ADVERSE REACTIONS TO PHARMACOLOGICAL AGENTS USED IN STRESS MYOCARDIAL PERFUSION IMAGING STUDIES: DIFFERENCES IN OLDER AND YOUNGER PATIENTS IN A SOUTH AFRICAN POPULATION COHORT

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University of Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree of
Master of Medicine
in the branch of Nuclear Medicine

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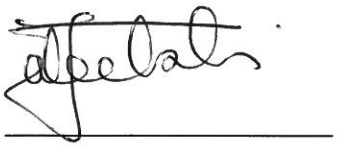
Declaration

I, Jaleelat Imoitseme Momodu declare that this Research Report is my own work. It is being submitted for the degree of Master of Medicine at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.



(Signature of candidate)

11 TH day of NOVEMBER 2020 in Johannesburg.

Dedication

My Lord, the Most Gracious, the Most Merciful.

Abubakar: My best friend, my rock. This wouldn't have been possible without your love, prayers, encouragement and support. Thank you for always believing in me.

Rashad and Adiba: My world. Thank you for understanding. I love you two immensely.

My parents and Abdul-Razak: Thank you for being there every step of the way. I am forever grateful for your prayers and support.

Abstract

Myocardial perfusion imaging (MPI) is a non-invasive nuclear medicine technique that plays a valuable role in the evaluation of coronary artery disease (CAD). In patients who are unable to tolerate exercise, pharmacological stress MPI with coronary vasodilators is widely used as an alternative to achieve coronary hyperemia.

This study aimed to assess age-related differences in patient tolerance to coronary vasodilators (adenosine and dipyridamole), as well as compare their side effect profiles in a South African population cohort. In addition, other factors that may influence tolerability to coronary vasodilators were identified.

Two hundred and sixty-four patients undergoing pharmacological stress MPI between August 2018 and November 2019 were prospectively observed for the development of adverse effects during or immediately after the intravenous vasodilator infusion. One hundred and forty seven patients (55.7%) received adenosine while 117 patients (44.3%) received dipyridamole. An age threshold of 60 years was used to divide the study population into two groups; <60 years (Group A) and $\geq$ 60 years (Group B).

Adverse effects occurred in 62.1% of the study population, majority of which were mild and moderate adverse effects and required no intervention. Only 3 patients (1%) developed severe adverse effects which required reversal with intravenous aminophylline. Older study participants (Group B) were 42% less likely to develop adverse effects compared to younger study participants (Group A) (OR = 0.58; 95% CI= 0.35-0.97; p=0.036). For adenosine, chest pain and dyspnea were the most common adverse effects in Group A and B, respectively. For dipyridamole, headache was the most common adverse effect in both age groups. Adenosine was three times as likely to cause adverse effects compared to dipyridamole (OR = 3.23; 95% CI= 1.93-5.43) (p<0.001). However, dipyridamole showed a higher propensity to cause higher grade adverse effects despite more participants receiving adenosine (p<0.001).

Pharmacological stress MPI with intravenous vasodilators is an overall safe method for assessing CAD. Side effects are more common in younger patients but are largely tolerable and resolve spontaneously after termination of the vasodilator infusion.

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Nomenclature and Abbreviations

1. ASNC: American Society of Nuclear Cardiology
2. BMI: Body mass index
3. CAD: Coronary artery disease
4. CHBAH: Chris Hani Baragwanath Academic Hospital
5. CHD: Coronary heart disease
6. CMJAH: Charlotte Maxeke Johannesburg Academic Hospital
7. COPD: Chronic obstructive pulmonary disease
8. DALYs: Disability-adjusted life years
9. ECG: Electrocardiogram
10. IAEA: International Atomic Energy Agency
11. IHD: Ischemic heart disease
12. INOCA: Ischemia and no obstructive coronary artery disease
13. MBF: Myocardial blood flow
14. MPI: Myocardial perfusion imaging
15. SISEs: Severe and intolerable side effects
16. SPECT: Single photon emission computed tomography
17. WHO: World Health Organization

Note: The terms “adverse effects” and “side effects” are used interchangeably throughout this research report.

CHAPTER ONE

1.0 INTRODUCTION

Coronary artery disease (CAD), which is also known as coronary heart disease (CHD), is characterized by the presence of obstructive atherosclerotic plaques in coronary vessels (1). A cascade of pathophysiological processes may either lead to vascular obstruction by a thrombus or a ruptured atherosclerotic plaque, resulting in reduced myocardial oxygen supply, manifesting as myocardial ischemia and angina (1,2). This definition recognizes a causal relationship between CAD and ischemic heart disease (IHD) and centers the diagnosis, risk assessment and treatment of IHD on the presence and severity of the atherosclerotic plaque (1). On this basis, CHD, CAD and IHD have generally been used interchangeably in the literature.

Contrary to this generally accepted concept, however, multiple studies have shown an increasing number of patients with IHD who do not have obstructed coronary arteries (3). This theory identifies atherosclerosis as a single factor in the complex pathophysiological process of IHD that includes inflammation, endothelial dysfunction, microvascular dysfunction, thrombosis and angiogenesis (3). Indeed, IHD can occur in the absence of CAD, a concept defined as ischemia and no obstructive coronary artery disease (INOCA) (4). This concept is yet to gain widespread clinical acceptance and is still undergoing studies (4).

For the purpose of this research report and based on general clinical practice, CAD, CHD and IHD are considered synonymous and will be referred to as CAD.

Coronary artery disease is a non-communicable disease with worldwide prevalence and significant global impact. The global distribution of CAD mortality in males and females is shown in figures 1.1 and 1.2 respectively (2). Global CAD burden is projected to rise from around 47 million disability-adjusted life years (DALYs) in 1990 to 82 million DALYs in 2020 (5). In low and middle income countries, mortality associated with CAD has been

rising in recent years (6). Lifestyle changes, urbanization and longevity are recognized as factors responsible for this trend (5).

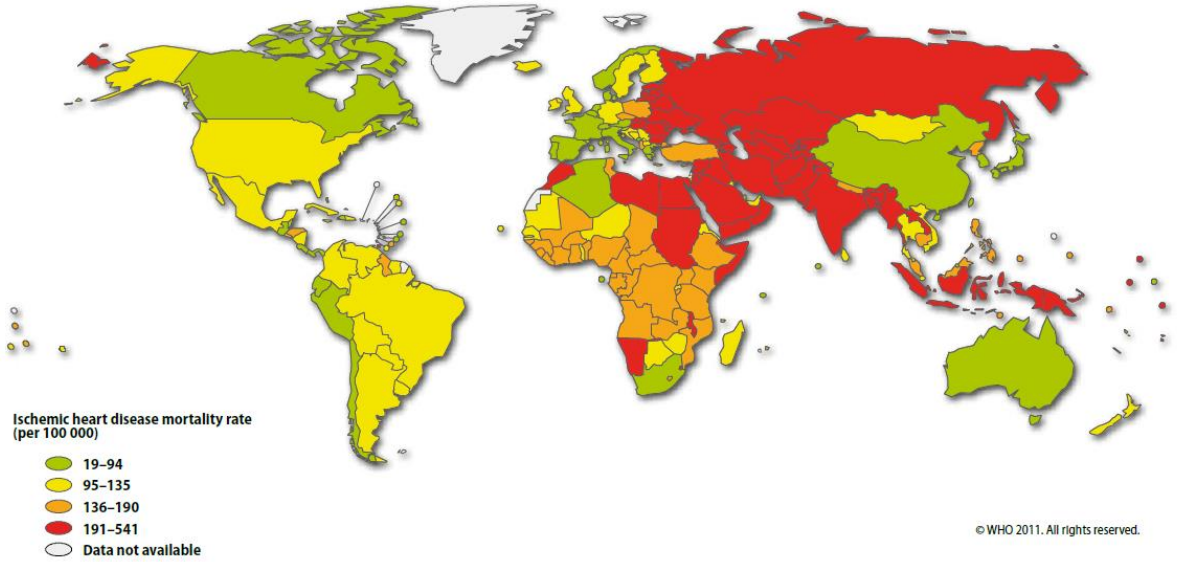


Figure 1.1 *Global distribution of coronary artery disease mortality rates in males [age standardized rates, per 100,000]*
From: WHO Global atlas on cardiovascular disease prevention and control

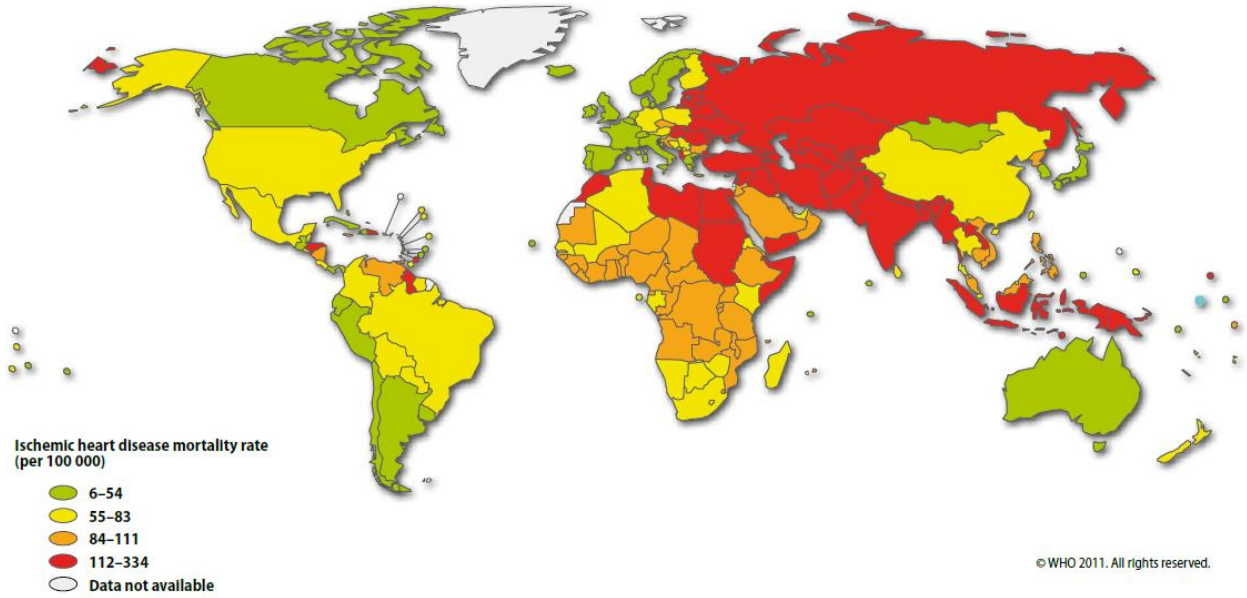


Figure 1.2 *Global distribution of coronary artery disease mortality rates in females [age standardized rates, per 100,000]*
From: WHO Global atlas on cardiovascular disease prevention and control

In South Africa, CAD was one of the ten leading causes of mortality between 2015 and 2017, accounting for 2.9% (12,766) of all deaths in 2017 (7). The prevalence is higher in people aged 65 years and above (7) and known risk factors for mortality include tobacco smoking, physical inactivity and unhealthy diets (5).

1.1 BACKGROUND

Myocardial perfusion imaging (MPI), a non-invasive nuclear medicine technique for assessing myocardial blood flow (MBF) plays a valuable role in the diagnosis, risk assessment and prognosis of CAD (8). Single photon emission computed tomography (SPECT) MPI is one of the most frequently performed nuclear cardiology investigations worldwide for the evaluation of confirmed or suspected CAD (9). In 2016, the International Atomic Energy Agency (IAEA) estimated that 15-20 million studies were performed annually globally and due to technological improvements and rising interest in early disease detection, the number of studies is expected to continue increasing globally (6).
MPI assesses the adequacy of cardiovascular flow reserve in response to hyperemia. In the hyperemic state, stenotic blood vessels are unable to dilate sufficiently to maintain coronary blood flow, resulting in a perfusion disparity between normal and diseased vessels (10).

Physical exercise (treadmill or ergometry) is the ideal method for inducing hyperemia as it provides additional clinical diagnostic information such as patient's exercise tolerance, hemodynamic response, heart rate recovery and electrocardiogram (ECG) changes during exercise (10). Maximal myocardial hyperemia depends on patient's ability to achieve at least 85% of the age-adjusted maximal predicted heart rate (220 beats per minute minus patient age), a workload of more than 5 metabolic equivalents and at least 3 minutes of exercise to completion of stage 1 of the standard Bruce protocol (11). Rate pressure product (heart rate x systolic blood pressure) may be applied as a surrogate marker for myocardial hyperemia and values >25,000mmHg/min indicate good hyperemia (11).

A high prevalence of CAD is noted in the elderly population who are more likely to have reduced exercise tolerance due to advanced age, severe debility and obesity (10). Other

factors that limit a patient's ability to tolerate exercise stress include: musculoskeletal diseases, peripheral vascular disease, severe pulmonary diseases, cardiac rhythm disturbances and medications (10). In these patients, intravenous pharmacological stress agents are the alternatives used to induce hyperemia (12).
Pharmacological stress agents include vasodilators (adenosine, dipyridamole, regadenoson) and inotropic agents such as dobutamine (11).
Vasodilator stress test, in particular is preferred in cases of cardiopulmonary limitations such as left bundle branch block and ventricular pacing, to reduce the chance of false positive MPI scans (13).

The safety profile, diagnostic and prognostic value of vasodilator MPI in different patient groups has been demonstrated and shown to be similar to exercise MPI (14–18). A review of the literature did not reveal any studies focused on the tolerability of vasodilator MPI in the South African patient population.

Records show that approximately 1000 SPECT MPI studies are performed annually in both nuclear medicine departments at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH). Of these, about 30-40% are pharmacological vasodilator stress tests and studies assessing MPI in general have been done in the local population from these institutions (19–21).

1.1.1 Mechanism of action of vasodilator stress agents

Adenosine

Adenosine causes a 3.5- to 4-fold increase in MBF by activating A2a receptors resulting in direct coronary arteriolar vasodilation (Figure 1.3) (22). The activation of A1, A2b and A3 receptors results in atrioventricular block (A1 receptor), peripheral vasodilation (A2b receptor) and bronchospasm (A2b and A3 receptors) which are responsible for the side effects of adenosine. Peak vasodilation occurs about 60-120 seconds after commencing the intravenous infusion. Because of its half-life of approximately 10 seconds, side effects are typically short-lived and resolve within a few seconds of stopping the infusion. Adenosine

either undergoes phosphorylation to adenosine monophosphate by adenosine kinase or is degraded to inosine by adenosine deaminase (22). The minor side effects of intravenous adenosine (flushing, chest pain, dyspnea, nausea and symptomatic hypotension) are common, occurring in up to 80% of patients (22). The more severe but very rare side effects – atrioventricular block, ST segment depression $\geq$ 1mm, fatal or non-fatal myocardial infarction and atrial fibrillation (22) will not be considered in this study.

Dipyridamole

Dipyridamole has an indirect coronary vasodilatory effect by inhibiting the intracellular reuptake and deamination of adenosine, resulting in increased tissue levels of adenosine and a 3.8- to 7-fold rise in MBF (Figure 1.3) (22). Peak vasodilation occurs about 6.5 minutes after the start of intravenous infusion (22). Due to its half-life of 30-45 minutes, dipyridamole-induced hyperemia may last more than 50 minutes resulting in prolonged side effects, sometimes referred to as severe and intolerable side effects (SISEs) (18). Dipyridamole undergoes metabolism in the liver to a glucuronic acid conjugate which is excreted in bile (22).

The minor side effects of intravenous dipyridamole (chest pain, headache, dizziness, nausea, hypotension and flushing) are common, occurring in up to 50% of patients (22). The more severe but very rare side effects – atrioventricular block, ST segment changes and fatal or non-fatal myocardial infarction (22) will not be considered in this study.

Adenosine and dipyridamole are known to cause a modest drop in blood pressure and a rise in heart rate (23). The increase in heart rate is attributable to a reflex response to their vasodilatory effect on the systemic circulation, resulting in a complex cascade of events that ultimately increase sympathetic discharge (23).

Aminophylline, a non-selective adenosine receptor antagonist, administered as a slow intravenous push is effective for the reversal of SISEs from vasodilator stress (6,24).

Regadenoson (Rapiscan®), a selective A2a receptor agonist with a low affinity for other adenosine receptors is less associated with side effects (22). However, it is not routinely used in our department and was not included in this study.

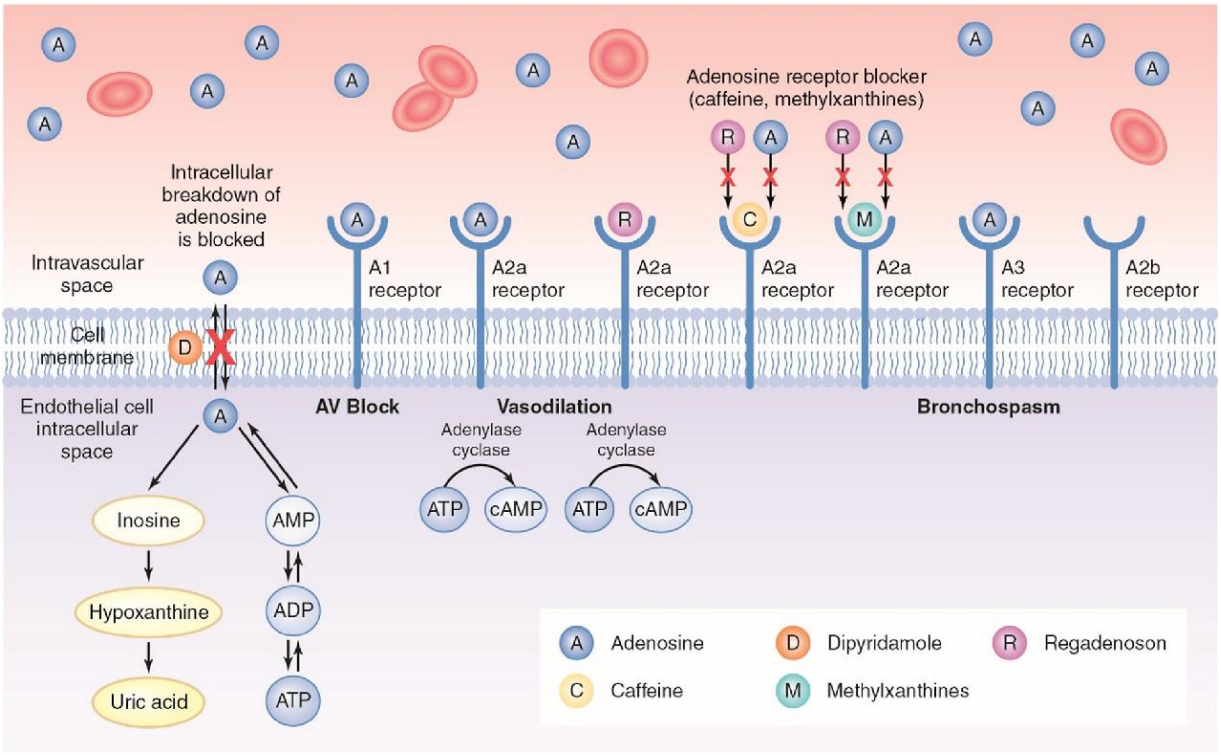


Figure 1.3 *Mechanism of action of coronary vasodilators.*
ADP, adenosine diphosphate; AMP, adenosine monophosphate; ATP, adenosine triphosphate; AV, atrioventricular; and cAMP, cyclic adenosine monophosphate.
From: ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols and tracers

1.1.2 Vasodilator stress protocols

Our departmental vasodilator stress protocols have been adopted from the Association of Nuclear Cardiology (ASNC) guidelines (22).

Adenosine is administered as a continuous intravenous infusion at the rate of 140mcg/kg/min over 6 minutes. The radiotracer is injected at 3 minutes and the adenosine infusion continues for 3 minutes after tracer injection (Figure 1.4).

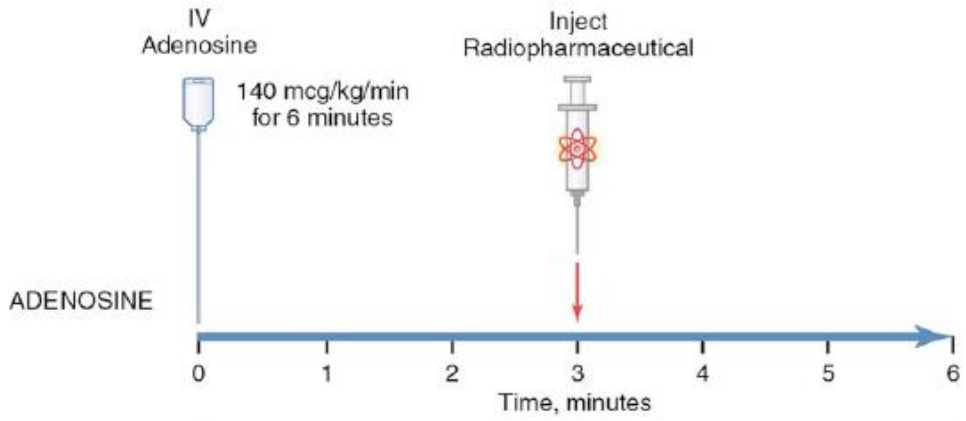


Figure 1.4 *Adenosine protocol.*
IV, intravenous; kg, kilogram; mcg, microgram; min, minute.
From: ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols and tracers

Dipyridamole is administered intravenously at a dose of 0.56mg/kg over 4 minutes. The radiotracer is then injected at 7 minutes (Figure 1.5).

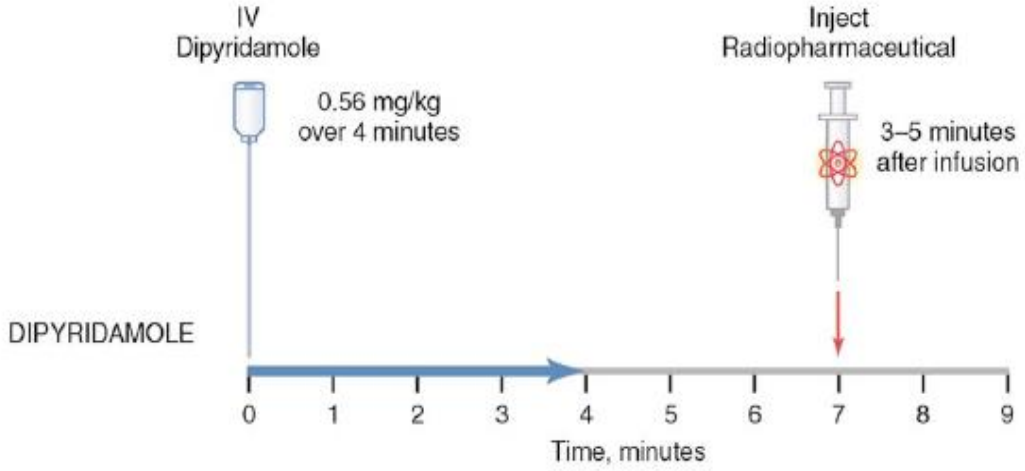


Figure 1.5 *Dipyridamole protocol.*
IV, intravenous; kg, kilogram; mg, milligram.
From: ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols and tracers

1.2 STUDY OBJECTIVES

In order to guide appropriate selection of intravenous vasodilators for pharmacological stress in our patient population, the goals of this study are:

Primary

- To assess age-related differences in patient tolerance to coronary vasodilators-adenosine and dipyridamole
- To compare the tolerance profiles of adenosine and dipyridamole in our patient population

Secondary

- To identify other factors that may influence tolerability to coronary vasodilators. These factors include race, cigarette smoking and co-morbidities such as hypertension, diabetes mellitus and chronic renal failure.

1.3 LITERATURE REVIEW

1.3.1 Safety profile of adenosine and dipyridamole

The Adenoscan Multicenter Trial Registry was a prospective, phase III trial of 9,256 consecutive patients conducted at 21 clinical sites in the United States of America, between January 1989 and March 1992 (25). Till date, this is the largest prospective study recorded in the literature that demonstrates the occurrence of adverse events during and immediately after intravenous adenosine infusion. There was a high incidence of minor cardiac and non-cardiac adverse effects (81.1%) which were generally well tolerated and resolved spontaneously upon termination of the adenosine infusion. Only 0.8% of patients developed adverse effects severe enough to warrant aminophylline reversal. Chest pain, flushing and shortness of breath were the most common adverse effects, reported in an estimated 70-80% of the study population. This trial also demonstrated the higher risk of developing adverse effects in patients younger than the median age of 65 years, females (OR=1.78) and patients with body weight above the median (OR=1.47).

In a study conducted in Greece to evaluate the tolerability, safety and prognostic implications of intravenous adenosine as a pharmacological vasodilator in octogenarians (aged $\geq$ 75 years), most patients tolerated the standard 6-minute infusion and no deaths occurred during the adenosine infusion or in the short-term post infusion period (26). Angina-like chest pain which was the most common adverse effect, requiring premature termination of the adenosine infusion, was reported in 7% of the study population. There was one case of pulmonary oedema which required oxygen, loop diuretics and intravenous aminophylline for reversal. All other side effects resolved spontaneously within a few minutes of terminating the vasodilator infusion (26). The authors demonstrated that adenosine stress MPI is well tolerated in their study population.

Gnanasegaran G et al. (27), in a retrospective study to assess the safety of adenosine MPI in elderly patients found that flushing, chest pain and neck pain were less common in those over 65 years of age ($p<0.05$). Other adverse effects observed (headache, abdominal discomfort, nausea and/or vomiting) were also less common in those over 65 years of age. The exception noted was dyspnea, which was more common in the elderly than those patients who were less than 65 years of age. No significant difference was noted in hemodynamic changes (heart rate and blood pressure) in the two age groups. The study concluded that adenosine stress MPI is a safe method for the evaluation of CAD in elderly patients and is well tolerated.

Due to the activation of A2b receptors on bronchial smooth muscles, adenosine and dipyridamole both have the potential to cause severe bronchoconstriction (28,29); a major concern in patients with asthma and chronic obstructive pulmonary disease (COPD). Reyes E et al (17), in a case-control study demonstrated the safety of adenosine in these patients. All subjects in this study received prophylactic pre-treatment with an inhaled beta-2-adrenergic agonist prior to the intravenous infusion of adenosine. Bronchospasm occurred in 5 patients but resolved spontaneously, shortly after termination of the adenosine infusion. Reversal with intravenous aminophylline was not required in any case.

Although relatively less highlighted in the literature, a higher incidence of adverse effects to vasodilator stress has been noted in females (30). In one of the earliest studies to

demonstrate this finding, Thomas et al (31) reported more adverse effects in their female study population compared to males (5.7% vs 1.8%; p=0.004) using adenosine for pharmacological stress. The reason for this gender disparity has remained unexplained and there are no concrete data to demonstrate that measures to reduce vasodilator side effects are equally effective in males and females (30).

Miner R (32), in a prospective study of 119 patients (58 male and 61 female) assessing the influence of demographic factors on the frequency and severity of side effects to dipyridamole found a high incidence of side effects (77%) in their study population. About 33% of males experienced no side effects; this was twice the frequency of females experiencing no side effects (p=0.034). Headache, which was demonstrated in 50% of the study population was the most common side effect. The occurrence and severity of headache was influenced by age and BMI. There was a strong negative correlation between headache and age, and a positive correlation with BMI. Other common side effects noted were dizziness (26%), flushing (24%), chest pain (19%), and nausea (18%). The administration of intravenous aminophylline to all patients at the end of the stress test is a possible confounding factor (32).

The Multicenter Dipyridamole Safety Study was a retrospective study to determine the incidence of major adverse reactions to intravenous dipyridamole stress MPI (33). The study which involved 73,806 patients in 59 hospitals across 19 countries demonstrated the low risk of serious dipyridamole-induced adverse effects. Multivariate analysis revealed that chest pain; one of the study end-points, was more common in patients less than 70 years old (p=0.0017). Minor non-cardiac side effects were more frequent in females (p=0.0001) and less frequent among those older than 70 years of age (p=0.0053). There was significant hypotension post dipyridamole infusion which was asymptomatic in most cases.

1.3.2 Comparison of Adenosine and Dipyridamole

A retrospective study to compare the hemodynamic changes and side effects associated with vasodilators for pharmacologic stress testing in 2000 patients revealed a high incidence of adverse effects (78% in the adenosine study group and 50% in the dipyridamole study group; $p<0.0001$) (34). Chest pain was the most common side effect reported for both vasodilators. Although adverse effects were found to occur less often in the dipyridamole group, they were more difficult to manage, requiring reversal with intravenous aminophylline in 16% (compared to <1% in the adenosine study group). With adenosine, more patients demonstrated a decrease in systolic blood pressure (from baseline to the end of infusion) of 30mmHg or more compared with dipyridamole ($p<0.0001$).

CHAPTER TWO

2.0 MATERIALS AND METHODS

Ethics approval was obtained from the University of Witwatersrand Human and Research Ethics Committee (HREC), ethics clearance number M180510 (Appendix 7.1). Permission was obtained from the Chief Executive Officers of both Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH) for the use of patients' information (Appendix 7.2, 7.3).

2.1 Study Design

This is a prospective, observational two-center study involving patients with known or suspected coronary artery disease referred to nuclear medicine for myocardial perfusion imaging (MPI) between August 2018 and November 2019. Patients seen at both the CMJAH and CHBAH nuclear medicine departments were included in the study.

2.2 Study Population

All patients for MPI who were candidates for pharmacological stress testing according to standard local protocol were approached to take part in the study. Every patient received an information sheet with details of the study and its procedure (Appendix 7.4). Subsequently, signed consent was obtained from all study participants (Appendix 7.5). Patients who did not give consent and those who underwent low dose exercise prior to vasodilator administration were excluded from the study. In total, 264 participants (84 from CMJAH and 180 from CHBAH) were enrolled.

Table 2.1 *Inclusion and exclusion criteria*

Inclusion Criteria	Exclusion Criteria
● All patients referred for stress MPI in whom vasodilator pharmacological stress was indicated	● Patients who declined consent for the study ● Low dose exercise prior to administration of intravenous vasodilator ● Patients in whom dobutamine stress was indicated ● Patients who underwent exercise stress test

2.3 Allocation of study participants

Although simple randomization was initially proposed, the choice of vasodilator for pharmacological stress MPI was eventually determined by availability in the two hospitals. Intravenous adenosine (Adenocor®) was administered to all study participants at CMJAH. Intravenous dipyridamole (Persantin®) was initially administered to the study participants at CHBAH but was changed to adenosine (Adenocor®) when dipyridamole (Persantin®) went out of stock in the hospital pharmacy.

2.4 Study protocol

Patients referred to the nuclear medicine department underwent routine history taking and clinical assessment to determine those who were candidates for vasodilator pharmacological stress. After the procedure was thoroughly explained, patients gave written consent to participate in the study. Pharmacological stress testing was conducted per departmental standard protocols (Appendix 7.6).

Participants' demographic data (age, race, gender and body mass index) were recorded on a questionnaire (Appendix 7.7). In addition, co-morbidities and risk factors (hypertension, diabetes mellitus, cigarette smoking and chronic renal failure) were recorded on the

questionnaire. Heart rate and blood pressure at baseline and at the end of the vasodilator infusion were also noted to monitor hemodynamic changes.

Each participant was monitored and questioned by the examining doctor for side effects during and immediately after termination of the vasodilator infusion. The presence of side effects as well as reversal with intravenous aminophylline was recorded in the questionnaire. Common side effects that the examining doctor evaluated were chest pain, nausea, vomiting, abdominal discomfort, wheezing, dyspnea, flushing, headache and impending syncope. Reported side effects that were not included in the pre-designed questionnaire were also recorded.

2.5 Statistical Analysis

Data was entered into a secure Microsoft Excel software.
Categorical variables were expressed as frequencies and percentages while continuous variables were expressed as means.

An age cut-off of 60 years (being the mean/median age) was used to divide the study population into younger and older age groups.

Cross-tables were generated to determine the association between age and other categorical variables (gender, race, co-morbidities and risk factors) using Pearson's chi squared test. Student t-test was used to compare the means of the groups for patient characteristics expressed as continuous variables.

Factors associated with age and side effects were analyzed using univariate logistic regression analysis, reporting odds ratio and 95% confidence interval. A p value <0.05 was considered significant throughout.

The analyses were performed using STATA statistical software [StataCorp. 2017. *Stata Statistical Software:* Release 15. College Station, TX: StataCorp LLC].

CHAPTER THREE

3.0 RESULTS

Two hundred and sixty-four patients gave consent to participate in the study, of which 147 (55.7%) received intravenous adenosine and 117 (44.3%) received intravenous dipyridamole.

The age threshold used for comparison of data in this study is 60 years. Forty-three percent of the population belonged to the younger age group (<60 years, [Group A]) while about 57% belonged to the older age group (≥60 years, [Group B]).

Patient Characteristics

Demographic and clinical characteristics of the study population are presented in Table 3.1a.

Table 3.1a *Characteristics of the study population*

VARIABLES	FREQUENCY	PERCENT
Age (years)		
Mean±SD	59.7±13	
Range	12 – 88	
Age group (years)		
< 60 years (Group A)	114	43.2
≥ 60 years (Group B)	150	56.8
Gender		
Male	142	53.79
Female	122	46.21
Race		
Black	156	59.09
White	62	23.48
Indian	31	11.74
Colored	15	5.68
Body Mass Index (BMI)		
Mean±SD	29.5±8.4	
Co-morbidities		
Hypertension	232	87.88
Diabetes mellitus	98	37.12
Chronic renal failure	22	8.33
Cigarette smoking		
No	213	80.68
Yes	51	19.32
Pack years		
Mean±SD	24±13	

SD (Standard deviation)

Study participants from both age groups were matched for body mass index, the presence of co-morbidities (chronic renal failure) and cigarette smoking (Table 3.1b). The older age group (≥60 years, [Group B]) accounted for 55.8% and 58.1% of study participants receiving intravenous adenosine and dipyridamole respectively.

Table 3.1b *Comparison of demographics and risk factors between the two age groups*

	Group A (<60years) n=114 (%)	**Group B (≥60years) n=150 (%)**	**p value**
Age			
Mean±SD	48.1±10.2	68.6±6.5	
Range	12-59	60-88	
Gender			
Male	70 (49.3)	72 (50.7)	**0.030***
Female	44 (36.1)	78 (63.9)	
Race			
Black	78 (50.0)	78 (50.0)	
Colored	8 (53.3)	7 (46.7)	**0.017***
Indian	10 (32.3)	21 (67.7)	
White	18 (29.0)	44 (71.0)	
BMI (kg/m²)			
Mean±SD	30.4±9.3	28.8±7.6	0.134
Co-morbidities			
Hypertension	95 (41.0)	137 (59.0)	**0.049***
Diabetes Mellitus	32 (32.7)	66 (67.3)	**0.008***
Chronic renal failure	13 (59.1)	9 (40.9)	0.116
Cigarette smoking	22 (43.2)	29 (56.8)	0.668
Pack years			
Mean±SD	20.9±13.6	27.0±12.6	0.107
Pharmacological agent			
Adenosine	65 (44.2)	82 (55.8)	0.703
Dipyridamole	49 (41.9)	68 (58.1)	

BMI (Body mass index), SD (Standard deviation), * (Statistically significant p<0.05)

Study Indications

Accounting for about two-thirds of the study population (161 patients), diagnosis of coronary artery disease was the most common indication for SPECT MPI. Only 3 patients were referred for risk stratification post myocardial infarction. Indications for the study are shown in Figure 3.1.

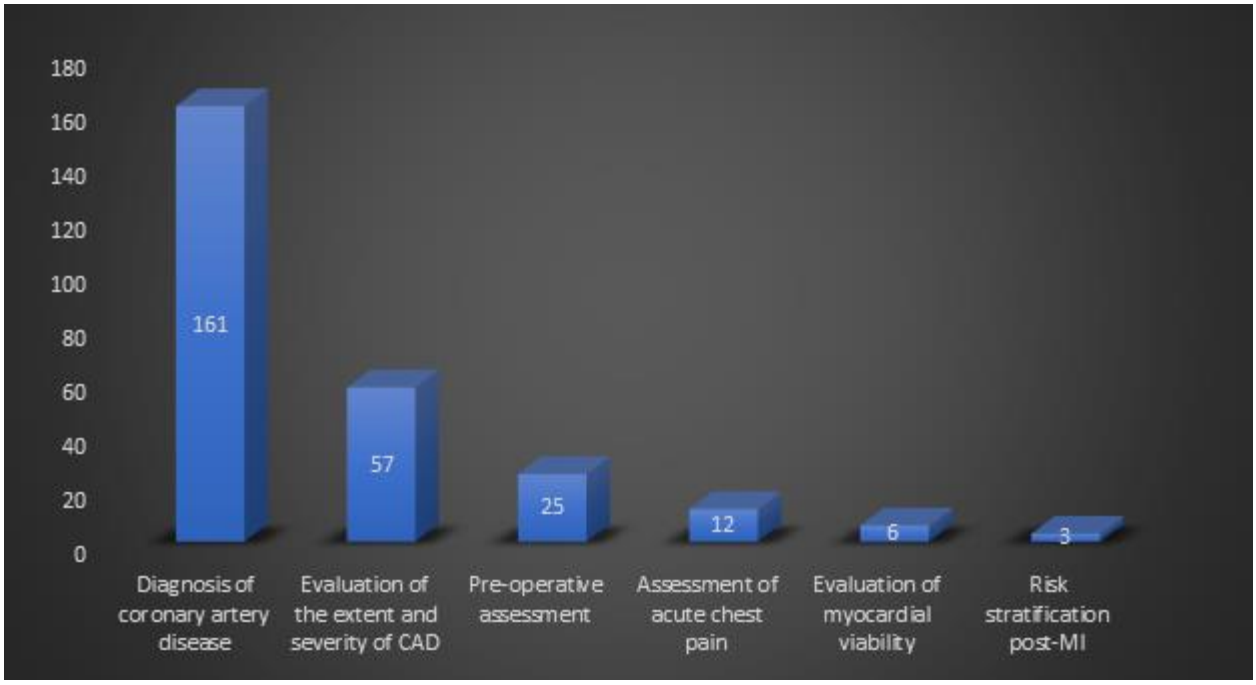


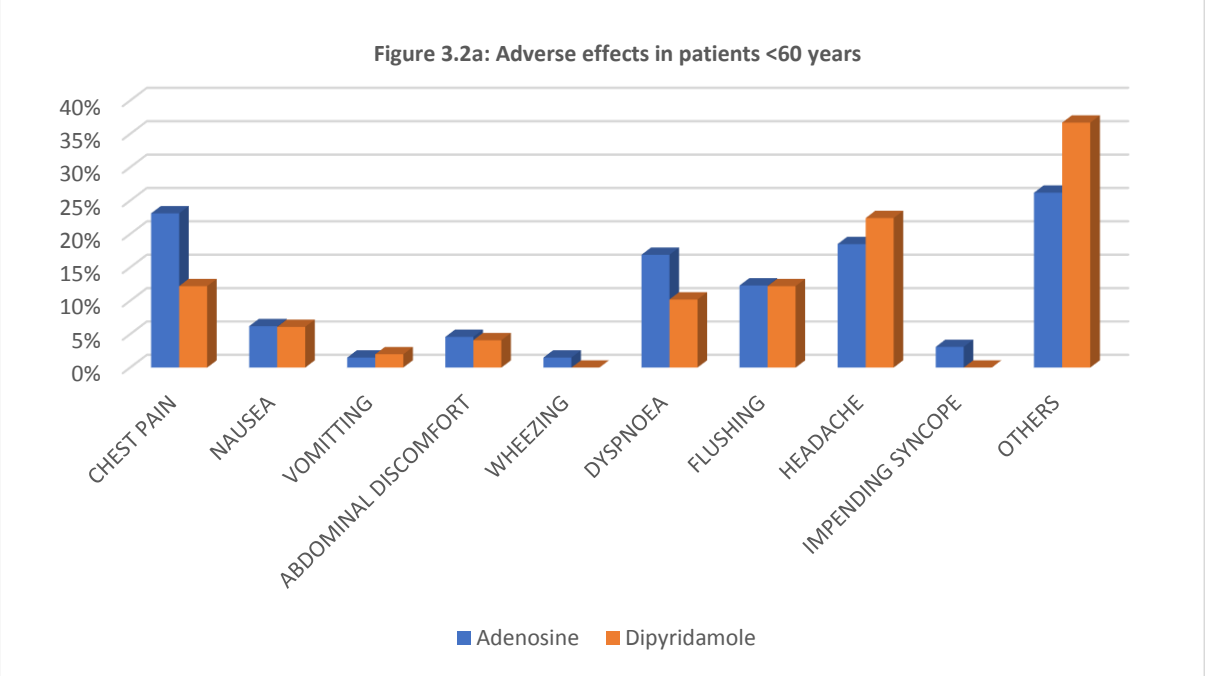
Figure 3.1 *Indications for SPECT MPI.*

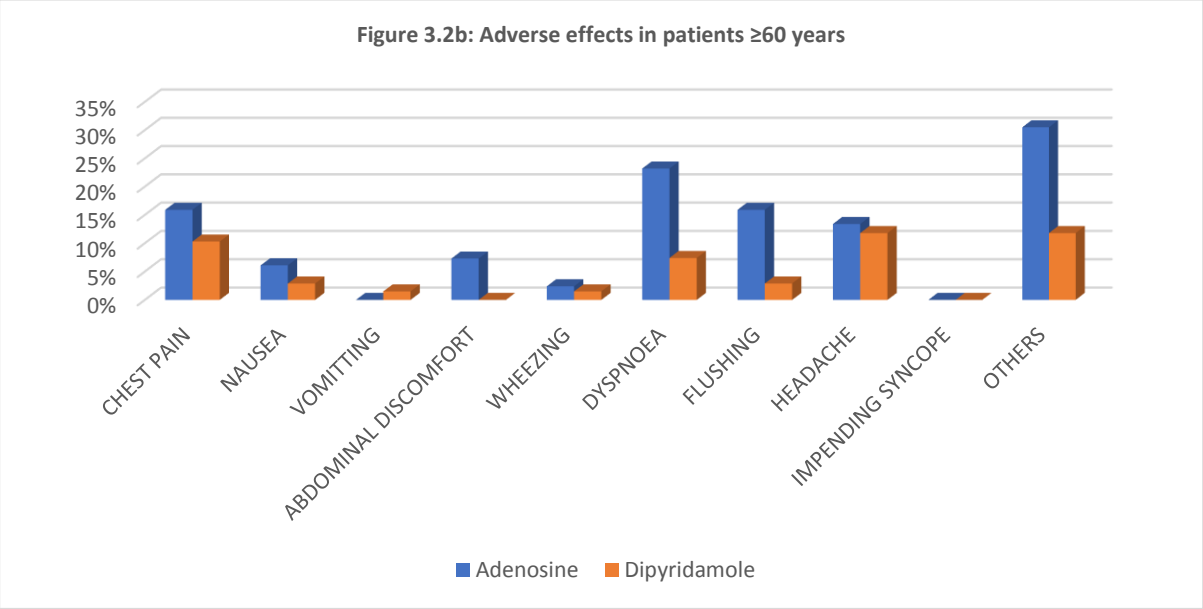
Frequency of adverse effects

The majority of the study participants (62.1%) developed adverse effects; the most frequently reported was headache which occurred in 16% of the study population. Chest pain and dyspnea were each reported in 15% of the study population. Other reported adverse effects were dry mouth, nausea, abdominal discomfort, vomiting and wheezing.

For adenosine, chest pain and dyspnea were the most common adverse effects in Group A and B, respectively. For dipyridamole, headache was the most common adverse effect in both age groups.

The distribution of adverse effects in the two age groups is represented in figures 3.2a and 3.2b.





Figures 3.2a & b *Adverse effects from pharmacological vasodilators in different age groups.*

Grading of adverse effects

Previous studies have relied on the investigators' clinical judgment for grading side effects (25,35). This approach presents a possibility of subjectivity and inter-observer variability. In order to objectively assess the severity of adverse effects, a four-point grading scale, which focused on the number of side effects was developed as follows:

Grade 0: no adverse effects

Grade 1: less than 3 adverse effects (mild)

Grade 2: 3-6 adverse effects (moderate)

Grade 3: >6 adverse effects (severe) or SISEs requiring reversal with intravenous aminophylline

The majority of participants reported mild adverse effects (Grade 1); only 3 participants, representing about 1% of the study population, manifested Grade 3 side effects (Figure 3.3). All three participants with severe adverse effects required reversal with intravenous aminophylline. The side effects noted in this group were nausea, flushing, headache and dizziness.

Using this grading scale, there was no statistically significant difference when age groups were compared with the different grades of side effects (p=0.184).

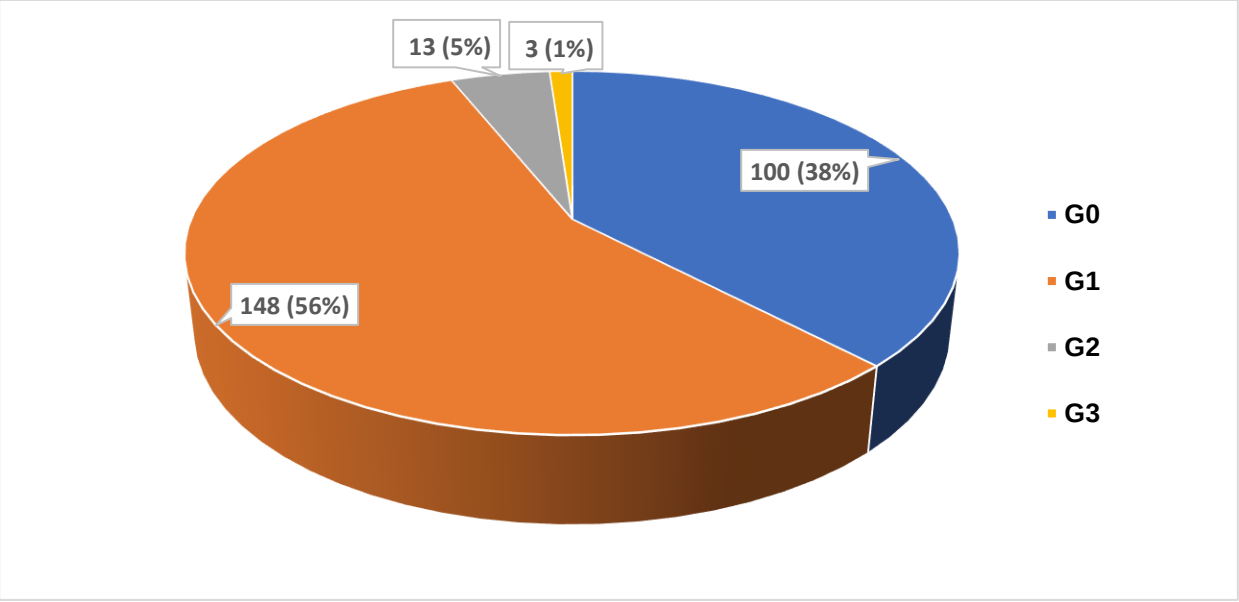


Figure 3.3 *Distribution of adverse effects by grade.*

Tolerability and safety profile

Of the study participants who reported adverse effects, 79 belonged to Group A and 85 to Group B (Table 3.2).

Study participants in the older age group (Group B) were 42% less likely to develop side effects compared to participants in the younger age group (Group A). This was a statistically significant finding (OR = 0.58; 95% CI= 0.35-0.97; p=0.036) (Table 3.2).

Table 3.2 *Associations of socio-demographic characteristics, risk factors and pharmacological vasodilators with adverse effects*

	Adverse effects				
	Total	**No**	**Yes**	**OR (95% CI)**	**p value**
	N=264 (%)	**n=100 (%)**	**n=164 (%)**		
Age in years					
<60 (Group A)	114 (100.0)	35 (30.7)	79 (69.3)	1.00 (Reference)	
≥60 (Group B)	150 (100.0)	65 (43.3)	85 (56.7)	0.58 (0.35-0.97)	**0.036***
Gender					
Male	142 (100.0)	60 (42.3)	82 (57.7)	1.00 (Reference)	
Female	122 (100.0)	40 (32.8)	82 (67.2)	1.50 (0.91-2.48)	0.115
Race					
Black	156 (100.0)	62 (39.7)	94 (60.3)	1.00 (Reference)	
Colored	15 (100.0)	7 (46.7)	8 (53.3)	0.75 (0.26-2.18)	0.603
Indian	31 (100.0)	11 (35.5)	20 (64.5)	1.20 (0.54-2.68)	0.657
White	62 (100.0)	20 (32.3)	42 (67.7)	1.39 (0.74-2.58)	0.304
BMI (kg/m²) Mean ± SD	29.5±8.4	27.6.±7.8	30.7±8.5	1.05 (1.01-1.09)	**0.003***
Pharmacological agents					
Dipyridamole	117 (100.0)	62 (53.0)	55 (47.0)	1.00 (Reference)	
Adenosine	147 (100.0)	38 (25.8)	109 (74.2)	3.23 (1.93-5.43)	**<0.001***
Hypertension					
No	32 (100.0)	9 (28.1)	23 (71.9)	1.00 (Reference)	
Yes	232 (100.0)	91 (39.2)	141 (60.8)	0.61 (0.27-1.37)	0.229
Diabetes mellitus					
No	166 (100.0)	65 (39.2)	101 (60.8)	1.00 (Reference)	
Yes	98 (100.0)	35 (35.7)	63 (64.3)	1.16 (0.69-1.94)	0.578
Chronic renal failure					
No	242 (100.0)	89 (36.8)	153 (63.2)	1.00 (Reference)	
Yes	22 (100.0)	11 (50.0)	11 (50.0)	0.58 (0.24-1.40)	0.225
Smoking					
No	213 (100.0)	80 (37.6)	133 (62.4)	1.00 (Reference)	
Yes	51 (100.0)	20 (39.2)	31 (60.8)	0.93 (0.50-1.74)	0.827

OR (Odds ratio), 95% CI (95% confidence interval), BMI (Body mass index), SD (Standard deviation), * (Statistically significant p<0.05)

Although females represent a lower proportion of the study population (46.2%), they were 50% more likely to develop side effects compared to males (Table 3.2). There was however not so strong evidence for this causation as it was not a statistically significant finding (p=0.115).
The mean body mass index (BMI) of the study population (29.5±8.4) falls in the overweight range. For every unit increase in BMI, there was a 5% increased chance of developing adverse effects (OR = 1.05; 95% CI= 1.01-1.09; p=0.003) (Table 3.2).

Adenosine was three times more likely to cause adverse effects compared to dipyridamole (OR = 3.23; 95% CI= 1.93-5.43) (p<0.001). However, dipyridamole showed a higher propensity to cause higher grade adverse effects as all participants with Grade 3 adverse effects received dipyridamole (p<0.001).

Hypertension and chronic renal failure were 39% and 42% less likely to cause adverse effects respectively. Smokers had a 7% lower chance of developing side effects compared to non-smokers (Table 3.2). Diabetes mellitus was 16% more likely to cause adverse effects (Table 3.2). There was no strong evidence for causation when race, hypertension, diabetes mellitus, chronic renal failure and cigarette smoking were compared with adverse effects (Table 3.2).

Using age group as the stratification variable (Table 3.3), study participants with adverse effects were 42% less likely to be in the older age group (Group B) than in the younger age group (Group A). This a statistically significant finding (OR=0.58; 95% CI=0.35-0.97; p=0.037), confirming that younger patients are more likely to develop adverse effects.
Another important observation is that females had a 72% chance of being in the older age group (OR = 1.72; 95% CI= 1.05-2.83; p=0.03) (Table 3.3).
Although there was no strong evidence for causation when compared with adverse effects, participants with hypertension and diabetes mellitus had a significantly higher chance of being in the older age group (Table 3.3).

Table 3.3 *Association of the adverse effects, gender and risk factors with age*

	Age group				
	Total n=264 (%)	**Group A n=114 (%)**	**Group B n=150 (%)**	**OR (95% CI)**	**p value**
Adverse Effects					
No	100	35 (35.0)	65 (65.0)	1.00 (Reference)	
Yes	164	79 (48.2)	85 (51.8)	0.58 (0.35-0.97)	**0.037***
Gender					
Male	142	70 (49.3)	70 (50.7)	1.00 (Reference)	
Female	122	44 (38.1)	78 (63.9)	1.72 (1.05-2.83)	**0.030***
Hypertension					
No	32	19 (59.4)	13 (40.6)	1.00 (Reference)	
Yes	232	95 (40.9)	137 (59.1)	2.11 (0.99-4.47)	**0.049***
Diabetes Mellitus					
No	166	82 (49.4)	84 (50.6)	1.00 (Reference)	
Yes	98	32 (32.7)	66 (67.3)	2.01 (1.20-3.39)	**0.008***
Chronic renal failure					
No	242	101 (41.7)	141 (58.3)	1.00 (Reference)	
Yes	22	13 (59.1)	9 (40.9)	0.50 (0.20-1.20)	**0.116**

OR (Odds ratio), BMI (Body mass index), SD (Standard deviation), * (Statistically significant p<0.05)

Hemodynamic response

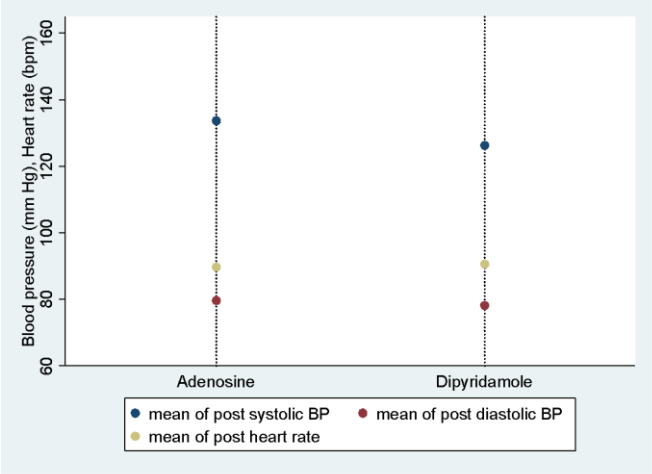
With both vasodilators, there was a drop in mean systolic and diastolic blood pressures and a rise in mean heart rate from baseline to end of vasodilator infusion (Table 3.4).

Table 3.4 *Hemodynamic changes during vasodilator stress*

	Pharmacologic vasodilators		
Hemodynamic variables	**Adenosine Mean ± SD**	**Dipyridamole Mean ± SD**	**p value**
Baseline systolic BP (mmHg)	138.20 ± 22.83	132.42 ± 20.04	**0.032**
Peak systolic BP (mmHg)	133.76 ± 24.84	126.35 ± 19.88	**0.009**
Baseline diastolic BP (mmHg)	81.85 ± 14.20	83.14 ± 11.69	0.427
Peak diastolic BP (mmHg)	79.67 ± 14.76	78.17 ± 11.81	0.374
Baseline heart rate (bpm)	83.68 ± 16.36	84.51 ± 15.62	0.676
Peak heart rate (bpm)	89.72 ± 17.04	90.64 ± 18.30	0.674

*BP (Blood pressure), *Peak (end of vasodilator infusion)

The differences in mean systolic blood pressures between adenosine and dipyridamole was statistically significant (p=0.032 for baseline; p=0.009 for peak blood pressures) (Figure 3.4; Table 3.4). The drop in diastolic blood pressures and rise in heart rate noted for both vasodilators were not statistically significant.



*BP (Blood pressure)

Figure 3.4 *Dot plot showing the mean values of hemodynamic variables post-pharmacologic stress, comparing adenosine and dipyridamole.*

CHAPTER FOUR

4.0 DISCUSSION

Consistent with previous reports in the literature (13,17,25,27,36), this study demonstrates the tolerability and safety of adenosine and dipyridamole as pharmacologic vasodilators in all age groups. Although there is an overall high incidence of side effects (62.1%), the majority of participants had mild (56%) and moderate (5%) adverse effects that were tolerated with or without adjustment of the infusion dose and did not require premature termination of the vasodilator infusion. Only 1% (3 participants) of the study population developed severe symptoms that required extra monitoring time and administration of intravenous aminophylline. This is in keeping with the documented low rates of SISEs (1-10%) associated with vasodilator stress MPI (24,27,35). Neither death nor other known severe adverse effects were reported.

Age-related differences in adverse effects and tolerability

Consistent with previous similar studies (13,22,25,27,34), there is a high incidence of adverse effects in our study population (62.1%); headache, chest pain and dyspnea being the most common in both age groups.

Using age thresholds ranging from 65 to 75 years, studies have shown a higher incidence of adverse effects in younger patients compared to older patients (25–27,32). In this study, with a lower age threshold of 60 years, the results are comparable, with a significantly higher rate of adverse effects noted in the younger age group ($p=0.036$). The reasons for this age-related difference are largely speculative but differences in vasodilator metabolism and receptor sensitivity are cited as possible factors (25).

Younger participants (Group A) had the highest rates of chest pain and headache while older participants (Group B) had the higher rates of dyspnea and flushing. This is comparable to the study by Gnanasegaran G et al. (27) where chest pain was more prevalent in patients below 65 years of age.

Vasodilator-induced chest pain may represent severe CAD, particularly multi-vessel disease or it may also occur in healthy patients (37). It is thought to be caused by direct activation of myocardial nociceptors and endothelial dysfunction associated with hypertension and diabetes (38).

Other factors associated with adverse effects

Although this was not a statistically significant finding, we noted that female participants were more prone to developing side effects compared to their male counterparts. This is consistent with the findings by Thomas et al (31), the Adenoscan Multicenter Trial Registry (25) and the Multicenter Dipyridamole Safety Study (33). The reasons for this gender-based difference are probably related to higher prevalence of obesity in females of the older age group (39,40). Same holds true for this study where there was a significantly higher mean BMI in females (31.2kg/m^2; 95% CI=29.2-32.8kg/m^2) compared to males (28.0kg/m^2; 95% CI=26.7-29.2 kg/m^2), (p=0.0018). The higher percentage body fat is thought to result in relatively higher plasma concentration of water soluble adenosine due to the smaller volume of distribution in females (31).

Similar to findings in the literature (25,32), a unit rise in BMI was associated with a 5% increase in the odds of developing side effects. The reasons are likely related to obesity as discussed above.

Though not statistically significant, this study shows that Caucasians have higher odds of developing adverse effects compared with Africans. Also, those with a history of diabetes mellitus demonstrated a higher odds of developing side effects compared to those without. These associations have not been previously documented in the literature and require further studies to determine their relevance.

Differences between Adenosine and Dipyridamole

The general spectrum of common side effects noted in this study (chest pain, dyspnea, headache, flushing) is comparable to the literature. As reported by Miner et al. (32), headache was found to be the most common adverse effect associated with dipyridamole in young and older patients.

It was also noted that adenosine is three times more likely to cause side effects than dipyridamole (OR=3.23, 95% CI=1.93-5.43; $p<0.001$). It is unlikely that the reason for this is the fact that a higher proportion of the study population received adenosine (55.7% versus 44.3% who received dipyridamole) as it is consistent with the literature. Johnston et al. (34) reported adverse effects in 78% of the adenosine group and 50% of the dipyridamole group in their study with an equal number of patients in both groups. Higher systemic vasodilation noted with adenosine as compared to dipyridamole has been proposed as the reason for this finding (34).

Dipyridamole had a greater propensity to cause higher grade adverse effects ($p<0.001$). All three patients with Grade 3 side effects in this study had received dipyridamole and required reversal with intravenous aminophylline. This is consistent with two large studies that have compared adenosine and dipyridamole (25,34) and has been attributed to the long half-life of dipyridamole. Unlike with adenosine where adjustment of the infusion rate provides symptom relief because of its short half-life, the adverse effects from dipyridamole are more persistent and do not respond to infusion rate adjustments (25).

Adenosine was associated with a more significant drop in systolic blood pressure from baseline (138.2 ± 22.8mmHg) to end of infusion (133.76 ± 24.48mmHg) compared to dipyridamole ($p<0.009$). A similar trend was noted in previous studies (25,34,35) and is attributable to adenosine's significant systemic vasodilation which causes a decrease in systolic blood pressure (41). The drop in mean systolic blood pressure with adenosine was 4.4mmHg in this study, compared to 9mmHg in the Adenoscan Multicenter Trial Registry (19), 17.1mmHg in the study by Abreu et al (35) and $\geq$30mmHg in the study by Johnston et al (34). This difference may be attributed to the comparatively smaller sample size of this

study or differences in the demographics of the study population as all studies used the same protocol for vasodilator infusion.

Methods of reducing adverse effects

Adjunctive low-level exercise simultaneously or prior to vasodilator infusion has proven effective in ameliorating adverse effects and improving image quality in SPECT MPI studies (13,31,42) but may be a potential challenge for older patients and those who are physically unable to exercise. Assessing the effects of low level exercise is outside the scope of this study.

Secondly, a reduced duration of the vasodilator infusion can decrease the frequency and duration of adverse effects as demonstrated by Treuth M et al. (43) who showed that an abbreviated 3 minute infusion of intravenous adenosine was better tolerated than the standard 6 minute infusion.

Regadenoson, a selective A2a receptor antagonist with a simple usage protocol and good tolerability is now commonly used for pharmacologic testing especially in the United States of America (36). Compared to adenosine, regadenoson has a more tolerable side effect profile. Unfortunately, it is not currently available for routine use in our center due to cost limitations.

4.1 STUDY LIMITATIONS

Simple randomization was initially proposed as the method of selecting patients who will receive intravenous adenosine and dipyridamole. Unfortunately, by the time the study began only intravenous adenosine was available at CMJAH. Consequently, all patients for vasodilator stress MPI at CMJAH received adenosine while those at CHBAH received dipyridamole. During the course of the study, dipyridamole was no longer available at CHBAH and the rest of the patients received adenosine. This lack of radomization likely introduced some bias to the study.

The global molybdenum-99 shortage that occurred in late 2018 adversely impacted our department's generator supply. As a consequence, a significantly lower number of SPECT MPI studies were conducted between October 2018 and January 2019. Data collection had to be extended from August 2019 to November 2019 in order to achieve the desired sample size.

CHAPTER FIVE

5.0 CONCLUSION

Adenosine and Dipyridamole are pharmacologic vasodilators with a good safety profile and are valuable alternatives to exercise stress test for SPECT MPI studies in patients who have limitations to physical exercise.

Consistent with previous similar studies, this prospective study has demonstrated an age related difference in the tolerability of adenosine and dipyridamole, with patients less than 60 years old having a higher chance of developing adverse effects.
In addition, with fewer severe adverse effects, adenosine has demonstrated a better safety profile compared to dipyridamole.

This study has provided information to guide nuclear physicians in individualizing their choice of vasodilator when conducting pharmacological stress SPECT MPI as demographic and physical factors have a significant effect on the development of adverse effects in our patient population. For instance, adenosine will be preferred in older females and patients with obesity as dipyridamole has a higher propensity to cause adverse effects in these patient groups.
It is important to note that in our setting, the choice of vasodilator will also depend on availability of the product and other logistical factors.

In addition, the nuclear physician is better equipped to inform patients on what adverse effects they may experience. This has the potential to reduce anxiety and optimize patient cooperation during the stress test.

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APPENDIX

Appendix 7.1

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr J Momodu

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M180510

NAME: (Principal Investigator)	Dr J Momodu
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Nuclear Medicine and Molecular Imaging Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Adverse reactions to pharmacological agents used in stress myocardial perfusion imaging studies: differences in older and younger patients in a South African population cohort
DATE CONSIDERED:	25/05/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professor MDTHW Vangu
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	02/08/2018

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 Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/We fully understand the conditions under which I am/we are authorised 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 to the Committee. **I agree to submit 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).

Principal Investigator Signature

03/05/2018
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 7.2

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. N. Mzila
Office of the Clinical Director
Tell: (011): 488-4812
Email: Nolwazi.Mzila@gauteng.gov.za
8th August 2018

GP_201708_004

Dear Dr. J. Momodu

STUDY TITLE: Adverse Reactions to Pharmacological Agents Used In Stress Myocardial Perfusion Imaging Studies: Differences in Older and Younger Patients in a South African Population Cohort.

Permission is granted for you to conduct the above recruitment activities as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not anyway incur or inherit costs as result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall be observed at all times.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported/~~not supported~~

Dr. M.I. Mofokeng
Clinical Director
DATE: 06/08/2018

Approved/not approved

Ms. G. Bogoshi
Chief Executive Officer
Date: 08.08.2018

Appendix 7.3

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 24th April 2018

TITLE OF PROJECT:

Adverse reactions to pharmacological agents used in stress myocardial perfusion imaging studies: differences in older and younger patients in a S.A. Population Cohort

UNIVERSITY: Witwatersrand

Principal Investigator: Dr. Jaleelat Momodu

Department: Nuclear Medicine

Supervisor : Dr K Purbhoo

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

.....
Recommended
(On behalf of the MAC)
Date: 24/04/2018

.....
Approved/Not Approved
Hospital Management
Date: 26/04/18

Appendix 7.4

INFORMATION DOCUMENT

Study title: Adverse Reactions to Pharmacological Agents Used in Stress Myocardial Perfusion Imaging Studies: Differences in Older and Younger Patients in a South African Population Cohort

Good Day,

Introduction:

I, Dr Jaleelat Momodu, am conducting a research on medications used for cardiac testing, for the purposes of a Masters degree at the University of the Witwatersrand. The aim is to find out which patients may most likely develop side effects to these drugs.

Invitation to participate:

I am Dr JI Momodu, a registrar in the Nuclear Medicine department at the CM Johannesburg hospital and would like to invite you to join this study.

To help you to decide whether to take part in this study you should fully understand what is involved. If you have any questions, which are not fully explained in this information sheet, do not hesitate to ask the doctor. You should not agree to take part unless you are completely happy about the procedure involved.

What is involved in this study?

This is a study that is done to identify which patients are more likely to develop side effects to the medications used for cardiac stress testing that you will have in our department.

Based on your history and physical examination, a medication rather than exercise is the best alternative for your cardiac stress test.

Two medications namely Adenosine and Dipyridamole will be used for this study. The choice of medication to be used will be based on random selection.

Your cardiac stress test will be carried out in the usual manner based on current guidelines. The doctor carrying out the test will ask you and observe to know if you develop any side effects. The possible side effects are headache, chest pain or chest tightness, flushing, neck pain, nausea and vomiting. You may not develop any side effects, or you may develop some. These effects usually resolve spontaneously within a few minutes after stopping the administration of the medication. Your doctor may give you another medication to reverse the effects if you remain uncomfortable.

This study will not affect your clinical management in any way and there will be no cost to you by accepting to participate in this study. You are not required to fill out a questionnaire. Should you decline or withdraw your consent, your treatment will not be affected, and your decision will not influence your future care and continued treatment in this hospital.

This study will involve patients at CM Johannesburg Academic Hospital and CHB Academic Hospital. No patients outside South Africa will be recruited into the study.

At the end of this research we will be able to better anticipate and plan for side effects in patients referred for similar cardiac test.

Efforts will be made to keep personal information confidential. However, absolute confidentiality cannot be guaranteed, in the following very rare exceptional circumstances:

1. Personal information may be disclosed if required by law
2. the Human Research Ethics Committees of the University may exceptionally require personal data to respond to a formal complaint, or for a compliance audit
3. the South African Health Products Regulatory Authority (SAHPRA), which is the successor body to the South African Medicines Control Council (SAMCC), might conceivably require access to personal data, if conducting an investigation into a drug trial

For further information please contact me, Dr Momodu, on tel no. 082 265 7349, or my Supervisor, Professor Vangu, on 011 488 3500.

This study has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg ("Committee"). A principal function of this Committee is to safeguard the rights and dignity of all human subjects who agree to participate in a research project and the integrity of the research.

If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Professor Clement Penny, who may be contacted on telephone number 011 717 2301, or by e-mail on Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za

Thank you for reading this Study Information Sheet.

Date: August 2018

Appendix 7.5

Written Consent Form

STUDY TITLE: Adverse Reactions to Pharmacological Agents Used in Stress Myocardial Perfusion Imaging Studies: Differences in Older and Younger Patients in the South African Population

Name of Patient:……

Patient Number:……

The aims and procedures of this study have been explained to me by the doctor. I have read and understood the subject information sheet provided.

I have had the opportunity to ask questions and to consider the answers given to me.

I understand that participation in this study is voluntary, that I may decline my consent and if I choose not to participate my decision will not affect my care and future visits at the hospital.

I hereby freely give my informed consent to taking part in this study.

NAME: ……..

DATE: ……

SIGNATURE: ……..

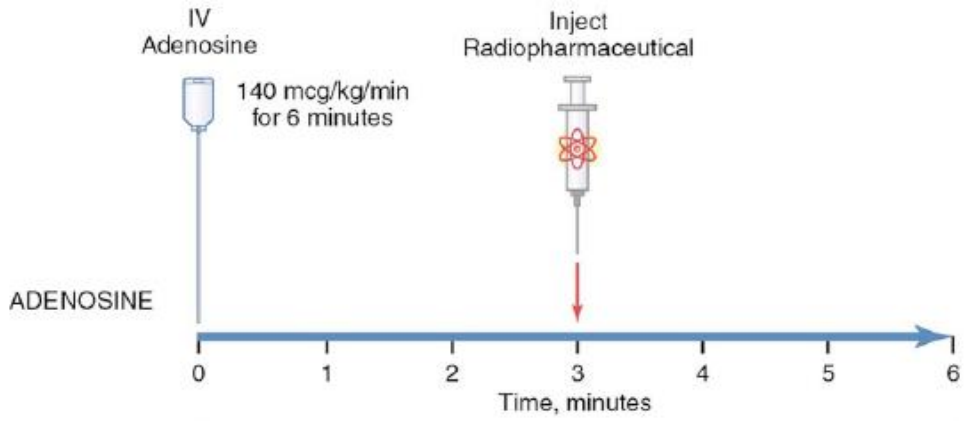
I confirm that I have fully explained the nature of the study and the procedure to be performed to the above-named patient.

NAME: …….

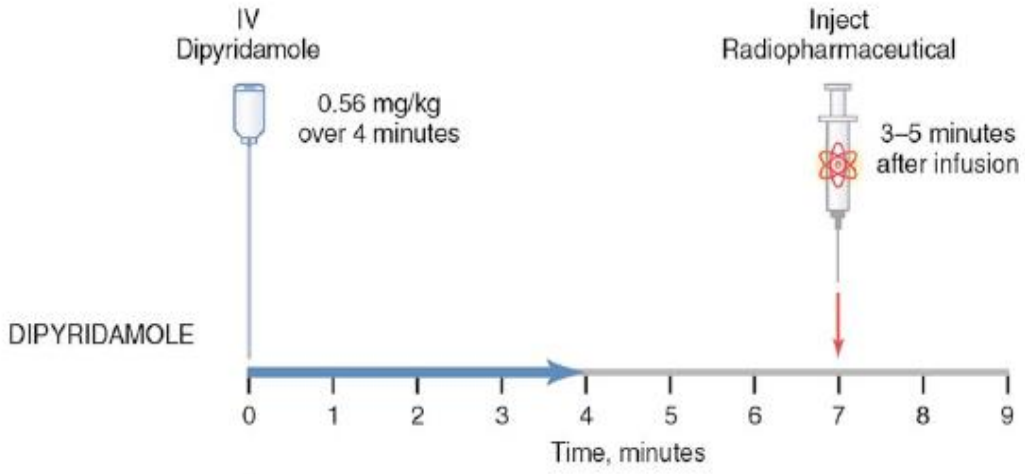
DATE: ……..

SIGNATURE: …….

Standard Departmental Protocols for Vasodilator Stress Testing



Adenosine protocol.
IV, intravenous; kg, kilogram; mcg, microgram; min, minute.
From: ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols, and tracers



Dipyridamole protocol.
IV, intravenous; kg, kilogram; mg, milligram.
From: ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols, and tracers

Appendix 7.7

QUESTIONNAIRE- SIDE EFFECTS OF PHARMACOLOGICAL STRESS AGENTS

BIODATA

Code:
Age:
Gender:
Race: Please tick (✓) appropriate box

Black	
White	
Indian	
Colored	
Other	

Weight (kg):
Height (m):

INDICATION FOR STUDY:

RISK FACTORS AND CO-MORBIDITIES: Please tick (✓) if present and leave blank if absent

Hypertension	
Diabetes mellitus	
Cigarette smoking (if yes, number of packs per day)	
-Number of years smoking	
Chronic renal failure (pre-transplant assessment)	

PHARMACOLOGICAL AGENT:

Adenosine	
Dipyridamole	

SIDE EFFECTS AND SEVERITY

Please tick (✓) appropriate box

Symptom	Yes	No	Reversal with IV Aminophylline	
			Yes	No
Chest pain (angina)				
Nausea				
Vomiting				
Abdominal discomfort				
Wheezing				
Dyspnea				
Flushing				
Headache				
Impending syncopal attack				
Other:				

PR AND BP

	Pulse Rate (bpm)	Blood Pressure (mmHg)
Baseline		
Post-infusion		

Appendix 7.8

DataCol Web: Form for requesting permission to reproduce, reprint or translate WHO copyrighted material

==========

ID: 361140

Section: Contact details

---

* Title
* Dr

---

* First name
* Jaleelat

---

* Family name
* Momodu

---

* Organization/affiliation
* University of Witwatersrand

---

* Web site address
*

---

* Type of organization
* University/Academic

---

* If other, please specify
*

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* If STM signatory, please select
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* Position
*

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* +27822657349

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Department of Nuclear Medicine,
Faculty of Health Sciences,
University of the Witwatersrand,
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Appendix 7.9

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Institution name	UNIVERSITY OF WITWATERSRAND, SOUTH AFRICA
Expected presentation date	Oct 2020
Portions	Figure 1 on page 609; Figure 2 on page 610; Figure 4 on page 614
Requestor Location	Dr. Jaleelat Momodu Division of Radiation Sciences Faculty of Health Sciences University of the Witwatersrand Johannesburg, Gauteng Private Bag 3, WITS 2050 South Africa Attn: Dr. Jaleelat Momodu
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