

Hyperinsulinemic Euglycemic Clamp for Cardiac PET

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Abstract

The aim of this study was to assess the adequacy of Hyperinsulinemic Euglycaemic clamp to yield technically adequate and clinically meaningful cardiac scans. The F-18 Fluorodeoxyglucose scans obtained in diabetic patients are of sub-optimal quality as high level of glucose competes with radioactive Fluorodeoxyglucose for cardiac uptake. Thus to allow quick stabilization of metabolic environment and to get superior quality images, insulin clamp is an accepted technique. Thirty patients (20 males and 5 females) with ages ranging from 43 to 69 years, who were referred for post-myocardial infarction estimation of myocardial viability, were evaluated in this study. All patients reported for the test after 6 hours of fasting. At first myocardial perfusion studies were carried out in all patients with Tc-99m Tetrofosmin on a GE dual head gamma camera. Blood glucose levels were checked. The blood sugar levels in the patients were in the range of 130 - 190 mg%. Insulin clamp was applied depending upon the glucose level obtained, according to ASNC guidelines for PET Myocardial Glucose Metabolism and Perfusion Imaging. On stabilization of blood glucose levels, 10 mCi of F-18 FDG was injected and imaging was performed at 1 hour on a dedicated 16 slice STE GE PET – CT scanner. Three patients had incidence of hypoglycemia as a side effect during the procedure, their blood sugar falling to 40 mg%. They were treated with 25ml of 25% dextrose intravenously following which there was stabilization of

blood sugar. Entire procedure including Tetrofosmin imaging took approximately 4-6 hours. Good quality images were obtained after the use of insulin clamp. Infusion of insulin and glucose gives stable plasma glucose levels during imaging. The insulin clamp technique makes it possible to adjust and maintain a metabolic steady state during the PET study. It does not alter F-18 FDG uptake patterns in different myocardial areas and gives superior quality images. The technique is safe and should improve both the clinical use and cost effectiveness of FDG-PET imaging for identification of injured but viable myocardium.

Key words: Diabetes Mellitus, F-18 Fluorodeoxyglucose Cardiac PET, Hyperinsulinemic Euglycaemic Clamp

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Introduction

Over the past few years, Cardiac PET using F-18 Fluorodeoxyglucose (F-18 FDG) has become a useful tool in the post-myocardial infarction assessment of patients for myocardial viability. PET has several advantages over SPECT techniques in the assessment of myocardial viability (1). These include the very basis of PET imaging, which allows for accurate performance of attenuation correction. The higher energy of positron emitters (511 keV) provides better tissue penetration. Besides it is possible to incorporate the positron emitting isotopes into substances of physiological interest. Cardiac PET allows accurate estimation of viable segments in injured myocardium using metabolic tracers. It is possible to simultaneously determine myocardial perfusion and left ventricular ejection fraction using Gated myocardial SPECT – thereby obtaining detailed and comprehensive information regarding myocardial viability and the need for revascularization.

F-18 FDG is the most extensively used tracer in cardiac PET because of the central role of glucose in myocardial metabolism. The 110 minute physical half life allows the tracer to be transported from the site of manufacture (cyclotron) to a distant site for clinical use. Cardiac PET can be performed in both diabetic and non-diabetic patients.

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However, in diabetic patients, F-18 FDG scans are of sub-optimal quality as high level of glucose competes with fluorodeoxy glucose for cardiac uptake. Such patients have limited ability to produce endogenous insulin in response to glucose or because their cells are less able to respond to insulin stimulation. The use of Hyperinsulinemic Euglycaemic clamp has been advocated to bring down the sugar levels to acceptable range and to allow quick stabilization of metabolic environment in order to obtain superior quality images (2).

Materials and Methods

A total of 30 diabetic patients (Males=24, Females=5, Age range=43-69 years) were included in this study. All of them were patients of post-myocardial infarction, and were referred to nuclear medicine for the assessment of myocardial viability.

The patients were required to report for the test following a period of fasting of at least 6 hours prior to the study. All patients were instructed to omit their regular medications including their morning dose of insulin on the day of the test. All patients underwent at first a resting myocardial perfusion imaging study following an intravenous injection of 20 mCi of Tc-99m Tetrofosmin. SPECT myocardial imaging was performed in each case at 1 hr after the administration of Tc-99m Tetrofosmin on a Millenium MG dual head gamma camera (GE healthcare Technologies, Milwaukee, Wisconsin, U.S.A). The images were acquired on a 64 x 64 matrix using step and shoot technique in 18 steps (Each shooting angle=6 degrees; Each step = 40 seconds). The starting angle was 45 degree. The time required for imaging was approximately 15 minutes. The images were acquired with simultaneous registration of patient's electrocardiogram. Images were reconstructed using filtered back-projection technique.

Blood glucose levels were measured using glucometer and the levels of blood sugar ranged from 140 to 190 mg%. Insulin clamp was applied depending upon the glucose level obtained, as per the guidelines provided by American Society of Nuclear Cardiology for PET Myocardial Glucose Metabolism and Perfusion Imaging (3).

On stabilization of blood glucose levels, which took about 45-90 minutes depending upon the initial blood sugar level, 10 mCi F-18 FDG was injected intravenously. PET Images were acquired at 60 minutes after intravenous injection of the PET tracer, on a dedicated 16 slice STE GE PET – CT scanner. Acquisition was done with the patient lying in supine position keeping the hands above the shoulders. 2-D acquisition was done (to get better resolution of images) with pixel size of 3mm. Total acquisition time of the PET images was 13 minutes. The images were coupled with electro cardiographic gating. Attenuation correction was done by CT and reconstruction was by iterative method. Entire procedure including tetrofosmin imaging took approximately 4 to 6 hours.

Technique of Insulin Clamp

The diabetic patients were primed with 6 units of human Actrapid insulin given as intravenous bolus, when blood sugar was less than 140 mg% or with 10 units when the blood sugar was more than 140 mg%. Insulin solution was prepared by adding 100 units of human Actrapid insulin to 500ml of normal saline. First 50cc of solution was discarded to prevent the adsorption of insulin in the rubber tubing.

Insulin drip was started at a rate (ml/min) determined by the following formula by taking into consideration the weight of the patient: $(1.2 \times \text{Weight in kg})/60 \text{ min}$.

Blood sugar was checked every 15 minutes.

Once the blood sugar fell down to below 140 mg %, 20% dextrose drip was started through separate intravenous line (to avoid mixing of the fluids). The dextrose drip rate (ml/min) was determined by the following formula: $(1.8 \times \text{Weight in kg})/60 \text{ min}$.

Blood sugar was monitored every 15 minutes.

After stabilization of blood sugar and confirming with two successive measurements showing the levels between 80-140 mg%, 10.0 mCi of F-18 FDG was injected intravenously.

Insulin drip was run for another 15 minutes to facilitate FDG uptake. Dextrose drip was run for another 30 minutes to prevent hypoglycemia with continuous monitoring of blood sugar. PET imaging was performed at 30 minutes after stopping the drips as per the imaging protocol mentioned previously.

Results

Good quality images were obtained in all patients after the use of insulin clamp. Three patients had incidence of hypoglycemia as side effect during the procedure, their blood sugar falling down to 40 mg%. They were given 25ml of 25% dextrose intravenously following which there was stabilization of blood sugar. Myocardial viability was assessed by analyzing the results of perfusion and metabolic imaging. Myocardial viability was diagnosed wherever there were presence of mismatched myocardial perfusion and metabolic abnormalities (Figures 1). Very poor quality images were obtained in those patients on whom imaging procedures were performed without the use of insulin clamp.

Discussion

The myocardium utilizes a variety of substrates, predominantly fatty acids, glucose and lactate as sources of energy (4). Under normal aerobic conditions, 50 - 70% of total energy is obtained from oxidation of fatty acids, with the rest being primarily obtained from carbohydrates (glucose and lactate). The proportional contribution of these various substrates to myocardial energy metabolism primarily depends upon availability of substrate, hormonal

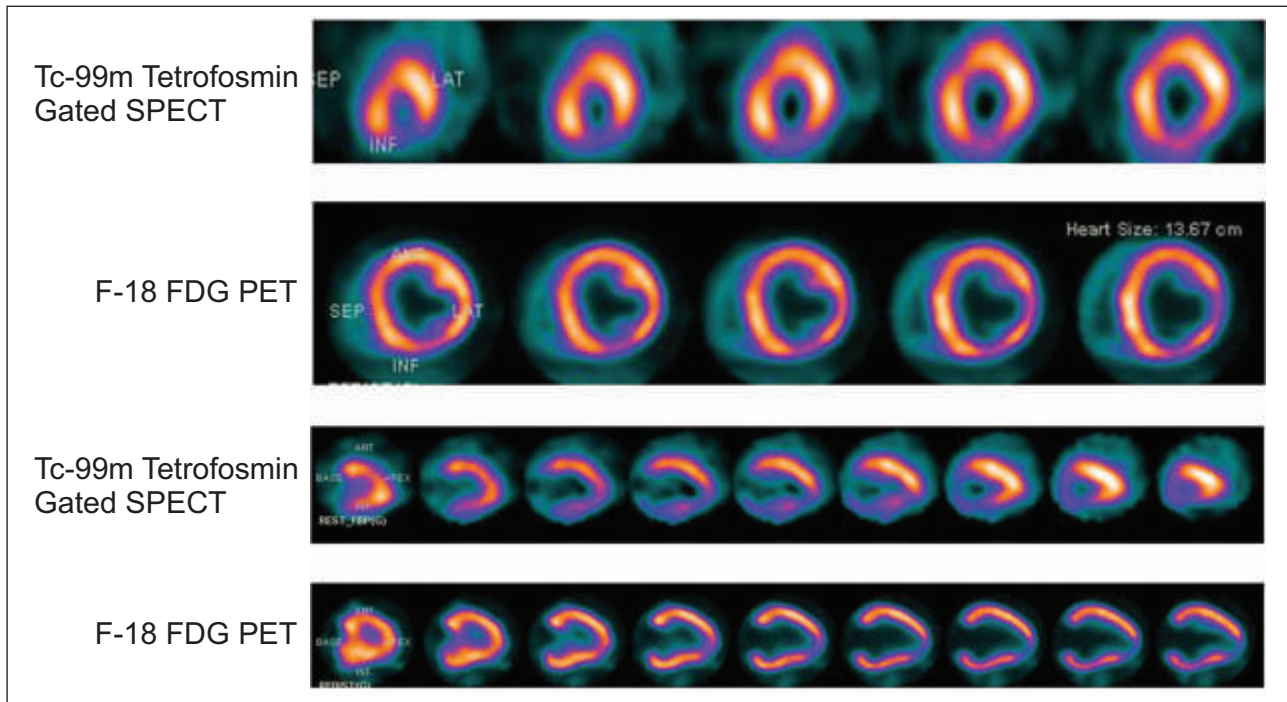


Figure 1. Tc-99m Tetrofosmin Myocardial Perfusion SPECT and F-18 FDG PET scans of a 46 year old male patient with old inferior wall myocardial infarction (MI) and recent anterior wall MI. He had angiographic evidence of triple vessel disease. Patient was referred for assessment of myocardial viability. There is evidence of mismatched myocardial perfusion and metabolism, which indicate presence of viable myocardium.

levels, level of myocardial work and level of myocardial blood flow. For example, under fasting conditions, myocardium utilizes fatty acids as main source of energy. This is because plasma insulin levels fall, resulting in increased lipolysis in peripheral adipose tissue and thus increased plasma fatty acid levels. The increased fatty acid delivery to the myocardium increases myocardial fatty acid levels, thereby shifting the substrate utilization in favor of fatty acids. This decreases the transport of glucose into the myocytes, as well as its oxidation leading to decrease in overall glucose metabolism. Conversely, under fed conditions, there is a rise in plasma insulin levels leading to translocation of glucose transporters 1 and 2 (GLUT 1 and GLUT 2, respectively) to external sarcolemmal sites, increasing glucose uptake and its oxidation. The increased insulin levels also inhibit lipolysis as a result of which, plasma fatty acid levels decrease which in turn reduces myocardial fatty acid metabolism. Increase in cardiac work and catecholamine stimulation also shifts metabolism in favor of glucose utilization. However, an overdependence on myocardial fatty acid metabolism with a parallel decline in carbohydrate use is characteristic of myocardial metabolic adaptation in diabetes mellitus. This shift occurs as a result of markedly increased plasma free fatty acids and triglyceride levels in diabetic patients, hypoinsulinemia causing microsomal localization of glucose transporter and acetyl coenzyme A carboxylase activity, combined effects of increased fatty acids and hypoinsulinemia leading to reduction in activity of pyruvate dehydrogenase complex and decreased neuronal function. All these factors shift the

myocardial substrate utilization to fatty acid oxidation with a marked decline in overall glucose utilization.

To image with F-18 FDG, the myocardial substrate utilization has to be shifted to glucose in diabetic patients, this can be done by giving 25 to 50 gram of oral glucose load to the patients. However, the response is inadequate as patients have limited ability to produce endogenous insulin in response to glucose load or they have insulin resistance (Inability of the cells to respond to glucose stimulation). This difficulty can be overcome by giving the patient supra-physiological levels of insulin by using insulin clamp. This yields clinically meaningful scans.

Ideally, the myocardial metabolism using PET tracers should be compared with PET perfusion tracers. However, this is still not a viable option in India due to cost constraints. Therefore, the myocardial perfusion imaging using SPECT tracers were compared with PET images obtained using metabolic tracers. SPECT images suffer from attenuation artifacts due to lack of uniform attenuation artifact correction software, as well as lower resolution. Therefore while evaluating SPECT perfusion images with FDG PET metabolic images, consideration has to be given to patient motion, attenuation artifacts and reconstruction artifacts. GE software for FDG viability which was used to compare the perfusion and metabolism images, however, yielded technically adequate images.

The main drawbacks of the study were the long time required for the procedure, multiple pricks for measurement of blood glucose levels and hypoglycemia. The procedure is also technically demanding. To

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decrease the incidence of hypoglycemia, patient is advised to have a snack before leaving the department. Patient is also warned about the risk of late hypoglycemia.

Conclusion

Insulin clamp technique makes it possible to adjust and maintain a metabolic steady state during PET imaging. It gives superior quality images; stable plasma glucose and serum insulin levels during imaging and permits the use of smaller F-18 FDG patient doses. The technique is safe and should improve both the clinical use and cost effectiveness of FDG-PET imaging for identification of injured but viable myocardium.

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