THE EFFECT OF FATTY MEAL, MILK AND WATER ON THE SUB-DIAPHRAGMATIC ACTIVITY IN TC-99M TETROFOSMIN MYOCARDIAL PERFUSION IMAGING

BY

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DECLARATION

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

NOORAISHAH BINTI SAADON

P-IPM 0025/19

Date: May 15th, 2024

DISCLAIMER

I hereby declare that this dissertation records the results of the study performed by me and that it is of my own composition. I declare that I have no financial interest in the instruments or materials used in this study.

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May Allah S.W.T. grant everyone hidayah, aafiyah and jannah. For indeed to Him we belong and to Him we will return.

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LIST OF ABBREVIATIONS

AC	Attenuation correction
ACS	Acute coronary syndromes
ASNC	American Society of Nuclear Cardiology
AV	Atrioventricular node
CAD	Coronary artery disease
CT	Computed tomography
EANM	European Association of Nuclear Medicine
JEPeM	Jawatankuasa Etika Dan Penyelidikan Manusia
keV	Kiloelectron volts
LAD	Left anterior descending artery
LCA	Left coronary artery
LCx	Left circumflex artery
mCi	Millicurie
MPI	Myocardial perfusion imaging
NAC	Non-attenuation correction
PDA	Posterior descending artery
RCA	Right coronary artery
ROI	Region of interest
SA	Sinoatrial node
SPECT	Single photon emission computed tomography
Tc-99m	Technetium-99[metastable]
Tl-201	Thalium-201 chloride
USM	Universiti Sains Malaysia

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ABSTRAK

Latarbelakang: Terdapat beberapa cara untuk mendiagnosa penyakit arteri koronari dan Skan Perfusi Jantung (MPI) adalah salah satu alat diagnostiknya. Salah satu cabaran praktikal dalam tafsiran imbasan ini ialah aktiviti sub-diafragma yang mengganggu dengan visualisasi jantung yang sesuai. Pendekatan yang berbeza dinilai untuk menangani masalah ini. Kaedah yang agak biasa ialah penggunaan makanan yang mengandungi lemak sebelum pengimejan. Walau bagaimanapun, makanan berlemak boleh menyebabkan beberapa masalah bagi sesetengah pesakit, serta kos tambahan. Kajian ini bertujuan untuk menyiasat kesan makanan berlemak, susu, dan air sebagai kaedah persediaan sebelum MPI dan seterusnya dalam penilaian keputusan dan laporan.

Metodologi: Seramai 150 pesakit (umur 58.86 ± 12.05 tahun) telah mendaftar dalam kajian ini. Pesakit secara rawak dibahagikan kepada tiga kumpulan. Pesakit-pesakit ini menjalani protokol dua hari MPI. Pada hari ujian tekanan farmakologi, mereka diberi makanan berlemak dan semasa ujian rehat, individu dalam Kumpulan 1 diberi makanan berlemak; mereka yang berada dalam Kumpulan 2 350ml susu; dan Kumpulan 3 350ml air. Kedua-dua teknologis dan pembuat laporan (pakar) tidak dimaklumkan berkenaan kumpulan persediaan bagi setiap pesakit. MPI dilakukan untuk semua pesakit dan aktiviti sub-diafragma ditentukan secara visual pada imej yang dibina semula.

Keputusan: Kedua-dua penilaian visual dan separa kuantitatif bagi semua kumpulan menunjukkan perbezaannya tidak signifikan secara statistik.

Kesimpulan: Kajian ini menunjukkan bahawa skan yang dilakukan dengan persediaan makanan berlemak, susu, dan air sebelum skan perfusi jantung mempunyai hasil yang setanding dari segi kualiti imej dan laporan skan.

ABSTRACT

Background: There are multiple methods available for diagnosing coronary artery disease (CAD), including myocardial perfusion imaging (MPI). One of the challenges to interpret MPI findings is the interfering sub-diaphragmatic activity with appropriate cardiac visualisation. Various methodologies were assessed in order to overcome this issue. A relatively common method is the consumption of fatty meals before proceeding with the scan. Nevertheless, consumption of high-fat meals may result in adverse effects for certain patients, in addition to incurring additional expenses. The aim of this study is to investigate the impact of consuming a high-fat meal, milk, or water before undergoing MPI and to aid in the interpretation of the results.

Methods: A total of 150 patients (age 58.86 ± 12.05 years) were enrolled in this study. The patients were randomly divided into three groups. These patients underwent a two-day protocol of MPI. During the day of the pharmacological stress study, they were given a fatty meal. During the rest study, fifty the patients in Group 1 were given a fatty meal, fifty in Group 2 were given 350 ml of milk and fifty patients in Group 3 were given 350 ml of water. The study was double blinded for both patients and interpreters. Stress and rest MPI studies were performed for all patients and the sub-diaphragmatic activity was determined visually, and semi-quantitatively on the reconstructed images.

Results: The difference between all groups, as determined by semi-quantitative and visual evaluations, is not statistically significant.

Conclusion: The findings of this comparative study indicated that scans conducted after preparing fatty meal, milk, and water prior to MPI yielded similar interpretations and image quality.

CHAPTER 1

INTRODUCTION

Coronary artery disease (CAD) is acknowledged as the leading cause of illness and death from non-communicable diseases (NCD) worldwide, including in Malaysia. CAD has a wide spectrum of symptoms, from asymptomatic individuals to those with acute coronary syndromes (ACS) and sudden cardiac death. Angina in CAD results from a transient and correctable mismatch between the heart muscle's oxygen demand and oxygen supply, causing myocardial ischemia. In an ACS, the blood clotting related to the ruptured plaque becomes the main focus over the entire disease process and symptoms.

Utilising single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) using technetium 99m (Tc-99m) -labelled radiopharmaceuticals with exercise or pharmacological stress is a recognised diagnostic tool for diagnosing, predicting outcomes, monitoring treatment effectiveness, and evaluating myocardial wall viability in patients with coronary artery disease. This diagnostic method can identify CAD with a sensitivity of 90% and a specificity exceeding 80%. MPI is a complex physiological imaging technique that is vulnerable to a range of potential mistakes and artefacts that could impede its effectiveness and analysis. Challenges may arise throughout any stage of the imaging process and can be classified as problems related to patients, equipment, or technologists (Heinle and Siraj, 2009).

Besides Thalium-201 chloride (Tl-201) and Tc-99m Sestamibi, other radiopharmaceutical used for SPECT MPI is Tc-99m-1,2-bis[bis(2-ethoxyethyl) phosphino] ethane, also known as Tc-99m Tetrofosmin (Brand name: Myoview). This radiopharmaceutical is a lipophilic cation that specifically accumulates and remains in the mitochondria of the heart muscle cell. The substance has a decay half-life of 6 hours and releases gamma rays with an energy of 140 keV. After intravenous delivery, the chemical rapidly clears from the bloodstream and is swiftly absorbed by the myocardium. The extraction of this radiopharmaceutical increases in direct correlation with the rate of blood flow. Heart-to-lung and heart-to-liver ratios rise with time due to the chemicals being cleared by the liver and kidneys. It exhibits quicker hepatic clearance, enabling early imaging (Verberne et al., 2015).

Sub-diaphragmatic activity, also referred to as infra-cardiac and extra-cardiac activity, originates from organs such as the liver, biliary tract, stomach, or bowel. This activity can cause misinterpretation of results due to the proximity of these organs to the heart, which is situated just above the left lobe of the liver and close to the bowel (Malek et al., 2015; Qutbi, 2018). Tc-99m agents like Tetrofosmin or Sestamibi can accumulate below the diaphragm, potentially causing interference with activity in the perfusion patterns of the inferior myocardial wall, leading to an inferior wall artefact. Several methods have been suggested to improve the approach of reducing this artefact and its undesired effects, that involves extended stays at the facility for repeat scanning, which could lead to increased discomfort or the need for a new appointment if the scan is not interpretable due to low image quality.

CHAPTER 2

LITERATURE REVIEW

2.1 Normal anatomy of heart

The heart is a central mediastinal organ encased by the pericardium. The heart consists of three layers: the epicardium (outside lining), myocardium (middle and thickest muscular layer), and endocardium (innermost layer). The heart is divided by a septum into the right and left atria and ventricles. The atria receive blood from the venous system and lungs, then contract to push the blood into the ventricles. The ventricles then push the blood either to the lungs or around the body.

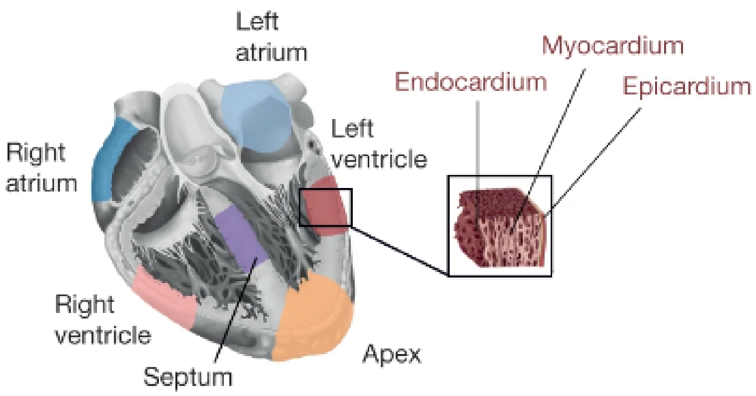

Figure A Human heart and the layer (Litviňuková et al., 2020).

The heart consists of four valves: the aortic, pulmonary, mitral, and tricuspid valves. The heart's conduction system comprises the sinoatrial node (SA node), atrioventricular node (AV node), atrioventricular bundle, right and left terminal branches, and Purkinje fibres.

2.2 Coronary arteries and regions

The heart receives blood from the left mainstem, commonly referred to as the left coronary artery (LCA), and the right coronary arteries (RCA). The LCA divides into the left anterior descending artery (LAD) and left circumflex artery (LCx). It provides blood to the front two-thirds of the interventricular septum, the apex, and the front part of the right and left ventricles. In 10 to 15% of individuals, the LCx connects with the RCA to create the posterior descending artery (PDA). It provides blood to the left atrium and the lateral wall of the left ventricle.

The main branches of the RCA include the PDA which supplies blood to the back of the interventricular septum and the AV node, the sinoatrial nodal branch providing blood to the right atrium and the SA node, and the right marginal branch supplying a section of the right ventricle and the lower wall of the left ventricle. In two-thirds of cases, the RCA is the main artery due to the provision of a branch known as the PDA. One-third of patients exhibit a left dominant circulation, in which the left circumflex artery branches to the posterior descending artery.

The disruption or obstruction of the coronary arteries, mainly termed as CAD, will affect the blood flow and perfusion, supplied to the designated regions. The anatomical coronary artery regions form the basis of the 17-segment model commonly used in cardiac imaging for identifying this problem, including Nuclear Medicine's MPI.

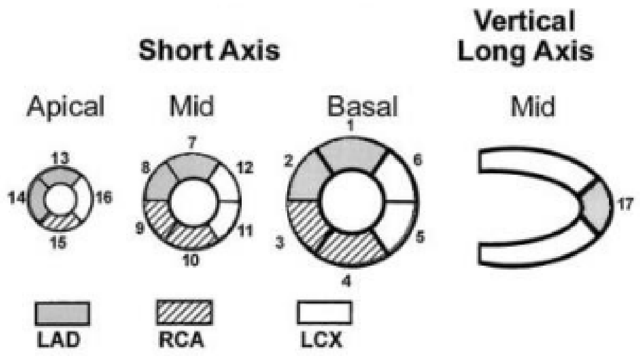

Figure B Coronary artery territories in a 17-segment model. Standard myocardial segmentation, assigning all 17 myocardial segments to the territories of the left anterior descending (LAD), right coronary artery (RCA), and left circumflex (LCX) (Verberne et al., 2015).

2.3 Definition and pathophysiology of coronary artery disease

CAD is a medical condition marked by the constriction or blockage of the heart's blood arteries caused by the accumulation of fatty deposits called plaque. Myocardial ischemia is a condition that reduces blood supply to the heart muscle, leading to various symptoms and potential complications. CAD presents a variety of clinical symptoms, ranging from asymptomatic atherosclerosis to stable angina, ACS, and congestive heart failure. Common risk factors for CAD are diabetes mellitus, hypertension, hypercholesterolemia, obesity, smoking, physical inactivity, and a family history of heart disease or metabolic disorders such diabetes mellitus.

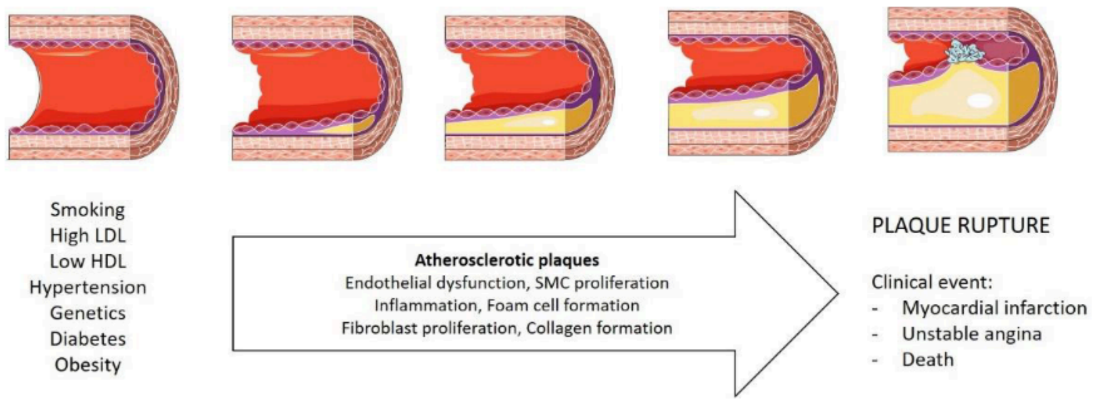

Figure C Coronary artery disease progression. LDL, low-density lipoproteins; HDL, high-density lipoproteins; SMC, smooth muscle cells (Conceição et al., 2020).

The symptoms of CAD vary according to the extent of blockage in the coronary arteries. Symptoms can vary from chest pain or discomfort (angina) to shortness of breath, exhaustion, dizziness, palpitations, and potentially a heart attack if blood flow is fully obstructed. Diagnosing CAD often includes assessing medical history, doing a physical examination, blood tests, and several imaging procedures like electrocardiography, echocardiography, stress test, CT scan, angiography, and MPI.

Treatment approaches for CAD focus on alleviating symptoms, enhancing cardiovascular circulation, and minimising the risk of adverse cardiac events. The primary treatment approach involves lifestyle modifications such as adopting a nutritious diet, engaging in consistent physical activity, quitting smoking, and managing other risk factors. Following the prescribed prescriptions and adhering to them will help manage blood pressure, decrease cholesterol levels, lessen the heart's workload, and prevent blood clots. Angioplasty or coronary artery bypass grafting may be necessary invasive procedures to restore blood flow to the heart. Early detection and appropriate management of CAD can greatly reduce the chances of complications and improve long-term outcomes.

2.4 Disease burden of coronary artery disease

In Malaysia, CAD has been the primary cause of death for both males and females for over a decade. There has been a small decrease in mortality rates in recent years according to the Ministry of Health in 2018. This ailment ranks as the fourth leading cause of hospitalisation in government hospitals under the Ministry of Health Malaysia, accounting for 8.01% of cases. It also stands as the primary cause of death, representing 15.0% of the 109164 medically certified deaths in 2019, with males at 17.3% and females at 11.4%. In 2020, the World Health Organisation estimated that 36729 individuals in Malaysia died from CAD, accounting for 21.86% of all fatalities. In most Western countries, death from CAD has been reducing gradually due to efficient primary prevention measures, improved diagnosis technologies, and rapid treatment.

2.5 Myocardial Perfusion Imaging

2.5 Myocardial Perfusion Imaging

MPI has been used to diagnose cardiovascular disease, assess patients' risk levels for prognosis, measure the effectiveness of medicine, and track the perfusion and vitality of the myocardium. The sensitivity of this method for diagnosing CAD is 90% and the specificity is 84% (MOH, 2018). Zanial et al (2023) found that 50.9% of patients sent to the Nuclear Medicine Department at Hospital Kuala Lumpur for CAD screening had abnormal MPI values. Despite the usefulness, MPI is a complex physiological imaging technique that has some potential limitations and artefacts that could limit its utility for research (Heinle and Siraj, 2009). These artefacts can occur at any point in the MPI process and can be categorised as difficulties pertaining to the patient, the equipment, or the technician. The causes consist of insufficient preparation, patient-related illnesses such as cardiomyopathy, gastritis, and obesity, mobility, radiopharmaceutical injections, image processing, machine condition, and limitations. Errors must be identified and rectified to get a high-quality image that can assist in the diagnosis.

In recent years, CT-based attenuation correction (CTAC) using hybrid systems has become the predominant method of attenuation correction (AC) according to the standards of the Society of Nuclear Medicine and Molecular Imaging (SNMMI) (Dorbala et al., 2015). Farrell et al. (2021) conducted a systematic review on CTAC and its effects on MPI, outlining both the advantages and drawbacks of this approach. CT offers advantages over gadolinium line source by eliminating downscatter concerns and reducing statistical noise, resulting in higher diagnostic accuracy compared to non-AC imaging (NAC). CTAC results in increased radiation exposure for patients, as well as the potential for co-registration mistakes and truncation artefacts. Plachinska et al. (2016) conducted a retrospective investigation using the AC to remove soft tissue artefacts. This attenuation artefact can hinder the effectiveness of MPI in detecting and predicting CAD. This study showed that utilising AC considerably improves the diagnostic precision of MPI in diagnosing CAD and pinpointing coronary arteries with severe constriction. Raza et al. (2016) found that CT-based attenuation corrected SPECT MPI notably enhanced the RCA territory in comparison to non-attenuation corrected imaging, despite diaphragmatic and breast attenuation being the most well-documented artefacts.

2.6 Sub-diaphragmatic activity

Sub-diaphragmatic activity denotes to any movement or activity occurring beneath the diaphragm, a muscle that divides the chest and abdominal compartments. This phrase is commonly employed when investigating gastrointestinal motility and digestive functions. This area comprises organs like the stomach, small intestine, large intestine, liver, gallbladder, and pancreas, which are essential for digestion, absorption, and metabolism.

During tests utilising MPI, activity below the diaphragm is frequently detected in the liver and colon. This is due to the elimination of radiopharmaceuticals via the hepatobiliary system. Sub-diaphragmatic activity in the stomach can occur via reflux of radiopharmaceuticals from the duodenum into the gastric lumen or the absorption of free Tc-99m pertechnetate by the gastric mucosa (Heinle and Siraj, 2009). This activity can result in increased or decreased activity in the adjacent myocardium and could lead to an artificial, permanent, or temporary reduction in blood flow. To minimise the presence of substandard wall artefact in the investigation, several preparations can be made. The pre-operation instructions involve fasting for at least 4 hours, abstaining from food and water, putting the patient in a prone posture during imaging, delaying the imaging process, and using CTAC.

2.7 The adjunct in minimising sub-diaphragmatic activity

Nuclear Medicine Facilities in Malaysia follow the standard operating procedure for MPI, which is derived from the European Association of Nuclear Medicine (EANM) and the American Society of Nuclear Cardiology (ASNC). The worldwide boards suggested using fatty meal, milk, and water as supplements to reduce sub-diaphragmatic activity in MPI. The suggestion does not specify any particular sort of food or a certain method of preparation. No prior research has been done in Malaysia to examine the specific food types, the use of single preparation, and the impact of the described method on sub-diaphragmatic activity.

An analysis by Anijdan et al. (2018) found that gender, age, and BMI did not have a significant effect on the quality of MPI. There is a significant difference only in the group that drinks milk compared to the control group. Therefore, different substances can be compared to milk. Mohsen Qutbi's (2018) case study showed that consuming 2 to 4 glasses of water before imaging can reduce extracardiac activity. Purbhoo et al. (2015) found that consuming milk significantly reduces infra-cardiac activity compared to a group that did not receive any intervention. Malek et al. (2015) investigated how milk, water, and lemon juice affect sub-diaphragmatic activity-related artefacts. It was found that drinking milk can decrease these interfering artefacts, resulting in enhanced image quality.

Several aspects can influence the uptake of radioactivity in organs, which in turn affects the quality of images obtained. The therapies mentioned are erythromycin, solid food, soda water, water, and milk. Additionally, a full stomach can apply pressure on the intestines, forcing them to shift downward and creating a physical gap between the intestines and the heart. Iqbal et al. (2020) found that milk can help remove toxins from the liver and bile ducts and decrease activity below the diaphragm. A study by Azadbakht et al. (2020) found that water produced similar results to a group ingesting a high-fat meal in terms of affecting extracardiac activity and image quality. Moreover, they conclude that water can be a suitable alternative because of its ease of use and lower cost.

The indicated studies that examined the impact of various preparations on sub-diaphragmatic activity referenced research by Hofman et al (2006). This study examined the effectiveness of milk versus water in decreasing infra-cardiac activity in

MPI using a scale to grade infra-cardiac activity. They referenced a much earlier study by Rehm et al. (1996). This study is the first to establish a grading system for evaluating the relative strength of abdominal activity in comparison to neighbouring myocardium and its impact on image interpretation.

CHAPTER 3

OBJECTIVES

3.1 Problem statement

In the Nuclear Medicine Department at Hospital Kuala Lumpur, the common method to reduce sub-diaphragmatic artefact is by consuming a high-fat meal and drinking milk. Some individuals may have intolerance to these preparations and may experience negative effects from consuming excessive amounts of fatty meals or milk, such as abdominal discomfort and diarrhoea. Some patients do not adhere to these instructions, leading to instances where they overeat and experience discomfort. This study aims to investigate how fatty meals, milk, and water can reduce sub-diaphragmatic activity and improve the quality of images produced. No prior research has been carried out in Malaysia to examine the specific food types, the utilisation of single preparation, and the impact of these methods on sub-diaphragmatic activity.

3.2 General objectives

To investigate the effects of fatty meal, milk, and water as the method of preparations prior to MPI.

3.3 Specific objectives

i. To evaluate either fatty meal, milk and water able to produce comparable image quality.

ii. To determine either the methods proposed in this study, which are the fatty meal, milk and water, could minimise sub-diaphragmatic activity.