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A Retrospective Analysis of the Utility of Myocardial Perfusion Imaging using Single Photon Emission Computed Tomography (SPECT) for Differentiating Ischaemic from Non-Ischaemic Left Ventricular Dysfunction

Alosha Singh

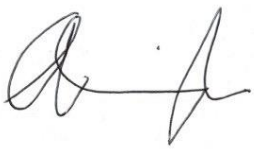
A research report submitted to the Faculty of Health Sciences in fulfilment of the requirements for the degree of Master of Medicine, in Internal Medicine at the University of Witwatersrand, Johannesburg.

September 2017

DECLARATION

I, Alosha Singh, declare that this dissertation is my own, unaided work, except where otherwise acknowledged. It is being submitted for the degree of Masters in Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.

Signed this 31st day of August 2017



Dr. A Singh

DEDICATION

To all the students at the University of Witwatersrand who work tirelessly to achieve their goals and to my parents who have always believed in me and inspired me.

ABSTRACT

Differentiating ischaemic left ventricular dysfunction (ILVD) from non-ischaemic left ventricular dysfunction (NILVD) is crucial since appropriately selected patients may benefit from coronary revascularisation. The aim of this study was to evaluate the diagnostic utility of myocardial perfusion imaging (MPI) in patients presenting with left ventricular dysfunction using coronary angiography (CA) as the gold standard.

Methods

This single centre retrospective study was conducted in 52 patients with heart failure with a reduced ejection fraction (EF< 40%) who had both MPI as well as CA at CHBAH between January 2005 and December 2012. ILVD was diagnosed when the distribution and severity of coronary disease on CA was sufficient to account for the degree of left ventricular dysfunction.

Results

From a total of 52 patients, 33 (63%) had ILVD and 19 (37%) had NILVD. As compared to patients with NILVD, those with ILVD were more likely to be Indian and White (p=0.0014), have more coronary risk factors (5(2) vs 3(2), $p < 0.0001$) and more commonly have q waves on the ECG (0% vs 55%, $p < 0.0001$). MPI had a sensitivity of 100% (95% CI 66-100%) and specificity of 52.63% (95% CI 30.18 - 75.08) for the diagnosis of ILVD. The presence of fixed perfusion defects on MPI was the best predictor of ILVD.

Conclusion

MPI has high sensitivity but low specificity for the diagnosis of ILVD. This makes it a useful screening test for the exclusion of coronary artery disease in patients presenting with heart failure.

ACKNOWLEDGEMENTS

Thank you to my kind and loving sister Jyotika Singh for her time, effort and patience in helping me with the statistical analysis.

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LIST OF ACRONYMS

CA	Coronary Angiography
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CHBAH	Chris Hani Baragwanath Academic Hospital
CMR	Cardiac Magnetic Resonance Imaging
DCMO	Dilated Cardiomyopathy
ECG	Electrocardiogram
EF	Ejection Fraction
FPD	Fixed Perfusion Defects
HFpEF	Heart Failure with Preserved EF
HFrEF	Heart Failure with Reduced EF
HIV	Human Immunodeficiency Virus
ICMO	Ischaemic Cardiomyopathy
ILVD	Ischaemic Left Ventricular Dysfunction
IHD	Ischaemic Heart Disease
LAD	Left Anterior Descending
LCX	Left Circumflex Artery
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MPI	Myocardial Perfusion Imaging
NILVD	Non-ischaemic Left Ventricular Dysfunction
PET	Positron Emission Tomography
RCA	Right Coronary Artery

RPD	Reversible Perfusion Defects
RWMA	Regional Wall Motion Abnormalities
SPECT	Single Photon Emission Computed Tomography

CHAPTER 1

1. Introduction and Literature Review

1.1. Introduction and Epidemiology

Heart failure is a common and complex clinical syndrome with a multitude of causes, either structural or functional, which impairs the ability of the heart to eject a sufficient volume of blood to meet metabolic requirements. It is a major health problem worldwide with significant morbidity and mortality and poses a significant economic burden on healthcare systems. Heart failure has a prevalence of over 5.8 million in the United States and this economy spends about 35 billion dollars of their annual health budget on managing the disease [(1), (2)]. Although precise data on the economic impact of heart failure in Sub Saharan Africa is insufficient, we know that between 3 to 7 percent of hospital admissions are attributable to heart failure in Southern Africa and it has been estimated that it costs approximately 1 percent of the health budget [(3)]. Furthermore, this negatively impacts the economy since heart failure in developing countries commonly occurs in the economically active young population[(3)].

Heart failure results from diseases that impair left ventricular (LV) function such as diseases of the pericardium, myocardium, endocardium, heart valves, great vessels or metabolic abnormalities. Heart failure occurs within a large range of ejection fractions (EF), which is defined as the volume of blood ejected from the heart within one cardiac cycle. The EF is used to classify patients with heart failure into two groups - heart failure with preserved EF (HFpEF) (in which the LV size is normal and EF usually more than 50%) and heart failure with reduced EF or HFrEF (which has a dilated LV

typically with an EF< 40%). These two groups have been shown to have different patient demographics, co-morbid conditions, prognosis and responses to treatment [4].

Epidemiology studies suggest that the most common causes of heart failure with reduced EF (HF-REF) are ischaemic heart disease (IHD), idiopathic dilated cardiomyopathy (DCMO), hypertension and valvular heart disease [5].

The prognosis of heart failure patients remains generally poor with a 5-year mortality rate of 45-60% [1]. Distinguishing non-ischaemic left ventricular dysfunction (NILVD) from ischaemic left ventricular dysfunction (ILVD) is difficult but important since these groups have different prognoses and therapeutic implications [6].

1.2. Ischaemic and Non-ischaemic Dilated Cardiomyopathy

It has been shown in a large single center study that ischaemic cardiomyopathy has a significantly worse prognosis than idiopathic dilated cardiomyopathy [6]. In a large study from John Hopkins University looking at the association between the cause of cardiomyopathy and the long term prognosis, it was shown that patients with peripartum cardiomyopathy had the best survival rates as compared to idiopathic DCMO. The worst survival rates (with highest hazard ratio for death) were amongst patients with cardiomyopathy due to infiltrative myocardial diseases, Human Immunodeficiency Virus (HIV) infection, doxorubicin therapy and ischaemic heart disease [6].

Heart failure in Sub Saharan Africa shows different trends from developed countries, the majority of causes being due to rheumatic heart disease, idiopathic dilated cardiomyopathy, and hypertensive heart disease [3], [7]. Ischaemic cardiomyopathy accounts for a minority of cases. However, urbanisation of sub-Saharan Africa, with the adoption of a western lifestyle, has led to an increase in the prevalence of cardiovascular risk factors for IHD such as hypertension, diabetes mellitus, hyperlipidaemia, cigarette smoking and obesity [7], [8], [9], [10]. These are some of the major risk factors known to be associated with the development of heart failure [1]. Thus, the rate of IHD and ILVD are expected to increase within the population. ILVD by definition, occurs in patients with heart failure who have had a documented myocardial infarction or have viable but dysfunctional myocardium due to severe ischaemia [11].

Data from developed countries show that ischaemic heart disease causing ILVD is the most common cause for heart failure [2]. As mentioned above, even though described as rare, rates of ILVD are expected to rise within developing populations. These patients have a shorter survival than patients with non-ischaemic heart failure [6]. The management of ILVD is also uniquely different and reperfusing viable segments of the heart via percutaneous intervention or Coronary Artery Bypass Grafting (CABG) may significantly improve LV function and hence morbidity and mortality in these patients [12], [13]. Thus, it is of the utmost importance that these patients are correctly identified, investigated and treated.

1.3. Diagnosis of Ischaemic Left Ventricular Dysfunction (ILVD)

The current recommendations for diagnosing and managing ILVD rely on demonstrating clinically significant coronary artery disease (CAD) via coronary angiography unless the patient is not eligible for revascularisation [4]. Since contrast CA is invasive, has certain risks, is expensive and not universally available, non-invasive imaging such as MPI may be used as a screening method for CAD. Other advantages of MPI include the ability to quantify the amount of ischaemia, measure ventricular function and to determine myocardial viability [4], [14].

Hibernating myocardium is a term given to ischaemic heart muscle which has down-regulated its contractility in order to match its decreased blood supply. It is thought to be a compensatory or adaptive mechanism and it leads to decreased LV function and heart failure. If blood supply to hibernating myocardium is restored, LV function and symptoms of heart failure are expected to improve [15], [16]. Stunned myocardium is also viable myocardium that has been salvaged by reperfusion (spontaneous or induced) but exhibits prolonged post-ischaemic dysfunction. Imaging helps to define whether dysfunctional myocardium in the ILVD patient is infarcted or hibernating or a combination of both. This knowledge would then allow for treatment decisions to be made as revascularisation of viable hibernating myocardium in patients with ILVD improves survival and LV function compared to medical therapy [16], [17].

1.4. Imaging modalities used in ILVD

There are a number of accepted non-invasive cardiac imaging modalities in patients with ischaemic heart disease. These include dobutamine stress echocardiography (DSE),

coronary computed tomography (CCT), cardiac magnetic resonance Imaging (CMR), single photon emission computed tomography (SPECT) and positron emission tomography (PET). The optimal imaging modality is ultimately governed by accuracy, cost and availability. DSE is the most widely available and low-cost imaging modality. However, the disadvantages are that a good echo window and reliable expertise are required, making it less reproducible. CCT has a high negative predictive value in excluding CAD but does not provide information on viability. CMR has the advantage of no radiation burden but is, however, very expensive and not readily available. SPECT and PET are more readily available, reproducible and provide certain advantages including yielding information on LV function, viability, ischaemia and infarction. The disadvantage includes radiation exposure [18]. At Chris Hani Baragwanath Academic Hospital, SPECT MPI is performed routinely using several tracers including Sestamibi and Thallium.

1.5. SPECT MPI

Single photon emission computerised tomography is a nuclear scintigraphy technique in which a radio-tracer (e.g., thallium-201 chloride and Tc-99m Sestamibi) is injected intravenously. The radio-tracer is then taken up by viable myocytes from the blood stream. The radio-tracer emits photons in proportion to the amount of radio-tracer that is taken up. A gamma camera is used to capture the emitted gamma ray photons and software converts this into digital data that is represented on a screen showing tomographic images (slices of the heart). Thus, well perfused areas will show up brightly on the screen and poorly perfused or infarcted areas will show up as perfusion defects [19]. Rest studies will show baseline perfusion of the myocardium. Images done

at stress might show a change in perfusion and thus denote a reversible perfusion defect. If a perfusion defect does not change then this implies a fixed perfusion defect representing infarction. Hibernating myocardium will show reduced but still adequate perfusion, indicating viability [19]. Examples of these changes are shown in Figure 1.1.

In positron emission tomography computed tomography (PET CT) images, viable myocardium will be evidenced by normal or increased metabolic activity (Fluorodeoxyglucose F 18 or F18-DG uptake in these viable segments). As mentioned above, these patients will benefit a significantly from revascularisation techniques. By using Electrocardiogram (ECG) gating together with SPECT MPI, information regarding wall motion abnormalities during systole as well as EF can be obtained. Areas of the myocardium that are infarcted or hibernating in the ischaemic patient have poor contractility and can be identified. In non-ischaemic cardiomyopathy, the study is expected to show a more diffuse poorly contracting myocardium, although can also have segmental wall motion abnormalities [20].

In order to standardise tomographic imaging of the heart, a 17-segment model is used. This divides the left ventricle into 17 segments described according to the long-axis of the heart as well as its circumferential location. Each segment is also assigned to one of the 3 epicardial arteries with the recognition that there is anatomic variability. These are the Left Anterior Descending (LAD), Right Coronary Artery (RCA) and the Left Circumflex Artery (LCX) [21]. The segments as well as their coronary artery territory are demonstrated in Figure 1.3.

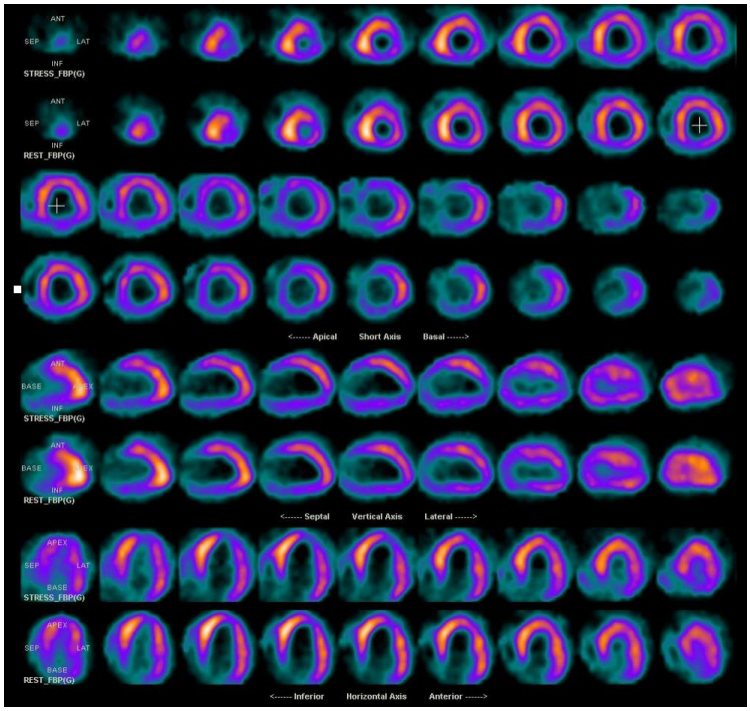
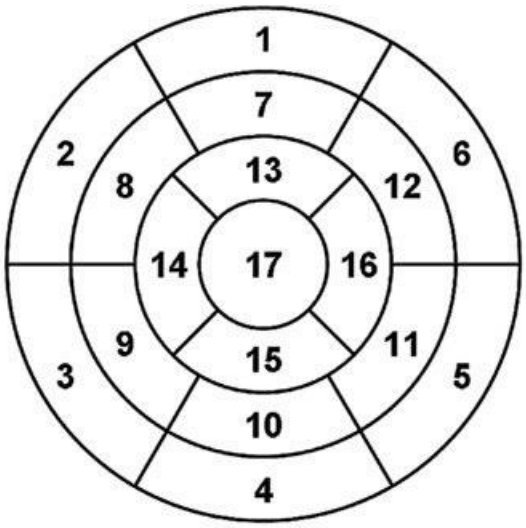


Fig 1.1: SPECT imaging performed before and after pharmacological stress (Image courtesy of Division of Nuclear Medicine, CHBAH. See Appendix E)



1. basal anterior
2. basal anteroseptal
3. basal inferoseptal
4. basal inferior
5. basal inferolateral
6. basal anterolateral
7. mid anterior
8. mid anteroseptal
9. mid inferoseptal
10. mid inferior
11. mid inferolateral
12. mid anterolateral
13. apical anterior
14. apical septal
15. apical inferior
16. apical lateral
17. apex

Fig 1.2: Left Ventricular Segmentation [21].

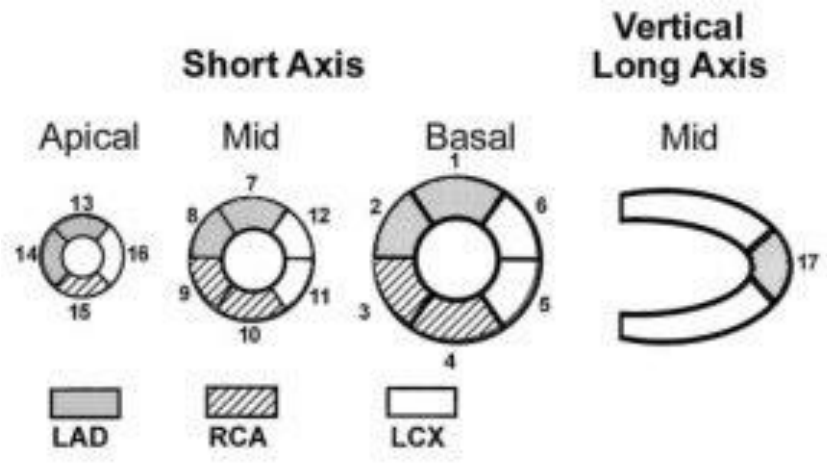


Fig 1.3: Coronary Artery Territories.

1.6. Distinguishing ILVD from NILVD

Distinction between ILVD and NILVD may be clinically challenging. Both groups of patients typically present with heart failure. Patients with ILVD may not have chest pain and patients with NILVD may have ischaemic-type pain due to high LV filling pressures. Although the ECG in ILVD may show evidence of ischaemia or infarction, this is not always the case. Furthermore, focal wall motion abnormalities may not be present in ILVD (due to diffuse coronary artery disease [CAD] or triple vessel disease) and may often occur in NILVD [(20)]. This may be due to associated bundle branch block causing asynchronous wall activation. Other causes may be due to focal myocarditis and fibrosis [(22)]. Differentiating these two groups is important for prognostic and management purposes.

Coronary angiography (CA) is the gold standard to diagnose coronary artery disease, and hence ILVD. It can reliably distinguish ILVD from NILVD. CA, however, is an invasive test and incurs a small risk. Furthermore, it is expensive and may not be readily available at all hospitals. This study sought to evaluate the efficacy of SPECT-MIBI in

distinguishing NILVD from ILVD. MPI has a benefit over CA in that it is non-invasive, has fewer risks to the patient and does not require the usage of contrast agents which are potentially nephrotoxic [14].

Due to epidemiological transition, the incidence of coronary disease and its complications have risen dramatically in South Africa [11]. Idiopathic cardiomyopathy and hypertensive heart disease are also common. Heart failure is a common presentation at Chris Hani Baragwanath Academic Hospital and it is often unclear what the underlying etiology is. Accurate identification of the different etiologies is crucial since the management is disease specific.

Previous studies have shown that 99mTc-MIBI MPI may be reliable in distinguishing ILVD from NILVD [22, 25]. A Lithuanian study by Ragaisyte et al demonstrated that the number as well as severity of perfusion defects in DCMO patients were far less than that found in ICMO patients. They showed a sensitivity in predicting DCMO of 94.44% and a specificity of 88.24%. This study was however performed using rest images only [22].

Perfusion abnormalities on MPI are a hallmark of ILVD because of myocardial ischaemia and infarction. However, perfusion abnormalities may also be seen in DCMO patients with normal coronary arteries. Several hypotheses have been suggested to account for this including, microvascular dysfunction as well as mitochondrial dysfunction (functional mitochondria are required to trap the nuclear tracer Sestamibi).

Van Den Heuvel et al. looked specifically at myocardial blood flow in idiopathic DCMO patients using Positron Emission Tomography (PET). They demonstrated impaired myocardial blood flow in this group compared to healthy control subjects. In addition, they showed that impaired blood flow reserve was positively related to the severity of heart failure as well to the left ventricular wall stress [(23)].

A study from Japan by Maeba et al. investigated perfusion as well as wall motion abnormalities on MPI (using rest-gated SPECT) in differentiating ICMO from DCMO. They also found that the ischaemic group showed a significantly larger number of poorly perfused areas. A cut-off value of more than 4 segments provided 88% sensitivity and 91% specificity for distinguishing ICMO. On the other hand, regional wall motion defects were not able to reliably distinguish the groups in this study [(24)].

Danias et al. looked at SPECT MPI in differentiating these two groups. They retrospectively studied 164 patients with an EF<40% and compared the SPECT data between the two groups (all being correctly identified as ICMO or non-ischaemic cardiomyopathy by coronary angiography). They found that sensitivity of stress SPECT in diagnosing ICMO was 87%, with a specificity of 63%. If they included wall motion data, it increased sensitivity to 88% and decreased specificity to 45%. If reversibility was also taken into account then SPECT MPI had a 94% sensitivity and 45% specificity in diagnosing ICMO. Thus, Danias et al. demonstrated that ECG-gated SPECT combining perfusion as well as regional wall motion abnormalities is very sensitive for detection of ischaemic cardiomyopathy [(25)].

The previously discussed studies were all performed in caucasian patients with a high pre-test probability of coronary artery disease. Although CAD is on the rise in black

South African patients, the overall incidence is still less than seen in other population groups. Non-ischaemic left ventricular dysfunction is also common in black South Africans. The non-invasive distinction between ILVD and NLVD is thus critical and utility of SPECT-MIBI in this setting has not been tested.

1.7. Objectives

1. To compare the clinical characteristics of patients with ischaemic and non-ischaemic left ventricular dysfunction.
2. To determine the difference in perfusion abnormalities (fixed and reversible defects) on SPECT MPI between ischaemic and non-ischaemic myocardium in patients with moderate to severe left ventricular dysfunction.
3. To determine the difference in wall motion abnormalities on SPECT MPI between ischaemic and non-ischaemic myocardium in patients with moderate to severe left ventricular dysfunction.
4. To determine the sensitivity and specificity of MPI using SPECT (with MIBI) in identifying ILVD compared to the gold standard of coronary angiography.

1.8. Ethics Approval

Ethics approval from the Ethics committee, University of the Witwatersrand was obtained in 2012, with the clearance certificate number M120535. Please see Ethics Clearance certificate in Appendix D.

CHAPTER 2

2. Methodology

This was a single-centre retrospective observational study conducted on patients with a reduced ejection fraction (EF< 40%) who had both an MPI SPECT scan as well as a coronary angiogram done at CHBAH.

2.1 Patient Selection

The study population comprised all patients recorded on the department of nuclear medicine's database who underwent MPI at CHBAH hospital between 2005 and 2012 who satisfied the inclusion and exclusion criteria for this study.

2.1.1 Inclusion Criteria

The inclusion criteria for this study was

- patients who had an EF<40%
- patients who had both an MPI SPECT scan as well as a coronary angiogram done at CHBAH.

2.1.2 Exclusion Criteria

The exclusion criteria for this study was

- the presence of significant co-morbidities such as severe or uncontrolled hypertension, pericardial disease or significant valvular abnormalities.
- lack of complete data on either the MPI SPECT scan or the coronary angiogram

A total of 52 patients were found who fulfilled the selection criteria. These patients were assigned study numbers and their data was recorded from both the SPECT MPI report (example in Appendix A) and angiogram (example in Appendix B) reports in a data sheet (example in Appendix C).

2.1 SPECT MPI protocol

2.2.1 Patient preparation

A two-day protocol was used as suggested by the European Association of Nuclear Medicine (EANM) guidelines [(26), (27)]. The stress study was performed on the first day, and the rest study was done on the second day. Patients were requested to fast on both days and avoid any caffeine or methylxanthine containing medications for 24 hours before the first day. All patients were routinely requested to stop any beta blocker or calcium channel blocker medications 48 hours prior to the stress test.

2.2.2 Stress Protocol

A treadmill exercise test and/or a Dipyridamole vasodilator test was performed according to the accepted guideline [(26), (27)]. Patients were then injected with an activity of 740MBq Tc99m-Sestamibi at peak stress on the first day and the same on the rest (second) day. Combined protocols using both exercise as well as pharmacologic vasodilator agents were occasionally performed to decrease adverse side effects of vasodilators, that is, flushing, dizziness, headache and hypotension. This may also improve image quality due to decreased extra-cardiac tracer uptake (19,26).

Stress images were then acquired 30-45 minutes after 99mTc-Sestamibi injection, and the rest images were acquired 45-60 minutes after injection. Patients were imaged in both the supine as well as prone positions.

2.2.3 Imaging protocol

A dual head rotating, large field of view Gamma camera was used for the SPECT images (GE medical systems Infinia hybrid system), using a low energy high resolution collimator. A 64 x 64 matrix size was used and 60 images (25 seconds duration for rest and 20 seconds duration for stress) were acquired over a semi-circular 180° arc. The images were re-constructed using filtered back projection with a low resolution Butterworth filter. No attenuation or scatter correction was applied. After reconstructing the trans-axial tomograms, the images were reorientated into three sets of orthogonal slices for each study, namely the short axis, horizontal long axis and vertical long axis.

2.3 Data recorded from the database

Data recorded from the MPI report included patient demographics (age, gender, race), ischaemic risk factors, findings on resting ECG (rhythm and signs of infarction), stress ECG data and nuclear scintigraphy data at rest and at stress. The risk factor data (hypertension, dyslipidaemia, smoking history, obesity, family history, diabetes, known IHD and post-menopausal) that was already recorded on the database were gathered from the request form from the referring physician.

The MPI report on the stress ECG findings were used to record the type of symptoms patients experienced during the test. The test was defined as positive or negative based

on the findings recorded by the reporting nuclear physician. A positive stress test was based on the findings of the nuclear physician with regard to abnormal ECG findings suggestive of ischaemia, with or without the development of accompanying symptoms. Further data from the MPI report included the development of symptoms during pharmacological or exercise stress. The data recorded with regard to perfusion scintigraphy included the presence and number of fixed perfusion defects and the presence and number of reversible perfusion defects. Information related to gated imaging were recorded and included the presence and number of segments displaying regional wall motion abnormalities of the LV at rest and during stress as well as the Left Ventricular Ejection Fraction (LVEF) at rest and at peak stress. Criteria for the diagnosis of suspected ILVD on the MPI study included the presence and extent of perfusion defects (reversible or fixed) as well as accompanying regional wall motion abnormality. Taking these variables into account, the nuclear physician reported the study as either being negative (NILVD) or positive (evidence of ischaemia or infarction). The positive studies were classified as ILVD by MPI.

2.4 Data recorded from the angiogram report

The reports of patients who underwent coronary angiography were analysed and the presence or absence of coronary artery disease was recorded. In patients with coronary artery disease the anatomical location and severity of lesions were recorded. Criteria for the diagnosis of ILVD was based on accepted criteria proposed by Felker et al. (angiographic luminal narrowing of $\geq$ 75% in 2 or more epicardial arteries, or $\geq$ 75% stenosis in the left main or proximal LAD and or a history of myocardial infarction or

revascularisation via CABG or PCI) [11]. If these criteria were not met, the patient was classified as NILVD.

2.5 Statistical Analysis

Data was captured in an Excel spreadsheet and analysed by Statistica. Results were presented by measures of mean, median and standard deviation. Continuous data was compared by a Students T-test. Categorical data was compared by Fishers exact test. Significance was observed at a p-value of < 0.05. Outcomes of the 2 tests (Angiogram and MPI using SPECT) were compared via sensitivity and specificity with the gold standard test being the angiogram. From this, a positive predictive value and negative predictive value was obtained with confidence intervals.

CHAPTER 3

3. Results

3.1 Clinical Characteristics

A total of 52 patients were included in the study. Coronary angiography identified 19 patients with NILVD and 33 with ILVD. No difference was noted between ILVD and NILVD with regard to age while a greater proportion of ILVD patients were male. The distribution of ILVD and NILVD was associated with ethnicity with a p-value of 0.0014. The diagnosis of ILVD was more common in Indian and White patients whereas in Black and Coloured patients, a similar proportion of patients had either ILVD or NILVD (Figure 3.2).

No differences were noted between the ILVD and NILVD groups with regard to the presence of hypertension, diabetes, obesity and family history. However, patients with ILVD were more likely to be smokers ($p=0.0001$), have dyslipidaemia ($p=0.03$), a prior history of ischaemic heart disease ($p<0.001$) and have a greater cumulative number of risk factors ($p<0.0001$) (Table 3.1).

Table 3.1: Patient demographics and Risk Factors

Characteristics:	NILVD: (n = 19)	ILVD: (n = 33)	P-value:
Age:	57.32±9.84	58.39±11.47	0.7245
Males:	9 (47.37%)	25 (75.76%)	0.04*
Females:	10 (52.63%)	8 (24.24%)	
Post-Menopausal:	9 (47.37%)	8 (15%)	0.09
Hypertension:	18 (94.74%)	25 (75.76%)	0.08
Diabetes:	6 (31.58%)	12 (36.36%)	0.73
Obesity:	9 (47.37%)	24 (72.73%)	0.7
Smoking:	4 (21.05%)	25 (75.76%)	0.0001*
Family History:	5 (26.32%)	11 (33.33%)	0.6
Hypercholesterolaemia:	4 (21.05%)	21 (63.64%)	0.003*
Known IHDs:	0 (0%)	30 (100%)	<0.0001*
Total Risk Factors:	3(±2)	5(±2)	< 0.0001*

Age is expressed as mean ± SD. Data are expressed as proportion and (%). Total risk factors is expressed as median and interquartile range. (*Significant)

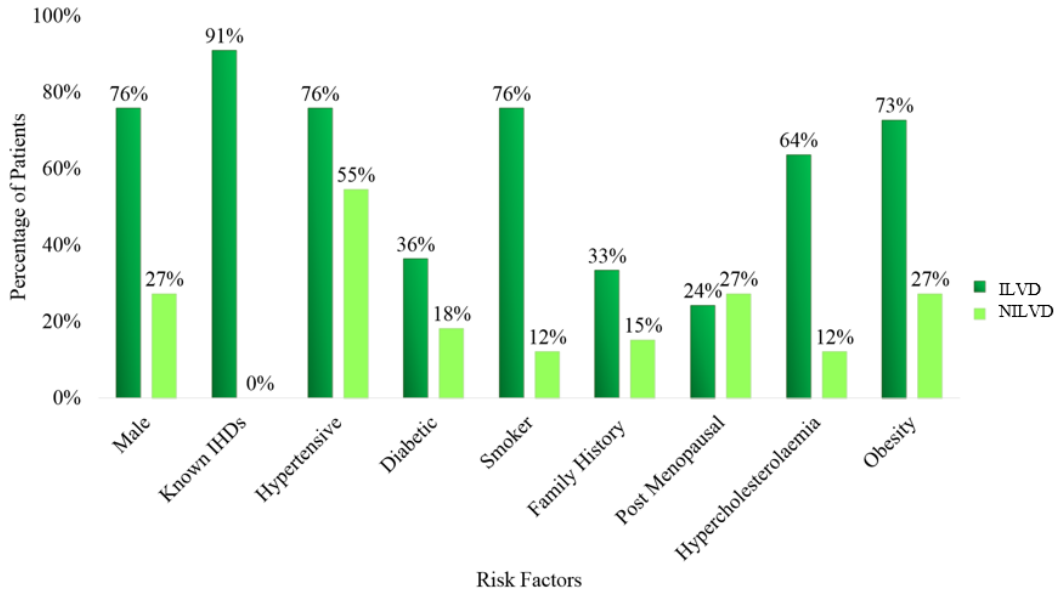


Fig 3.1: Atherosclerotic risk factor profile

3.2 ECG and Stress test findings

Evidence of infarction (Q waves) on the resting ECG was highly significant in predicting ILVD with a p-value of < 0.0001. Resting ST segment and T wave changes were not found to be good predictors of ILVD (p = 0.47). In this cohort, 30 (58%) patients underwent exercise stress MPI, 14 (27%) had only persantin stress MPI and 8 (15%) had both. A positive stress ECG did not predict ILVD (p 0.61) (Table 3.2). The development of fatigue during stress occurred in both groups but chest pain occurred exclusively in the ILVD group while shortness of breath was more common in NILVD (Table 3.3, figure 3.3).

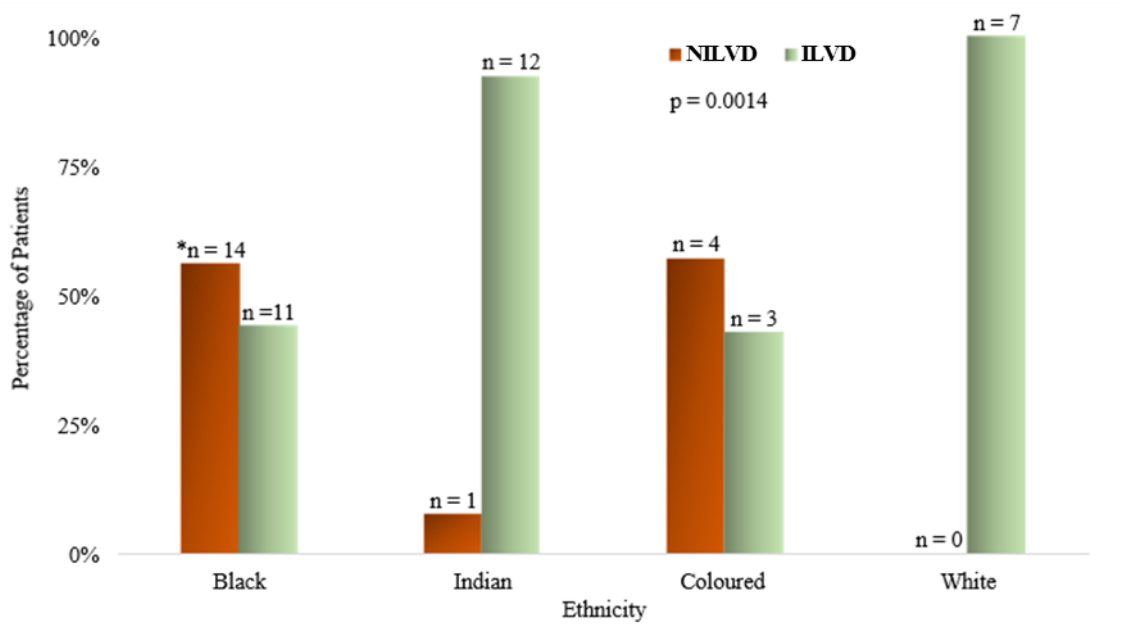


Fig 3.2: Ethnic Division in Each Group, *p < 0.01 Black vs. Indians

Table 3.2: ECG Results

	NILVD	ILVD	p-value
Resting ECG showing Infarction	0/19	18/33	<0.0001
Resting ECG showing ST and T wave abnormality	4/19	10/33	0.47
Positive Stress ECG	3/19	6/33	0.61

Table 3.3: Stress Symptoms between the two Groups

	NILVD (n = 19)	ILVD (n = 33)	p-value
SOB	1 (5.26%)	8 (24.24%)	0.08
Headache	2 (10.53%)	0 (0%)	0.13
Fatigue	9 (47.37%)	13 (39.4%)	0.58
Chest Pain	0 (0%)	6 (18.18%)	0.07

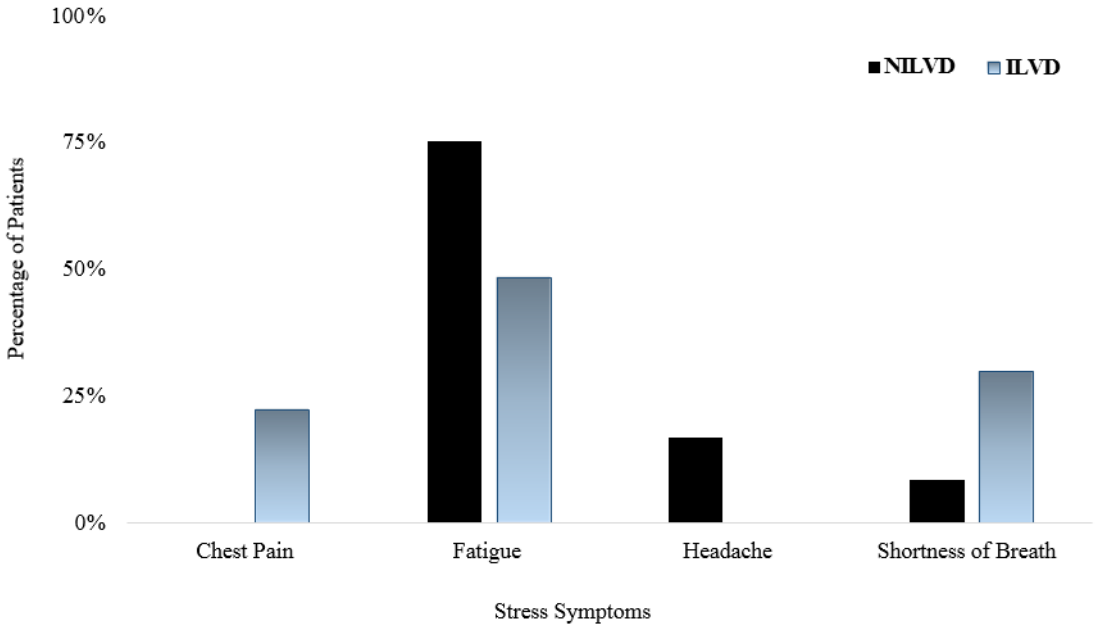


Fig 3.3: Comparison of Stress Symptoms between 2 Groups

3.3 SPECT MPI findings

Analysis of MPI revealed that ILVD patients had significantly more fixed perfusion defects compared to NILVD patients (Table 3.4 and figure 3.5). The presence of reversible perfusion defects were also more common in ILVD but this difference was not significant ($p = 0.4$). There was no difference between ILVD and NILVD groups with regard to regional wall motion abnormalities at rest and at stress.

3.4 Sensitivity and Specificity

According to the SPECT MPI, 10 patients were assessed to likely have NILVD and 42 ILVD. Myocardial perfusion imaging using SPECT had a sensitivity of 100% (95% CI 66-100%) and a specificity of 52.63% (95% CI 30.18-75.08%). The positive predictive value was 0.78 (95% CI 0.66 - 0.91) and the negative predictive value was 1 (95% CI 0.69 - 1) (Figure 3.4).

Table 3.4: MPI Results Table

	NILVD	ILVD	p-value
Reversible Perfusion Defects (RPD) (0 - 17)*	0(3)	2(4)	0.40
Fixed Perfusion Defects (FPD) (0 - 17)*	3 (5)	4 (3)	0.007
Regional Wall Motion Abnormalities (RWMA) (Stress) (0 - 17)*	5 (14)	7 (7)	0.75
RWMA (Rest) (0 - 17)*	5 (14)	7 (7)	0.98
Left ventricular ejection fraction (LVEF) (Stress) (%)#	25 (9)	24 (9)	0.88
LVEF (Rest) (%)#	25 (9)	24 (11)	0.88

Data* are expressed as median and interquartile range.
Data# are expressed as mean and standard deviation.
(0-17) denotes the number of involved segments according to standardised 17-segment model

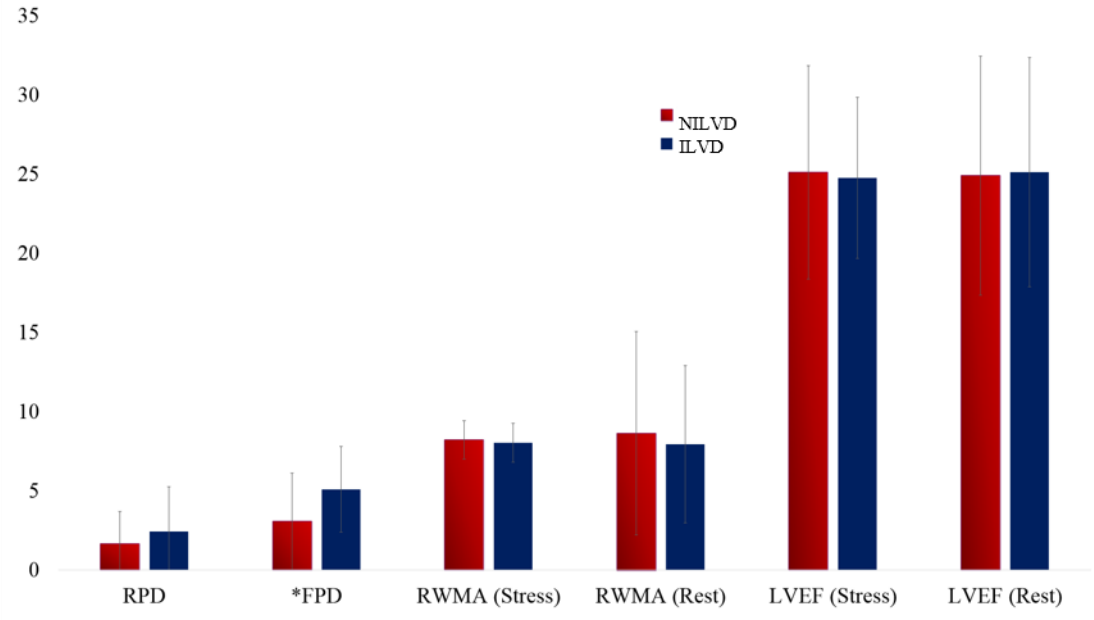


Fig 3.4: Summary of the MPI Results (*Significant)

Table 3.5: Sensitivity and Specificity of MPI

		Patients with IHD as confirmed on angiography		
		Condition Positive	**Condition Negative**	
Myocardial Perfusion Imaging Outcome	**Test Outcome Positive**	**True Positive** TP = 33	**False Positive** FP = 9	**Positive Predictive Value** =TP/(TP+FP) =0.7857 =78.57%
	Test Outcome Negative	**False Negative** FN = 0	**True Negative** TN = 10	**Negative Predictive Value** =TN/(FN+TN) = 1 = 100%
		Sensitivity =TP/(TP+FN) =1 =100%	**Specificity** =TN/(FP+TN) =0.5263 =52.63%	
		95% CI 66 - 100%	95% CI 30.18-75.08%	

CHAPTER 4

4. Discussion

4.1 Main findings

In this population of patients with heart failure and reduced ejection fraction, MIBI had a high sensitivity but a low specificity for differentiating ILVD from NILVD. The presence of fixed perfusion defects were indicative of ILVD but reversible perfusion defects and wall motion abnormalities were not. The high sensitivity of MPI makes it a useful screening test in patients with heart failure but a positive result needs to be confirmed with invasive coronary angiography.

The rationale for excluding coronary artery disease as the cause of HF-rEF is to identify patients in whom revascularisation will be of benefit. This benefit may relate to improvement of LVEF, reversal of heart failure and in some instances a survival benefit. Furthermore, patients with CAD benefit from strategies of secondary prevention which result in a reduction of recurrent MI. The latter is an important contributing factor to mortality in these patients. However, the distinction between coronary artery disease as the predominant cause of LV dysfunction and non-ischaemic LV dysfunction is challenging. In this study, we evaluated the differences in clinical, ECG and myocardial scintigraphic findings between patients with ILVD and NILVD. The major differences in the clinical and ECG characteristics of patients with ILVD vs NILVD in this study relates to three key areas — race, clustering of atherosclerotic risk factors and the presence of Q waves on the resting ECG. In addition, we found that MPI had a very high sensitivity but low specificity for the diagnosis of ILVD versus the gold standard.

4.2 Differences in Clinical Characteristics

ILVD was more common in Indians and White patients. This is expected since the prevalence of coronary risk factors and ischaemic heart disease are much higher in these populations. [28]. A second factor may well be that referral bias occurred. We speculate that race may have influenced referring physicians whereby Indian and white patients with a reduced EF were more likely to be referred to exclude CAD and thus underwent both MIBI and coronary catheterisation. Nevertheless, with the rising incidence of coronary disease in Black patients, it becomes imperative that the clinical suspicion and further investigation of the patients include tests to rule out myocardial ischaemia.

4.3 Differences in ECG findings

The finding that patients with ILVD had more Q waves is not unexpected. The presence of Q waves has traditionally been viewed as synonymous with transmural myocardial infarction and would be more likely to be found in patients with coronary artery disease causing a reduced EF. However, Q waves are not specific for myocardial ischaemia and have been reported in up to 26% of NILVD patients [29]. ECG abnormalities recorded at stress and at rest showed significant overlap between both groups of patients, which contributes to the diagnostic dilemma for the treating physician. Q wave formation on the ECG was more frequent in the ischaemic group and is a useful differentiating feature. The lack of difference between stress ECG findings is not unexpected although the development of chest pain had a trend towards distinguishing ILVD from DCMO ($p=0.07$). This may be a more significant finding if the study population was larger. Furthermore, while this finding only occurred in this study in 18.8% of patients with ILVD, none of the patients with DCMO developed chest pain.

4.4 SPECT MPI Findings

This study demonstrated that patients with ILVD had a greater number of fixed perfusion defects compared to patients with NILVD. Previous studies have shown that patients with ILVD may not have fixed perfusion defects and conversely, fixed defects on MPI may be seen in those with NILVD [23], [30], [31]. An understanding of MPI and the pathobiology of ischaemic left ventricular dysfunction serve to account for some of these shortcomings. Firstly, myocardial dysfunction in patients with coronary disease represents the summed effect of ischaemia, stunned and hibernating myocardium and irreversibly damaged myocardial scar [15], [30]. In patients with predominant and severe ischaemia and little infarction, MPI may not demonstrate a fixed perfusion defect. Furthermore, demonstration of abnormal perfusion of the myocardium by MPI is dependant on relative differences in uptake of the tracer by the tissue. Patients with global ischaemia may therefore not show perfusion defects resulting in a false negative study. On the other hand, many cardiac conditions other than ischaemia are accompanied by significant replacement fibrosis and may therefore give rise to false positive MPI perfusion defects. McCrohon et al demonstrated that 41% of DCMO patients had either sub-endocardial or mid-wall late gadolinium enhancement which reflect fibrosis. Similarly, at autopsy, patients with DCMO may have endocardial and transmural fibrosis which can be indistinguishable from myocardial infarction [31]. Another potential cause in severe left ventricular enlargement is due to attenuation artefact related to supine imaging [32], [33]. In addition, even in the absence of epicardial coronary abnormality, ischaemia may arise from microcirculation dysfunction and abnormal vasodilator reserve which has been well documented in these patients [23], [30], [31]. A further contributing factor in this study relates to the frequent presence of

hypertension in 94.74% and diabetes in 31.58% of the NILVD patients, both of which are associated with endothelial dysfunction and coronary microcirculation abnormality in the absence of flow limiting epicardial coronary disease

In this study, we could not demonstrate a significant difference in reversible perfusion defects between patients with ILVD and NILVD. This may reflect a relatively small sample size or alternatively a selection bias since these were patients presenting mainly with heart failure and low EF rather than with ischaemia or an acute coronary syndrome.

The presence of regional wall abnormality at rest or stress was also not significantly different between the two groups. Several factors could account for this. Firstly, analysis of wall motion abnormality is slightly more difficult and requires the careful acquisition of gated SPECT images. Patients with arrhythmia may pose a particular problem in this regard. However, none of the patients in this study had any arrhythmias. Secondly, progressive left ventricular remodeling following a myocardial infarction may result in a chamber that is globally dilated with the phenotype of a non ischaemic cardiomyopathy. Thirdly, many patients with NILVD have conduction abnormalities and may demonstrate segmental wall motion abnormalities that are not due to underlying ischaemia. In this study 8 patients showed left bundle branch block (LBBB) and 3 patients right bundle branch block (RBBB). Finally, regional wall abnormality at rest may also relate to several other factors including abnormal ventricular interaction due to right ventricular systolic overload and the presence of areas of focal fibrosis as a result of myocarditis.

The pathophysiology of resting fixed perfusion defects and resting regional wall abnormality in ischaemic heart disease occurs primarily due to infarction. However, the presence of fixed perfusion defects on nuclear scintigraphy may occur in DCMO patients because of areas of fibrosis.

Thus, the absence of perfusion abnormalities and regional wall abnormality at rest or stress would suggest the diagnosis of NILVD [30]. However, the presence of these factors cannot solely distinguish ILVD from NILVD. Our findings are in agreement with the findings of previous studies [22), (24), (25)]. One of the major limitations of this study with regard to perfusion and regional wall abnormality is that the reporting of these studies was performed by documenting the presence or absence of the abnormality in a binary fashion and counting the segments that were abnormal. Most recent studies in this field differ in their methodology with regard to the manner of image analysis [25, 30, 34)].

The ability of new software programs to offer a semi quantitative assessment of both perfusion and regional wall abnormality and the use of reporting these results in relation to predicted coronary territories has been used in several studies [30]. A 17-segment model was used and perfusion defects were expressed as summed stress, rest and reversibility perfusion defect scores in these studies. This allows for individual perfusion scores to be applied to each segment and graded as normal perfusion, mild, moderate or severe defects or absent perfusion at rest and during stress [25, 30, 34)]. Similarly, regional wall motion abnormality maybe graded on a scale of 0 - 5 (0 = normal, 1 = mild, 2 = moderate, 3 = severe, 4 = akinesia, 5 = dyskinesia). These semi

quantitative algorithms allow for a more robust way of reporting perfusion scores and regional wall abnormality. Several studies that utilised semi-automatic algorithms have demonstrated that ILVD patients are more likely to have more severe and more extensive perfusion and regional wall motion abnormalities resulting in higher summed scores than NILVD patients [33, 35]. This is also more suggestive of ILVD when interpreted in relation to coronary territory.

4.5 Sensitivity and Specificity of SPECT MPI using MIBI

The major finding in this study was that nuclear scintigraphy had a sensitivity of 100% with a specificity of 52% for the diagnosis of ICMO compared to the gold standard. The usefulness of this test was limited by the number of false positives that were identified. A screening test for medical conditions that are important and that would significantly change management strategies should be characterised by high sensitivity since a false negative result will have important adverse clinical consequences. Despite the low specificity of MPI in this study, the 100% sensitivity implies that it would be a useful screening test and obviate the need for invasive coronary angiography in many patients. This would have important economic implications especially in busy units where waiting lists for coronary angiography are long or in settings where a catheterisation laboratory is not available. The finding of a high sensitivity and a modest specificity are in keeping with other studies which used myocardial perfusion imaging to detect coronary artery disease in heart failure patients [25, 30].

We believe an important advantage of this study is that coronary angiography was used as the gold standard for the diagnosis of ILVD [7]. Apart from a few limitations, CA is regarded as the most accurate estimate of epicardial coronary disease. Firstly, there may

be concerns regarding the accuracy and reproducibility of the coronary stenosis measurement in the manner that was employed in this study (visual estimation of stenosis). Secondly, the physiological significance of a coronary lesion relates not only to the degree of stenosis of the coronary artery but to several other factors which include endothelial function, length of the lesion, presence or absence of collaterals and amount of myocardium subserved by the diseased vessels. Nevertheless, most experts and guidelines are in agreement regarding the value of coronary angiography for the diagnosis of ischaemic left ventricular dysfunction [(4)].

4.6 Study Limitations

1. This study was limited by being retrospective in design and not blinded.
2. There may have been a reporting bias associated with prior knowledge of angiogram or SPECT-MIBI study.
3. The sample size was small.

4.7 Conclusions

Ischaemic left ventricular dysfunction (ILVD) was more common in Indians and Whites and was associated with more cumulative risk factors for ischaemic heart disease compared to non-ischaemic left ventricular dysfunction (NILVD) patients. Patients with ILVD had a greater number of fixed perfusion defects but no difference with regard to reversible defects or regional wall abnormalities. In this population of patients, myocardial perfusion imaging (MPI) had a high sensitivity but a low specificity for the diagnosis of ILVD. The high negative predictive makes MPI a useful screening test to rule out coronary artery disease and reduces the need for further coronary angiography.

4.8 Recommendations

1. Tc-99m sestamibi SPECT MPI may be considered as a first line diagnostic strategy in excluding significant ischaemic heart disease in the heart failure population in whom the aetiology is uncertain.
2. Future prospective studies looking at the ability of SPECT-MPI in larger cohorts would be useful.

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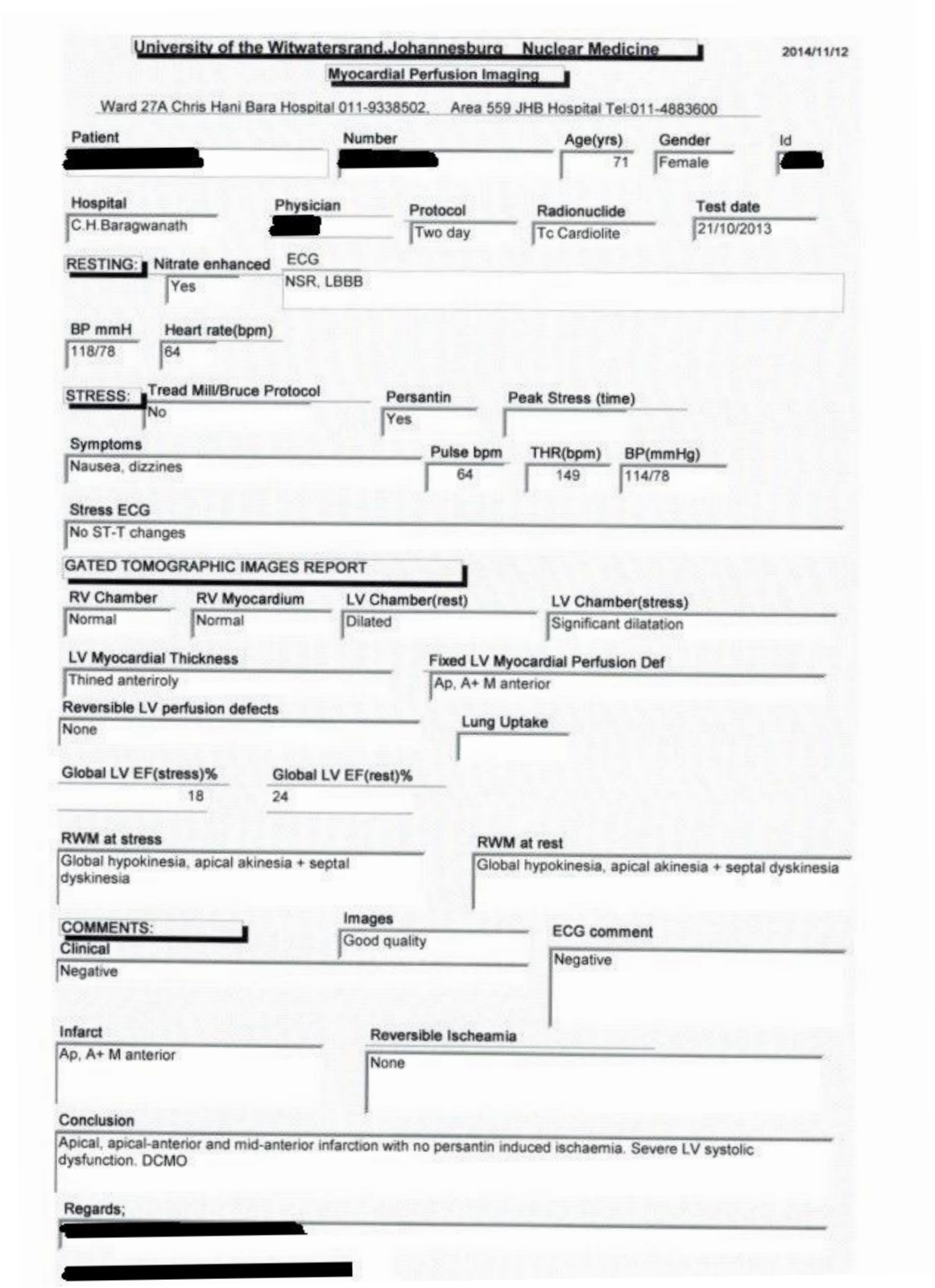
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APPENDIX A - Myocardial Perfusion Imaging



University of the Witwatersrand,Johannesburg Nuclear Medicine 2014/11/12

Myocardial Perfusion Imaging

Ward 27A Chris Hani Bara Hospital 011-9338502. Area 559 JHB Hospital Tel:011-4883600

Patient	Number	Age(yrs)	Gender	Id
[redacted]	[redacted]	71	Female	[redacted]

Hospital	Physician	Protocol	Radionuclide	Test date
C.H.Baragwanath	[redacted]	Two day	Tc Cardiolite	21/10/2013

RESTING: Nitrate enhanced: Yes; ECG: NSR, LBBB

BP mmH: 118/78; Heart rate(bpm): 64

STRESS: Tread Mill/Bruce Protocol: No; Persantin: Yes; Peak Stress (time):

Symptoms: Nausea, dizzines; Pulse bpm: 64; THR(bpm): 149; BP(mmHg): 114/78

Stress ECG: No ST-T changes

GATED TOMOGRAPHIC IMAGES REPORT

RV Chamber	RV Myocardium	LV Chamber(rest)	LV Chamber(stress)
Normal	Normal	Dilated	Significant dilatation

LV Myocardial Thickness: Thined anteriroly

Fixed LV Myocardial Perfusion Def: Ap, A+ M anterior

Reversible LV perfusion defects: None

Lung Uptake:

Global LV EF(stress)%: 18

Global LV EF(rest)%: 24

RWM at stress: Global hypokinesia, apical akinesia + septal dyskinesia

RWM at rest: Global hypokinesia, apical akinesia + septal dyskinesia

COMMENTS:

Images: Good quality

ECG comment: Negative

Clinical: Negative

Infarct: Ap, A+ M anterior

Reversible Ischeamia: None

Conclusion: Apical, apical-anterior and mid-anterior infarction with no persantin induced ischaemia. Severe LV systolic dysfunction. DCMO

Regards;

[redacted]

APPENDIX B - Diagnostic Coronary Angiography

CH BARAGWANATH CARDIAC UNIT

P.O. BERTSHAM JOHANNESBURG 2013 Ph: 0027-11-933 8197 Fx: 0027-11-938 8945 email:

CORONARY ANGIOGRAM REPORT

NAME: REFERRING MD:

AGE OPERATOR/S:
TEL NO

SEX: Male DATE:

HOSP.NO: CATN NO:

INDICATIONS DCMO
MIBI shows small area of infarction in RCA territory, no Ischaemia. However patient complains of CCII angina on medical therapy. Level of infarction out of keeping with level of LV dysfunction.
Risk factors: male, smoker, hypertensive
ECG: sinus, rate 80 BPM, poor R wave progression
Echo: EF 20%, functional MR, anterior mid and apical hypokinesia, right side normal
Results:FBC/U/E/INR normal
Current meds: Aspirin, Simvastatin, coversyl, Carloc, lasix, Aldactone, digoxin

PRE-MEDICATION:
DRUGS: None
CATHETERS: Diagnostic: 6F JL4, JR4, Pigtail

APPROACH: Rt Femoral artery
HEMODYNAMICS

	PRE-ANGIOPLASTY
HR:	85
AO (s/d/m):	114/90/102
LV (s/m/edp):	120/16/36

CORONARY ANGIOGRAPHY
OVERALL GOOD QUALITY VESSELS

- LEFT MAIN: normal, short
- LEFT ANTERIOR DESCENDING: normal
- CIRCUMFLEX: normal, non dominant
- RIGHT CORONARY: normal, dominant
- LEFT VENTRICLE: Omitted due to high EDP

CONCLUSIONS: DCMO. Antifailure therapy and follow up at DCMO clinic

Contrast: Jopamiron, 100ml

ARE ssop/15

APPENDIX C - Data Sheet

Data Sheet

Patient Number:

Age: **Sex:** M F

Race: Black White

Indian Coloured

Comorbid Disease:

Hypertensive: Diabetic:

History of MI: Smoker:

Other (specify):

ECG (Rest/Stress):

Sinus Rhythm (Yes/No):

Evidence of Previous Infarction - Q waves (Yes/No): If yes, Location:

Stress ECG showing Ischaemic changes - (Yes/No): If yes, Location:

Symptoms at stress present (Yes/No): If yes:

Headache: Fatigue:

Chest pain: Shortness of Breath:

MPI (SPECT) findings:

Reversible Perfusion Defects (1-17): Total number of affected areas:

Fixed Perfusion Defects (1-17): Total number of affected areas:

Wall Motion Abnormalities:

Areas (1-17): Total number of affected areas:

LVEF:

Angiogram Findings:

Significant CAD (>75% stenosis) (Yes/No):

Number of Stenotic Vessels (1,2,3):

LVEF:

APPENDIX D - Ethics Certificate



UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Alosha Singh

CLEARANCE CERTIFICATE	**M120535**
PROJECT	A Retrospective Analysis of the Utility of Myocadial Perfusion Imaging (MPI) using Single Photon Emission Computed Tomography (SPECT) For Differentiating Ischaemic from Non-Ischaemic Left Ventricular Dysfunction
INVESTIGATORS	Dr Alosha Singh
DEPARTMENT	Department of Family Medicine Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED	25/05/2015
DECISION OF THE COMMITTEE*	Approved unconditionally Title Change (08/03/2017)

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof M Essop

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in May and will therefore be due in the month of May each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

APPENDIX E – Permission Letter Nuclear Medicine

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DEPARTMENT OF HEALTH
CHRIS HANI BARAGWANATH
ACADEMIC HOSPITAL

DEPARTMENT OF RADIATION SCIENCES
DIVISION OF NUCLEAR MEDICINE
P.O BERTSHAM
JOHANNESBURG, 2013
PHONE: +2711 933 8502/9381
FAX: +2711 933 8227

21 August 2017

To: Whom it may concern

RE: Dr Alosha Singh Mmed

This letter serves to allow Dr Singh to utilize an image from our archive of a myocardial perfusion scan that was completed.

The patient's details have remained anonymous and therefore patient confidentiality was maintained.

Kind regards,

Dr Khushica Purbhoo
Specialist Nuclear Physician
Chris Hani Baragwanath Academic Hospital
+27 11 933 0843