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Large Vessel Vasculitis

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Pieter H. Nienhuis, Elisabeth Brouwer, and Riemer H. J. A. Slart

Introduction

Large vessel vasculitis (LVV) is a collection of chronic autoimmune conditions characterized by inflammatory lesions in the vessel wall of large- and medium-sized arteries. These vessel wall lesions may result in aneurysm formation, rupture, and dissection in the aorta and stenosis as well as end-organ damage in the medium-sized arteries [1]. There are two major variants of LVV: Takayasu arteritis (TAK) and giant cell arteritis (GCA). TAK is characterized by inflammation of the aorta and its major branches and affects patients under 50 years of age. In GCA, the aorta and its major branches may likewise be affected, but less commonly than in TAK. Instead, the third to fifth-order branches of the aorta such as the temporal and vertebral arteries are affected [2]. Additionally, GCA only presents in patients over 50 years of age, hence age being the main discriminator between the two diseases [3].

Apart from the above-mentioned complications associated with aortic involvement which presents in both TAK and GCA, the frequently affected vessels determine many of the clinical features. In TAK, subclavian artery occlusion leads to limb claudication and pulselessness. Such a clinical course may subsequently be complicated by peripheral ischemia. In GCA, occlusion of cranial arteries leads to headache and jaw claudication. Associated possible complications include vision loss and stroke.

Systemic symptoms such as fever, weight loss, and arthralgia are present in both types of

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LVV. GCA patients presenting with pain and stiffness of the shoulder or hip girdle are frequently diagnosed with concomitant polymyalgia rheumatica (PMR), belonging to the same disease spectrum as GCA. As many as half of the GCA patients have evidence of PMR [4].

Although both diseases are primarily diagnosed based on clinical suspicion and raised inflammatory markers, various imaging modalities are now frequently used to aid the diagnostic process. In recent recommendations, the early use of imaging in the diagnostic process of GCA has been favored over a temporal artery biopsy, which has historically been considered the diagnostic gold standard [5].

In patients with high clinical suspicion, a positive imaging test may confirm a diagnosis of GCA or TAK. Imaging modalities used to investigate LVV include ultrasonography, magnetic resonance angiography (MRA), computed tomography angiography (CTA), and [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET). Ultrasonography showing a "halo sign" is highly suggestive of GCA. MRA is the primary imaging modality to diagnose TAK by way of showing vessel wall thickening and edema. Additionally, MRA of the cranial arteries may be used to diagnose GCA. CTA may equally be used to detect vessel wall inflammation in the large arteries.

Despite the proven value of the current diagnostic tools, negative results from any diagnostic tool cannot definitively exclude the presence of LVV. For example, a patient may have a negative temporal artery biopsy, ultrasonography without a halo sign, magnetic resonance imaging and computed tomography without wall thickening, but still have LVV as evidenced by a positive FDG-PET/CT.

FDG-PET is a functional imaging technique that is based on detecting enhanced glucose uptake. It is an established tool in the field of oncology, detecting the high glycolytic activity of malignant cells. To anatomically locate FDG uptake, FDG-PET is always used in conjunction with another imaging method, most commonly low-dose CT.

FDG-PET/CT also plays a role in imaging infectious and inflammatory diseases, by detecting the increased glycolytic activity of inflammatory cells such as macrophages [6]. This way, vessel wall inflammation in LVV may be detected on FDG-PET/CT. Given FDG-PET/CT is usually conducted as a whole-body scan, it enables detection of LVV in many regions throughout the body. Using FDG-PET/CT to assess inflammation of the aorta and its first-order branches is already well established in daily clinical practice. Its use to assess vessel wall inflammation in the cranial arteries had always been regarded unfeasible due to the small diameter of these arteries. For example, the superficial branch of the temporal artery has an average diameter of 2 mm, for which PET camera systems did not have sufficient resolution [7]. Additionally, cranial artery uptake was difficult to distinguish from the high physiological FDG uptake of the brain [8]. However, recent studies have shown that procedural adaptions and higher resolution PET camera systems can reveal inflammation in the cranial arteries as well [9–11].

Apart from detecting vessel wall inflammation, FDG-PET/CT may assist the differential diagnosis by enabling the identification of other inflammatory processes that may explain the patient's clinical presentation.

Much remains unknown about how FDG uptake may be interpreted in inflammatory diseases. Increased FDG uptake is mainly noticed in active disease processes with a high rate of metabolism. In LVV, this may be observed in the early phase of the disease process, before anatomic changes in the vessel wall manifest. Therefore, FDG-PET/CT may not show the vessel wall destruction resulting from inflammation and subsequently not capture all clinically significant findings.

In this chapter, the current application of FDG-PET/CT in LVV will be discussed. The technical approach to FDG-PET procedure and image interpretation as well as the role of FDG-PET/CT in the diagnostic workup of LVV forms the backbone of this chapter. Additionally, potential pitfalls of FDG-PET/CT in LVV will be reviewed.

FDG-PET Procedure

The FDG-PET procedure for patients with LVV determines the quality and, therefore, the readability of the FDG-PET images. Important factors in the FDG-PET procedure are patient preparation, image acquisition, and image reconstruction. Standardization of the FDG-PET procedure is paramount to ensure optimal image quality for diagnosis, enable comparison with follow-up imaging, and allow validation of research outcomes [8, 12]. The recommended procedural parameters are summarized in Table 7.1.

Patient Preparation

The main goal of patient preparation is to reduce physiologic tracer uptake in healthy tissues while maintaining or enhancing tracer uptake in inflamed tissues. Because FDG is a glucose analog, glucose may competitively inhibit FDG uptake in tissues. Indeed, serum glucose levels have been found to alter the biodistribution of FDG and lower the diagnostic sensitivity of FDG-PET [13, 14]. Ideally, serum glucose levels do not exceed 7 mmol/L before the FDG administration. For this reason, patients are instructed to fast 6 h before FDG administration. Unlike for certain malignancies, FDG-PET may still enable the detection of inflammatory disorders despite high serum glucose levels [15]. Therefore, hyperglycemia is not considered an absolute contraindication, and patients with (poorly controlled) diabetes may still undergo an FDG-PET [8].

Glucocorticoids form the initial mainstay in the treatment of LVV [16]. Especially when GCA is suspected, glucocorticoid treatment needs to be given without delay to decrease the risk of ischemic complications such as vision loss. For this reason, glucocorticoid treatment may already be started before a diagnosis of LVV can be confirmed by imaging.

However, glucocorticoid treatment may decrease the detectability of LVV on US and FDG-PET imaging [17]. Research revealed that FDG-PET imaging maintains its accuracy for detecting LVV when performed within 3 days of starting glucocorticoid therapy. FDG-PET imaging performed after 10 days of glucocorticoid treatment significantly decreases its diagnostic sensitivity [18]. Glucocorticoids may also increase liver uptake of FDG, resulting in lower diagnostic sensitivity when scoring vascular FDG uptake compared to the liver [19]. Scoring methods will be discussed further below, under "Image Interpretation."

Table 7.1 Summary of recommended patient preparation and image acquisition parameters for FDG-PET/CT in LVV

Parameter	Recommendation
Dietary preparation	Fast for at least 6 h prior to FDG administration Consider a carbohydrate lacking diet for 12–24 h prior to the scan in case of fever of unknown origin or suspected cardiac involvement
Blood glucose levels	Preferably ≤7 mmol/L (126 mg/dL)
Glucocorticoids	Withdraw or delay therapy until after PET, unless there is a risk of ischemic complications
Scan range	Head down to the feet
Incubation time after FDG injection	Standard 60 min

Modified from Slart et al. [8]

PET Acquisition Procedure

The interval time, defined as the time between FDG injection and acquisition, is one of the main influencing factors of the imaging result. Interval times of approximately 60 min are most frequently used in LVV imaging. Extended interval times of 120 min are more frequently used in atherosclerosis, another type of vessel wall inflammation. In LVV, extended interval times have been shown to decrease FDG uptake in the blood pool, possibly resulting in enhanced detectability of vessel wall uptake due to lower background activity. Interval times of 120 min may identify more patients with clinically active LVV [20]. An

important comparative advantage of FDG-PET imaging is its ability to allow assessment of virtually all medium- and large-sized vessels. Imaging from head to knee or from head to feet (whole-body imaging) is, therefore, recommended. Additionally, doubling the imaging time and applying a larger matrix increases the resolution of the images. A higher resolution may be especially beneficial when imaging the arteries of the head and neck due to their smaller size [8].

Image resolution also depends on the chosen image reconstruction settings. Increasing the number of iterations increases the resolution, but also increases image noise. Time-of-flight information must be used during reconstruction and image filtering should be minimized [8].

Interpretation and Reporting of FDG-PET/CT

Arterial FDG uptake may be influenced significantly by several factors. Over the years, several interpretation methods have been proposed for use in clinical practice. The simplest method of FDG-PET interpretation is based on a visual first impression by an experienced reader. This method, also described in literature by the German word "Gestalt," gives fast results, but highly subjective and, subsequently, not standardizable [19]. The interpretation methods are summarized in Table 7.2.

Visual Grading Scales

Visual grading scales may be used to overcome this subjectivity bias, by creating uniform, reproducible, and easy-to-use criteria. Additionally, visual grading scales may also correct for individual differences in systemic FDG uptake by comparing vascular wall uptake to a background organ. To achieve more standardization in clinical practice, 2018 recommendations propose the use of a 0-to-3 visual grading scale that compares

Table 7.2 Summary of FDG-PET/CT interpretation methods for large vessel vasculitis

FDG-PET/CT LVV interpretation methods		
Visual interpretation		
Grading compared to background	Grade 0 (no vascular uptake)	
	Grade 1 (vascular uptake < background)	
	Grade 2 (vascular uptake = background uptake)	
	Grade 3 (vascular uptake > background uptake) Background: Liver Blood pool Lungs Surrounding tissue	
Uptake pattern	Focal (atherosclerosis)	
	Diffuse (vasculitis)	
Semiquantitative interpretation (visual)		
Total vascular score (TVS)	= [Grade Target 1] + [Grade Target 2] + …	
	Vascular targets:	
	Large vessels	Ascending aorta
		Aortic arch
		Descending aorta
		Abdominal aorta
		Pulmonary arteries
		Innominate artery
		Subclavian arteries
		Axillary arteries
		Subclavian arteries
		Iliac arteries
		Femoral arteries
	Cranial vessels	Temporal arteries
		Maxillary arteries
		Vertebral arteries
		Occipital arteries

Table 7.2 (continued)

FDG-PET/CT LVV interpretation methods		
Semiquantitative (SUV)		
Target-to-background ratio (TBR)	= SUV_{max} vascular target/$SUV_{max/mean}$ background	
	Vascular targets:	
	Same as above	
	Background:	
	Blood pool	Superior caval vein
		Inferior caval vein
	Liver	Right lobe

(PET/)CTA/MRA LVV interpretation methods
Regular vascular wall thickness (mm)
Contrast enhancement
Presence of stenosis and/or aneurysm

Modified from Slart et al. [8]

vascular wall uptake to liver [8]. This method is illustrated in Fig. 7.1 and works as follows: grade 0 = no uptake; grade 1 = vascular uptake inferior to liver; grade 2 = vascular uptake equal to liver; grade 3 = vascular uptake superior to liver uptake. Examples of visual grading scores for the large vessels are shown in Fig. 7.1. In active LVV, a smooth linear and segmental pattern of grade 3 visual FDG uptake in the wall of large- and medium-sized arteries is considered a positive FDG-PET. Under immunosuppressive therapy, a grade 2 may be considered positive. In addition to the liver, the blood pool in the vena cava may also be used as background for comparison.

In LVV, all medium- and large-sized vessels may be affected. For FDG-PET interpretation of LVV, it is useful to make a distinction between the large systemic vessels affected in TAK and

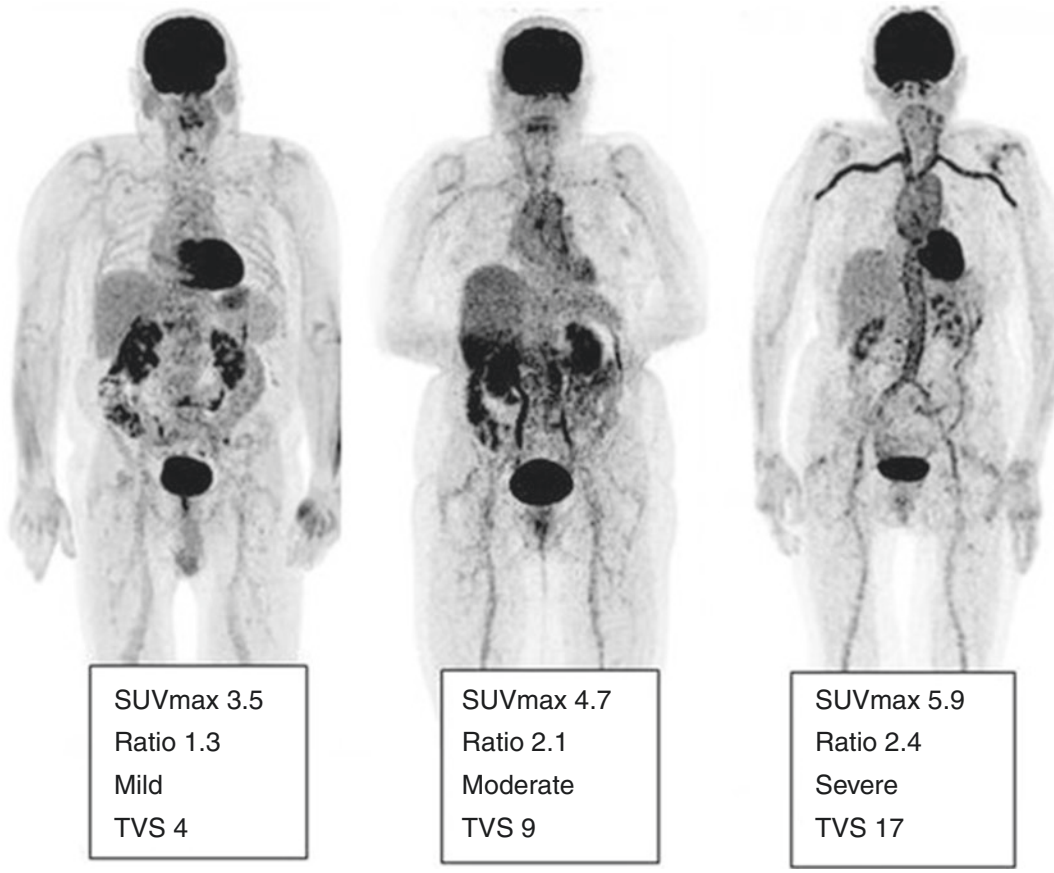

Fig. 7.1 FDG-PET. Mild (grade 1), moderate (grade 2), and severe (grade 3) FDG uptake patterns including SUVmax values of the thoracic aorta in patients with GCA. Ratio is defined as average SUVmax of the thoracic aorta divided by the liver region. The total vascular score (TVS) is the highest for the right-positioned patient. (Modified from Slart et al. [8])

large vessel-GCA (LV-GCA), and between the medium-sized cranial vessels in C-GCA. The initial use of FDG-PET in LVV was based on the assessment of increased tracer uptake in the large systemic vessels [21]. FDG-PET/CT imaging and assessment of the aorta and the common carotid, subclavian, axillary, iliac, and femoral arteries were, increasingly used in the diagnostic workup of GCA and TAK, although to a lesser extent in TAK. Importantly, FDG-PET imaging was not deemed feasible to assess the cranial arteries and, for that reason, not suitable to diagnose C-GCA [22].

Cranial Artery Assessment

Due to procedural adaptions and technical advancements in PET systems in recent years, PET image resolution has increased. The use of digital PET systems and especially systems with time-of-flight capabilities allow for the assessment of extra-cranial artery involvement in GCA. Also, a slight increase in acquisition time of the head/neck area (5 min instead of 2–3 min) improves the visualization of extra-cranial arteries. Diagnosis of C-GCA is possible due to combined assessment of the temporal, maxillary, vertebral, and occipital arteries and may be reported like the visual scoring previously described [9–11] (Fig. 7.2).

Quantification

Until now, only scoring by visual assessment has been discussed. Other types of (semi) quantitative scoring may also be used and may be considered more objective methods of FDG-PET interpretation. Standardized uptake value (SUV) metrics may be calculated by drawing regions of interest (ROI) or volumes of interest (VOI) around the vascular lesions. Additionally, SUV metrics of the target vascular lesion may also be corrected for systemic uptake. By dividing the SUV of the target vascular lesion by the SUV of a background region, a correction can be made for individual differences of tracer uptake depending on weight, injected radiotracer dose, blood glucose levels, and renal clearance. Frequently used background regions are the liver and the blood pool as measured in the superior or inferior vena cava.

Importantly, semiquantitative measurements using SUV metrics are currently recommended for use in research only [23]. Although studies have shown that SUV metrics can be used for diagnosis, this has not been proven in any large-scale, prospective studies [20, 24, 25]. Moreover, SUV metrics are highly dependent on the FDG-PET imaging procedure, which may make generalization and comparable multicenter diagnostic implementation difficult. Equally, the use of SUV metrics in FDG-PET as a monitoring biomarker or as a predictive tool may provide additional benefit. However, this has not been investigated yet.

Diagnostic Performance

The diagnostic performance of FDG-PET imaging in LVV is good to excellent. The sensitivity of FDG-PET/CT to detect LV-GCA is 80–90% and its specificity is 89–98%, depending on the criteria for reference diagnosis [8, 26]. Diagnostic performance is similar when assessing the cranial arteries in C-GCA, with a sensitivity of 82% and a specificity approaching 100% [9, 10]. In comparison, diagnostic accuracy is lower in TAK patients, a sensitivity of 87% and a specificity of 73%. As stated before, the diagnostic accuracy of FDG-PET in LVV decreases if patients have already been treated with glucocorticoids for more than 3 days [18].

The use of a visual grading scale, as described above, can be extended by calculating a total vascular score (TVS). The TVS is calculated by adding up the visual grading scores of multiple vessels and vascular segments. As expected, a TVS of 4 aortic segments (ascending, arch, descending, and abdominal) and 4 branch arteries (carotid and subclavian) is significantly higher in LVV patients than in controls [27]. It is currently unknown whether TVS also illustrates the disease extent or severity. A recent study concluded that the TVS may be correlated with the global assessment of a physician, but not with patient-reported disease severity [23]. Likewise, it

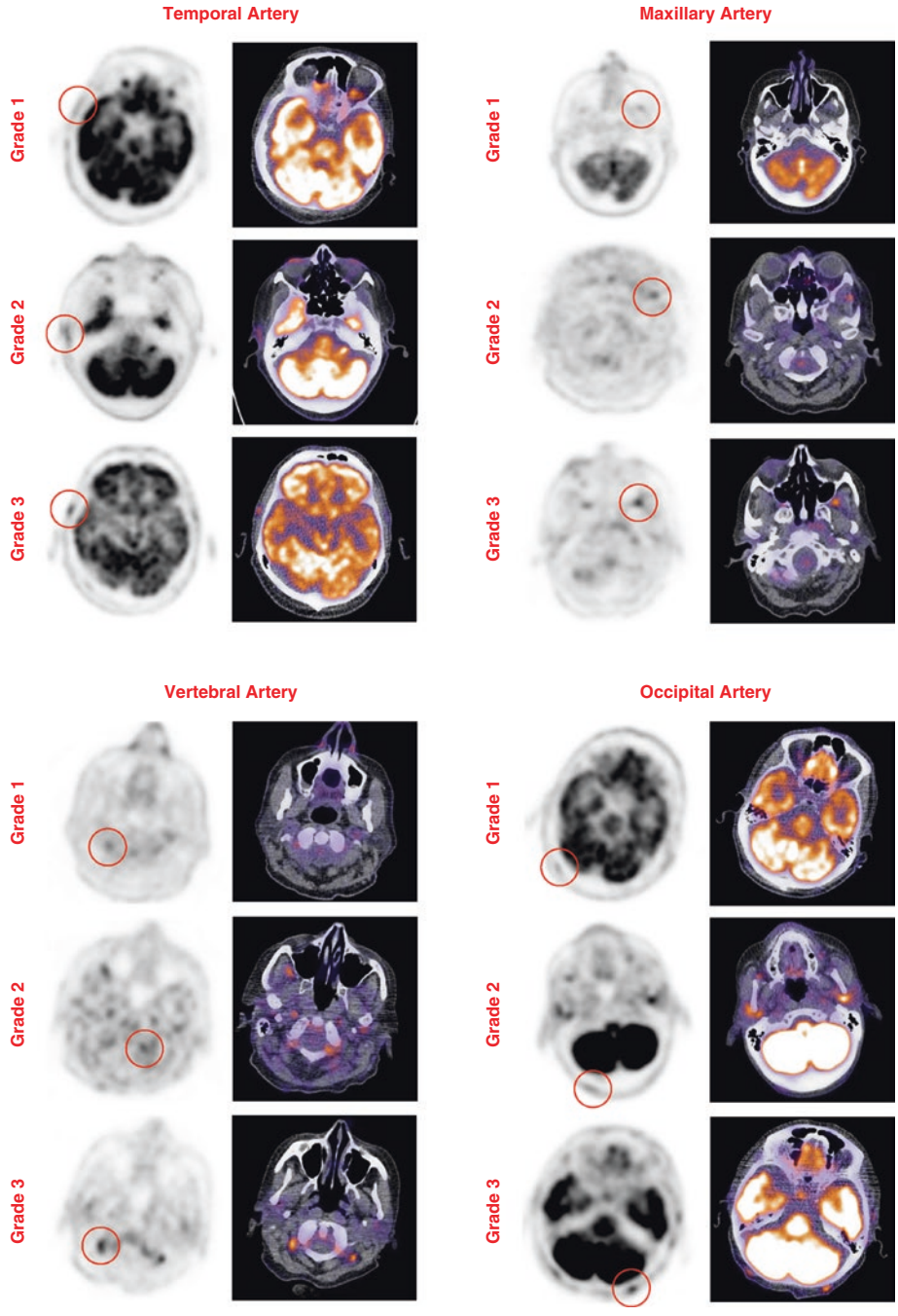

Fig. 7.2 FDG-PET/CT. Mild (grade 1), moderate (grade 2), and severe (grade 3) cranial FDG uptake patterns: temporal artery, maxillary artery, vertebral artery, and occipital artery. The red circle highlights the visually determined area of increased uptake

remains unclear whether including less frequently involved vessels such as the axillary, iliac, and femoral arteries increases the discriminatory value of the TVS. Similarly, including the cranial vessels may increase diagnostic performance [11].

Monitoring and Follow-Up

As described in the introduction, clinical symptoms, physical signs, and laboratory tests are unreliable to diagnose LVV [24]. Similarly, the same holds true for establishing relapsing disease. Over 50% of patients with LVV will experience relapsing disease [16].

The value of serial FDG-PET investigations as an imaging biomarker for LVV is still up for debate [11, 27]. Follow-up FDG-PET/CT imaging may be able to differentiate clinically active and inactive disease by, respectively, higher and lower TVS. Additionally, there may be no correlation between the glucocorticoid dose and TVS, nor between patient-reported assessment and TVS [23]. In studies looking at follow-up FDG-PET scans in LVV patients, FDG uptake was variable in patients with persistent clinical remission, ranging from patients with decreased FDG uptake to patients with increased uptake compared to baseline [25, 28]. Conversely, other studies demonstrated mainly decreased FDG uptake on follow-up scans [29, 30].

Likewise, some research suggests that a high TVS may be predictive for future clinical relapse. However, this predictive ability may depend on the TVS calculation, the number of vascular beds included, the reconstruction techniques used, and the background organ that is used for semiquantitative scoring.

PET Combined with CTA or MRA

Standard FDG-PET/CT imaging in LVV makes use of low-dose CT for attenuation correction and also of anatomic reference for the PET signal. As an imaging tool in LVV, low-dose CT has little added value by itself but can be helpful to distinguish LVV from atherosclerotic activity [31].

Alternatively, PET imaging may be complemented by vascular imaging with angiography, either in the form of CT angiography (CTA) or MR angiography (MRA). When used in conjunction with these imaging techniques, FDG-PET provides visualization of ongoing inflammatory processes, whereas the CTA and MRA can visualize the morphologic changes in the vessel wall, such as wall thickening, aneurysm formation, and arterial stenosis assessment.

Currently, CTA and MRA are used in different situations. Thickening of the vessel wall (>2–3 mm) or aorta dilatation (3–4 cm) on CTA may be indicative of LVV and shows particularly high diagnostic accuracy in TAK [26]. Its use for investigation of the cranial arteries in C-GCA is limited. Conversely, MRA is an established method to investigate mural inflammation in the cranial arteries. By itself, it may also be used to investigate inflammation of the intracerebral arteries, which are precluded from investigation on FDG-PET due to high FDG uptake by the brain. Combined FDG-PET/MRA may synergistically improve diagnosis of C-GCA due to its combined morphologic and functional imaging accompanied by lower radiation burden [32].

Potential Pitfalls in LVV FDG-PET Imaging

Potential pitfalls regarding FDG-PET imaging in LVV have already been mentioned in this chapter. Many aspects of the FDG-PET procedure influence the resulting image, highlighting the importance of procedure standardization. Patient factors, such as blood glucose levels, glucocorticoid use, and body mass, may all influence FDG uptake in the tissues. Other factors, such as renal clearance, metabolic disease, and the use of immunosuppressive drugs may also influence imaging results. Procedural factors such as injected tracer dosage and imaging time delay also influence the FDG-PET image [20].

Image interpretation may also present some challenges. Implementation of the recommended

visual scoring methods described above may require additional training. Interpretation of cranial artery uptake may be especially challenging because of the anatomic localization. However, high diagnostic accuracy and reader consensus may be achieved with training [9].

Like LVV, atherosclerosis may show FDG uptake in the arterial wall. Therefore, it may be difficult to distinguish between atherosclerosis and LVV, especially where both diseases may overlap [31]. Hence, one should interpret vascular inflammation in patients with marked calcification on CT with caution. No definitive methods have been devised to differentiate between these types of vascular inflammation, but atherosclerosis seems to present with less intense and patchier FDG uptake compared to LVV, as the latter is a more intense and diffuse pattern [31] (Fig. 7.3).

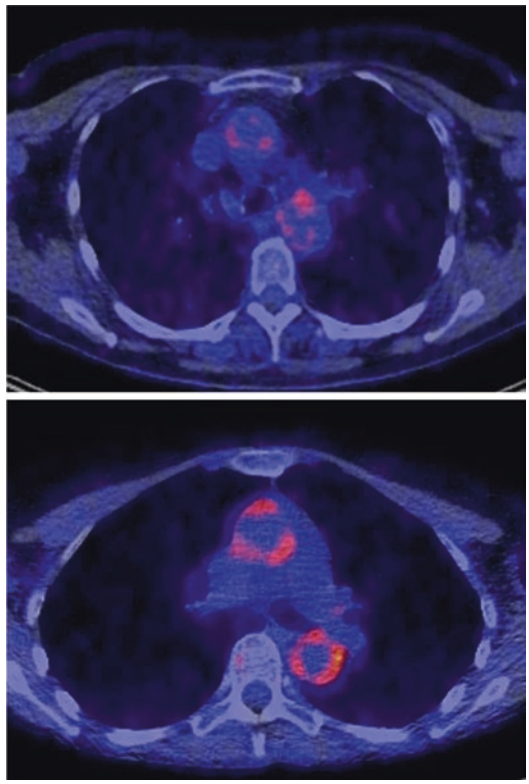

Fig. 7.3 Transverse FDG-PET/CT images of atherosclerotic FDG uptake (above) and vasculitic FDG uptake (below) in the aorta. Vasculitic FDG uptake is characteristically more intense and circumferential compared to atherosclerotic FDG uptake

Perspectives in LVV Imaging

Based on the currently available literature, FDG-PET/CT plays an important role in the diagnosis of LVV, but additional randomized studies are needed to validate the existing evidence. To increase the reproducibility of future research and the generalizability of its results, future studies should take the latest international recommendations on FDG-PET/CT imaging in LVV into account.

Future research should focus on including real-world prospective data and the implementation of FDG-PET/CT with existing diagnostic (imaging) investigations. The development of diagnostic algorithms may further clarify the role of FDG-PET/CT in the diagnostic process and its position within such algorithms. New semiquantitative approaches to FDG-PET/CT interpretation, focusing on SUV metrics, and including TVS, may be of particular benefit in monitoring and prediction of the LVV disease course. An example of a novel semiquantitative metric may be found in the calculation of the total lesion glycolysis (TLG). TLG measurements are already used in oncology and also take the volume of an inflammatory lesion into account, rather than only the intensity of FDG uptake. Although not yet extensively investigated, TLG may prove to be of value in monitoring disease activity [33].

Whole-body PET imaging presents opportunities for truly systemic investigations of LVV, a systemic disease that may present in virtually all large- and medium-sized arteries throughout the body. The availability of the FDG tracer allows for the widespread use and implementation of FDG-PET/CT investigations in LVV. However, FDG remains nonspecific in the investigation of inflammatory processes and cannot provide any information about the nature of inflammation. Additionally, high FDG uptake in the brain precludes FDG-PET from assessing inflammatory processes in the brain, but extra-cranial arteries can be visualized on digital high-resolution PET/CT camera systems.

New PET tracers targeting specific immune cells may open new areas for basic research into LVV as well as more specific characterization

and recognition of inflammatory lesions. Macrophage targeting PET tracers, such as ^{18}F-PEG-Folate, and tracers targeting the translocator protein (TSPO) have shown promising results in (auto) inflammatory and vascular diseases [34]. Similarly, tracers targeting the fibroblast activation protein inhibitor (FAPI) are promising, demonstrating low uptake in healthy tissues and showing promise in monitoring disease activity [35, 36].

Importantly, FDG-PET/CT may play an increasing role in clinical practice. Its implementation may be further aided by additional physician training on the interpretation of FDG-PET/CT scans in LVV. Furthermore, the role of FDG-PET/CT in LVV may change in the future, possibly for monitoring and predicting disease course. As the array of investigative (and therapeutic) options increases, and as management will become more personalized, a vasculitis multidisciplinary expert team may ensure optimal use of FDG-PET/CT in LVV. Also training in optimal reading of the FDG-PET/CT for the imager should be supported by the affiliated medical societies.

A patient-centered and multidisciplinary approach has to be accounted for in research too. Therefore, for future research to be built into clinical practice, clinical relevance and patient well-being are essential. This includes minimizing the diagnostic burden where possible and utilizing the strengths of FDG-PET/CT—its high diagnostic performance and whole-body assessment—where necessary.

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