylline, an adenosine receptor antagonist
Dipyridamole	Flushing (3%) Dyspnoea (3%) Chest pain (20%) Headache (12%) THESE MAY LAST FOR UP TO 6 HOURS	The side effects can be reversed by the administration of aminophylline, an adenosine receptor antagonist (75-250mg intravenously).
Dobutamine	Chest pain (31%) Premature ventricular contractions (15.3%) Dyspnea (14%) Nausea (8%) Premature atrial contactions (7.7%) Anxiety (6%) Headache (4%)	Side effects of dobutamine can be reverted by metoprolol (1-5mg) or esmolol intravenously,
Arbutamine	Tremor (22%) Dizziness (11%) Headache (11%) Paraesthesia (7%) Arrhythmias (6%) Hypotension (4%)	Side effects of arbutamine can be reverted by metoprolol (1-5mg) or esmolol intravenously,

TABLE 8.

High-risk markers associated with stress testing and perfusion imaging

Stress test markers	SPECT markers
• Ischemic ECG changes at a low (5 METS) workload	- Elevated lung heart ratio (>0.50 for Tl-201, >0.43 for Tc-99m Sestamibi)
• Typical angina occurring at a low (5 METS) workload	- Transient ischemic dilatation of the left ventricle during stress
• Ischemic ECG changes or typical angina persisting late into the recovery phase	- Transient right ventricular visualization during stress
• Hypotensive blood pressure response to exercise	- Perfusion defects in multiple vascular territories
• Ischemic ECG changes during adenosine/dipiridamole infusion	- Large, severe perfusion defects
• Development of ventricular tachycardia/fibrillation	
• Development of pulmonary edema	

TABLE 9.

Distribution of diabetics' characteristics with regard to race

	Blacks	Whites& Indians	Total (%)
Asymptomatic	94	50	144 (61.54)
Symptomatic	45	45	90 (38.46)

TABLE 10.

Demographics		
Characteristics	Number	Percentage
Female	123	52.6
Male	111	47.4
Age (mean±SD,year)	62± 8	
Asymptomatic diabetics		
Female black	53	56.4
Male black	41	43.6
Female W+I	24	48.0
Male W+I	26	52.0
Symptomatic diabetics		
Female black	26	57.8
Male black	19	42.2
Female W+I	20	44.5
Male W+I	25	55.5

W+I: white and Indian

TABLE 11.

Differences in demographics of diabetic participants

	Asymptomatic			Symptomatic		
	Black	W+I	p-value	Black	W+I	p-value
Age (mean±SD)	60±7.2	64±7.7	0.003	59.7±9.3	65.3±9.4	0.006
Gender						
Female (%)	53 (56.4)	24 (48)	0.43	26 (57.8)	20 (44.5)	0.30
Male (%)	41(43.6)	26 (52)		19 (42.2)	25 (55.5)	

W+I: white and Indian

TABLE 12.

Reversibility of perfusion from rest to stress MPI

	Asymptomatic		Symptomatic	
	Black	W+I	Black	W+I
	N (%)		N (%)	
None	81 (86.2)	36 (72)	36 (80)	30 (66.7)
Mild	11 (11.7)	12 (24)	4 (8.9)	8 (17.8)
Moderate	1 (1.1)	2 (4)	4 (8.9)	7 (15.6)
Severe	1 (1.1)	0 (00)	1 (2.2)	0 (00)

W+I: whites and Indians

TABLE 13.

Fixed perfusion defects on MPIs	Asymptomatic		Symptomatic	
	Black	W+I	Black	W+I
	N (%)		N (%)	
Small	2 (2.1)	1 (2)	7 (15.6)	2 (4.4)
Medium	10 (10.6)	5 (10)	5 (11.1)	6 (13.3)
Large	7 (7.4)	7 (14)	7 (15.6)	16 (35.6)

W+I: whites and Indians

TABLE 14.

Means ±SD of biomarkers measured within weeks of MPIs

	Asymptomatic		Symptomatic	
variables	Black	W+I	Black	W+I
Hb1ac	8.4±.2	7.2±2	9.5±.3	8.1±2
Chol	4.5±1	4.5±1	4.5±2	4.4±1
TG	1.4±0.7	1.4±0.7	1.8±1.4	1.6±0.7
HDL	1.3±0.3	1.3±0.4	1.2±0.4	1.2±0.4
LDL	2.5±0.9	2.5±0.8	2.3±1	2.6±1

W+I: whites and Indians; Hb1ac: haemoglobin A1c (expressed in %) ;Chol: cholesterol; TG: triglyceride; HDL:high density lipoprotein; LDL: low density lipoprotein (all measured in mmol/L)

TABLE 15.

Values of LVEF measured on MPI both at rest and in post stress

Characteristic (N)	Rest EF (%) (mean±SD)	Post stress EF (%) (mean±SD)
All (234)	50.3±16.7	50.2±17.3
Asymptomatic Black (94)	51.6±13.6	51.72±15.2
Asymptomatic White and Indian (50)	52.1±19.2	53.4±19.3
Symptomatic Black (45)	46.2±17.57	49.9±18.6
Symptomatic White and Indian (45)	45.3±18.9	48.3±17.3

Fig 1. Normal rest and stress MPI in asymptomatic diabetic black participant. Note the lack of perfusion change from rest to stress.

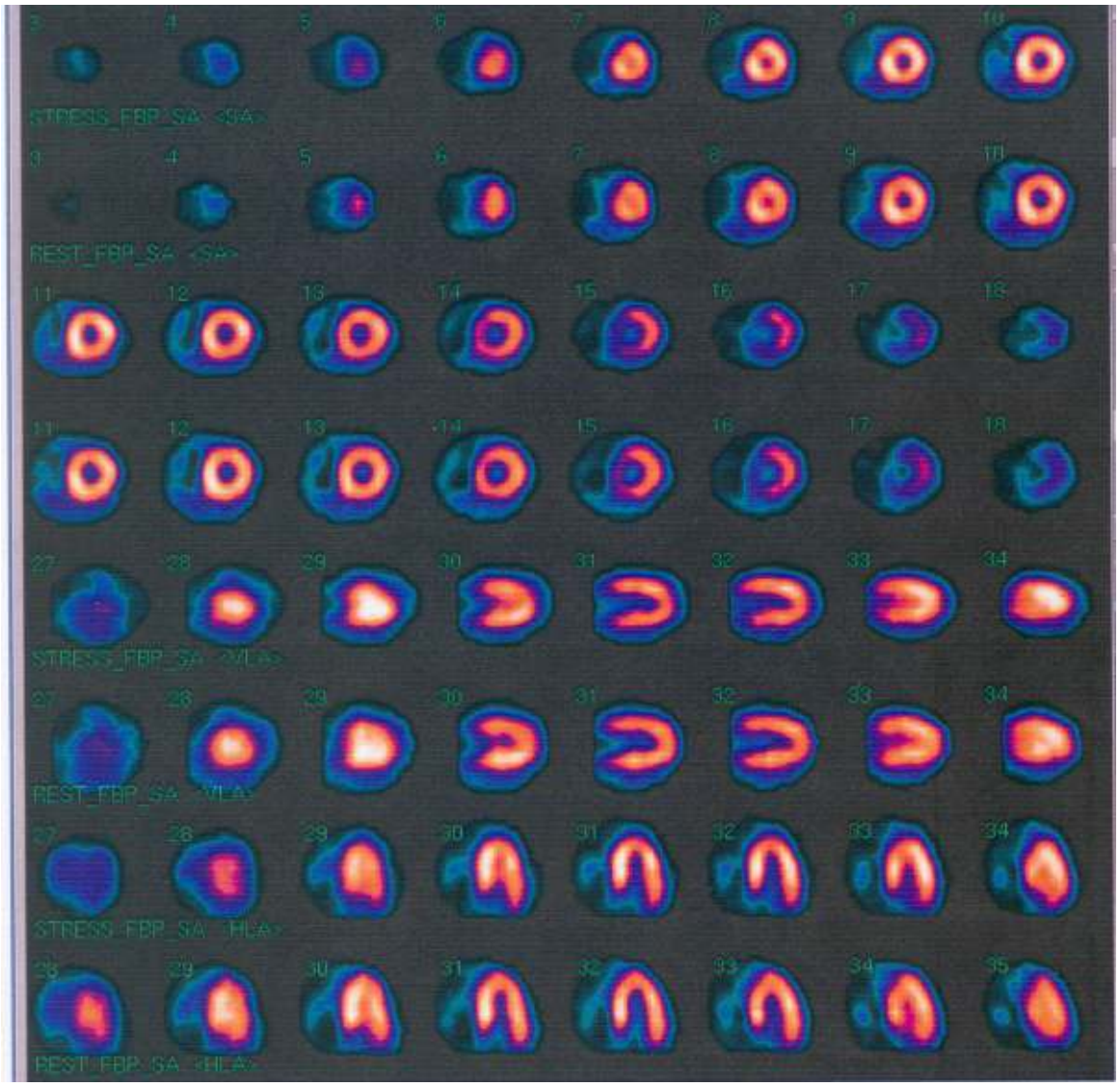
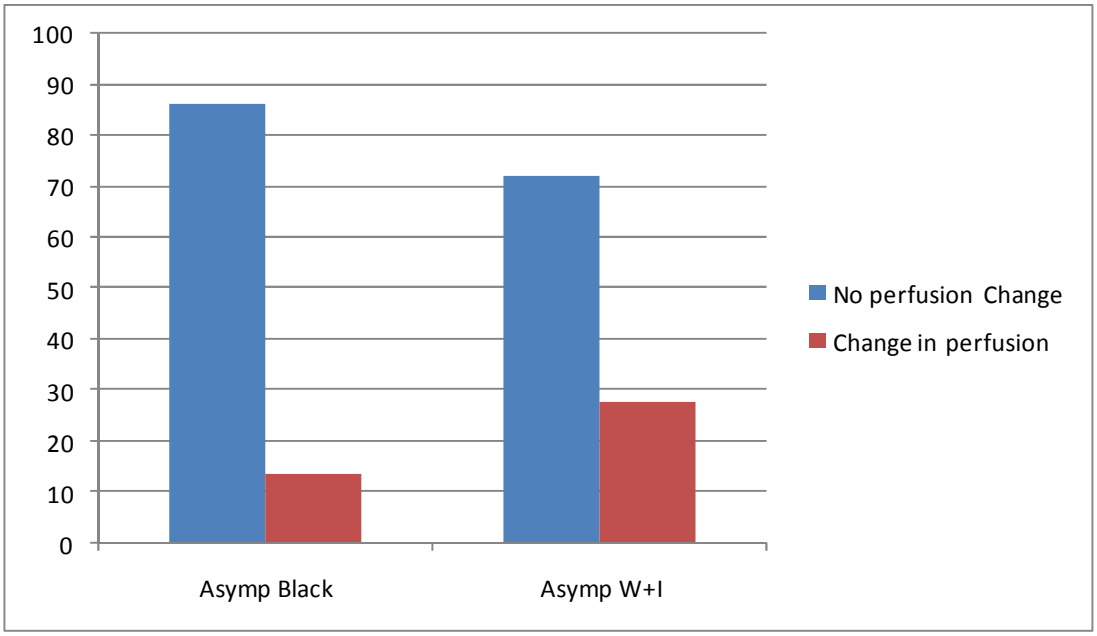


Fig 2. Percentage on the improvement noted on the perfusion from rest to stress MPI in both groups of asymptomatic participants.



W+I: white and Indian

Fig 3. Reversibility of perfusion from rest to stress MPI that was consistent with mild stress induced apical inferior myocardial ischemia in asymptomatic diabetic participant. The summed difference score (SDS) was 6.

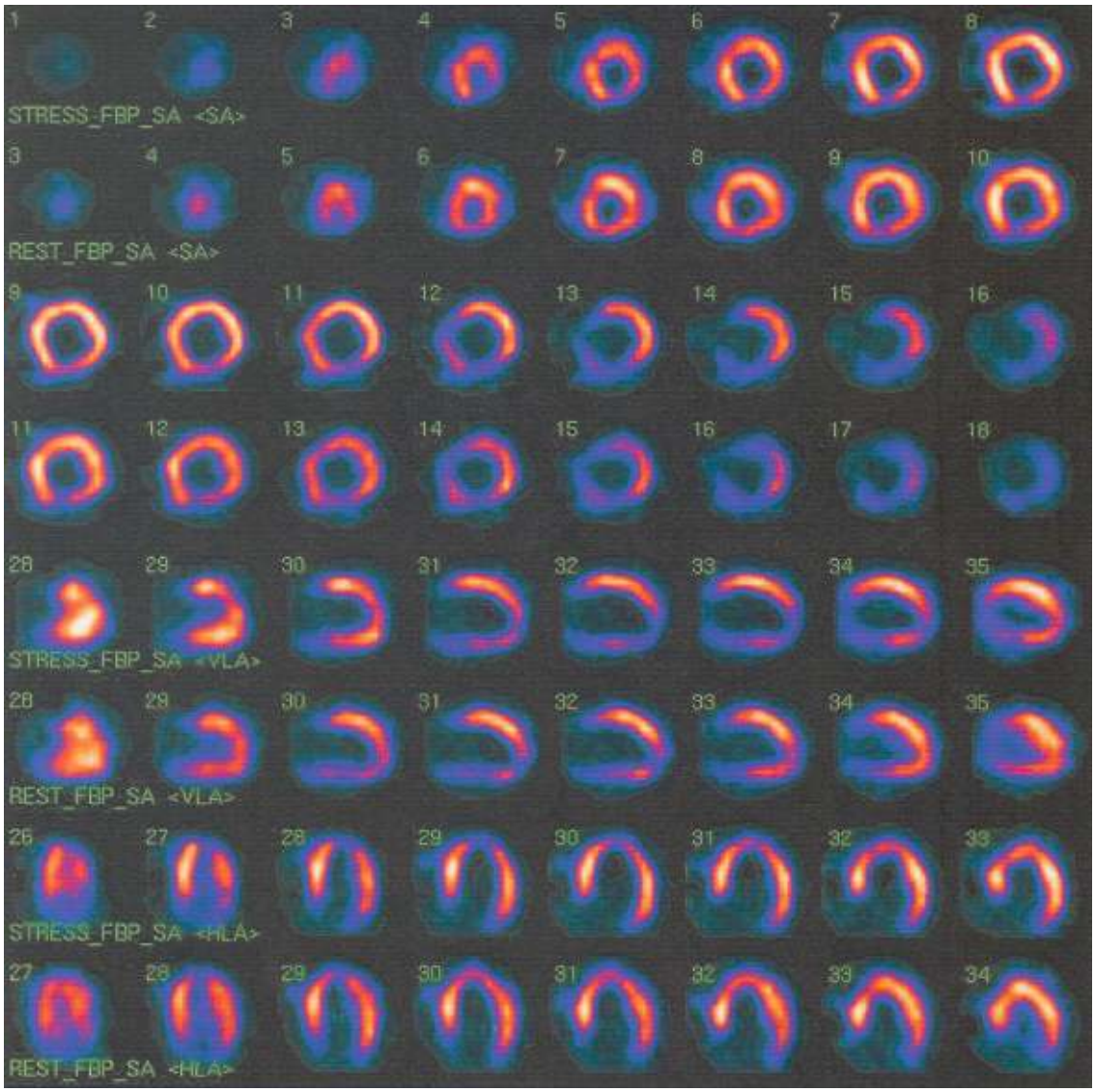


Fig 4. This asymptomatic diabetic participant showed a reversible perfusion consistent with stress induced moderate inferior ischaemia and the SDS was 10.

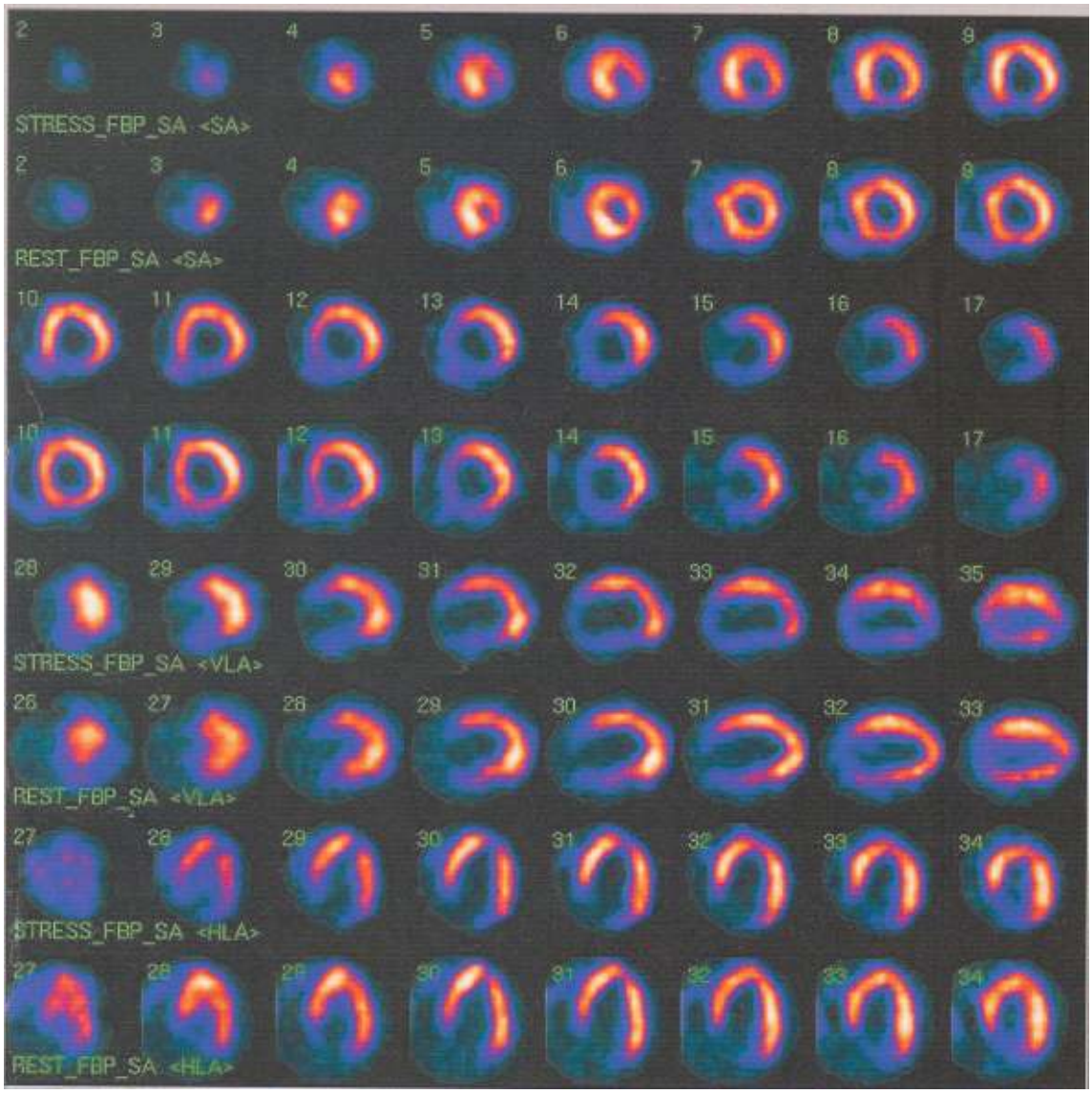


Fig 5. Severe lateral and inferior stress induced ischaemia with a SDS of 15.

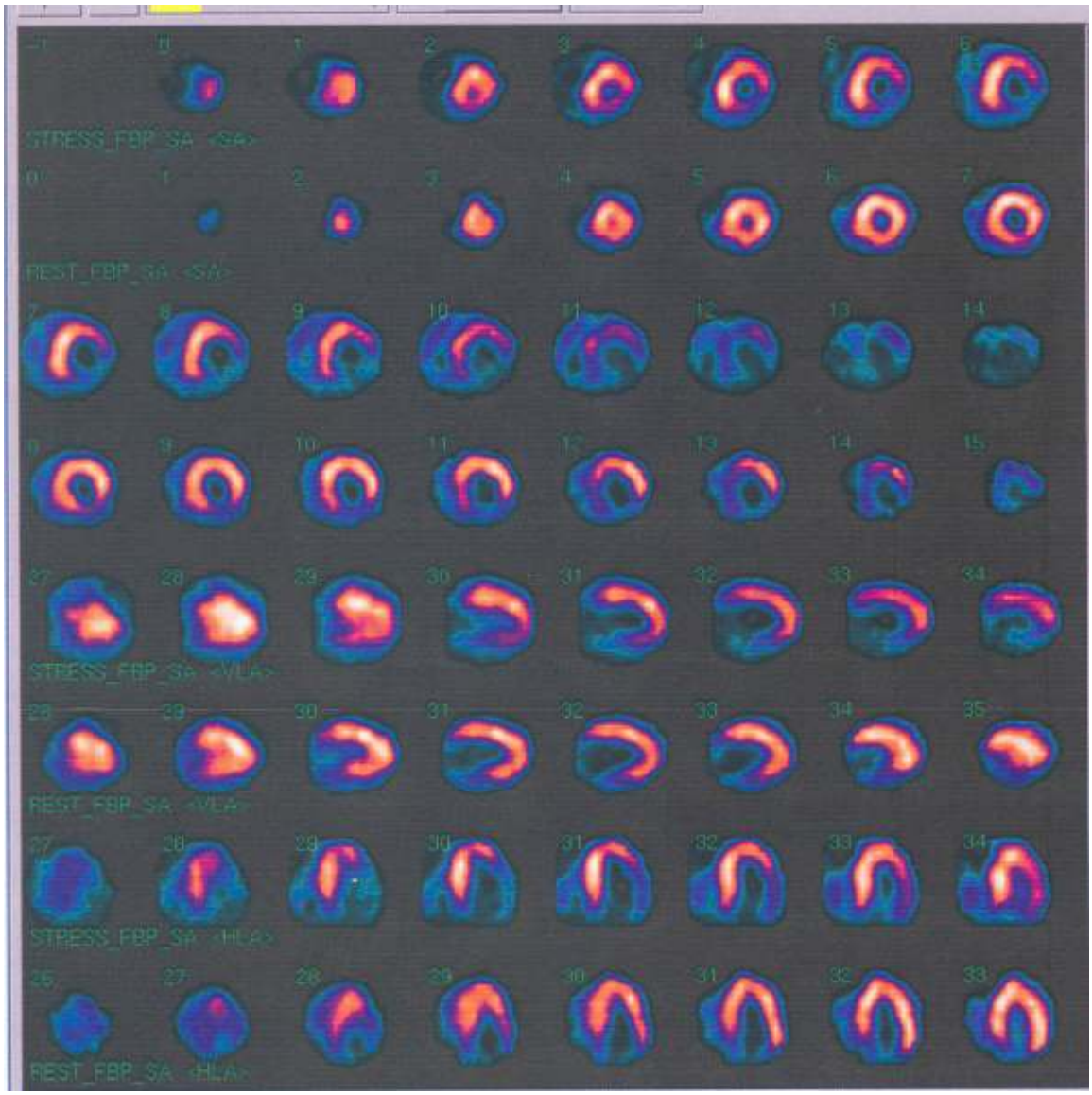

STRESS_FBP_SA <SA>
REST_FBP_SA <SA>
STRESS_FBP_SA <VLA>
REST_FBP_SA <VLA>
STRESS_FBP_SA <HLA>
REST_FBP_SA <HLA>

Fig 6. Different degree of perfusion improvement noted in both groups of asymptomatic participants.

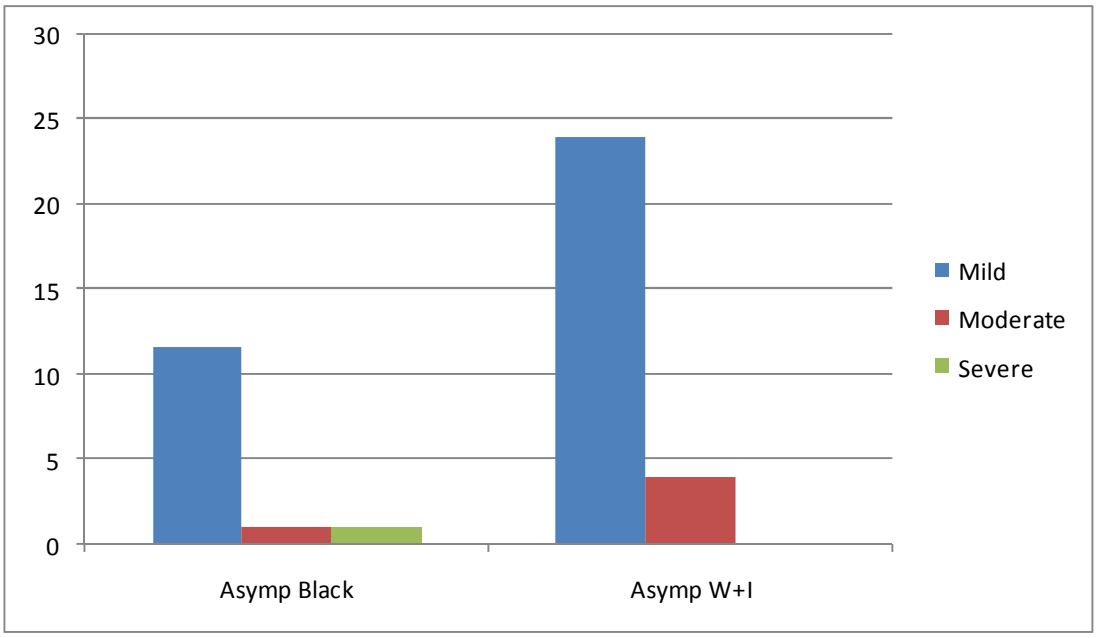
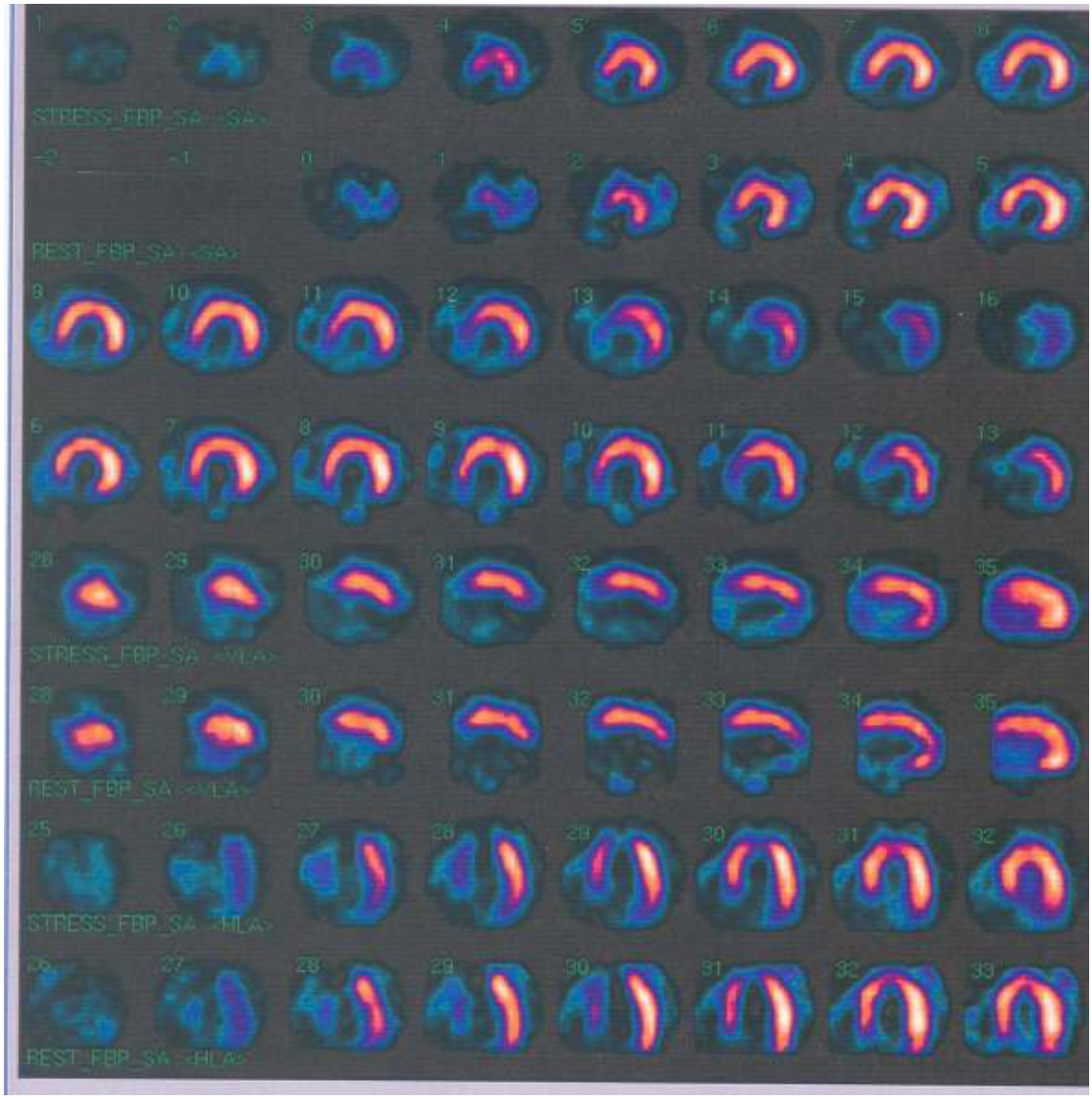


Fig 7. No change is noted on the perfusion from rest to stress MPI but there is a large fixed perfusion defect noted in the apical inferior, septal and inferior walls.



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