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Does positron emission tomography/computed tomography aid the diagnosis of prosthetic valve infective endocarditis?

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Abstract

A best evidence topic was constructed according to a structured protocol. The question addressed was whether ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) aids the diagnosis of prosthetic valve endocarditis (PVE)? A total of 107 publications were found using the reported search, of which 6 represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. The reported outcome of all studies was a final diagnosis of confirmed endocarditis on follow-up. All the six studies were non-randomized, single-centre, observational studies and thus represented level 3 evidence. The diagnostic capability of PET/CT for PVE was compared with that of the modified Duke Criteria and echocardiography, and reported in terms of sensitivity, specificity and positive and negative predictive values. All studies demonstrated an increased sensitivity for the diagnosis of PVE when PET/CT was combined with the modified Duke Criteria on admission. A higher SUV_{max} on PET was found to be significantly associated with a confirmed diagnosis of endocarditis and an additional diagnostic benefit of PET/CT angiography over conventional PET/non-enhanced CT is reported due to improved anatomical resolution. However, PET/CT was found to be unreliable in the early postoperative period due to its inability to distinguish between infection and residual postoperative inflammatory changes. PET/CT was also found to be poor at diagnosing cases of native valve endocarditis. We conclude that PET/CT aids in the diagnosis of PVE when combined with the modified Duke Criteria on admission by increasing the diagnostic sensitivity. The diagnostic ability of PET/CT can be potentiated by the use of PET/CTA; however, its use may be unreliable in the early postoperative period or in native valve endocarditis.

Keywords: Positron emission tomography/computed tomography • Valve surgery • Infective endocarditis

INTRODUCTION

A best evidence topic was constructed according to a structured protocol as fully described in *ICVTS* [1].

THREE-PART QUESTION

In [patients with previous prosthetic valve implantation] does [the use of PET/CT] aid [the diagnosis of infective endocarditis]?

CLINICAL SCENARIO

A 54-year old gentleman is admitted with low-grade fever and general malaise at 6 months following aortic valve replacement for infective endocarditis. On admission, he is noted to have an ejection systolic murmur in keeping with his tissue aortic valve and no obvious sources of infection. His inflammatory markers are raised, and blood cultures on admission grew *Staphylococcus aureus*. Transoesophageal echocardiography demonstrates moderate aortic regurgitation and no obvious vegetations. You suspect the patient may have prosthetic valve endocarditis (PVE) and have heard that positron emission tomography/computed tomography (PET/CT) scanning has been reported as aiding diagnosis in this setting. You are not aware of the current evidence supporting its use and decide to review the literature.

SEARCH STRATEGY

A literature search of Medline was performed using the Pubmed interface with the terms (positron [All Fields] AND emission [All Fields] AND tomography [All Fields]) AND (endocarditis [All Fields]).

SEARCH OUTCOME

A total of 107 publications were found using the reported search. Of these, six represented the best available evidence to answer the clinical question. These are summarized in Table 1.

Table 1: Best evidence papers

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Saby *et al.* (2013), J Am Coll Cardiol, France [2] Prospective observational study (level III evidence)	72 patients with PVE	Diagnosis of PVE on 3-month follow-up (classified as definite, possible or rejected)	Diagnostic ability for PVE PET/CT alone: sensitivity 73%; specificity 80%; PPV 85%; NPV 67% Diagnostic ability of Duke Criteria (DC) vs that of Duke Criteria + PET Sensitivity of DC: 70% (95% CI 83–99%) Sensitivity of DC + PET: 97% (95% CI 52–83%) *P* = 0.0008 Specificity of DC: 50% (95% CI 30–70%) Specificity of DC + PET: 40% (95% CI 22–61%) *P* = 0.5 SUV_{max} increased in cases of 'definite PVE' in comparison with 'possible PVE' or 'rejected PVE' *P* < 0.05	The addition of PET/CT as a major criterion in the Duke Criteria increased its sensitivity without a significant reduction in specificity With the addition of PET/CT to echocardiography, no patients with 'definite PVE' were misdiagnosed
Bartoletti *et al.* (2013), BMC Res Notes, Italy [3] Case series (level III evidence)	6 patients with suspected aortic PVE–TEE negative	PVE confirmed or not confirmed	PET/CT indicated PVE in all 6 cases. Four cases operated—PVE confirmed on histology on resected tissue. All 6 showed regression on PET following their surgery	Very small numbers but consistent results. Showed a reduction in SUV_{max} following antibiotic therapy on serial PET/CT
Ricciardi *et al.* (2014), Int J Infect Dis, Italy [4] Retrospective observational study (level III evidence)	22 patients with IE and PET/CT + TTE/TEE results Group 1: 15 patients with suspected PVE and PET/CT + TTE/TEE results Group 2: 7 patients with native valve endocarditis (NVE)	IE confirmed/not confirmed	Overall comparison of diagnostic ability for PVE DC: sensitivity 70%; specificity 100%; PPV 100%; NPV 25% Echocardiography: sensitivity 80%; specificity 100%; PPV 100%; NPV 33% PET/CT: sensitivity 55%; specificity 100%; PPV 100%; NPV 18% Comparison for Group 1 (PVE) DC: sensitivity 77%; specificity 100%; PPV 100%; NPV 40% Echocardiography: sensitivity 69%; specificity 100%; PPV 100%; NPV 33% PET/CT: sensitivity 85%; specificity 100%; PPV 100%; NPV 50% Comparison for Group 2 (NVE) DC: sensitivity 57%; specificity[a]; PPV 100%; NPV[a] Echocardiography: sensitivity 100%; specificity[a]; PPV 100%; NPV[a]	In the whole population of PVE and NVE, echocardiography had a higher sensitivity than PET/CT. For PVE, PET/CT was the most sensitive modality and increased ability to rule out IE

Continued

Table 1: (*Continued*)

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
			PET/CT: sensitivity[a]; specificity[a]; PPV[a]; NPV[a]	
Rouzet *et al*. (2014), J Nucl Med, France [5] Retrospective observational (level III evidence)	39 patients with suspected PVE undergoing both PET/CT and SPECT imaging	Definite, possible or excluded PVE	Overall comparison of diagnostic ability for PVE PET/CT: sensitivity 93%; specificity 71%; PPV 68%; NPV 94%; accuracy 80% SPECT: sensitivity 64%; specificity 100%; PPV 100%; NPV 81%; accuracy 86% Excluding patients imaged in first 2 months following valve implantation (n = 9) PET/CT: sensitivity 92%; specificity 100%; PPV 100%; NPV 93%; accuracy 96%. SPECT: sensitivity 57%; specificity 100%; PPV 100%; NPV 67%; accuracy 77%	PET/CT was found to have higher sensitivity than SPECT but reduced specificity Specificity was improved by excluding all patients who were within 2 months of valve implantation to avoid false-positives from postoperative inflammation
Pizzi *et al*. (2015), Circulation, Spain [6] Prospective observational (level III evidence)	Overall 92 patients with suspected PVE and CDE Group 1: 64 patients with suspected PVE Group 2: 28 patients with suspected CDE Group 3: 76 patients with suspected PVE and CDE who underwent CTA	Definite, possible or rejected PVE	Group 1 (PVE): comparison of diagnostic ability for PVE Duke Criteria: sensitivity 51%; specificity 92%; PPV 91%; NPV 55%. PET/CT: sensitivity 87%; specificity 92%; PPV 95%; NPV 82%. DC + PET/CT: sensitivity 90%; specificity 88%; PPV 92%; NPV 85% Group 2 (CDE): comparison of diagnostic ability for CDE Duke Criteria: sensitivity 50%; specificity 100%; PPV 100%; NPV 61% PET/CT: sensitivity 88%; specificity 100%; PPV 100%; NPV 86% DC + PET/CT: sensitivity 94%; specificity 100%; PPV 100%; NPV 92% Group 3: overall comparison of diagnostic ability for PVE including PET/CTA Duke Criteria: sensitivity 55%; specificity 94%; PPV 92%; NPV 61% PET/CT: sensitivity 86%; specificity 88%; PPV 90%; NPV 83% PET/CTA: sensitivity 91%; specificity 91%; PPV 93%; NPV 88%	PET/CT had improved sensitivity for the diagnosis of IE in both PVE and CDE PET/CTA was found to have additional benefit over conventional PET/NECT A positive correlation was shown between median SUV_{max} and confirmed diagnosis of PVE

Continued

Table 1: (*Continued*)

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
			DC + PET/CT: sensitivity 89%; specificity 84%; PPV 88%; NPV 85% DC + PET/CTA: sensitivity 91%; specificity 88%; PPV 91%; NPV 88% Relationship between median SUV_{max} and final diagnosis of PVE Definite PVE: median SUV_{max}: 7.36 Possible PVE: median SUV_{max}: 2.37 Rejected PVE: median SUV_{max}: 0.5	
Fagman *et al.* (2015) Int J Cardiovasc Imaging, Sweden [7] Prospective observational (level III evidence)	8 patients with definite PVE 19 control patients without PVE	Definite PVE	Diagnostic ability for PVE by visual inspection of PET/CT Sensitivity: 75%, specificity 84%, likelihood ratio (+) 4.8 and likelihood ratio (−) 0.3 Semi-quantitative analysis: Definite PVE vs control SUV_{max}: 5.8 (IQR 3.5–6.5) vs 3.2 (IQR 2.8–3.8) ($P < 0.001$) SUV ratio: 2.4 (IQR 1.7–3.0) vs 1.5 (IQR 1.3–1.6) ($P < 0.001$)	FDG uptake in non-infected prosthetic valves is low PET/CT has showed good diagnostic performance for PVE. However, there was no comparison with other modalities (e.g. Echo or Duke's Criteria)

FDG: ^{18}F-fluorodeoxyglucose; PPV: positive predictive value; NPV: negative predictive value; TTE: transthoracic echocardiography; TEE: transoesophageal echocardiography; DC: Duke Criteria; IE: infective endocarditis; PVE: prosthetic valve endocarditis; CDE: cardiac device-related endocarditis; PET/CTA: PET/CT angiography; PET/NECT: PET/non-enhanced CT; SPECT: single-photon emission computed tomography.
[a]Non-evaluable due to the value of '0' used as a numerator or denominator in calculation.

RESULTS

All studies compared the diagnostic ability of PET/CT scan with a 'final diagnosis' gold standard. The exact method of determining this gold standard varied between studies but in all cases was based on a combination of the modified Duke's Criteria, imaging and microbiological findings over the follow-up period (ranging from hospital discharge to 3 months). Where further information such as intraoperative findings and histology were available, these were included in the final diagnostic criteria.

Saby *et al.* [2] were the first to conduct a study of the diagnostic impact of PET/CT in the setting of PVE. In their prospective observational study of 72 patients with suspected PVE on admission, the addition of a positive PET/CT scan as a major criterion in the modified Duke Criteria (DC) significantly increased its sensitivity from 70 to 97% ($P < 0.008$) without a significant reduction in specificity. This increase was attributed to a significant reduction in cases classified as 'possible PVE' from 40 to 23 ($P < 0.0001$). However, it should be noted that part of this reclassification resulted in 10 of 22 patients originally correctly classified as 'possible PVE' being incorrectly reclassified as 'definite PVE'. The clinical implications of this are not known. The SUV_{max} on PET/CT in cases of 'definite PVE' was also significantly increased in comparison with cases of possible or rejected PVE ($P < 0.05$).

Bartoletti *et al.* [3] reported a small case series of 6 patients with suspected aortic PVE and negative echocardiographic findings. Final diagnoses were based on histology in 4 cases and by clinical response to treatment in the remaining 2 cases. PET/CT successfully diagnosed PVE in all 6 cases and showed a consistent reduction in SUV_{max} on repeat scanning following antibiotic therapy.

Ricciardi *et al.* [4] conducted a retrospective study of 22 patients with suspected endocarditis (15 PVE and 7 native valve endocarditis). PET/CT had a greater sensitivity for detecting confirmed PVE at 85% compared with 77% for transthoracic echocardiography/transoesophageal echocardiography and 77% for DC on admission. However, in 7 patients with native valve endocarditis, PET/CT failed to detect infection in all cases ($P < 0.001$). As such, the authors advise against the use of PET/CT in this setting.

Rouzet *et al.* [5] compared PET/CT and single-photon emission computed tomography (SPECT) in the diagnosis of 92 cases of suspected PVE with inconclusive echocardiographic results. PET/CT was found to be a more useful initial test due to its greater sensitivity for PVE (93 vs 64%) although SPECT had a greater specificity (100 vs 71%). This reduced specificity was in part due to 6 cases of false-positive PET/CT results, all of which were within 2 months of

valve implantation. The authors conclude that postoperative ^{18}F-fluorodeoxyglucose uptake in inflammatory tissues can mimic infection and result in false-positives in this time period. When patients within 2 months of prosthetic valve implantation were excluded from the analysis, the sensitivity and specificity of PET/CT for detecting PVE were 92 and 100%, respectively.

Pizzi *et al.* [6] analysed the relative performance of PET/CT and PET/CT angiography (PET/CTA) in the diagnosis of patients with suspected PVE and cardiac device-related endocarditis. They report that adding PET/CT to modified DC on admission significantly increased diagnostic sensitivity for patients with PVE from 51 to 90% (*P*-value not quoted). PET/CTA was found to confer an additional advantage of PET/non-enhanced CT (PET/NECT) by reducing the number of possible cases on PET/NECT from 20 to 8% ($P < 0.001$). PET/CTA offers additional diagnostic ability due to its use of ECG-gated, contrast-enhanced anatomical images. In a similar result to that demonstrated by Saby *et al.*, SUV_{max} was significantly higher in cases of definite PVE (median SUV_{max} of 7.36 for definite PVE; 2.37 for possible PVE and 0.5 for rejected PVE).

Fagman *et al.* [7] performed a prospective study that included a control group of patients with prosthetic valves undergoing PET scan for malignancy. They showed that SUV_{max} and SUV ratio were both significantly lower in this cohort than in a cohort of 8 patients with a final diagnosis of definite PVE. They also showed good diagnostic ability of PET/CT for PVE, but this result was not contextualized by comparison with any other methods such as the modified DC or echocardiography.

CLINICAL BOTTOM LINE

Current evidence suggests that PET/CT aids the diagnosis of PVE when combined with the modified DC on admission by increasing the diagnostic sensitivity. The diagnostic ability of PET/CT can be potentiated by the use of PET/CTA. However, PET/CT is unreliable in the early postoperative period or in native valve endocarditis.

Conflict of interest: none declared.

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