## we are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists



122,000

135M



Our authors are among the

TOP 1%





WEB OF SCIENCE

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

### Interested in publishing with us? Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected. For more information visit www.intechopen.com



### **FDG-PET in Large Vessel Vasculitis**

Quinn K.T. Ng<sup>1</sup>, Bernd Klaeser<sup>1</sup>, Ulrich A. Walker<sup>2</sup> and Martin A. Walter<sup>1</sup> <sup>1</sup>Institute of Nuclear Medicine University Hospital Haller Building Freiburgstrasse 4 CH-3010 Bern <sup>2</sup>Department of Rheumatology Felix-Platter Spital Burgfelderstr. 101 CH-4012 Basel Switzerland

#### 1. Introduction

[<sup>18</sup>F]FDG-PET, a non-invasive metabolic imaging technique, is based on the regional distribution of fluorine-18-fluorodeoxyglucose ([<sup>18</sup>F]FDG) reflecting increased glucose consumption of tissues. This technique has become increasingly important over the years in the management of patients with malignancies, as many malignant tumors show an enhanced glucose metabolism<sup>1</sup>. [<sup>18</sup>F]FDG uptake in infections and other inflammatory changes seen during oncologic imaging showed indications for the versatility of [<sup>18</sup>F]FDG-PET. Activated leukocytes also overexpress glucose transporters and avidly accumulate glucose and [<sup>18</sup>F]FDG <sup>2,3</sup>, providing an important rationale for its use in vasculitis. Remarkable images of patients with active vasculitis have been generated through [<sup>18</sup>F]FDG-PET scans<sup>4-12</sup>. Such images demonstrate the potential of [<sup>18</sup>F]FDG-PET for a variety of applications which implies that it may also be useful in the future for the routine evaluation of patients with several forms of vasculitis, particularly for large vessel vasculitis.

The family of vasculitides is categorized with reference to the size of vessels involved into large, medium, and small vessel vasculitis (**Table 1**). Of interest with respect to [<sup>18</sup>F]FDG-PET imaging is the group of large vessel vasculitides (giant cell arteritis and Takayasu's arteritis), other causes of aortitis and potentially also chronic periaortitis. Patients of both of these diseases regularly present a set of non-specific symptoms and laboratory tests which make their diagnosis and follow-up quite challenging. Consequently, patients may receive delays or even unsuccessful diagnostic work-up regarding their condition. The use of whole-body scanning via [<sup>18</sup>F]FDG-PET may provide a sensitive metabolic imaging modality that could lead to a more successful and shorter diagnostic workup.

The total amount of available data on [<sup>18</sup>F]FDG-PET in large vessel vasculitis is however still limited **(Table 2)**. In addition, no standardized guidelines are in place for the placement of [<sup>18</sup>F]FDG-PET imaging in the sequence of the diagnostic workup, its performance, interpretation and description. This chapter summarizes current clinical data in order to assist nuclear medicine and rheumatology practitioners in recommending, performing and interpreting the results of [<sup>18</sup>F]FDG-PET in patients with suspected large vessel vasculitis.

#### 2. Giant cell arteritis

Giant cell arteritis was first described by Hutchinson in 1890 as a granulomatous vasculitis of large and medium sized arteries <sup>13</sup>. Giant cell arteritis usually affects the cranial branches

of the arteries originating from the aortic arch, particularly the superficial temporal artery; however, involvement of the entire aorta and of its main branches also occurs in about 15% <sup>14</sup>. Giant cell arteritis is common in the Caucasian population, with an incidence of about 18 per 100,000 over 50 years of age <sup>15-17</sup>and affects women twice as often as men <sup>15-17</sup>. Autopsy studies however suggest that it may be much more common than is clinically apparent <sup>18</sup>.

Size of vessels	Type of vasculitis	Classification Criteria*
Large	Giant cell arteritis	Age at onset of disease ≥50 yr
		New headache
		Temporal artery abnormality
		Elevated erythrocyte sedimentation rate
		Abnormal findings on biopsy of temporal artery
	Takavasu's arteritis	Age at onset of disease $\leq 40$ vr
		Claudication of an extremity
		Decreased brachial artery pulse
		Difference in systolic blood pressure between arms
		A bruit over the subclavian arteries or the aorta
		Narrowing or occlusion of the entire aorta at
		angiography
Medium	Peri-arteritis nodosa	
	Kawasaki's arteritis	
	Primary CNS vasculitis	
	Buerger's disease	
Small	Wegener's disease	
	Churg-Strauss syndrome	
	Microscopic polyangiitis	
	Henoch-Schonlein purpura	
	Essential cryoglobulinaemic vasculitis	
	Cutaneous leukocytoclastic angiitis	
*Diamaai	is of giant call automitics at la	ast 2/E anitoria. Caraitinity -02 E% Craaifinity -00 E%

\*Diagnosis of giant cell arteritis: at least 3/5 criteria; Sensitivity =93.5%, Specificity =90.5% \*Diagnosis of Takayasu's arteritis: at least 3/6 criteria; Sensitivity =91.2%, Specificity =97.8%

#### Table 1. Classification of vasculitis

Currently, the etiology of giant cell arteritis still remains unknown. Classic histological pictures of giant cell arteritis show granulomatous inflammation wherein giant cells are usually located at the connection between the intima and media. However, panarteritides with mixed-cell inflammatory infiltrates of lymphomononuclear cells, occasional neutrophils and eosinophils, but without giant cells are also found <sup>19</sup>. The focal arteritic lesions cause ischemia which subsequently leads to the sudden or gradual onset of symptoms and a variety of systemic manifestations. A variety of systemic symptoms may be present <sup>20,21</sup>, and include myalgia, neck pain, scalp tenderness, jaw claudication, fever,

58

tenderness of the temporal arteries, transient ischemic attacks, general malaise, fatigue, anorexia, weight loss, depression, and night sweats <sup>20,22,23</sup>. Headache is probably the most frequent symptom which occurs in two thirds of patients <sup>21</sup>.

Authors	Year	Takayasu arteritis (number of patients)	Giant cell arteritis (number of patients)	Follow-up PETs	Reference
Blockmans et al.	1999	-	11*	)(  )	63
Blockmans et al.	2000	-	25*		64
Belhocine et al.	2002	-	3	3	65
Meller et al.	2003	5	-	-	52
Meller et al.	2003	1	14	7	48
Bleeker-Rovers et al.	2003	1	7*	1	45
Webb et al.	2004	18	-	8	44
Brodman et al.	2004	-	22	-	46
Moosig et al.	2004	-	12*	8	47
Andrews et al.	2004	6	-	6	43
Scheel et al.	2004	-	8	8	53
Kobayashi et al.	2005	14	-	7	50
Walter et al.	2005	6	20	4	49
Blockmans et al.	2006	-	35*	22	66
Blockmans et al.	2008	-	46	25	67
Both et al.	2008	-	25	9	68
Hautzel et al.	2008	-	18	-	69
Henes et al.	2008	3	10	-	70
Janssen et al.	2008	-	11	-	71
Arnaud et al.	2009	28	-	8	72
Lee et al.	2009	32	-	-	73
Vista et al.	2010	4	-	-	74
Lehmann et al.	2011	3	17	-	75

\*Giant cell arteritis and polymyalgia rheumatica patients

Table 2. Clinical studies on PET in the detection of large vessel inflammation: the present literature

#### 3. Takayasu's arteritis

Takayasu's arteritis is named after Mikito Takayasu, who in 1908 had reported the peculiar wreath-like arteriovenous anastomoses around the papillae in a young woman with pulseless disease <sup>24</sup>. This large vessel vasculitis primarily affects the aorta, its main branches, and the coronary and pulmonary arteries. The incidence rate of the disease is about 2 per 1,000,000 with its onset at a mean of 35 years of age <sup>25-27</sup>. Takayasu's arteritis occurs worldwide, although it is considered to be more common in the Orient <sup>28</sup> and is 10 times more prevalent in females than in males. The etiology of Takayasu's arteritis also remains unresolved, while the clinical course includes both an early and a late phase. Pathology studies in the early phase reveal granulomatous or diffuse productive

inflammation in the media and adventitia, with secondary thickening of the intima and occasional perivascular inflammation <sup>29</sup>. In the clinic, it is commonly the setting of fever of unknown origin with non-specific systemic symptoms. Contrary to the early phase, pathology studies in the late phase show marked thinning of the media, with disruption of elastic fibers, fibrotic thickening of the adventitia, and marked intimal proliferation<sup>29</sup>. The resulting variable ischemic symptoms secondary to arterial stenosis, occlusion, or arterial dilatation and aneurysmal formation cause various clinical conditions, such as arm claudication, decreased arterial pulses, carotodynia, visual loss, stroke, aortic regurgitation and arterial hypertension<sup>30</sup>. Topological classification of Takayasu's arteritis is based on the vascular provinces that are affected <sup>31</sup>, with either affection of the branches of the aortic arch (Type I), the ascending aorta, aortic arch and its branches and the thoracic descending aorta (Type IIB), the thoracic descending aorta, abdominal aorta, and/or renal arteries (Type III), the abdominal aorta and/or renal arteries (Type IV) or combined features of types IIB and IV.

#### 4. Diagnostic work-up in large vessel vasculitis

Giant cell arteritis and Takayasu's arteritis are both usually present with a wide clinical spectrum with no specific laboratory finding. The American College of Rheumatology has established a set of clinical, radiological and histological criteria to classify cases of biopsy-proven arteritis (**Table 1**) <sup>32,33</sup>. The presence of at least three of the described criteria is required for classifying a patient as having either Takayasu's arteritis or giant cell arteritis. These criteria provide a sensitivity of 93.5% with a specificity of 90.5% for diagnosing giant cell arteritis and a sensitivity of 91.2% with a specificity of 97.8% for diagnosing Takayasu's arteritis in biopsy-positive patients.

Although these criteria were originally designed for research purposes to help distinguish between different types of vasculitis; they are in clinical practice also frequently used for diagnosing an individual patient <sup>34</sup>. Nevertheless, the fact that frequent symptoms of giant cell arteritis such as jaw claudication, diplopia, neck pain, and elevated C-reactive protein are not included in the criteria, limits their widespread clinical application. Criteria that are included, such as headache and scalp tenderness can also be due to various other diseases. A normal erythrocyte sedimentation rate does not rule out giant cell arteritis, as it has been found in up to 30% of patients with biopsy-proven giant cell arteritis <sup>35,36</sup>. Furthermore, several patients with giant cell arteritis do only display nonspecific symptoms that does not apply to any set of criteria. Systemic giant cell arteritis symptoms such as fever, anorexia, weight loss and malaise may focus the diagnostic work-up towards a suspected malignancy, especially in older patients <sup>37</sup>.

Frequent clinical features of Takayasu's arteritis such as fever, postural dizziness, arthralgias, weight loss, headache, hypertension, elevated erythrocytes sedimentation rate and anemia were also not included in the classification criteria of the American College of Rheumatology. In contrast, angiographic findings and non-congruent blood pressure measurements between both arms are included as part of the diagnostic criteria although they may be false negative in early vasculitis <sup>38,39</sup>, or when the arteritis is restricted to the abdominal aorta, its branches, or to the pulmonary artery.

The wide clinical spectrum and the diagnostic limitations of giant cell arteritis and Takayasu's arteritis frequently cause delay in their diagnosis and subsequent treatment.

60

#### 5. [<sup>18</sup>F]FDG-PET and [<sup>18</sup>F]FDG-PET/CT

[<sup>18</sup>F]FDG-PET is an operator-independent, non-invasive imaging modality which examines the regional distribution of fluorine-18-fluorodeoxyglucose. Deoxyglucose is labeled with the positron emitting radionuclide, <sup>18</sup>Fluorine, and is intravenously administered to patients. [<sup>18</sup>F]FDG initially distributes in proportion to the perfusion of the organs, where it follows the same route of uptake as glucose. After entering cells through specific carriers, [<sup>18</sup>F]FDG is phosphorylated to [<sup>18</sup>F]FDG-6-phosphate, trapped intracellularly, but not metabolized further. The emitted positrons can be detected by a scanner and are displayed as a bright signal in the [<sup>18</sup>F]FDG-PET scan, reflecting an increased glucose requirement.

Heightened glucose metabolism is a property of many malignancies, a fact which has fostered the use of [<sup>18</sup>F]FDG-PET studies in the staging and follow-up in various types of cancers <sup>1</sup>.

Modern PET-CT scanners combine PET scanners with a computed tomography scanner in a single gantry system. With these scanners, images are taken sequentially with both devices in the same session and the reading can be done with the single co-registered image. As a consequence, the functional image obtained by PET, can be correlated more precisely with the anatomic structures. PET/CT has shown an incremental diagnostic value over CT and PET alone and there is emerging evidence of a substantial impact of PET/CT imaging on patient management <sup>40</sup>.

#### 6. [<sup>18</sup>F]FDG-PET scanning protocols for large vessel vasculitis

The American and the European Association of Nuclear Medicine have both established procedure guidelines for tumor imaging with [<sup>18</sup>F]FDG-PET <sup>41,42</sup>. The guidelines of the American Association of Nuclear Medicine from 1998 recommend fasting at least 4 hours prior to the scan. Low blood glucose levels are recommended, the injected activity should total 350 to 750 MBq [<sup>18</sup>F]FDG, and image acquisition should start 30 to 40 minutes after injection. In contrast, the guidelines of the European Association of Nuclear Medicine from the year 2003 advocate fasting at least 6 hours prior to the scan. Blood glucose level should not exceed 130mg/dl, the injected [<sup>18</sup>F]FDG activity should be 6 MBq/kg body weight, and acquisition should be started 60 minutes after injection.

Both professional associations however, have not established guidelines for the PET imaging of inflammation and consequently, the present studies **(Table 2)** have used several different protocols. Pre-scan fasting intervals of 4 hours <sup>43,44</sup>, 6 hours <sup>45-47</sup>, and overnight fasts <sup>48-50</sup> were applied. Body-weight adapted protocols for the applied [<sup>18</sup>F]FDG dose with 5 <sup>49</sup>, 6 <sup>50</sup> or 6.5 MBq <sup>46,51</sup> [<sup>18</sup>F]FDG per kilogram bodyweight were used. However, fixed doses of 296 MBq <sup>52</sup>, 370 MBq <sup>48</sup>, and 450 MBq <sup>47</sup> were also employed. To accelerate renal [<sup>18</sup>F]FDG elimination, one group also routinely administered additional furosemide <sup>45</sup>. Most studies on [<sup>18</sup>F]FDG-PET in large vessel vasculitis did not restrict scanning by maximal glucose levels and only three studies tolerated maximum serum glucose levels of 100mg/dl <sup>48,52</sup> and 180mg/dl <sup>49</sup>. Large differences in the time interval between [<sup>18</sup>F]FDG application and image acquisition were also shown as [<sup>18</sup>F]FDG-uptake periods of 45 minutes <sup>49,50</sup>, 60 minutes <sup>45,46,48,51,52</sup>, or 90 minutes <sup>43,44,47</sup> were reported. Dedicated PET scanners with full-ring detectors were generally used; nevertheless, hybrid cameras have also been successfully employed <sup>48,52,53</sup>. Reports on the use of combined [<sup>18</sup>F]FDG-PET-CT scanners in large vessel vasculitis are available <sup>50,54,55</sup>.

The average radiation dose from the [<sup>18</sup>F]FDG-PET scan is 7mSv, the average dose from the CT scan is 18mSv. The CT dose, however, can be lowered by the use of low-dose acquisition protocols.

This summary indicates that despite a lack of standardization, [<sup>18</sup>F]FDG-PET is a reliable imaging modality of large vessel vasculitis.

#### 7. [<sup>18</sup>F]FDG-PET and atherosclerosis

The accumulation of glucose analogues has not only been demonstrated in vasculitic vessels, but also in atherosclerotic plaques (**Figure 1**) <sup>56</sup>. Consequently, a modest large vessel [<sup>18</sup>F]FDG accumulation at the level of the major vessels occurs in about 50% of all PET-scans, with increased prevalence in older people <sup>57</sup>. This vascular uptake might be explained by smooth muscle metabolism in the media, subendothelial smooth muscle proliferation from senescence, and the presence of macrophages within the atherosclerotic plaque. Therefore, vascular uptake found in the [<sup>18</sup>F]FDG-PET scan is not specific for vasculitis.



Fig. 1. 71-year-old female patient that underwent FDG-PET/CT to evaluate a suspicious lung nodule. Focal FDG uptake was found in the thoracic and abdominal aorta corresponding to circumscribed artherosclerotic and aneurysmatic wall changes (arrow; from the Institute of Nuclear Medicine, University Hospital, Bern, CH)

Nevertheless, atherosclerotic lesions can be differentiated from vasculitic lesions by taking into account the vascular distribution, [<sup>18</sup>F]FDG uptake pattern, and the intensity of the [<sup>18</sup>F]FDG accumulation. For example, the internal carotid artery demonstrates atherosclerotic changes more frequently, while the external carotid artery more often reveals inflammatory changes. The uptake pattern of atherosclerotic mediastinal great vessels sometimes can be identified as ring-shaped structures, while contrary to this, the uptake pattern in the arteries of the abdomen and lower extremities are often linear and continuous <sup>58</sup>. Most discriminatingly, atherosclerotic lesions rarely demonstrate intense uptake of FDG <sup>48,49</sup>.

To distinguish vasculitis from atherosclerosis, a visual scoring of vascular [<sup>18</sup>F]FDG-uptake compared to the liver [<sup>18</sup>F]FDG-accumulation has been established. Three grades of large vessel [<sup>18</sup>F]FDG-uptake are differentiated **(Figure 2)**: a) Grade I: uptake present but lower than liver uptake, b) Grade II: similar to liver uptake, and c) Grade III: uptake higher than liver uptake. Proposed by Meller et al. <sup>48</sup>, this scale was subsequently validated to represent the severity of inflammation <sup>49</sup>.



Fig. 2. The visual arteritis score as proposed by Meller et al. <sup>48</sup>. The severity of large vessel [18F]FDG-uptake is visually graded: **A**) Grade 1: uptake present but lower than liver uptake; **B**) Grade 2: similar to liver uptake; **C**) Grade 3: uptake higher than liver uptake (images derived from reference <sup>49</sup>).

So far, this score has been employed in two reference collectives without clinical symptoms or laboratory signs of large vessel inflammation in order to determine the uptake in non-vasculitic vessels <sup>48,49</sup>. Grade I vessel uptake was frequently found in the thoracic part of the aorta which was most likely due to atherosclerosis. Accordingly, only Grade II or III [<sup>18</sup>F]FDG-uptake in the thoracic aorta and any visible uptake in other segments should routinely be judged as active large vessel inflammation. In this manner, the majority of lesions can be ruled out as due to atherosclerosis. On the other hand, computed quantification of [<sup>18</sup>F]FDG-uptake using the [<sup>18</sup>F]FDG *standardized uptake value* (SUV) has not shown to be useful in discriminating atherosclerosis from vasculitis yet.

#### 8. [<sup>18</sup>F]FDG-PET for diagnosing giant cell arteritis

The diagnosis of giant cell arteritis is currently based mainly on clinical evaluation, laboratory results, and temporal biopsy, but a gold standard is lacking. Despite recent advances, no imaging modality has been included in the American College of Rheumatology diagnostic criteria for giant cell arteritis **(Table 1)**. Nevertheless, [<sup>18</sup>F]FDG-

PET has indicated its usefulness clinically for a number of studies through better evidence, as compared to Takayasu's arteritis, due to the higher frequency of the disease **(Table 2)**.

The uptake pattern in large vessels affected by giant cell arteritis was linear, continuous, and was predominantly of Grade II. The thoracic vessels were most frequently affected, followed by the abdominal vessels <sup>48,49</sup>. In the published studies, the ability of [<sup>18</sup>F]FDG-PET to detect large vessel inflammation differed considerably. In studies employing patients with polymyalgia rheumatica and giant cell arteritis, sensitivities between 56% and 100% were reported <sup>45,46,51,53</sup>, with a specificity between 77% and 98% <sup>51</sup>. The large differences seen between the studies can partially be explained by dissimilar disease activity; as suggested by one study demonstrating that the sensitivity depends on the degree of inflammation (**Figure 4**). C-reactive protein has shown to be a better predictor for the sensitivity of [<sup>18</sup>F]FDG-PET in giant cell arteritis than the erythrocyte sedimentation rate <sup>49</sup>.

Studies employing [<sup>18</sup>F]FDG-PET and Magnetic Resonance Imaging (MRI) revealed comparable sensitivities for both methods. [<sup>18</sup>F]FDG-PET may have the advantage that it simultaneously identifies more affected vessels <sup>48,53</sup>, possibly reflecting the fact that metabolic changes normally precede morphologic changes in giant cell arteritis. Additionally, [<sup>18</sup>F]FDG-PET might also allow new insights into the pathology of giant cell arteritis and polymyalgia rheumatica. A study demonstrated inflammation of the aorta or its major branches in 92% of patients with polymyalgia rheumatica. Tracer uptake was strongly correlated with the erythrocyte sedimentation rate and the C-reactive protein. These data underline that polymyalgia rheumatica frequently may be accompanied by subclinical vasculitis <sup>47</sup>.

[<sup>18</sup>F]FDG-PET also offers the possibility of whole-body screening in one procedure which may become helpful in the follow-up of patients with giant cell arteritis. The results of computed quantification of vascular [<sup>18</sup>F]FDG accumulation correlate well and better than Magnetic Resonance Imaging with the clinical course also at longitudinal follow up <sup>47</sup>,<sup>48</sup>.

The value of [<sup>18</sup>F]FDG-PET for diagnosing temporal arteritis has however been questioned in a study of 22 patients, 17 of which had involvement of the temporal arteries which was not detected by [<sup>18</sup>F]FDG-PET <sup>46</sup>. The high [<sup>18</sup>F]FDG uptake of the brain and the small diameter of the temporal arteries limited its sensitivity in the detection of cranial vessel involvement with the whole-body PET technique used. Newer generation PET/CT scanners offer an image resolution corresponding to a three-fold improvement compared to the technology used in the aforementioned study (2mm vs. 7mm), potentially allowing to image even smaller arteries as the temporal arteries. Further clinical studies must are warranted to clarify the potential role of PET in the non-invasive work-up of temporal vasculitis.

#### 9. [<sup>18</sup>F]FDG-PET for diagnosing Takayasu's arteritis

The diagnosis of Takayasu's arteritis frequently integrates imaging and angiographic **(Table 1)**. However, angiographic alterations usually occur in the late phase of Takayasu's arteritis while metabolic changes are already present in the early phases. The data on the use of [<sup>18</sup>F]FDG-PET in Takayasu's arteritis are less robust compared to those in giant cell arteritis **(Table 2)**, accounting for the different prevalences of both vasculitides.

During the early phase of Takayasu's arteritis, the [<sup>18</sup>F]FDG uptake pattern is linear and continuous (**Figure 3A**), while in the late phase the pattern can become patchier rather than continuous but still remains in a linear distribution <sup>44</sup>. Three studies reported sensitivities of [<sup>18</sup>F]FDG-PET between 83% and 100% <sup>43,44,52</sup>, which is comparable to Magnetic Resonance

64

Imaging. Additionally, metabolic imaging using [18F]FDG-PET for Takayasu's arteritis has identified more affected vascular regions than morphologic imaging using Magnetic Resonance Imaging <sup>52</sup>. However, unlike Magnetic Resonance Imaging, [<sup>18</sup>F]FDG-PET does not give any information about the wall structure or the lumen of affected vessels.

Similarly to giant cell arteritis, there is a clear correlation between the activity of vessel inflammation and the sensitivity of [18F]FDG-PET. [18F]FDG-PET positive patients have shown significantly higher erythrocyte sedimentation rates and C-reactive protein levels as compared to [18F]FDG-PET negative patients, with the C-reactive protein being the superior marker<sup>44</sup>.

Follow-ups in Takayasu's arteritis only based on clinical symptoms alone have shown to be of limited accuracy. In a previous report, biopsies showed active inflammation in 44% of patients thought to be in clinical remission <sup>59</sup>. However, [<sup>18</sup>F]FDG-PET is able to detect more sites than just those that were clinically active <sup>44</sup>. This makes [<sup>18</sup>F]FDG-PET a promising candidate to be regularly employed in the follow-up of Takayasu's arteritis (Figure 3) due its high sensitivity and the good correlation with the outcome 43,44,49.



Fig. 3. A) [18F]FDG-PET of a patient with Takayasu's arteritis with markedly abnormal uptake of [18F]FDG in the aortic arch and carotide arteries (arrows). B) [18F]FDG-PET scan of the same patient in clinical remission after treatment with prednisone and intravenous cyclophosphamide (from reference <sup>43</sup>)

#### 10. [<sup>18</sup>F]FDG-PET-CT in large vessel vasculitis

The combination of [18F]FDG-PET scanners with Computed Tomography (CT) has gained importance in the management of patients with malignancies 60-62 by allowing the integration of morphologic and metabolic information for detection, staging, and therapy control. Rapidly increasing availability of [18F]FDG-PET-CT scanners are also opening new opportunities for its application in rheumatology by allowing the investigation of both morphologic and metabolic activity while significantly improving the localization of affected vessels. Two case reports have already indicated the value of [18F]FDG-PET-CT

65



Fig. 4. Sensitivity of Large Vessel Vasculitis [<sup>18</sup>F]FDG-PET as a function of C-reactive protein (CRP)levels and erythrocyte sedimentation rate (ES§), respectively. High sensitivity for detection of large vessel vasculitis is reached at high CRP and ESR levels (from reference <sup>49</sup>).



Fig. 5. 52 year-old female patient with clinical suspision of a large vessel vasculitis. The FDG-PET/CT shows intense tracer uptake along the aortic arch, the supraaortic branches and the supraclavicular arteries. There is also uptake along the abdominal aorta and femoral arteries and branches.



Fig. 6. FDG-PET/CT of a 67-year-old male patient with recent loss of weight and continious deterioration of his general condition. The PET/CT performed did not support the clinical suspicion of a malignant tumor but showed intense vessel uptake (**A**). Additional high-resolution PET images of the chest and neck illustrate the ability of state-of-the-art PET machines to visualize circumscribed wall inflammation even in medium sized arteries as the carotic sinus and the vessel wall of the aortic arch (**B**)

scanners in large vessel vasculitis <sup>53,54</sup> and one clinical trial has investigated its value in 14 patients <sup>50</sup>. The co-registered CT scan was most useful for the anatomic identification of vascular [<sup>18</sup>F]FDG-uptake, especially in case of rather moderate [<sup>18</sup>F]FDG-accumulation. Furthermore, the anatomic identification of mediastinal [<sup>18</sup>F]FDG uptake, particularly in the pulmonary arteries was significantly improved **(Figure 5)**. The coregistered CT scan allows for a sensitive detection of calcified plaques to discriminate vasculitis from inflammatory arteriosclerotic changes.

#### **11. Conclusions**

In conclusion, whole-body imaging with [<sup>18</sup>F]FDG-PET is highly effective in assessing the extent of giant cell arteritis and Takayasu's arteritis, respectively.

[<sup>18</sup>F]FDG-PET has shown to have identified more affected vascular regions than morphologic imaging with Magnetic Resonance Imaging in both diseases.

A unique feature and strength of FDG-PET is the opportunity to monitor disease activity non-invasively. In contrast to other imaging modalities PET allows for an immediate assessment of response to anti-inflammatory treatment and is suitable to guide therapy.

Recent developments in PET technology such as integrated PET/CT machines and increased image resolution of the PET submodality imply significant improvements for vaculitis imaging with FDG.

Further studies are warranted to evaluate the diagnostic benefit of these newer technical developments.

[<sup>18</sup>F]FDG-PET has the clear potential to develop into a valuable tool in the diagnostic workup of both giant cell arteritis and Takayasu's arteritis, and may become a first-line investigation technique for non-invasive therapy monitoring. However, consensus regarding the imaging procedures as well as further clinical evidence is urgently needed.

#### 12. References

- [1] Been LB, Suurmeijer AJ, Cobben DC, Jager PL, Hoekstra HJ, Elsinga PH. [18F]FLT-PET in oncology: current status and opportunities. Eur J Nucl Med Mol Imaging 2004;31(12):1659-72.
- [2] Ishimori T, Saga T, Mamede M, Kobayashi H, Higashi T, Nakamoto Y, Sato N, Konishi J. Increased (18)F-FDG uptake in a model of inflammation: concanavalin A-mediated lymphocyte activation. J Nucl Med 2002;43(5):658-63.
- [3] Jones HA, Cadwallader KA, White JF, Uddin M, Peters AM, Chilvers ER. Dissociation between respiratory burst activity and deoxyglucose uptake in human neutrophil granulocytes: implications for interpretation of (18)F-FDG PET images. J Nucl Med 2002;43(5):652-7.
- [4] Turlakow A, Yeung HW, Pui J, Macapinlac H, Liebovitz E, Rusch V, Goy A, Larson SM. Fludeoxyglucose positron emission tomography in the diagnosis of giant cell arteritis. Arch Intern Med 2001;161(7):1003-7.
- [5] Blockmans D, Van Moer E, Dehem J, Feys C, Mortelmans L. Positron emission tomography can reveal abdominal periaortitis. Clin Nucl Med 2002;27(3):211-2.
- [6] Wenger M, Gasser R, Donnemiller E, Erler H, Glossmann H, Patsch JR, Moncayo R, Schirmer M. Images in cardiovascular medicine. Generalized large vessel arteritis visualized by 18fluorodeoxyglucose-positron emission tomography. Circulation 2003;107(6):923.
- [7] Brodmann M, Lipp RW, Aigner R, Pilger E. Positron emission tomography reveals extended thoracic and abdominal peri-aortitis. Vasc Med 2003;8(2):127-8.
- [8] Wiest R, Gluck T, Schonberger J, Scholmerich J, Eilles C, Muller-Ladner U. Clinical image: occult large vessel vasculitis diagnosed by PET imaging. Rheumatol Int 2001;20(6):250.
- [9] De Winter F, Petrovic M, Van de Wiele C, Vogelaers D, Afschrift M, Dierckx RA. Imaging of giant cell arteritis: evidence of splenic involvement using FDG positron emission tomography. Clin Nucl Med 2000;25(8):633-4.
- [10] Hara M, Goodman PC, Leder RA. FDG-PET finding in early-phase Takayasu arteritis. J Comput Assist Tomogr 1999;23(1):16-8.
- [11] Malik IS, Harare O, A AL-N, Beatt K, Mason J. Takayasu's arteritis: management of left main stem stenosis. Heart 2003;89(3):e9.
- [12] Walter MA, Melzer RA, Graf M, Tyndall A, Muller-Brand J, Nitzsche EU. [18F]FDG-PET of giant-cell aortitis. Rheumatology (Oxford) 2005;44(5):690-1.
- [13] Hutchinson J. On a peculiar form of thrombotic arteritis of the aged which is sometimes productive or gangrene. Arch Surg 1890;1:323-329.
- [14] Klein RG, Hunder GG, Stanson AW, Sheps SG. Large artery involvement in giant cell (temporal) arteritis. Ann Intern Med 1975;83(6):806-12.
- [15] Salvarani C, Gabriel SE, O'Fallon WM, Hunder GG. The incidence of giant cell arteritis in Olmsted County, Minnesota: apparent fluctuations in a cyclic pattern. Ann Intern Med 1995;123(3):192-4.

- [16] Franzen P, Sutinen S, von Knorring J. Giant cell arteritis and polymyalgia rheumatica in a region of Finland: an epidemiologic, clinical and pathologic study, 1984-1988. J Rheumatol 1992;19(2):273-6.
- [17] Gonzalez-Gay MA, Alonso MD, Aguero JJ, Bal M, Fernandez-Camblor B, Sanchez-Andrade A. Giant cell arteritis in Mediterranean countries: comment on the article by Salvarani et al. Arthritis Rheum 1992;35(10):1249-50.
- [18] Ostberg G. An arteritis with special reference to polymyalgia arteritica. Acta Pathol Microbiol Scand [A] 1973;237:Suppl 237:1-59.
- [19] Lie JT. Illustrated histopathologic classification criteria for selected vasculitis syndromes. American College of Rheumatology Subcommittee on Classification of Vasculitis. Arthritis Rheum 1990;33(8):1074-87.
- [20] Weyand CM. The Dunlop-Dottridge Lecture: The pathogenesis of giant cell arteritis. J Rheumatol 2000;27(2):517-22.
- [21] Salvarani C, Macchioni PL, Tartoni PL, Rossi F, Baricchi R, Castri C, Chiaravalloti F, Portioli I. Polymyalgia rheumatica and giant cell arteritis: a 5-year epidemiologic and clinical study in Reggio Emilia, Italy. Clin Exp Rheumatol 1987;5(3):205-15.
- [22] Huston KA, Hunder GG. Giant cell (cranial) arteritis: a clinical review. Am Heart J 1980;100(1):99-105.
- [23] Calamia KT, Hunder GG. Giant cell arteritis (temporal arteritis) presenting as fever of undetermined origin. Arthritis Rheum 1981;24(11):1414-8.
- [24] Takayasu M. Case with unusual changes of the central vessels in the retina. Acta Soc Ophthal Jpn 1908;12:554-5.
- [25] Waern AU, Andersson P, Hemmingsson A. Takayasu's arteritis: a hospital-region based study on occurrence, treatment and prognosis. Angiology 1983;34(5):311-20.
- [26] Hall S, Barr W, Lie JT, Stanson AW, Kazmier FJ, Hunder GG. Takayasu arteritis. A study of 32 North American patients. Medicine (Baltimore) 1985;64(2):89-99.
- [27] el-Reshaid K, Varro J, al-Duwairi Q, Anim JT. Takayasu's arteritis in Kuwait. J Trop Med Hyg 1995;98(5):299-305.
- [28] Lande A. Abdominal Takayasu's aortitis, the middle aortic syndrome and atherosclerosis. A critical review. Int Angiol 1998;17(1):1-9.
- [29] Nasu T. Pathology of pulseless disease. A systematic study and critical review of twenty-one autopsy cases reported in Japan. Angiology 1963;14:225-42.
- [30] Matsunaga N, Hayashi K, Sakamoto I, Ogawa Y, Matsumoto T. Takayasu arteritis: protean radiologic manifestations and diagnosis. Radiographics 1997;17(3):579-94.
- [31] Moriwaki R, Noda M, Yajima M, Sharma BK, Numano F. Clinical manifestations of Takayasu arteritis in India and Japan--new classification of angiographic findings. Angiology 1997;48(5):369-79.
- [32] Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, Edworthy SM, Fauci AS, Leavitt RY, Lie JT and others. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33(8):1122-8.
- [33] Arend WP, Michel BA, Bloch DA, Hunder GG, Calabrese LH, Edworthy SM, Fauci AS, Leavitt RY, Lie JT, Lightfoot RW, Jr. and others. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum 1990;33(8):1129-34.

- [34] Rao JK, Allen NB, Pincus T. Limitations of the 1990 American College of Rheumatology classification criteria in the diagnosis of vasculitis. Ann Intern Med 1998;129(5):345-52.
- [35] Salvarani C, Hunder GG. Giant cell arteritis with low erythrocyte sedimentation rate: frequency of occurence in a population-based study. Arthritis Rheum 2001;45(2):140-5.
- [36] Hayreh SS, Zimmerman B. Management of giant cell arteritis. Our 27-year clinical study: new light on old controversies. Ophthalmologica 2003;217(4):239-59.
- [37] Gonzalez-Gay MA, Garcia-Porrua C, Salvarani C, Olivieri I, Hunder GG. The spectrum of conditions mimicking polymyalgia rheumatica in Northwestern Spain. J Rheumatol 2000;27(9):2179-84.
- [38] Lambert M, Hachulla E, Hatron PY, Perez-Cousin M, Beregi JP, Warembourg H, Devulder B. [Takayasu's arteritis: vascular investigations and therapeutic management. Experience with 16 patients]. Rev Med Interne 1998;19(12):878-84.
- [39] Lambert M, Hatron PY, Hachulla E, Warembourg H, Devulder B. Takayasu's arteritis diagnosed at the early systemic phase: diagnosis with noninvasive investigation despite normal findings on angiography. J Rheumatol 1998;25(2):376-7.
- [40] Czernin J, Benz MR, Allen-Auerbach MS. PET/CT imaging: The incremental value of assessing the glucose metabolic phenotype and the structure of cancers in a single examination. Eur J Radiol;73(3):470-80.
- [41] Schelbert HR, Hoh CK, Royal HD, Brown M, Dahlbom MN, Dehdashti F, Wahl RL. Procedure guideline for tumor imaging using fluorine-18-FDG. Society of Nuclear Medicine. J Nucl Med 1998;39(7):1302-5.
- [42] Bombardieri E, Aktolun C, Baum RP, Bishof-Delaloye A, Buscombe J, Chatal JF, Maffioli L, Moncayo R, Mortelmans L, Reske SN. FDG-PET: procedure guidelines for tumour imaging. Eur J Nucl Med Mol Imaging 2003;30(12):BP115-24.
- [43] Andrews J, Al-Nahhas A, Pennell DJ, Hossain MS, Davies KA, Haskard DO, Mason JC. Non-invasive imaging in the diagnosis and management of Takayasu's arteritis. Ann Rheum Dis 2004;63(8):995-1000.
- [44] Webb M, Chambers A, A AL-N, Mason JC, Maudlin L, Rahman L, Frank J. The role of 18F-FDG PET in characterising disease activity in Takayasu arteritis. Eur J Nucl Med Mol Imaging 2004;31(5):627-34.
- [45] Bleeker-Rovers CP, Bredie SJ, van der Meer JW, Corstens FH, Oyen WJ. F-18fluorodeoxyglucose positron emission tomography in diagnosis and follow-up of patients with different types of vasculitis. Neth J Med 2003;61(10):323-9.
- [46] Brodmann M, Lipp RW, Passath A, Seinost G, Pabst E, Pilger E. The role of 2-18F-fluoro-2-deoxy-D-glucose positron emission tomography in the diagnosis of giant cell arteritis of the temporal arteries. Rheumatology (Oxford) 2004;43(2):241-2.
- [47] Moosig F, Czech N, Mehl C, Henze E, Zeuner RA, Kneba M, Schroder JO. Correlation between 18-fluorodeoxyglucose accumulation in large vessels and serological markers of inflammation in polymyalgia rheumatica: a quantitative PET study. Ann Rheum Dis 2004;63(7):870-3.
- [48] Meller J, Strutz F, Siefker U, Scheel A, Sahlmann CO, Lehmann K, Conrad M, Vosshenrich R. Early diagnosis and follow-up of aortitis with [(18)F]FDG PET and MRI. Eur J Nucl Med Mol Imaging 2003;30(5):730-6.

- [49] Walter MA, Melzer RA, Schindler C, Muller-Brand J, Tyndall A, Nitzsche EU. The value of [18F]FDG-PET in the diagnosis of large-vessel vasculitis and the assessment of activity and extent of disease. Eur J Nucl Med Mol Imaging 2005;32(6):674-81.
- [50] Kobayashi Y, Ishii K, Oda K, Nariai T, Tanaka Y, Ishiwata K, Numano F. Aortic wall inflammation due to Takayasu arteritis imaged with 18F-FDG PET coregistered with enhanced CT. J Nucl Med 2005;46(6):917-22.
- [51] Blockmans D, Stroobants S, Maes A, Mortelmans L. Positron emission tomography in giant cell arteritis and polymyalgia rheumatica: evidence for inflammation of the aortic arch. Am J Med 2000;108(3):246-9.
- [52] Meller J, Grabbe E, Becker W, Vosshenrich R. Value of F-18 FDG hybrid camera PET and MRI in early takayasu aortitis. Eur Radiol 2003;13(2):400-5.
- [53] Scheel AK, Meller J, Vosshenrich R, Kohlhoff E, Siefker U, Muller GA, Strutz F. Diagnosis and follow up of aortitis in the elderly. Ann Rheum Dis 2004;63(11):1507-10.
- [54] Kroger K, Antoch G, Goyen M, Freudenberg LS, Veit P, Janicke I, Bockisch A, Forsting M. Positron emission tomography/computed tomography improves diagnostics of inflammatory arteritis. Heart Vessels 2005;20(4):179-83.
- [55] Antoch G, Freudenberg LS, Debatin JF, Kroger K. Images in vascular medicine. Diagnosis of giant cell arteritis with PET/CT. Vasc Med 2003;8(4):281-2.
- [56] Rudd JH, Warburton EA, Fryer TD, Jones HA, Clark JC, Antoun N, Johnstrom P, Davenport AP, Kirkpatrick PJ, Arch BN and others. Imaging atherosclerotic plaque inflammation with [18F]-fluorodeoxyglucose positron emission tomography. Circulation 2002;105(23):2708-11.
- [57] Yun M, Jang S, Cucchiara A, Newberg AB, Alavi A. 18F FDG uptake in the large arteries: a correlation study with the atherogenic risk factors. Semin Nucl Med 2002;32(1):70-6.
- [58] Yun M, Yeh D, Araujo LI, Jang S, Newberg A, Alavi A. F-18 FDG uptake in the large arteries: a new observation. Clin Nucl Med 2001;26(4):314-9.
- [59] Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, Rottem M, Hoffman GS. Takayasu arteritis. Ann Intern Med 1994;120(11):919-29.
- [60] Sachelarie I, Kerr K, Ghesani M, Blum RH. Integrated PET-CT: evidence-based review of oncology indications. Oncology (Williston Park) 2005;19(4):481-90; discussion 490-2, 495-6.
- [61] Macapinlac HA. FDG PET and PET/CT imaging in lymphoma and melanoma. Cancer J 2004;10(4):262-70.
- [62] Frank SJ, Chao KS, Schwartz DL, Weber RS, Apisarnthanarax S, Macapinlac HA. Technology insight: PET and PET/CT in head and neck tumor staging and radiation therapy planning. Nat Clin Pract Oncol 2005;2(10):526-33.
- [63] Blockmans D, Maes A, Stroobants S, Nuyts J, Bormans G, Knockaert D, Bobbaers H, Mortelmans L. New arguments for a vasculitic nature of polymyalgia rheumatica using positron emission tomography. Rheumatology (Oxford) 1999;38(5):444-7.
- [64] Blockmans D, Baeyens H, Van Loon R, Lauwers G, Bobbaers H. Periaortitis and aortic dissection due to Wegener's granulomatosis. Clin Rheumatol 2000;19(2):161-4.
- [65] Belhocine T, Kaye O, Delanaye P, Corman V, Baghaie M, Deprez M, Daenen F, De Barsy C, Beckers C, Gomez P and others. [Horton's disease and extra-temporal vessel

locations: role of 18FDG PET scan. Report of 3 cases and review of the literature]. Rev Med Interne 2002;23(7):584-91.

- [66] Blockmans D, Ceuninck Ld, Vanderschueren S, Knockaert D, Mortelmans L, Bobbaers H. Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: A prospective study of 35 patients. Arthritis Care & Research 2006;55(1):131-137.
- [67] Blockmans D, Coudyzer W, Vanderschueren S, Stroobants S, Loeckx D, Heye S, De Ceuninck L, Marchal G, Bobbaers H. Relationship between fluorodeoxyglucose uptake in the large vessels and late aortic diameter in giant cell arteritis. Rheumatology 2008;47(8):1179-1184.
- [68] Both M, Ahmadi-Simab K, Reuter M, Dourvos O, Fritzer E, Ullrich S, Gross WL, Heller M, BĤhre M. MRI and FDG-PET in the assessment of inflammatory aortic arch syndrome in complicated courses of giant cell arteritis. Annals of the Rheumatic Diseases 2008;67(7):1030-1033.
- [69] Hautzel H, Sander O, Heinzel A, Schneider M, Muller H-W. Assessment of Large-Vessel Involvement in Giant Cell Arteritis with 18F-FDG PET: Introducing an ROC-Analysis-Based Cutoff Ratio. J Nucl Med 2008;49(7):1107-1113.
- [70] Henes J, Müller M, Krieger J, Balletshofer B, Pfannenberg A, Kanz L, Kötter I. [18F] FDG-PET/CT as a new and sensitive imaging method for the diagnosis of largevessel vasculitis. Clinical and experimental rheumatology 2008;26(3).
- [71] Janssen SP, Comans EH, Voskuyl AE, Wisselink W, Smulders YM. Giant cell arteritis: Heterogeneity in clinical presentation and imaging results. Journal of Vascular Surgery 2008;48(4):1025-1031.
- [72] Arnaud L, Haroche J, Malek Z, Archambaud F, Gambotti L, Grimon G, Kas A, Costedoat-Chalumeau N, Cacoub P, Toledano D and others. Is 18Ffluorodeoxyglucose positron emission tomography scanning a reliable way to assess disease activity in takayasu arteritis? Arthritis & Rheumatism 2009;60(4):1193-1200.
- [73] Lee SG, Ryu JS, Kim HO, Oh JS, Kim YG, Lee CK, Yoo B. Evaluation of disease activity using F-18 FDG PET-CT in patients with Takayasu arteritis. Clinical nuclear medicine 2009;34(11):749.
- [74] Vista EGS, Santos Estrella PV, Lichauco JJT. Flourine-18 flourodeoxyglucose Positron Emission Tomography as a non-invasive test of disease activity in Takayasu's arteritis -- A report of four cases. Autoimmunity Reviews 2010;9(7):503-506.
- [75] Lehmann P, Buchtala S, Achajew N, Haerle P, Ehrenstein B, Lighvani H, Fleck M, Marienhagen J. 18F-FDG PET as a diagnostic procedure in large vessel vasculitis – a controlled, blinded re-examination of routine PET scans. Clinical Rheumatology 2011;30(1):37-42.[



#### Advances in the Diagnosis and Treatment of Vasculitis Edited by Dr. Luis M Amezcua-Guerra

ISBN 978-953-307-786-4 Hard cover, 366 pages Publisher InTech Published online 09, November, 2011 Published in print edition November, 2011

This book represents the culmination of the efforts of a group of outstanding experts in vasculitis from all over the world, who have endeavored to draw themselves into this volume by keeping both the text and the accompanying figures and tables lucid and memorable. The book provides practical information about the screening approach to vasculitis by laboratory analysis, histopathology and advanced image techniques, current standard treatment along with new and more specific interventions including biologic agents, reparative surgery and experimental therapies, as well as miscellaneous issues such as the extra temporal manifestations of "temporal arteritis" or the diffuse alveolar hemorrhage syndrome. The editor and each of the authors invite you to share this journey by one of the most exciting fields of the medicine, the world of Vasculitis.

#### How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Quinn K.T. Ng, Bernd Klaeser, Ulrich A. Walker and Martin A. Walter (2011). FDG-PET in Large Vessel Vasculitis, Advances in the Diagnosis and Treatment of Vasculitis, Dr. Luis M Amezcua-Guerra (Ed.), ISBN: 978-953-307-786-4, InTech, Available from: http://www.intechopen.com/books/advances-in-the-diagnosis-and-treatment-of-vasculitis/fdg-pet-in-large-vessel-vasculitis



#### InTech Europe

University Campus STeP Ri Slavka Krautzeka 83/A 51000 Rijeka, Croatia Phone: +385 (51) 770 447 Fax: +385 (51) 686 166 www.intechopen.com

#### InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai No.65, Yan An Road (West), Shanghai, 200040, China 中国上海市延安西路65号上海国际贵都大饭店办公楼405单元 Phone: +86-21-62489820 Fax: +86-21-62489821 © 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the <u>Creative Commons Attribution 3.0</u> <u>License</u>, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

# IntechOpen

# IntechOpen