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EFFECTS OF ORAL FATTY ACID ON LEFT VENTRICULAR 2-[18F] FLUORO-2-DEOXY-D-GLUCOSE UPTAKE DURING WHOLE BODY POSITRON EMISSION AND COMPUTED TOMOGRAPHY

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillments of the Requirement for the Degree of Master of Science

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Master of Science.

EFFECT OF ORAL FATTY ACID ON LEFT VENTRICULAR 2-[^{18}F] FLUORO-2-DEOXY-D-GLUCOSE (^{18}F-FDG) UPTAKE DURING WHOLE BODY POSITRON EMISSION AND COMPUTED TOMOGRAPHY

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August 2016

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Background: There are two main myocardial metabolic pathways including glucose oxidative pathway and free fatty acid (FFA) oxidative pathway. FFA is the major source of energy for the heart, generating 60% to 90% of energy while glucose metabolism produces the rest 10% to 40% of energy depending on physiological conditions. **Objective:** This study was carried out to observe the intensity and to analyze the differences in the intensity of ^{18}F-FDG uptake in the wall of LV WITH and WITHOUT oral ingestion of edible oils during whole body (WB) ^{18}F-FDG PET/CT study. **Methodology:** This is a prospective study involving patients undergoing modified WB ^{18}F-FDG PET/CT protocol; [Group A (n=12) : WB + oral ingestion of 50ml virgin coconut oil (VCO); Group B (n=9) : WB + oral ingestion of 50ml olive oil(OO)]. And Group C (n=9) applied standard preparation protocol for WB ^{18}F-FDG PET/CT examination. The ^{18}F-FDG uptake in the wall of LV was qualitatively and quantitatively assessed. **Results:** The mean age for group A, B, and C were 49.25 ± 13.19, 56.11 ± 11.66 and 64.33 ± 7.50. The mean BMI were 22.46 ± 3.83, 25.68 ± 5.66 and 26.74 ± 4.26 respectively, while the mean FBS were 5.80 ± 1.23, 5.60 ± 1.61 and 5.73 ± 0.51 respectively. The LV uptake of ^{18}F-FDG was significantly higher in Group C patients. There was a significant difference in mean SUVmax at mid (2.58 ± 3.97 vs 2.28 ± 2.75 vs 6.59 ± 2.09, p=0.002), basal (6.43 ± 8.57 vs 4.87 ± 3.08 vs 13.89 ± 3.77, p=0.005) and apical (6.37 ± 8.27 vs 5.33 ± 3.22 vs 11.42 ± 4.66, p=0.002) of LV. The mean normalized ^{18}F-FDG distribution in 20-segment polar map expressed in percentage for Group B was lower in comparison to Group A and Group C (66.37% vs 63.13% vs 68.78%, p=0.04). **Conclusion:** Oral ingestion of edible oils leads to preference towards fatty metabolism of myocardium hence reduction in glucose uptake.

Keywords : Glucose uptake; myocardium; ^{18}F-FDG PET/CT; edible oils

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

KESAN ORAL ASID LEMAK KE ATAS PENGAMBILAN 2- [18F] FLUORO-2-DEOXY-D-GLUKOSA (^{18}F-FDG) DI VENTRIKEL KIRI SEMASA PANCARAN POSITRON DAN TOMOGRAFI BERKOMPUTER SELURUH BADAN

Oleh

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Pengerusi : Prof. Abdul Jalil Nordin, PhD
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Latar Belakang: Terdapat dua laluan metabolik miokardium iaitu laluan oksidatif glukosa dan laluan oksidatif asid lemak bebas (FFA). FFA adalah sumber tenaga utama untuk jantung, menjana 60% hingga 90% daripada tenaga manakala metabolisma glukosa menghasilkan selebihnya 10% kepada 40% daripada tenaga bergantung kepada keadaan fisiologi. **Objektif:** Kajian ini dijalankan untuk menilai dan menganalisis perbezaan keamatan pengambilan ^{18}F-FDG di dinding ventrikel kiri (LV) DENGAN dan TANPA pengambilan minyak secara oral semasa pemeriksaan seluruh badan (WB) ^{18}F-FDG PET / CT. **Metodologi:** Ini merupakan kajian prospektif yang melibatkan pesakit yang menjalani pengubahsuaian protokol WB ^{18}F-FDG PET / CT; [Kumpulan A (n=12) : WB + pengambilan 50ml oral minyak kelapa dara (VCO); Kumpulan B (n=9) : WB + pengambilan 50ml oral minyak zaitun (OO)]. Dan Kumpulan C (n=9) menggunakan protokol penyediaan standard prosedur WB ^{18}F-FDG PET/CT. Pengambilan ^{18}F-FDG di dinding ventrikel kiri (LV) dinilai secara kualitatif dan kuantitatif. **Keputusan:** Min umur kumpulan A, B, dan C ialah 49.25 ± 13.19, 56.11 ± 11.66 dan 64,33 ± 7.50. Min BMI masing-masing ialah 22.46 ± 3.83, 25.68 ± 5.66 dan 26.74 ± 4.26, manakala min FBS masing-masing adalah 5.80 ± 1.23, 5.60 ± 1.61 dan 5.73 ± 0.51. Pengambilan ^{18}F-FDG adalah jauh lebih tinggi di kalangan pesakit Kumpulan C. Terdapat perbezaan yang signifikan dalam min SUVmax pada bahagian tengah (2.58 ± 3.97 vs 2.28 ± 2.75 vs 6.59 ± 2.09, p = 0.002), basal (6.43 ± 8.57 vs 4.87 ± 3.08 vs 13.89 ± 3.77, p = 0.005) dan apikal (6.37 ± 8.27 vs 5.33 ± 3.22 vs 11.42 ± 4.66, p = 0.002). Min taburan normal ^{18}F-FDG dalam 20 segmen *polar map* yang dinyatakan dalam peratusan bagi Kumpulan B adalah lebih rendah berbanding dengan kumpulan A dan C (66.37% vs 63.13% vs vs 68.78%, p = 0.04). **Kesimpulan:** Pengambilan minyak makan secara oral membawa kepada keutamaan terhadap metabolisma lemak oleh miokardium sekaligus pengurangan dalam pengambilan glukosa.

Kata kunci: Pengambilan glukosa ; miokardium; ^{18}F-FDG PET/CT; minyak makan

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

^{18}F-FDG	2-[^{18}f] Fluoro-2-Deoxy-D-Glucose
ATP	Adenosine Triphosphate
BMI	Body Mass Index
CAD	Coronary Artery Disease
CDNI	Centre For Diagnostic Nuclear Imaging
cFFAs	Circulating Free Fatty Acids
CHD	Coronary Heart Disease
cm	Centimetre
CMV	Cytomegalovirus
coA	Coenzyme A
CS	Citrate Synthase
CT	Computed Tomography
CVD	Cardio Vascular Disease
F18	Fluorine-18
FAO	Food And Agriculture Organization
FBG	Fasting Blood Glucose
FFAs	Free Fatty Acids
g	Gram
GBq	Gigabecquerel
H^+	Hydrogen
HDL	High Density Lipoprotein
JKEUPM	Jawatankuasa Etika Universiti Melibatkan Manusia
kBq/ml	Kilobecquerel/mililitre
keV	Kiloelectron Volts
kg	Kilogram
kVp	Peak Kilovoltage
LAD	Left Anterior Descending
LCFAs	Long Chain Fatty Acids
LCX	Left Circumflex Artery

LDL	Low Density Lipoprotein
LV	Left Ventricle
mA	Miliampere
MCFAs	Medium Chain Fatty Acids
MCTs	Medium Chain Triglycerides
MDCT	Multi-Detectors Ct
mm	Milimetre
mmol/L	Milimol/Litre
MRI	Magnetic Resonance Imaging
MUFAs	Monounsaturated Fatty Acids
NAD	Nicotinamide Adenine Dinucleotide
NADP	Nicotinamide Adenine Dinucleotide Phosphate
O_2	Oxygen
OHADH	Beta-Hydroxyacyl Coenzyme-A Dehydrogenase
OO	Olive Oil
PDH	Pyruvate Dehydrogenase
PET	Positron Emission Tomography
PET/CT	Positron Emission Tomography/Computed Tomography
pH	Power Of Hydrogen
PO4	Phosphate
PPARa	Peroxisome-Proliferator-Activated Receptor A
PPDN	Pusat Pengimejan Diagnostik Nuklear
Rb	Rubidium
RCA	Right Coronary Artery
ROI	Region of Interest
SPECT	Single Photon Emission Computed Tomography
SUV	Standardized Uptake Values
SUVmax	Maximum Standardized Uptake Value
UPM	Universiti Putra Malaysia
VCO	Virgin Coconut Oil
VLDL	Very-Low-Density Lipoprotein

WB	Whole Body
WHO	World Health Organization
β+	Beta

CHAPTER 1

INTRODUCTION

1.1 Background

Myocardium is the muscular layer of the middle wall of the heart. It triggers the blood circulation in the heart by stimulating heart contractions to pump blood from the ventricles. Then the heart relaxes to allow the atria to receive blood. The beating heart leads the cardiac cycle which delivers blood to the whole body including the cells and tissues. Myocardium consists of spontaneously contracting cardiac muscle fibers which allow the heart to contract. This is the autonomic (involuntary) function of the peripheral nervous system. Epicardium, which is the outer layer of the heart and the endocardium (inner layer of the heart) coat the myocardium.

According to the latest data published by World Health Organization (WHO) in May 2014, deaths in Malaysia caused by coronary heart disease ranks the 33rd position in the world with the age adjusted death Rate of 150.00 per 100,000 population. In Malaysia this has reached 29,363 or 23.10% of total deaths. As heart diseases have continued to rise through the years, it has become more critical than ever to advocate healthy lifestyle to the public. Perhaps this is closely related to the Heart Foundation of Malaysia's study which found Coronary Heart Disease as number one leading cause of death in this country.

The broad concept of myocardial viability needs to be scrutinized in relation to atherosclerosis. Atherosclerosis happens when plaque is built up within the wall of coronary arteries. Plaque is waxy substance that can restrict the blood flow into the heart muscle. The arteries that are blocked by plaque are those that are supposed to supply oxygen-rich blood to the heart muscle which is the most important substance needed for the heart to continue beating.

In worst case scenarios, the plaques or atherosclerosis that grow after many year will eventually cause damaging effects leading to death. Continuous deposition of plaques in the coronary artery may jeopardize the coronary circulation and potentially lead to myocardial ischemia, myocardial infarction, and hibernating myocardium. By understanding the pathophysiological cause, effect and function on each one of the above mentioned clinical entity, then only one can appreciate the clinical importance of imaging myocardial viability.

There are several clinical imaging techniques available (Schinkel et al., 2007) to assess cardiac function like chest X-ray, echocardiography (ECG), CT scan, Magnetic Resonance Imaging (MRI), coronary angiography, Gamma camera, and single photon emission computed tomography (SPECT) camera. Chest x-ray provides morphological informations only, while ECG can be useful for early functional assessment. Both are widely available in most healthcare centers. However, the capacity of these techniques is relatively poor in providing adequate information on myocardial viability when compared to other non -invasive imaging techniques (Moir et al., 2004).

According to Schuijf et al. (2006), more recently, multi- slices computed tomography (MSCT) has emerged as a potential modality for non-invasive evaluation of coronary circulation through CT angiography technique. Cardiac computed tomography (CCT) offers superb spatial and contrast resolution, resulting in excellent endocardial definition (Sugeng et al., 2006). But, the flipside of these conveniences is high radiation exposure to patient affected by the scan length, scan protocols, and parameters used (Hunold et al., 2003). Patients with diabetes or kidney diseases may experience kidney failure when using CT contrast media especially when the dye is mainly excreted for elimination through renal tubular excretion into urine.

In the past decade MRI has become the standard of reference for quantification of left ventricular function due to technical improvements by increasing the temporal resolution while providing reasonable spatial resolution and the different signal intensities between blood- filled cavities and surrounding myocardium (Rathi & Biedermann, 2004; Thomas et al., 2005). Its non-invasiveness, the lack of ionizing radiation and the excellent soft-tissue contrast without IV contrast material injection render MRI highly attractive for patients with various cardiac diseases with compromised left ventricular function (Schlosser et al., 2005).

However, cardiac MR is still limited with regard to restricted scanner availability, relatively high costs, and generally long examination times (Schlosser et al., 2005). Contra- indications for CMR are metal implants, irregular heart rhythm, and claustrophobia (Salm et al., 2005). As a matter of fact, gadolinium containing MR contrast has been recently found complicating long term nephrofibrosis and renal failure.

Technical improvement in myocardial viability imaging has recently been observed using radionuclide imaging tools. There have been several exciting advances in SPECT hardware and software upgrade that can provide faster acquisition time and currently, lower dosimetry, and improved image quality. However, its typical protocol is inefficient, often taking 3 to 5 hours to complete (Bateman, 2012).

PET/CT study applying metabolic tracers such as 2-[^{18}F] Fluoro-2-Deoxy-D-Glucose (^{18}F-FDG) enables detection of metabolic changes at cellular level associated with ischemia. ^{18}F-FDG PET/CT is considered as one most effective and accurate noninvasive techniques to identify non-viable myocardial segment (Nordin et al., 2012). It gives a biological signal on cellular viability. The CT data are used to calculate the attenuation correction for the PET scan to provide anatomic information for comparison with the PET scan (Schinkel et al., 2007).

1.2 Problem Statement

PET/CT imaging using fluorine-18 fluorodeoxyglucose (^{18}F-FDG) is a clinically feasible method to assess myocardial viability in patients with impaired left

ventricular function (Knuuti et al., 2002). Although various tracers have been used in combination with PET (^{11}C-acetate and ^{82}Rb), ^{18}F-FDG is the tracer most frequently used to assess myocardial viability. ^{18}F- FDG is used to evaluate cardiac glucose use, and the tracer is a glucose analog (one OH group is replaced by an F atom) (Schinkel et al., 2007).

Knuuti et al. (2002) applied ^{18}F-FDG and positron emission tomography (PET) in his study to evaluate myocardial glucose utilization. Clinical PETCT imaging method is considered as the most reliable tool to study and identify cardiovascular disorders ranging from hypertrophic and idiopathic dilated cardiomyopathy (Grover-McKay et al., 1989) to unstable angina (Araujo et al., 1988), myocardial infarction (Schwaiger et al., 1986) and chronic ischemic left ventricular (LV) dysfunction (Maddahi et al.,1994).Most myocardial viability assessments using ^{18}F-FDG PETemphasized on patients with chronic coronary artery disease and LV dysfunction (Maddahi et al., 1994). ^{18}F-FDG is used in these patients to determine the extent of myocardial viability or potentially reversible contractile dysfunction in response to revascularization as well as the extent of scar tissue or irreversible contractile dysfunction.

In chronically and severely disabled patient, the non- invasive viability assessment and hibernation is mainly defined in patient whose prognosis without intervention is poor but the risk of revascularization is high (Schöder et al., 1999).

The American Society of Nuclear Cardiology and the Society of Nuclear Medicine (Bacharach et al., 2003) published several methods using ^{18}F-FDG PETCT imaging in myocardial viability assessment including fasting, oral or intravenous glucose loading, hyperinsulinemic euglycemic clamping, and free fatty acid inhibition.

The majority of cardiac ^{18}F-FDG studies have been performed after fasting and oral glucose loading, which is simple and effective approach. Fasting can be a simple clinical method since it does not require any substrate manipulation provided patients strictly follow instructions (Schinkel et al., 2007). With this approach, some areas may portray as defect in ^{18}F-FDG uptake due to the preferential free fatty acid (FFA) utilization even without infarction. In addition, the quality of myocardial FDG images can be poor in fasting condition due to reduced FDG uptake and slower clearance of FDG from the blood stream (Beanlands et al., 1997). Fast bolus intravenous injection of glucose is painful with high risk of thrombo-phlebitis and embolism while slow insulin infusion technique using the pump is time consuming and clinically meticulous (Bax et al., 1997; Vitale et al., 2001).

Despite variety of protocols published on PET/CT myocardial viability assessment, many are accompanied with restrictions and inconsistent outcome.

Thus the aim of this study is to explore the effect of oral fat supplement

ingestion towards myocardial glucose utilization. This is a proof of concept study, with an intention to find an alternative method for clinical myocardial functionality assessment by using fatty acid in comparison to glucose metabolic pathway assessment.

1.3 Significance Of The Study

The study will provide a visible effect of myocardial glucose metabolism following fat ingestion. This can be a preliminary evidence on fatty acid metabolism as an alternative to glucose metabolic pathway.

The results from this study can be explored further to create new non-invasive imaging method in myocardial functional assessment using fatty acid precursors as bio-markers.

1.4 Study Objectives

General Objective :

i. To investigate the myocardial uptake of ^{18}F-FDG in high fatty acid environment through oral fat ingestion during WB ^{18}F-FDG PET/CT study

Specific Objectives :

i. To analyze the demographic, BMI and FBS distribution of the study population.

ii. To compare the intensity of glucose uptake by myocardium during whole body ^{18}F-FDG examination WITH and WITHOUT oral ingestion of edible oils.

iii. To measure the differences in the intensity of glucose uptake by myocardium during whole body ^{18}F-FDG examination with and without oral ingestion of edible oils using 20-segment polar map.

1.5 HYPOTHESIS

Ingestion of edible oils will lead to preference towards fatty acid metabolism of myocardium hence reduction in glucose (^{18}F-FDG) uptake.

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