

REVIEW

PET/CT IMAGING IN AUTOIMMUNE DISORDERS

The role of PET/CT in large vessel vasculitis and related disorders: diagnosis, extent evaluation and assessment of therapy response

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ABSTRACT

Large vessel vasculitides (LVV) are defined as chronic inflammatory disorders that affect the arteries with two major variants being distinguished: giant cell arteritis (GCA) and Takayasu's arteritis (TAK). These often present with nonspecific constitutional symptoms which makes an accurate diagnosis often challenging. Nevertheless, timely diagnosis is of utmost importance to initiate treatment and to avoid potential life-threatening complications. [¹⁸F]FDG-PET/CT is nowadays widely accepted as useful tool to aid in the diagnosis of large vessel vasculitis. However, its role to monitor disease activity and to predict disease relapse during follow-up is less obvious since vascular [¹⁸F]FDG uptake can be detected in the absence of clinical or biochemical signs of disease activity. In addition to the two major variants, [¹⁸F]FDG-PET/CT has shown promise in (peri-)aortitis and related disorders. This article aims to provide an update on the current knowledge and limitations of [¹⁸F]FDG-PET/CT for the diagnosis and assessment of treatment response in LVV. Furthermore, other radiopharmaceuticals targeting key components of the vascular immune system are being discussed which could provide an interesting alternative to image vascular inflammation in LVV.

(Cite this article as: Jamar F, Gormsen LC, Yildiz H, Slart RH, van der Geest KS, Gheysens O. The role of PET/CT in large vessel vasculitis and related disorders: diagnosis, extent evaluation and assessment of therapy response. Q J Nucl Med Mol Imaging 2022;66:182-93. DOI: 10.23736/S1824-4785.22.03465-3)

KEY WORDS: Positron emission tomography computed tomography; Fluorodeoxyglucose F18; Vasculitis; Aortitis.

Vasculitides encompass a wide spectrum of disorders, with all in common the feature of inflammation of blood vessels. The primary vasculitides are categorized as a function of the vessels' size: large, medium and small vessels.¹ Medium and small vessel vasculitides usually require pathological confirmation on biopsies. Large vessel vasculitis (LVV) is characterized by inflammation of large to medium-sized vessels and is associated with a triad of

pathophysiological features: arterial occlusion, aneurysm formation and in some cases arterial dissection (aorta). These pathological mechanisms may lead to severe symptoms such as transient or definitive loss of vision, strokes, or acute peripheral occlusive symptoms. Two main forms of LVV are well identified, giant cell arteritis (GCA) and Takayasu arteritis (TKA). Besides, aortitis of various aetiologies have been reported. Large vessel vasculitis (LVV)

occurs in vessels large enough to be accessible to non-invasive imaging. Positron emission tomography with computed tomography using 2-deoxy-2-[¹⁸F]fluoro-D-glucose ([¹⁸F]FDG-PET/CT) is a whole-body functional imaging modality widely used in oncology and has also demonstrated its versatility in inflammatory disorders, initially by serendipity.^{2, 3} [¹⁸F]FDG-PET was shown in experimental models and in the clinics to enable detection of increased glucose uptake in immune cells and fibroblasts in inflamed vessel walls.^{2, 4, 5} This review deals with the potential of functional imaging with a focus on [¹⁸F]FDG-PET/CT, to help in the diagnosis of LVV, but also the extent evaluation and the assessment of response to therapy, essentially in the two major forms, with a few words about atypical vasculitis presentations. In addition, potential future developments of functional imaging using other pathophysiological imaging pathways will be discussed in LVV.

Clinical spectrum of LVV and related disorders

Vasculitis is a group of disorders affecting both arteries and veins. According to the International Chapel Hill consensus conference in 2012, the term “large vessel” refers to the aorta and its major branches.¹ GCA and Takayasu arteritis (TAK) are the most common causes of LVV. Isolated aortitis is also considered as a LVV but classified as single-organ vasculitis compared to TAK and GCA which are potentially (multi)-systemic vasculitides.¹ Both LVV subtypes mainly differ in terms of epidemiological aspects (ethnic distribution, age of onset, gender), distribution pattern, treatment response to the same drug and prognosis. They however share clinical, imaging and histopathological features.⁶⁻⁸

A prompt recognition and treatment of GCA and TAK is essential to avoid irreversible complications/damage. Histopathologically, GCA and TAK are characterized by large vessel wall infiltration by inflammatory cells such as mononuclear cells and macrophages.^{9, 10} However, the clinical presentation is different. GCA mainly affects patients of ≥ 50 years of age while TAK occurs in young women ≤ 40 years of age.^{11, 12} TAK and GCA are characterized by nonspecific symptoms such as fever, fatigue, malaise, weight loss but also more typical symptoms such as headache, jaw claudication, and scalp tenderness in GCA versus limb claudication (with loss of pulse) and carotidynia in TAK. Furthermore, GCA may occur simultaneously with polymyalgia rheumatic (PMR) and TAK with inflammatory bowel disease, sarcoidosis

or ankylosing spondylitis.¹¹⁻¹³ The most striking clinical presentation of GCA is loss of vision, sometimes but not always preceded by transient loss, so called amaurosis fugax or just resulting in sudden irreversible blindness, stroke, aorta aneurysm or dissection in large vessel GCA (LvGCA). The main complications of TAK are transitory ischemic attack, stroke and large vessel steno-occlusive lesions as well as renovascular hypertension due to renal artery stenosis, pulmonary thrombosis and aortic regurgitation.¹⁴ Nonspecific constitutional symptoms, together with markers of systemic inflammation such as C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) make the diagnosis of LVV very challenging and prompt to additional diagnostic criteria.^{15, 16} The American College of Rheumatology 1990 criteria for GCA, are based on clinical and histological features, but are not suitable for individual patients.^{17, 18} In all cases, early imaging, such as ultrasound, MRI, CT and [¹⁸F]FDG-PET/CT is highly recommended to avoid delay in diagnosis and therapeutic actions as highlighted in the latest EULAR imaging recommendations, the latter being discussed in this paper.¹⁹ The treatment of these diseases is based on corticosteroids as a first line and followed with disease-modifying antirheumatic drugs (DMARDs)/immunosuppressive agent(s) as a second or subsequent line.²⁰

Besides the two typical LVV, non-infectious aortitis is a third entity that can be either isolated or related to several systemic disorders.²¹ Such association has been shown for instance with Behçet's disease, Cogan's syndrome, immunoglobulin G4-related diseases (IgG4-RD), relapsing polychondritis, granulomatosis with polyangiitis (GPA), spondyloarthritis, PMR, etc.¹³ Aortitis can also be the only (initial) manifestation of a systemic LVV and if no etiology is found, the aortitis is classified as “clinically isolated aortitis.”²¹ The constitutional symptoms are similar to those encountered in GCA or TAK. More specific symptoms can be present according to the underlying systemic disease, for example, 1) chondritis of ear and nasal cartilage with or without scleritis in relapsing polychondritis; 2) genital and mouth ulcers, uveitis in Behçet's disease; 3) interstitial keratitis and vestibuloauditory symptoms in Cogan's syndrome; 4) bilateral swelling of lacrimal or salivary glands, orbital pseudotumor in IgG4-RD. Histopathological findings are usually similar to those reported in GCA or TAK. In IgG4-RD though, the pathological findings comprise dense lymphoplasmocytic inflammation, storiform fibrosis, obliterative phlebitis and eosinophilia.²² The main complications of aortitis are the formation of aneurysm and dissection.

The role of PET-CT in LVV: diagnosis, extent evaluation and therapy response assessment

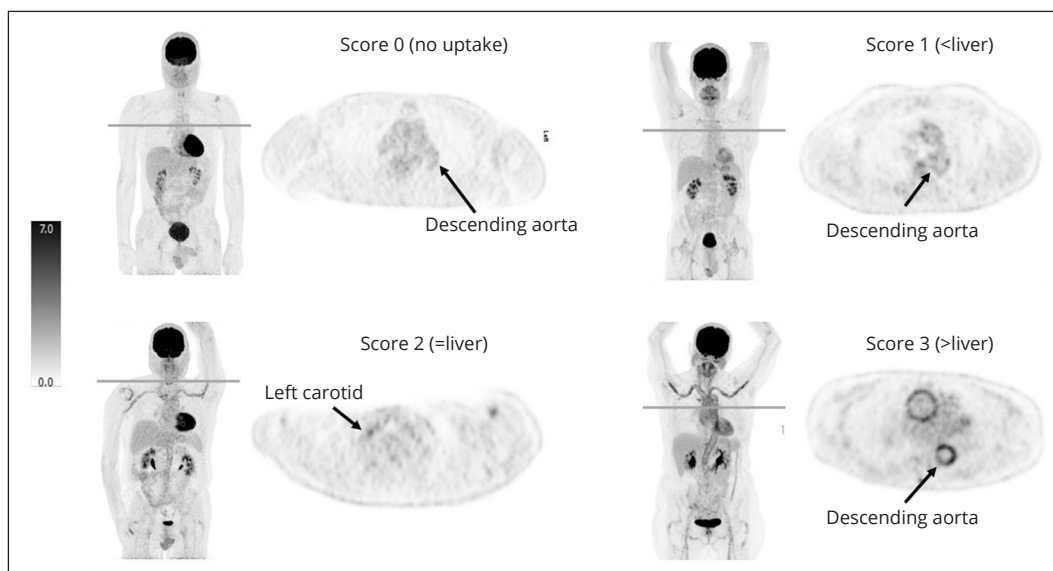
Diagnostic value of [^{18}F]FDG-PET/CT and extent evaluation

[^{18}F]FDG-PET/CT imaging is considered a good diagnostic tool for LVV, even though its exact diagnostic accuracy is difficult to determine due to a lack of an independent reference standard. In addition, meta-analyses on the diagnostic performance of [^{18}F]FDG-PET or [^{18}F]FDG-PET/CT are mainly based on retrospective data. The meta-analysis by Soussan *et al.* including 4 studies in GCA patients and 7 studies in TAK patients reported a pooled sensitivity of 90% and 87% and pooled specificity of 98% and 73%, respectively.²³ Another meta-analysis of 8 studies reported an overall pooled sensitivity of 76% and pooled specificity of 93% for diagnosing LVV (GCA and TAK) and a sensitivity of 83% and specificity of 90% for the GCA subgroup.²⁴ The diagnostic performance of [^{18}F]FDG-PET/CT was further investigated in two more recent studies that included patients undergoing [^{18}F]FDG-PET/CT for suspected LVV. Larivière *et al.* found a sensitivity of 67% and specificity of 100% of [^{18}F]FDG-PET/CT for a diagnosis of LvGCA and Moragas Solanes *et al.* reported a sensitivity of 96% and specificity of 97% for a diagnosis of LVV (GCA and TAK).^{25, 26} Although FDG uptake patterns may show strong similarities between individual patients with GCA and TAK, it has been shown that differences in distribution exist between the two main forms of LVV on a group level.^{27, 28} Aortic involvement is a promi-

nent feature in both conditions. However, involvement of abdominal arteries and predominant involvement of the subclavian / carotid arteries is more frequently observed in TAK. Patients with GCA more often present with diffuse vascular involvement or bilateral axillary/subclavian artery involvement. Pulmonary artery involvement on [^{18}F]FDG-PET/CT has also been described in a series of patients with TAK.²⁹ Till recently, studies on [^{18}F]FDG-PET/CT have been restricted to assess LVV involvement in patients with systemic vasculitis, although increasing evidence indicates that improved resolution of the newest generation (digital) PET scanners allows for assessing inflammation of cranial arteries, such as the vertebral, temporal and maxillary arteries, in patients with cranial GCA (cGCA). Two independent studies reported a sensitivity of 79%-83% and specificity of 75-100% of [^{18}F]FDG-PET/CT for cGCA.^{30, 31}

To date, there is no sufficient evidence that semiquantitative [^{18}F]FDG-PET/CT parameters may outperform visual assessment to diagnose (extracranial) LVV.³² Visual analysis (arterial uptake compared to a reference organ) should be preferred in routine clinical practice. The recommended visual analysis is a standardized 4-point grading scale with grade 0: no uptake, grade 1: vascular uptake less than liver, grade 2: vascular uptake equal to liver and grade 3: vascular uptake greater than liver as illustrated in Figure 1. When applying this 4-point grading scale, a diffuse and segmental grade 3 uptake in the wall of the aorta and/or its main branches (including the carotid bifurcation and vertebral arteries) is considered positive for LVV while a grade 2 uptake may be indicative of LVV.³³ In addition, a

Figure 1.—Representative maximum intensity projection and transverse [^{18}F]FDG PET images illustrating the 4-point visual grading scale.



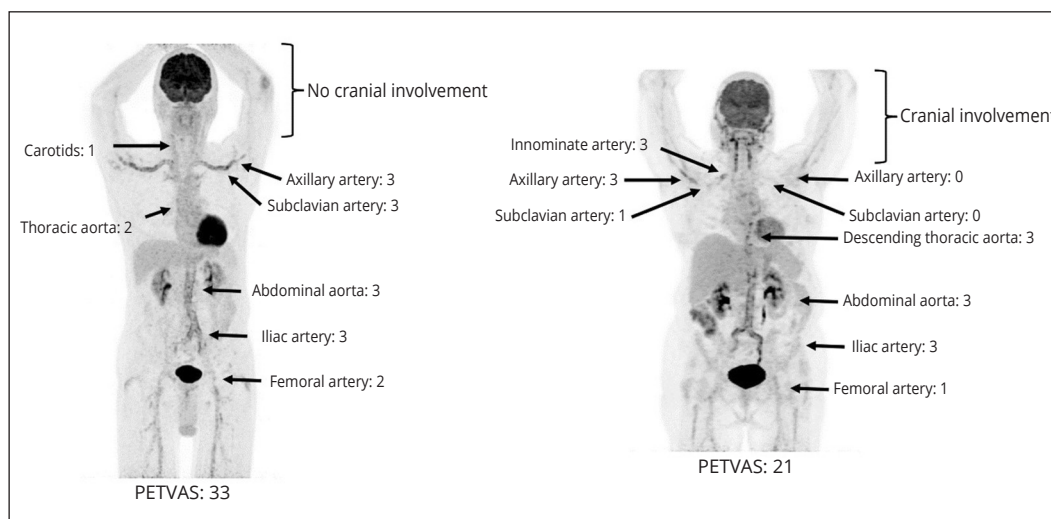


Figure 2.—Representative maximum intensity projection [^{18}F]FDG PET images illustrating the PET vascular activity score (PETVAS) in a LvGCA patient with symmetric [^{18}F]FDG uptake in the aorta and most larger branches without cranial involvement (left panel). LvGCA and cGCA patient with more asymmetrical [^{18}F]FDG uptake in the aorta and its branches (right panel). In addition, there was extensive and involvement of the cranial arteries (typically not considered in the PETVAS).

quantitative composite score based on a visual analysis of individual segmental territories, such as the PET vascular activity score (PETVAS) could be applied as illustrated in Figure 2. Such visual assessment has been shown highly reproducible among observers, which is essential in daily practice for clinical decision-making based on the scan report.³⁴ In this regard, it is important to acknowledge that the diagnostic accuracy of [^{18}F]FDG-PET/CT is impaired in patients on immunosuppressive treatment. Stellingwerff *et al.* demonstrated an increase in sensitivity from 83% to 92% without affecting specificity when patients receiving glucocorticoids were excluded from the analysis.³⁵ This can, at least partially, be explained by a treatment-induced reduction or normalization of arterial wall uptake in combination with a trend towards higher liver uptake. Several groups have indeed argued that the liver uptake might not be the most suitable reference organ in those patients.^{36, 37} Nevertheless, Nielsen *et al.* have shown that the sensitivity of [^{18}F]FDG-PET/CT for diagnosing LVV was not affected after 3 days of high-dose oral glucocorticoid treatment while nearly two-thirds of patients showed a normalization of wall uptake after 10 days. This suggests that [^{18}F]FDG-PET/CT can be performed within 72 hours of glucocorticoid initiation without attenuating its diagnostic performance.³⁸ Prospective data in the 3-10 days window are currently lacking: accordingly, as of today, adhering to the 72 hours window is recommended.

Since [^{18}F]FDG-PET/CT is a whole-body imaging modality and considerable overlap exists between GCA and PMR, typical uptake patterns for PMR are frequently found in patients eventually diagnosed with GCA. Promi-

nent findings suggestive of PMR include [^{18}F]FDG uptake at the shoulders, sternoclavicular joints, hips, trochanteric and ischial bursae, and interspinous regions of the cervical and lumbar spine. A composite score of visual uptake at these sites provided a sensitivity of 85-90% and specificity of 84-88% according to two reports.^{39, 40} In addition, bilateral diffuse capsular uptake at the knees is present in a large proportion of PMR patients.⁴¹

Taken together, [^{18}F]FDG-PET/CT is a valuable tool for diagnosis and assessment of disease extent in patients with GCA and TAK.

[^{18}F]FDG-PET/CT to evaluate disease activity and response to treatment in LVV

Whereas the value of [^{18}F]FDG-PET/CT to aid in the diagnosis of LVV is well-established, it is far less obvious to what extent – if any – [^{18}F]FDG-PET/CT could play a role in monitoring disease activity. There are several reasons for this, not least the generally low quality of studies investigating the impact of immunosuppressive treatment on vascular wall [^{18}F]FDG uptake in LVV patients. Most studies are cross-sectional, drug dosing varies widely or may even not be reported, disease duration at the time of the [^{18}F]FDG-PET/CT differs, and the interpretation criteria (visual or semi-quantitative metrics) used to evaluate pathological vessel uptake are often not properly described. Furthermore, various criteria for assessment of clinical disease activity are used in these studies. For patients in clinical remission, it is often unclear how long this has been the case at time of the follow-up scan. Nevertheless, a few longitudinal, observational studies have

been published from which some interesting lessons may be drawn (reviewed recently by van der Geest *et al.*).⁴²

The plethora of arguments for introducing imaging to evaluate treatment response in patients with LVV is compelling though. If not properly controlled, LVV is associated with serious vascular complications such as aortic dilation (and dissection), claudication and potentially strokes.^{43, 44} For decades, the mainstay of treatment has been corticosteroids, which are associated with a number of adverse effects, in particular diabetes and osteoporosis.²⁰ Treating physicians will therefore try to taper and ultimately discontinue corticosteroid treatment as soon as possible. However, there are currently no reliable biomarkers or definite clinical signs of relapsing or residual active LVV disease, and patient and physician perception of disease does not always align.^{45, 46} Consequently, treatment with corticosteroids or corticosteroid-sparing drugs such as methotrexate or tocilizumab is often continued well beyond the necessary time-period.⁴⁷ In this context, functional imaging with [¹⁸F]FDG-PET/CT appears to be a logical choice to aid in the decision-making, since [¹⁸F]FDG is a marker of cell metabolism and generally reflects disease activity in both malignant and non-malignant diseases.

Ideally, [¹⁸F]FDG-PET/CT performed in LVV patients during treatment should therefore facilitate: 1) differentiation between active and inactive disease; 2) prediction of relapse risk; and 3) choosing whether to continue, escalate or de-escalate instituted treatment. Using [¹⁸F]FDG-PET/CT in these scenarios would closely mimic the use of [¹⁸F]FDG-PET/CT in malignant lymphoma, which is currently a widely accepted clinical indication for using [¹⁸F]FDG-PET/CT in treatment response evaluations.⁴⁸ However, previously published [¹⁸F]FDG-PET/CT studies in LVV only contain limited data concerning the first point and a few scattered observations concerning the second point. To the best of our knowledge, no properly conducted studies have been performed, which could potentially back up the third point.

Vessel wall [¹⁸F]FDG-uptake during treatment

Vessel wall [¹⁸F]FDG uptake in patients with active LVV is thought to mostly reflect infiltrating activated macrophages and lymphocytes causing both transmural panarteritis and adventitial periarteritis.⁹ Therefore, vessel wall uptake should decrease in tandem with decreased leukocyte activity when immunosuppressive therapy is instituted. Since the aim of immunosuppressive therapy is to control the inflammatory activity rather than to cure it, the [¹⁸F]FDG-

PET/CT report should provide an overall measurement/assessment of inflammatory disease burden, similar to the metabolic tumor volume used in oncology. To address this issue, the PETVAS has been proposed in which [¹⁸F]FDG uptake is rated in the most commonly affected vascular territories using a visual 4-point scale ranging from 0-3 allowing for a maximum score of 27.⁴⁹ Depending on the number of segments chosen (typically between 7 and 15), the PETVAS Score can yield a maximum score of 21 to 45. This approach has proven robust with little inter-observer variability and is currently widely endorsed for disease evaluation in treatment response studies.³³ As an alternative, various target-to-background [¹⁸F]FDG-PET ratios of the most active vessel may be used as proposed by Meller *et al.*, but these are less suitable for longitudinal studies compared to the PETVAS since they do not convey the extent of disease, but only the severity.⁵⁰

Overall, a few short- and long-term longitudinal studies in patients with both GCA and TAK have demonstrated a rapid reduction of vessel wall [¹⁸F]FDG uptake in response to treatment. A first proof-of-concept study was performed by Blockmans *et al.* who showed a significant decrease in vascular [¹⁸F]FDG uptake at 3 months after glucocorticoid initiation in patients with GCA.⁵¹ However, no further changes in vascular [¹⁸F]FDG uptake were observed at 6 months even though all patients were in clinical remission and PETVAS was not able to identify patients at high risk for relapse. Similarly, Nielsen *et al.* demonstrated that 10 days treatment with 60 mg prednisone reduces vascular [¹⁸F]FDG uptake by ~40%, and Rimland *et al.* observed a ~20% reduction in PETVAS after a median of 6 months corticosteroid treatment.^{38, 52} The treatment effect on vessel wall [¹⁸F]FDG uptake is not restricted to corticosteroids as attested by the strikingly similar reduction observed in patients treated with tocilizumab.⁵³⁻⁵⁵ Compared to the effect of corticosteroids, methotrexate or tocilizumab revealed a tendency towards a greater reduction in vascular inflammation as reflected by PETVAS.⁵⁶ Regardless of the PET metric used, vascular [¹⁸F]FDG uptake generally tends to decrease between 20% and 60% from diagnosis to time of treatment response evaluation but in a manner not linearly correlated with the duration of treatment.^{56, 57} However, in contrast to the often completely absent [¹⁸F]FDG uptake by residual lymphomatous lesions during/after chemotherapy, vessel wall [¹⁸F]FDG uptake is only rarely completely normalized in patients with LVV during treatment. As a consequence, the pooled proportion of [¹⁸F]FDG-PET scans still indicative of active LVV in patients in clinical remission (putatively false

positive scans) has been estimated to be at least ~25% (as reviewed by van der Geest *et al.*⁴²) with values up to 58% as reported in a recent study.⁵⁸ To add further complexity to the read-out of [¹⁸F]FDG-PET scans during treatment, biomarkers that are often used to substantiate the patient's remission status (CRP and ESR) have been demonstrated to correlate poorly with vessel wall [¹⁸F]FDG uptake.^{59, 60} The pathophysiological importance of persistent vascular [¹⁸F]FDG uptake and the lack of association between this uptake and biochemical inflammatory markers remains unknown. The residual [¹⁸F]FDG uptake observed on follow-up PET studies may relate to other processes than the inflammatory cell associated vessel wall [¹⁸F]FDG uptake at diagnosis or prior to treatment. Vessel wall fibrosis and remodeling, low-grade inflammation caused by atherosclerosis, and hypoxia have been suggested as possible sources of persistent vessel wall [¹⁸F]FDG uptake in the absence of clinical or biochemical signs of disease relapse.⁶¹⁻⁶³ Regardless of the underlying cause, a recent meta-analysis on the diagnostic performance of [¹⁸F]FDG-PET/CT during immunosuppressive treatment reported a modest pooled sensitivity of 77% and specificity of 71% to detect active LVV disease.⁴² Such a moderate diagnostic accuracy (based on only four studies and with wide confidence intervals) does not merit using [¹⁸F]FDG-PET/CT to singularly either rule-in or rule-out active LVV.

In addition to monitoring changes in vascular uptake during treatment, several studies have explored whether [¹⁸F]FDG-PET/CT performed during clinical remission may predict disease relapse. Grayson *et al.* observed that patients with a high PETVAS (>20) were more likely to experience a relapse (45% *vs.* 11%) than patients with low PETVAS (<20) with a median follow-up time of 15 months.⁵⁸ Along the same line, Rimland *et al.* observed disease relapse in 11 patients in clinical remission who had PETVAS scores above 20 with a median follow-up time of 6 months.⁵² It should be noted though, that a PETVAS score of 20 (with 27 being the highest PETVAS value) implies that at least some of the vascular territories still had a significant [¹⁸F]FDG uptake (above liver uptake). Vascular FDG uptake of that magnitude would in many studies have been interpreted as active disease. In this context, it is thought-provoking that PETVAS did not significantly increase from clinical remission to clinical relapse in the study by Rimland *et al.*⁵² Therefore, evidence of increased vessel wall [¹⁸F]FDG uptake during clinical remission does not allow discriminating between *subclinical* active disease and *risk* of future relapse.

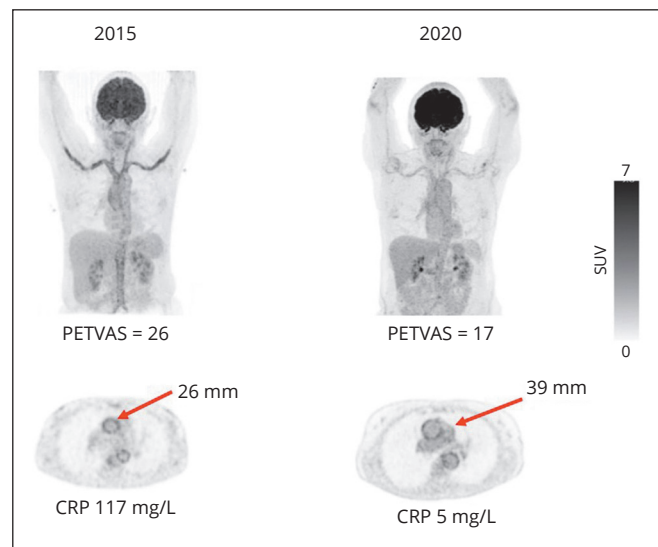


Figure 3.—Patient diagnosed with LGGCA in 2015, treated with corticosteroids and methotrexate. Inflammatory disease burden assessed by PETVAS was 26 (left panel). Five years after the pre-treatment [¹⁸F]FDG-PET/CT and in a period of clinical and biochemical remission, she was referred for a staging [¹⁸F]FDG-PET/CT for an unrelated disease. Vessel wall FDG uptake was still above liver in the aorta and the PETVAS had not normalized (score of 17). Of note, an increasing diameter of the ascending aorta was noted on the second scan reflecting progressive aortic dilation despite immunosuppressive treatment.

In summary, vessel wall [¹⁸F]FDG uptake decreases during immunosuppressive treatment in patients with LVV, but not to an extent that allows for robust discrimination between active and inactive disease as illustrated in Figures 3, 4. Some data indicate that a high PETVAS during clinical remission is associated with an elevated risk of later disease relapse, but it is evenly possible that a high PETVAS during clinical remission simply reflects subclinical active LVV. Finally, there are currently no studies available that support the use of [¹⁸F]FDG-PET/CT to de-escalate or escalate immunosuppressive treatment. As outlined above, a complex relationship exists between clinical, laboratory and imaging findings in assessing disease activity during treatment in patients with LVV and these different disease activity parameters do not always align. Treatment decisions for individual patients should thus be based on all disease activity parameters available and guided by the disease features and existence of comorbidities in those patients. Therefore, future studies are warranted to develop and validate more comprehensive composite outcome measurements for assessing disease activity during treatment, to define the optimal timing at which repeat imaging should be performed, to guide treatment, and to predict disease relapse.

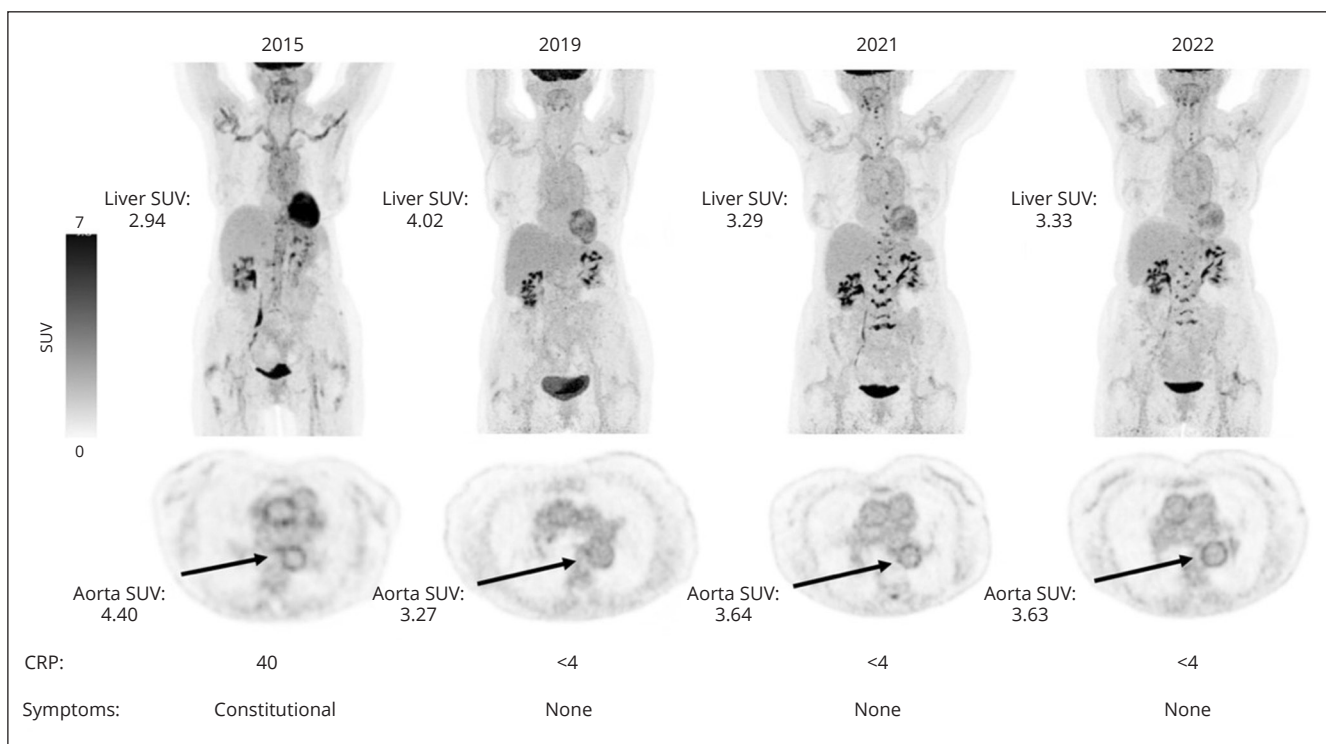


Figure 4.—Patient referred for a ^{18}F FDG-PET/CT scan for suspicion of LvGCA, which was confirmed (left panel). She was treated with corticosteroids for a total of 18 months. In the following 7 years, three additional ^{18}F FDG-PET/CT's were performed as surveillance of an unrelated disease. In these, aortic vessel wall ^{18}F FDG uptake gradually increased to above liver level. In addition, marked ^{18}F FDG uptake was noted in the interspinous ligamentous bursae. At no point after the initial tapering of corticosteroid therapy did the patient experience clinical relapse and inflammatory markers were not elevated. CRP is in mg/L.

^{18}F FDG-PET/CT in other vasculitides and peri-aortitis

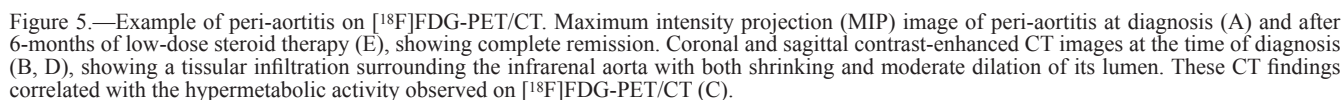
Besides the two main forms of vasculitis, there are numerous reports of the use of ^{18}F FDG-PET/CT in aortitis and related disorders. Most are anecdotal or merged in heterogeneous series comprising mainly LVV and TAK. Chen *et al.*, recently reported the performance of ^{18}F FDG-PET/CT in large-, medium- and small-vessel vasculitis: in a series of 71 patients, ^{18}F FDG-PET/CT was positive in 93% of the patients, showing vascular and extravascular involvement in 64% and 53%, respectively.⁶⁴ In Behçet's disease, most prospective publications deal with brain involvement. An interesting case report showed multiple cardiovascular involvements in a patient with Behçet's disease.⁶⁵ The interest of ^{18}F FDG-PET/CT however goes well beyond vascular hypermetabolism, for it enables to show both vascular and extravascular involvement as illustrated in a small series by Cho *et al.*⁶⁶ Behçet's disease was widely present in series of patients with pyrexia of unknown origin, although to the best of our knowledge, no prospective trial has been conducted in this particular disease.⁶⁷

^{18}F FDG-PET/CT also showed its efficacy in detecting extravascular and vascular involvement in anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis.⁶⁸

Recently, there has been growing interest in IgG4-RD. This versatile disorder may affect large and medium vessels but also various organs. The differential diagnosis stays among that of inflammation of unknown origin and hence a whole-body functional imaging method such as ^{18}F FDG-PET/CT is of interest. Tsuji *et al.* showed a correlation between ^{18}F FDG uptake and histopathology in 21 patients with IgG4-RD.⁶⁹ Interestingly, they reported a SUVmean of 4.07 as being the threshold for lesions to be biopsied for a definite diagnosis. This was confirmed by other authors who identified the role of ^{18}F FDG-PET/CT in IgG4-RD to assess organ involvement, guide biopsy and monitor disease response.⁷⁰ There is now ample data about the potential of ^{18}F FDG-PET/CT in IgG4-RD, but limited evidence suggests that vasculitis is relatively uncommon in IgG4-RD.⁷¹ In a recent report, only 15% of the patients with IgG4 presented with aortitis or periaortitis, mainly with involvement of the abdominal aorta.⁷²

to evaluate patients with RPF.⁷⁸ This paper showed a better identification of patients who would respond to treatment based on the baseline SUV_{max}. Finally, the study by Fernando *et al.* reported on the negative and positive predictive value in RPF.⁷⁹ They concluded that [¹⁸F]FDG-PET/CT enables to discriminate between cancer-related *versus* not cancer related RPF. Ruhlmann *et al.* showed that [¹⁸F]FDG-PET/MRI had a potential as a one-stop diagnostic procedure for the assessment of active RPF.⁸⁰ More recently, [⁶⁸Ga]-FAPI PET/CT may also prove useful in RPF.⁸¹

As discussed above, [^{18}F]FDG-PET/CT is an established technique to diagnose patients with LVV, but its role for evaluating response to treatment and identifying residual active disease needs to be further clarified. [^{18}F]FDG is taken up by all metabolically active cells that primarily use glucose as substrate and as such is not limited to inflammatory cells (e.g. lymphocytes and macrophages). As consequence, metabolically active cells that are not part of the inflammatory response may, at least to some degree, contribute to the origin of the vascular [^{18}F]FDG uptake. Lower background activity, thereby increasing target-to-background ratio and the imaging accuracy is of additional value. Also aiding the design of personalized treatment regimens especially with emerging novel immunotherapies is more important these days. Therefore, alternative radiotracers targeting key components of the vascular immune system could provide an interesting alternative to image vascular inflammation in general. Furthermore, one



can envision the development of PET tracers targeted to specific cell receptors that are important during the inflammatory or healing process, but the major challenge remains the exquisite selectivity of such a PET tracer for a particular cell type. Nevertheless, many novel radiotracers for inflammation imaging have been applied in the field of cardiovascular diseases including vasculitis.

Since LVV is a chronic inflammatory disease characterized by the presence of macrophages, several groups have evaluated PET tracers targeting macrophages in patients with LVV.⁸²⁻⁸⁴ Pugliese *et al.* reported that the TSPO ligand [¹¹C]-PK11195 was taken up in the arterial wall of all symptomatic patients (N.=6) with clinical suspicion of vasculitis while none of the asymptomatic control patients showed any tracer uptake.⁸² Since PK11195 has a moderate affinity for TSPO and low specific binding, second generation TSPO radioligands with higher affinity have been developed.⁸⁵ However, a recent pilot study evaluating such novel generation TSPO ligand, [¹¹C]-PBR06, did not show any uptake in three patients with LVV.⁸⁶ Another target on macrophages is the somatostatin receptor 2 (SST²) which can be interrogated by [⁶⁸Ga]DOTATATE or [¹⁸F]FET-βAG-TOCA. In the first two patients with TAK, SST² PET/MRI imaging accurately identified arteritis with a pattern similar to the findings on [¹⁸F]FDG or MRI.⁸⁷ Other interesting targets on macrophages include the folate receptor β that is exclusively expressed on activated macrophages, or the CXCR4 receptor that could be imaged using [¹⁸F]-PEG-folate and [⁶⁸Ga]-Pentixafor, respectively.^{88, 89} Other targets may be used in the future such as the IL-2 receptor agonists or antagonists, or B-cell targeting radiotracers, *i.e.* to CD20, with radiolabelled rituximab. However, further studies are warranted to evaluate their usefulness for the diagnosis and treatment monitoring of patients with vasculitis.

Conclusions

Functional imaging, *per se*, has become part of standard of care in patients with suspected vasculitis. Vasculitis encompasses a wide spectrum of disorders, among which GCA and TAK have been widely studied in the past decade. Even though expert opinion has highlighted its use to aid in the diagnosis of LVV, [¹⁸F]FDG-PET/CT is currently not recommended for follow-up evaluation in recent clinical guidelines. Visual assessment and semi-quantitative evaluation for diagnosis and assessment of disease activity were presented herein with their advantages and drawbacks. In addition, [¹⁸F]FDG-PET has also shown

promising in other types of vasculitides, including peri-aortitis and related disorders. Other tracers may become available in the near future, for this constellation of disorders, such as those targeting activated macrophages or the fibroblast activating protein.

In all cases, regardless of the tracer used, prospective and multicentric studies are necessary to strengthen the role of functional and metabolic imaging across the wide spectrum of vasculitides and related disorders.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—François Jamar has given substantial contributions to the conception and the design of the manuscript, François Jamar, Lars C. Gormsen, Halil Yildiz, Riemer H. Slart, Kornelis S. van der Geest and Olivier Gheysens to acquisition, analysis and interpretation of the data. All authors have participated to drafting the manuscript, Olivier Gheysens and François Jamar revised it critically. All authors read and approved the final version of the manuscript.

History.—Manuscript accepted: June 13, 2022. - Manuscript revised: May 31, 2022. - Manuscript received: April 5, 2022.