

## Review Article

# The role of <sup>18</sup>F-fluorodeoxyglucose PET/computed tomography in the diagnosis and monitoring of large vessel vasculitides - a review article

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**Abstract:** In the last two decades, advancements in positron emission tomography (PET) technology have increased the diagnostic accuracy of patients with large-vessel vasculitis (LVV). Numerous systematic reviews and meta-analyses have been conducted, and patients suspected of having LVV can be diagnosed earlier with <sup>18</sup>F-FDG PET. Two subtypes, giant cell arteritis (GCA) and Takayasu arteritis (TA), will progress when their response to corticosteroids and enhanced immunosuppression is inadequate. In the majority of patients, disease activity cannot be monitored solely through laboratory procedures; consequently, glucose metabolism may be a source of potential biomarkers. In this article, we discuss the current state of <sup>18</sup>F-FDG PET/CT imaging standards.

**Keywords:** PET scan, computed tomography, vasculitis

## Introduction

Vasculitis is a heterogeneous group of disorders characterized by inflammation and fibrinoid necrosis of blood vessel walls [1]. Large vessel vasculitis (LVV) is a disease predominantly affecting the large arteries and main branches. Pathologic specimens from patients show granulomatous infiltration of various inflammatory cells within the vessel walls of the thoracic and abdominal aorta and their branches [2-4]. Patients with LVV often present with non-specific clinical symptoms including fatigue, malaise, weight loss, anorexia, fever, and night sweats. Two subtypes, Takayasu arteritis (TA) and giant cell arteritis (GCA), are known. In most patients, the development of LVV is a progressive process that is an inefficient and impermanent response to treatment [5]. Diagnostic procedures including ultrasound, computed tomography (CT), magnetic

resonance imaging (MRI), and angiography often give inconclusive results in patients with LVV [6, 7].

Over the past few years, positron emission tomography (PET) imaging with the radiolabeled tracer <sup>18</sup>F-fluorodeoxyglucose (FDG), a glucose analogue, has emerged as a promising modality in the evaluation of patients with LVV [8]. The ability of <sup>18</sup>F FDG-PET/CT to detect early vascular inflammation, even before arterial narrowing occurs, and to monitor response to therapy contributed to the marked interest invested in this modality for LVV [9, 10].

This review will first present an overview of the pathophysiology and traditional investigation of LVV. Then, the technical aspects of <sup>18</sup>F FDG-PET/CT imaging for LVV will be briefly discussed, followed by a review of its diagnostic performances, prognostic value, and role in evaluation of response to therapy.

## Large-vessel vasculitis

### *Giant cell arteritis (GCA)*

GCA is a chronic idiopathic granulomatous autoimmune vasculitis affecting medium and large arteries. It is the most frequent cause of LVV, with a prevalence estimated between 1 and 33 cases per 100,000 persons, depending on geographical location and ethnicity. As opposed to TA, GCA affects patients over the age of 50 [11]. Large-vessel GCA (LV-GCA) is part of the GCA clinical syndrome, which comprises a spectrum of overlapping phenotypes, including cranial GCA, LV-GCA, and polymyalgia rheumatica (PMR) [12, 13]. Cranial GCA corresponds to the classical description of GCA, often referred to as temporal arteritis or Horton's disease, in which patients present with headaches, sudden changes in vision, and jaw claudication [14]. At the other end of the spectrum, PMR is characterized by peripheral musculoskeletal symptoms, such as arthritis involving the neck, shoulders, hips, and knees; morning stiffness; pitting edema; and tenosynovitis. LV-GCA tends to affect younger patients compared with cranial GCA and PMR, with a marked female predominance [15].

In all three phenotypes, acute-phase reactants and constitutional symptoms are often present. Importantly, the phenotypes are frequently overlapping, and large-vessel inflammation can develop in patients with apparently isolated PMR or cranial GCA [16]. In these patients, the prevalence of vascular complications is relatively high, emphasizing the need for large vessel inflammation screening, especially in PMR [17].

### *TAayasu's arteritis*

TA is a chronic idiopathic granulomatous autoimmune panarteritis affecting patients younger than 50 years old. TA is rare, with an estimated incidence of 1 case per million people per year [18]. It typically affects women of childbearing age and has a higher incidence in the Asian population [19]. In TA, the ascending aorta as well as the carotid, subclavian, renal, and splanchnic arteries are more frequently involved [20]. Coronary artery involvement is seen in 15 to 25% of cases. The disease is characterized by intimal hyperplasia, which leads to stenosis or occlusion in over 90% of cases, while aneu-

rysms are seen in roughly 25% of cases [21]. Two phases of TA arteritis have been described: the acute (systemic) and chronic (occlusive) phases. The acute phase is characterized by constitutional symptoms associated with active vascular inflammation. In the chronic phase, vascular morphological abnormalities cause signs and symptoms, such as absent or weak peripheral pulses, claudication, and blood pressure discordance between the arms [18]. The diagnosis of TA is usually delayed because of the non-specific presentation and low clinical suspicion, especially during the acute phase. Most frequently, the diagnosis is established during the chronic phase, once irreversible vascular damage has already occurred [22].

Interestingly, reports dating back to the 1970s suggest that TA, GCA, and PMR are different manifestations of the same disease. This hypothesis is based on several similarities between those diseases [23]. First, GCA/PMR and TA have overlapping histopathological features, making it impossible to distinguish the two on tissue sampling alone. In fact, differentiation between GCA/PMR and TA usually relies on patient's age. Second, all three conditions present with similar clinical manifestation and both show drastic response to steroid therapy. Finally, one condition might precede the other. Hence, the investigations of patients with suspicion of TA and GCA are very similar [24].

## The role of 18F FDG-PET/CT in LVV diagnosis

### *18F FDG-PET/CT*

FDG is a radioactive sugar labeled with the positron-emitting isotope fluorine-18. FDG is extensively used in oncology for the diagnosis and staging of numerous cancers. Additionally, it is used in a wide range of infectious and inflammatory disorders [10]. As a glucose analog, FDG crosses cell membranes with glucose transporter proteins (GLUT) before it is phosphorylated by glucose-6-phosphatase. Once phosphorylated, the FDG does not undergo further metabolism through the glycolysis pathway, as would glucose, and therefore accumulates in the cells [25].

FDG accumulation in tissue is proportional to glycolytic activity, which can be associated with the upregulation of GLUT, increased hexokinase activity, and reduced glucose-6 phosphatase activity.

tase activity. In inflammation, FDG accumulates mainly in macrophages due to their high glycolytic activity [26]. On histopathology, both GCA and TA are characterized by activated macrophage infiltration, which accounts for the accumulation of FDG in the inflamed vascular wall [27]. 18F FDG-PET/CT is a marker of active inflammation, as opposed to most imaging modalities, which show chronic morphological changes secondary to inflammation. Indeed, FDG accumulates in various inflammatory diseases before morphological abnormalities can be identified on CT and MRI [28].

### *Imaging protocol*

A fasting period of at least 6 h is necessary prior to radiotracer injection. Vigorous physical activity should be avoided during the 24 h preceding the test to avoid significant skeletal muscle uptake. Also, to minimize brown fat uptake, injection is performed in a temperature-controlled room, and warm blankets can be provided. Imaging is performed 60 to 120 min post FDG injection [29, 30]. At time of injection, a serum glucose level of 7 mmol/L or less is preferable. Higher serum glucose levels can result in greater blood pool activity, limiting the ability to visualize the vascular wall uptake. In the presence of significant blood pool activity, delayed images can be acquired 120 to 180 min post-injection and better visualize the vessel wall [31].

Whole-body PET/CT acquisition extending from the head to the knees is recommended. As there is significant overlap between GCA and PMR, identification of inflamed joints can be contributory to the diagnosis. Furthermore, whole-body imaging allows for identification of other pathology that could explain the symptoms of patients [32]. A detailed description of the recommended imaging protocol has been proposed in a recent joint procedural recommendation paper. In patients investigated for fever of unknown origin (FUO) or if myocardial inflammation or endocarditis is suspected, a myocardial suppression protocol should be used to minimize physiological myocardial uptake. If coronary vasculitis is suspected, in addition to the myocardial suppression preparation, an ECG-gated acquisition should be obtained to minimize the blurring of the coronary vessels due to cardiac motion [33].

### *Interpretation criteria*

On FDG PET/CT, LVV often presents as diffuse increased uptake affecting the aorta and its branches. Several interpretation criteria have been described to assess the presence of LVV. Some rely on visual interpretation while others use semi-quantitative or quantitative methods [34]. Quantitative methods were shown to be more specific but less sensitive compared with semi-quantitative approaches. Visual interpretation comparing vascular to liver uptake has been shown to have better diagnostic accuracy compared with various quantitative metrics [34, 35]. A standardized 4-point scale system comparing vascular uptake to liver uptake is recommended. When using this 4 point-scale system, the study is considered positive for LVV when uptake is greater than liver (grade 3); when uptake is equal to liver (grade 2), it is indicative of LVV. Uptake less than liver (grade 1) or completely absent (grade 0) is considered negative for LVV [34]. In addition to maximizing diagnostic accuracy, such standardized approaches have been shown to improve inter-observer agreement and facilitate comparisons of multiple studies [36].

### **The role of 18F FDG-PET/CT in GCA diagnosis**

GCA encompasses cranial and extracranial manifestations. Constitutional symptoms and elevated inflammatory markers are present in > 90% of cases, and patients may present with a fever of unknown origin as the initial symptom in 15% of cases [37]. Cranial manifestations such as headaches may present in two-thirds of patients. The most severe acute complication, visual loss, is described in around 20% of cases, but this has been reduced with early recognition of the disease and the use of temporal artery ultrasound [38]. Pseudomyalgia rheumatica (PMR) is the most common extracranial manifestation in GCA and occurs in 45-50% of GCA patients [39]. Clinical manifestations of large vessel involvement (limb claudication, thoracic pain) may develop in one-fifth of GCA patients [40].

A temporary artery biopsy (TAB) was initially recommended in every case of suspected GCA and was considered the gold standard. However, results are delayed, and a biopsy may be negative in up to 42% of patients with pre-

dominantly large vessel GCA (LV GCA) [41]. Temporal artery ultrasound has shown very good performance, with a pooled sensitivity of 77% and a pooled specificity of 96% as compared with the clinical diagnosis of GCA [42]. It is also cost-effective compared to TAB but remains limited to the exploration of the aorta and visceral arteries. Thus, it is the first-line recommended imaging technique for suspected predominantly cranial GCA. Nevertheless, TAB remains strongly recommended over imaging in the ACR 2021 guidelines [43]. Recently, the 2022 American College of Rheumatology/EULAR GCA classification criteria emphasized the use of 18F FDG-PET/CT as well as other investigative methods, such as ultrasound and MRI, for use in clinical practice. PET, MRI, and CT are equally proposed to detect large vessel inflammation in GCA in recommendations from different scientific societies: the ACR, EULAR, the British Society for Rheumatology, and the French Study Group for Large Vessel Vasculitis [44, 45].

18F FDG-PET/CT is also a useful imaging technique to assess large vessel involvement in patients with suspected GCA and negative TAB. In a retrospective study of 63 patients with suspected GCA and negative TAB, large vessel involvement with 18F FDG-PET/CT was observed in 14 patients (22%). The final diagnosis of GCA was based on the presence of clinical symptoms, laboratory results, imaging data compatible with GCA, and good response to corticosteroid therapy [46].

18F FDG-PET/CT may visualize inflammation of the larger arteries in patients with extracranial GCA, in whom the temporal artery is spared but there is involvement of the aorta and its branches [47]. 18F FDG-PET/CT is the best imaging examination in cases of an atypical clinical presentation with a broad differential diagnosis, as it is a very effective imaging technique to identify LVV when it is unexpected [48]. Detection of temporal artery inflammation was considered impossible on 18F FDG-PET/CT because of its anatomical location next to the FDG-consuming brain, its superficial location, and its small vessel diameter. However, more recently, visualization of temporal artery inflammation has been reported on the newest 18F FDG-PET/CT engines and is also correlating with cranial symptoms and histological findings compatible with GCA [49, 50]. FDG-uptake in

the larger arteries is very specific for vasculitis, but atherosclerosis may complicate the interpretation of 18F FDG-PET/CT images. Vasculitis is shown as a linear, smooth FDG uptake, in contrast to atherosclerosis, which has a spotty appearance, corresponding to the atherosclerotic plaques. FDG-uptake of the thoracic aorta and its main branches has a very high specificity of 95% to 100% for vasculitis. The specificity decreases to 70% to 80% when only the abdominal aorta or lower limb arteries are considered, because these vessels are more disposed to atherosclerosis. In GCA, symmetrical FDG-uptake is typically noted, and the arteries are affected bilaterally in equal measure. The vessels that are most frequently affected include the subclavian arteries (75%), the thoracic and abdominal aortas (50%), and the axillary, carotid, iliac, and femoral arteries (30-40%) [48]. When GCA is suspected, 18F FDG-PET/CT should be performed as soon as possible. The sensitivity and specificity of 18F FDG-PET/CT decrease after initiating treatment, and up to 50% of 18F FDG-PET/CT may become negative after 10 days.

Performing the 18F FDG-PET/CT imaging within 3 days after oral glucocorticoid initiation is warranted [51]. Moreover, there are no data on the sensitivity and specificity of 18F FDG-PET/CT after 3 days of high-dose intravenous corticosteroid administration, which is required in the case of visual disturbances [6].

### The role of 18F FDG-PET/CT in TA diagnosis

There is no gold standard for diagnosis of TA and artery biopsy is not routinely available. Diagnosis is mainly based on the presence of characteristic imaging of large arteries in young patients under 50 years with clinical signs and/or elevated inflammatory markers [52]. Patients with TA may present with vascular symptoms attributable to arteritis but also systemic symptoms or “non-vascular” symptoms. Systemic symptoms may precede the vascular phase and are non-specific. They encompass fever, skin manifestations, arthralgia, episcleritis. Also, TA may be associated with other inflammatory diseases, such as sarcoidosis, spondylarthritis, or Crohn disease [53]. TA predominantly affect subclavian and common carotid arteries but aorta and all its branches may be involved. The disease is often diagnosed during the vascular phase which results from vascular compli-

cations: stenosis in > 90% of cases, aneurysm in 20% of cases [34].

Appropriate imaging is the mainstay for the diagnosis of TA. Based on its performance to investigate mural inflammation and/or luminal changes and the young age of the patients, European guidelines recommend angio-MRI as the first line imaging option replacing angiography [54]. Moreover, to assess peripheral artery disease, French guidelines propose vascular doppler ultrasound to evaluate vessel wall morphology and blood flow [55]. Based on current clinical practice, recent 2022 ACR/EULAR classification criteria for TAayasu arteritis fully integrate evidence of vasculitis in the aorta or branch arteries confirmed by vascular imaging: CT/catheterbased/magnetic resonance angiography (MRA), ultrasound and PET [56, 57].

### **The diagnostic performance of 18F FDG-PET/CT**

In a meta-analysis of 21 studies totalizing 413 subjects, FDG PET imaging was shown to detect LVV accurately for both TA and GCA. The pooled sensitivity and specificity obtained for GCA were 90 and 98%, respectively. Pooled sensitivity and specificity were slightly lower in patients with TA, at 84% [58]. Another meta-analyses assessing the diagnostic accuracy of FDG PET/CT for both TA and GCA showed similar results with a pooled sensitivity and specificity of 83.9 and 92.4%, respectively [59]. These results have been confirmed in subsequent studies. For example, in a study comparing visual and semi-quantitative interpretation of FDG PET/CT in patients with LV-GCA, visual analysis alone was shown to be superior to other semi-quantitative methods. Using the standard visual interpretation comparing vascular uptake to liver activity, sensitivity and specificity were 83 and 91%, respectively. When excluding patients receiving glucocorticoid therapy, the sensitivity increased to 92%, while the specificity remained at 91% [60]. This can be explained in part by the ability of FDG PET/CT to normalize with effective therapy. In another study of FDG PET/CT for GCA, both visual and semi quantitative methods were equivalent with positive and negative predictive values greater than 92% [61].

Different hypotheses have been proposed to account for the slightly lower accuracy of FDG PET/CT in TA. For instance, in TA, vascular

inflammation is predominant in the early phase of the disease, and patients presenting during the chronic phase might have morphological abnormalities, such as stenosis and aneurysm with minimal to no inflammation [34]. In those cases, FDG PET/CT will be considered a false-negative study, while in fact, there is no active inflammation to be detected. On the other hand, increased vascular uptake is sometimes observed in subjects without biological or clinical evidence of active disease. Although they are considered to be false positive studies, a subset of these cases likely represent early disease. Indeed, the diagnostic gold standard used in most studies is the ARC criteria, which are positive late in the chronic phase of the disease process as discussed above [34, 62]. Because macrophage accumulation in the vascular wall occurs early in the pathophysiology of LVV, before ARC criteria are met, FDG PET/CT can detect disease that does not meet the gold standard definition of the disease [34, 62].

### **18F FDG-PET/CT versus other imaging**

Prior to the accessibility of PET scanners, molecular imaging of LVV was performed with SPECT radiopharmaceuticals. FDG PET/CT was shown to be significantly more sensitive to detect vascular inflammation compared with SPECT radiotracers, such as 67gallium-citrate and white blood cells labeled with 99mTc or 111In [25]. At present, where available, FDG PET/CT is the molecular imaging modality of choice and recommended for investigation of LVV.

In patients imaged for initial diagnosis of GCA, both computed tomography angiography (CTA) and FDG PET/CT were shown to be able to detect the presence of LVV with excellent concordance and high sensitivity and specificity [63]. However, on per segment analysis, FDG PET/CT detected a significantly higher number of involved vascular territories compared with CTA [33]. While sensitivity of the two modalities was comparable for the aorta, FDG PET/CT was superior at evaluating disease extent with higher sensitivity for detection of aortic branch involvement [63]. Similar results were obtained in small studies, showing higher sensitivity of FDG PET/CT compared with MRA [64, 65]. In a recent larger prospective study comparing MRA and FDG PET/CT, the two modalities were shown to yield complementary information on the disease status; FDG PET/CT provides infor-

**Table 1.** Comparison of sensitivity and specificity rates of index tests in different studies

Study	Year	Study type	Study population	Mean of age, year $\pm$ SD	Type of LVV	CRP/ESR available	Reference standard	Index test	Performance
Blockmans et al.	2000	Retrospective	69	69 $\pm$ 9	GCA	Yes	Clinical criteria and positive TAB	Visual intensity of FDG uptake	Sensitivity: 56% Specificity: 98% PPV: 93% NPV: 80%
Soussan et al.	2015	Meta-analysis	127	55.4 $\pm$ 11	GCA	Yes	ACR criteria or positive TAB	Visual intensity of FDG uptake	GCA: Sensitivity: 90% Specificity: 98% PRL: 28.7 NRL: 0.15
Lariviere et al.	2016	Prospective	24	72.7 (51-85)	GCA	Yes	Positive TAB	Visual intensity of FDG uptake	Sensitivity: 66% Specificity: 100% PPV: 100% NPV: 64%
Sammel et al.	2019	Prospective	64	69 (50-90)	GCA	Yes	Positive TAB	Visual intensity of FDG uptake	Sensitivity: 92% Specificity: 85% PPV: 61% NPV: 98% AUC: 88%
Santhosh et al.	2014	Retrospective	51	30 $\pm$ 12	TA	Yes	ACR criteria	Intensity of FDG uptake	Sensitivity: 83% Specificity: 90%

PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio; AUC, area under the curve; TAB, temporal artery biopsy.

mation on the disease activity, while MRI provides information on vascular damage [66]. Because FDG PET/CT findings relate to an earlier and different stage of the disease, it should be viewed as complementary to other imaging modalities rather than an alternative [66, 67]. Finally, FDG PET/CT is able to accurately detect other causes of systemic symptoms. Because patients investigated for LVV often have non-specific clinical presentations and systemic symptoms, underlying infection or neoplasia remains a possible diagnosis, which can be identified with whole-body FDG PET/CT. The studies are summarized in **Table 1**.

### Conclusion

In patients with a suspicion of vasculitis, functional imaging has become part of the standard of care. Vasculitis encompasses a broad spectrum of diseases, including GCA and TAK, which have been intensively researched over the past decade. In patients with a clinical suspicion of LVV, 18F-FDG-PET/CT may be helpful in the diagnosis of LVV, particularly in cases of early disease onset or non-specific symptoms. Prior to steroid therapy, irreversible ischemic complications (e.g., stroke, vision loss, myocardial infarction) almost always manifest in the early stages of LVV. In addition, the presence of 18F-FDG-PET/CT activity in the vasculature can precede angiographic change and progression

in the LVV. However, prospective and multicentric investigations are required to strengthen the role of functional and metabolic imaging across the broad spectrum of vasculitis and associated disorders.

### Disclosure of conflict of interest

None.

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