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Jelena Šaponjski[1†], Dragana Šobić-Šaranović[1,2], Nebojša Petrović[1,2], Strahinja Odalović[1,2], Vera Artiko[1,2], Milica Stojiljković[1], Nevena Ranković[1], Miloš Veljković[1], Milica Vukićević[3], Nikola Bogosavljević[4], Danilo Jeremić[4], Dušan Šaponjski[5]

Hybrid imaging of vascular graft infection by positron emission tomography with computed tomography using fluorine-18-labeled fluorodeoxyglucose: Serbian National PET Center Experience

Хибридни имиџинг инфекције васкуларног графта помоћу позитронске емисионе томографије са компјутеризованом томографијом користећи флуор-18-обележену флуордеоксиглукозу: искуство националног ПЕТ центра Србије

[1]Clinical Center of Serbia, Center for nuclear medicine, Belgrade, Serbia;
[2]University in Belgrade, Faculty of Medicine, Belgrade, Serbia;
[3]Clinical Center of Serbia, Cardiac surgery clinic, Belgrade, Serbia;
[4]Institute for orthopedic surgery "Banjica", Belgrade, Serbia;
[5]Clinical Center of Serbia, Center for radiology and magnetic resonance, Belgrade, Serbia

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†**Correspondence to:**
Jelena ŠAPONJSKI
Center for nuclear medicine, Clinical Center of Serbia
Višegradska 26, 11000 Belgrade, Serbia
Email: **jelena.saponjski1@gmail.com**

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SUMMARY

Introduction Positron emission tomography with computed tomography using fluorine-18-labeled fluorodeoxyglucose (^{18}F-FDG PET/CT) is a hybrid diagnostic method based on the cell's glucose uptake detection, which correlates with the degree of disease activity. While other diagnostic procedures fail to evaluate functional tissue, ^{18}F-FDG PET/CT can be helpful in discovering active disease in patients with vascular graft infection.

Methods This cohort retrospective study included 22 patients (17 male, five female; aged 61.7 ± 16.1) with suspected vascular graft infection. Blood analyses, Computed tomography/ultrasound were performed in all patients. Degree of glucose uptake was evaluated visually and semiquantitatively using maximal standardized uptake value (SUVmax). Findings were considered positive if focal fluoro-deoxyglucose (FDG) accumulation was greater in vascular graft projection than other parts of the blood vessel and liver.

Results Sights of active disease were found in 19 patients (86%) (16 male, three female) in projection of implanted vascular grafts: six aortobifemoral (27%), four aortoiliac (18.2%), four of abdominal aorta (18.2%), two of thoracic aorta (9.1%), two femoral (9.1%), one femoropopliteal (4.5%) (SUVmax 7.9 $\pm$ 2.4). Two patients were considered true and one false negative- due to antibiotic usage, which reduces FDG uptake. PET/CT helped in treatment alteration of 12 patients, seven (31.8%) started new medicament therapy, five (22.7%) had a surgical graft replacement. Overall sensitivity of this method is 95%, specificity 100%, positive predictive value 100%, negative predictive value 66.6%, accuracy 95.4%.

Conclusion ^{18}F-FDG PET/CT is a useful diagnostic method in detection of active vascular graft infection with high diagnostic accuracy, which is important in avoiding unnecessary surgery and appropriate therapy planning.

Keywords: ^{18}F-FDG PET/CT; SUVmax; vascular graft; infection

САЖЕТАК

Увод Позитронска емисиона томографија са комјутеризованом томографијом користећи флуор 18-обележену флуордеоксиглукозу (*^{18}F-FDG PET/CT*) је хибридна дијагностичка метода базирана на детекцији ћелијског накупљања глукозе, који корелира са степеном активности болести. Док друге дијагностичке медоде немају могућност процене функције ткива, *^{18}F-FDG PET/CT* може бити од помоћи у откривању активне болести код пацијената са инфекцијом васкуларног графта.

Методе У овој кохортној ретроспективној студији је било укључено 22 пацијента (17 мушкараца, пет жена; година старости 61,7 ± 16,1) са суспектном инфекцијом васкуларног графта. Анализе крви, *CT*/ултразвук су урађени свим пацијентима. Степен преузимања глукозе је процењен визуелно и семиквантитативно користећи *SUVmax*. Налази су сматрани позитивним уколико је фокално појачано накупљање FDG било интензивније у нивоу васкуларног графта него у другим деловима крвног суда и јетри.

Резултати Активна болест је уочена код 19 пацијената (86%) (16 мушкараца, три жене) у нивоу уграђеног васкуларног графта: шест аортобифеморалног (27%), четири аортоилијачног (18,2%), четири (18,2%) абдоминалне и две (9,1%) торакалне аорте, две феморалног (9,1%) и једна феморопоплитеалног (4,5%) (*SUVmax* 7,9 $\pm$ 2,4). Два пацијента су сматрана стварно и један лажно негативним- услед коришћења антибиотика који смањују накупљање *FDG*. *PET/CT* је допринео даљем лечењу 12 пацијената, код седам (31,8%) је започета медикаментна терапија, а код пет (22,7%) хируршка замена графта. Свеукупна сензитивност ове методе је 95%, специфичност 100%, позитивна предиктивна вредност 100%, негативна предиктивна вредност 66.6%, тачност 95,4%.

Закључак *^{18}F-FDG PET/CT* је корисна метода у детекцији инфекције васкуларног графта са високом дијагностичком тачношћу, што је битно за избегавање непотребних операција и планирање одговарајуће терапије.

Кључне речи: *^{18}F-FDG PET/CT*; *SUVmax*; васкуларни графт; инфекција

INTRODUCTION

Cardiovascular disease is the leading cause of death worldwide [1]. Endovascular interventions rarely end up with infection, but in cases of infected prosthetic vascular graft, morbidity and mortality are high [2].

Infection and inflammation of cardiovascular system can be clinically presented by numerous nonspecific symptoms, which make them even more difficult to be recognized. Right diagnosis is made based on blood tests, hemoculture, ultrasound, and Computed tomography (CT) [3, 4]. The most common causes of an infection are bacteria *Staphylococcus aureus*, Methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella* and *Enterococcus* [5, 6]. Medicament treatment implies elimination of an infective agent by various antibiotics (Tetracycline, Methicillin, Penicillin), but the treatment of choice for graft infections is surgical removal and graft replacement [7, 8], which is why an accurate diagnosis is important to avoid unnecessary surgery.

Nowadays, positron emission tomography with computed tomography using fluorine-18-labeled fluorodeoxyglucose (^{18}F- FDG PET/CT) is used to assess the sights of an increased metabolism of glucose, such as in neoplastic cells, which is why Positron emission tomography – Computed tomography (PET/CT) is mostly used in oncology [9, 10]. However, PET/CT can identify the source of an infection or inflammation relying on its ability to recognize functional changes of the tissue, unlike radiologic modalities, which evaluate only morphology [11, 12]. Therefore, our aim was to evaluate the importance of ^{18}F-FDG PET/CT in patients with suspected vascular graft infection, to detect a cause and the extent of active disease.

METHODS

Patients

In this cohort retrospective study were included 22 patients (17 male and five female; aged 61.7 ± 16.1) with persistent systemic manifestations (fever, weakness, chills, muscle pain), who were referred to ^{18}F-FDG PET/CT examination, to National PET Center of Clinical Center of Serbia, in the period between September 2012 to June 2018, to confirm vascular graft infection. Biochemical blood analyses, hemoculture, CT and ultrasound were performed in all patients. Inclusion criteria and indications for ^{18}F-FDG PET/CT scan were: suspicion of a recurrent cardiovascular infection, positive medical history of graft implantation, fever of unknown origin, positive hemoculture and blood analyses (elevated C-reactive protein, sedimentation), as well as the patients with follow up of at least six months. The criteria for exclusion were blood glucose level above 11 mmol/l, application of corticosteroid therapy, the existence of malignant disease and recent chemo/radiotherapy.

^{18}F-FDG PET/CT examination

A 64-slice hybrid PET/CT (Biograph, TruePoint64, Siemens Medical Solutions, Inc. USA) was used for scanning, which was initiated one hour after intravenous injection of fluorine-18 labeled fluorodeoxyglucose. Imaging was performed from the base of the skull to the mid tights, by non-contrast-enhanced low dose CT and PET. CT, PET and fused PET/CT images were then demonstrated for interpretation on the workstation. Level of metabolic activity was analyzed visually and semiquantitatively using the maximal standardized uptake value (SUVmax), which was calculated according to the patient's weight and radioactivity admitted. ^{18}F-FDG PET/CT findings were found to be positive in cases of focal glucose uptake that is higher in a projection of implanted vascular graft than the accumulation in other parts of the blood vessel and liver.

Findings of ^{18}F- FDG PET/CT examination were compared to the bacterial culture results of an infected vascular graft from surgery, biochemical parameters, other diagnostic methods (CT/ US) and therapy response during clinical follow-up six months after PET/CT scan.

Statistical analyses

The results were showed as mean ± standard deviation (SD). The ^{18}F-FDG PET/CT and CT/US diagnostic values were calculated by specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV) and accuracy.

This study was done in accord with the standards of the institutional Committee on Ethics.

RESULTS

Sights of pathological FDG uptake were found in 19 out of 22 patients (86.4%) (16 male and three female), which were considered true positive. Increased metabolism was showed in a projection of implanted vascular grafts: six aortobifemoral (27%), four aortoiliac (18.2%), four of abdominal aorta (18.2%) (Figure 1), two of thoracic aorta (9.1%), two femoral (9.1%) and one femoropopliteal (4.5%) (Figure 2). Mean SUVmax value of an active disease was 7.9 $\pm$ 2.4 (Table 1). Out of 19 true positive patients, 13 (68.4%) had manifested symptoms such as fever, swelling and pain of the limb affected, weakness and 11 (57.9%) had leukocytosis and elevated C-reactive protein.

Out of three negative patients, two were considered true negative and one was false negative – due to antibiotic usage in a period of examination, which reduces FDG uptake.

PET/CT helped in a treatment alteration of 12 patients, 7 (31.8%) started a new medicament therapy (antibiotic) and 5 (22.7%) had a surgical graft replacement during which

infective agent was proved (Staphylococcus species) and seven patients remained on the same therapy as the disease was still active on PET/CT (Table 2).

Only four patients (three men and one woman) had a control ^{18}F-FDG PET/CT to evaluate a therapy response. Recurrent disease was found in two patients after the antibiotic interruption.

Results of other radiological modalities (CT and US) failed to detect graft infection in 14 patients (63.3%). In seven patients (31.8%) the results correlated to PET/CT, five (22.7%) were true positive and two true negative. Calculated sensitivity of CT is very low 26.3% and specificity 66.7%. While overall sensitivity of PET/CT is 95%, specificity 100%, positive predictive value 100%, negative predictive value 66.6%, accuracy 95.4%.

DISCUSSION

Mortality of vascular graft infection has high rates, which is why the appropriate diagnosis is a priority, especially when infection is asymptomatic. Because of the high glucose uptake of inflammatory cells, FDG PET/CT is an appropriate tool to use in detecting suspected inflammation and infection [13].

Diagnostic tool of choice in a progressive vascular graft infection is CT; however, the frequency of false negative results is relatively high which is why FDG PET/CT was introduced as an alternative modality for infectious lesions [14]. In our study, 63.6% of findings were false negative on CT, in comparison to one false negative on PET/CT. This can be explained by the fact that both sensitivity and specificity of CT decrease in chronic infection [4, 15].

False-negative finding in one patient was a result of antibiotic therapy used in a period of PET/CT examination. In a study of Guenther et al. [16], one patient was also considered false negative for the same reason, while 80% of other patients had been treated with

antibiotics prior to PET/CT. Antibiotics reduce inflammation and accumulation of radiopharmaceutical, which can undermine the diagnostic accuracy. In addition, subacute and low-grade infections may also be problematic to interpret, which is why it is important to take everything into account – clinical, biochemical and diagnostic findings in the final conclusion [17].

The results of our study show high sensitivity 95% and specificity 100% of FDG PET/CT in detection of vascular graft infection, similar to those in the paper of Keidar et al. [18], who reported sensitivity of 93% and specificity of 91%, as well in other papers [19, 20]. In some studies specificity may vary, which can be explained by physiological uptake in postoperative inflammation, healing tissue or chronic inflammatory reactions induced by the graft [15, 16, 21]. FDG PET/CT had better diagnostic performance than CT in this study [4, 22].

One of this study's exclusion criteria was high glucose level, over 11 mmol/L. However, a study by Rabkin et al. [23] proved that hyperglycemia might reduce the sensitivity of FDG PET/CT but in cases of malignancy, while in those with infection/inflammation no meaningful impact on the false negative results was found.

Symptoms and elevation of inflammatory parameters do not have to be presented in all of the patients with an infected vascular graft. In this study, out of 86.4% positive patients on FDG PET/CT, 57.9% had leukocytosis and elevated C-reactive protein. In a study by Wassélius et al. [24] was reported that CRP was normal or discretely elevated in 13 out of 15 patients and vascular graft infection was confirmed in only one patient

FDG PET/CT helped in treatment alteration of 63.2% of the patients, who started a new antibiotic therapy or had a surgical graft replacement, while other patients with still active disease did not interrupt further treatment. PET/CT is a tool that can help to avoid unnecessary surgery and contributes to the optimal treatment [15, 25].

CONCLUSION

According to our results, ^{18}F-FDG PET/CT is a useful diagnostic method in the detection of active vascular graft infection with high diagnostic accuracy. This is very important in avoiding unnecessary surgery, appropriate therapy planning and in the assessment of therapy effectiveness. It was proven superior to CT, because of its ability to evaluate morphology and functional tissue using SUVmax, which gives an objective assessment of sights and level of the disease activity. However, FDG PET/CT has a limited role in detection of active vascular graft infection in patients who are treated with antibiotics.

Conflict of interest: None declared

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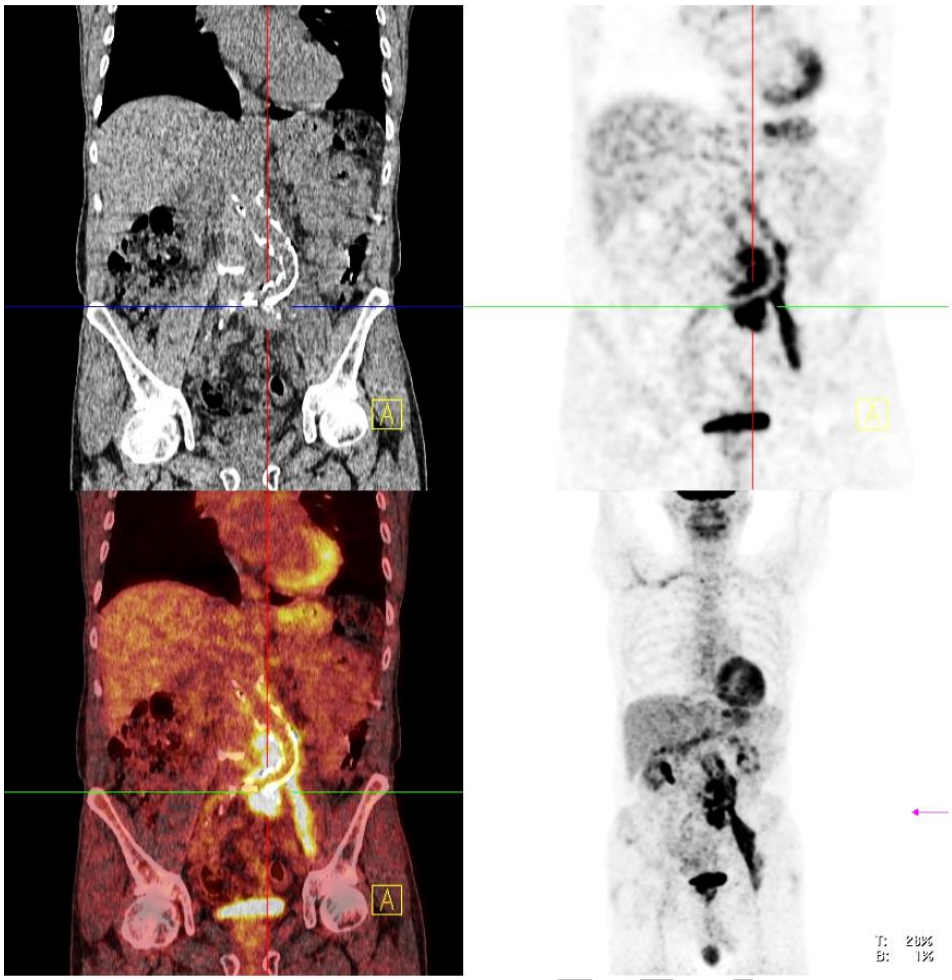

Figure 1. Coronal plane of unenhanced low dose CT, PET, fused PET/CT and MIP (maximal intensity projection). Focally increased uptake of FDG is seen in a projection of soft tissue lesions along vascular graft of abdominal aorta (SUVmax 9.3).

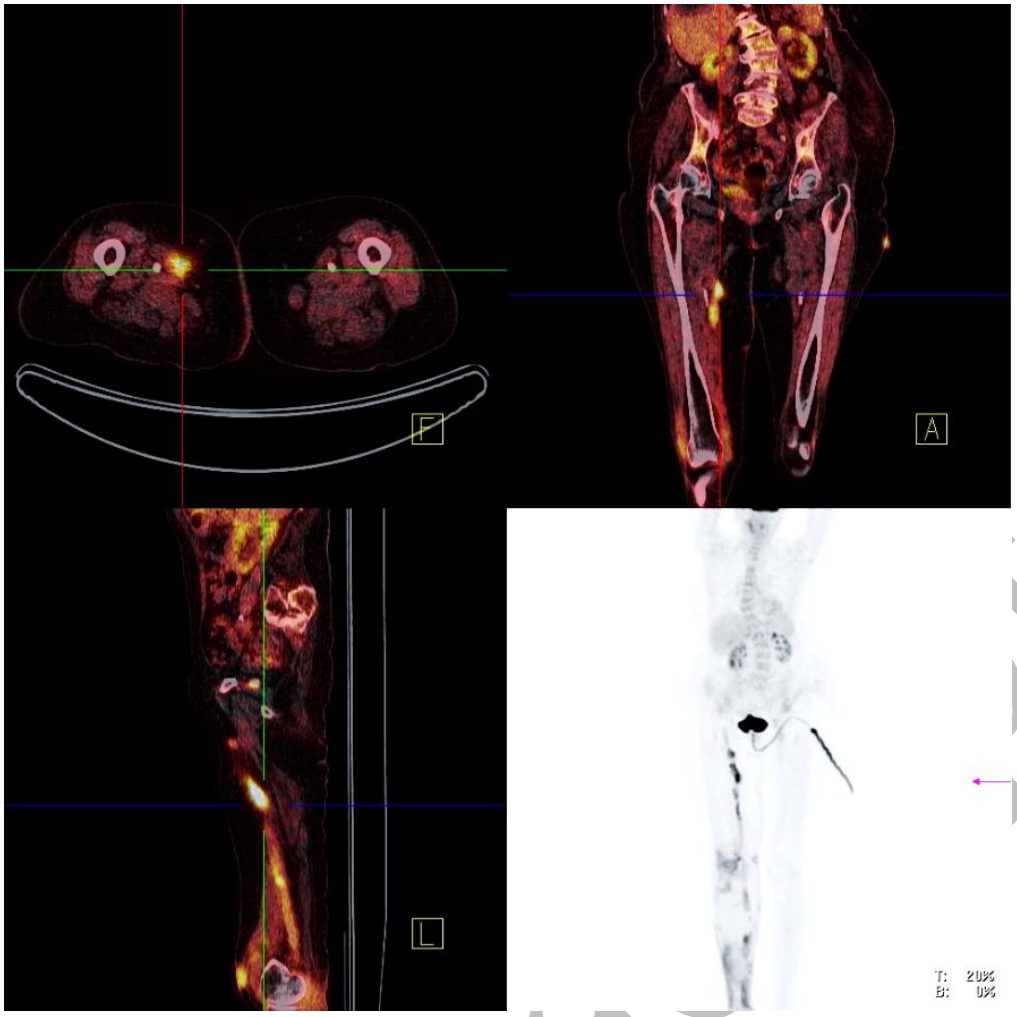

Figure 2. Transversal, coronal, and sagittal plane of FDG PET/CT and MIP (maximal intensity projection). Focally increased accumulation of FDG is showed in a projection of right femoropopliteal vascular graft (SUVmax 6.1).

Table 1. Average values of SUVmax based on PET/CT finding

Parameters	**True positive**	**True negative**	**False negative**
n (%)	19 (86.4%)	2 (9.1%)	1 (4.5%)
SUVmax ± SD	7.92 ± 2.40	1.1 ± 0.2	1.9

SUVmax – maximal standardized uptake value; SD – standard deviation.

Table 2. Number of patients who received a new treatment or prolonged with the same therapy after 18F- FDG PET/CT examination

Parameters	**Antibiotics**	**Surgery**	**Total**
New treatment	7	5	12
No change in treatment	7	0	7
Total	14	5	19

