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Delayed Dual-Time Point Imaging Protocol Improving Myocardial Uptake of 18-Fluorine Flouro Deoxyglucose (^{18}F-FDG) During Viability Screening of Diabetes Mellitus Type 2 Patients Using Integrated Positron Emission Tomography/Computed Tomography (PET/CT) Imaging

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MNN, AJN, FFAS and HRAR designed the research planning. Authors AJN, FFAS and HRAR were responsible for subject recruitment. Author MNN carried out the data analysis and manuscript preparation. Author AJN was a responsible author and gave final approval of the version to be published. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aims: To investigate the effect of delayed imaging protocol and hypoglycemic agent on quantitative values obtained during myocardial viability ^{18}F-FDG PET/CT assessment.
Presentation of Case: Mr. A, a 72 year-old man, Madam B, a 73 year-old woman and Madam C, a

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64 year-old woman, presented to the Centre for Diagnostic Nuclear Imaging, Universiti Putra Malaysia for myocardial viability assessment. All were diagnosed Diabetes Mellitus type II on oral hypoglycemic agent.

Discussion: Our study showed an increased ^{18}F-FDG uptake in the wall of LV after the delayed protocol was applied to the patients. One hour time elapsed before ^{18}F-FDG injection is to allow optimal level of niacin in the blood for its action to lower the plasma FFA levels and encourage myocardial preference towards glucose metabolism. Oral glucose loading is given to stimulate insulin secretion and increase glucose utilization as the metabolic substrate. The approach of premedicating nicotinic acid like niacin can be a reliable hypolipidemic agent in shifting myocardial metabolism to glucose oxidative pathway in ^{18}F-FDG PET/CT myocardial viability assessment. Delayed enhancement imaging has been shown to be effective, in both animals and humans, in identifying the presence, location, and extent of acute and chronic myocardial infarction in patients with ischemic cardiomyopathy. Furthermore, this technique may also be useful in assessing myocardial injury in patients with non-ischaemic heart disease.

Conclusion: Delayed imaging is superior to early imaging. The improvement of the image quality leads to accurate assessment of the viable or non-viable myocardium.

Keywords: Cardiac viability; hypoglycemic agent; ^{18}F-FDG PET/CT; delayed imaging.

1. INTRODUCTION

PET/CT merges two fundamentally different imaging technologies into one new device. This combined imaging facility provides simultaneous structural and metabolic (biochemical) information in a single seating. In PET/CT myocardial imaging, ^{18}F-FDG is the most frequently used tracer to assess myocardial viability. There have been several exciting advances in PET/CT hardware and development to further improve the image quality.

Many literatures have published the improving clinical value of PET/CT relating to the outcome of myocardial viability assessment in comparison to conventional nuclear imaging technique using gamma camera, SPECT or SPECT CT systems. ^{18}F-FDG PET/CT has been proven to be clinically sensitive with higher accuracy in segregating hibernating from infarcted segments.

The cases in this study series demonstrate the potential use of delayed dual-time point imaging protocol in anticipating improved myocardial ^{18}F-FDG uptake.

2. PRESENTATION OF CASE

This study was conducted under the purview of local ethic committee [reference number: PPDN (FR14)CT001] at the Centre for Diagnostic Nuclear Imaging (CDNI), University Putra Malaysia (UPM).

Mr. A, a 72 year-old man, Madam B, a 73 year-old woman and Madam C, a 64 year-old woman, presented to the Centre for Diagnostic Nuclear Imaging, Universiti Putra Malaysia for myocardial viability assessment. All were diagnosed Diabetes Mellitus type II on oral hypoglycemic agent.

They were prepared using modified glucose loading protocol as recommended by Martin et al. [1] (Fig. 1). All were instructed to be fasted for at least 8 hours before the examination. In the morning of the study they were advised to continue oral hypoglycaemic medication as usual. The body weight and fasting sugar levels measured and included in the calculation of maximum Standardized Uptake Value (SUVmax). Consent obtained prior to the study.

Oral Niacin tablet (200 mg stat) was given one hour before intravenous injection of 8 mCi of ^{18}F-FDG. The blood sugar level was monitored, alternating with intramuscular injection of short-acting insulin while the hydration was maintained via intravenous slow normal saline infusion (Fig. 1). Following intravenous injection of ^{18}F-FDG, subject remained in resting state for a period of at least 1 hour before PET/CT scanning procedure.

All studies performed using Siemens Biograph True Point PET-CT Somatom Sensation 64-slice multi detector computed tomography (MDCT) integrated with luteum oxysilicate PET camera. Prior to the study, patients were required to remove all metals (e.g., bracelets, dental braces, pants with zippers, etc.) that could lead to streak artifacts on the CT transmission scan. Subjects were positioned comfortably on the examination table with their arms raised above the heads

including support devices to aid comfortable positioning (e.g., knee, head and neck, and arm supports) limiting involuntary motion.

The field of study was focusing on to the chest area. A topogram acquired using low dose CT parameter for attenuation correction and anatomical correlation followed by list mode PET acquisition emission scan. Patient was scanned with identical parameters, which included 120 kVp, 150 mA, 0.5-second gantry rotation time, 5.0 mm table feed per gantry rotation, 0.8 pitch, and a section profile of 2.5 mm (full width at half maximum) with a 3.0 mm section interval and a standard reconstruction algorithm.

The result of all imaging studies were analyzed using cardiac software. The first set of imaging results fail to trace any ^{18}F-FDG myocardial uptake. A thorough check was performed in retrospect on the steps of examination protocol and precautions including oral intake of hypoglycaemic agents.

Upon ensuring the standard preparation and examination procedures, image acquisition and post processing, patients were advised to wait for another hour following the first scanning procedure.

A repeat CT and PET imaging procedure were performed followed by image reconstruction and post processing.

2.1 Image Analysis

The reconstructed left ventricular (LV) images from Patient A, B and C were systematically reviewed. The ^{18}F-FDG uptake in the wall of LV was qualitatively and quantitatively assessed.

The mean normalized percentage of ^{18}F-FDG distribution derived from 20-segment polar map of each patient was tabulated as shown in Figs. 2(c) and 2(d). The quantification value of ^{18}F-FDG uptake into the LV in both protocols was compared using both assessment methods.

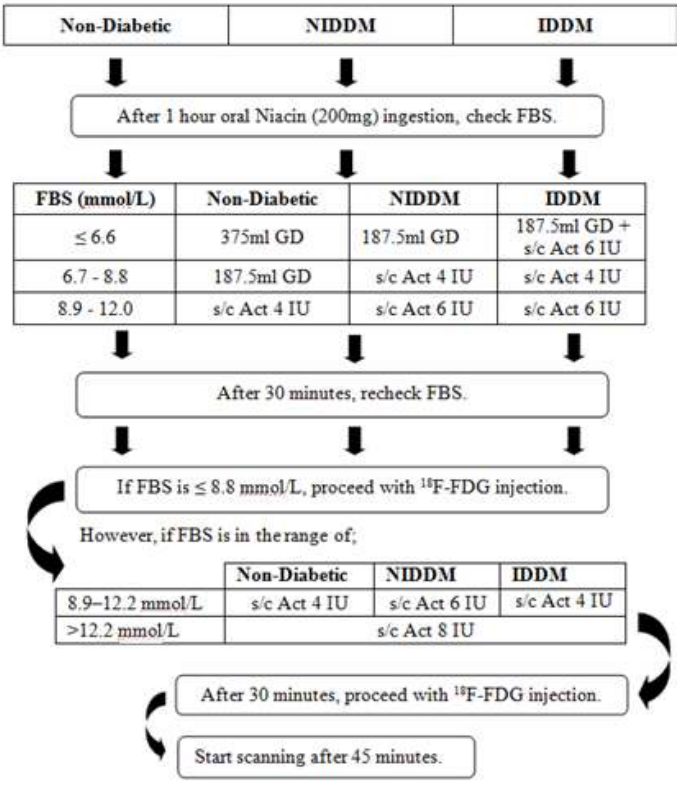

Fig. 1. The combined oral niacin and glucose loading protocol at the Centre for Diagnostic Nuclear Imaging (CDNI) [2]

***IDDM, Insulin Dependent Diabetes Mellitus; NIDDM, Non-Insulin Dependent Diabetes Mellitus; FBS, Fasting Blood Sugar; s/c, subcutaneous; IU, International Unit; Act, actrapid **Glucose Drink : 20% glucose in 500 mls of saline*

3. RESULTS AND DISCUSSION

Coronary artery disease (CAD) can be defined as a narrowing of the coronary arteries, the vessels that supply blood to the heart muscle. Generally, CAD can be caused by atherosclerosis, which is the buildup of plaques in the arterial walls. Compositions of plaques are cholesterol-rich fatty deposits, collagen, other proteins, and excess smooth muscle cells.

Atherosclerosis, which usually progresses very gradually over a lifetime, thickens and narrows the arterial walls, impeding the flow of blood and depriving the heart of the oxygen and essential nutrients it needs (also called "ischemia"). This can cause angina, a muscle cramp-like chest pain. Continuous deposition of plaques in the coronary artery may lead to jeopardized circulation like myocardial ischemia, myocardial infarction and hibernated myocardium.

The total delayed imaging in these 3 patients was approximately 2 hours.

Glucose is a prime energy generating substrate for living tissue to sustain viability [2]. 2-[^{18}f] fluoro-2-deoxy-d-glucose or well known as ^{18}F-FDG is a modified glucose molecule. The tissue uptake of ^{18}F-FDG follow similar glucose metabolic pathway, thus, FDG uptake by myocardium almost being regarded as a gold standard indicator for tissue viability provided the environment is favorable for myocardial glucose metabolism [3-6].

Although this glucose analogue is commonly used as oncology tracer during whole body PET/CT study, the added value of ^{18}F-FDG, as a viability agent in myocardial assessment together with the delayed imaging protocol is highlighted in this study. In view of myocardial capability to use alternative substrates to generate energy, the LV during ^{18}F-FDG WB PET/CT often demonstrates inconsistent uptake pattern indicating an alternative fatty acid oxidative pathway being chosen for metabolism [2]. Fasting is a simple clinical method to enhance

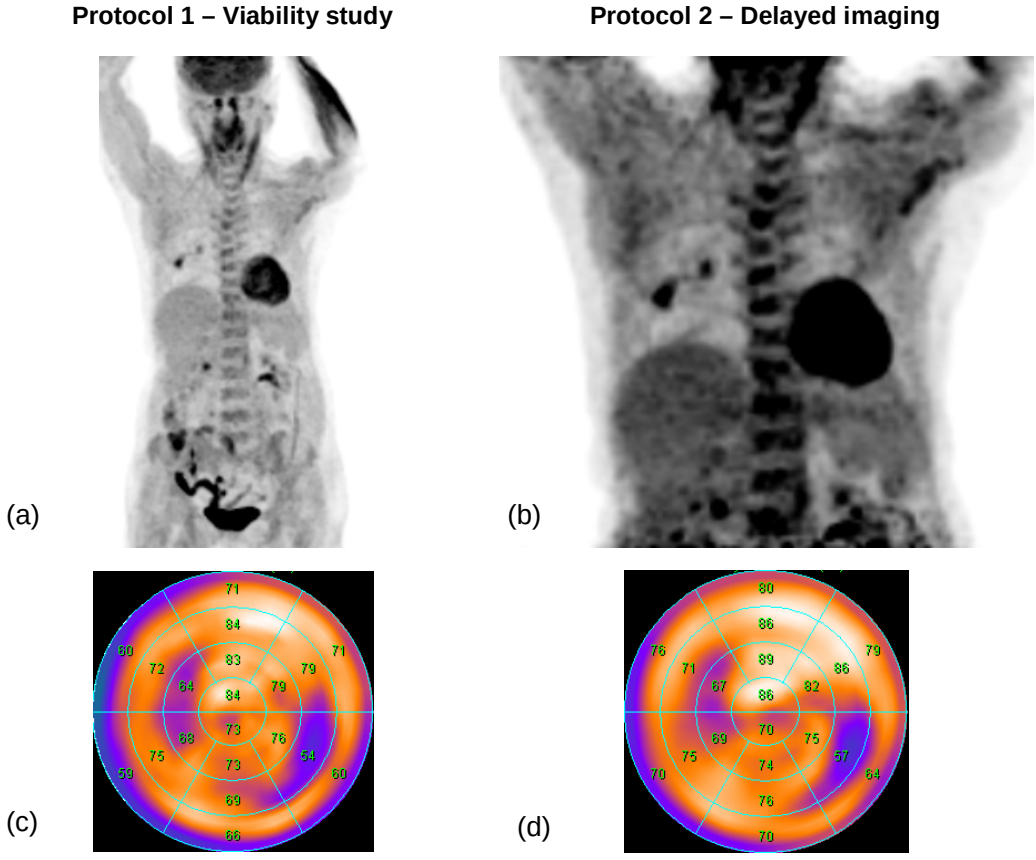

Fig. 2. A 20-segment polar map demonstrating percentage perfusion of FDG activity in Patient B for protocol 1 (c) and protocol 2 (d)

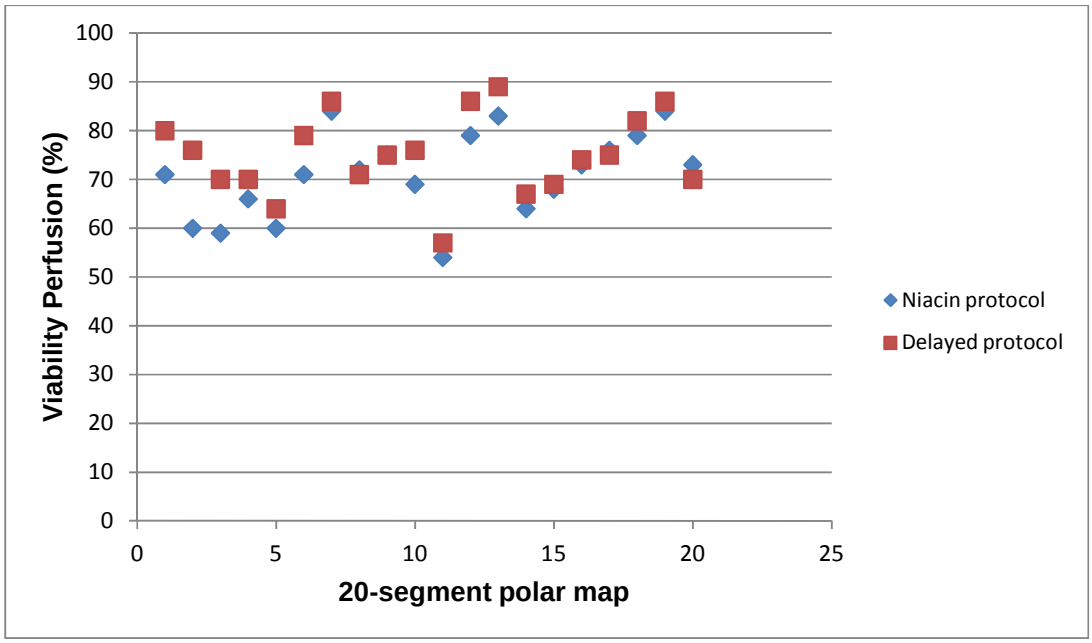

Fig. 3. Mean percentage SUVmax from polar map of Patient B

myocardial uptake of ^{18}F-FDG since it does not require any substrate manipulation provided patients strictly follow instructions. 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 ^{18}F-FDG images can be poor in fasting condition due to reduced ^{18}F-FDG uptake and slower clearance of ^{18}F-FDG from the blood stream [7].

In this study, we observed significant difference of the ^{18}F-FDG uptake to the myocardium. One hour time elapsed before ^{18}F-FDG injection is to allow optimal level of niacin in the blood for its action to lower the plasma FFA levels and encourage myocardial preference towards glucose metabolism. Oral glucose loading is given to stimulate insulin secretion and increase glucose utilization as the metabolic substrate. Knuuti et Al. [3] recommended the use of up to 75 g of glucose to improve homogeneity of myocardial FDG uptake. We gave subcutaneous short acting insulin in our protocol in cases where blood sugar level is found to be raised above 6.5 mmol/L to improve the free plasma glucose uptake into the muscle and myocardium and later promote ^{18}F-FDG uptake in the myocardium of LV.

This method was proven to be clinically feasible and reproducible [8] besides providing consistent image quality [9]. In a preliminary study by Nordin A, et al. [8], he found the approach of premedicating niacin can be a reliable hypolipidemic agent in shifting myocardial metabolism to glucose oxidative pathway in ^{18}F-FDG PET/CT myocardial viability assessment.

Furthermore, our study showed an increased in ^{18}F-FDG uptake in the wall of LV after the delayed protocol was applied to the patients (Fig. 2).

The blood glucose level should be checked before ^{18}F-FDG administration. Tumor uptake of ^{18}F-FDG is reduced in hyperglycemic states. Most institutions reschedule the patient if the blood glucose level is greater than 150–200 mg/dL. Reducing the serum glucose level by administering insulin can be considered, but the administration of ^{18}F-FDG should be delayed after insulin administration depending on the type and route of insulin administration [10].

Additionally, delayed enhancement imaging has been found to be effective, in both animals and humans [11,12]. This technique is capable in identifying the presence, location, and extent of acute and chronic myocardial infarction and provides scar size measurements that are closely related with positron emission tomography (PET). In patients with ischemic cardiomyopathy [13], the images obtained

were superior to single photon emission computed tomography (SPECT) in patients with small myocardial infarctions [14]. It can also be used to predict improvement in contractile function after revascularization in patients with acute or chronic coronary artery disease [15].

4. CONCLUSION

Delayed imaging is superior to early imaging. The improvement of the image quality leads to accurate assessment of the viable or non-viable myocardium. These findings, if duplicated among other readers and centers, may form the basis of imaging recommendations for ^{18}F-FDG myocardial viability.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all studies have been examined and conducted under the purview of local ethic committee [reference number: PPDN (FR14)CT001] at the Centre For Diagnostic Nuclear Imaging (CDNI), University Putra Malaysia (UPM).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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