The additional role of 18F-FDG PET/CT in prosthetic valve endocarditis

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Abstract. – **OBJECTIVE:** The purpose of the present review is an update on the diagnosis of prosthetic valve endocarditis (PVE), evaluating the additional value of 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) to the standard modified DUKE criteria on which for a long time is based the diagnostic strategy of the disease.

MATERIALS AND METHODS: We did a comprehensive research on the studies reported in the literature and regarding the employment of 18F-FDG PET/CT in the early diagnosis of PVE in patients with suspected disease. Scientific databases have been examined such as Medline and PubMed, followed by a review of citations and reference lists. The research included the following terms: infective endocarditis, prosthetic heart valve and cardiac valve replacement infections, 18F-FDG PET/CT and endocarditis.

RESULTS: The recent studies reported in the literature on the PVE diagnostic approaches showed elevated sensitivity and specificity values of 18F-FDG PET/CT ranging from 73 to 96.6% and from 80 to 94%, respectively, reducing the number of misdiagnosed patients. The usefulness of the radioisotopic procedure is even more important when the other diagnostic conventional diagnostic tools, such as echocardiography, are inconclusive or negative in patients in whom the diagnosis of PVE is definitively ascertained. However, false negative and positive results of 18F-FDG PET/CT were also ascertained in some studies interfering with image interpretation even if such limitation can be reduced with an adequate patient preparation, with a better knowledge of clinical course of the disease, of the treatment in progress and of the different technical aspects of the method.

CONCLUSIONS: In different studies reported in the literature, 18F-FDG PET/CT proved to improve the diagnostic accuracy of the conventional modified DUKE criteria in patients with suspected IE, and in particular with PVE, giving the highest diagnostic performance and providing additional diagnostic benefits. Thus, the radioisotopic hybrid procedure should be included in the diagnostic protocol of PVE as complementary tool to modified DUKE criteria. Finally, the usefulness of 18F-FDG PET/CT in monitoring the response to antibiotic therapy, although the few data reported in the literature are encouraging, needs more numerous studies and with a major number of cases.

Key Words:
Infective endocarditis, Prosthetic valve endocarditis, Modified Duke criteria, 18F-FDG PET/CT.

Introduction

The diagnosis of infective endocarditis (IE) represents a very complicate challenge because of the various clinical features and the difficult interpretation of the conventional echocardiography procedures as well as of the not easy identification of the different microorganisms responsible of the infection, the most predominant bacteria detected being streptococci, including more rarely the type viridans[1], staphylococci (in particular *staphylococcus aureus* and coagulase-negative staphylococci) and enterococci. The diagnosis and management of IE requires a multidisciplinary approach by cardiologists, cardiac imaging specialists, heart surgeons, infection disease physicians and microbiologists[2].

Despite the significant advances in both diagnostic and therapeutic procedures for this condition, IE remains characterized by a poor prognosis because of the possible serious complications[3] and also with high risk of mortality that is not decreased in the last 30 years[4].

Approximately 20% of IE patients had intracardiac devices, such prosthetic valves (PV) or implantable cardiac electronic devices (ICEDS),

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defibrillators or pacemakers. These patients comprise a special IE population with clear predisposing factors of epidemiologic profiles and higher mortalitity[5]. The incidence of prosthetic valve endocarditis (PVE) has increased of 50%[6], and patients with heart PV seem to be exposed to an approximately rate of 3 cases of IE per 1.000 patients every year[7]. PVE is mostly associated with infection rates ranging from 1-6 to 15% with higher frequency in revision surgery[8].

Generally, the clinical approach to PVE is based on the association of a recent valve substitution with an infection syndrome; PVE can occur as result of contamination during surgery, of hematogeneous dissemination or contiguous infection. However, 13% of PVE has been described as blood culture-negative endocarditis reaching more than 47% of mortality, especially following bacteremia from *staphylococcus aureus*[9-11]. The diagnosis of IE has been long based on the modified DUKE criteria[12]; these criteria are principally founded on clinical symptoms and biological findings, blood microbiologic cultures and echocardiography with a reported sensitivity value of 80%[13,14]. However, in clinical practice, the accuracy of these criteria is lower in IE, especially in presence of PVE, a defibrillator and a pacemaker where echocardiography can result negative for infection or inconclusive in more than 30% of cases[15]. In particular, trans-thoracic echocardiography (TTE) and trans-esophageal echocardiography (TEE) are employed and the former imaging procedure is often inconclusive or of difficult interpretation in patients with PVE or ICEDS, thus the infection remaining undiagnosed[16]. In the last years, the hybrid procedure 18F-fluorodeoxyglucose positron emission tomography with computed tomography based attenuation tomography correction (18F-FDG PET/CT), proved as an important diagnostic tool in oncology, has presented in the last years an increased use also for the diagnosis of infection diseases including IE, particularly in patients with PVE. 18F-FDG PET/CT proved useful both for differentiating between normal and pathological findings and for the qualitative visualization of the lesion and the semi-quantitative measurement of lesion metabolic activity, giving more useful information to achieve the correct diagnosis[17].

Recent studies[17,18] have demonstrated that 18F-FDG PET/CT may improve the detection of IE with a consequent positive impact on the sensitivity of modified DUKE criteria, in particular in cases of difficult diagnosis. The procedure has been added to the European Society of Cardiology Guidelines for the diagnosis and management of infective endocarditis.

The aim of the present review is to underline the adjunctive value by 18F-FDG PET/CT in PVE diagnosis, in particular when conventional diagnostic tools have failed, and to evaluate whether the procedure may also be useful in the follow-up after treatment.

Materials and Methods

We performed a review of the published studies inherent the clinical approach to PVE and the advantages and limitations of 18F-FDG PET/CT employment in PVE diagnosis in addition to the modified DUKE criteria, also evaluating the possibility of total quality management implementation. Our comprehensive research was done examining scientific databases, such as Medline and PubMed, followed by a review of citations and reference lists. The research included the following terms: infective endocarditis, FDG, prosthetic heart valve and cardiac valve replacement infections, 18F-FDG PET/CT and endocarditis.

Results

Advantages of 18F-FDG PET/CT in PVE Diagnosis

The introduction of the hybrid imaging technology 18F-FDG PET/CT proved an important adjunctive diagnostic tool to standard procedures in the evaluation of patients with suspected IE, particularly in presence of PVE. 18F-FDG is actively incorporated *in vivo* by activate leukocytes, monocyte-macrophages and CD4 + T-lymphocytes, all of these accumulating in the sites of infection.

The most accurate 18F-FDG PET/CT procedure, before intravenous injection of a tracer dose standard of 370 MBq, is preceded by an accurate preparation of the patient. A diet is followed with meal rich in fat and low in carbohydrates in the days prior to the exam. A fasting period for at least 12 hours is recommended since after the standard 6 hours fast, generally considered for the usual methodology, it makes difficult to delineate FDG uptake caused by the infection. Moreover, an intravenous injection of 50 IU/kg of unfractioned heparin is also performed by some researchers 15 min before FDG injection to reduce the physiologic uptake of the tracer by myocardium[19,20]. The addition of heparin pre-administration of FDG improves cardiac glucose metabolism suppression over low carbohydrate diet alone in 18F-FDG PET/CT imaging. Blood glucose levels are measured and the values must be less than 150 mg/dl. 60 min after FDG injection, with patients supine and their arms raised above the head, a whole body PET/CT is acquired in 3-dimensional mode and for 3 min per bed position. Both visual and semi-quantitative analyses of the images in transaxial, coronal and sagittal views were made. In visual analysis, tracer focal increased uptakes are considered in both attenuation corrected and uncorrected images. In semi-quantitative analysis, standard uptake maximum value (SUV max) in the foci of suspected infection is calculated. The mean SUV is also obtained in the blood pool (superior vein cava) and in the liver to establish SUV ratios. The suppression of myocardial uptake is classified in 3 different inhibition sub-groups: less or equal to liver (complete), focally above the liver (partial), diffusely superior to liver uptake (absent).

In the last years different published studies highlighted the promising results of 18F-FDG PET/CT in patients with suspected IE and, in particular, PVE; as an example of the use of this procedure, Figure 1 illustrates one case, belonging to the casuistry of the authors of the present review, showing an elevated uptake of the tracer in the sites of PVE in a biologic prosthesis, and a complete suppression of myocardium.

Saby et al[18] prospectively studied 72 patients with suspected PVE who underwent clinical, microbiological and echocardiographic exams; in all cases, a cardiac 18F-FDG PET/CT was added at admission and, globally, sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 73%, 80%, 85%, 67%, and 76%, respectively. However, adding the abnormal FDG uptake around the prosthetic valve as a new major criterion together with other clinical, microbiological and echocardiographic pa-

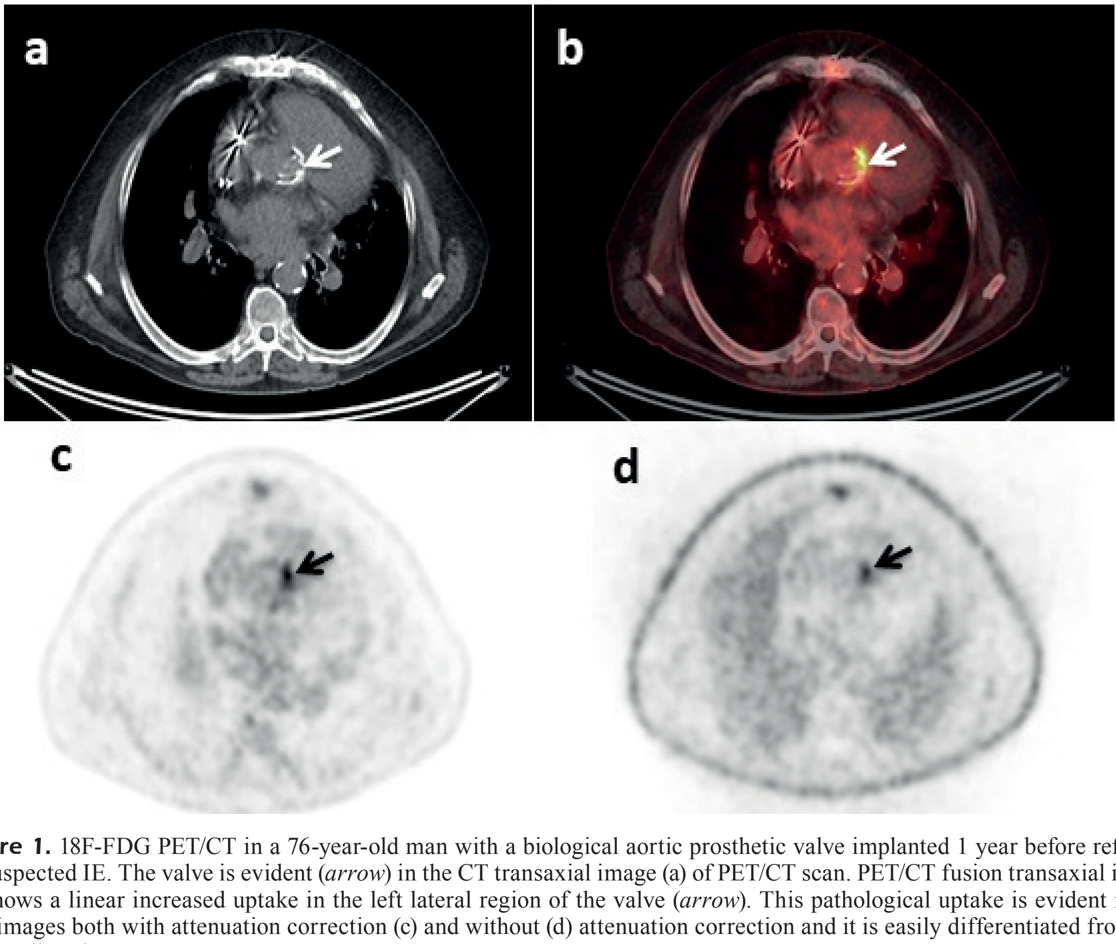

Figure 1. 18F-FDG PET/CT in a 76-year-old man with a biological aortic prosthetic valve implanted 1 year before referred for suspected IE. The valve is evident (*arrow*) in the CT transaxial image (a) of PET/CT scan. PET/CT fusion transaxial image (b) shows a linear increased uptake in the left lateral region of the valve (*arrow*). This pathological uptake is evident in the PET images both with attenuation correction (c) and without (d) attenuation correction and it is easily differentiated from the surrounding tissue.

rameters, the sensitivity of the modified DUKE criteria at admission significantly and dramatically increased achieving 97% without compromising specificity value. This result was due to a significant reduction of the number of possible PVE cases from 56 to 32%. The major contribution of 18F-FDG PET/CT to the early diagnosis of PVE appears to be related to patients in whom the initial echocardiographic analysis is negative. However, notwithstanding the encouraging data, some false positive results were observed because of the execution of the exam in too early phase after the implantation of the prosthetic valve, as also reported by other authors[21]. Furthermore, false negative results were also ascertained for lower inflammation activity or for having performed PET/CT in too long time after initiating antibiotic therapy. The authors of the study suggested that the sensitivity of the modified DUKE criteria to diagnose PTV can be enhanced if PET/CT results are incorporated into an approach including clinical, microbiological and echocardiographic parameters. 18F-FDG PET/CT proved useful for diagnosing PVE and might also have an impact on therapeutic strategy and clinical outcomes in the future. However, the procedure cannot be a substitute for clinical, microbiological and echocardiographic evaluation, but it could be implemented in the global assessment of patients with suspected PVE.

Millar et al[11] reviewed more than 30 published papers on the potential advantages of 18F-FDG PET/CT in IE. In the majority of the cases, blood cultures played a major role in the diagnosis of IE (87.7%) and there was a good correlation with 18F-FDG PET/CT findings (85.7%), a large proportion of the patients with infection being related to PVE. In contrast, the contribution played by echocardiography (21.1%) was less evident positive for the presence of vegetation. This was a significant finding since the negative predictive value of TEE has been reported previously to be very high ranging from 86 to 97%, thus ruling out the diagnosis of IE.

In a study of Graziosi et al[22] in 27 consecutive patients with implantable device, 18F-FDG PET/CT was positive in 10 patients with final diagnosis of definite IE in 7/10 cases, of possible IE in 1 case and of rejected IE in 2; in the remaining 17 patients, PET/CT was true negative in 13 cases and false negative in 4, but 3/4 of whom were studied after having started antibiotic therapy. The study seems to confirm that in patients with cardiac device 18F-FDG PET/CT increases the diagnostic accuracy of the modified DUKE criteria for IE, particularly in the group of patients with possible IE at DUKE criteria but of difficult management.

Bartoletti et al[23] described a series of 6 patients with suspected aortic PVE where initial TEE was negative in all cases and only in 2 of these became positive later. 18F-FDG PET/CT was positive in all 6 cases, in 4 of which valve replacement was performed with histology confirming PVE. After an adequate course of antibiotic therapy, also in the 2 patients not selected for surgery 18F-FDG PET/CT showed resolution of PVE in all cases.

Ricciardi et al[24] further highlighted the limitation of echocardiography in the diagnosis of PVE and the potential advantage of 18F-FDG PET/CT showing a sensitivity of 85% in PVE patients *vs.* 69% for TEE and 77% for the DUKE modified criteria. Moreover, 89% of confirmed PVE resulted 18F-FDG PET/CT positive.

Chen et al[25] in a review reported the results of recent publications on the use of 18F-FDG PET/CT in patients with suspected cardiac mechanical device or prosthetic valve infection, particularly when anatomy based imaging studies, such as echocardiography or CT, are uncertain or negative. A potential advantage of 18F-FDG PET/CT is in its detection of inflammatory cells early in the infection process, before morphologic damages ensue. However, the authors identified many unanswered questions in the literature. There is the necessity of standardization amongst the various imaging studies, such as dietary preparation, duration and timing of image acquisition, image processing with and without CT attenuation correction, and more importantly image interpretation criteria.

Pizzi et al[26] analyzed 92 patients with suspected PVE or cardiac device IE, all submitted to echocardiography and 18F-FDG PET/CT and 76/92 also to PET/CT angiography (PET/CTA). Echocardiography was positive in 42 cases, negative in 33 and doubtful in 17. PET/CT significant increased the sensitivity from 52 to 90.7%. PET/CT+DUKE modified criteria (DC) enabled reclassification of 90% of cases initially classified as possible IE with DC alone and provided a conclusive diagnosis (definite/rejected) in 95% of cases. Using PET/CTA even better diagnostic performance values than PET/non-enhanced CT was obtained reducing the rate of doubtful cases from 20 to 8%. Thus, the study seems to demonstrate that 18F-FDG PET/CT improves the diagnostic accuracy of the modified DUKE criteria in patients with suspected IE and prosthetic valves or cardiac devices. Moreover, PET/CTA proved the highest diagnostic performance and provided additional diagnostic benefits.

Granados et al[20] published a cross-sectional study of 80 patients with suspected IE sub-divided in native valve endocarditis (NVE), PVE and ICED infection in whom the definitive diagnosis of infection was established in 31 cases, 6 NVE, 12 PVE (5 biologic valves and 7 mechanical valves) and 8 ICED. The performance of 18F-FDG PET/CT was elevated achieving sensitivity, specificity, positive predictive value, negative predictive value of 82%, 96%, 94%, and 87%, respectively. When only patients with intra-cardiac prosthetic material were considered, these values changed in 96.6%, 94%, 93%, and 97%, respectively. 18F-FDG PET/CT was able to reclassify 90% of patients initially classified as possible IE by modified DUKE criteria. Moreover, PET/CT changed possible to definite IE in 26% of cases and modified possible to rejected IE in 64%. Given high negative predictive value (97%), the procedure was useful in selecting which device should be removed. However, 2 false positive and 7 false negative results were observed; 6 of the latter were NVE and only 1 PVE. In addition, PET/CT was useful in visualizing peripheral septic embolic and metastatic infectious episodes. The authors suggested that the appearance of abnormal activity of FDG around the implantation site after three months from surgery could be proposed as a major criterion in suspecting PVE. On the basis of the data obtained in this study, it is resulted that 18F-FDG PET/CT improved the diagnostic accuracy of the modified DUKE criteria; thus, the procedure should be included in the algorithm-flowchart for early diagnosis of PVE and ICED infection reducing the rate of misdiagnosed patients. Finally, the authors also suggested that PET/CT imaging could be considered as parameter for monitoring the antibiotic therapy response, but the data for this application are still few.

In 2016, Gomes et al[27], on the basis of the numerous studies reported in the literature, strongly think that the time has arrived to propagate the clear message to implement 18F-FDG-PET/CT in the diagnostic protocol of patients with suspected prosthetic valve and ICED infections. The radioisotopic imaging technique should be used as an additional tool providing complementary information to both transthoracic (TTE) and transesophageal (TEE) echocardiography data locally as well as whole body information on extracardiac foci and complications. Moreover, more data are necessary to estimate the effect of antimicrobial therapy before PET/CT as well as the usefulness of the procedure for the monitoring of therapy. A further goal is the possibility to provide a valid guidance on when performing 18F-FDG PET/CT, both in the diagnostic protocol and in the therapeutic setting of the individual patient. Whether the procedure is beneficial to shorten hospitalization, to reduce clinical complication and costs, needs to be evaluated in prospective studies. Finally, the authors underline another interesting future development such as the use of the hybrid PET/MRI imaging camera; this system could be potentially useful because of its lower radiation exposure than PET/CT, the specific and unique MRI characteristics, and the possibility for repetitive scanning, although metal devices need to be MRI-compatible. However, the availability of the equipment is still very low and the spatial resolution is lower in comparison with current CT scans. Most available reports on the use of 18F-FDG PET/CT are focalized on the visual interpretation of the images to differentiate between normal and pathological findings. Moreover, a semi-quantitative analysis of the metabolic activity of the suspect lesion can also be obtained calculating the standardized uptake value (SUV), which could offer an objective cut-off value to discriminate normal from pathological images, relying less on subjective interpretation. However, SUV is dependent on a large number of variables regarding both acquisition and reconstruction parameters rendering difficult a proper standardization which has been proposed in different ways and it is still under study.

For example, Kelly et al[28] proposed the method of reference SUV (SUVref) which is related to a reconstruction-protocol specific phantom-optimized filter to clinical PET scan and reduces reconstruction-dependent variations in SUV measurement. A comparative evaluation in the interpretation of PET images between qualitative visual method and semi quantitative method has been carried out by Jimenez-Ballvè et al[29]. In 41 patients with suspected PVE and ICED infection using the modified DUKE criteria and who underwent 18F-FDG PET/CT, the diagnostic value of this procedure was highly dependent on the method used for image interpretation besides patient preparation. The maximum sensitivity, specificity and accuracy value achieved was 88%, 80% and 84%, respectively, using qualitative analysis; with semi quantitative analysis SUV max was higher in areas of confirmed IE than in those without IE and a value of 5.5 of SUV max was the optimal threshold for IE diagnosis using ROC curve analysis.

Limitation Factors of the Performance of 18-FDG PET/CT

In the interpretation of PET/CT images, some factors may interfere such as the combined cardiac-respiratory motion since the coronary arteries have been described to move from 8 to 23 mm during the cardiac cycle, whereas the values reported for the respiratory motion of the heart coronaries during free breathing range between 4.9 and 9.0 mm. To face the reduction of resolution related to the cardiac-respiratory motion, the use of electrocardiography (ECG) and respiratory-gated techniques could be useful.

In this way, Martinez-Möller et al[30] conducted a dual cardiac-respiratory gated PET study in 12 patients. Respiratory motion of the heart was quantified by measuring the displacement between the inspiratory and expiratory images in the diastolic phase by means of intensity-based non-rigid image registration. In these cases, dual gated PET series were successfully acquired showing better-resolved myocardial walls.

Buther et al[31] studied different methods of cardiac and respiratory gating PET in patients with coronary diseases; in association with ECG, the authors used a sensitive video method without auxiliary measurements by dividing the list mode stream in 50-ms frames and then either determining the number of coincidences, and center-of-mass method computing the axial center of mass and SD of the measured counting rates in the same frames. It resulted that all methods successfully captured the respiratory movements and decreased the respiratory-related blur. In essence, the study quality could be improved by using respiratory and ECG gated techniques, thus minimizing imaging artifacts.

Other factors can interfere with the interpretations of 18F-FDG PET/CT images; some of these, however, can be overcome, for example, with a careful preparation of the patients such an adequate fasting period and an appropriate diet and better with addition of heparin before FDG injection, as above. It is also important to pay particular attention not to perform PET/CT too shorty after cardiac surgery to avoid false positive results because of the regeneration process with nonspecific inflammation. Notwithstanding it is still debated whether the previous antibiotic therapy may reduce PET/CT accuracy, probably it would be more suitable to perform the imaging procedure before beginning therapy to avoid eventual false negative results. Moreover, misinterpretations by SUV could be correctly modified with standardization of this parameter. However, other factors are due to the characteristics of PET device, such as the low spatial resolution to detect too small size oscillating valve vegetation, the artifacts for the metal devices as well as the not negligible exposition to radiation due to CT which should be addressed with radiation dose reduction measures; with regard to the latter aspect, however, the potential advantages of PET/CT overcome this drawback in seriously ill patients in whom a prompt diagnosis may have a critical impact on their prognosis.

Discussion

Infective endocarditis is a serious disease with poor prognosis and high risk of fatal events owing to the acute complications due to cerebral and coronary embolization from vegetation. The incidence of the disease is increasing because of growing of the number of treatments that employ prosthetic material implanted in the heart. In particular, PVE represents one of the most challenges in both diagnosis and treatment. Its outcome is highly related to an early identification, an accurate evaluation of the risk and a careful follow-up after therapy. The modified DUKE criteria, based on clinical, microbiological and anatomic parameters with echocardiographic procedures, have been used as tools for diagnosing patients with suspected PVE. However, the sensitivity of these criteria is not elevated in daily clinical practice because of the probability that echocardiography fails in more than 30% of cases. In the light of the serious consequences in terms of morbidity and mortality for the failed diagnosis, it is crucial to increase the sensitivity of DUKE criteria and, in particular, supporting transthoracic and transesophageal echocardiography with other imaging procedures which can evaluate both structural and pathophysiological abnormalities at the cellular/molecular level.

Recently, many studies advocate the use of 18F-FDG PET/CT particularly when echocardiography and blood culture results are inconclusive or negative making a definitive PVE diagnosis difficult. The radioisotopic procedure is based on in *vivo* FDG labeling of the pre-existing cells at the infection site. With the stimulation of cytokines, these cells (macrophages, neutrophils and lymphocytes) overexpress the glucose transporter-1 and accumulate FDG with high concentration.

Published studies in the last years highlighted the important role of 18F-FDG PET/CT in PVE diagnostic approach, given its elevated sensitivity and specificity, ranging from 73% to 96.6% and from 80% to 94%, respectively, thus reducing the number of misdiagnosed patients. These favorable results have suggested that the procedure has been incorporated in the latest European Society of Cardiology Endocarditis Guidelines.

However, 18F-FDG PET/CT can present some false positive and negative results interfering with the interpretation of the images; such a limitation, however, can be reduced with an adequate preparation of the patient, with a better knowledge of clinic course of the disease and of the treatments in progress, besides the different technologic aspects; the latter include the standardization of SUV for semi quantitative analysis and the use of cardiac and respiratory gating reducing eventual artifacts and improving the quality of the images.

Conclusions

Although echocardiography still remains a reference test for the initial evaluation of PVE, 18F-FDG PET/CT clearly proved to be an important diagnostic tool for an early diagnosis of disease and can play an additional complementary role to echocardiography, particularly for cases of difficult diagnosis. Thus, the radioisotopic procedure should be included in the diagnostic protocol of PVE to associate with the modified DUKE criteria.

With regard to the usefulness of 18F-FDG PET/CT in monitoring the response to antibiotic therapy, the studies reported in the literature, although encouraging, are still few and include a small number of patients. Thus, more data are necessary for suggesting the employment of 18F-FDG PET/CT also for this important aspect of the management of patients affected by PVE.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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