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ORIGINAL ARTICLE

^{18}F-fluorodeoxyglucose positron emission tomography combined with whole-body computed tomographic angiography in critically ill patients with suspected severe sepsis with no definite diagnosis

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Abstract
Purpose Timely identification of septic foci is critical in patients with severe sepsis or septic shock of unknown origin. This prospective pilot study aimed to assess ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), combined with whole-body computed tomographic angiography (CTA), in patients with suspected severe sepsis and for whom the prior diagnostic workup had been inconclusive.
Methods Patients hospitalized in an intensive care unit with a suspected severe sepsis but no definite diagnosis after 48 h of extensive investigations were prospectively included and referred for a whole body FDG-PET/CTA. Results from FDG-PET/CTA were assessed according to the final diagnosis obtained after follow-up and additional diagnostic workup.
Results Seventeen patients were prospectively included, all on mechanical ventilation and 14 under vasopressor drugs. The FDG-PET/CTA exam 1) was responsible for only one desaturation and one hypotension, both quickly reversible under treatment; 2) led to suspect 16 infectious sites among which 13 (81 %) could be confirmed by further diagnostic procedures; and 3) triggered beneficial changes in the medical management of 12 of the 17 study patients (71 %). The FDG-PET/CTA images showed a single or predominant infectious focus in two cases where CTA was negative and in three cases where CTA exhibited multiple possible foci.
Conclusion Whole-body FDG-PET/CTA appears to be feasible, relatively safe, and provides reliable and useful information, when prospectively planned in patients with suspected severe sepsis and for whom prior diagnostic workup had been inconclusive. The FDG-PET images are particularly helpful when CTA exhibits no or multiple possible sites.

Keywords Sepsis · Diagnosis · FDG-PET imaging · Computed tomographic angiography

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Introduction

The timely identification and localization of septic sites is critical in patients with severe sepsis or septic shock of unknown origin. This identification may remain a challenge despite extensive workup including clinical examination, laboratory investigations and conventional ultrasound and X-ray imaging. The use of biomarkers has been proposed in this setting, but still remains of little help [1].

Stimulated immune cells, especially macrophages and neutrophils, overexpress glucose transporter 1 (GLUT1) receptors [2–4]. As such, uptake of the ^{18}F-fluorodeoxyglucose (FDG) by these cells is high in inflammatory/infectious sites [5]. Thus, in addition to cancer, another promising application of FDG-PET has emerged in the evaluation of patients with infections. FDG-PET, associated with X-ray computed tomographic imaging (CT), has been shown to be helpful for the diagnosis of osteo-articular, prosthetic, and vascular graft infections, as well as in cases of fever of unknown origin [6, 7]. FDG-PET/CT has also been investigated in the setting of severe sepsis with bacteremia. In particular, Vos et al. reported on the usefulness of FDG-PET/CT in a case–control study of 115 (non-critically ill) patients presenting with a Gram-positive bacteremia [8]. Of interest, mortality was lower than that of an historical control group. However, data remain scarce in critically ill patients hospitalized in intensive care units (ICU). In two recent studies, Simons et al. and Kluge et al. described their experience with FDG-PET/CT in ICU patients with sepsis of unknown origin [9, 10]. Although very encouraging, the retrospective nature of these studies limited the generalization of their findings. In addition, no angiography was assigned with CT imaging, whereas CT angiography is currently recommended for detecting infectious foci, especially within the abdomen and pelvis [11].

This pilot study, therefore, aimed to assess the feasibility and usefulness of FDG-PET combined with CT angiography in patients with suspected severe sepsis and for whom prior diagnostic workup had been inconclusive.

Materials and methods

The study was approved by the regional ethics committee (Comité de Protection des Personnes-Est III) and written informed consent of the patient or the patient's relatives was obtained before inclusion. (Clinical Trial Registration: www.clinicaltrials.gov, NCT00791310).

Patients

During a 2-year period, all consecutive patients were screened for eligibility. Inclusion was possible when a severe sepsis i) was suspected according to conventional criteria [12], and ii) remained of unknown origin after 48 h of extensive investigations. A unique procedure was not imposed for these diagnostic investigations, as they were dependent on clinical context. However, in addition to clinical examination, chest X-ray and conventional laboratory investigations (blood cultures, urine analysis, detection of soluble antigens, bronchoalveolar lavage fluid [BALF] culture, serology), most patients benefited from an echocardiography (transthoracic and/or transesophageal), an abdominal echography and whole body CT-scan before inclusion. Main exclusion criteria were i) recent (<30 days) surgery, ii) hemodynamic instability, as determined by the clinician in charge of the patient, iii) severe hypoxia (PaO_2/FiO_2<150), iv) known allergy to iodinated contrast products, v) pregnancy, and vi) age<18 years.

Recording of FDG-PET/CTA images

FDG-PET/CTA was performed within 24 h of inclusion after an overnight fast, after having withdrawn any perfusion solution containing glucose and after having confirmed that glycemia was $<1.6\ g\ l^{-1}$, with no insulin added. The patients were transported from the ICU to the Department of Nuclear Medicine by an intensive care team, involving at least one senior physician and one nurse. Thereafter, the patients were placed in supine position on the bed of the hybrid PET camera, which included a six-detector CT (Biograph 6 True Point, SIEMENS, Knoxville, Tennessee, USA). Patients were mechanically ventilated and continuously monitored (ECG, blood pressure, SaO_2) during the overall procedure, from the time of FDG injection to the end of image recording (a total of approximately 90 min).

An activity of 5.5 MBq/kg of FDG was injected intravenously and a whole body CT recording, used for attenuation correction, was initiated 60 min later. The latter was followed by a 3D whole-body FDG-PET recording, which involved six to eight bed positions lasting 3 min each. FDG-PET images were reconstructed by the OSEM method (three iterations and eight subsets) with corrections for diffusion and attenuation, and displayed in a 168×168 matrix with 3.0×3.0×3.0 mm^3 voxels [13]. The standardized uptake value (SUV) was calculated by dividing the activity measured in each voxel by the total injected activity, which was expressed per gram of body weight and corrected for radioactive decay.

Thereafter, a whole body CTA was recorded after the intravenous injection of 1.5 to 2 mL/kg of iodinated contrast at a iodine concentration of 320 mg/mL Iodixanol (VISIPAQUE^{TM}), General Electric Healthcare, Velizy-Villacoublay, France) followed by 20 to 60 mL of saline solution. Main parameters were as follows: 130 kV, intensity adapted to noise index, 512×512 matrix, 2 mm slice thickness and pitch of 1.

Analysis of FDG-PET/CTA images

Body CTA was analyzed immediately after completion of the FDG-PET/CTA recording by an experienced radiologist who was blinded to the FDG-PET images, but not to the patient's other medical data (clinical history, previous biological and imaging tests), similarly to standard practice when only a CTA is prescribed in this setting. The possible infectious foci were reported.

Thereafter, the whole FDG-PET/CTA images were analyzed in a consensual manner by two observers and with a paired display of both CTA and fused FDG-PET/CTA images provided on an Esoft station (Siemens, Knoxville, Tennessee, USA). One of these observers was the radiologist, who had already analyzed the CTA images, and the other was a physician in Nuclear Medicine, who had extensive experience in FDG-PET imaging. The possible infectious foci were determined on the basis of the presence of a clear enhancement in FDG uptake and with the knowledge of all other medical data. These foci were described and immediately communicated to the ICU staff, such that additional diagnostic procedures could be quickly implemented.

Follow-up and judgment criteria

All diagnostic tests and therapeutic changes were recorded during follow-up and those based on the results of the FDG-PET/CTA were pointed out (oriented bacteriological sampling, surgery, changes in antibiotic treatments, device removal, etc.).

At the end of follow-up, which was defined as the date of death or ICU discharge, a final diagnosis was given on the actual presence and location of infectious diseases. This diagnosis was made by experienced physicians and according to results from further diagnostic procedures.

Results from FDG-PET/CTA were considered 'true positive' when the reported infectious foci corresponded to actual infectious site as evidenced by results from further procedures. 'False positives' pointed to reported sites for which infection could not be proven by further procedures. FDG-PET/CTA exams, for which no infectious site was reported, were considered 'true negative' when infection could definitely be ruled out after diagnostic workup and clinical follow-up, and 'false negative' in cases of evidence of focal or systemic infection.

Statistical analysis

Results are expressed as medians (IQR). FDG-PET/CTA sensitivity, specificity, and positive and negative predictive values for the diagnosis of sepsis were calculated.

Results

Patient characteristics

During the 2-year study period, sepsis was suspected in 630 patients. Among these, the source of infection remained unknown in 49 (7.8 %) despite extensive clinical, biological and imaging examinations. These 49 patients were thus eligible for inclusion in this study; however, hemodynamic instability (n=15), absence of consent (n=8), or FDG unavailability (n=9) yielded a final enrolment of 17 patients in this pilot study.

There were 10 men and 7 women (age: median 55 years, range: 19–82 years). The delay time between ICU admission and FDG-PET/CTA was variable, ranging from 2 to 125 days with a median of 7 days. This delay was longer in patients who were not initially admitted for a suspected severe sepsis and for whom this diagnostic was only suspected later (see Table 1 for more details). At the time of FDG-PET/CTA, all but one patients received antibiotics for a median of 4 (2–17) days, 14 received vasopressor drugs (suspicion of septic shock) and all were under mechanical ventilation. Severity was high as assessed by an elevated Sequential Organ Failure Assessment (SOFA) score (median value: 10 [2–16]). Six patients died in the ICU (35 %).

Extensive microbiological testing (blood, urine, bronchoalveolar lavage fluid [BALF]) had been performed within 48 h before PET imaging: blood culture was positive in six patients while urine and BALF remained negative in all patients.

Before inclusion, all patients underwent conventional chest X-rays, 16 had abdominal ultrasonography, 14 had transthoracic or transesophageal echocardiography and 10 had a previous whole body CT scan.

Adverse events

Only two patients had adverse events in relation to the FDG-PET/CTA that, in both cases, occurred when the patients were moved to be placed on the camera bed. They were quickly reversible on treatment: a <90 % oxygen desaturation requiring an increase in FiO_2 and a drop in systolic arterial pressure <90 mmHg necessitating an increase in norepinephrine dosage.

Diagnostic performance of FDG-PET/CTA

As detailed in Table 1, FDG-PET/CTA images led to suspect a total of 16 infectious sites in 14 patients: seven pneumonia, one pulmonary abscess, one cervical cellulitis, two osteitis, one pyelonephritis, one abdominal parietal abscess, one abscess of an abdominal aortic stent graft, one endometritis, and one central venous catheter infection. Two different infectious sites were suspected in one patient with pneumonia and stent graft infection (#8 in Table 1), and in a second patient with pulmonary abscess and cervical cellulitis in the setting of a Lemierre syndrome (#11 in Table 1, Fig. 1).

Thirteen of the 16 suspected infection sites (81 %) could be confirmed by further diagnostic procedures leaving three presumably false positive results. These were 1) a suspected infection of a central venous

Table 1 main parameters collected in individual patients

#	Age (years)	Suspected diagnosis at admission	Delay time from admission to PET/CTA (days)	Previous medical imaging*	Blood cultures	Suspected infectious sites at PET/CTA	Confirmation (or not) of suspected sites	Therapeutic changes
1	59	Pancreatitis, mesenteric ischemia	38	CxR, AE	/	Bilateral pneumonia	Yes: *P. aeruginosa* pneumonia	Antibiotics modification
2	78	Septic shock	10	CxR, AE	/	Central venous catheter	No	/
3	41	ARDS	7	CxR, WB-CT	/	Pneumonia of right inferior lobe	Yes: *E. cloacae* pneumonia	Antibiotics modification
4	41	Endocarditis	11	CxR, AE, TEE, TTE, WB-CT	/	Bilateral pneumonia	No	/
5	77	ARDS	50	CxR, AE, TEE, TTE, WB-CT	*E. cloacae*	Pneumonia of right inferior lobe (and lung cancer)	Yes: endobronchial biopsy and *E. cloacae* pneumonia	/
6	56	Septic shock	2	CxR, AE, TEE, TTE	/	Left abscessed pyelonephritis	Yes: *E. coli* pyelonephritis	Antibiotics modification
7	55	Septic shock	5	CxR, AE, TTE	/	/	Yes	Stop antibiotics
8	82	Septic shock	4	CxR, AE, TEE, TTE	/	Peri-prosthetic infection, bilateral pneumonia	Yes: *S. aureus* pneumonia	Antibiotics modification
9	62	Cardiogenic pulmonary edema	125	CxR, AE, TTE, WB-CT	*P. aeruginosa*	Right tibial osteitis	Yes: surgical biopsy grew *P. aeruginosa*	Antibiotics modification, Surgery
10	36	Septic shock	2	CxR, AE, TEE, TTE, WB-CT	*H. influenzae*	Left pneumonia	Yes: *H. influenzae* pneumonia	Antibiotics modification
11	22	Septic shock	4	CxR, AE, TTE, WB-CT	*S. mitis*	Pulmonary abscesses, cervical cellulitis	Yes: Lemierre syndrome	Antibiotics modification
12	35	Septic shock	2	CxR, AE, TTE	*E. coli*	/	No	/
13	47	Acute pancreatitis	14	CxR, AE, TTE, WB-CT	/	Right pneumonia	Yes: *P. aeruginosa* pneumonia	Antibiotics modification
14	73	Hemorrhagic shock	4	CxR, AE, TTE	/	Endometritis	No: *C. koserii* pneumonia	/
15	34	Septic shock	14	CxR, AE, TTE, WB-CT	/	Ischiatic osteitis	Yes: surgical biopsy grew *P. aeruginosa*	Antibiotics modification
16	59	Septic shock	42	CxR, AE, TTE, TEE, WB-CT	*K. pneumoniae*	Parietal abdominal abscess	Yes: *K. pneumoniae* abscess	Surgery
17	19	Shock state	2	CxR, AE, TTE, WB-CT	/	/	Yes	/

AE abdominal echography, *ARDS* Acute respiratory distress syndrome, *CxR* Chest X-Ray, *TTE* transthoracic echocardiography, *TEE* transesophageal echocardiography, *WB-CT* whole-body computed tomography

*: performed in the 48 h preceding FDG-PET/CTA

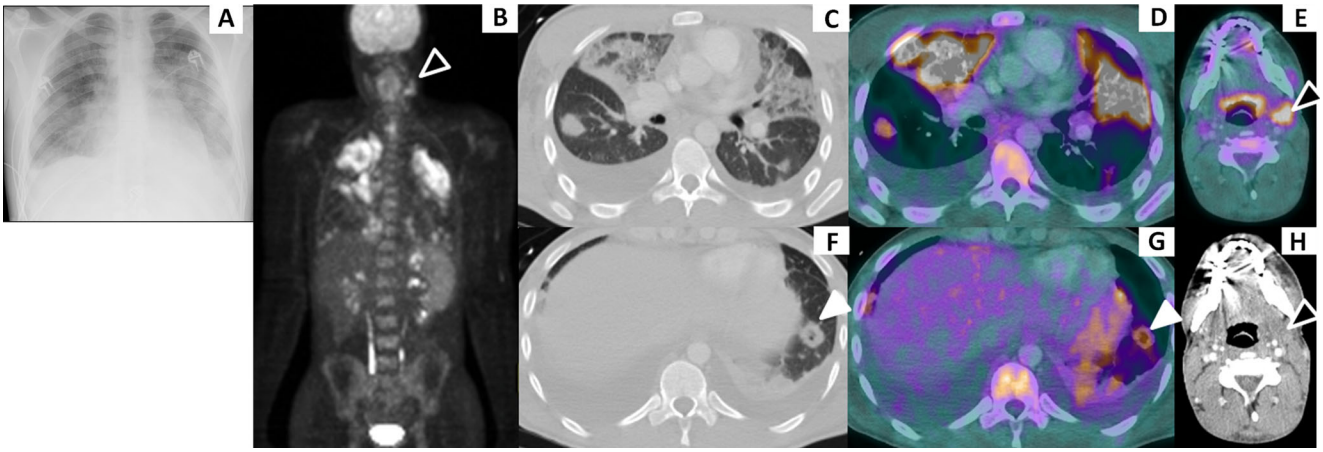

Fig. 1 This 22-year old patient (#11 in Table 1), admitted for a septic shock, was finally diagnosed with Lemierre syndrome. Anterior view of a 3D-MIP from FDG-PET (**b**) and fused FDG-PET/CTA images (**d**, **g**) revealed bilateral lung hypermetabolism predominant in the upper and middle lobes, while corresponding CTA images (**c**, **f**) confirm the diagnostic of bilateral pneumonia with an abscess in the left lower lobe (*arrowhead*) and pleurisy. FDG-PET/CTA also showed findings consistent with a cervical cellulitis (**e**, **h**): enlargement of cervical nodes and local inflammation together with a hypermetabolic thrombosis of the left facial vein indicative of an infective clot (*black arrowheads*). The presence of these infection foci could not be established on a previous unenhanced CT. The chest X-ray, which was previously recorded in bed (**a**), was abnormal, but not typical of pneumonia and it was initially associated with negative BALF sampling. CTA: computed tomographic angiography; FDG-PET: ^{18}F-fluorodeoxyglucose positron emission tomography; MIP: maximum intensity projection

catheter in which subsequent catheter culture was negative, and for which the relation with the method of FDG injection could be discussed (FDG was injected through this catheter because of a very poor venous access, #2 in Table 1); 2) a suspected pneumonia in which repeated BALF cultures remained negative (#4); and 3) a suspected endometritis in which gynecological examination was normal and bacterial cultures were negative (#14).

In three patients, FDG-PET/CTA did not show any obvious infectious site. This likely corresponded to true-negative results in 2 of them but to a false negative result in the 3rd patient who had positive blood cultures for *E. coli* (#12 in Table 1). A second false negative was documented in patient #14 for whom an endometritis was falsely suspected by FDG-PET/CTA whereas subsequent BALF cultures yielded evidence of a *C. koserii* ventilator-associated pneumonia.

When compared to CTA analysis only, additional analysis of FDG-PET images added crucial information in five patients. In two of these patients, the actual infectious sites were only identified with FDG-PET: one osteitis (#9 in Table 1), one infection of an aortic stent graft (#8). In the three other patients, multiple possible infectious sites were documented at CTA (from two to four sites). Abdominal infection sites were additionally suspected by CTA in patient #1, who had a previous history of pancreatitis and prior abdominal surgery (Fig. 2), and in patient #13, who also had a previous history of pancreatitis. For patient #6, a pneumonia had been additionally suspected by CTA.

It should also be pointed out that in one patient, FDG-PET/CTA led to unmasking a right lung carcinoma in addition to pneumonia of the right inferior lobe.

On a patient basis, the sensitivity of FDG-PET/CTA in identifying patients with a definite severe sepsis was 85 % (11/13), specificity was 50 % (2/4), positive predictive value was 85 % (11/13) and negative predictive value was 50 % (2/4) (Table 2). On an infected-site basis, sensitivity was 87 % (13/15) and positive predictive value was 81 % (13/16).

Therapeutic implications

Treatments for 12 out of the 17 patients (71 %) were usefully modified according to the additional analyses triggered by the FDG-PET/CTA results. In five cases, antibiotics were changed to broaden or reduce their spectrum, according to the information obtained after sampling and culture of the unmasked infectious sites. Antibiotic treatments were prolonged to treat an osteitis and an aortic prosthesis infection, while suppressed in one patient who had no infection site at FDG-PET/CTA. Surgery was performed in order treat an osteitis in one patient and a parietal abscess in another patient.

Discussion

In this prospective pilot study, whole body FDG-PET/CTA was found 1) to be feasible and relatively safe in severe sepsis

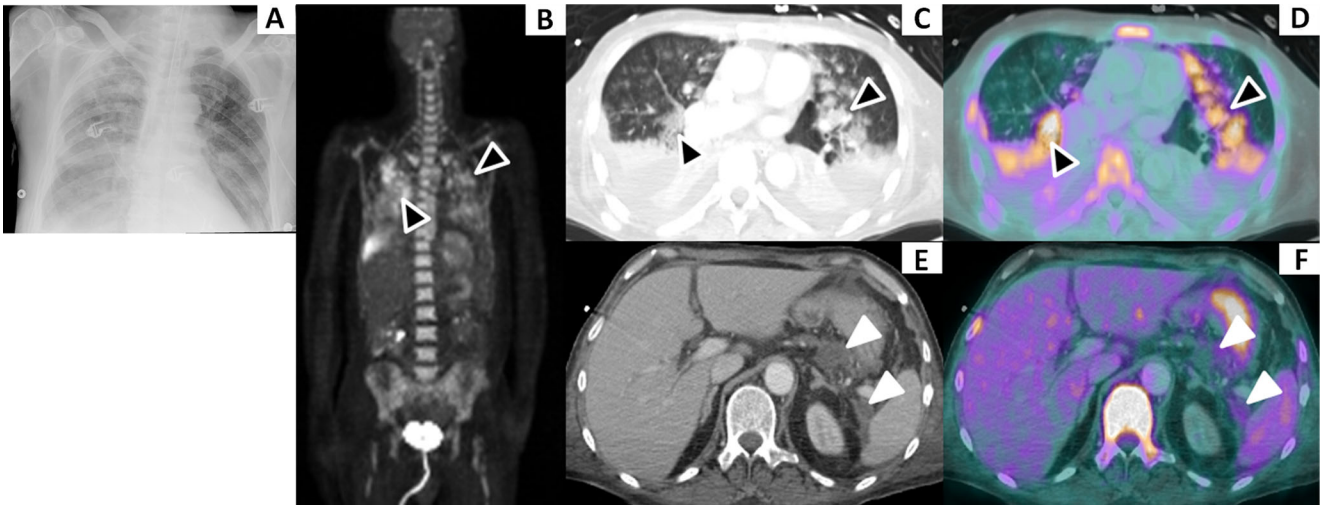

Fig. 2 In this 59-year old patient, admitted for pancreatitis 38 days before (#1 in Table 1), FDG-PET images revealed bilateral pneumonia with concordant images from CTA (*black arrowheads*; **b**: anterior view of a 3D-MIP from FDG-PET; **c**: CTA images **d**: fused FDG-PET and CTA images). FDG-PET images also ruled out abdominal infection, revealing no hypermetabolism of the collections lying in the pancreatic region (*white arrowheads*; **e**: axial slice of CTA and **f**: corresponding fused FDG-PET/CTA image). The chest X-ray, which was previously recorded in bed (**a**), was abnormal but not typical of pneumonia and it was initially associated with negative BALF sampling. CTA: computed tomographic angiography; FDG-PET: ^{18}F-fluorodeoxyglucose positron emission tomography; MIP: maximum intensity projection

patients, and 2) to unmask numerous infection sites, leading to high rates of useful therapeutic changes.

The seven unmasked infections were very diverse, corresponding to osteitis, cellulitis, pyelonephritis, parietal abscess, pulmonary abscess or stent graft abscess. Moreover, pneumonia was involved in seven additional infections. Of note, the diagnosis of pneumonia could not be established by prior chest X-rays and BALF sampling in all seven cases, and by a previous CT scan in four instances. It is well known that pneumonia is often difficult to diagnose in patients who are treated by antibiotics and under mechanical ventilation (see the pleural effusions and the diffuse abnormalities on the in bed chest X-ray of patients from Figs. 1 and 2). It is likely that the positive results from FDG-PET/CTA played a major role in the decision to quickly repeat the BALF sampling, leading to positive culture results.

Table 2 FDG-PET accuracy to diagnose patients with actual infectious sites

	Confirmation +	Confirmation -	Total
FDG-PET/CTA +	11 (TP)	2 (FP)	13
FDG-PET/CTA -	2 (FN)	2 (TN)	4
Total	13	4	

TP true positive, *FP* false positive, *TN* true negative, *FN* false negative

Of note, patient #14, who was finally diagnosed with bacterial pneumonia, was considered a false negative result in the per-patient analysis, even though FDG-PET/CTA was positive. This was, however, a falsely positive result, leading to suspect endometritis, a possible source of time wasting for medical management

Despite the fact that almost all patients were under antibiotic treatment, the sensitivities of FDG-PET/CTA were sufficiently high to identify both the sites and patients with definite diagnosis of sepsis (87 % and 85 %, respectively). Only two infected patients were missed: 1) one with repeated *E. coli* bacteremia, and for whom no final diagnosis could be obtained regarding the actual infected site, and 2) one other patient, who was finally identified as having pneumonia. In addition, the positive predictive value was also high, with only three presumably false positive results among the 16 suspected infected sites (81 %).

Specificity and negative predictive value (NPV) were likely to be lower here, although they could not be reliably estimated, with only three patients being finally considered to have no infectious disease. It should be pointed out that specificity has already been shown to be lower than sensitivity in two other FDG-PET/CT studies, which were previously performed in this setting but in a retrospective manner and without the systematic use of CT angiography (CTA). In 33 mechanically ventilated patients, Simons et al. found an impressive 100 % sensitivity and 78 % specificity for the diagnosis of infection with FDG-PET/CT [9]. Kluge et al. found similar results in 18 patients suffering from severe sepsis of unknown origin with 100 % sensitivity and 62.5 % specificity [10].

In addition, our data clearly show that the combined analysis of FDG-PET and CTA is more efficient than analysis with CTA alone. FDG-PET images were indeed able to reveal serious infections missed by whole body

CTA analysis, including one osteitis and one aortic stent graft infection. In three other patients, multiple possible foci had been identified by body CTA while FDG-PET images enabled to focus on the actual infectious sites. Therefore, the recording of FDG-PET images could be particularly useful when CTA is not or only poorly conclusive and showing either no evident infectious focus or multiple possible foci.

This FDG-PECT study is the first to prospectively enroll patients with suspicion of severe sepsis and where FDG-PET was combined with whole-body CTA. This enrolment was proceeded after at least a 48-h period of extensive diagnostic workup in order to avoid including patients with an obvious diagnosis. The FDG-PET/CTA had to be performed no later than 24 h after inclusion in order to lower the effects of treatment (especially antibiotics) on its interpretation.

Several limitations, nevertheless, deserve consideration. First, it is likely that only a small proportion of patients with suspected severe sepsis are potentially concerned. Indeed, after a 48-h period of usual investigations, the diagnosis of sepsis or infectious site remained uncertain in only 49 (7.8 %) of our screened patients. Among these 49 patients, 32 could not be referred to FDG-PET due not only to the lack of informed written consent, but also because of FDG unavailability (on weekends) or because of an unstable hemodynamic status. Second, the initial diagnostic workup (prior to FDG-PET/CTA scan) was not protocolized, but rather performed ad hoc and conducted by the clinician in charge of the patient, similarly to standard practice. Nevertheless, all patients benefited from extensive microbiological sampling (blood, urine, BALF) as well as several imaging procedures prior to inclusion in this study. Third, a final diagnosis could not be obtained in two patients with a negative FDG-PET/CTA scan. Notwithstanding, these patients responded well without further antibiotics. Fourth, although there were very few severe adverse events, it should be recognized that transport of a severe septic patient from the ICU to the Department of Nuclear Medicine may be problematic in terms of logistics and medical staff requirements. Finally, this being only a pilot study, further prospective studies with a greater number of patients are warranted for a more accurate evaluation.

Conclusion

Whole-body FDG-PET/CTA appears feasible, relatively safe and provides reliable and useful information, when prospectively scheduled in patients with suspected severe sepsis, but no definite diagnosis. FDG-PET images would be particularly helpful when CTA exhibits no or multiple possible sites.

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Conflict of interest The authors state that they have no conflict of interest.

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