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INVITED REVIEW

FDG-PET/CT Imaging of Large Vessel Vasculitis

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ABSTRACT

Large vessel vasculitis (LVV) is a heterogeneous group of disorders characterized by inflammation of large and medium-sized blood vessels. When not properly diagnosed and treated, it may lead to severe morbidity due to ischemic events. ^{18}F-florodeoxyglucose (FDG) PET/CT can be helpful in the assessment of disease activity before treatment as well as monitor therapeutic effect or detect relapse of the disease. Proper preparation of the patients before FDG-PET scan and standart interpretation methods are crucial part of the evaluation. New technologies like whole body and digital PET or new PET radiotracers may further increase the clinical value of PET imaging.

INTRODUCTION

Large vessel vasculitis (LVV) is defined as inflammation of large arteries. It usually involves the internal and external carotid arteries, aorta, and its main branches more centrally in the thorax [1]. Takayasu arteritis (TA) and giant cell arteritis (GCA) are the two main forms of vasculitis. Although they share some common features, TA and GCA are different diseases with different ages of onset, ethnic distribution, immunogenic background, distribution, and therapy response. TA generally affects the aorta and its branches, but GCA affects cranial arteries[2] as well as the aorta. These vasculitides may also co-exist with other rheumatological diseases. GCA and polymyalgia rheumatica (PMR) often coexist in the same patient. PMR can be seen in half of the patients with GCA, while approximately 20% of patients with PMR have concomitant GCA [3]. These vasculitides have important outcomes that lead to severe morbidity and mortality, therefore, appropriate treatment is necessary [4]. Optimal vasculitis imaging is critical to solve clinical dilemmas and avoid disease-related complications. Imaging with ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) are routinely used to identify the source of inflammation. However, these modalities lack enough specificity and accuracy. Metabolic imaging of LVV with ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) combined with CT or MRI helps in the diagnosis and follow-up of inflammation [5]. It acts as a clinical problem-solving tool in the difficult scenarios of inflammation and is recommended by several organizations like the American College of Radiology [6-8].

In this paper, imaging of large vessel vasculitis is described in the following topics; FDG-PET imaging procedure, patient preparation, mechanism of action, imaging features and clinical value of FDG on disease course, and future aspects.

^{18}F-FDG Imaging

FDG is a positron-emitting radiotracer that behaves similarly to the human body's glucose. The radiotracer enters the cell via glucose transporters (GLUTs); it is phosphorylated and no longer metabolized [9,10]. Positron emission of trapped FDG in the cell enables PET imaging, thus leading to visualization of tissues' glucose metabolism [10]. Active inflammatory cells, especially macrophages, in inflamed arterial walls and synovia/bursa show increased glucose metabolism and FDG uptake [11].

Table 1. Patient preparation for FDG-PET/CT

Dietary preparation	Fast for at least six hours before FDG administration
Blood glucose levels	Preferably <126 mg/dL for non-diabetic and <200 mg/dL) for diabetic patients
Drugs	Glucocorticoids: Withdraw or delay therapy until after PET unless there is a risk of ischemic complications. FDG-PET within three days after the start of GC is optional as a possible alternative
PET acquisition	Patient positioning: Supine, arms next to the body Scan range: Whole body (Head down to the feet) Scan duration 3D: 2–3 min/bed position Dose of FDG injection: 3-5 MBq/kg body weight Incubation time after FDG injection: Standard 60 min PET/CT: Low-dose non-contrast CT for attenuation correction and anatomical reference.

FDG uptake of tissues is directly related to glucose metabolism and some patient characteristics also interfere with FDG uptake, so optimal patient preparation is crucial (Table 1). The optimal biodistribution of FDG depends on blood insulin and glucose levels. Patients must be fasting for at least 6 hours before FDG injection, and measured blood glucose levels should be <126 mg/dL for non-diabetic patients and <200 mg/dL for diabetic patients. In addition, strenuous physical activities should be avoided within 24 h before FDG administration to avoid muscle uptake. After administration of FDG, patients should relax in an adequately temperature-controlled room to minimize physiologic uptake in muscles and brown fat [11]. In some cases, FDG uptake in brown fat can be reduced by beta-blocking drugs, e.g., orally administered 20 mg propranolol one h before FDG injection.

Glucocorticoids (GC) may reduce vascular wall uptake of FDG; the available data regarding the effect of GC withdrawal on FDG uptake are scarce. Nielsen et al. recently confirmed that diagnostic accuracy of LVV with FDG-PET remained for three days after initiation of GC. After three days, a significant decrease in radiotracer uptake was detected. If active LVV is suspected, FDG-PET/CT should be performed before GCs are started in case of no ischemic complication risk or within the first three days of treatment [12].

Before PET scan, patients wait for 60-90 min. to get enough uptake and reduce the background blood pool activity after the injection. The patient must be well hydrated and void before scan.

The PET scan from vertex to feet takes around 15 to 20 minutes. At the same time, CT or MRI sections are also obtained. After the scan, no isolation for radiation protection is required [11,13-16].

For FDG-PET/CT imaging, a low-dose non-contrast CT must be performed for attenuation correction and anatomical localization. Alternatively, a diagnostic contrast-enhanced CT may be performed according to applicable local protocols and guidelines. If intravenous contrast is going to be used, renal function tests must be checked to avoid toxicity.

Special imaging techniques could be performed to increase the accuracy of FDG-PET. The detection of smaller vascular structures in the head and neck region can be improved by increasing the acquisition time and matrix size per bed position [17].

Imaging inflammation

The pathophysiology of inflammation is quite complex. In theory, there are many molecular pathways to target for imaging. At inflammatory focus, inflammatory cells like macrophages, neutrophils, and monocytes upregulate in their GLUT transporters, thus showing increased glucose metabolism. FDG-PET can non-invasively detect this increased population of inflammatory cells with increased glucose metabolism [6,7,9,10].

FDG-PET has been used for several etiologies of inflammation. Infective endocarditis, IgG4 related disease, osteomyelitis, and large vessel vasculitis are major indications of FDG-PET. Two forms of large vessel vasculitis, TA and GCA, can be imaged by FDG-PET scan [7,8,11,18-20].

Large Vessel Vasculitis and ^{18}F-FDG PET/CT

TA and GCA generally affect medium-large vessels like the aorta and its branches, referred to as large

Table 2. Main findings of available meta-analyses on the diagnostic accuracy of FDG-PET in patients with large-vessel vasculitis

LVV	Publication	Studies included	Number of patients	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio	Negative likelihood ratio	AUC
GCA	Lee et al. [24] 2016	3	66	83.3 (72–91)	89.6(80–96)	7.10(2.91–17.36)	0.2(0.11–0.34)	0.88
	Soussan et al. [23] 2015	4	57	90 (79–96)	98(94–99)	28.7(11.5–71.6)	0.15(0.07–0.29)	0.98
	Besson et al. [46] 2011	6	101	80 (63–91)	89(78–94)	6.73(3.55–12.77)	0.25(0.13–0.46)	0.84
TA	Soussan et al. [23] 2015	7	191	87 (78–93)	73(63–81)	4.2(1.5–12)	0.2(0.1–0.5)	0.91
	Cheng et al. [25] 2013	6	76	70.1(58.6–80)	77.2(64.2–87.3)	2.31(1.11–4.83)	0.34(0.14–0.82)	0.805
LVV	Lee et al. [24] 2016	8	170	75.9(68.7–82.1)	93(88.9–96)	7.27(3.71–14.24)	0.3(0.23–0.4)	0.86

vessel vasculitis [2]. On conventional imaging with MRI or contrast-enhanced computed tomography (CECT), thickening of the vessel wall or aneurism formation can be seen [21]. Anatomic imaging can not give adequate functional data about disease activity [8]. Molecular and functional imaging helps in these clinical situations. One of the recent meta-analyses showed FDG-PET/CT has a sensitivity and specificity of 88% (95% CI: 79–93) and 81% (95% CI: 64–91)[22] (Table 2). The diagnostic performance of FDG-PET was higher for the detection of GCA than TA (87% vs. 58%, respectively; $p < 0.0001$)[23,24] Similarly, in a meta-analysis of four pooled studies, for the diagnosis of patients with GCA, FDG-PET demonstrated high pooled sensitivity (90%) and specificity (98%), without significant heterogeneity [23].

In TA, FDG-PET demonstrated pooled sensitivity of 87% and specificity of 73% for the assessment of disease activity in a recent meta-analysis of seven studies including 191 patients with TA, with significant heterogeneity [23]. These findings are in line with a previous meta-analysis including TA patients evaluated by FDG-PET, showing pooled sensitivity and specificity of 70% and 77%, respectively [25]. The specificity of FDG-PET increased to 84% when considering studies using National Institutes of Health (NIH) criteria [26] as the disease activity assessment scale [23]. Visual analysis showed that high FDG uptake correlated well with the presence of markers of disease activity in TA, but vascular uptake was observed in up to 67% of TA patients without markers of activity [23]. Another meta-analysis showed FDG performance is related to serum acute phase reactants (APR) like C-reactive protein and also FDG uptake is an independent biomarker [27,28]. However the sensitivity and accuracy of the FDG-PET are impaired in patients under GC and/or immunosuppressive treatment at the time of imaging [23].

Imaging Features of LVV

A standardized evaluation and a common language between disciplines were created for the interpretation of FDG-PET images. These are qualitative and semiquantitative, but a combination of them by nuclear medicine physicians makes interpretation more accurate (Table 3). Slart et al. proposed using 0-to-3 grading system as follows "0 = no uptake (≤ mediastinum); 1 = low-grade uptake (< liver); 2 = intermediate-grade uptake (= liver), 3 = high-grade uptake (> liver), with grade 2 possibly indicative and grade 3 considered positive for active LVV" [29].

Also, a total vascular score can be calculated from seven different locations: thoracic aorta, abdominal aorta, subclavian arteries, axillary arteries, carotid arteries, iliac arteries, and femoral arteries. Scoring of these regions from 0-to-3 is: 0 for negative, 1(mild), 2 (moderate), and 3 (high) for positive (see Figure 1-2) [29]. Additionally several semiquantitative methods have also been proposed, from simple standard uptake value (SUV) metrics to target-to-background ratios (TBR) (Table 3). The clinical utility of SUV or TBR for the initial diagnosis of LVVor PMR is currently unvalidated and not routinely recommended. However, their relevance for recurrence or follow-up evaluation may be a matter of further research [30].

Table 3. Recommended PET interpretation criteria

For clinical use	Grade 0: No vascular uptake (≤ mediastinum) Grade 1: Vascular uptake < liver uptake Grade 2: Vascular uptake = liver uptake, may be PET-positive Grade 3: Vascular uptake > liver uptake, considered PET-positive
PET semiquantitative analysis*	Target: Average SUVmax artery of the vascular ROIs Blood pool: Average SUVmean of several vein ROIs TBR = average SUVmax artery / average SUVmean vein Liver: SUVmax of a liver region, preferably the right lobe TBR = average SUVmax artery / SUVmax of a liver region
Vascular targets:	- Carotid arteries - Subclavian arteries - Axillary arteries - Vertebral arteries - Ascending aorta - Aortic arch - Pulmonary arteries - Descending aorta - Abdominal aorta
Joints:	Scapulae and pelvic girdles, knees, cervical and lumbar interspinous bursae, trochanteric and ischial bursae

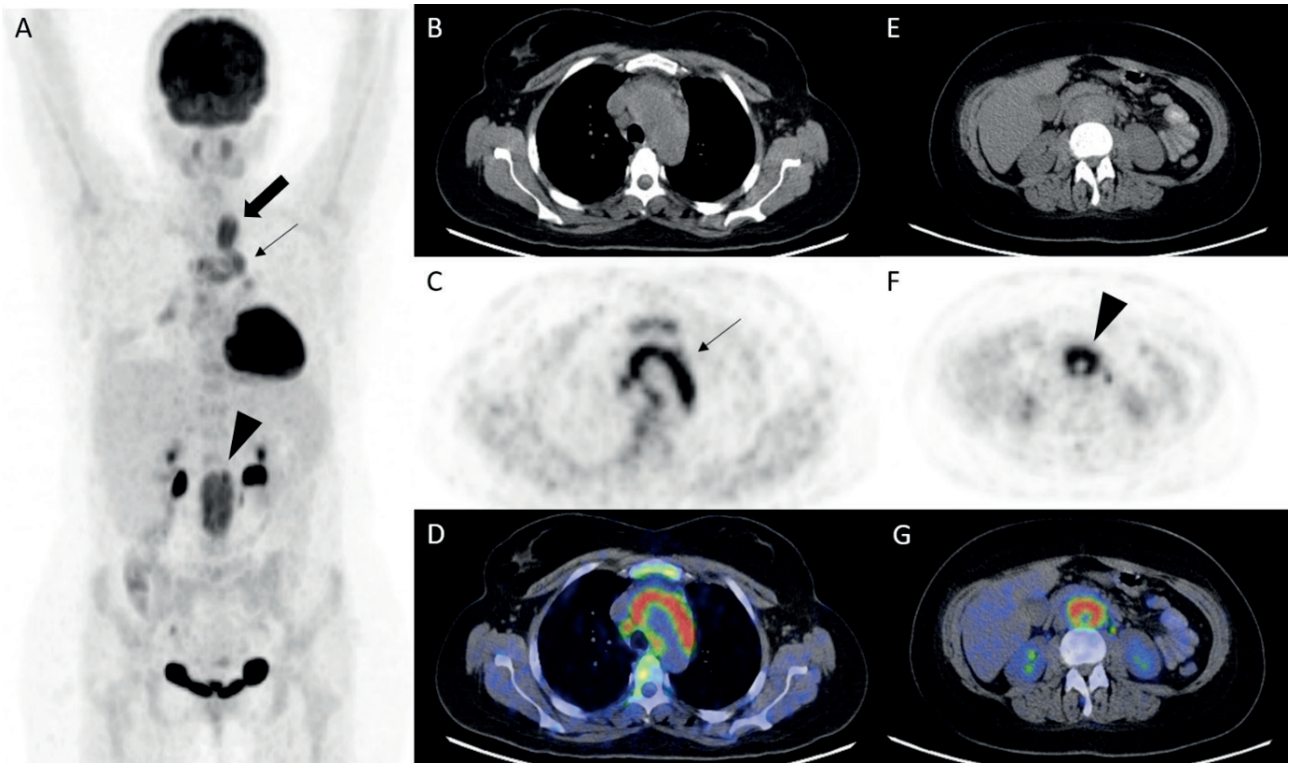

Figure 1. The maximum intensity image(a) and axial CT, PET and PET/CT fusion images showing FDG uptake of left subclavian artery (a, thick arrow), arcus aorta (a, b, c, d thin arrow) and abdominal aorta (a, e, f, g arrowhead). Grade 3 LVV with marked vessel wall FDG uptake greater than liver; total vascular score of this patient is 9 (left subclavian artery, 3 points; thoracic aorta, 3 points; abdominal aorta, 3 points). Ratio of SUVmax(thoracic aorta/liver) is 3.2.

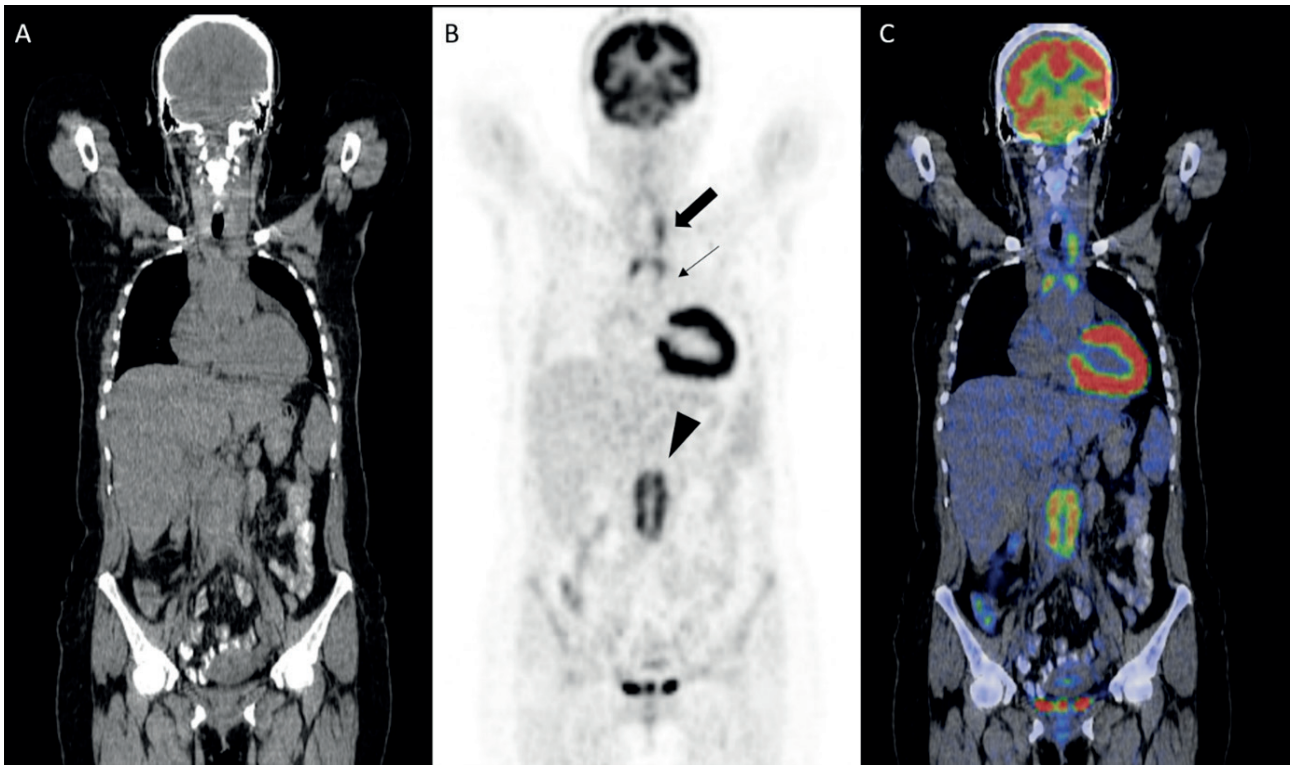

Figure 2. The coronal CT(a), PET(b) and PET/CT fusion(c) images showing FDG uptake of subclavian artery (thick arrow), thoracic aorta (thin arrow) and abdominal aorta (arrowhead).

In general, FDG-PET classically appears as a smooth linear pattern involving the aorta and its main branches (subclavian, carotid or vertebral arteries, pulmonary arteries specifically in TA), but not all main branches have to be involved. Arterial wall uptake must be higher than venous blood pool activity [31,32].

Frequencies of affected vessels detected with FDG-PET/CT are subclavian artery, aorta, iliac and femoral artery, decreasing order 74%, 50%, and 37%, respectively [33].

Special care must be taken for the atheromatous vessel walls, which might be a source of false-positive findings. Despite a classical patchy uptake pattern, atherosclerotic vascular uptake which is frequent with aging may be a source of false positivity for LVV evaluation. Uptake in iliofemoral arteries should be interpreted cautiously because this is a frequent site of atherosclerosis [34]. Generally, intraabdominal and pelvic vessels are affected by atherosclerosis, and supradiaphragmatic vessel uptake is more specific for LVV [35-37]. As stated above, GCA may also co-occur with other rheumatological diseases. As PMR and GCA frequently overlap, typical FDG joint uptake patterns, especially in pelvic and scapular girdles should be reported [29,38].

Follow up and Prognosis

Generally, there is certain decrease in FDG uptake of arterial walls in correlation with patient symptomatology and signs of disease activity. With the data from RIGA study, Schonau et al. showed that follow up of LVV with FDG-PET/CT is valuable. Symptoms and AFRs sometimes can be non-specific but FDG-PET/CT correlates with disease activity [39]. It is reported that complete normalization of vessel walls after treatment occurs [40]. And also, high uptake after initial therapy is related with refractory and/or relapsing vasculitis [37]. But 25% of the patients showed residual mild FDG uptake on the vessel walls which may be related with vascular wall remodeling or smoldering vasculitis [37,41].

Since PET is a whole-body modality, despite its cost, using it for diagnosis and follow-up helps clinicians to control the disease activity in all main vessels simultaneously. This may lead to changes in clinical management that, hopefully, result in patients' benefit.

Future Perspectives

As technology improves logarithmically, new devices and new tracers come into use. Long axial field-of-view total-body PET/CT systems are

changing the paradigm nowadays. Total-body PET is a cutting-edge device that increases the sensitivity of scan around 40-fold while reducing scan time, allowing whole-body dynamic imaging that offer simultaneous angiography [42,43]. New PET/MRI systems use digital PET technology, which increases the resolution and sensitivity of the PET scan. Combined MR angiography and digital FDG-PET data may decrease equivocal cases [21,44].

New tracers also may take place in inflammation imaging. Fibroblast-activation-protein inhibitors (FAPI) are a member of the serine proteinase family that bind cancer-associated fibroblast, which is also found in chronic inflammation sites. Wu et al. showed a patient whose FDG scan was normal but overt FAPI positive vessel walls diagnosed as TA. FAPI PET is promising for imaging inflammation as well as malignancy [45].

CONCLUSION

FDG-PET/CT has an important role in diagnosing and following patients with large vessel vasculitis. Optimal preparation of patient and standard interpretation of FDG-PET-CT are crucial. Further prospective studies involving large cohorts of vasculitis are needed to investigate and validate the role of PET.

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