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Artículos originales

Evaluation of [^{18}F]FDG distribution and uptake via micro PET/CT in a murine model of myocardial infarction

Evaluación de la distribución y captación de [^{18}F]FDG mediante microPET/CT en un modelo murino de infarto de miocardio

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Conflict of interests

No conflict of interest is reported in the submission of this manuscript.

Resumen

Introducción: Evaluar la distribución de [^{18}F]Fluodesoxiglucosa ([^{18}F]FDG) en un modelo murino de infarto de miocardio (IM), utilizando Tomografía por Emisión de Positrones y Tomografía Computarizada (PET/CT) para validar este enfoque para su uso en la evaluación de nuevas terapias para el tratamiento del IM.

Método: El IM fue inducido por ligadura permanente de la arteria coronaria descendente anterior izquierda. El estudio incluyó un grupo control, un grupo con 7 días de infarto (infarto agudo) y otro con 21 días de infarto (infarto crónico). Antes de la eutanasia, aproximadamente 60 minutos después de la inyección de [^{18}F]FDG se obtuvieron las imágenes mediante el PET/CT. Los valores de la región de interés y del valor de captación estándar se obtuvieron mediante la CT para evaluar las diferencias entre los grupos en la captación de [^{18}F]FDG en el corazón, el cerebro y la vejiga.

Resultados: Se observó una distribución cardíaca homogénea del radiofármaco en el grupo sano, mientras que en los grupos infartados hubo ausencia de captación en la zona del infarto. Mediante el análisis de ANOVA y la prueba de Kruskal-Wallis, se detectaron diferencias estadísticamente significativas entre los grupos de infarto sano y agudo y los grupos de infarto agudo y crónico. No hubo diferencias significativas entre los tres grupos a nivel cerebral ni en la eliminación de radiofármacos.

Conclusiones: La técnica de microPET/CT tiene la sensibilidad para detectar IM en el modelo murino. Además, nos permite cuantificar la captación de [^{18}F]FDG por los órganos de los diferentes grupos estudiados.

Palabras clave: PET/TC; modelos animales; infarto agudo de miocardio; 18FDG

Abstract

Introduction: To evaluate [^{18}F]Fluodeoxyglucose ([^{18}F]FDG) distribution in a murine model of myocardial infarction (MI), using Positron Emission Tomography and Computed Tomography (PET/CT) to validate this approach for use in evaluating new therapies for MI treatment.

Method: MI was induced by permanent ligation of the left anterior descending coronary artery. The study included a sham group, a group with 7 days infarction (acute infarction) and another with 21 days infarction (chronic infarction). Prior to euthanasia, each group was imaged by PET/CT approximately 60 minutes after injection of [^{18}F]FDG. Total and maximal Region of Interest and Standard Uptake Value values were obtained using CT, which enables more precise delineation of the anatomy to assess between-group differences in [^{18}F]FDG uptake in the heart, brain and bladder.

Results: Following distribution of [^{18}F]FDG throughout the body, at 60 minutes after injection homogeneous cardiac distribution of the radiopharmaceutical was observed in the healthy group, while in the infarcted groups there was an absence of uptake in the infarct area. Using ANOVA analysis and the Kruskal-Wallis test, statistically significant differences were detected between the healthy and acute infarction groups and the acute and chronic infarction groups. There were no significant differences between the three groups in brain uptake or radiopharmaceutical clearance.

Conclusions: The microPET/CT technique has the sensitivity to detect infarcted areas in the murine model. Moreover, it allows us to quantify [^{18}F]FDG uptake and thus assess uptake by the organs in the different groups studied.

Keywords: PET/CT; Animal Models; Myocardial Infarction; 18FDG.

Highlights

Current scientific knowledge supports the use of microPET/CT to evaluate [^{18}F]FDG distribution in murine models of MI. This method allows identifying infarcted areas with high sensitivity, quantifying glucose uptake and evaluating differences depending on the state of the infarct. The study validates the use of microPET/CT to detect and quantify [^{18}F]FDG uptake in infarcted areas in a murine model, providing a precise tool to evaluate new therapies in MI. The results support the use of microPET/CT as an accurate tool to evaluate therapies in MI, facilitating preclinical research and improving the development of innovative cardiovascular treatments.

Introduction

Cardiovascular pathologies represent one of the leading causes of morbidity and mortality at the global level⁽¹⁾. They are considered complex multifactorial pathologies involving both genetic and environmental factors, which makes it difficult to establish prevention criteria covering all risk factors⁽²⁾. Lifestyle habits (smoking, alcohol consumption, diets and lack of physical activity) and individual health factors (blood pressure, cholesterol, blood glucose) also exert a decisive influence on cardiovascular health⁽¹⁾.

Myocardial infarction (MI) is a cardiovascular pathology caused by thrombotic occlusion of a coronary artery. The first line of treatment for patients with ST-segment elevation MI is rapid coronary revascularization to restore nutrient and oxygen supply to the myocardium⁽³⁾. As a consequence of the ischemia-reperfusion process, an inflammatory response is triggered that facilitates the removal of necrotic cardiomyocytes and remnants of the infarcted tissue matrix⁽⁴⁾ and the subsequent formation of a collagen-based fibrotic scar⁽⁵⁾.

Animal models are an interesting method to study the pathophysiological aspects of disease and to evaluate new therapeutic and preventive options⁽²⁾. Over the last two decades, the mouse model of MI has become the preclinical model of choice to study the molecular mechanisms of human heart physiology and disease⁽⁶⁾.

Despite substantial differences from humans in heart size, heart rate, and myocardial structure, other characteristics of this species position it as an interesting animal model, including the lower cost of procedures and the capacity to manipulate the genome⁽²⁾. In addition, the results obtained in the preclinical phase using this animal model can be transferred to clinical phase studies always taking in consideration the differences between animal model and , which has increased interest in this model, especially for developing new therapies⁽⁸⁾.

Imaging techniques are non-invasive methods which enable us to assess not only myocardial metabolism and viability⁽⁹⁾ but also the distribution, pharmacodynamics and toxicity of new drugs⁽¹⁰⁾. Among these, positron emission tomography (PET) with [^{18}F]Fluorodeoxyglucose ([^{18}F]FDG), chosen for its sensitivity, is considered an effective technique to study myocardial viability⁽¹¹⁾. [^{18}F]FDG is a radiopharmaceutical that behaves metabolically like glucose, but unable to continue with the glycolytic pathway because it lacks a hydroxide in position 2, it is retained inside the cell, which allows us to analyse the real consumption of glucose in the tissue under study (Figure 1).

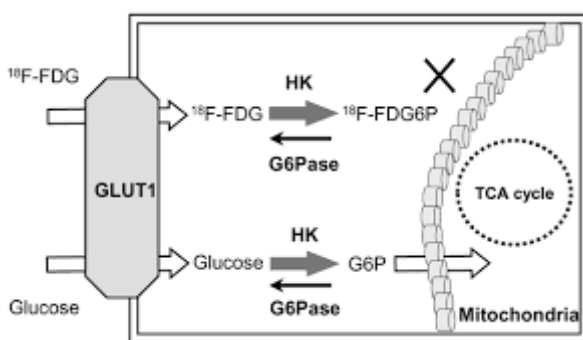


Figure 1. Uptake of [^{18}F]fluorodeoxyglucose ([^{18}F]FDG)⁽¹²⁾

Whole-body PET images taken one to two hours after administration of [^{18}F]FDG indicate radiopharmaceutical accumulation occurs mostly in the brain, heart and urinary tract. In the postprandial state, the myocardium has a similar uptake of [^{18}F]FDG to the brain, but in prolonged fasting state (more than 12 hours), myocardial uptake of this drug is reduced because myocardial metabolism shifts to

fatty acid consumption as an energy source. [^{18}F]FDG is eliminated by renal excretion and in the absence of intense hydration, diuretics and urinary catheterization, can easily localize in the bladder and upper urinary tract⁽¹³⁾.

Although PET after [^{18}F]FDG administration enables some anatomical structures to be visualized, the spatial resolution provided by this technique is generally inadequate to accurately localize pathology. However, combining the PET technique with a high-resolution technique such as computed tomography (CT) helps to improve anatomical identification of injured tissues⁽¹⁴⁾ the spatial resolution is generally inadequate for accurate anatomic localization of pathology. However, combining the PET technique with a high-resolution technique such as computed tomography (CT) helps to improve anatomical identification of injured tissues⁽¹⁴⁾.

Employing a murine model of acute MI, the main aim of this study was to evaluate [^{18}F]FDG uptake in the heart, brain and bladder using the micro PET/CT imaging technique to analyse possible alterations in the distribution of the radiopharmaceutical caused by the pathology.

Methods

Ethical Statement

This study was approved by the Research Ethics and Animal Experimentation Committee of the Universitat de València (protocol number: 2017/VSC/PEA/00106) and was performed following the guidelines of Directive 2010/63/EU.

Murine model and induction of myocardial infarction

The study was performed with C57BL/6J mice (Charles River Laboratories, Châtillon-sur-Chalaronne, France) aged 16 ± 2 weeks and weighing 22.144 ± 2.35 grams. The animals were bred in the animal house of the University of Valencia and maintained under specific pathogen-free conditions at a constant temperature of 22 ± 2 °C and humidity of 60-65 % with a 12-hour light/dark cycle and with free access to a standardized diet (Teklad Global Rodent Diets, Inotiv) and autoclaved water.

The animals included in the study were randomly distributed into three groups; group I ($n = 24$): control (healthy group); group II ($n = 10$): acute infarction (1–7 days), and group III ($n = 14$): chronic infarction (14–21 days). Infarction in both groups (acute and chronic) was induced by permanent ligation of the left anterior descending coronary artery⁽¹⁵⁾. The knot was tightened with consequent occlusion of coronary flow. Ischemia was confirmed for all animals included, no animals were excluded, by ST-segment elevation on the electrocardiogram. The animals were kept under fasting conditions for 4–6 hours with free access to water before imaging. The main difference between groups II and III is the time elapsed from infarct provocation to imaging and subsequent animal sacrifice, which was 7 days for the acute phase infarction group (group II) and 21 days for the chronic phase (group III). Intraperitoneal buprenorphine (0.05 mg/kg, twice daily) and meloxicam (0.3 mg/kg, once daily) was administrated for 5 days after surgery.

PET/CT Protocol

PET/CT images were performed prior to euthanasia, which was 7 days for the acute infarction group and 21 days for the chronic infarction group. To have a homogeneous study, control group was also imaged at 7 and 21 days. For it, the images were obtained as explained below.

Anesthesia

Both radiopharmaceutical injection and image acquisition were performed under anesthesia induced with the aid of an anesthesia machine (Cyprante Keighleit) and flow-meter for oxygen supply. This anesthesia was administered by inhalation and consisted of two stages⁽¹⁶⁾ achieving prolonged immobility for sensitive imaging modalities (magnetic resonance imaging for instance. The first phase (induction) was performed with 3–4 % isoflurane (Zoetis-IsoFlo® 100 % w/w) and 100 % from a medical oxygen

cylinder (Nippongases, Valencia). This reduces animal stress and prevents this factor from affecting subsequent uptake of the radiopharmaceutical. During the second phase (maintenance), the inhalation mixtures contained 1–2.5 % isoflurane and oxygen was maintained at 100 %.

Administration of [^{18}F]FDG

The [^{18}F]FDG used was produced and supplied by CuriumTM Life Forward, and was administered intraperitoneally [IP]⁽¹⁷⁾ the impact of dietary conditions, mode of anesthesia, and ambient temperature on the biodistribution of ^{18}F -FDG in mice has not been systematically studied so far. The aim of this study was to determine how these factors affect assessment of tumor glucose use by ^{18}F -FDG PET and to develop an imaging protocol that optimizes visualization of tumor xenografts. Methods: Groups of severe combined immunodeficient (SCID using a dose of between 200–300 μCi in all animals included in the study. After administration of the radiopharmaceutical, the animals were kept at rest for 60 ± 10 minutes to allow complete and homogeneous distribution of the radiopharmaceutical around the body, after which the images were obtained.

Acquisition and reconstruction of images using microPET/CT

Image acquisition was performed following the Albira Acquierer protocol (New Albira Suite 3.0 - Rheinstetten, Germany) with microPET/CT equipment (Albira I, Bruker Biospin PCI GmbH Rinstetten, Germany), equipped with a spatial resolution of 70 microns for CT and 1mm for PET. Sequential whole-body images were obtained, with a duration of 7 minutes for CT and 15 min of two frames for PET.

PET and CT images were processed and reconstructed in 2D and 3D with the Albira Reconstructor program (New Albira Suite 3.0 software - Rheinstetten, Germany), using a cross OSEM algorithm and CT Rec. Alg algorithm, respectively. Visualization and fusion of both images with AMIDE version 1.0.4 software (A medical Imaging Data Examiner, Boston, MA 02111-1307-USA) enabled more precise anatomical localization of radiopharmaceutical uptake observed by PET.

Quantification of radiopharmaceutical uptake and consumption

The images obtained were used to delimit the contour or area of interest (ROI) around each specific organ. This delimited region is used to evaluate the amount of the radiopharmaceutical that accumulates in each organ by calculating the Standard Uptake Value (SUV)⁽¹⁸⁾. Both parameters allow quantification of the consumption/uptake of [^{18}F]FDG, providing information on the distribution of the radiopharmaceutical in the organism and on the physiological function of each organ. Quantification was performed with the PMOD program (Technologies[®] LLC, Zurich, Switzerland). The ROI and SUV values for each organ studied were analyzed in absolute and relative terms expressed as a percentage of radiopharmaceutical uptake in each organ in relation to total uptake in the organism (sum of the values obtained in the three organs studied). After digitizing the images, the quantification of all PET-CT images were performed in a dedicated laboratory by a trained observer unaware of the experimental protocol applied.

Calculation of ROI

Using CT (figure 2), the organ of interest or ROI is completely delimited, and the PET image is hybridized over this region. Next, the uptake values of [^{18}F]FDG in the total ROI expressed in kBq/cm^3 are obtained using the statistics application. To calculate the maximum ROI (ROI_m), the area of maximum radiopharmaceutical uptake is located, and several measurements are performed to obtain the value of this parameter expressed in kBq/cm^3 .

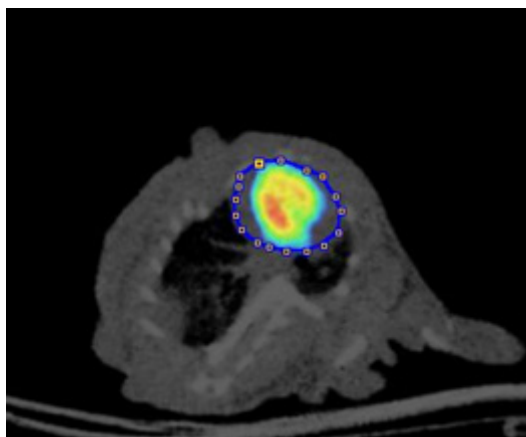


Figure 2. Region of interest (ROI) drawn on the Computed Tomography to delimit the total area of the heart (ROI_T) and the maximum uptake area (ROI_M).

SUV calculation

The total SUV (SUV_T) and maximum SUV (SUV_M) values of the heart, brain and bladder were calculated from the uptake values obtained in each ROI. The calculation was performed by dividing the ROI value by a correction factor (Activity [KBq]/Animal weight [g])⁽¹⁸⁾ [equation 1]:

$$SUV = \frac{ROI[kBq/cm^3]}{Activity[kBq]/Animal\ weight[g]} \text{ equation (1)}$$

To compare [¹⁸F]FDG distribution in each group studied, the two parameters (ROI and SUV) were analyzed in relative terms according to the following equation (equation 2):

$$ROI(\%) = \frac{ROI_{Organ} \cdot 100}{ROI_{Heart} + ROI_{Brain} + ROI_{Bladder}} \text{ equation (2)}$$

Histology study

Once the animal was sacrificed, the heart was extracted and cut into 1-mm-thick short-axis slices. Sections of the sectioned myocardium (5μm) were fixed using 4 % paraformaldehyde acid, embedded in paraffin, and mounted on double gelatin-coated glass slides. To facilitate histological analysis and quantification of infarct size, samples were stained with hematoxylin-eosin (Sigma Aldrich, St. Louis, MO) before observation with Leica DM3000 light microscope (Leica Microsystems, Wetzlar, Germany). Scoring was performed blinded on coded slides.

Statistical Analysis

Statistical analysis of the results was performed using the IBM SPSS version 25 program. We assessed normality of distribution with the Kolmogorov – Smirnov test. The parameters obtained in each organ and test group were expressed using the mean, standard deviation and 95 % confidence interval. To determine whether the study parameters showed statistically significant health status-related differences, ANOVA was performed after testing for normal distribution of the variable using the Shapiro Wilk test and homogeneity of variance (Levene's test). If the variance was not homogeneous, the Kruskal Wallis nonparametric test was used. The level of statistical significance was set at p<0.05.

Results

PET-CT images

Figure 3 shows hybrid images captured with PET/CT of the heart in axial, coronal and sagittal planes. The figure shows that cardiac uptake of [^{18}F]FDG differs according to the animal group studied. Thus, in group I (healthy animals, image 3a) cardiac uptake is homogeneous, whereas in acutely and chronically infarcted animals (group II, image 3b and III, image 3c, respectively) there is an absence of radiopharmaceutical uptake around infarcted tissue.

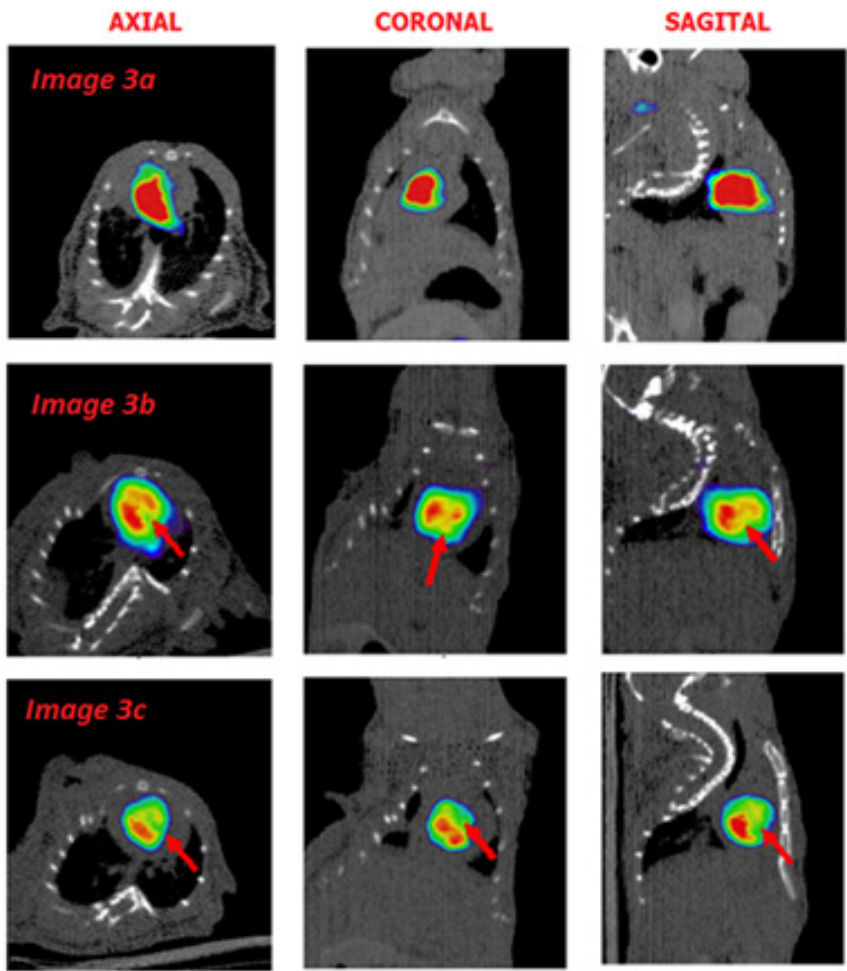


Figure 3. Cardiac images of the three axial, coronal and transverse slices. Image 3a shows a healthy mouse. Images 3b and 3c show samples from an acutely and chronically infarcted mouse, respectively (arrow: area of absence of uptake of [^{18}F]fluorodeoxyglucose ([^{18}F]FDG)).

In figure 4, the mean values of the ROI_T and SUV_T parameters and their distribution in each organ and group tested are shown in figures 4.1 and 4.2, respectively. No statistically significant differences in [^{18}F] FDG uptake in brain and bladder were detected in ANOVA statistical analysis. However, cardiac uptake of [^{18}F]FDG showed statistically significant differences, with higher uptake in animals with acute phase infarction (group II) than in healthy animals (group I) or animals with chronic phase infarction (group III) [Kruskal-Wallis, $p<0.001$].

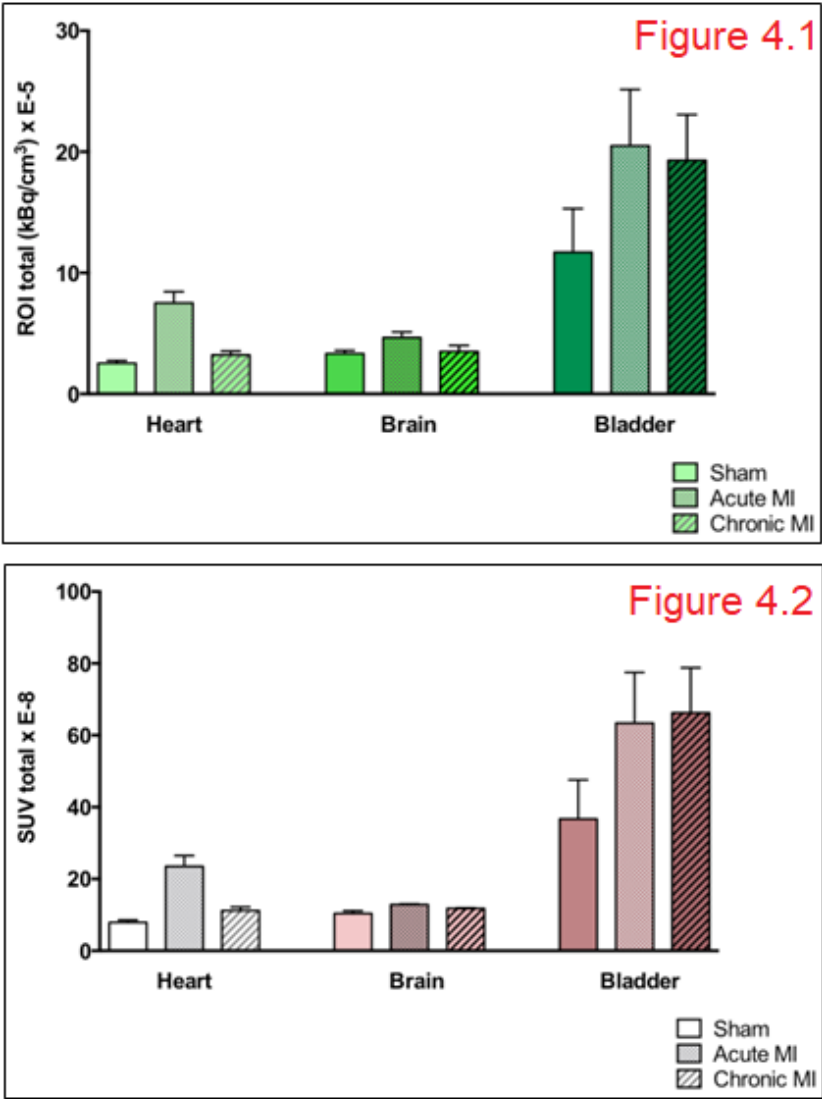


Figure 4. For each study group and organ MI, in figure 4.1, mean values and dispersion of Region of Interest (ROI_T). In figure 4.2, mean values and dispersion of Standard Uptake Value (SUV_T). MI: myocardial infarction.

The mean values of the relative ROI_T and SUV_T for each organ and group studied are shown in figure 5. As can be seen, the bladder was the organ with the highest uptake in all three of animal groups. Furthermore, in healthy animals (group I) brain uptake was slightly higher than cardiac uptake, a relationship that was inverted in animals with acute infarction (group II).

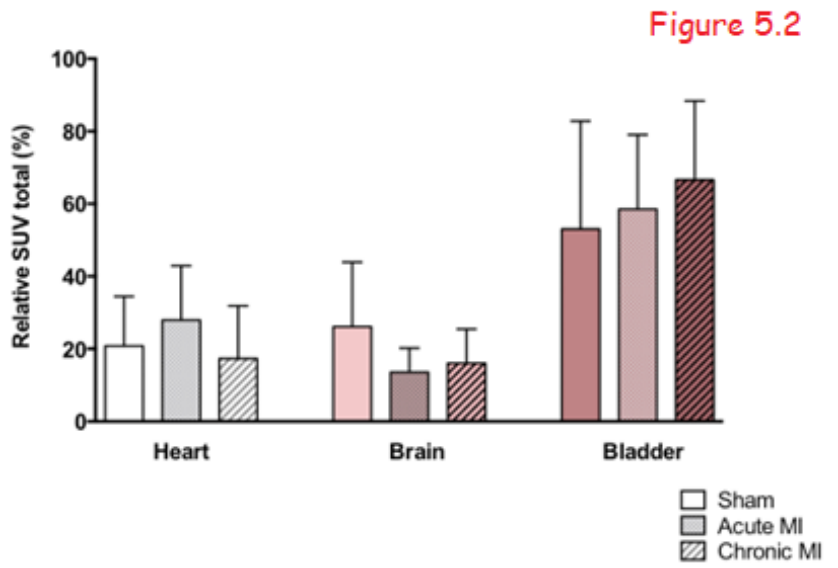
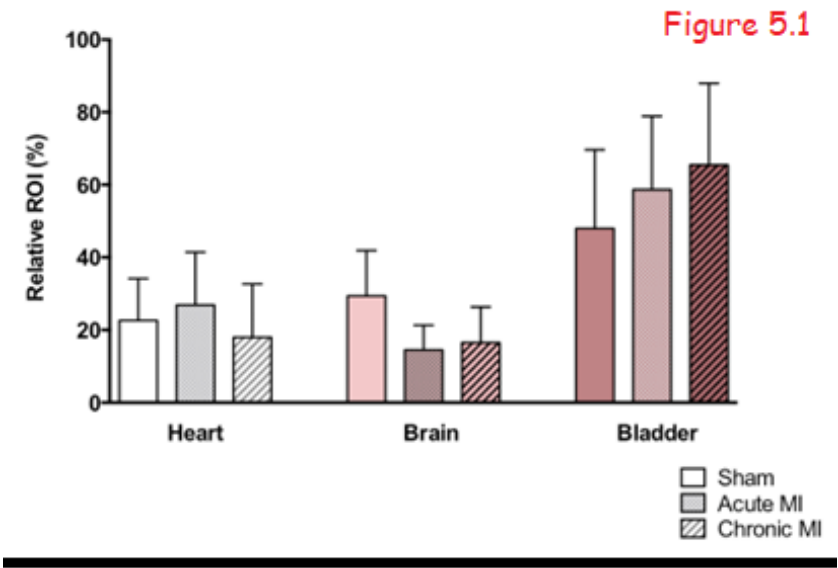


Figure 5. Figure (5.1) total Region of Interest (ROI_T) and Figure (5.2) total Standard Uptake Value (SUV_T) values in each organ expressed as a percentage in each animal group in the study. MI: myocardial infarction.

Histological study

Figure 6 shows both the histological sections of the cardiac tissue and the images taken with the Leica DM3000 optical microscope for each animal group, revealing healthy cardiomyocytes in the control group (group I), inflammatory cells in the acute phase (group II), and collagen fibers and myofibroblasts in the animals with chronic phase infarction (group III).

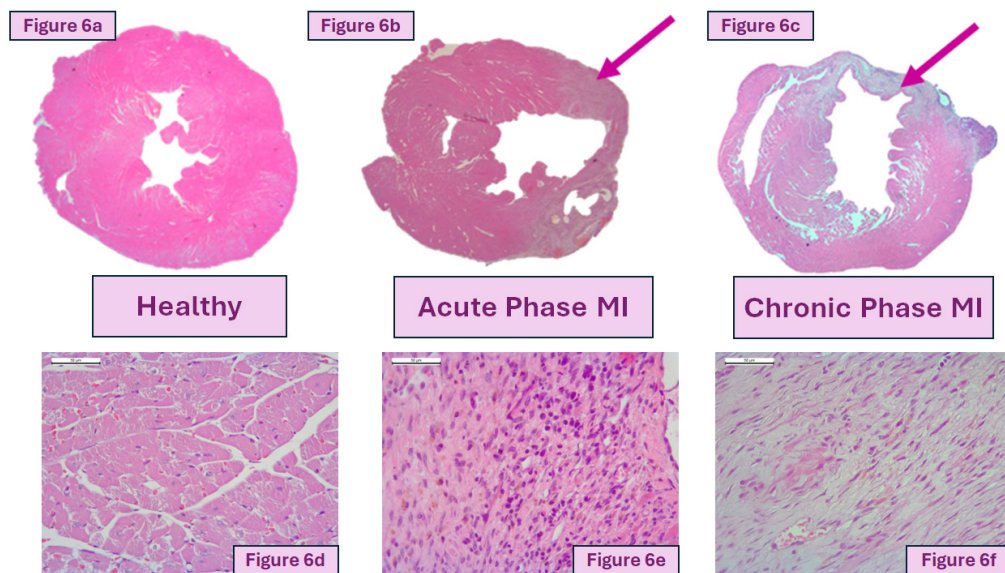


Figure 6. Histological sections of a healthy (7a), Acute phase MI (7b) and Chronic phase MI heart (7c) – Arrows shows infarction zone. Figures 7d, 7e and 7f show a microscopic image of cardiac tissue (50µm) from animals in the study groups. MI: myocardial infarction

Discussion

MI is a pathology with high incidence and is one of the leading causes of death worldwide^(19,20). Animal models aimed at understanding natural disease evolution and/or the effect of drugs to minimize cardiac injury is crucial⁽²¹⁾. The animal species most commonly used in models available for MI study is the mouse⁽²²⁾, which has a small heart and high heart rate. These models have proven useful for studying the temporal evolution of cardiac tissue after MI induction, and radiopharmaceuticals are optimal for monitoring alterations taking place in the tissue, given that radiopharmaceutical distribution and energy consumption requirements change significantly in response to MI-related damage⁽²³⁾.

Imaging techniques (ultrasound) for detecting MI present several limitations for studying disease evolution, including difficulty in measuring the size of the infarcted tissue and the need for acquisition angle-dependent analysis⁽²⁴⁾. Furthermore, cardiac function and myocardial viability maintained after infarction cannot be accurately determined by these techniques. Finally, use of this technique in mice is complicated by their small heart size and high heart rate⁽²⁵⁾. These drawbacks have prompted recourse to imaging techniques in nuclear medicine, such as PET, which require the use of radiopharmaceuticals.

Among the radiopharmaceuticals currently available that have shown to be suitable for diagnosis and localization of ischemia and/or myocardial infarction are compounds labeled with metastable technetium-99 (99mTc), such as 99mTc-Tetrofosmin and 99mTc-Sestamibi⁽²⁶⁾. However, single-photon emis-

sion computed tomography (SPECT) must be used to image these compounds⁽²⁷⁾. The limitations of this technique include the need for additional reconstruction to obtain 3D images, which only permits semi-quantitative assessment, and the lower sensitivity of SPECT compared to PET⁽²⁷⁾. Overall, PET provides better resolution and detection sensitivity, less attenuation and fewer image artifacts than SPECT⁽²⁸⁾. We selected the radiopharmaceutical [¹⁸F]FDG for this study as it is a widely used radiopharmaceutical whose time course in the body is known⁽²⁹⁾ and which is indicated for cardiological studies⁽³⁰⁾.

PET with [¹⁸F]FDG is a technique capable of detecting and differentiating damaged areas of the heart thanks to differences in radiopharmaceutical consumption and uptake by the myocardium⁽³¹⁾ and can also be used to quantify MI magnitude by measuring the parameters of the ROI and SUV⁽¹⁸⁾. Furthermore, combining PET with CT⁽²³⁾ allows for a more precise anatomical localization of these uptake areas. Homogeneous [¹⁸F]FDG uptake is observed in the absence of injury, whereas no uptake is observed when there is cellular damage in tissue⁽³²⁾ thus allowing qualitative/visual localization of tissue injury.

The results obtained in this study based on [¹⁸F]FDG uptake in the heart, brain and bladder in the three groups indicated no statistically significant differences ($p > 0.05$) by ANOVA in [¹⁸F]FDG uptake in the brain and bladder after induction of MI. In the heart, however, the distribution and uptake of [¹⁸F]FDG presented statistically significant differences ($p < 0.001$) between healthy animals (group I) and those in the acute infarction phase (group II), as well as between the two infarcted animal groups (acute and chronic). That no significant differences were observed in [¹⁸F]FDG uptake by the cardiac tissue of healthy and chronically infarcted animals could be explained by changes in the pathophysiology of cardiac tissue after infarction development. At around day 3–7 post-infarction, massive inflammation occurs in the myocardium to eliminate apoptotic cardiomyocytes due to lack of blood supply. Subsequently, this inflammation resolves and the process of fibrosis begins⁽³³⁾, consisting of the differentiation of myofibroblasts that synthesize collagen in the infarcted area to replace the dead cells removed. The images obtained at 7 and 21 days would thus correspond to the inflammatory and fibrosis phases, respectively⁽³⁴⁾.

The values of the ROI_T and SUV_T expressed in relative terms (figure 5) indicate that in healthy animals (group I) brain glucose consumption is slightly higher than cardiac consumption, which may be because to obtain energy during the fasting period undergone by all the study animals, the heart consumes more fatty acids as opposed to the brain, which requires glucose for energy. However, in animals in acute phase infarction (group II), the heart takes up more than the brain, which may be due to massive migration of macrophages that consume glucose occurring during the post-surgical inflammatory process, while in animals in chronic phase infarction (group III) radiopharmaceutical uptake is similar in the heart (17 %) and in the brain (16 %).

Histologically, the extracellular matrix of cardiac tissue is a three-dimensional network composed of fibers and ground substance that participates in providing structural support to cardiomyocytes, and in regulating survival, migration, proliferation, and inflammatory response. After acute MI, a series of changes occur at the extracellular matrix level aimed at eliminating necrotic cardiomyocytes through a controlled inflammatory response and at subsequent fibrotic scar formation. The remodelling process of the cardiac interstitium after infarction must be perfectly controlled in time and form given that its dysregulation has been associated with adverse ventricular remodelling and the appearance of heart failure.

This study confirms that the PET/CT technique using [¹⁸F]FDG as a radiopharmaceutical in the murine model is highly effective in detecting cardiac lesions and quantifying the affected area. Our results are in agreement with those obtained by other authors⁽³⁵⁾ who demonstrated its utility as a noninvasive technique for determining cardiovascular function by measuring [¹⁸F]FDG uptake in a murine model of permanent ligation ischemia after genetic deletion⁽²⁾. Nonetheless, in order to extrapolate the results obtained in the murine animal of MI it is crucial to have a well-defined and standardized protocol in terms of anesthesia, preparation, radiopharmaceuticals, etc.⁽²³⁾, like the one used in this study.

Conclusion

MicroPET after [^{18}F]FDG administration provides qualitative and quantitative information on glucose consumption in the heart, brain and bladder. Combined with CT, it facilitates a more precise localization of the organs, helping to delimit the quantitative parameters (ROIs and SUVs) used to highlight the differences in distribution caused by the cardiac pathology studied, especially at the level of myocardial tissue. Micro PET/CT may therefore be of great practical interest for assessing the extent of MI-related cardiac injury, as well as for evaluating new therapies using animal experimental models.

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