ADVERSE EFFECTS DURING DIPYRIDAMOLE STRESS MYOCARDIAL PERFUSION IMAGING (MPI) AND ITS ASSOCIATION WITH ECG FINDINGS AND SCINTIGRAPHY OUTCOMES IN HOSPITAL KUALA LUMPUR (HKL)

BY

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DECLARATION

I hereby declare that this research was sent to Universiti Sains Malaysia (USM) for the degree of Master of Medicine (Nuclear Medicine). It has not been sent to any other universities. With that, this research can be used for consultation and photocopied as a reference.

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ABBREVIATIONS

ACS	Acute coronary syndrome
BNMS	British Nuclear Medicine Society
CAD	Coronary artery disease
CAG	Coronary angiography
CVD	Cardiovascular disease
CZT	Cadmium zinc telluride
EANM	European Association of Nuclear Medicine
ECG	Electrocardiogram
EST	Exercise stress test
HKL	Hospital Kuala Lumpur
IV	Intravenous
keV	kiloelectronvolt
LV	left ventricle
Mbq	Megabecquerel
mSv	millisievert
MI	Myocardial infarction
MPI	Myocardial perfusion imaging
MRI	Magnetic resonance imaging
MSCT	Multi-slice computed tomography
NCVD-ACS	National Cardiovascular Disease-Acute Coronary Syndrome
PET	Positron emission tomography
SPECT	Single photon emission computed tomography
STEMI	ST-elevation myocardial infarction
Tc-99m	Technetium-99m

ABSTRAK

Pengenalan: *Dipyridamole* adalah sejenis ubat yang digunakan untuk mengembangkan salur darah koronari dan secara tidak langsung ia digunakan sebagai satu cara untuk menguji tekanan kepada jantung. Ubat ini mempunyai banyak kesan sampingan di mana ia mungkin berkait atau pun tidak berkaitan dengan masalah jantung.

Objektif: Kajian ini bertujuan untuk mengesan kemungkinan kesan sampingan *dipyridamole* dan kaitannya dengan elektrokardiografi (EKG) dan skan perfusi jantung.

Kaedah: Kajian prospektif ini dilakukan ke atas 363 pesakit yang telah menjalani ujian tekanan skan perfusi jantung menggunakan *dipyridamole*. Kesan sampingan ubat *dipyridamole* dan perubahan dalam EKG direkodkan. Pengimejan perfusi jantung dijalankan mengikut protokol.

Keputusan: Seramai 363 pesakit dengan purata umur 59.9 ($\pm$ 11.10) tahun telah dianalisa. 251orang pesakit (69.1%) mengalami kesan sampingan dipyridamole semasa prosedur dijalankan. Sakit kepala menunjukkan peratusan kesan sampingan yang paling tinggi (32.8%) diikuti dengan sakit dada dan sakit perut (masing-masing 24.6% dan 23.5%). Walau bagaimanapun, hanya sakit dada yang menunjukkan nilai statistik yang signifikan dengan kedua-dua penemuan EKG dan MPI yang tidak normal ($p < 0.05$).

Kesimpulan: Enam puluh sembilan peratus pesakit mengalami kesan sampingan dari ujian tekanan jantung menggunakan dipyridamole. Dalam banyak-banyak kesan sampingan, hanya sakit dada yang mempunyai kaitan yang signifikan dengan perubahan dalam EKG dan keputusan pengimejan perfusi jantung yang tidak normal.

ABSTRACT

Introduction: Dipyridamole is an indirect coronary artery vasodilator which is one of the drugs used in pharmacological stress test during myocardial perfusion imaging (MPI). It has many adverse effects which could be or could not be related to the diseased myocardium.

Objective: The purpose of this study is to investigate the adverse effects of dipyridamole and its correlation with ECG and myocardial perfusion imaging findings.

Methods: This prospective study includes 363 patients who have undergone dipyridamole myocardial perfusion stress imaging. Dipyridamole adverse effects were documented. ECG changes were recorded. Stress and rest myocardial perfusion imaging were done as per protocol.

Results: A total of 363 patients with mean age of 59.8 (±11.10) were analysed. 251 patients (69.1%) demonstrated some forms of adverse effects. The most prevalent of these adverse effects was headache (32.8%) followed by chest pain and abdominal pain (24.6% and 23.5% respectively). However, only chest pain showed significant statistical value with both abnormal ECG and MPI findings ($p < 0.05$).

Conclusion: Sixty-nine percent of the patients experience adverse effects during dipyridamole myocardial perfusion stress imaging. Among all adverse effects, only chest pain is significantly related to ECG changes and abnormal MPI findings.

CHAPTER 1

RESEARCH BACKGROUND

1.1 Introduction

Myocardial perfusion imaging (MPI) is recognised as one of the modalities used in diagnosing and follow up of coronary artery disease (CAD) patients (Fihn et.al., 2012). It is performed in nuclear medicine facilities using intravenous injection of Technetium-99m (Tc-99m) sestamibi or tetrofosmin. MPI is divided into stress study and rest study which may be scheduled on the same day, a day ahead or after. For stress study it could be done using exercise machine like treadmill or ergometer; or pharmacology using vasodilator like dipyridamole, adenosine or regadenoson; or inotropic and chronotropic stressor for instance dobutamine or arbutamine (Henzlova et.al., 2016).

In a diseased state, stress-MPI helps to differentiate the differences in blood flow between normal and diseased coronary arteries. The differences in blood flow is induced either by increasing oxygen demand during exercise or forced vasodilatation through pharmacological reaction.

However, stress-MPI has its own limitation. Patients who are unable to achieve an adequate heart rate and blood pressure response either due to non-cardiac physical limitation (such as pulmonary, peripheral vascular or musculoskeletal abnormalities) or due to lack of motivation will result in lower diagnostic value (Henzlova et.al., 2016). As a consequences, pharmacologic stress-MPI is preferred over exercise stress test (EST) in patients whom unable to complete the EST (Leppo., 1994).

Even though the radiopharmaceuticals used for MPI have evolved over the years, most of the nuclear medicine facilities in Malaysia including our center in Hospital Kuala Lumpur (HKL) is still using dipyridamole during stress-MPI procedure due to its availability and cost effectiveness. Furthermore, other vasodilator agent like regadenosone is not readily available in local setting.

Dipyridamole is an indirect coronary artery vasodilator. It has many adverse effects such as chest discomfort, palpitation, abdominal discomfort, difficulty in breathing and others. Nausea or headaches are not uncommon and approximately 20% to 30% of patients may experience chest pain (Ziessman et.al., 2013). Most of the time these adverse effects have no correlation with acute ECG changes, but sometimes it does. In this study, we would like to see if patients who experienced dipyridamole adverse effects would have abnormal MPI findings. Hence, this study is conducted to look at dipyridamole adverse effects during stress MPI and its correlation with acute ECG changes and MPI findings.

1.2 Literature Review

1.2.1 Myocardial Perfusion Imaging (MPI)

MPI is considered as a non-invasive diagnostic procedure (Gupta et.al, 2019). For the last 25 years, MPI using single photon emission computed tomography (SPECT) has risen through its rank in establishing its role as coronary angiography gatekeeper worldwide (Sabharwal et.al., 2003). In Malaysia, Clinical Practice Guidelines for Myocardial Infarction has stated that MPI using SPECT was among the main tool for the assessment of CAD (Panel., 2007).

MPI provides functional imaging of the myocardium (Schuijf et.al., 2005). The relative regional distribution of perfusion can be assessed at stress, rest or both. The stress and rest study can be done as 1-day or 2-day protocol. The stress-MPI uses an intravenously administered radiopharmaceutical during some form of cardiovascular stress to map the blood flow distribution in the myocardium. Tc-99m sestamibi and Tc-99m tetrofosmin are the common radiotracers used in Malaysia and the latter in particular is used in nuclear medicine department, HKL. Pharmacological stress agents are valuable for patients who are unable to carry out physical exercise for variety of causes, including physical restrictions, some drugs, respiratory disease, peripheral vascular disease, motivational limitation and aortic aneurysms (Leppo., 1994). Vasodilator agents such as dipyridamole or adenosine, or inotropic and chronotropic agents such as dobutamine or arbutamine are the method of choice to increase coronary blood flow (Botvinick., 2009). In the beginning of the 21st century, regadenosone; a new class of selective adenosine 2A receptor agonist (FDA approval on April 10, 2008) was introduced (Saab et.al., 2017). It produces coronary vasodilatation and increases coronary blood flow, the same way adenosine and dipyridamole produce coronary vasodilation.

MPI is done using SPECT or SPECT in combination with computed tomography (CT). The low-dose CT is used for anatomical localisation as well as for attenuation correction of the single photon emission data. Dedicated cardiac SPECT cameras equipped with cadmium zinc telluride (CZT) detectors has been introduced in recent years, that could allow more accurate and faster evaluation of regional myocardial perfusion (Liga et.al., 2019). Through MPI stress and rest study, areas of comparatively reduced myocardial perfusion during stress study can be evaluated as ischemia or infarction, depending on the comparative images in the rest study.

A technologist's guide on myocardial perfusion imaging published by European Association of Nuclear Medicine (Lezaic., 2014), stated the indications for MPI are:

1. Diagnosis of CAD: presence, area of coronary territory, and disease extent (number of vascular territories involved).
2. Prognostic risk assessment in patients: both after myocardial infarction and preoperatively for major surgery that may be a risk for coronary events.
3. Assessment of myocardial viability: differentiating ischaemia from scar, and predicting improvement of left ventricular (LV) function after interventions.
4. Monitor the treatment effect post coronary revascularisation procedures.

1.2.2 Dipyridamole Stress-Myocardial Perfusion Imaging

1.2.2.1 Mechanism of Action

Dipyridamole is an indirect coronary artery vasodilator (Ziessman et.al., 2013). The dipyridamole administration used during stress-MPI has broadly been practiced simulating the effects of physical exercise in person who are unable to perform a conventional exercise stress test. It works by:

1. inhibiting the degradation of naturally occurring adenosine
2. indirectly increasing adenosine level in the blood
3. activating all adenosine receptor subtypes (A1, A2a, A2b and A3)

Collateral vessels and resting vasodilatation will maintain resting blood supply in ischaemic myocardium. Vasodilator (such as dipyridamole or adenosine) or increased oxygen demand (such as in exercise or due to inotropic agent) may cause flow difference between normal

and diseased vessels (stenosed). Further blood flow difference will expose the coronary flow reserve which cause significant difference between maximum and resting flow rates. Coronary steal phenomenon may further impact the decreased of relative and absolute blood flow in the stenosed vessels. These schematic representations of general pharmacologic stress-MPI were described in Figure 1.1.

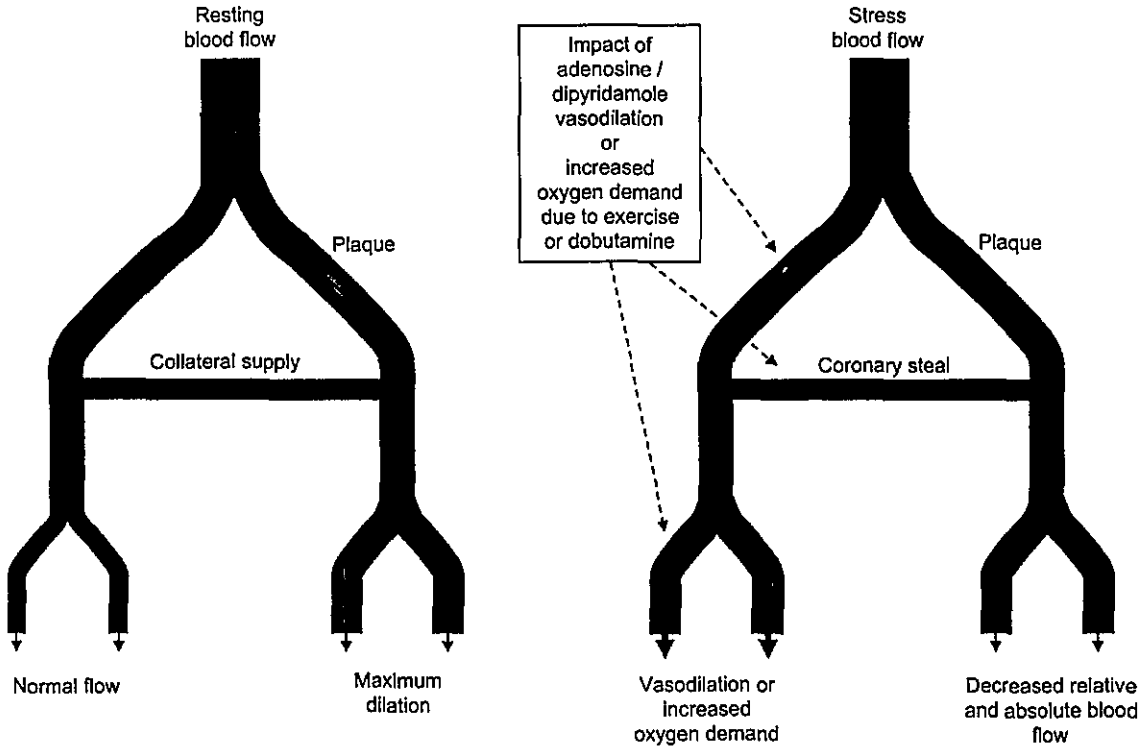


Figure 1.1. Schematic representation of general principle of pharmacologic stress in myocardial perfusion imaging. (Adapted from tech.snmjournals.org accessed on February 25, 2020).

With the infusion of dipyridamole, myocardial areas supplied by normal or near normal arteries will experience an increase in the blood flow up to 3 to 5 times above the baseline levels due to reduced coronary vascular resistance (Lezaic., 2014). In contrast to myocardium supplied by stenosed vessels may only have limited reserve capability to dilate thus cannot raise the blood flow at the same rate as seen in more normal territories.

An actual coronary steal can occur if the area distal to a severe stenosis is dependent on collateral flow for normal resting blood flow supply. With a pharmacologic stressor, the collateral flow may be significantly reduced, resulting in an absolute decrease in nutrient blood flow and subsequent production of acute myocardial ischemia. However, the production of true ischemia is not essential in order to produce a disproportion in regional blood flow that can be detected by MPI (Leppo., 1994).

However, some organs may express receptor subtypes heavily when compared to others as shown in Figure 1.2. These adenosine receptor subtypes activation causing a significant adverse effect to the patients. Some of the symptoms of adverse effects are chest discomfort, palpitation, shortness of breath, headache and others. Half-life of dipyridamole is approximately 30 to 45 minutes and the symptoms including flushing, chest pain, dyspnea and nausea are usually mild and transient. Throughout the procedure, patient is monitored accordingly, and intravenous aminophylline (antidote) is given if symptoms persist (Johnson et.al., 2010).

Expression level	A_1 receptors	A_{2A} receptors	A_{2B} receptors	A_3 receptors
High expression	Brain (cortex, hippocampus, cerebellum), spinal cord, eye, adrenal gland, atria (Poulsen and Quinn, 1998)	Blood platelets, olfactory bulb Spleen, thymus, leukocytes (Fredholm et al., 2002)	Cecum, colon, bladder (Cacciari et al., 2005)	Testis (rat), mast cells (rat) (Poulsen and Quinn, 1998)
Intermediate expression	Other brain regions, skeletal muscles, liver, kidney, adipose tissue (Poulsen and Quinn, 1998)	Heart, lung, blood vessels, peripheral nerves (Fredholm et al., 2002)	Lung, blood vessels, eye, mast cells (Cacciari et al., 2005)	Cerebellum, hippocampus (Poulsen and Quinn, 1998)
Low expression	Lungs (but probably higher in bronchi), pancreas (Poulsen and Quinn, 1998)	Other brain regions (Fredholm et al., 2002)	Adipose tissue, adrenal gland, brain, kidney (Cacciari et al., 2005)	Thyroid, most of brain adrenal gland, spleen, liver, kidney, heart (Poulsen and Quinn,

Figure 1.2 Distribution and expression of adenosine receptor (Adapted from: https://www.researchgate.net/figure/Distribution-and-expression-of-adenosine-receptors_tbl1_255987597 accessed February 23, 2020).

1.2.3 Adverse Effects During Dipyridamole Stress-Myocardial Perfusion Imaging

According to British Nuclear Medicine Society, there is low incidence of any serious events occurring during MPI-stress test when supervised by a physician as demonstrated in Table 1.1 (Wechalekar., 2012).

Table 1.1: Adverse effects rates during physician lead stress testing. (Adapted from British Nuclear Medicine Society, BNMS 2012).

Stress Types	Exercise N=518,448	Adenosine N= 9256	Dipyridamole N= 73,806	Dobutamine N= 1022
Death	25.9 (0.005%)	0	7 (0.01)	0
MI or serious arrhythmias	457 (0.08%)	647 (7%)	19 (0.03%)	42 (4.2%)

Flushing, chest pain, headache, dizziness, or hypotension are example of symptoms of adverse effects in 50% of patients during dipyridamole stress-MPI (Henzlova et.al., 2006). However, the incidence is fewer with adenosine infusion. The occurrence of AV block with dipyridamole about 2% which is less than adenosine. Myocardial infarction (either fatal or non-fatal) is very uncommon which account for only 0.26% of dipyridamole stress-MPI (Henzlova et.al., 2016, Lette et.al., 1995). They recommended the availability of intravenous aminophylline throughout the stress procedure to counter any of the adverse events which comes handy when needed (Gupta et.al, 2019).

Boehringer Ingelheim Limited 2015 listed dipyridamole adverse effects from very common to the least as below (adapted from :https://www.drugs.com/uk/ persantin-ampoules-10mg-2ml-solution-for-infusion-leaflet.html accessed February 1, 2020):

- Very common (1 in 10 cases)
    - Headache
    - Chest pain
    - Dizziness
- Common (less than 1 in 10 but more than 1 in 100 cases)
    - Palpitation
    - Paraesthesia
    - Hot flushes
    - Nausea
- Uncommon (less than 1 in 100 but more than 1 in 1000 cases)
    - Difficulty in breathing/wheezing
    - Abdominal discomfort
- Rare (less than 1 in 1000 but more than 1 in 10000)
    - Shortness of breath
- Very rare (less than 1 in 10000)
    - Serious allergy reaction
    - Fits
    - Stroke
    - Cardiac arrest
    - Ventricular fibrillation
    - Not known

Recent study by Lee et.al., (2017) on dynamic evaluation upon dipyridamole-induced adverse effects during MPI demonstrated that 96 patients or 69.6% suffer from drug adverse effects. The most common symptoms recorded were dizziness, chest tightness, abdominal discomfort and headache which accounted about 42.8%, 24.6%, 18.1% and 15.2% respectively. This study has shown that aminophylline treatments were given to 18 patients due to the following symptoms of adverse reactions upon the stress procedure. Thirty-six minutes was the median duration of symptom which were generally acceptable for clinical use.

Eighty-eight patients or about 14.9% complained of at least one adverse effect during infusion of dipyridamole, as reported by Javadi et.al., (2010). The most frequent complaint was chest discomfort which accounted for 5.2% of the patients.

In a recent study by Amer et.al., (2017) on a comparison of the frequency of adverse effects in patients undergoing MPI with regadenoson and dipyridamole, they found that patients whom received dipyridamole infusion experienced lower proportion of an adverse effects than those who were in regadenoson group (56.7% vs 84.9%, $p<0.0001$). However, none of the patient in both groups needed early termination of stress-MPI due to severe adverse reactions. There were no significant differences between both groups regarding aminophylline reversible effect or other management to treat adverse reactions. In the post-conversion dipyridamole group, the overall drug cost saving was $51,526. Hence, the study has shown that for patients undergoing MPI-stress test, dipyridamole showed lesser adverse events compared to regadenoson and it offers a safe and cost-effective alternative to regadenoson for myocardial perfusion imaging.

1.2.4 Adverse Effects During Dipyridamole Stress-Myocardial Perfusion Imaging with ECG Changes

Javadi et.al., (2010) reported that abnormal ECG findings were seen in 191 patients (32.4%). In their study, abnormal ECG was defined as a 0.1-mV horizontal or down-sloping ST segment depression of 80ms after the J point. The incidence of adverse effects was seen in patients with abnormal ECG findings than those patients with normal ECG findings, 32.9% and 6.2% respectively. The adverse effects that correlated with abnormal ECG findings were chest discomfort, headache and shortness of breath.

1.2.5 Adverse Effects during Dipyridamole Stress-Myocardial Perfusion Imaging with Abnormal Scintigraphic Findings

Myocardial ischaemia is seen as perfusion defect at stress images that resolves in rest images while myocardial infarction is seen as perfusion defect at both stress and rest images. Both of these findings are considered abnormal MPI. Besides these, a grossly dilated heart is also considered abnormal. Left ventricular ejection fraction in normal subjects' ranges from 50% to 75% (Ziessman et.al., 2013).

Javadi et.al., (2010) reported that abnormal MPI findings were seen in 287 patients (48.6%). Patients whom developed adverse effect during dipyridamole infusion were associated with higher abnormal MPI findings compared to patients with normal MPI findings (22.6% vs. 7.5%; p value = 0.05). They defined abnormal MPI as findings other than normal.

Meyers et.al. had retrospectively investigated on 933 patients who had undergone dipyridamole stress-MPI and demonstrated that 44.3% of them had adverse effects. The most prevalent adverse effects were headache (37.1%), followed by chest pain (12.1%) and nausea (11.1%). They also revealed that patients who experienced adverse effects during dipyridamole infusion had 10% more risk to show abnormal perfusion imaging (Meyers et.al., 2002b).

1.3 Rationale / Benefit of the Study

Adverse effects of dipyridamole were described before. Shortness of breath, chest pain and headache were some of the many adverse effects of dipyridamole that we were familiar with. This study was conducting prospectively to document any adverse effects which were probably not documented before. Most studies related to dipyridamole did not associate the adverse effects with both ECG changes and MPI scintigraphic findings. Hence, I took the initiative to find any correlation between the adverse effects of dipyridamole with ECG changes and also MPI scintigraphic findings.

If this study is able to demonstrates a correlation between adverse effects of dipyridamole with ECG and abnormal scintigraphic findings, early intervention and precaution can be taken during the stress procedure by the attending doctor. Thus, it helps to prevent further deterioration and carry out an optimum patient's care.

CHAPTER 2

OBJECTIVE AND HYPOTHESIS

2.1 General Objective

To evaluate the adverse effects during dipyridamole stress-myocardial perfusion imaging and its significance

2.2 Specific Objectives

- To associate the adverse effects during dipyridamole stress-MPI with ECG findings
- To evaluate the adverse effects during dipyridamole stress-MPI with scintigraphic findings

2.3 Hypothesis

- Null hypothesis: There is no correlation between adverse effects during dipyridamole stress-MPI with ECG and/or scintigraphic findings.
- Alternate hypothesis: There is a correlation between adverse effects during dipyridamole stress-MPI with ECG and/or scintigraphic findings.

CHAPTER 3

MATERIAL AND METHODS

3.1 Study Design and Sampling Method

This is a prospective study with convenient sampling method.

3.2 Study Location, Recruitment Period and Study Sample

This study was done in Department of Nuclear Medicine, Hospital Kuala Lumpur (HKL) from April 2018 until November 2019. All patients scheduled for dipyridamole stress-MPI was included in this study. The referrals received were mainly from in-house medical department and other departments or from other primary or secondary district hospitals in West Malaysia.

3.3 Inclusion Criteria

Patients scheduled for dipyridamole stress-MPI.

3.4 Exclusion Criteria

- Recent myocardial infarction (MI) within seven days.
- Patients who were contraindicated to dipyridamole such as history of asthmatic, bronchospasm or known allergic to dipyridamole.
- Consumed caffeine or xanthine less than 24 hours prior to study.
- Pregnancy or breast-feeding woman.
- Patients who were unable to complete the MPI study.

3.5 Study Samples and Sample Size Calculation

Reference population was the patients undergoing MPI study in Kuala Lumpur, Malaysia. Source population was the patients undergoing MPI in HKL. The sampling population was all patients who were referred to Department of Nuclear Medicine, HKL for MPI. Study subjects were from all consented patients referred for dipyridamole stress-MPI study.

To investigate the adverse effects during MPI dipyridamole stress test, sample size estimation was performed using 1 population proportion formulae (Lemeshow, Hosmer, Klar, Lwanga, & Organization, 1990). Prior data (Lee et.al, 2017) indicated that the proportion of adverse effects during Dipyridamole stress-MPI was 0.697. If the Type I error probability and precision are 0.05 and 0.05, 326 samples need to be studied. With an additional of 10% dropout rate, the sample size is 363 samples.

Therefore, to meet the objectives of this study, the sample size of 363 was used.

3.6 Research Tool

Data collections in this study were recorded into: Patient's information data sheet (Refer to Appendix 2).

3.7 Data Analysis

All analyses were carried out using SPSS (IBM Corp. Released 2011 IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). All p values < 0.05 are considered statistically significant.

Demographics of the patients were summarised using descriptive studies. Continuous variables were described by summary statistics (means and standard deviations) for normally distributed variables. If the distribution is not normal, median with inter-quartile range will be reported instead. Other descriptive statistics, such as minimum and maximum values will be reported when necessary. Categorical (nominal/ordinal) variables were described by frequencies with percentages.

Chi-Squared test or Fisher Exact test (when minimum expected count is less than 5) was used for categorical variables. Comparison of proportion for categorical data were performed using Chi-square test. A p value < 0.05 is considered statistically significant. Univariate analysis using binary logistic regression was used to determine the association between independent variables and dependent variables. The result would produce crude odd ratio with 95% confident interval and p value < 0.05 was considered to be significant. Multivariate analysis was carried out for variables with p value < 0.05.

For analytic purposes, MPI findings which showed both (ischemic and infarct features) were not included in the statistical analysis.

3.8 Variables Definition

- Adverse effects were defined as undesired harmful effects resulting from medication or other intervention. Dipyridamole adverse effects from very common to the least was adopted from Boehringer Ingelheim Limited 2015.
    - Very common (1 in 10 cases)
        - Headache
        - Chest pain

- Common (less 1 in 10 but more than 1 in 100 cases)
    - Palpitation
    - Hot flushes
    - Nausea
- Uncommon (less than 1 in 100 but more than 1 in 1000 cases)
    - Difficulty in breathing
    - Abdominal discomfort

Very common to uncommon (1 in 10 to 1 in 1000 cases) were included in this study. While sweating, vomiting and neck pain were observed in our department during dipyridamole stress-MPI procedure, thus they were included in this study. Rare and very rare adverse effects were not included (occur in 1 in 10 000 cases).

- Electrocardiography (ECG) records the electrical activity of the heart.
    - Abnormal ECG was defined as one showing a 0.1-mV horizontal or down-sloping ST segment depression of 80ms after the J point (Javadi et.al., 2010).
    - Whereas ECG manifestation of acute changes in this study were defined as:
        - ST depression > 2 mm from baseline.
        - ST elevation > 1 mm from baseline.

Those patient with other ECG changes that were different from baseline such as arrhythmias, any Q wave, any T wave inversion, premature ventricular contraction (PVC), premature atrial contraction (PAC) or bundle block changes were recorded as no ST segment changes.

- MPI findings were categorised as:
  - Normal is defined as myocardium without fixed or reversible defect on MPI.
  - Abnormal MPI was divided into myocardial ischaemia and myocardial infarction:
    - Myocardial ischaemia is defined as defects at stress with complete or partial reperfusion at rest study.
    - Myocardial infarction is defined as fixed perfusion defect in both stress and rest study.

3.9 Data Collection and Procedure

All patients referred for MPI using dipyridamole stress study were eligible for recruitment. Patients that meet the inclusion criteria were recruited.

Nuclear Medicine Department, HKL follows a two days' protocol for MPI study. Patients were explained regarding the procedure and risk. Written consent was obtained from patients. In our center, symptoms of patients receiving dipyridamole for MPI stress study were recorded in the patient's file throughout the procedure.

The images were reviewed separately by two independent nuclear medicine physicians who were blinded to the clinical findings. Disagreements between reviewers were resolved by discussion or third reviewer when necessary.

Data was collected by principal investigator from the clinical records provided by the referring specialist, history taking from patients and reported imaging.

3.9.1 Dipyridamole Stress- MPI and Rest Protocol

The procedure for dipyridamole stress-MPI study were done according to Nuclear Medicine Department, HKL protocol. Dipyridamole was administered at 0.56mg/kg intravenously over a 4-minute period (142ug/kg/min):

- IV Tc -99m tetrofosmin 15mCi was administered at the 7th minute as shown in figure 3.1. According to (Einstein et.al., 2015) characterization of patient radiation doses from MPI and the use of radiation optimizing best practices worldwide found 36mCi is the highest recommended activity in guidelines. Whereas, Henzlova et al., (2016) recommended 8-12mCi.
- Patients were monitored continuously throughout the procedure up to 15 minutes with 12 lead ECG monitoring.
- The ECG, heart rate and blood pressure of all patients were recorded both before and after dipyridamole administration; every 2 minutes for at least 15 minutes once stress test began
- All symptoms were observed and recorded upon the procedure of dipyridamole stress-MPI study. Antidote (aminophylline) was given accordingly. Record was written if aminophylline had been used to relieve adverse effects.
- After stress procedure, patients were asked to take foods preferably "fatty meals" and to wait in the rest area for another 1 hour before proceeding with the imaging.
- Approximate duration of each patient to complete the MPI stress study was up to 4 hours from registration to imaging.

For rest study, Tc-99m IV Tetrosfosmin 15mCi was administered on a different day (within 4 weeks following the dipyridamole stress-MPI) and the imaging was performed after 1 hour of post injection.

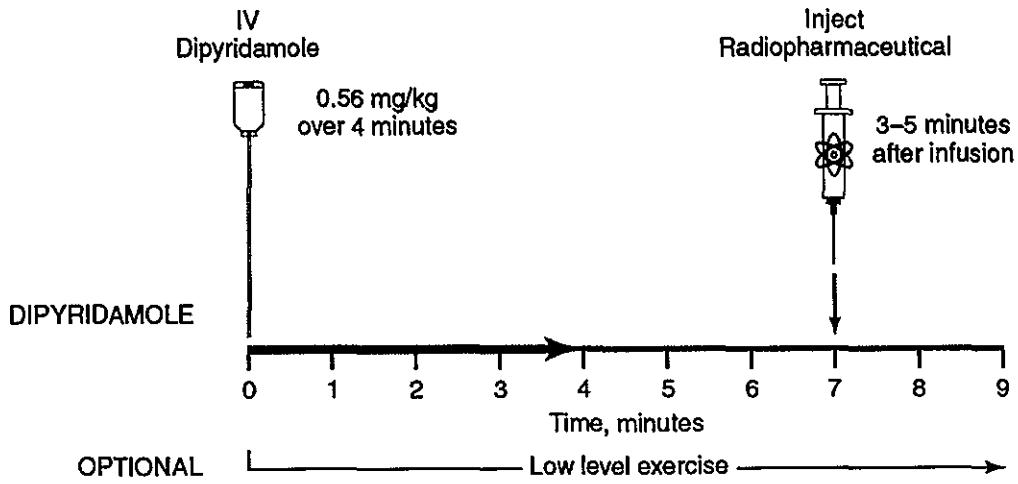


Figure 3.1: Dipyridamole protocol. *IV,* Intravenous; *kg,* kilogram; and *mg,* milligram (adapted from Henzlova et.al., 2016 accessed February 20, 2020).

3.9.2 ECG Analysis

ECG interpretation was done by the nuclear medicine physician and medical officer without knowing the results of MPI. ECG interpretation was done according to the criteria outlined as described earlier in variables definition. It was then entered into data collection form (Appendix 2).

3.9.3 Acquisition Protocol of SPECT Gamma Camera

The patient underwent ECG gated stress-rest study. Images were acquired using Siemens e.cam (Siemens Medical Solutions) dual-head gamma camera equipped with low-energy high resolution (LEHR), photo peak at 140 keV with 20% energy window, parallel-hole collimators and 128 x 128 matrix. Myocardium images were acquired over 180° orbit (starting from 45-degree right anterior oblique to 135 degree left posterior oblique). The images were then reconstructed using a standardised setting filter (180 filtered back projection and ramp filter). During the procedure, patient was in supine position with left arm raised.

3.9.4 Image Analysis

Raw datasets were reviewed in cinematic display to determine any artifact due to patient motion or any extra cardiac uptake. The commonest artefact was motion related artefact which manifested as discontinuities or breaks in the normally smooth curvature of the sonogram. The stress and rest images were displayed simultaneously. Static images were displayed in the short-axis, vertical long-axis, and horizontal long-axis views. The interpreter was allowed to modify the alignment of the images, the window, and the intensity, in order to select the most appropriate display of static slices.

Interpreter rated the perfusion of the segments for both stress and rest using a 5-point scoring system (0 = normal, 1 = mildly decreased, 2 = moderately decreased, 3 = poor uptake, and 4 = absent uptake). Defects with similar perfusion at stress and rest were designated as "fixed"; defects at stress with complete normalization or partial improvement at rest, "reversible"; and no defects at stress and rest, "normal". The MPI findings was finally concluded as normal or abnormal (ischaemia or infarction).

3.10 Ethical Consideration

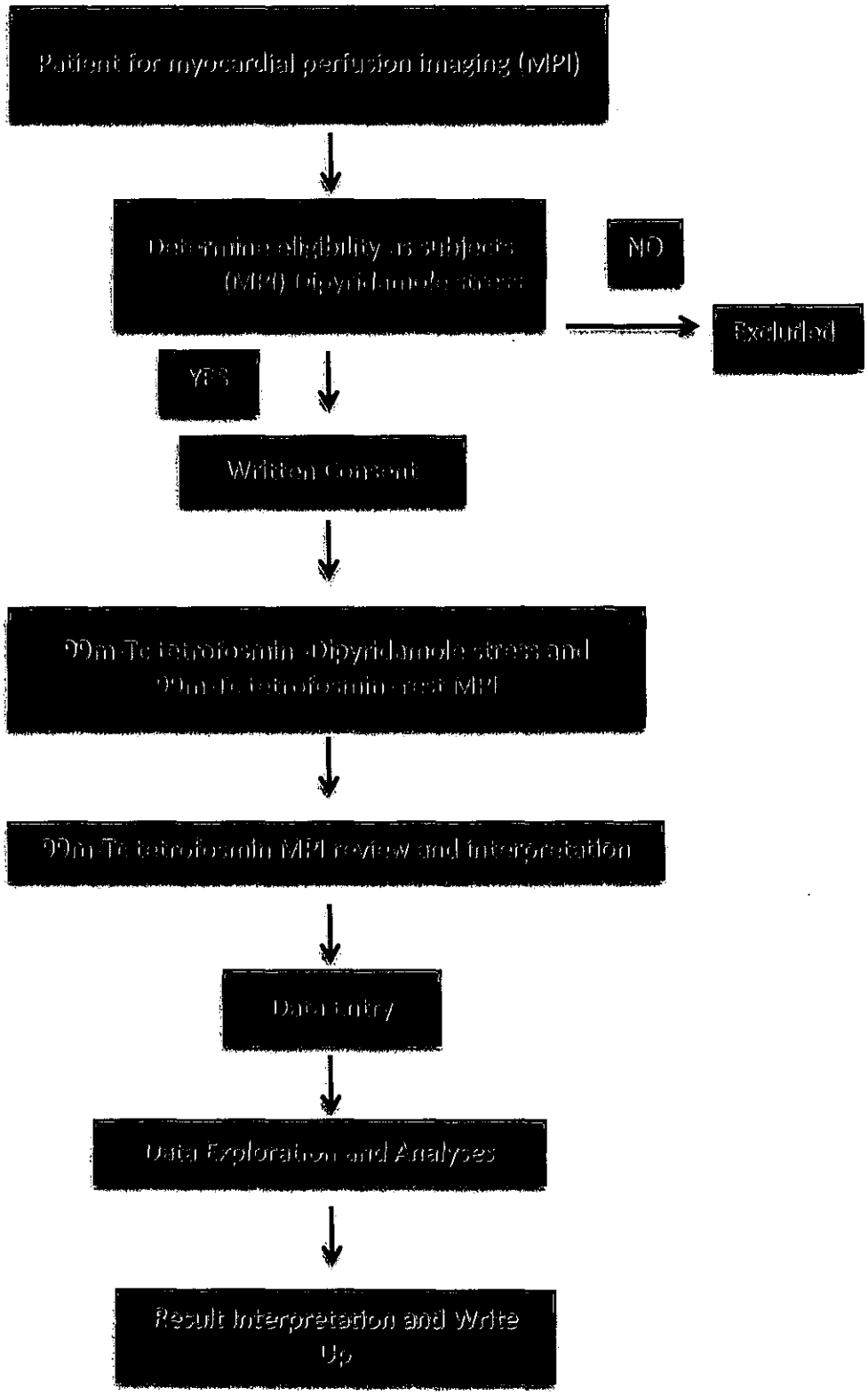
This study has been approved by Human Research Ethics Committee USM and Clinical Research Centre, National Institutes of Health in the Ministry of Health, Malaysia (Appendix 1a and 1b). Information and data collected during the research period is kept confidential. Written informed consent for this Tc99m-tetrofosmin dipyridamole stress-MPI was obtained from patients. Patients were allowed to refuse consent to participate in this study.

This study did not involve any investigational products. Dipyridamole stress-MPI study has been widely practiced and recognised as a safe procedure. This is a routine procedure and risks are related to the procedure per se not to the study or conduct of the study.

3.11 Privacy and Confidentiality

Subject's names were kept on a password-protected database and were linked only with a study code number for this research. All data have been entered into a computer that is password protected. On completion of study, data in the computer have been copied to CDs. CDs and any hardcopy data were stored in a locked office of the investigators and would be kept for a minimum of three years after the completion of the study. The CDs and data would be destroyed after that period of storage.

3.12 Study Flow Chart



4.2 Adverse Effects During Dipyridamole Stress-MPI

Out of 363 patients, more than half of the patients (n=251; 69.1%) developed symptoms (adverse effect of dipyridamole) during the study. The number and percentage of patients having adverse effect during the study are shown in Table 4.2.

Table 4.2: To study the adverse effects during dipyridamole stress-MPI

Adverse Effects	Number of patients (n)	(%)
Yes	251	69.1%
No	112	30.9%
Total	363	100%