

¹⁸F-FDG PET/CT for the Detection of Septic Embolisms in Patients with Infectious Endocarditis

An important complication of infectious endocarditis is secondary septic embolisms caused by hematogenous spreading of the microorganism to distant sites. In this issue of *The Journal of Nuclear Medicine*, Kestler et al. (1) report their experience with ¹⁸F-FDG PET/CT in diagnosing septic embolisms in a group of 47 patients with infectious endocarditis. Their results confirm that ¹⁸F-FDG PET/CT is a valuable technique in diagnosing these septic embolisms, shown by the sensitivity, specificity, positive predictive value, and negative predictive value of 100%, 80%, 90%, and 100%, respectively. In patients with infectious endocarditis, up to 44% may have septic embolisms and metastatic infection (2). Early detection of these septic embolisms is important because the morbidity and mortality of infectious endocarditis

See page 1093

are higher in the presence of these foci. Known risk factors for developing metastatic infectious foci are community acquisition of the bacteremia, unknown portal of entry, time span longer than 48 h between the first symptoms and initiation of antibiotic therapy, the presence of foreign body material, persistent fever after 72 h, and positive follow-up blood cultures at 24–96 h (3,4). Because septic embolisms need prolonged antibiotic therapy and possibly surgical intervention, failure to identify these metastatic complications may lead to early cessation of therapy and relapse of bloodstream infection and unfavorable outcome (5). However, timely identification of septic embolisms is often difficult. Often these septic foci are not suspected in the absence of positive blood cultures or when blood cultures are obtained during antibiotic treatment. Furthermore, up to 50% of patients with septic embolisms do not have any localizing signs and symptoms (6,7). In the current study, more than half (60%) of the patients with an infectious complication were asymptomatic. ¹⁸F-FDG PET/CT was the only initially positive imaging technique in 55.5% of true-positive cases (1). To date, a structural protocol for diagnosis of septic embolisms is lacking.

Besides the study of Kestler et al., other investigators have shown evidence that ¹⁸F-FDG PET/CT could be of diagnostic value in patients with septic embolisms. Several case reports have shown the value of ¹⁸F-FDG PET/CT in the diagnosis of extra-

cardiac foci in patients with infectious endocarditis (8). A small study of 24 patients with 25 episodes of infectious endocarditis investigated the value of ¹⁸F-FDG PET/CT in diagnosing septic embolisms. ¹⁸F-FDG PET/CT revealed a septic embolism in 11 episodes (44%) and detected 7 positive cases (28%) in which there was no clinical suspicion (2). In a previously published study investigating 71 patients with suspected infectious endocarditis, ¹⁸F-FDG PET/CT detected unexpected extracardiac septic embolisms in 17 patients (24%) (9). In the study of Kestler et al., ¹⁸F-FDG PET/CT was able to detect septic embolisms in 57.4% of the 47 patients with definite infectious endocarditis.

A large clinical study of ¹⁸F-FDG PET/CT in detecting metastatic infection in 115 patients was published in *The Journal of Nuclear Medicine* in 2010 by Vos et al. (7). In that study, the diagnostic value of ¹⁸F-FDG PET/CT was investigated in 115 non-neutropenic patients with Gram-positive bacteremia and a high risk of complications, of whom 21 patients (18.3%) were diagnosed with infectious endocarditis. High risks of metastatic complications were community acquisition of the bacteremia, signs of infection more than 48 h before initiation of appropriate treatment, fever more than 72 h after initiation of appropriate treatment, and positive blood cultures more than 48 h after initiation of appropriate treatment. Results were compared with a matched historical control group of 230 patients on whom no ¹⁸F-FDG PET/CT was performed; of these patients, 19 (8.3%) were diagnosed with infectious endocarditis. Sensitivity, specificity, positive predictive value, and negative predictive value of ¹⁸F-FDG PET/CT for the detection of metastatic infection were 100%, 87%, 89%, and 100%, respectively. Significantly more patients were diagnosed with metastatic infections in the study group (67.8% vs. 35.7% in the control group, $P < 0.01$). Relapse rates decreased from 7.4% in the control group to 2.6% in the study group ($P = 0.09$) and from 8.9% to 1.4% in patients with *Staphylococcus aureus* bacteremia ($P = 0.04$). In the study of Kestler et al., ¹⁸F-FDG PET/CT also led to a significant increase in the diagnosis of infectious complications: 57.4% in the study group and 18.0% in the control group ($P = 0.0001$). Furthermore, ¹⁸F-FDG PET/CT was associated with a 2-fold reduction in the number of relapses: 4.2% in the study group and 9.6% in the control group ($P = 0.25$). These findings are similar to the results of Vos et al., adding more support to the diagnostic value of ¹⁸F-FDG PET/CT in diagnosing septic embolisms.

In the study of Kestler et al., the impact of ¹⁸F-FDG PET/CT on mortality in patients with infectious endocarditis and septic embolisms was not investigated. The data of Vos et al. suggest that ¹⁸F-FDG PET/CT significantly decreases relapse rates and overall mortality in patients with Gram-positive bacteremia (7). It would be interesting to further explore the value of ¹⁸F-FDG PET/CT relating to relapse rate and mortality rate in patients with infectious endocarditis and septic embolisms.

A cost-effectiveness analysis for ¹⁸F-FDG PET/CT in the study of Vos et al. (10) was performed and showed a cost-effectiveness ratio of \$72,487 per prevented death, which is within the range

Received Apr. 13, 2014; revision accepted Apr. 14, 2014.
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 Published online May 8, 2014.
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 DOI: 10.2967/jnumed.114.140707

that is considered to be efficient by Dutch guidelines. The cost increase was due to in-hospital treatment of metastatic infectious foci. Kestler et al. showed that, on the basis of data from Spanish health authorities, the mean extra cost of a major complication of a systemic infection is €20,241 (~\$27,940). Early diagnosis of infectious complications with ^{18}F -FDG PET/CT is cost-effective, as ^{18}F -FDG PET/CT costs €658 (~\$908) per patient. In this study, the length of hospital stay was similar in the study group and the control group because of an outpatient parenteral antibiotic treatment program.

In the last decade, the use of ^{18}F -FDG PET/CT in diagnosing infectious diseases has been increasing. ^{18}F -FDG PET/CT has shown great results in fever of unknown origin and in identification of inflammatory foci in soft-tissue and bone structures (11). Besides the fact that ^{18}F -FDG PET/CT is more suitable as a screening method than conventional radiologic techniques because of its whole-body imaging without increasing radiation exposure, it also detects early metabolic activity and has a lack of artifacts due to metallic hardware. Furthermore, no adverse reactions to ^{18}F -FDG are described. In contrast to conventional nuclear imaging, ^{18}F -FDG PET/CT is a high-resolution technique that enables precise localization of sites of infectious foci, and the procedure is completed in a few hours with a relatively low radiation dose.

In patients with infectious endocarditis, ^{18}F -FDG PET/CT is frequently considered to be unsuitable for the detection of infectious cardiac foci because of high physiologic ^{18}F -FDG uptake by the normal myocardium. Infectious endocarditis is currently diagnosed using the revised Duke criteria, which are based on microbiologic results, echocardiography, and certain signs and symptoms (12). The specificity of these criteria is high, but sensitivity is limited in clinical practice. More recently, reports have been published showing that ^{18}F -FDG PET/CT could be a valuable diagnostic technique in patients with suspected endocarditis (13,14). Kestler et al. did not evaluate ^{18}F -FDG uptake in the heart valves of patients with infectious endocarditis. A recent study (15) investigated the diagnostic value of ^{18}F -FDG PET/CT in infectious endocarditis in 72 patients with Gram-positive bacteremia. All patients underwent both ^{18}F -FDG PET/CT and echocardiography. Infectious endocarditis was defined according to the revised Duke criteria. For ^{18}F -FDG PET/CT, sensitivity was 39%, specificity was 93%, PPV was 64%, and NPV was 82%. Because of this low sensitivity, ^{18}F -FDG PET/CT is currently unsuitable for diagnosing endocarditis, but its high specificity is promising. Newer PET/CT scanners have improved resolution, and there is also promising evidence that a low-carbohydrate fat-allowed diet will adequately suppress cardiac ^{18}F -FDG uptake (16,17). Also, because intracardiac septic foci can be very small, delayed imaging could increase the diagnostic accuracy of this technique, as demonstrated by a case recently published (18). These improvements may increase sensitivity in future studies.

The results of the study by Kestler et al. add to the body of evidence demonstrating that ^{18}F -FDG PET/CT is a valuable diagnostic technique in patients with infectious endocarditis and detection of septic foci and confirm that ^{18}F -FDG PET/CT can accurately localize these infectious foci. Because ^{18}F -FDG PET/CT overcomes many shortcomings of other imaging techniques, it should be considered the imaging modality of choice in this clinical context.

DISCLOSURE

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

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