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REVIEW ARTICLE

Molecular Imaging in the Diagnosis of Infectious Endocarditis – the Role of PET and SPECT

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Abstract

18-fluorine-fluorodeoxyglucose positron emission computed tomography (18F-FDG PET/CT) and single-photon emission computed tomography (SPECT) using radiolabeled white blood cells (WBC) are non-invasive techniques widely used in the diagnosis of infections, like endocarditis. The aim of our paper was to provide a systematic review of the published data on the use of 18F-FDG PET/CT and SPECT in infective endocarditis (IE). A comprehensive literature search of the PubMed/MEDLINE, Scopus, Embase and Cochrane library databases was conducted to find relevant published articles about the diagnostic performance of SPECT using WBC and 18F-FDG PET/CT in the diagnosis of infectious endocarditis. Twenty papers were included, with a total of 1,154 patients (166 studies with WBC SPECT and 988 with 18F-FDG PET/CT). From the analyses of the studies, the following results were obtained: both SPECT and PET/CT had good diagnostic accuracy in the study of endocarditis. 18F-FDG PET/CT had good specificity (85.8%) and lower sensitivity (68%), with high heterogeneity among the studies; WBC SPECT/CT had an overall sensitivity of 80% and specificity of 98%. Specific preparations for PET/CT can affect the diagnostic accuracy of the test. Both 18F-FDG PET/CT and WBC SPECT are useful for the diagnosis of IE, and WBC SPECT appears to be slightly more specific than 18F-FDG PET/CT. A specific diet could influence the diagnostic performance of PET/CT.

Keywords

Endocarditis,Infectious/ diagnostic imaging; Positron Emission Tomography Computed/methods; Positron Emission Tomography Computed Tomography/ methods; Radiommunodetect/ methods; Leukocytes.

Introduction

Infectious endocarditis (IE) is a serious, potentially life-threatening condition, and a challenge for clinicians due to difficulties in its diagnosis.[1,2] The current diagnostic approach often revolves around the modified Duke criteria, which are composed of a composite of clinical criteria, blood cultures and echocardiographic findings,[3] but cases of uncertain diagnosis are still significant.

Cardiac infections include a group of conditions involving the heart muscle, the pericardium or the endocardial surface of the heart. Infections can extend to the prosthetic material or the leads in case of device implantation. The heterogeneity of clinical presentations requires, besides the diagnostic criteria, a discussion by a multidisciplinary team.

IE is a representative example where the use of nuclear medicine has evolved as an important diagnostic tool.[4,5]

Single photon emission computed tomography (SPECT) using radiolabelled white blood cell (WBC) and fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) have been widely used in the diagnosis of infections and in IE, with controversial findings.

The aim of this review is to provide a systematic review of published data about the role of WBC SPECT and 18F-FDG PET/CT in the diagnostic work-up of patients with IE.

Materials and Methods

The present meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (see supplementary material for PRISMA Checklist).[6]

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Search strategy

A comprehensive literature search of the PubMed/MEDLINE, Scopus, Embase and Cochrane library databases was conducted to find relevant published articles about the diagnostic accuracy of WBC SPECT and 18F-FDG PET/CT in patients affected by IE. We used a search algorithm based on a combination of the terms: a) ''SPECT" OR "Single-photon emission computed tomography" OR "WBC" OR "radiolabeled leukocytes" OR "PET" OR "positron emission tomography" AND b) "endocarditis" OR "heart infection". No beginning date limit was used; the search was updated until August 31, 2019. Only articles in the English language were selected; pre-clinical or not *in vivo* studies, review, letters, editorials and conference proceedings were excluded. To expand our search, references of the retrieved articles were also screened for additional studies. Studies considering cardiovascular implantable electronic device infections were excluded by this review. All literature studies collected were managed using EndNote Web 3.3.

Study selection

All articles reporting patients with IE evaluated by WBC SPECT and 18F-FDG PET/CT in clinical setting were eligible for inclusion. Two researchers (DA and FB) independently reviewed the titles and abstracts of the retrieved articles. The same two researchers then independently reviewed the full-text version of the remaining articles to determine their eligibility for inclusion. Disagreements were resolved by a third opinion (RG). Moreover, in case of studies that included the same population, the report with the highest number of enrolled patients was considered for the analysis.

Data abstraction

For each included study, the following data were extracted – authors' names, year of publication, type of study, number of patients, diagnostic test, diagnostic criteria, reference standard, diagnostic performance. The main findings of the articles included in the review are reported in the Results section.

Results

Literature search

The comprehensive computer literature search revealed 665 articles (Figure 1). On reviewing the titles and abstracts, 645 articles were excluded because the data reported data were not within the field of interest of this review. Twenty articles were selected and retrieved in full-text version[7-25]; no additional study was found when screening the references of these articles. In total, 20 articles were included in the systematic review, four about WBC SPECT[7-10] and 16 about 18F-FDG PET/CT[11-25]

Qualitative analysis

Characteristics of the studies are detailed in Tables 1 and 2. The IE group included 16 [18F] FDG PET/CT (overall 988 patients) and four SPECT/CT studies (overall 166 patients). Among the PET/CT studies, seven analyzed only prosthetic valve endocarditis (PVE),[9,13,15,16,19-21] two only native valve endocarditis (NVE),[11,23] and the remaining seven analyzed a mixed population or the type of endocarditis was not reported.[12,14,17,18,22,24,25] Among SPECT studies, two included only PVE,[8,9] and the remaining two papers included both NVE and PVE.[7,10] In only one paper,[9] both SPECT and PET/CT techniques were used to study IE.

The pooled sensitivity of 18F-FDG PET/CT was 68% (95% CI 55–87), with a high heterogeneity (I2 = 94%, $p < 0.001$), whereas pooled sensitivity of WBC SPECT was 80% (95% CI 67–94) with a lower heterogeneity (I2 = 75%, p = 0.017). The pooled specificity of 18F-FDG PET/CT was 86.8% (95% CI 82–95) with a high heterogeneity (I2 = 86%, $p < 0.001$), whereas WBC SPECT showed a pooled specificity of 98% (95% CI 94–100) with no heterogeneity (I2 = 0%, p = 0.625). In a sub-analysis, pooled sensitivity of 18F-FDG PET/CT and WBC SPECT for NVE was 71% (95% CI 49–93) with a high heterogeneity (I2 = 95%, $p < 0.001$), while pooled sensitivity for PVE was 81% (95% CI 78–93) with a significant heterogeneity (I2 = 67%, $p < 0.001$). Pooled specificity of 18F-FDG PET/CT and WBC SPECT for NVE was 96% (95% CI 93-100) with a low heterogeneity (I2 = 52%, p = 0.016), while pooled specificity for PVE was 92% (95% CI 86-96) with a significant heterogeneity (I2 = 79%, $p < 0.001$).

Of 17 manuscripts considering the diagnostic performance of 18F-FDG PET/CT, 11 showed specific preparation before PET/CT scan [9,13,15-18,21-25] and five did not.[11,12,14,19,20] In six studies,[9,13,21-24] participants underwent dietary preparation to promote myocardial suppression (high-fat, low-carbohydrate diet), without heparin injection; in two studied only heparin injection was suggested;[16,18] in the remaining three works,[15,17,25] both myocardial suppression and heparin injection were done. Despite this, there was strong heterogeneity in

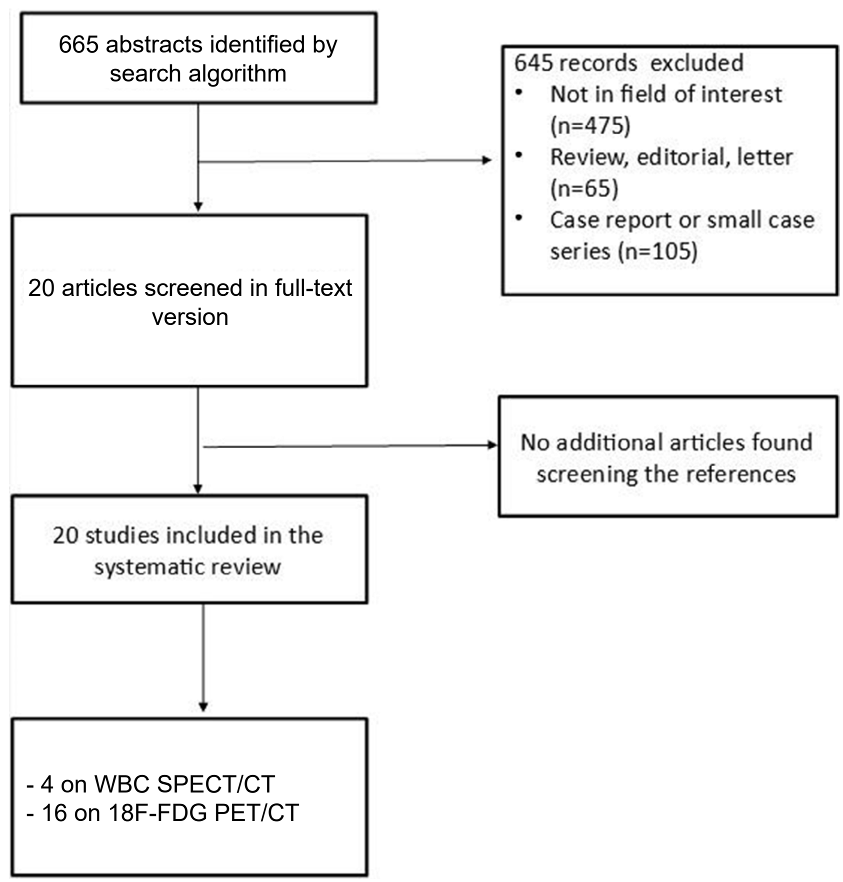

Figure 1 - Flow-chart of the search strategy.

Table 1 - Characteristics of the studies on single photon emission computed tomography using radiolabelled white blood cell and infectious endocarditis

Author	Year	Design study	N pts	Clinical setting	Sensitivity	Specificity	Accuracy	Diagnostic criteria	Reference standard
Erba et al.	2012	Retrospective	51	16 NVE, 35 PVE	90%	nr	90%	Visual analysis	Microbiological analysis or clinical follow-up
Hyafil et al.	2013	Retrospective	42	42 PVE	nr	100%	nr	Visual analysis	Pre-operative macroscopic analysis and bacteriological analysis + clinical follow-up
Rouzet et al.	2014	Retrospective	39	39 PVE	65%	100%	86%	Visual and semiquantitative analysis	Combination of modified Duke criteria and clinical follow-up
Caobelli et al.	2017	Retrospective	34	12 NVE, 22 PVE	86%	95%	91%	Visual analysis	Microbiological analysis + combination of modified Duke criteria and clinical follow-up

NVE: native valve endocarditis; PVE: prosthetic valve endocarditis; nr: not reported.

Table 2 - Characteristics of the studies on fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) and infectious endocarditis

Author	Year	Design study	N pts	Clinical setting	Sensitivity	Specificity	Accuracy	Diagnostic criteria	Reference standard
Van Riet et al.	2010	Prospective	25	25 NVE	12%	100%	18%	Visual analysis	Clinical follow-up
Ozcan et al.	2013	Retrospective	72	12 PVE, 52 NVE	18%	nr	18%	Visual analysis	Clinical follow-up
Saby et al.	2013	Prospective	72	72 PVE	73%	80%	76%	Visual analysis (AC and NAC)	Modified Duke criteria and clinical follow-up
Kouijzer et al.	2013	Prospective	72	nr	39%	93%	nr	Visual analysis	Modified Duke criteria
Rouzet et al.	2014	Retrospective	39	39 PVE	93%	71%	80%	Visual (AC and NAC) and semiquantitative analysis	Modified Duke criteria and clinical follow-up
Ricciardi et al.	2014	Retrospective	27	27 PVE	55%	100%	nr	Visual (AC and NAC) and semiquantitative analysis	Modified Duke criteria and clinical/ microbiological follow-up
Pizzi et al.	2015	Prospective	92	92 PVE	87%	92%	nr	Visual (AC and NAC) and semiquantitative analysis	Modified Duke criteria and clinical follow-up
Jimenez-Ballvè et al.	2016	Prospective	41	39 PVE, 2 NVE	88%	79%	85%	Visual (AC and NAC)	Modified Duke criteria and clinical/ microbiological follow-up
Granados et al.	2016	Prospective	51	29 PVE, 21 NVE	82%	96%	nr	Visual (AC and NAC) analysis	Clinical, imaging and microbiological follow-up
Fagman et al.	2016	Retrospective	30	30 PVE	75%	86%	83%	Visual (AC and NAC) and semiquantitative analysis	Modified Duke criteria and clinical/ microbiological follow-up
Guenther et al.	2017	Retrospective	26	26 PVE	94%	29%	76%	Visual and semiquantitative analysis	Modified Duke criteria and clinical follow-up
Salomaki et al.	2017	Prospective	23	16 PVE, 7 NVE	100%	71%	91%	Visual (AC and NAC) and semiquantitative analysis	Modified Duke criteria and clinical/ microbiological follow-up
Kouijzer et al.	2018	Retrospective	88	88 NVE	45%	100%	87.5%	Visual (AC and NAC) analysis	Modified Duke criteria and clinical/ microbiological follow-up
de Camargo et al.	2019	Prospective	303	188 PVE, 115 NVE	93% PVE 70% NVE	90% PVE 93% NVE	91% PVE 69% NVE	Visual (AC and NAC) and semiquantitative analysis	Modified Duke criteria
El-Dalati et al.	2019	Retrospective	14	8 PVE, 6 NVE	nr	100%	nr	Visual (AC and NAC) and semiquantitative analysis	Histological diagnosis

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Table 3 - Preparations for fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography described in the studies included in the review

Author	N pts	Diet	Heparin	Specific preparation
Van Riet et al.	25	no	no	4-hour fasting
Ozcan et al.	72	no	no	6-hour fasting (4-hour for diabetic patients)
Saby et al.	72	yes	no	HFLW (only one meal) diet, 12-hour fasting
Kouijzer et al.	72	no	no	6-hour fasting
Rouzet et al.	39	yes	no	HFLW (only one meal) diet, 12-hour fasting
Ricciardi et al.	27	yes	yes	HFLW diet, 6-hour fasting
Pizzi et al.	92	no	yes	12-hour fasting, 50 IU/Kg heparin bolus 15 min before FDG
Jimenez-Ballvè et al.	41	yes	yes	48-hours HFLC diet, 12-hour fasting, 50 IU/Kg heparin bolus 15 min before FDG
Granados et al.	51	no	yes	12-hour fasting, 50 IU/Kg heparin bolus 15 min before FDG
Fagman et al.	30	no	no	18-hour fasting
Kokalova et al.	13	no	no	6-hour fasting
Guenther et al.	26	yes	no	HFLW diet, 12-hour fasting
Salomaki et al.	23	yes	no	24-hour HFLW diet, 10-hour fasting
Kouijzer et al.	88	yes	no	24-hour HFLW diet, 6-hour fasting
de Camargo et al.	303	yes	no	24-hour HFLW diet, 8-hour fasting
El-Dalati et al.	14	yes	yes	36-hour HFLC diet, 30 IU/kg of heparin administered in three boluses (10 IU/kg) at 10 min before FDG and 5 and 20 min after FDG

MS: myocardial suppression; HFLW: High-fat low-carbohydrate; NR: not reported.

preparation for PET/CT, with different time of fasting or diet for myocardial suppression (Table 3). Pooled sensitivity of PET/CT was 47% (95% CI 18-81) in patients without specific protocol and 78% (95% CI 45-99) in patients who performed specific preparation (myocardial suppression diet and/or heparin injection).

Pooled sensitivity of PET/CT was 76% (95% CI 64–88) and 72% (95% CI 46–99) in patients with and without specific preparation, indicating a high heterogeneity. Also, a pooled specificity of 93% (95% CI 70-100) was observed in the first group and 91% (95% CI 85-94) in the second group.

Discussion

An accurate diagnosis of IE is critical for clinical decision making and represents a challenge for clinicians; in the latest update of the European Society of Cardiology Guideline,[26] nuclear medicine imaging was integrated in the diagnostic flow-chart of IE. Although blood cultures and echocardiography continue to play a crucial role in the diagnosis and the subsequent clinical management of IE, they have limitations, with a significant number of doubtful reports. Also, ultrasound may have difficulties to study prosthetic valves and inconclusive results have been reported in up to 30% of cases.[27]

In this context, WBC SPECT and 18F-FDG PET/CT studies have demonstrated a significant impact on the study of both PVE and NVE. In particular, in case of suspected PVE, abnormal 18F-FDG PET/CT and WBC SPECT/CT uptake should be considered as a pathological finding. In this systematic review we included 19 studies, with a total of 1,115 patients. Overall, 18F-FDG PET/CT had good specificity (86%) and low sensitivity (68%), with high heterogeneity among papers, while WBC SPECT had high specificity (98%) and good sensitivity (80%) but a small number of patients evaluated.

Our results are similar to those reported in previous reviews and meta-analysis.[4,5]

The 18F-FDG PET/CT has the advantage to be a whole-body study that allows the assessment of extracardiac sites of the disease, including clinically unsuspected distant foci, and more appropriate and timely intervention, including antibiotic therapy. In fact, whole-body 18F-FDG PET/CT leads to treatment modification in up to 35% of patients with IE.[28] Several factors, such as antimicrobial therapy, small vegetation size and elevated blood glucose level may impact the accuracy of PET/CT and increase the number of false negative findings. The difficulty to detect small vegetations is directly related to the resolution power of the PET/CT device (about 4-5 mm), which is aggravated in case of high FDG uptake in the surrounding myocardium.

Physiological uptake of FDG is a common problem in the evaluation of heart infection; for this reason, preparation protocols before and/or after FDG injection were suggested, like dietary preparation for MS and heparin injection. However, different diets have been proposed in the literature, without consensus (Table 3). These MS protocols include patient preparation with the use of a low-carbohydrate and high-fat diet plus fasting for at least 6 hours, and use of heparin prior to imaging. Prolonged fasting and low-carbohydrate, high-fat diets lead to decreased insulin and blood glucose levels, and increased free fatty acid levels, reducing physiological FDG uptake. Heparin induces lipolysis and leads to an increase in free fatty acid levels.

Another possible limitation affecting FDG evaluation of IE is the time between valve surgical procedure and PET/CT scan; PET/CT studies performed shortly after cardiac procedures can also be affected by the presence of inflammation foci near to the prostheses.

Although 18F-FDG PET/CT is generally considered a method with higher accuracy than SPECT due to higher spatial resolution and detection efficiency, this was not observed in our results. In fact, in our analysis, both sensitivity and specificity of WBC SPECT were better than PET/CT. 18F-FDG PET/CT has several clear advantages over SPECT imaging such as the lack of blood handling, a shorter study time and high target-to-background ratio; however, a high specificity of 18F-FDG PET/CT requires specific protocols to increase diagnostic accuracy.[29,30]

Limitation of the studies

Several limitations affect the quality of our review on the role of SPECT and PET in IE such as the lack of multicenter studies, the low number of patients evaluated (also due to the rarity of this disease), and the heterogeneity of included papers. This heterogeneity arises from the diversity of patients' characteristics, methodological aspects, reference standards and global quality of the studies.

Conclusion

Our findings support the utility of both WBC SPECT and 18F-FDGPET/CT as diagnostic tools in the study of IE, particularly in patients with prosthetic valve. Specific protocols including diet and/or heparin injection may improve the diagnostic performance of PET/CT.

Author contributions

Conception and design of the research: Bertagna F, Giubbini R. Acquisition of data: Albano D. Analysis and interpretation of the data: Albano D, Bertagna F, Giubbini R. Statistical analysis: Albano D. Writing of the manuscript: Albano D. Critical revision of the manuscript for intellectual content: Albano D, Bertagna F, Giubbini R.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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