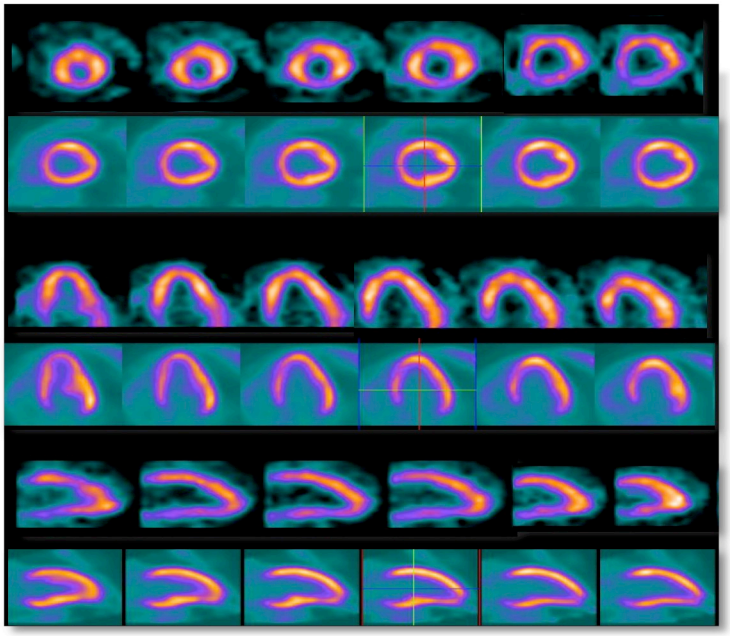
THE PREVALENCE OF MYOCARDIAL VIABILITY AS DETECTED BY ^{18}F-FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY



Dr Dineo Mpanya MBChB(UCT), FCNP(SA)

Professor Carlos Libhaber MD, FCNP(SA), PhD

Dr Nqoba Tsabedze MBBch(Wits), FCP(SA), Cert Cardio (SA)

Miss Brenda Kagodora, MSC

Professor Mboyo-Di-Tamba Vangu MD, MMed, MSC, PhD

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

Johannesburg, October 2017

CONTENTS PAGE

Declaration iii

Acknowledgements v

Nomenclature v

Research report 1-10

Appendices

a. Figure 1: Flow chart showing segment analysis 11
b. Table 1: Baseline characteristics 12
c. Table 2: Viable segments 15
d. Table 3: Multivariate logistic regression 17
e. Protocol 18
f. Ethical clearance certificate 28
g. Turnitin Report 29
h. Letter confirming submission from Journal 41

DECLARATION

I, Dineo Mpanya, declare that this research report is my own work. This research report is being submitted for the degree of Master of Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Dr Dineo Mpanya

11th day of October 20 17 in Parktown

Re: Dr. Dineo Mpanya
Student number: 878824
A0036448
MMed Nuclear Medicine

This letter serves to certify that Dr Dineo Mpanya has done her research in Nuclear Medicine. Her topic is: **The prevalence of myocardial viability as detected by ^{18}F-fluorodeoxyglucose positron emission tomography.**

She compiled and analysed the data herself with the assistance of a statistician and followed the protocol for her study accordingly.

The research report was entirely written by her with input from the co-authors.

Kind regards,

Professor MDTHW Vangu

Professor CD Libhaber

Dr NI Tsabedze

Miss Brenda Kagodora

ACKNOWLEDGEMENTS

I would like to express my gratitude to my supervisors Professors Vangu and Libhaber for the support, guidance and wisdom they imparted to me. I am humbled by the support from my family and friends.

NOMENCLATURE

FDG: Fluorodeoxyglucose

PET: Positron Emission Tomography

SPECT: Single Photon Emission Tomography

MBq: Megabecquerel

ABSTRACT

Background: Positron Emission Tomography (PET) is an imaging modality that guides the revascularization management of patients with left ventricular systolic dysfunction secondary to coronary artery disease. Segments of the myocardium demonstrating reduced perfusion and increased or preserved ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) uptake are considered to be viable and thus suitable for revascularization. The aim of our study was to determine the prevalence of myocardial viability as determined by FDG-PET in our local cohort and to compare our prevalence of myocardial viability to data published elsewhere.

Methods: We retrospectively reviewed 240 consecutive ^{99m}Tc-sestamibi myocardial perfusion Gated Single Photon Emission Tomography (SPECT) and ^{18}F-FDG PET reports of patients referred for evaluation of myocardial viability between January 2009 and June 2015.

Results: 236 patients met the inclusion criteria. There were 194 (82.2%) males. The mean age was 59.1 (SD 11.0) years. A total of 4012 segments of the left ventricle were analyzed on the gated SPECT and reduced perfusion was noted in 1862 (46.4%) segments. Perfusion-metabolism mismatch (viable myocardium) was observed in 586 (31.5%) out of 1862 perfusion defects. The prevalence of myocardial viability in the study population was 61.4%. On the multivariate logistic regression model, aspirin intake [OR:0.37; CI:0.16-0.83; p=0.016] and hypertension [OR:0.26; CI:0.12-0.58; p=0.001] were associated with the presence of viable myocardium. Smoking was associated with the likelihood of having non-viable myocardium [OR:2.31; CI:1.01-5.29; p=0.048]

Conclusion: The prevalence of myocardial viability as detected by ^{18}F FDG PET in our local cohort is similar to prevalence rates reported in the developed world.

1. INTRODUCTION

The incidence of coronary artery disease in sub-Saharan Africa is on the rise (1). In the developed world, patients presenting with acute coronary syndromes have access to primary percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) timeously. This is not the case in sub-Saharan Africa, where a delay has been observed between the time of onset of chest pain to the

performance of coronary angiography (2). A need to assess for the presence of myocardial viability therefore exists in our clinical setting. A number of imaging modalities are available for assessment of myocardial viability, namely stress echocardiography, cardiac magnetic resonance imaging and Positron Emission Tomography (3).

Positron Emission Tomography identifies patients with myocardial contractile dysfunction secondary to ischaemic heart disease that is more likely to demonstrate an improvement in the left ventricular function after coronary revascularization (4). Myocytes exposed to reduced blood flow preferentially use glucose for cellular metabolism instead of free fatty acids (5). The rationale for using fluorodeoxyglucose (FDG), a glucose analogue, is to detect glucose utilization in areas of the myocardium with reduced perfusion. Areas of the myocardium with reduced perfusion and increased or preserved ^{18}F-FDG uptake are considered to represent viable tissue (6).

Johannesburg, the economic hub of Southern Africa has a population of approximately 4 million. The city covers an area of 1 645 km^2 (7). A vast majority of people in this region rely on public health services (7). In Johannesburg, there is only one public health centre equipped with PET.

The aim of our study was to determine the prevalence of myocardial viability as determined by ^{18}F-FDG PET in our local cohort and to compare our determined prevalence of myocardial viability to data published elsewhere. To the best of our knowledge, this is the first study investigating the prevalence of myocardial viability using Positron Emission Tomography in the sub-Saharan African region.

2. MATERIALS AND METHODS

2.1 Study Design and Population

We reviewed Gated Single Photon Emission Tomography (SPECT) myocardial perfusion and metabolic (cardiac PET) imaging reports of 240 consecutive patients referred for assessment of myocardial viability between January 2009 and June 2015. All patients had ischaemic heart diseases as evidenced by a clinical history of

myocardial infarction and or coronary angiography. All patients above 18 years who had both the resting perfusion study with ^{99m}Tc-sestamibi and metabolic imaging with ^{18}F-FDG PET were included in the study. The referral centres included the Charlotte Maxeke Johannesburg Academic Hospital, Chris Hani Baragwanath Academic Hospital and the Helen Joseph Hospital. These centres are all part of the clinical academic complexes of the University of the Witwatersrand. Ethics approval was sought from the University of the Witwatersrand Human Research Ethics Committee and relevant hospital authorities.

2.1.1 Resting Gated SPECT Myocardial Perfusion Data and Cardiac PET Data:

Prior to the acquisition of gated SPECT images, patients received an empiric dose between 555-1110 megabecquerels (MBq) of ^{99m}Tc-sestamibi intravenously. After a delay of approximately 60 minutes, supine myocardial perfusion images were acquired with a dual head gamma camera (General Electric Hawkeye; GE) equipped with a low energy high resolution collimator.

We reviewed resting myocardial perfusion reports and documented demographic data, risk factors for coronary artery disease, the status of the left ventricle chamber (normal or dilated), segments of the myocardium with evidence of perfusion defects, the resting left ventricular ejection fraction (LVEF) and evidence of regional wall motion abnormalities. A 17-segment model was used to document the presence of perfusion defects and both visual and quantitative analysis were used to report on the presence of perfusion defects. Patients with evidence of transmural perfusion defects demonstrating contractile dysfunction were selected for further imaging using Positron Emission Tomography.

Prior to the acquisition of cardiac PET images, patients were requested to fast overnight. On the day of the study, all patients received 25-75 g of dextrose monohydrate glucose powder (Medicolab) orally. This was done to stimulate the endogenous release of insulin, and thus enhance FDG uptake by the myocytes. Thereafter, an intravenous dose of ^{18}F-FDG between 185-370 MBq was administered. After a delay of approximately 45-60 minutes from the time of tracer injection, a Siemens Biograph Somaton Sensation 40 PET/CT camera was used for the acquisition of images. From the cardiac PET data, we documented the patients' serum glucose levels before and after oral glucose loading, and the presence of metabolic defects. We compared each segment with reduced

perfusion on Gated SPECT with cardiac PET findings to assess for perfusion-metabolism match or mismatch. Based on the conclusion available from the reports sent to the cardiologist, we classified patients into two groups, one group with evidence of viable segments of the myocardium and another group without any viable segments.

2.1.2 Coronary Angiography

Coronary angiography data was available in 145 (61.4%) patients. The data was obtained from study requisition forms, angiogram reports and patient discharge summaries. Where reported coronary angiography data was not available, the archived coronary angiogram cine images were retrieved and reviewed by an independent cardiologist, blinded to the myocardial viability results.

2.2 Statistical Analysis

The statistical analyses were generated using STATA MP version 13.0 (StataCorp, Texas). Normally distributed continuous variables were summarized as mean and standard deviation, whereas for the non-normally distributed data, the median and interquartile range was used. The Chi- square test was used to compare categorical variables. Both univariate and multivariate logistic regression analyses were done. We included the following parameters: age, gender, ethnicity, hypertension, diabetes mellitus, dyslipidaemia, smoking, family history of coronary artery disease, the size of the left ventricle lumen at rest, regional wall motion abnormalities and concomitant oral medication. Pearson's correlation was utilized to find a relationship between two groups. Differences were considered statistically significant at a p value of < 0.05. Confidence intervals were calculated at 95% interval levels.

3. RESULTS

The study population comprised of 236 patients. Out of 240 consecutive reports reviewed, four patients were excluded from the study. One patient had viability assessment performed after the administration of Thallium-201 chloride and another patient had a resting perfusion study done outside the academic sector. The other two patients had reports with inconclusive findings.

There were 194 (82.2%) males. The mean age was 59.1 (SD 11.0) years. The majority, 53.0% of the study population were classified as white and 30.1% were Indian. There were 32 (13.6%) study participants classified as black. Hypertension was the most common risk factor for coronary artery disease. This finding was observed in 48.3% of the participants. In this cohort, there were only 4 patients reported to have a history of infection with Human Immunodeficiency Virus (HIV) (Table 1).

Overall, 145 (61.4%) patients had evidence of viable myocardium and 55.5% of the patients had evidence of viability in more than 10% of the myocardium (17 segment model).

A total of 4012 segments of the left ventricle were analyzed for the presence of perfusion defects. Reduced perfusion was noted in 1862 (46.4%) segments. A perfusion-metabolism mismatch (viable myocardium) pattern was evident in 586 out of 1862 segments (31.5%). The basal inferoseptal (p=0.021) and mid inferior (p=0.030) segments were the only two segments associated with the presence of viable myocardium (Table 2). Seventy percent of the patients in the study population had a dilated left ventricle at rest.

The mean resting LVEF on Gated SPECT was 28.9% (SD 11.4) One hundred and sixty-eight (71.2%) patients had a resting LVEF less than or equal to 35% and 19.9% had a LVEF between 36-49%. There were 15 patients with normal resting LVEF. The LVEF was not available in 6 patients, due to gating errors. Global hypokinesia was observed in 52.2%, akinesia in 27.5% and dyskinesia in 34.0%. The dyskinetic segments were seen in 70.0% of patients with resting LVEF less than or equal to 35%.

Angiographic data was available in 145 (61.4%) patients. Sixty (41.4%) had triple vessel disease, 37.9% had double vessel disease and 20.7% had single vessel disease. The left anterior descending artery was diseased in 54.2%, the right coronary artery in 48.7% and the left circumflex in 31.4%.

One hundred and three patients (43.6%) were taking oral beta-blocker medication, 40.3% were on statins, 26.3% were on calcium antagonists, 19.1% were on oral nitrates and 42.0% were taking aspirin.

Multivariate logistic regression analyses showed an association between aspirin intake [OR:0.37; CI:0.16-0.83; p=0.016] and the presence of viable myocardium. An association was also noted between hypertension [OR: 0.26; CI:0.12-0.58; p=0.001] and the presence of myocardial viability. Smoking was associated with the likelihood of having non-viable myocardium [OR: 2.31; CI:1.01-5.29; p=0.048] (Table 3).

4. DISCUSSION

The prevalence of myocardial viability in our local cohort is similar to prevalence rates reported in the developed world. This is despite limited access to resources in our clinical setting. Schinkel et al. assessed the prevalence of myocardial viability in a population in Netherlands and reported a prevalence of 61% (8). The matching prevalence rates are likely related to the comparable patient characteristics such as the mean age, the predominance of white race in our cohort and the proportion of patients with a LVEF less than or equal to 35%. Similarly, Auerbach et al. reported a prevalence of 55% elsewhere in the developed world (9).

Hypertension was the most common risk factor for coronary artery disease. We noted that patients with hypertension were more likely to have viable myocardium. The hypertrophied heart, which is commonly seen in hypertensive patients has been found to demonstrate an impairment in energy metabolism, which may manifest as increased glucose utilization and glycolysis (10). Furthermore the sub-endocardial region of the myocardium in hypertensive patients is prone to ischaemia as a result of a blunted or absent coronary vasodilatory reserve (11). We hypothesize that this region could possibly hibernate and survive on less oxygen supply, thus protecting it in the event of occlusive coronary artery disease.

Smoking is another well-established independent risk factor for cardiovascular disease. Our study demonstrated that smokers were twice as likely to have non-viable myocardium. This finding enforces the need to implement smoking cessation programs in smokers with coronary artery disease, more importantly before any revascularization techniques. There was no association between the presence of non-viable myocardium and diabetes mellitus, dyslipidaemia and a family history of coronary artery disease.

The contribution of the Human Immunodeficiency virus to the burden of coronary artery disease in sub-Saharan Africa remains relatively small (12). In our study, there were only 4 (1.7%) patients with HIV. To the best of our knowledge, there has been no study demonstrating a higher prevalence of coronary artery disease in patients with HIV in South Africa despite a growing volume of data confirming this association in the developed world (13, 14).

This study has supported the benefit of Aspirin intake in patients known with coronary artery disease. Aspirin prevents arterial thrombosis and the occurrence of serious vascular events (15). In our study, patients taking Aspirin were more likely to have viable myocardium, compared to patients not on Aspirin.

In our resource-poor setting, it would have been ideal to find parameters on Gated SPECT myocardial perfusion imaging that could allow us to select patients for further imaging with PET. This study failed to demonstrate parameters on perfusion imaging that could independently predict the presence of viable myocardium. Nevertheless, we noted that the basal inferoseptal and mid inferior segments were more likely to have viable myocardium.

The main limitation of this study is its retrospective nature. Data was collected from clinical records and imaging reports. Some of the important risk factors associated with coronary artery diseases such as obesity, could not be assessed. Secondly, the inter-observer variability among the Nuclear Physicians in our department may have also affected the imaging findings documented on the imaging reports. Lastly, the presence of viable myocardium was solely considered on the observation of the perfusion-metabolism mismatch pattern. An ideal end-point would have been a prospective follow-up of these patients to establish how many had an improvement in their anginal symptoms and or left ventricular systolic function following revascularization if done.

5. CONCLUSION

The prevalence of myocardial viability as detected by ^{18}F FDG PET in our local cohort is 61.4%. This suggests that two-thirds of our population could potentially benefit from revascularization. This finding supports the clinical utility of PET in our setting.

6. ACKNOWLEDGEMENTS

The authors would like to thank Professor Jonathan Levin for assistance, the Head of the Division of Epidemiology and Biostatistics in the School of Public Health at the University of the Witwatersrand. We also acknowledge the support from staff members at the Department of Nuclear Medicine and Molecular Imaging department at Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Academic Hospital.

7. REFERENCES

1. Onen CL. Epidemiology of ischaemic heart disease in sub-Saharan Africa. Cardiovasc J Afr. 2013;24(2):34-42.
2. Tsabedze N, McCutcheon K, Mkhwanazi L, Garda R, Vachiat A, Ramjee R, et al. Periprocedural myocardial infarction during percutaneous coronary intervention in an academic tertiary centre in Johannesburg. Int J Cardiol. 2017;230:175-80.
3. Allman KC. Noninvasive assessment myocardial viability: current status and future directions. J Nucl Cardiol. 2013;20(4):618-37; quiz 38-9.
4. Orlandini A, Castellana N, Pascual A, Botto F, Cecilia Bahit M, Chacon C, et al. Myocardial viability for decision-making concerning revascularization in patients with left ventricular dysfunction and coronary artery disease: a meta-analysis of non-randomized and randomized studies. Int J Cardiol. 2015;182:494-9.
5. Kobylecka M, Maczewska J, Fronczewska-Wieniawska K, Mazurek T, Plazinska MT, Krolicki L. Myocardial viability assessment in 18FDG PET/CT study (18FDG PET myocardial viability assessment). Nucl Med Rev Cent East Eur. 2012;15(1):52-60.
6. Misko J. Evaluation of myocardial perfusion and viability in coronary artery disease in view of the new revascularization guidelines. Nucl Med Rev Cent East Eur. 2012;15(1):46-51.
7. Statistics South Africa. Available at: http://www. statssa.gov.za. Accessed June 10, 2017.
8. Schinkel AF, Bax JJ, Sozzi FB, Boersma E, Valkema R, Elhendy A, et al. Prevalence of myocardial viability assessed by single photon emission computed tomography in patients with chronic ischaemic left ventricular dysfunction. Heart. 2002;88(2):125-30.
9. Auerbach MA, Schoder H, Hoh C, Gambhir SS, Yaghoubi S, Sayre JW, et al. Prevalence of myocardial viability as detected by positron emission tomography in patients with ischemic cardiomyopathy. Circulation. 1999;99(22):2921-6.
10. Kolwicz SC, Jr, Tian R. Glucose metabolism and cardiac hypertrophy. Cardiovasc Res. 2011;90(2):194-201.
11. Strauer BE. The concept of coronary flow reserve. J Cardiovasc Pharmacol. 1992;19 Suppl 5:S67-80.

12. Sliwa K, Carrington MJ, Becker A, Thienemann F, Ntsekhe M, Stewart S. Contribution of the human immunodeficiency virus/acquired immunodeficiency syndrome epidemic to de novo presentations of heart disease in the Heart of Soweto Study cohort. Eur Heart J. 2012;33(7):866-74.
13. Paisible AL, Chang CC, So-Armah KA, Butt AA, Leaf DA, Budoff M, et al. HIV infection, cardiovascular disease risk factor profile, and risk for acute myocardial infarction. J Acquir Immune Defic Syndr. 2015;68(2):209-16.
14. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrinol Metab. 2007;92(7):2506-12.
15. Antithrombotic Trialists C. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324(7329):71-86.

Figure 1

Flow chart outlining left ventricular segment analysis

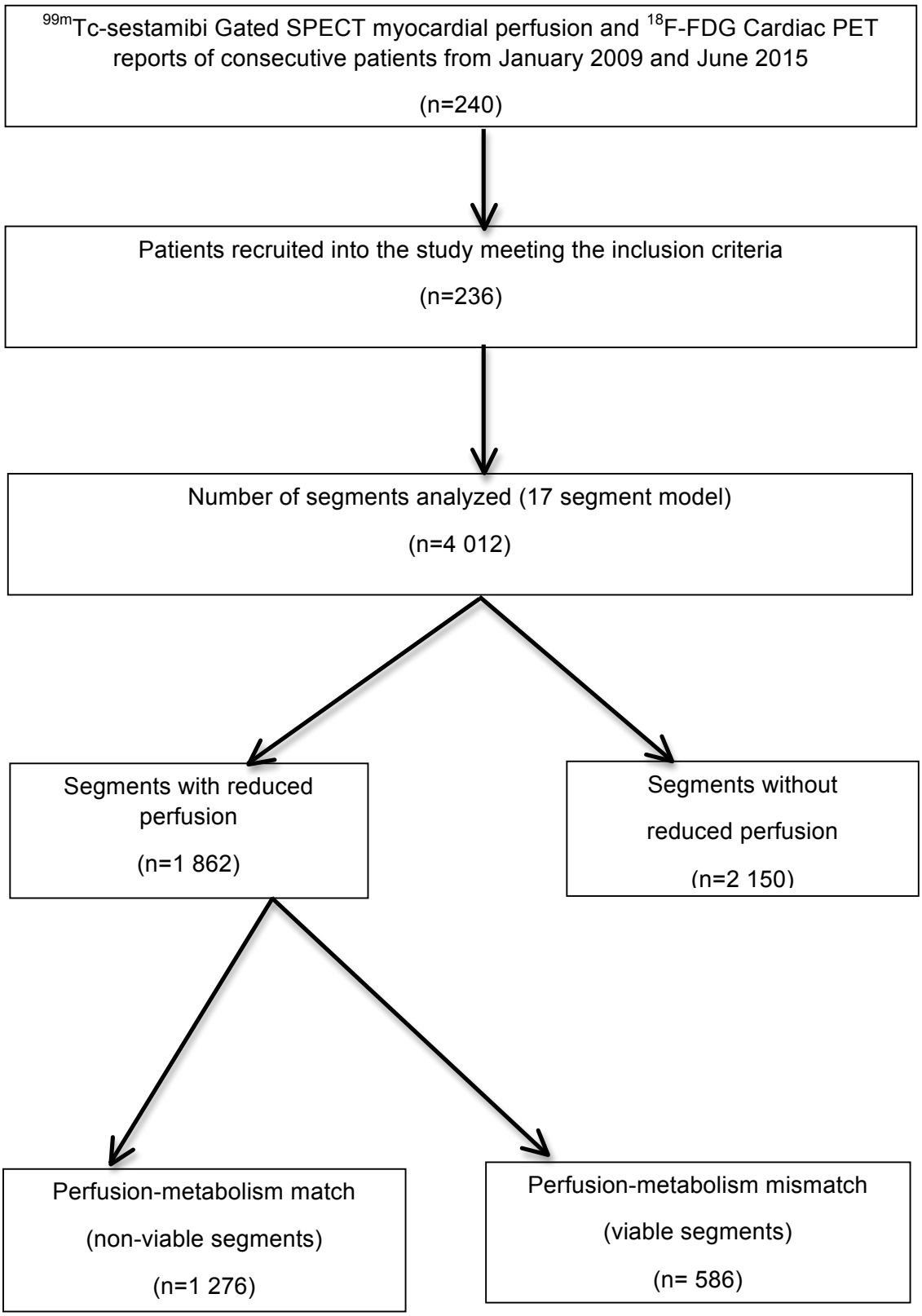


Table 1
Baseline characteristics of patients according to myocardial viability

Variable	Overall population (n=236)	Myocardial viability		p-value
		No (n=91) (38.6%)	Yes (n=145) (61.4%)	
Age (years)	59.1 SD 11.0	57.7 SD 11.4	60.0 SD 10.7	0.163
20-39	11 (4.7)	5 (5.5)	6 (4.1)	
40-49	36 (15.3)	16 (17.6)	20 (13.8)	
50-59	70 (29.7)	33 (36.3)	37 (25.5)	
60-69	78 (33.1)	22 (24.2)	56 (38.6)	
70+	41 (17.4)	15 (16.5)	26 (17.9)	
Male	194 (82.2)	75 (82.4)	119 (82.1)	0.524
Ethnicity:				0.164
White	125 (53.0)	56 (61.5)	69 (47.6)	
Indian	71 (30.1)	21 (23.1)	50 (34.5)	
Black	32 (13.6)	12 (13.2)	20 (13.8)	
Cardiovascular risk factors:				
Hypertension	114 (48.3)	33 (36.3)	81 (55.9)	0.003
Diabetes Mellitus	61 (25.9)	17 (18.7)	44 (30.3)	0.046
Dyslipidaemia	91 (38.6)	28 (30.8)	63 (43.5)	0.051

Smoking	91 (38.6)	34 (37.4)	57 (39.3)	0.765
Family history of CAD	58 (24.6)	17 (18.7)	41 (28.3)	0.096
HIV	4 (1.7)	2 (2.2)	2 (1.4)	0.635
Concomitant medication:				
Beta Blockers	103 (43.6)	29 (31.9)	74 (51.0)	0.004
Aspirin	99 (42.0)	27 (29.7)	72 (49.7)	0.002
Statins	95 (40.3)	27 (29.7)	68 (46.9)	0.009
ACE Inhibitor	76 (32.2)	24 (26.4)	52 (35.9)	0.129
Calcium Channel Blocker	62 (26.3)	19 (20.9)	43 (29.7)	0.136
Nitrates	45 (19.1)	13 (14.3)	32 (22.1)	0.138
Regional wall motion:				
Akinesia	65 (27.5)	29 (31.9)	36 (24.8)	0.239
Dyskinesia	80 (34.0)	24 (26.4)	56 (38.6)	0.053
Global hypokinesia	124 (52.5)	49 (53.9)	75 (51.7)	0.751
Resting LVEF (SPECT):	28.9 SD 11.4	27.1 SD 10.4	30 SD 11.8	0.123
LVEF ≥ 50	15 (6.4)	4 (4.4)	11 (7.6)	
LVEF = 41-49	25 (10.6)	5 (5.5)	20 (13.8)	
LVEF = 36-40	22 (9.3)	8 (8.8)	14 (9.7)	
LVEF ≤ 35	168 (71.2)	70 (76.9)	98 (67.6)	

Data are shown as mean, standard deviation (SD) for continuous variables and absolute numbers (percentage) for dichotomous variables.

CAD: coronary artery disease; ACE: HIV: Human Immunodeficiency Virus; Angiotensin Converting Enzyme; SPECT: single photon emission tomography; LVEF: left ventricular ejection fraction

Table 2
Segments with viable myocardium

Segment	Overall population (n=236)	Myocardial viability		p-value
		No (n=91) (38.6%)	Yes (n=145) (61.4%)	
Apex	187 (79.2)	67 (73.6)	120 (82.8)	0.092
Anterior wall:				
Apical anterior	163 (69.1)	60 (65.9)	103 (71.0)	0.409
Mid anterior	136 (57.6)	48 (52.8)	88 (60.7)	0.229
Basal anterior	55 (23.3)	17 (18.7)	38 (26.2)	0.183
Septal wall:				
Apical septal	121 (51.3)	49 (53.9)	72 (49.7)	0.531
Mid anteroseptal	132 (55.9)	48 (52.8)	84 (57.9)	0.435
Basal anteroseptal	91 (38.6)	30 (33.0)	61 (42.1)	0.162
Mid inferoseptal	111 (47.0)	39 (42.9)	72 (49.7)	0.308
Basal inferoseptal	100 (42.4)	30 (33.0)	70 (48.3)	0.021
Lateral wall:				
Apical lateral	79 (33.5)	26 (28.6)	53 (36.6)	0.206
Mid anterolateral	47 (19.9)	16 (17.6)	31 (21.4)	0.477
Basal anterolateral	29 (12.3)	8 (8.8)	21 (14.5)	0.195

Mid inferolateral	69 (29.2)	23 (25.3)	46 (31.7)	0.289
Basal inferolateral	70 (29.7)	23 (25.3)	47 (32.4)	0.243
Inferior wall:				
Apical inferior	194 (82.2)	75 (82.4)	119 (82.1)	0.946
Mid inferior	145 (61.4)	48 (52.8)	97 (66.9)	0.030
Basal inferior	133 (56.4)	45 (49.5)	88 (60.7)	0.090

Data shown as absolute numbers (percentage)

Table 3

Multivariable Logistic Regression Analysis
Independent predictors of myocardial viability

Variables	OR	95% CI	Z	p-value
Hypertension	0.26	0.12 – 0.58	-3.28	0.001
Diabetes mellitus	0.75	0.30 – 1.86	-0.62	0.534
Dyslipidaemia	0.94	0.41 – 2.18	-0.14	0.890
Smoking	2.31	1.01 – 5.29	1.98	0.048
Family history of CAD	0.81	0.32 – 2.02	-0.45	0.650
Aspirin	0.37	0.16 – 0.83	-2.40	0.016
Dyskinesia	0.50	0.23 – 1.07	-1.80	0.073

CAD; coronary artery disease

PREVALENCE OF MYOCARDIAL VIABILITY AS DETECTED BY 18F-FLUORO DEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY

Student: Dr Dineo Mpanya, Student No. 878824

Supervisor: Prof MDTHW Vangu – Chief Specialist and Head of Radiation Sciences, University of Witwatersrand. Head of Nuclear Medicine, Charlotte Maxeke Johannesburg Academic Hospital. MD, MMed, MSC, PhD

Co-supervisor:Prof CD Libhaber, Specialist Nuclear Physician, Cardiologist, Charlotte Maxeke Johannesburg Academic Hospital. MD, FCNP (SA), PhD

1. INTRODUCTION

The ability of cardiac myocytes to reduce the contractile function of the heart in states of chronic hypoperfusion after myocardial infarction, and recover after restoration of optimal blood flow is a well described phenomenon, with the coined term of “hibernating myocardium.” Coronary revascularization, either percutaneously or with coronary artery bypass grafting (CABG) of patients with hibernating myocardium has been associated with an improvement in anginal symptoms and symptoms of heart failure as well as a decline in the number of hospitalization of patients with heart failure secondary to chronic coronary artery disease [1]. The accurate identification of such patients is crucial.

The cardiology units at Charlotte Maxeke Johannesburg Academic Hospital, Chris Hani Baragwanath Academic Hospital and Helen Joseph Hospitals refer patients

who have had a myocardial infarction (MI) to the Department of Nuclear Medicine at Charlotte Maxeke Johannesburg Academic Hospital, which is the only public hospital in Johannesburg equipped with a Positron Emission Tomography (PET) scan, for assessment of myocardial viability.

Positron Emission Tomography identifies patients with myocardial contractile dysfunction, who are likely to demonstrate an improvement in the left ventricular ejection fraction after coronary revascularization. Hibernating cells, with reduced perfusion, preferentially use glucose for cellular metabolism instead of free fatty acids. Areas within the myocardium with increased or normal ^{18}F-Fluorodeoxyglucose (F18-FDG) uptake signify the presence of viable tissue [2].

Prior to acquisition of PET images, patients will initially have myocardial perfusion imaging, which is performed with a gamma camera using Gated Single Photon Emission Tomography (Gated SPECT). During a rest study, Technetium-99m methoxy-isobutyl-isonitrile (MIBI) is administered intravenously, as the name implies, under rest conditions. Subsequently, patients are imaged with a gamma camera using gated SPECT. The technetium labelled tracer enters the cardiac myocytes by passive diffusion and localize in the cytoplasmic mitochondria and thereafter remain fixed within the mitochondria [3].

In circumstances where the presence of myocardial ischaemia along with viability is questioned, an exercise stress test may be performed with a treadmill or with pharmacological agents that induce hyperaemia in coronary arteries or increase the rate of contractility. The visualization of perfusion defects on the perfusion images is subsequently followed by assessment of viability [4, 5,6].

In contrast to the technetium labelled tracers, Thallium-201, a radionuclide that is also employed when imaging with gated SPECT, requires intact cellular membrane integrity to be able to localize in the myocytes[7]. Thallium enters the myocytes via the Na^+/K^+ pump. It is on such basis that assessment of viability is achievable with Thallium. The disadvantages of using Thallium include lower photon energy of 80 keV, making it an unfavourable tracer in imaging obese patients due to soft tissue attenuation of the photons. Thallium also has a higher radiation burden, thus limiting the amount of administered dose to 1 mCi (37 MBq). This undoubtedly results in poor spatial resolution.

Positron emission tomography blood flow tracers are used to assess myocardial blood flow, prior to assessment of cellular metabolism. However, these tracers are used in centres equipped with on-site cyclotrons as they have short physical half-lives or require frequent replacement of generators producing these radionuclides. In a retrospective study involving 283 patients with ischaemic cardiomyopathy, referred for myocardial viability imaging with ^{13}N ammonia/^{18}F FDG PET, the prevalence of myocardial viability was 55% [8].

Other modalities available for the assessment of myocardial viability include echocardiography and cardiac magnetic resonance imaging (CMR) [7]. Two-dimensional echocardiography assesses myocardial viability by assessing the response of contractile function to ionotropic stimulation after administering a low dose Dobutamine infusion intravenously. Improvement of baseline contractile function after the infusion, signifies viable myocardium [9]. Other parameters on echocardiography that are used to assess viability of myocytes are wall thickness, mitral deceleration time and strain rate[7].

Cardiac Magnetic Resonance imaging, along with the use of either Dobutamine or Gadolinium can differentiate between viable and infarcted myocytes. Gadolinium is an extracellular molecule, which does not cross intact cellular membranes. However, in conditions that disrupt the cellular membrane, such as myocardial infarction, accumulation and reduced washout of Gadolinium is seen in the intracellular environment, a hallmark of infarcted tissue [10].

Petrucci et al in a prospective study, assessed areas of scar tissue in the myocardium manifesting as delayed Gadolinium enhancement on CMR with intracoronary electrograms recorded during percutaneous coronary intervention. They concluded that intracoronary electrograms, based on voltage amplitude, could discriminate between viable and non-viable myocardium [11].

Failure to perform coronary revascularization is associated with higher morbidity and mortality rates, in comparison to groups with viable myocardium who are treated with medical therapy. In a meta-analysis involving 3 088 patients, patients with viable myocardium, who were revascularized had an annual mortality rate of only 3.2% compared to those treated medically, with an annual mortality rate of 16% [12].

The CMJAH nuclear medicine unit performs cardiac PET scans for patients in the Johannesburg Metropolitan. However, our local prevalence rate of myocardial viability has never been determined.

STUDY OBJECTIVES

Primary objectives:

a) To estimate the prevalence of myocardial viability as determined by PET.

b) To compare our prevalence rate of myocardial viability to published data/literature.

Secondary objective:

c) To describe the characteristics of patients referred for myocardial viability imaging.

2. METHODS

3.1 Study Design

This is a retrospective review of Tc-99m sestamibi and F18-FDG PET cardiac reports of patients who were referred for myocardial viability assessment between January 2009 and June 2015 at Charlotte Maxeke Johannesburg Academic Hospital.

3.2 Study Population, sampling and protocol

This study will be conducted at the Department of Nuclear Medicine. Electronic version and hard copies, where available of the Tc-99m sestamibi and F18-FDG PET cardiac reports of the consecutive patients referred for assessment of myocardial viability will be reviewed. The sample size will be dependent on the total number of patients referred for myocardial viability assessment between January 2009 and June 2015. We usually see about 32 patients on a yearly basis. A minimum of 230 patients will be reviewed.

3.3 Inclusion Criteria

a) Age > 18 years

b) Patients that had both a rest ^{99m}Tc sestamibi and ^{18}F FDG PET scan performed for assessment of myocardial viability.

3.4 Exclusion Criteria

a) Studies with incomplete data or missing variables.

3.5 Materials

The following variables, which will appear on the Tc-99m sestamibi and F18-FDG PET cardiac reports and clerking notes, will be recorded on RedCap data collection sheet (see attached appendix).

3.5.1 Demographics

Age (years), gender, ethnicity, weight (kg) and height (cm)

3.5.2 Risk factors (for coronary artery disease) and Co-morbidities

The following conditions will be considered for analysis: Diabetes, Hypertension, Chronic kidney disease, HIV, Peripheral vascular disease, Dyslipidaemia, Family history of ischaemic heart disease, previous myocardial infarction, smoking, Asthma and Chronic obstructive airway disease.

3.5.3 Concomitant medication

B-blockers, aspirin, Angiotensin Converting Enzyme Inhibitors, Calcium channel blockers, nitrates and statins.

3.5.4 F18-FDG cardiac PET findings

We will document all the following parameters of the PET findings: dose of oral glucose administered, minutes between tracer injection and image acquisition, serum glucose levels, segments showing improvement on cardiac PET, % recoverable total myocardium and % recoverable infarcted area.

3.5.5 Tc-99m sestamibi myocardial perfusion imaging findings

Similar to PET findings, we will also document the following parameters for gated SPECT: radionuclide employed, nitrate enhancement, type of exercise stress test, resting and stress systolic and diastolic pressures, pharmacological agents used and changes in heart rate response, evidence of perfusion defects, left ventricular ejection fraction and evidence of regional wall motion abnormalities.

3.5.6 Angiographic findings

Angiographic findings pertaining to the diseased vessel will be documented.

3.6 Data management and analysis

Descriptive statistics-frequency tables will be used to describe demographic and clinical parameters. Multivariate analysis of risk factors will be done. Chi-test and Fisher's exact will be used to compare categorical variables. Continuous variables will be summarized as mean +/- SD of median and Inter quartile range for non-normality distribution of the data. Student t- test and Wilcoxon rank sum test will be

used. STATA version 11 will be used for the data analysis. 95% confidence interval will be calculated for all data.

4. ETHICS AND CONFIDENTIALITY

This study will be conducted at Charlotte Maxeke Academic Hospital in the Department of Nuclear Medicine in fulfilment of the requirements of the Masters in Medicine research report. Ethics approval will be sought from the University of Witwatersrand Human Research Ethics Committee and relevant hospital authorities. Unique patient identifiers will be used on the data collection sheet to protect the identity of the study participants. Outcomes will be published in a peer review journal and will be used to make recommendations whenever necessary, and/or required.

5. TIMING

TASKS	**PROPOSED COMPLETION DATE**
Protocol assessment	July 2015
Ethics Application	August 2015
Data Collection	August 2015 to September 2015
Data analysis	October to November 2015
Write up	December to January 2016

6. FUNDING

This study is a low cost research project. Funding will not be required.

Photocopying and printing cost will be paid by myself.

7. REFERENCES

1. Juergen vom Dahl CA, Florence H Sheehan, Petra Buechin, Germot Schulz. Effect of Myocardial Viability Assessed by Technetium-99m-Sestamibi SPECT and Fluorine- 18-FDG PET on Clinical Outcome in Coronary Artery Disease. *Journal of Nuclear Medicine* 1996; **38**(5).

2. Misko J. Evaluation of myocardial perfusion and viability in coronary artery disease in view of the new revascularization guidelines. *Nucl Med Rev Cent East Eur* 2012; **15**(1): 46-51.

3. Arrighi JA, Dilsizian V. Multimodality imaging for assessment of myocardial viability: nuclear, echocardiography, MR, and CT. *Curr Cardiol Rep* 2012; **14**(2): 234-43.

4. Matsunari I, Kanayama S, Yoneyama T, et al. Electrocardiographic-gated dual-isotope simultaneous acquisition SPECT using 18F-FDG and 99mTc-sestamibi to assess myocardial viability and function in a single study. *Eur J Nucl Med Mol Imaging* 2005; **32**(2): 195-202.

5. Slart RH, Bax JJ, van Veldhuisen DJ, van der Wall EE, Dierckx RA, Jager PL. Imaging techniques in nuclear cardiology for the assessment of myocardial viability. *Int J Cardiovasc Imaging* 2006; **22**(1): 63-80.

6. Tsai JP, Yun CH, Wu TH, et al. A meta-analysis comparing SPECT with PET for the assessment of myocardial viability in patients with coronary artery disease. *Nucl Med Commun* 2014; **35**(9): 947-54.

7. Allman KC. Noninvasive assessment myocardial viability: current status and future directions. *J Nucl Cardiol* 2013; **20**(4): 618-37.

8. Martin Allen Auerbach HS, Carl Hoh, Sanjiv Sam Gambhir. Prevalence of Myocardial Viability as Detected by Positron Emission Tomography in Patients With Ischemic Cardiomyopathy. *Circulation* 1999; **99**.

9. Bax JJ, Delgado V. Myocardial viability as integral part of the diagnostic and therapeutic approach to ischemic heart failure. *J Nucl Cardiol* 2015; **22**(2): 229-45.

10. Arai AE. The cardiac magnetic resonance (CMR) approach to assessing myocardial viability. *Journal of Nuclear Cardiology* 2011; **18**.

11. Petrucci E, Balian V, Bocchieri A. Real-time assessment of myocardial viability in the catheterization laboratory using the intracoronary electrograms recorded by the PTCA guidewire in patients with left ventricular dysfunction: comparison with delayed-enhancement magnetic resonance imaging. *JACC Cardiovasc Interv* 2014; **7**(9): 988-96.

12. Kevin C. Allman LJS, James E Udelson. Myocardial Viability Testing and Impact of Revascularization. *Journal of the American College of Cardiology* 2002; **39**(7).

R14/49 Dr Dineo Mpanya

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150801

NAME: (Principal Investigator) Dr Dineo Mpanya

DEPARTMENT: Nuclear Medicine
Charlotte Maxeke Johannesburg Academic Hospital

PROJECT TITLE: The Prevalence of Myocardial Viability as Detected by Flourine-18 Flurodeoxyglucose Positron Emission Tomography

DATE CONSIDERED: 28/08/2015

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Prof Mboyo-di-tamba Vangu

APPROVED BY: Professor P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 02/09/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature

Date 01/10/2016

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Turnitin Originality Report

Turnitin.docx by Dineo Mpanya

From Dineo Mmed (EhFmtqmOPj43B8ZnJrk8q050bw0c1d052wKT9eBpCJ1vmS4G67cHGrle2k4semvUnHE05MDbzGkTs9jWZSGgai4694FLm

- Processed on 18-Jun-2017 11:09 PM SAST
- ID: 825877722
- Word Count: 4111

Similarity Index
11%
Similarity by Source

Internet Sources:
5%
Publications:
9% Student Papers:
1%

sources:

1 2% match (publications)
Tsabedze, Nqoba, Keir McCutcheon, Lancelot Mkhwanazi, Riaz Garda, Ahmed Vachiat, Rohan Ramjee, Jameel Moosa, Themba Maluleke, Gloria Mukeshimana, Saffiyyah Karolia, Dineo Mpanya, and Pravin Manga. "Periprocedural myocardial infarction during percutaneous coronary intervention in an academic tertiary centre in Johannesburg", International Journal of Cardiology, 2016.

2 1% match (publications)
"Poster Presentations", European Journal of Nuclear Medicine and Molecular Imaging, 08/08/2009

3 1% match (Internet from 05-May-2014)
http://www.heartfailureguideline.org/_assets/document/Guidelines.pdf

4 1% match (publications)
V. Dunet. "Abstracts", European Heart Journal Supplements, 04/01/2011

5 < 1% match (publications)
"EANM'15", European Journal of Nuclear Medicine and Molecular Imaging, 2015.

6 < 1% match (publications)
"Poster Presentations", European Journal of Nuclear Medicine and Molecular Imaging, 10/2011

7 < 1% match (publications)
Atlas of Nuclear Cardiology, 2013.

8 < 1% match (Internet from 15-Aug-2015)
http://www.wits.ac.za/academic/health/academicprogrammes/21494/foreignpostgraduatestudies.html

9 < 1% match (publications)
Pinheiro Pessoa. "Assessment of Takotsubo (Ampulla) Cardiomyopathy Using Iodine-123 Metaiodobenzylguanidine Scintigraphy", Acta Radiologica, 12/1/2006

10 < 1% match (Internet from 29-Oct-2013)
http://www.wits.ac.za/academic/health/clinicalmed/orthopaedicsurgery/orthopaedics-home/9734/orthopaedics_home.html

11 < 1% match (Internet from 29-Dec-2016)
http://rc.rcjournal.com/content/60/1/81.full

12 < 1% match (publications)
Jan Manolas. "Noninvasive detection of coronary artery disease by assessing diastolic abnormalities during low isometric exercise", Clinical Cardiology, 03/1993

13 < 1% match (Internet from 08-Sep-2015)
http://www.tdx.cat/bitstream/handle/10803/31864/TSMF.pdf?sequence=1

14 < 1% match (publications)
C VITALE. "Trimetazidine improves left ventricular function and quality of life in elderly patients with coronary artery disease", European Heart Journal, 10/2004

15 < 1% match (Internet from 29-Mar-2017)
http://www.ors.org/Transactions/57/2186.pdf

16 < 1% match (Internet from 22-Oct-2015)
http://www.aasmnet.org/jcsm/ViewAbstract.aspx?pid=28945

17 < 1% match (Internet from 03-May-2015)
http://www.cyprusjcardiol.com/uploads/1/1/9/9/11996983/chaapter5.pdf

18 < 1% match (Internet from 14-Feb-2017)
http://www.mdpi.com/2072-6643/9/2/103/pdf

19 < 1% match (Internet from 10-Mar-2016)
http://dare.ubvu.vu.nl/bitstream/handle/1871/19587/dissertation.pdf?sequence=1

20 < 1% match (Internet from 29-Oct-2016)
https://issuu.com/hmpg/docs/samj-1603

21 < 1% match (publications)
McCarthy, P.M.. "Surgical Therapies for Post-Myocardial Infarction Patients", The American Journal of Cardiology, 20080908

22 < 1% match (Internet from 14-Feb-2017)
http://www.jove.com/visualize?author=Ad+J+J+C+Bogers

23 < 1% match (Internet from 16-Oct-2016)
https://cardiab.biomedcentral.com/articles/10.1186/1475-2840-13-70

24 < 1% match (Internet from 28-Sep-2016)
http://www.omicsonline.org/carotid-intima-media-thickness-in-african-patients-with-critical-lower-limb-ischemia-infected-with-the-human-immunodeficiency-virus-2155-6113.1000167.php?aid=8983

25 < 1% match (publications)
James T, Dominic Y. "Chapter 1 Utilization of Functional Tests Prior to and Adherence to Guidelines on Coronary Angiography", InTech, 2011

---

26 < 1% match (publications)
Angelini, A.. "Coronary arterial wall and atherosclerosis in youth (1-20 years): a histologic study in a northern Italian population", International Journal of Cardiology, 199009

---

27 < 1% match (publications)
Schoos, Mikkel M., Roxana Mehran, George D. Dangas, Jennifer Yu, Usman Baber, Peter Clemmensen, Frederick Feit, Bernard J. Gersh, Giulio Guagliumi, E. Magnus Ohman, Stuart J. Pocock, Bernhard Witzenbichler, and Gregg W. Stone. "Sex Differences in Associations Between Intraprocedural Thrombotic Events During Percutaneous Coronary Intervention and Adverse Outcomes (From the ACUITY and HORIZONS-AMI Trials)", The American Journal of Cardiology, 2016.

---

28 < 1% match (publications)
Geske, J. B., J. M. Bos, B. J. Gersh, S. R. Ommen, B. W. Eidem, and M. J. Ackerman. "Deformation patterns in genotyped patients with hypertrophic cardiomyopathy", European Heart Journal - Cardiovascular Imaging, 2014.

---

29 < 1% match (publications)
Abdel-Salam, Zainab, and Wail Nammas. "Preditores de viabilidade em pacientes com resposta negativa à ecocardiografia de estresse com dobutamina de baixa dose", Arquivos Brasileiros de Cardiologia, 2011.

---

30 < 1% match (publications)
"VYTORIN[R] (ezetimibe/simvastatin) Significantly Reduced Cardiovascular Events More than Simvastatin", Business Wire, Nov 17 2014 Issue

paper text:

Background:

2**Positron Emission Tomography (PET)** is **an imaging**

modality that guides the revascularization

7**management of patients with left ventricular** systolic **dysfunction** secondary to **coronary artery disease.**

Segments of the myocardium demonstrating reduced perfusion and increased or preserved 18F-Fluorodeoxyglucose (18F-FDG) uptake are considered to be viable and thus suitable for revascularization. The

2**aim of** our **study was to determine the prevalence of myocardial**

viability as determined by FDG-PET in an African population and to compare our prevalence of myocardial viability to data published elsewhere. Methods: We retrospectively reviewed 240 99mTc-sestamibi

2**myocardial perfusion Gated Single Photon Emission Tomography (SPECT)**

and 18F-FDG PET reports of patients referred for evaluation of myocardial viability between January 2009 and June 2015. Results: 236 patients met the inclusion criteria. There were 194 (82.2%) males. The mean age was 59.1 (SD 11.0) years. A total of 4012 segments of the left ventricle were analyzed on the gated SPECT and reduced perfusion was noted in 1862 (46.4%) segments. Perfusion-metabolism mismatch (viable myocardium) was observed in 586 (31.5%) out of 1862 perfusion defects. The prevalence of myocardial viability in the study population was 61.4%. On the multivariate logistic regression model, aspirin intake [OR:0.37; CI:0.16-0.83; p=0.016] and hypertension [OR:0.26;

6**CI:0.** 12 **-0.** 58; **p=0.** 001] **were associated with**

the presence of viable myocardium. Smoking was associated with the likelihood of having non-viable myocardium [OR:2.31; CI:1.01-5.29; p=0.048] Conclusion: The

3**prevalence of myocardial viability as detected by** 18F FDG PET **in**

our African cohort is similar to prevalence rates reported in the developed world. 1. INTRODUCTION The incidence of coronary artery disease in sub-Saharan Africa is on the rise (1). In the developed world,

30**patients presenting with acute coronary syndromes**

have access to primary

17**percutaneous coronary intervention (PCI)** and **coronary artery bypass grafting (CABG)** timeously. This **is** not **the**

case in sub-Saharan Africa, where a delay has been observed between the time of

1**onset of chest pain to the** performance **of coronary angiography**

(2). A need to assess for the presence of myocardial viability therefore exists in our clinical setting. A number of imaging modalities are available for assessment of myocardial viability, namely

3**stress echocardiography, cardiac magnetic resonance imaging** and **Positron Emission Tomography**

(3). Positron Emission Tomography identifies patients with myocardial contractile dysfunction secondary to ischaemic heart disease that is more likely to demonstrate an improvement in the left ventricular function after coronary revascularization (4). Myocytes exposed to reduced blood flow preferentially use glucose for cellular metabolism instead of free fatty acids (5). The rationale for using fluorodeoxyglucose (FDG) a glucose analogue, is to detect glucose utilization

14**in areas of** the **myocardium with reduced perfusion.**

14**Areas of** the **myocardium with reduced perfusion**

and increased or preserved 18F-FDG uptake are considered to represent viable tissue (6). Johannesburg, the economic hub of Southern Africa has a population of ~ 4 million. The city covers an area of 1 645 km2 (7). A vast majority of people in this region rely on public health services (7). In Johannesburg, there is only one public health centre equipped with PET. Despite this resource constraint, the majority of patients in Johannesburg requiring assessment of myocardial viability are imaged with PET. The

2**aim of** our **study was to determine the prevalence of myocardial**

viability as determined by 18F-FDG PET in an African population and to compare our determined prevalence of myocardial viability to data published elsewhere.

13**To the best of our knowledge, this is the first** systematic **study** investigating **the** prevalence **of**

myocardial viability using Positron Emission Tomography in an African cohort.

18**2. MATERIALS AND METHODS 2.1 Study Design and Population We**

reviewed

2**Gated Single Photon Emission Tomography (SPECT) myocardial perfusion**

and metabolic (cardiac PET) imaging reports of 240 consecutive patients

6**referred for assessment of myocardial viability**

6**between January** 2009 **and June** 2015. All **patients had**

ischaemic heart diseases as evidenced by a clinical history of 2 myocardial infarction and or coronary angiography. All patients above 18 years who had both the resting perfusion study with 99mTc-sestamibi and metabolic imaging with

5**18F-FDG PET were included in the study.**

The referral centres included

8**the Charlotte Maxeke Johannesburg Academic Hospital, Chris Hani Baragwanath Academic Hospital and the Helen Joseph Hospital.**

These centres are all part of the clinical academic complexes of the University of Witwatersrand. Ethics approval was sought

20**from the University of Witwatersrand Human Research Ethics Committee**

and relevant hospital authorities. 2.1.1 Resting Gated SPECT Myocardial Perfusion Data and Cardiac PET Data: Prior to the acquisition of gated SPECT images, patients received an empiric dose between 555-1110 megabecquerels (MBq) of 99mTc-sestamibi intravenously. After a delay of ~ 60 minutes, supine myocardial perfusion images were acquired with

9**a dual head gamma camera (General Electric** Hawkeye; GE) **equipped with a low energy high resolution collimator.**

We reviewed resting myocardial perfusion reports and documented demographic data,

2**risk factors for coronary artery disease,**

the status of the left ventricle chamber (normal or dilated), segments of the myocardium with evidence of perfusion defects, the resting left ventricular ejection fraction (LVEF) and evidence of regional wall motion abnormalities. A 17-segment model was used to document the presence of perfusion defects and both visual and quantitative analysis were used to report on the presence of perfusion defects. Patients with evidence of transmural perfusion defects demonstrating contractile dysfunction were selected for further imaging using Positron Emission Tomography. Prior to the acquisition of cardiac PET images, patients were requested to fast overnight. On the day of the study, all patients received 25-75 g of dextrose monohydrate glucose powder (Medicolab) orally. This was done to stimulate the endogenous release of insulin, and thus enhance FDG uptake by the myocytes. Thereafter, an intravenous dose of 18F-FDG between 185-370 MBq was administered. After a delay of ~ 45-60 minutes from the time of tracer injection, a Siemens Biograph Somaton Sensation 40 PET/CT camera was used for the acquisition of images. From the cardiac PET data, we documented the patient's 3 serum glucose levels before and after oral glucose loading, and the presence of metabolic defects. We compared each segment with reduced perfusion on Gated SPECT with cardiac PET findings to assess for perfusion-metabolism match or mismatch. Based on the conclusion available from the reports sent to the cardiologist, we classified patients into two groups, one group with evidence of viable segments of the myocardium and another group without any viable segments. 2.1.2 Coronary Angiography Coronary angiography data was available in 145 (61.4%) patients. The data was obtained from study requisition forms, angiogram reports and patient discharge summaries. Where reported coronary angiography data was not available, the original coronary angiogram was retrieved and reviewed from the angiography suite data archives by a qualified cardiologist.

1**2.2 Statistical Analysis** The **statistical analyses were generated using STATA** MP **version 13.** 0 **(StataCorp, Texas).** Normally distributed **continuous variables were** summarized **as mean** and **standard deviation**

whereas, for the non-normally distributed data, the

11**median and interquartile range** was used. **The Chi- square test was used to compare categorical variables.**

1**Both univariate and multivariate logistic regression analyses were** done. We included **the following parameters:**

age, gender, ethnicity, hypertension, diabetes mellitus, dyslipidaemia, smoking, family history

4of coronary artery disease, the size of the

left ventricle lumen at rest, regional wall motion abnormalities and concomitant oral medication. Pearson's correlation was utilized to find a relationship

15between two groups. Differences were considered statistically significant at a p value of <0.05.

Confidence intervals were calculated at 95% interval levels. 3. RESULTS The study population comprised of 236 patients. Out of 240 consecutive reports reviewed, four patients were excluded from the study. One patient had viability assessment performed after the administration of Thallium-201 chloride and another patient had a resting perfusion study done outside the academic sector. The other two patients had reports with inconclusive findings. 4 There were 194 (82.2%) males. The mean age was 59.1 (SD 11.0) years. The majority, 53.0% of the study population were classified as white and 30.1% were Indian. There were 32 (13.6%) study participants classified as black. Hypertension was the most common risk factor for coronary artery disease. This finding was observed in 48.3% of the participants. In this cohort, there were only 4 patients reported to have a history of infection with Human Immunodeficiency Virus (HIV) (Table 1). Overall, 145 (61.4%) patients had evidence of viable myocardium and 55.5% of the patients had evidence of viability in more than 10% of the myocardium (17 segment model). A total of 4012 segments of the left ventricle were analyzed for the presence of perfusion defects. Reduced perfusion was noted in 1862 (46.4%) segments. A perfusion-metabolism mismatch (viable myocardium) pattern was evident in 586 out of 1862 segments (31.5%). The basal

28inferoseptal (p=0. 021) and mid inferior (p=0.

030) segments were the only two segments associated with the presence of viable myocardium (Table 2). Seventy percent of the patients in the study population had a dilated left ventricle at rest. The mean resting LVEF on Gated SPECT was 28.9% SD 11.4. One hundred and sixty-eight (71.2%) patients had a resting LVEF less than or equal to 35% and 19.9% had a LVEF between 36-49%. There were 15 patients with normal resting LVEF. The LVEF was not available in 6 patients, due to gating errors. Global hypokinesia was observed in 52.2%, akinesia in 27.5% and dyskinesia in 34.0%. The dyskinetic segments were seen in 70.0% of patients with resting LVEF less than or equal to 35%. Angiographic data was available in 145 (61.4%) patients. Sixty (41.4%)

12had triple vessel disease, 37.9% had double vessel disease and 20.7% had single vessel disease. The

left anterior descending artery was diseased in 54.2%, the

26right coronary artery in 48.7% and the left circumflex in

31.4%. One hundred and three patients (43.6%) were taking oral beta-blocker medication, 40.3% were on statins, 26.3% were on calcium antagonists, 19.1% were on oral nitrates and 42.0% were taking aspirin. Multivariate logistic regression analyses showed an association between aspirin intake [OR:0.37; CI:0.16-0.83; p=0.016] and the presence of viable myocardium. An association was also noted between hypertension [OR: 0.26; CI:0.12-0.58;

16p=0.001] and the presence of myocardial viability. Smoking was associated

with the

likelihood of having non-viable myocardium [OR: 2.31; CI:1.01-5.29; p=0.048] (Table 3). 4. DISCUSSION The prevalence of myocardial viability in our African cohort is similar to prevalence rates reported in the developed world. This is despite limited access to resources in our clinical setting. Schinkel et al. assessed the prevalence of myocardial viability in a population in Netherlands and reported a prevalence of 61% (8). The matching prevalence rates are likely related to the comparable patient characteristics such as the mean age, the predominance of white race in our cohort and the proportion of patients with a LVEF less than or equal to 35%. Similarly, Auerbach et al. reported a prevalence of 55% elsewhere in the developed world (9). Hypertension was the most common risk factor for coronary artery disease. We noted that patients with hypertension

25were more likely to have viable myocardium. In patients with hypertensive heart disease,

the sub-endocardial region of the myocardium is prone to ischaemia as a result of a blunted or absent coronary vasodilatory reserve (10). Our hypothesis is that this region could possibly hibernate and survive on less oxygen supply, thus protecting it in the event of occlusive coronary artery disease. There is thus a requirement for prospective studies assessing the relationship between myocardial viability and hypertension in an African population. Smoking is another well-established independent risk factor for cardiovascular disease. Our study demonstrated that smokers were twice as likely to have non- viable myocardium. This finding enforces the need to implement smoking cessation programs in smokers with coronary artery disease, more importantly before any revascularization techniques. The contribution of the Human Immunodeficiency virus to the burden of coronary artery disease in sub-Saharan Africa remains relatively small (11). In our study, 6 there were only 4 (1.7%) patients with HIV.

27To the best of our knowledge, there has been no study

demonstrating a higher

4prevalence of coronary artery disease in patients with

HIV in South Africa despite a growing volume of data confirming this association in the developed world(12, 13). This study has supported the benefit of Aspirin intake in patients known with coronary artery disease. Aspirin prevents arterial thrombosis and the occurrence of serious vascular events (14). In our study, patients taking Aspirin were more likely to have viable myocardium, compared to patients not on Aspirin. In our resource-poor setting, it would have been ideal to find parameters on Gated SPECT myocardial perfusion imaging that could allow us to select patients for further imaging with PET. This study failed to demonstrate parameters on perfusion imaging that could independently predict the presence of viable myocardium. Nevertheless, we noted that the basal inferoseptal and mid inferior segments were more likely to have viable myocardium. The main limitation of this study is its retrospective nature. Data was collected from clinical records and imaging reports. The inter-observer variability among the Nuclear Physicians in our department may have also affected the imaging findings documented on the imaging reports. Also, the presence of viable myocardium was solely considered on the observation of the perfusion-metabolism mismatch pattern. An ideal end-point would have been a prospective follow-up of these patients to establish how many had an improvement in their anginal symptoms and or

29left ventricular systolic function following revascularization

if done. 5. CONCLUSION The

3prevalence of myocardial viability as detected by 18F FDG PET in

our African cohort is 61.4%. This suggests that two-thirds of our population could potentially benefit from revascularization. This finding supports the clinical utility of PET in our setting. The ability of cardiac myocytes to reduce the contractile function of the heart in states of chronic hypoperfusion after myocardial infarction, and recover after restoration of optimal blood flow is a well described phenomenon, with the coined term of “hibernating myocardium.” Coronary revascularization, either percutaneously or with coronary artery bypass grafting (CABG) of patients with hibernating myocardium has been associated with an improvement in anginal symptoms and symptoms of heart failure as well as a decline in the number of hospitalization

3of patients with heart failure secondary to chronic coronary artery disease

1. The accurate identification of such patients is crucial. The cardiology units

10at Charlotte Maxeke Johannesburg Academic Hospital, Chris Hani Baragwanath Academic Hospital and Helen Joseph

Hospitals refer patients who have had a myocardial infarction (MI)

5to the Department of Nuclear Medicine

at

24Charlotte Maxeke Johannesburg Academic Hospital, which is the only public hospital in Johannesburg

equipped with a

5Positron Emission Tomography (PET) scan, for assessment of

myocardial viability. Positron Emission Tomography identifies patients with myocardial contractile dysfunction, who

7are likely to demonstrate an improvement in the left ventricular ejection fraction after coronary revascularization.

Hibernating cells, with reduced perfusion, preferentially use glucose for cellular metabolism instead of free fatty acids. Areas within the myocardium with increased or normal 18F- Fluorodeoxyglucose (F18-FDG) uptake signify the presence of viable tissue 2. Prior to acquisition of PET images, patients will initially have myocardial perfusion imaging, which is performed with a gamma camera using

4Gated Single Photon Emission Tomography (Gated SPECT). During a rest study,

Technetium-99m methoxy-isobutyl-isonitrile (MIBI) is administered intravenously, as the name implies, under rest conditions. Subsequently, patients are imaged with a gamma camera using gated SPECT. The technetium labelled tracer enters the cardiac 8 myocytes by passive diffusion and localize in the cytoplasmic mitochondria and thereafter remain fixed within the mitochondria 3. In circumstances where the presence of myocardial ischaemia along with viability is questioned, an exercise stress test may be performed with a treadmill or with pharmacological agents that induce hyperaemia in coronary arteries or increase the rate of contractility. The visualization of perfusion defects on the perfusion images is subsequently followed by assessment of viability 4, 5,6. In contrast to the technetium labelled tracers, Thallium-201, a radionuclide that is also employed when imaging with gated SPECT, requires intact cellular membrane integrity to be able to localize in the myocytes7. Thallium enters the myocytes via the Na+/K+ pump. It is on such basis that assessment of viability is achievable with Thallium. The disadvantages of using Thallium include lower photon energy of 80 keV, making it an unfavourable tracer in imaging obese patients due to soft tissue attenuation of the photons. Thallium also has a higher radiation burden, thus limiting the amount of administered dose to 1 mCi (37 MBq). This undoubtedly results in poor spatial resolution. Positron emission tomography blood flow tracers are used to assess myocardial blood flow, prior to assessment of cellular metabolism. However, these tracers are used in centres equipped with on-site cyclotrons as they have short physical half-lives or require frequent replacement of generators producing these radionuclides. In a retrospective study involving 283 patients with ischaemic cardiomyopathy, referred for myocardial viability imaging with 13N ammonia/18F FDG PET, the prevalence of myocardial viability was 55% 8. Other modalities available for the assessment of myocardial viability include echocardiography and cardiac magnetic resonance imaging (CMR) 7. Two-dimensional echocardiography assesses myocardial viability by assessing the response of contractile function to ionotropic stimulation after administering a low dose Dobutamine infusion 9 intravenously. Improvement of baseline contractile function after the infusion,
signifies viable myocardium 9. Other parameters on echocardiography that are used to assess viability of myocytes are wall thickness, mitral deceleration time and strain rate7. Cardiac Magnetic Resonance imaging, along with the use of either Dobutamine or Gadolinium can differentiate between viable and infarcted myocytes. Gadolinium is an extracellular molecule, which does not cross intact cellular membranes. However, in conditions that disrupt the cellular membrane, such as myocardial infarction, accumulation and reduced washout of Gadolinium is seen in the intracellular environment, a hallmark of infarcted tissue 10. Petrucci et al in a prospective study, assessed areas of scar tissue in the myocardium manifesting as delayed Gadolinium enhancement on CMR with intracoronary electrograms recorded during percutaneous coronary intervention. They concluded that intracoronary electrograms, based on voltage amplitude, could discriminate between viable and non-viable myocardium 11. Failure to perform coronary revascularization

22**is associated with** higher **morbidity and mortality rates, in**

comparison to groups with viable myocardium who are treated with medical therapy.

21**In a meta-analysis involving 3 088 patients,** patients **with**

viable myocardium, who were revascularized had an annual mortality rate of only 3.2% compared to those treated medically, with an annual mortality rate of 16% 12. The CMJAH nuclear medicine unit performs cardiac PET scans for patients in the Johannesburg Metropolitan. However, our local prevalence rate of myocardial viability has never been determined. STUDY OBJECTIVES Primary objectives: 10 a) To estimate the prevalence of myocardial viability as determined by PET. b) To compare our prevalence rate of myocardial viability to published data/literature. Secondary objective: c) To describe the characteristics of patients referred for myocardial viability imaging. 2. METHODS 3.1 Study Design This is a retrospective review of Tc-99m sestamibi and F18-FDG PET cardiac reports of patients who were referred for myocardial viability assessment between January 2009 and June 2015 at Charlotte Maxeke Johannesburg Academic Hospital. 3.2 Study Population, sampling and protocol This study will be conducted at the Department of Nuclear Medicine. Electronic version and hard copies, where available of the Tc-99m sestamibi and F18- FDG PET cardiac reports of the consecutive patients referred for assessment of myocardial viability will be

reviewed. The sample size will be dependent on the total number of patients referred for myocardial viability assessment between January 2009 and June 2015. We usually see about 32 patients on a yearly basis. A minimum of 230 patients will be reviewed. 3.3 Inclusion Criteria a) Age > 18 years b) Patients that had both a rest 99mTc sestamibi and 18F FDG PET scan performed for assessment of myocardial viability. 3.4 Exclusion Criteria a) Studies with incomplete data or missing variables. 3.5 Materials The following variables, which will appear on the Tc-99m sestamibi and F18-FDG PET cardiac reports and clerking notes, will be recorded on RedCap data collection sheet (see attached appendix). 3.5.1 Demographics Age (years), gender, ethnicity, weight (kg) and height (cm) 3.5.2 Risk factors (for coronary artery disease) and Co- morbidities The following conditions will be considered for analysis: Diabetes, Hypertension, Chronic kidney disease, HIV, Peripheral vascular disease, Dyslipidaemia, Family history of ischaemic heart disease, previous myocardial infarction, smoking, Asthma and Chronic obstructive airway disease. 3.5.3 Concomitant medication B-blocker therapy 3.5.4 F18-FDG cardiac PET findings We will document all the following parameters of the PET findings: dose of oral glucose administered, minutes between tracer injection and image acquisition, serum glucose 12 levels, segments showing improvement on cardiac PET, % recoverable total myocardium and % recoverable infarcted area. 3.5.5 Tc-99m sestamibi myocardial perfusion imaging findings Similar to PET findings, we will also document the following parameters for gated SPECT: radionuclide employed, nitrate enhancement, type of exercise stress test, resting and stress systolic and diastolic pressures, pharmacological agents used and changes in heart rate response. 3.6 Data management and analysis Descriptive statistics-frequency tables will be used to describe demographic and clinical parameters. Multivariate analysis of risk factors will be done. Chi-test and

23**Fisher's exact** will be **used to compare categorical variables.**

Continuous variables will be summarized as mean +/- SD of median and Inter quartile range for non-normality distribution of the data. Student t- test and Wilcoxon rank sum test will be used. STATA version 11 will be used for the data analysis. 95% confidence interval will be calculated for all data. 99mTc-sestamibi Gated SPECT myocardial perfusion and 18F-FDG Cardiac PET PerfusioSPnea-mgtiemeNnteautsnbmtorsbeliewcsrrmiutohitmfesadetigcnmhtoetnhtes astnuadlyyzmeede(Pt1in7egrsfutehsgeimoinne-cnmltrueemsdtiaooubdncoeecllidir)sitmpeermirafuissmioantch (viable s(eng=m2e1n5t0s)) (norne-dviuacbeled speegrfmuseinotns) (n(n==4203162)) reports of consecutive patients from January 2009 and June 2015 Segments without (n=240) Table 1 Baseline

1**characteristics of patients according to myocardial** viability **Variable Overall population (n=** 236) **Myocardial** viability p-value **No (n=**

91) (38.6%) Yes (n=145) (61.4%) Age (years) 59.1 SD 11.0 57.7 SD 11.4 60.0 SD 10.7 0.163 20-39 11 (4.7) 5 (5.5) 6 (4.1) 40-49 36 (15.3) 16 (17.6) 20 (13.8) 50-59 70 (29.7) 33 (36.3) 37 (25.5) 60-69 78 (33.1) 22 (24.2) 56 (38.6) 70+ 41 (17.4) 15 (16.5) 26 (17.9) Male 194 (82.2) 75 (82.4) 119 (82.1) 0.524 Ethnicity: 0.164 White 125 (53.0) 56 (61.5) 69 (47.6) Indian 71 (30.1) 21 (23.1) 50 (34.5) Black 32 (13.6) 12 (13.2) 20 (13.8) Cardiovascular risk factors: Hypertension 114 (48.3) 33 (36.3) 81 (55.9) 0.003 Diabetes Mellitus 61 (25.9) 17 (18.7) 44 (30.3) 0.046 Dyslipidaemia 91 (38.6) 28 (30.8) 63 (43.5) 0.051 Smoking 91 (38.6) 34 (37.4) 57 (39.3) 0.765 Family history of CAD 58 (24.6) 17 (18.7) 41 (28.3) 0.096 HIV 4 (1.7) 2 (2.2) 2 (1.4) 0.635 Concomitant medication: Beta Blockers 103 (43.6) 29 (31.9) 74 (51.0) 0.004 Aspirin 99 (42.0) 27 (29.7) 72 (49.7) 0.002 Statins 95 (40.3) 27 (29.7) 68 (46.9) 0.009 ACE Inhibitor 76 (32.2) 24 (26.4) 52 (35.9) 0.129 Calcium Channel Blocker 62 (26.3) 19 (20.9) 43 (29.7) 0.136 Nitrates 45 (19.1) 13 (14.3) 32 (22.1) 0.138 Regional wall motion: Akinesia 65 (27.5) 29 (31.9) 36 (24.8) 0.239 Dyskinesia 80 (34.0) 24 (26.4) 56 (38.6) 0.053 Global hypokinesia 124 (52.5) 49 (53.9) 75 (51.7) 0.751 Resting LVEF (SPECT): 28.9 SD 11.4 27.1 SD 10.4 30 SD 11.8 0.123 LVEF ≥ 50 15 (6.4) 4 (4.4) 11 (7.6) LVEF = 41-49 25 (10.6) 5 (5.5) 20 (13.8) LVEF = 36-40 22 (9.3) 8 (8.8) 14 (9.7) LVEF ≤ 35 168 (71.2) 70 (76.9) 98 (67.6)

1**Data are shown as mean, standard deviation (SD) for continuous variables**

and absolute numbers (percentage) for dichotomous variables. CAD: **coronary**

artery disease; ACE: HIV: Human Immunodeficiency Virus; Angiotensin Converting Enzyme;

19**SPECT: single photon emission tomography; LVEF: left ventricular ejection fraction**

Table 2 Segments with viable myocardium Segment Overall population (n=236) Myocardial viability p-value No (n=91) (38.6%) Yes (n=145) (61.4%) Apex 187 (79.2) 67 (73.6) 120 (82.8) 0.092 Anterior wall: Apical anterior 163 (69.1) 60 (65.9) 103 (71.0) 0.409 Mid anterior 136 (57.6) 48 (52.8) 88 (60.7) 0.229 Basal anterior 55 (23.3) 17 (18.7) 38 (26.2) 0.183 Septal wall: Apical septal 121 (51.3) 49 (53.9) 72 (49.7) 0.531 Mid anteroseptal 132 (55.9) 48 (52.8) 84 (57.9) 0.435 Basal anteroseptal 91 (38.6) 30 (33.0) 61 (42.1) 0.162 Mid inferoseptal 111 (47.0) 39 (42.9) 72 (49.7) 0.308 Basal inferoseptal 100 (42.4) 30 (33.0) 70 (48.3) 0.021 Lateral wall: Apical lateral 79 (33.5) 26 (28.6) 53 (36.6) 0.206 Mid anterolateral 47 (19.9) 16 (17.6) 31 (21.4) 0.477 Basal anterolateral 29 (12.3) 8 (8.8) 21 (14.5) 0.195 Mid inferolateral 69 (29.2) 23 (25.3) 46 (31.7) 0.289 Basal inferolateral 70 (29.7) 23 (25.3) 47 (32.4) 0.243 Inferior wall: Apical inferior 194 (82.2) 75 (82.4) 119 (82.1) 0.946 Mid inferior 145 (61.4) 48 (52.8) 97 (66.9) 0.030 Basal inferior 133 (56.4) 45 (49.5) 88 (60.7) 0.090 Data shown as absolute numbers (percentage) Table 3

1**Multivariable Logistic Regression Analysis Independent predictors of myocardial** viability **Variables OR 95% CI Z**

p-value Hypertension 0.26 0.12 – 0.58 -3.28 0.001 Diabetes mellitus 0.75 0.30 – 1.86 -0.62 0.534 Dyslipidaemia 0.94 0.41 – 2.18 -0.14 0.890 Smoking 2.31 1.01 – 5.29 1.98 0.048 Family history of CAD 0.81 0.32 – 2.02 -0.45 0.650 Aspirin 0.37 0.16 – 0.83 -2.40 0.016 Dyskinesia 0.50 0.23 – 1.07 -1.80 0.073 CAD; coronary artery disease 1 5 7 11 13 14 15 16 17 18 19 20 21 22 23 24 25 26

Successfully received: submission The prevalence of myocardial viability as detected by Flourine-18 Fluorodeoxyglucose Positron Emission Tomography in patients referred for evaluation of appropriateness of coronary revascularization in Johannesburg for...

International Journal of Cardiology [EviseSupport@elsevier.com]
Sent: Tuesday, June 13, 2017 7:42 AM
To: Dineo Mpanya

This message was sent automatically. Please do not reply.

Ref: IJC_2017_2937

Title: The prevalence of myocardial viability as detected by Flourine-18 Fluorodeoxyglucose Positron Emission Tomography in patients referred for evaluation of appropriateness of coronary revascularization in Johannesburg

Journal: International Journal of Cardiology

Dear Dr. Mpanya,

Thank you for submitting your manuscript for consideration for publication in International Journal of Cardiology. Your submission was received in good order.

To track the status of your manuscript, please log into EVISE® at: http://www.evise.com/evise/faces/p ages/navigation/NavController.jspx?JRNL_ACR=IJC and locate your submission under the header 'My Submissions with Journal' on your 'My Author Tasks' view.

Thank you for submitting your work to this journal.

Kind regards,

International Journal of Cardiology

Have questions or need assistance?

For further assistance, please visit our Customer Support site. Here you can search for solutions on a range of topics, find answers to frequently asked questions, and learn more about EVISE® via interactive tutorials. You can also talk 24/5 to our customer support team by phone and 24/7 by live chat and email.
