Positron Emission Tomography in Inflammatory Cardiovascular Diseases

Renata Christian Martins Felix[1,2,3], Clécio Maria Gouvea[1], Michel Pontes Carneiro[2], Claudio Tinoco Mesquita[3]

Instituto Nacional de Cardiologia[1], Instituto Nacional de Câncer[2], Rio de Janeiro, RJ – Brazil; Universidade Federal Fluminense[3], Niterói, RJ, Brazil

Introduction

The positron emission tomography (PET) is a technology in the field of Nuclear Medicine, designed in the late 1950s for the purposes of mapping brain function. The development of this technique and the production of new radiopharmaceuticals for positron emitters allowed its incipient employment in clinical practice from the years 1980-1990[1]. Lately, the equipment consists of a system that integrates PET and computed tomography (CT), bringing benefits of improved image quality and anatomic correlation of metabolic findings[2]. Its applicability has been expanded worldwide in recent years.

Fluorodeoxyglucose (^{18}F-FDG) is the most used radiopharmaceutical drug for conducting PET tests due to its relatively long physical half-life (110 minutes) compared to positron-emitting materials, while some others have a half-life of just a few minutes or even seconds; and also for playing a well-defined biological role in glycolytic metabolism[1].

Warburg observed in the 1930s that tumor cells preferentially use glucose as energetic substrate, opening the way for new investigations to demonstrate the potential of ^{18}F-FDG as a metabolic marker of tumor activity, with a different uptake according to the malignancy degree of the tumor[1].

^{18}F-FDG is a glucose derivative bound to the radioactive fluorine, which, after intravenous administration, is transported through the cell membrane through glucose transporters (GLUT). There are about 13 subtypes of GLUT, but only a few stand out, like GLUT 1, which presents an increased expression in tumor cells. Intracellularly, ^{18}F-FDG is metabolized by hexokinase, as well as glucose, ^{18}F-FDG-6-phosphatase, which does not continue in the metabolic pathway due to the presence of fluorine in its molecule. The cell membrane is impermeable to ^{18}F-FDG-6-phosphatase, causing an accumulation of this metabolite in metabolically active cells, allowing for the production of images[3].

The PET imaging technology allows quantifying the concentration of ^{18}F-FDG in tissues. The most commonly used parameter is the SUV (Standard Uptake Value). The SUV corresponds to the measurement of the concentration of ^{18}F-FDG performed by the equipment in a particular tissue divided by the material injected dose adjusted for the weight. This measure has demonstrated diagnostic and prognostic implications[4].

The main application of PET-CT is currently in the field of oncology. It is used for differentiating benign from malignant lesions, for staging and evaluation of treatment response of various tumors. The method has also been applied in the differential diagnosis between dementia and depression in neuropsychiatry; in the diagnosis, localization and follow-up of inflammatory and infectious processes, reflecting an increased energy demand of inflammatory cells; in cardiology, it has been used in myocardial viability research[2].

Many articles have demonstrated the role of this technology in the evaluation of inflammatory and infectious diseases of the cardiovascular system[5].

The purpose of this article is to provide a review of the literature on this topic to identify clinical situations in which there is evidence of the usefulness of PET-CT in diagnostic and therapeutic evaluation.

Methodology

A literature review was conducted on articles published using the following databases: PubMed and Medline.

The terms used were FDG, fluorodeoxyglucose, Positron Emission Tomography, PET/CT (AND) cardiovascular inflammation, cardiac sarcoidosis, endocarditis, pericarditis and myocarditis.

Through the evaluation of the abstracts, the articles that did not address the topic were excluded.

Results

By combining all the above terms, our research resulted in 1,676 articles in an inquiry made by June 30, 2014. Once any duplicate articles were excluded, 294 articles were selected according to a visual analysis of the correlation with the subject studied between 1999 and 2014.

Approximately 65% of the articles were published between 2011 and 2014, demonstrating the contemporary nature of the topic.

Eleven revision manuscripts were found. Just a few of them address the issue broadly, noting that some publications focus on atherosclerosis and others focus only on inflammatory diseases of other causes[5,6].

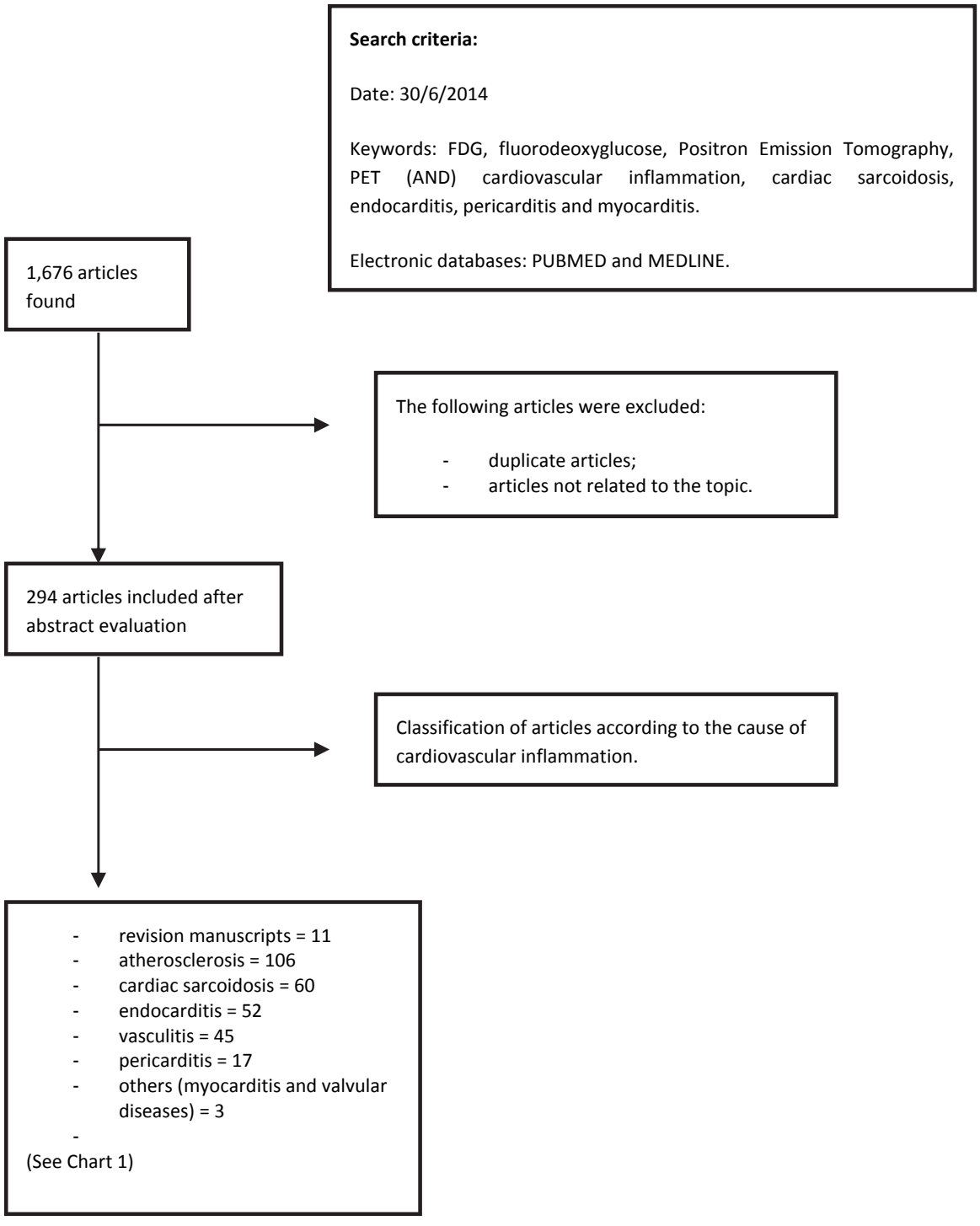
Research execution flowchart:

Keywords

Cardiovascular Diseases/etiology; Cardiovascular Diseases/complications; Inflammation; Positron-Emission Tomography.

Mailing address: Instituto Nacional de Cardiologia •
Rua das Laranjeiras, 374, 22240-006, Laranjeiras, Rio de Janeiro, RJ – Brazil
E-mail: renatafelix@cardiol.br/renata.felix@inc.saude.gov.br
Manuscript received on August 22, 2014; manuscript revised on August 25, 2014; approved on September 1, 2014.

DOI: 10.5935/2318-8219.20140034


Search criteria:
Date: 30/6/2014
Keywords: FDG, fluorodeoxyglucose, Positron Emission Tomography, PET (AND) cardiovascular inflammation, cardiac sarcoidosis, endocarditis, pericarditis and myocarditis.
Electronic databases: PUBMED and MEDLINE.
1,676 articles found
The following articles were excluded:
- duplicate articles;
- articles not related to the topic.
294 articles included after abstract evaluation
Classification of articles according to the cause of cardiovascular inflammation.
- revision manuscripts = 11
- atherosclerosis = 106
- cardiac sarcoidosis = 60
- endocarditis = 52
- vasculitis = 45
- pericarditis = 17
- others (myocarditis and valvular diseases) = 3
-
(See Chart 1)

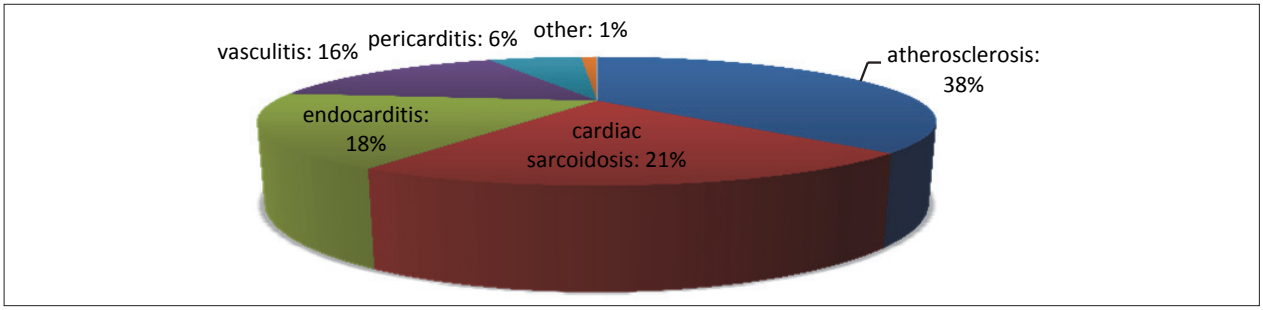


Chart 1 – *Distribution of articles according to the cause of cardiovascular inflammation. (Others: represents myocarditis and valvular heart diseases.)*

Because they are the most common issues, we will look into some evidence about the role of PET-CT in atherosclerosis, cardiac sarcoidosis, endocarditis and vasculitis. We will briefly mention other inflammatory processes.

Role of PET-CT in the evaluation of atherosclerosis

Atherosclerosis is a systemic inflammation associated with the formation of lipid plaques on vessel walls. Atherosclerotic plaque usually evolves over decades, comprising non-obstructive lesions, stable obstructive lesions and vulnerable (or unstable) plaques. The latter are susceptible to rupture and acute arterial thrombosis, which is responsible for cardiovascular events such as myocardial infarction and cerebral vascular accidents[7].

Vulnerable plaque is characterized by a thin fibrous cap and lipid-rich or necrotic core. Imaging techniques such as computed tomography and magnetic resonance imaging can estimate the density of the tissues and demonstrate such components; however, finding the plaques that are about to induce acute events is a challenge[7].

PET with ^{18}F-FDG has been evaluated as an imaging method able to play the role of a molecular marker of vulnerable plaque due to its ability to signal inflammatory processes in activity[8].

The first study using fluorodeoxyglucose to identify inflammation in plaques causing acute cardiovascular events was published in 2002[9]. ^{18}F-FDG uptake in the culprit plaque was demonstrated in all patients with recent transient ischemic attack and carotid obstruction of at least 70%. Despite the small number of individuals, this was the first direct evidence of atherosclerotic inflammation in culprit arteries.

Subsequently, Tawakol et al.[10] demonstrated that it is possible to correlate the degree of vascular ^{18}F-FDG uptake with the degree of vascular inflammation through the histology of atherosclerotic plaques removed during carotid endarterectomy, identifying differences in the content of macrophages associated with atherosclerotic inflammation[7].

One of the most interesting applications of ^{18}F-FDG in atherosclerosis is the assessment of therapeutic response. Tahara et al.[11] demonstrated a significant reduction in the intensity of carotid uptake after three months of treatment with simvastatin compared to dietary treatment, demonstrating the anti-inflammatory effect of the drug associated with reduced LDL cholesterol and increased HDL cholesterol.

One can not only associate cardiovascular risk factors with vascular uptake of ^{18}F-FDG[12], but also predict clinical outcomes, as demonstrated in a study with 513 cancer patients with risk factors for atherosclerotic disease who underwent PET-CT with ^{18}F-FDG and were evaluated for the presence of inflammation in the ascending aorta[13]. After a mean follow-up of four years, we observed a higher number of cardiovascular events in those with higher radiotracer uptake, even after adjustment for age and clinical factors, demonstrating the prognostic impact of the method.

Assessment of coronary atherosclerosis

The analysis of coronary arteries by PET-CT is especially challenging for two main reasons: the physiological uptake of the radiotracer by the myocardium[14], which makes it difficult to properly identify the coronary arteries and myocardial pathologies; and the small size of the coronary vessels, which are at the limit of the spatial resolution of the equipment and can only be properly seen when they present a strong intensity of uptake[15].

Many groups have been devoted to the subject and it seems that a satisfactory suppression of myocardial uptake enables the evaluation of proximal epicardial coronary arteries, hence decreasing the significance of spatial resolution. The strategies undertaken for this purpose employ the principle of myocardial metabolic shift to use of fatty acids instead of glucose[15] with satisfactory success[16,17].

Rogers et al. compared patients who underwent angioplasty with stenting for acute coronary syndrome (ACS) with those who underwent an elective procedure. Intense uptake of ^{18}F-FDG was demonstrated in coronary segments that received ACS stenting in contrast to those who were not in an acute process. Besides the uptake of the "culprit artery," patients with ACS had a higher uptake in the ascending aorta and in the left main coronary artery, underscoring the systemic aspect of the disease[18]. This study corroborated the role of ^{18}F-FDG as a marker of inflammatory activity in atherosclerotic coronary disease.

Besides the ^{18}F-FDG, ^{18}F-NaF (fluoride) has been studied as a marker of coronary atherosclerosis and other vessels[19]. Its main application is in the evaluation of the skeleton due to deposition of hydroxyapatite crystals that make up the bone matrix. It is capable of identifying areas of active calcification[20]. It seems that the uptake of fluoride in the vessels is associated with active plaque remodeling,

identifying its greater susceptibility[19]. Further studies are needed to determine its role in this scenario.

In order to establish the value of imaging methods in the identification and management of patients with vulnerable plaque, the prospective study BioImage — High Risk Plaque Initiative is underway. It is intended to include 6,500 volunteers who will undergo vascular ultrasound, magnetic resonance imaging, computed tomography and PET-CT, with three-year follow-up[21]. The results may provide insights that will assist us in assessing cardiovascular risk.

The role of PET-CT in cardiac sarcoidosis

Sarcoidosis is a systemic disease of an unknown cause characterized by the presence of noncaseating granuloma[22]. Cardiac involvement can be as frequent as 76% of patients, as observed in an autopsy study. However, severe underdiagnosis occurs in life. Myocardial involvement may be responsible for half of fatal cases[23].

Diagnosis of the disease is always confirmed by biopsy of a supposedly involved organ. However, as the disease progresses with remissions and relapses, it is important to identify whether the inflammatory process is going on, as this determines clinical management, whose main item is corticosteroid therapy[22].

The first reported use of ^{18}F-FDG for assessment of cardiac sarcoidosis was published in 2003[24]. The criteria for interpreting the images have ranged from visual analysis to the application of SUV and indexes of ^{18}F-FDG uptake. Visual analysis identifies as a disease in activity some patterns in which there is heterogeneous radiotracer uptake by the myocardium with focal areas of greater intensity, which has demonstrated a very high sensitivity but a variable specificity[24]. SUV semiquantification in myocardial segments or indices that compare the SUV of the heart with the SUV of blood has high sensitivity and better specificity[25,26].

A recent systematic review[27] showed 89% sensitivity and 78% specificity for the diagnosis of cardiac sarcoidosis by ^{18}F-FDG, using as a benchmark the criteria of the Japanese Ministry of Health, which are universally applied.

Comparison with other imaging methods suggests that ^{18}F-FDG is more sensible than ^{67}gallium citrate[24,28], a radiotracer employed in the study of inflammatory processes. Another advantage is the better spatial resolution of PET imaging and lower radiation exposure[28].

As for magnetic resonance imaging (MRI), ^{18}F-FDG has shown superior sensitivity; however, with lower specificity. It seems that both methods can be used in a complementary way, as the PET/CT can detect lesions in inflammatory activity while magnetic resonance imaging may demonstrate areas of fibrosis and estimate cardiac function. One of the advantages of Nuclear Medicine on magnetic resonance imaging is that it can be applied in patients with implantable cardiac devices[29].

In 2013, Mc Ardle et al. demonstrated[30] that there may be an association between the outcome of the ^{18}F-FDG study and the clinical presentation of cardiac sarcoidosis. They showed that patients with ventricular tachycardia present SUV quantifications with higher values than those with atrioventricular block. Among the latter, there was a greater proportion of basal septum uptake. This study suggests that the degree of radiotracer uptake and its location can help understanding the patient's condition and therapeutic management. Blankstein et al.[31] showed in 118 patients that those with perfusion defects and focal uptake of ^{18}F-FDG in the same topography are at increased risk of ventricular tachycardia and sudden death, demonstrating the role of PET-CT in the prognosis evaluation in cardiac sarcoidosis.

There is evidence that ^{18}F-FDG is useful in assessing therapeutic response[32], with a reduction of radiotracer uptake after corticotherapy associated with increase in left ventricular ejection fraction.

Figure 1 shows the PET images with ^{18}F-FDG in patients with previous diagnosis of cardiac sarcoidosis who had worsening of cardiac function, raising suspicions of disease reactivation. Heterogeneous radiotracer uptake in the left ventricle, even after physiological uptake suppression protocol, confirmed the clinical assumption. There was pain in the lower limbs. Anomalous radiotracer uptake in the leg muscles suggesting that inflammation in this topography as well.

The indications for use of PET-CT with ^{18}F-FDG in sarcoidosis[33], as adopted by the Institute of Cardiology, University of Ottawa, Canada, are described in Chart 1.

The role of PET-CT in infective endocarditis and infections of intracardiac devices

The diagnosis of infective endocarditis remains challenging despite the diagnostic apparatus available. A positive blood culture and the presence of vegetation on echocardiography are the pillars that support clinical suspicions. However, this combination is not always easily demonstrated. Because of its high morbidity and mortality, identifying infective endocarditis is imperative for proper treatment[34].

Thus, new diagnostic elements have been proposed in addition to the traditional Duke criteria[34]. Among them, there is the suggestion of inclusion of PET-CT imaging with ^{18}F-FDG[35].

In 2004, Yen et al.[36] demonstrated the uptake of ^{18}F-FDG in six patients diagnosed with endocarditis by the Duke criteria at the same sites demonstrated by echocardiography.

Since then, some case series have been published, demonstrating that PET/CT may be useful in infective endocarditis and may contribute to the diagnosis, especially when there is clinical suspicion; however, blood cultures and echocardiography are inconclusive in the treatment follow-up and in the evaluation of septic embolization due to full body images[37].

Besides the evaluation of the native valve, ^{18}F-FDG is applied in the diagnosis of prosthetic valve infection. Saby et al.[35], in a prospective analysis of 72 patients with suspected prosthetic infection, found a sensitivity of 73% and specificity of 85% for PET-CT[35]. In this important study, the addition of PET-CT to the Duke criteria allowed to establish definitive diagnosis of prosthesis endocarditis in 97% of the cases versus 70% when only traditional criteria were used.

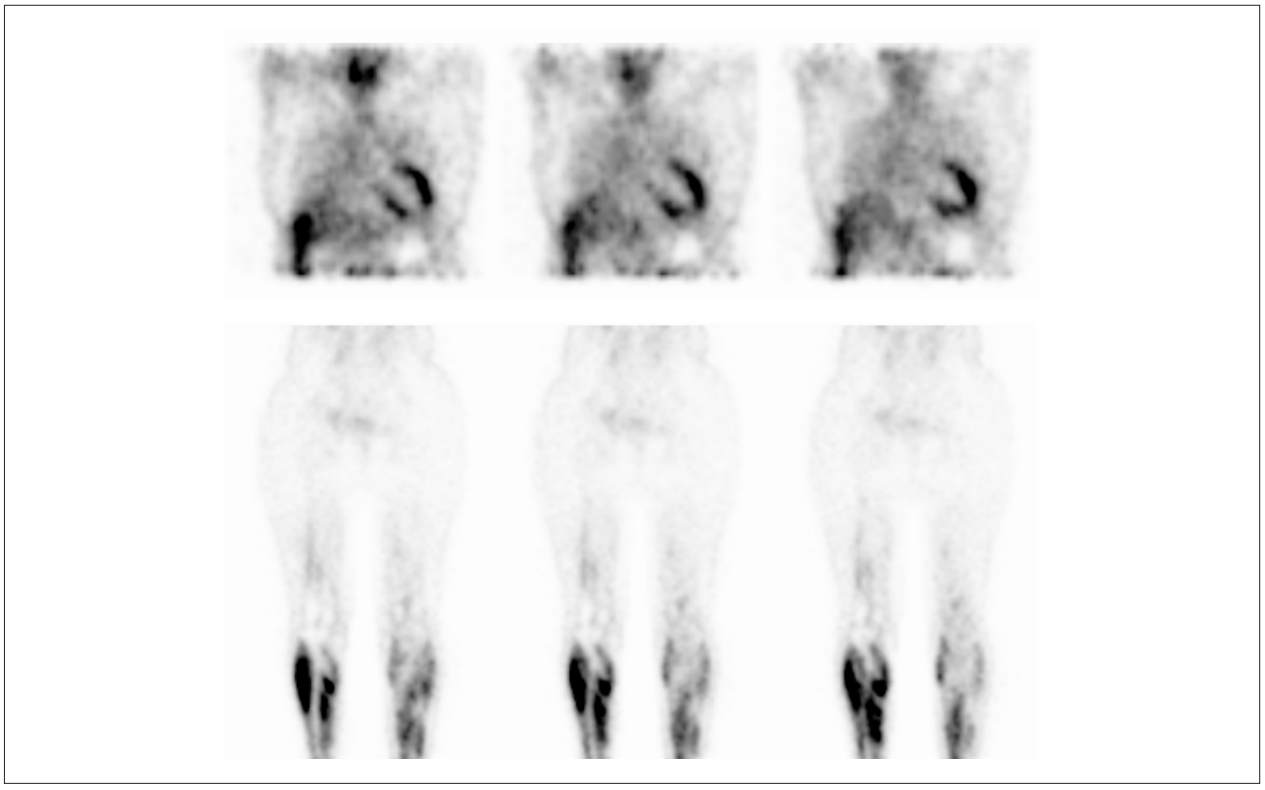


Figure 1 – *^{18}F-FDG test in patients diagnosed with cardiac sarcoidosis and reactivation of the disease.*

Chart 1 – Clinical situations in which we should consider the use of ^{18}F-FDG

Patient < 55 years, with 2nd or 3rd degree AVB of unknown etiology.
Unexplained monomorphic VT in the absence of atherosclerotic coronary artery disease and other known myocardial diseases.
Patient with extracardiac sarcoidosis, with ECG, echocardiography or abnormal Holter with suspected cardiac sarcoidosis; to guide the biopsy.
Patient with established cardiac sarcoidosis to evaluate the therapeutic response.

AVB: atrioventricular block; VT: ventricular tachycardia; ECG: electrocardiogram. Adapted from Mc Ardle et al.[33].

Limitations of the method in these cases are associated with small lesions, especially those smaller than 4 mm[38], and concomitant antibiotic therapy that may reduce the intensity of inflammation[39], besides the need for adequate suppression of myocardial physiological uptake, as previously said. Early after surgical procedures, radiotracer uptake may occur due to the inflammatory healing process, which can reduce the specificity of the method[40].

Millar et al.[37] published a review on the subject, suggesting an algorithm that includes PET-CT in the investigation of patients with suspected infective endocarditis (Algorithm 1).

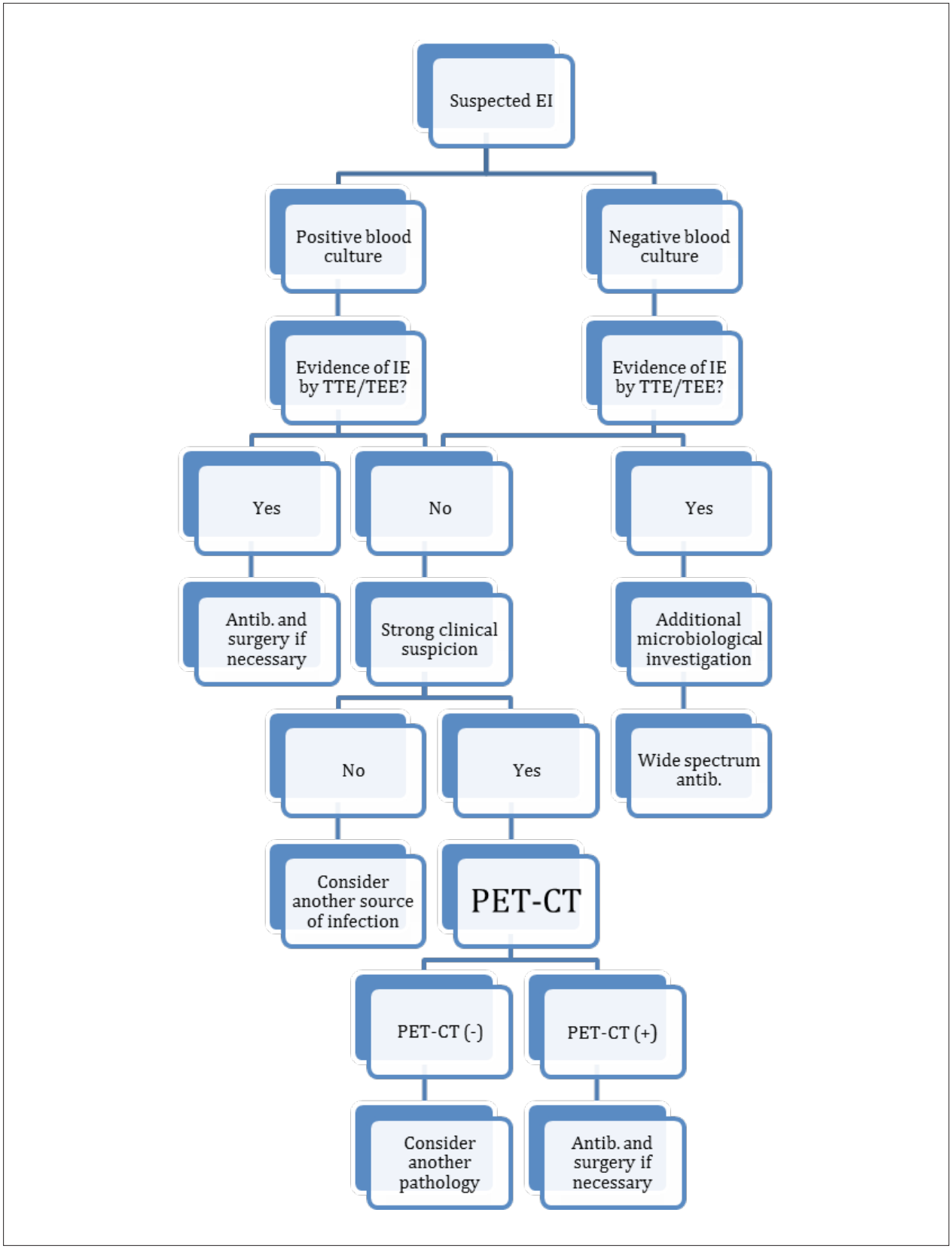
Patients with suspected infection of implantable cardiovascular devices such as a pacemaker or cardioverter-defibrillator can benefit from the study with fluorodeoxyglucose, both for diagnosing and for assessing the extent of infectious involvement, which has an impact on treatment decisions. Sarrazin et al.[41] found a sensitivity of 88% and specificity of 100%.

The indications for the use of PET-CT in infective endocarditis and infection of intracardiac devices are listed in Chart 2, as proposed by Millar et al.[37].

Studies demonstrate the usefulness of ^{18}F-FDG in the diagnosis of prosthetic valve infection, with diagnostic accuracy greater than 95%[42], which is higher than the computed tomography used alone[42,43]. The pattern of focal uptake at the prosthesis site shows high sensitivity and specificity for diagnosing the infection, whereas the presence of diffuse linear uptake can be interpreted as inflammation in the presence of prosthetic material[44].

The role of PET-CT in vasculitis

Vasculitis represents an inflammation of the blood vessels with leukocyte infiltration and no structural damage to the vessel wall and surrounding tissue. They are classified according to the size of the affected vessels. The main large-



Algorithm 1 – *Algorithm proposed for investigating infective endocarditis. Adapted from Plank et al. IE: infective endocarditis. Antib.: Antibiotic therapy.*

vessel vasculitis are giant cell arteritis and Takayasu's arteritis. Medium-vessel vasculitis includes polyarteritis nodosa in adults and Kawasaki disease in children. Other types of vasculitis involve small and medium vessels[45].

The diagnosis of these diseases can be challenging, especially in the early stages of the disease because the symptoms are usually nonspecific. This is confirmed by the biopsy; however, imaging studies play an important role in assessing the extension of inflammation and its consequences such as vascular stenosis[45].

Due to limited spatial resolution, PET-CT with ^{18}F-FDG has proven useful in cases of large vessel vasculitis, although there are isolated reports of its use in inflammation of smaller vessels[45].

Takayasu's arteritis affects the aorta and its major thoracic branches; mainly affecting young people or middle-aged adults. It commonly progresses with recurrences. The identification of inflammation activity is essential for the implementation of corticotherapy[46]. ESR and C-reactive protein are nonspecific markers of recrudescence of the inflammatory process[47]. PET-CT can establish whether the disease is active, quantify its intensity according to the degree of uptake and its extension due to its ability to take images of the entire body[48].

In the early stages of the disease, vascular uptake presents a linear pattern. The distribution along plaques at later stages is mostly common[48].

Tezuka et al.[46], using a semiquantitative evaluation with SUV, observed that values starting from 2.1 are associated with sensitivity of 92.6% and specificity of 91.7% for diagnosing and evaluating relapse of Takayasu, proving to be superior to serum inflammatory markers.

Meta-analysis of six studies[49] showed sensitivity of 70.1% and specificity of 77.2% of ^{18}F-FDG for the diagnosis of Takayasu arteritis, further emphasizing its additional value compared to current diagnostic methods. One of the main advantages of Nuclear Medicine is the ability to identify the inflammatory process before the evolution to vascular stenosis[48].

Reduced uptake of radiotracer is associated with clinical improvement and reduced thickening of the aortic wall[50].

In Figure 2, we present the case of a young man diagnosed with Takayasu arteritis, where the ^{18}F-FDG showed disease activity and improved uptake after implementation of therapy.

Giant cell arteritis or temporal arteritis affects people older than 50; involving the aorta and its branches, particularly the temporal artery. Due to its small size, PET-CT typically has difficulties in assessing the temporal artery; however, it can analyze the other branches involved[51]. The vessels typically demonstrate linear and continuous uptake of moderate intensity[52].

A meta-analysis using six studies described 80% sensitivity and 89% specificity for diagnosing the disease[52].

As in Takayasu's disease, decreased uptake correlates with clinical improvement and PET-CT appears to be more accurate than magnetic resonance imaging for clinical follow-up[53].

PET-CT may be indicated in the scenario of vasculitis, as suggested by Zerizer et al.[54], as shown in Chart 3.

The role of PET-CT in other cardiovascular inflammations

Diseases that involve the pericardium may present ^{18}F-FDG uptake. Although it is not possible to clearly identify the etiology of the process, the intensity of radiotracer uptake may help distinguish between infection/inflammation and neoplastic involvement. Pericarditis by neoplasia demonstrates intense uptake, while no neoplastic involvement usually demonstrates mild to moderate intensity[55].

Ozawa et al.[56] observed 100% sensitivity and specificity for the diagnosis of acute myocarditis with fluorodeoxyglucose compared to endomyocardial biopsy when the test was performed within two weeks from disease onset. After this period, there is a reduction in the detection of inflammation, which may be associated with the evolution of the pathophysiological mechanism.

In our literature research, we did not find any publication contemplating PET-CT in the Chagas' disease, demonstrating a gap in knowledge in this area, which may call for research projects in our country, where the disease remains endemic in some areas[57].

The role of PET-CT in cardiac transplantation

There is little evidence about the role of ^{18}F-FDG in rejection after heart transplantation.

Rejection is an inflammatory process that is always present in transplantation because there is no genetic compatibility between individuals who are not monozygotic twins. Therefore, systematic surveillance is done through endomyocardial biopsy. Noninvasive imaging methods available are not yet able to replace it in this evaluation[58].

In 1992, Hoff et al.[59] used ^{18}F-FDG to research acute graft rejection in heterotopic heart transplantation in rats. They found an increased uptake of ^{18}F-FDG in transplanted

Chart 2 – Indications for the use of PET-CT in cases of infective endocarditis and infection of intracardiac devices

Cases of infective endocarditis or infection of intracardiac devices, which are difficult to diagnose because of negative findings on echocardiography and/or blood culture.
Cases of fever of unknown origin or bacteremia of unknown focus in patients with intracardiac devices or in patients with a strong clinical suspicion of infective endocarditis.
Early detection and assessment of embolic events and metastatic infection in cases of infective endocarditis or infection of intracardiac device.
Assistance to decision in the extraction of intracardiac devices (generating source and/or cables) with infection.

IE: infective endocarditis. Adapted from Millar et al.[37].

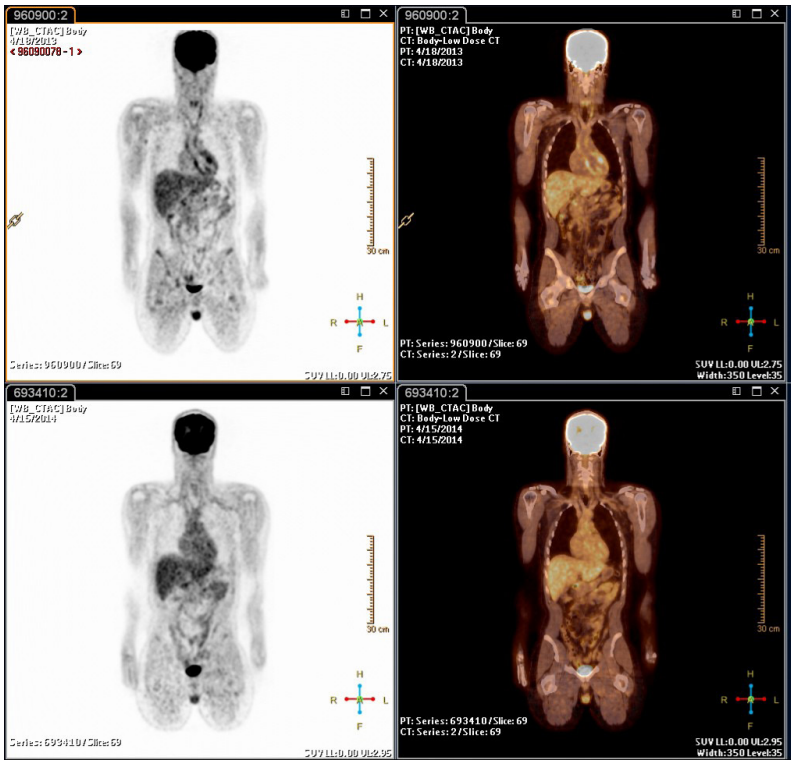


Figure 2 – *In the top row, there is uptake of ^{18}F-FDG in the thoracic aorta and its branches. At the bottom line, there is reduced intensity of uptake after initiation of therapy. On the left, PET images. On the right, the relevant PET-CT images.*

Chart 3 – Indications for ^{18}F-FDG in vasculitis

Initial diagnosis in patients with nonspecific symptoms and fever of unknown origin.
Identify areas of increased uptake that could be used as the site for biopsy.
Evaluate the extent of the disease, which will affect the treatment and identify sites at risk for complications.
Evaluate response to treatment.

Source: Adapted from Zerizer et al.[54].

hearts with mild to severe rejection compared to histological analysis. It was observed that in rats undergoing isograft with no rejection there was no significant uptake of radiotracer. The study suggests a diagnostic role of the method in post cardiac transplantation rejection.

In humans, Rechavia et al.[60] studied 10 men aged between 13 and 60 months after cardiac transplantation without rejection by endomyocardial biopsy and compared them with 9 healthy volunteers, observing that these had higher intensity of ^{18}F-FDG uptake than the control group. They suggest that the transplanted heart shows homogeneous increase of glucose metabolism, possibly due to inefficient use of metabolite or due to stimulus to uptake by increase of circulating catecholamines related to chronically denervated heart. These findings seem to become more challenging to suppress myocardial physiological uptake of the radiotracer in this group of patients; however, the researchers did not use any protocols that have proven effective in non-transplanted patients.

Hence, as there is no response to the use of fluorodeoxyglucose in post-heart transplantation rejection, the Instituto Nacional de Cardiologia is conducting a research project along with the cardiovascular science graduate program of Universidade Federal Fluminense in order to study this scenario.

Figure 3 shows the case of a patient with heart failure after heart transplantation with diagnosis of humoral rejection proven by endomyocardial biopsy. Study was performed

with ^{18}F-FDG. The test was performed after preparation for suppression of physiological uptake using diet low in carbohydrate and rich in fat. As there is no specific literature in this context, the images were interpreted according to criteria similar to those of cardiac sarcoidosis[26], in which heterogeneous radiotracer uptake by the myocardium is observed, adding importance to the areas of greatest intensity. Myocardial perfusion scintigraphy was performed with ^{99}mTc-sestamibi to assess potential areas of myocardial fibrosis. Upon completion of the project, it is expected to establish the best method of interpretation of the test in post-heart transplant rejection.

Conclusion

PET-CT with ^{18}F-FDG has proven to be a useful tool in diagnosing and monitoring various cardiovascular inflammatory processes.

This technology is widely available in our country and can assist the physicians in evaluating patients in this clinical scenario.

Authors' contribution

Research creation and design: Felix RCM; Data acquisition: Felix RCM, Gouvea CM, Carneiro MP; Data analysis and interpretation: Felix RCM; Statistical analysis: Felix RCM; Manuscript drafting: Felix RCM; Critical revision of the manuscript as for important intellectual content: Mesquita CT; Supervision: Mesquita CT.

Potential conflicts of interest

No relevant potential conflicts of interest.

Sources of funding

This study was funded by Instituto Nacional de Cardiologia – Fundacor.

Academic association

This article is part of the doctoral thesis of Renata Christian Martins Felix, from Universidade Federal Fluminense.

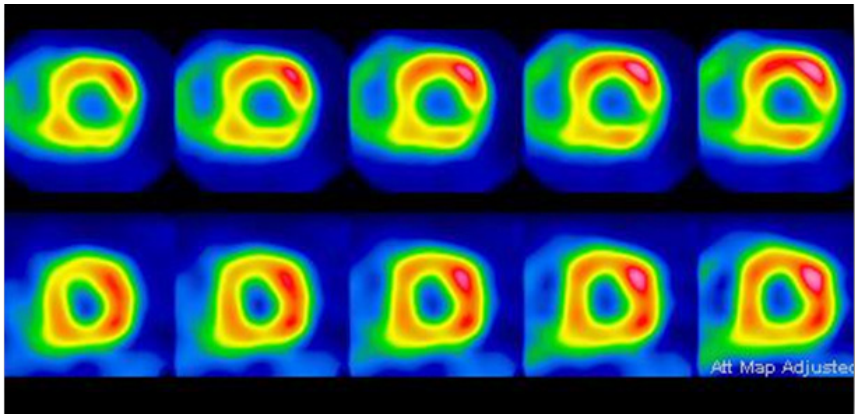


Figure 3 – *First line = study with ^{18}F-FDG demonstrating heterogeneous uptake of the radiotracer with greater intensity in the anterior and anterolateral walls, suggesting an inflammatory process in these regions. No uptake of radiotracer in the inferolateral wall and lower intensity in the inferior and inferoseptal walls. Second line = study with ^{99}mTc-sestamibi demonstrating preserved myocardial perfusion, including the inferolateral wall with no areas of myocardial fibrosis.*

References

1. Alavi A, Reivich M. Guest Editorial: The Conception of FDG-PET Imaging. Semin Nucl Med. 2002;32(1):2-5.
2. Mittra E, Quon A. Positron emission tomography/computed tomography: the current technology and applications. Radiol Clin N Am. 2009;47(1):147–60.
3. Plathow C, Weber WA. Tumor cell metabolism imaging. J Nucl Med. 2008; 49(Suppl 2):43S–63S.
4. Singh D, Miles K. Multiparametric PET/CT in oncology. Cancer Imaging. 2012;12:336-44.
5. Ben-Haim S, Gacinovic S, Israel O. Cardiovascular infection and inflammation. Semin Nucl Med. 2009; 39(2):103-14.
6. Joshi F, Rosenbaum D, Bordes S, Rudd JH. Vascular imaging with positron emission tomography. J Intern Med. 2011; 270(2):99-109.
7. Libby P. Inflammation in atherosclerosis. Nature. 2002; 420(6917):868-74.
8. Dunphy MP, Strauss HW. Molecular imaging of atherosclerosis. Curr Cardiol Rep. 2008; 10 (2):121-7.
9. Rudd JH, Warburton EA, Fryer TD, Jones HA, Clark JC, Antoun N, et al. Imaging atherosclerotic plaque inflammation with [18F]-fluorodeoxyglucose positron emission tomography. Circulation. 2002;105(23):2708-11.
10. Tawakol A, Migrino RQ, Bashian GG, Bedri S, Vermylen D, Cury RC, et al. In vivo 18F-fluorodeoxyglucose positron emission tomography imaging

provides a noninvasive measure of carotid plaque inflammation in patients. J Am Coll Cardiol. 2006;48(9):1818-24.

11. Tahara N, Kai H, Ishibashi M, Nakaura H, Kaisla H, Baba K, et al.. Simvastatin Attenuates Plaque Inflammation: evaluation by fluorodeoxyglucose positron emission tomography. J Am Coll Cardiol. 2006; 48(9):1825-31.

12. Antonopoulos AS, Margaritis M, Lee R, Channon K, Antoniades C. Statins as anti-inflammatory agents in atherogenesis: molecular mechanisms and lessons from the recent clinical trials. Curr Pharm Des. 2012;18(11):1519-30.

13. Figueroa AL, Abdelbaky A, Truong QA, Corsini E, MacNabb MH, Lavender ZR, et al. Measurement of arterial activity on routine FDG PET/CT images improves prediction of risk of future CV events. JACC: Cardiovasc Imaging. 2013;6 (12)1250-9.

14. Fukuchi K, Ohta H, Matsumura K, Ishida Y. Benign variations and incidental abnormalities of myocardial FDG uptake in the fasting state as encountered during routine oncology positron emission tomography studies. Br J Radiol. 2007;80(949):3–11.

15. Dunphy MP, Freiman A, Larson SM, Strauss HW. Association of vascular 18F-FDG uptake with vascular calcification. J Nucl Med. 2005;46(8):1278-84.

16. Wykrzykowska J, Lehman S, Williams G,. Parker JA, Palmer MR, Varkey S, et al. Imaging of inflamed and vulnerable plaque in coronary arteries with 18F-FDG PET/CT in patients with suppression of myocardial uptake using a low-carbohydrate, high-fat preparation. J Nucl Med .2009; 50(4):563–8.

17. Coulden R, Chung P, Sonnex E, Ibraim Q, Maguire C, Abele J. Supression of myocardial ^{18}F-FDG uptake with a preparatory "Atkins-style" low-carbohydrate diet. Eur Radiol. 2012;10(10):2221-8.

18. Rogers IS, Nasir K, Figueroa AL, Cury RC, Hoffmann U, Vermylen DA, et al. Feasibility of FDG imaging of the coronary arteries: comparison between acute coronary syndrome and stable angina. J Am Coll Cardiol Img .2010;3(4):388 –97.

19. Chen W, Dilsizian V. Targeted PET/CT imaging of vulnerable atherosclerotic plaques: microcalcification with sodium fluoride and inflammation with fluorodeoxyglucose. Curr Cardiol Rep. 2013;15(6):364.

20. Hawkins RA, Choi Y, Huang SC, Hoh CK, Dahlbom M, Schiepers C, et al. Evaluation of the skeletal kinetics of fluorine-18-fluoride ion with PET. J Nucl Med. 1992;33(5):633–42.

21. Muntendam P, McCall C, Sanz J, Falk E, Fuster V. The BioImage Study: novel approaches to risk assessment in the primary prevention of atherosclerotic cardiovascular disease - study design and objectives. Am Heart J. 2010; 160(1):49-57.

22. Newman LS, Rose CS, Maier LA. Sarcoidosis. N Engl J Med 1997;336(17):1224–34.

23. Perry A, Vuitch F. Causes of death in patients with sarcoidosis: a mor- phologic study of 38 autopsies with clinicopathologic correlations. Arch Pathol Lab Med. 1995;119(2):167-72.

24. Yamagishi H, Shirai N, Takagi M, Yoshiyama M, Akioka K, Takeuchi K, et al. Identification of cardiac sarcoidosis with (13)N- NH(3)/(18) F-FDG PET. J Nucl Med. 2003;44(7):1030–6.

25. Langah R, Spicer K, Gebregziabher M, Gordon L. Effectiveness of prolonged fasting 18f-FDG PET-CT in the detection of cardiac sarcoidosis. J Nucl Cardiol. 2009;16(5):801–10.

26. Tahara N, Tahara A, Nitta Y, Kodama N, Mizaguchi M, Kaida H, et al. Heterogeneous myocardial FDG uptake and the disease activity in cardiac sarcoidosis. J Am Coll Cardiol Img. 2010;3(12):1219–28.

27. Youssef G, Leung E, Mylonas I, Nery P, Williams K, Wisenberg G, et al. The use of 18F-FDG PET in the diagnosis of cardiac sarcoidosis: A systematic review and metaanalysis including the Ontario experience. J Nucl Med 2012;53(2):241-8.

28. Ohira H, Tsujino I, Yoshinaga K. 18F-Fluoro-2-deoxyglucose positron emission tomography in cardiac sarcoidosis. Eur J Nucl Med Mol Imaging. 2011; 38(9):1773–83.

29. Ishimaru S, Tsujino I, Sakaue S, Oyama N, Takei T, Tsukamoto E, et al. Combination of 18F-fluoro-2-deoxyglucose positron emission tomography and magnetic resonance imaging in assessing cardiac sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2005; 22(3):234–5.

30. Mc Ardle BA, Birnie DH, Klein R,de Kemp RA, Leung E, Renaud J, et al. Is there an association between clinical presentation and the location and extent of myocardial involvement of cardiac sarcoidosis as assessed by 18F- Fluorodoexyglucose Positron Emission Tomography? Circ Cardiovasc Imaging. 2013;6(5):617-26.

31. Blankstein R, Osborne M, Naya M, Waller A, Kim CK, Murthy VL, et al. Cardiac positron emission tomography enhances prognostic assessments of patients with suspected cardiac sarcoidosis. J Am Coll Cardiol. 2014;63(4):329–36.

32. Osborne MT, Hulten EA, Singh A,Waller AH, Bittencourt MS, Stewart GC, et al. Reduction in ^{18}F-fluorodeoxyglucose uptake on serial cardiac positron emission tomography is associated with improved left ventricular ejection fraction in patients with cardiac sarcoidosis. J Nucl Cardiol. 2014;21(1):166-74.

33. Mc Ardle BA, Leung E, Ohira H, Cocker MS, de Kemp RA, Da Silva J, et al. The role of F18-fluorodeoxyglucose positron emission tomography in guiding diagnosis and management in patients with known or suspected cardiac sarcoidosis. J Nucl Cardiol. 2013; 20(2):297–306.

34. Prendergast BD. The changing face of infective endocarditis. Heart. 2006; 92(7):879-85.

35. Saby L, Laas O, Habib G, Cammilleri S, Mancini J, Tessonnier C, et al. Positron emission tomography/computed tomography for diagnosis of prosthetic valve endocarditis - Increased Valvular 18F-Fluorodeoxyglucose Uptake as a Novel Major Criterion. J Am Coll Cardiol 2013;61(23):2374–82.

36. Yen RF, Chen YC, Wu YW, Pan MH, Chang SC. Using 18-fluoro-2-deoxyglucose positron emission tomography in detecting infectious endocarditis/endoarteritis: a preliminary report. Acad Radiol 2004;11(3):316–21.

37. Millar C, Prendergast BD, Alavi A, Moore JE. 18FDG-positron emission tomography (PET) has a role to play in the diagnosis and therapy of infective endocarditis and cardiac device infection. Int J Cardiol. 2013; 167(5):1724-36.

38. Plank F, Mueller S, Uprimny C, Hangler H, Feuchtner G. Detection of bioprosthetic valve infection by image fusion of (18) fluorodeoxyglucose-positron emission tomography and computed tomography. Interact Cardiovasc Thorac Surg. 2012;14(3):364–6.

39. Van Riet J, Hill EE, Gheysens O, Dymarkowski S, Herregods MC, Herygers P. 18F-FDG PET/CT for early detection of embolism and metastatic infection in patients with infective endocarditis. Eur J Nucl Med Mol Imaging. 2010;37)6):1189–97.

40. Abidov A, D'agnolo A, Hayes S, Kerman DS, Waxman AD.Uptake of FDG in the area of a recently implanted bioprosthetic mitral valve. Clin Nucl Med. 2004;29(12):848.

41. Sarrazin JF, Philippon F, Tessier M, Guimond J, Molin F, Champagne J, et al. Usefulness of fluorine-18 positron emission tomography/ computed tomography for identification of cardiovascular implantable electronic device infections. J Am Coll Cardiol .2012;59(18):1616–25.

42. Spacek M, Belohlavek O, Votrubova J, Sebesta P, Stadler P. et al. Diagnostics of "non-acute" vascular prosthesis infection using 18F-FDG PET/CT: our experience with 96 prostheses. Eur J Nucl Med Mol Imaging. 2009;36(5):850–8.

43. Fukuchi K, Ishida Y, Higashi M, Tsunekawa T, Ogino H, Minatoya K, et al. Detection of aortic graft infection by fluorodeoxyglucose positron emission tomography: comparison with computed tomography findings. J Vasc Surg. 2005;42(5):919–25.

44. Keidar Z, Pirmisashvili N, Leiderman M, Nitecki S, Israel O. 18F-FDG uptake in noninfected prosthetic vascular grafts: incidence, patterns, and changes over time. J Nucl Med. 2014; 55(3):392-5.

45. Pipitone N, Versari A, Hunder GG, Salvarani C. Role of imaging in the diagnosis of large and medium-sized vessel vasculitis. Rheum Dis Clin N Am. 2013; 39(3):593–608.

46. Tezuka D, Haraguchi G, Ishihara T, Ohigashi H, Inagaki H, Suzuki J, et al. Role of FDG PET-CT in Takayasu arteritis - sensitive detection of recurrences. J Am Coll Cardiol Img. 2012; 5(4):422–9.

47. Hoffman GS, Ahmed AE. Surrogate markers of disease activity in patients with Takayasu arteritis: a preliminary report from the International Network for the Study of the Systemic Vasculitis (INSSYS). Int J Cardiol 1998; 66(Suppl 1):S191–4.

48. Webb M, Chambers A, AL-Nahhas A, Mason JC, Maudlin L, Rahman L, et al. The role of 18F-FDG PET in characterizing disease activity in Takayasu arteritis. Eur J Nucl Med Mol Imaging. 2004;31(5):627-34.

49. Cheng Y1, Lv N, Wang Z,Chen B, Dang A. 18-FDG-PET in assessing disease activity in Takayasu arteritis: a meta-analysis. Clin Exp Rheumatol. 2013;31(1 Suppl 75):S22-7.

50. Derdelinckx I, Maes A, Bogaert J, Mortelmans L, Blockmans D. Positron emission tomography scan in the diagnosis and follow-up of aortitis of the thoracic aorta. Acta Cardiol 2000;55(3):193-5.

51. Glaudemans AWJM, de Vries EFJ, Galli F, Diercky RA, Slart RH, Signore A. The use of 18F-FDG-PET/CT for diagnosis and treatment monitoring of inflammatory and infectious diseases. Clin Dev Immunol. 2013; 2013:1-14.

52. Besson FL, Parienti JJ, Bienvenu B, Prior JC, Costa S, Bouvard G, et al. Diagnostic performance of 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a systematic review and meta-analysis. Eur J Nucl Med Mol Imaging. 2011; 38(9):1764-72.

53. Meller J, Strutz F, Siefker U, Scheel A, Sahman CO, Lehmann K, et al. Early diagnosis and follow-up of aortitis with [18F]FDG PET and MRI. Eur J Nucl Med Mol Imaging. 2003; 30(5):730–6.

54. Zerizer I, Tana K, Khan S,Barwick T, Marzola MC, Rubello D, et al. Role of FDG-PET and PET/CT in the diagnosis and management of vasculitis. Role of FDG-PET and PET/CT in the diagnosis and management of vasculitis. Eur J Radiol. 2010;73(3):504–9.

55. Erba PA, Sollini M, Lazzeri E, Mariani G. FDG-PET in cardiac infections. Semin Nucl Med. 2013;43(5):377-95.

56. Ozawa K, Funabashi N, Daimon M, Takaoka H, Takano H, Uehara M, et al. Determination of optimum periods between onset of suspected acute myocarditis and 18F-fluorodeoxyglucose positron emission tomography in the diagnosis of inflammatory left ventricular myocardium. Int J Cardiol. 2013;169(3):196–200.

57. Martins-Melo FR, Alencar CH, Ramos AN Jr, Heukelbach J. Epidemiology of mortality related to Chagas' disease in Brazil, 1999-2007. PLoS Negl Trop Dis. 2012;6(2):e1508.

58. Dec GW. Heart failure after cardiac transplantation: diagnostic evaluation and treatment options. ACC Curr J Rev. 2002;11(4):61-6.

59. Hoff SJ, Stewart JR, Frist WH, Kessler RM, Sandler MP, Atkinson JB, et al. Noninvasive detection of heart transplant rejection with positron emission scintigraphy. Ann Thorac Surg. 1992; 53(4):572-7.

60. Rechavia E, De Silva R, Kushwaha SS. Enhanced myocardial 18F-2-Fluoro-2-Deoxyglucose uptake after orthotopic heart transplantation assessed by positron emission tomography. J Am Coll Cardiol. 1997;30(2):533–8.