POTENTIAL APPLICATIONS OF PET/CT/MRI
IN INFLAMMATORY DISEASES – PART II
Cardiopulmonary and vascular inflammation

Running Title: PET/CT/MRI in inflammation II

Moozhan Nikpanah1, Sanaz Katal2, Thomas Q Christensen3, Thomas J Werner4, Søren Hess5,6, Ali Gholamrezanezhad7, Abass Alavi4, Babak Saboury1,4

Affiliations:
1. Department of Radiology and Imaging Sciences, Clinical Center, National Institutes of Health, Bethesda, MD, USA
2. Independent researcher
3. Department of Clinical Engineering, Region of Southern Denmark, Odense, Denmark
4. Department of Radiology, University of Pennsylvania, Philadelphia, PA, USA
5. Department of Radiology and Nuclear Medicine, Hospital Southwest Jutland, University Hospital of Southern Denmark, Denmark
6. Department of Regional Health Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark
7. Keck School of Medicine, University of Southern California (USC), Los Angeles, California, US

Corresponding Author:
Abass Alavi
3400 Spruce St, Philadelphia, PA 19104
Office number: 215-662-3069
Fax number: 215-573-4107
Email address: abass.alavi@pennmedicine.upenn.edu

Sources of Funding: ___

Declaration of conflict of interest: None
INTRODUCTION

As described in Part I of this double paper, the non-specificity of FDG which was originally considered a drawback now forms the basis of PET-hybrid imaging in systemic inflammatory disorders – the targets are molecular and cellular processes of inflammation, i.e. the so-called respiratory burst based on the same principles as the Warburg effect in malignant cells (1-4), but as mentioned, clinical implementation is still lacking despite the obvious potential from exceptional soft tissue contrast and reduced radiation dose (5, 6).

Some features of inflammatory diseases make them particularly interesting in the era of FDG and PET-based imaging. First, many inflammatory diseases including vasculitides are inherently systemic diseases but present with relatively non-specific symptoms and signs with few organ specific diagnostic clues, e.g. fever and general malaise. Thus, a high sensitivity whole body scan is a desirable first-line imaging modality, and it is perhaps not surprising that the most investigated clinical entities include the highly heterogeneous groups of unclarified fever of unknown origin and systemic bacteremia to find the focal origin (7). In these domains, the upfront implementation of routine whole-body FDG-PET/MRI is probably not yet warranted or logistically feasible. Nonetheless, the potential to supplement the initial whole-body FDG-PET/CT with focused PET/MRI of suspicious findings is not far-fetched in our time with novel fast reconstruction algorithms that allows for almost instantaneous image interpretation. The same is probably true for other whole-body disorders, where FDG-PET/CT is finding its place, but where the literature is still lacking, e.g. HIV, where studies have demonstrated correlation between FDG uptake pattern in lymph nodes, disease stage, and viral load (8, 9).

A specific challenge is the effect of treatment on FDG-uptake, which is exploited in monitoring treatment response, but also may cause false negative findings if patient preparation is not controlled sufficiently, especially in vasculitides. Thus steroid-naïve patients are preferable,
but if this is not possible scans should be performed within three days of treatment initiation or steroids should be discontinued for at least 2 weeks in any patients treated with doses above 10 mg pr. day (10).

This paper outlines the current potential for hybrid molecular imaging in cardiopulmonary and vascular inflammation with special focus on the potential for fused FDG-PET/CT/MRI.

**BRIDGING THE GAP: FDG-PET/MRI AS THE MODALITY OF CHOICE FOR IMAGING VASCULITIDES**

Systemic vasculitides are multisystemic diseases defined by inflammation in the walls of blood vessels of varying size, type and location (11). Categorization of noninfectious vasculitides is mainly based upon the predominant size of the affected vessels, namely, large, medium or small vessel size (Figure 1) (11). An important point in this classification is that overlaps exist within the size of the involved arteries, as arteries of any size can be affected by any of the three major categories of vasculitis (11).

Patients affected by systemic vasculitis might show a wide range of clinical presentations from organ-specific manifestations to generalized symptoms (12). In numerous instances, patients are diagnosed when showing late manifestations of the disease. While early diagnosis and therapy of systemic vasculitides can prevent life-threatening complications leading to organ failure (12). Moreover, even though inflammatory markers are mostly elevated in these patients, no particular laboratory test has been found useful as the solo biomarker for diagnosis confirmation (12). Additionally, systemic vasculitides can be mimicked by several inflammatory, infectious and neoplastic diseases (13). Therefore tissue biopsy has been considered as the gold standard in vasculitis diagnosis. However, sampling-error, invasiveness and infeasibility of
performing biopsy in some instances, emphasizes the need for a robust method for making the diagnosis, evaluating disease extension, and assessing the therapeutic response (12).

As vasculitis involves various regions of arteries simultaneously, understanding the extent and activity of the disease is essential for appropriate clinical response. Imaging has shown a critical role in detection of vascular abnormalities, assessing the extent of involvement and global evaluation of the affected patients and has helped broaden our knowledge of these disorders. Structural imaging modalities predominantly used for assessment of vasculitis include doppler ultrasound (US), MRI, CT, and angiography. US, CT, and MRI detect vessel wall and luminal changes associated with vasculitis (14), whereas angiography lacks the ability to evaluate vessel wall alterations, but may detect vascular stenosis and occlusions to guide interventional procedures (15).

All modalities contribute to various aspects of disease management in vasculitis, but each demonstrates specific advantages and disadvantages. MRI has exquisite soft tissue contrast that makes it useful for detecting edema, deep vascular involvement and perivascular changes (15, 16). CT-angiography is particularly useful for large vessel vasculitis due to its spatial resolution, and additionally for detecting and evaluation of pulmonary changes and osseous lesions associated with some vasculitides, although iodinated-contrast and radiation exposure are of concern in serial imaging (16, 17).

While FDG-PET has been shown to provide information about vascular inflammation, these findings should be interpreted by the experts who master nuances of diagnostic molecular imaging and understand the pitfalls; pattern-recognition is only rarely useful alone and extreme caution should be exercised since increased metabolic activity could be attributed to other subclinical or secondary processes such as hypoxia, vascular remodeling, or atherosclerosis (18).
In the following section we review applications of combined FDG-PET/MRI in diagnosis, assessment and follow-up of large, medium, and small vessel vasculitis, and speculate on the future role of this modality for management of patients within the spectrum of these disorders.

**Large Vessel Vasculitis**

Large vessel vasculitis (LVV) mainly affects arteries comprising intima, media and adventitia (19). Giant cell arteritis (GCA) and Takayasu arteritis (TAK) are well-known forms of LVV, characterized by involvement of the aorta and its major branches (11). Several studies have reported approximate sensitivity of 89.5% and 87% for GCA and TAK respectively, utilizing FDG-PET/CT (18, 20-24).

The role of PET/MRI as a potential tool to assess inflammatory processes in large vessel vasculitis has been investigated by previous studies. Einspieler et al. evaluated 12 patients with LVV including ten GCA and two TAK cases with FDG-PET/MRI and reported a significant correlation between CRP levels and disease activity on PET (p=0.00067) and FDG-PET/MRI (p<0.0001) (14). In a retrospective study of 23 LVV patients evaluated by FDG-PET/MRI, Padoan et al. reported increased SUVmax values in patients with different types of LVV, i.e. GCA, TAK, and isolated aortitis (25). Laurent et al. evaluated the application of FDG-PET/MRI in 13 LVV patients and found vascular wall inflammatory patterns on PET/MRI to correlate highly with disease activity in all TAK patients and 50% of GCA patients (Figures 2 and 3) (20). The authors highlighted the role of PET/MRI evaluation of LVV in characterizing disease burden.
**Giant Cell Arteritis (GCA)**

Giant cell arteritis is a chronic vasculitis defined by granulomatous inflammation of large and medium vessels including cranial arteries (known as temporal arteritis) (26). CGA is the most common systemic vasculitis and seen mainly in elderly white population (27). Incidence of GCA increases with aging in individuals older than 50 years with a peak at 70-79 years (28). GCA has a broad range of clinical manifestations from constitutional symptoms to new-onset headaches, jaw claudication, amaurosis fugax, and permanent vision loss (29-33). GCA diagnosis might be challenging, especially in cases with typical clinical features of GCA but negative results of temporal artery biopsy. Evaluating arterial involvement is of high importance for diagnosis confirmation in these patients (20).

Role of MRI as a non-invasive imaging modality has been probed in diagnosis and management of GCA with key features reported as arterial wall thickening and mural contrast enhancement of occipital and superficial temporal arteries (27). Bley et al. evaluated temporal arteries in 16 patients with biopsy-confirmed GCA by high resolution contrast enhanced MRI and confirmed visualization of mural inflammatory changes even in small arteries. Authors suggested T1-weighted sequences of up to 6 minutes can provide sufficient signal-to-noise ratio for detection of mural contrast enhancement that is a common sign of acute inflammatory change (Figure 4). They also investigated the use of unenhanced images without fat suppression that did not show diagnostic utility (34). In addition to commonly utilized sequences of MRI, functional sequences such as diffusion weighted imaging (DWI) has also been shown effective in detection of GCA-associated vascular inflammation (Figure 5). DWI is based on measuring random motion of water molecules known as Brownian motion. Due to strong infiltration of vessel walls
in patients with active vasculitis, DWI potentially reveals increased cellularity by measuring restricted water diffusion (35).

Studies have proven the value of FDG-PET to detect involvements in aorta, carotid, subclavian, brachiocephalic, and iliofemoral arteries (36). In a study by Hautzel et al. authors reported high sensitivity (89%) and specificity (90%) for FDG-PET in diagnosing associated aortic involvement in GCA. In a study by Meller et al. authors compared the performance of FDG-PET with MRI in 76 vascular regions from 14 patients undergoing PET and MRI clinically suspected for GCA; MRI and PET were comparable in early stages of aortitis, but 29 vascular regions were disconcordantly found positive on either MRI or PET, emphasizing the improved diagnostic capacity of a combined system (17, 37).

Takayasu Arteritis (TAK)

Takayasu arteritis, identified by granulomatous panarteritis, is a rare form of LVV that predominantly affects women younger than 40 years of age (38). Diagnosis is challenging due to non-specific primary symptoms like low grade fever and fatigue. Later in the disease course, onset of vascular involvement which predominantly includes aortic arch and its main branches, renal, mesenteric, and pulmonary arteries leads clinicians toward the diagnosis (17, 38). However, diagnosis of TAK needs histopathological confirmation which is not feasible in all patients (39).

Similar to GCA, MRI is an excellent tool in patients with Takayasu arteritis to evaluate both vessel lumen and wall for edema, particularly in aorta and its large branches. It could also be a useful supplement in follow-up for vascular anatomic changes. Desai et al. suggested hyperenhancement on delayed phase contrast-enhanced MRI might be useful in identifying inflammation in aortic wall (40). However, it has been argued that gadolinium contrast
enhancement could potentially indicate fibrosis as this is observed in patients in stable remission.
Papa et al. reported the effectiveness of the MRI contrast agent gadofosveset which contrary to
gadolinium does not enhance fibrous tissue and they found correlation between vessel wall
enhancement and active disease, a finding that warrants wider evaluation (41). However, studies
have reported a potential for false positive cases with MRI: In a study of 24 patients with TAK,
Tso et al. found vessel wall edema measured by increased MR signal intensity in 94% of
patients with active disease and >50% of patients with inactive disease or uncertain activity
status inferred from clinical judgement (Figure 6) (42).

FDG-PET has shown usefulness for early disease diagnosis in TAK patients, in treatment
follow-up, and detecting active disease. In a study by Tezuka et al. FDG-PET/CT was useful for
detecting inflammation not only in patients with active TAK but also in relapsing individuals
receiving immunosuppressive agents (43). Reported sensitivity and specificity of FDG-PET for
initial assessment of active vasculitis covers a wide range. A meta-analysis calculated a pooled
sensitivity and specificity of 70.1% and 77.2%, respectively, from retrospective studies and small
case series and speculated that inclusion of treated cases contributed to inferior accuracy of this
modality in TAK (41, 44). Tsuchiya et al reported on the extent and distribution of extra-vascular
findings on FDG-PET/CT in TAK patients in regions such as thyroid glands, lymph nodes, and
bone marrow of vertebrae and pelvis (45). Even though these findings cannot be attributed to
known pathophysiologic processes of the disease, it can increase our understanding of the
mechanisms of inflammation in TA.
Medium Vessel Vasculitis

Polyarteritis Nodosa (PAN)

Polyarteritis Nodosa is a systemic necrotizing vasculitis mainly involving medium-size muscular arteries; small muscular arteries may also be affected (11). PAN has a relative average age at onset of 50 years with peak in the 5th-6th decades of life (46, 47). PAN is a multisystemic disease mainly causing renal, nervous system, gastrointestinal, and cutaneous involvement, but for undetermined reasons spares the lungs (46, 48).

Even though the evaluation of medium arteries is mainly performed with angiography, the tissue effect of vascular injury and resultant manifestations have specific presentation in structural, physiologic, and molecular imaging. MRI can detect intracerebral hemorrhage and intracranial aneurysms, and aneurysms of other arteries such as hepatic, mesenteric, and renal arteries (microaneurysms create the appearance which is the origin of naming: nodosa (49)). In some cases the affected vessels are below the spatial resolution of MRI, however the downstream effect of vascular damage could be assessed by this modality, considering its high soft-tissue contrast resolution; MRI is particularly useful for assessment of subcutaneous fat, muscle, and visceral involvement (50, 51). In a study on MRI findings of muscle involvement in patients with PAN by Kang et al. authors concluded that differential diagnosis can be considered in cases with patchy diffuse muscle signal changes (Figure 7). Authors also reported fascial and periosteal involvement and enhancing lesions on vessels on contrast-enhanced images (52).

FDG-PET can detect signs of vasculitis in PAN (Figure 8) (53-55). FDG-PET is also a useful modality for non-vascular findings of PAN. Previous studies have found FDG-PET sensitive for detecting disseminated spots throughout subcutaneous tissue and muscle associated
with cutaneous polyarteritis nodosa (CPAN), a rare manifestation sometimes referred to as leopard skin appearance (56). CPAN is characterized by necrotizing vasculitis of medium and small arteries of the skin and is also associated with extra-cutaneous findings such as fever, malaise, and neuropathy but no visceral involvement (57).

**Kawasaki Disease (KD)**

KD (mucocutaneous lymph node syndrome) is one of the most prevalent forms of vasculitis in children younger than 5 years, barely affecting adults (58, 59). KD affects small and medium size vessels and presents as an acute febrile illness with symptoms of acute inflammation; typical clinical manifestations include cervical lymphadenopathy, bilateral non-exudative conjunctivitis, mucositis, rash, and edema of extremities (55, 56). KD is a self-limited disease that evolves over 10-12 days without therapy (59). However, affected children are highly vulnerable to life-threatening cardiovascular complications, the most concerning of which is coronary artery abnormalities leading to coronary artery aneurysms, arrhythmias, myocardial ischemia and infarction (60).

MRI has been shown to be useful in identification of coronary artery aneurysms in KD. In addition to coronary artery abnormalities, MRI provides clinically relevant information regarding myocardial inflammation, infarction and ischemia (61). In a previous study Tacke et al. evaluated the performance of MRI in assessment of 63 patients with KD. The authors concluded comparable performance to echocardiography for long term surveillance of patients with KD in identifying coronary artery pathology, ischemia, and myocardial infarction (Figure 9) (62).

There is limited information about the use of FDG-PET in patients with KD. There have been reports of persistent coronary arterial inflammation in patients with KD long after onset of
the disease (63, 64). Hauser et al. used $^{13}$N-ammonia-PET for noninvasive assessment of regional myocardial blood flow (MBF) and coronary flow reserve (CFR) in follow-up of functionality of coronary arteries in patients with normal epicardial coronary arteries after onset of KD. Authors reported significant reduction of CFR and attenuation of MBF after vasodilation in children with angiographically normal epicardial coronary arteries, and this lack in vasoreactivity could indicate residual damage of the coronary arteries (65).

**Small Vessel Vasculitis**

Small vessel vasculitides are characterized by involvement of arterioles, capillaries, and venules that are smaller in size comparing to arteries, but otherwise similar to other types of vasculitides; overlaps exist and small vessel vasculitis might also involve medium-size vessels (66). Small vessel vasculitides are mainly categorized on the basis of involvement of immune complexes. The main two categories are pauci-immune (ANCA associated) small-vessel vasculitis and immune complex small-vessel vasculitis (66).

A variety of immune mechanisms are thought to be involved in the inflammatory responses in small vessel vasculitis that mainly occur in vessels with substantial trafficking of cells and fluids between tissue and blood. The endothelia of these vessels are particularly responsive to pro-inflammatory signals, increasing the probability of association with cascades of events that includes endothelial damage, thrombosis, ischemia, and tissue necrosis (67, 68).

Even though imaging is limited with regards to direct assessment of these very small vessels, it plays a significant role in assessment of metabolic processes and tissue damages as a result of small-vessel vasculitis (69). MRI is particularly useful for revealing intra-abdominal involvements such as ischemia, bowel wall hemorrhage and edema. Additionally it can help with otorhinolaryngologic involvement such as mucosal inflammation and granulomatous tissue in the
paranasal sinus, mastoid, middle ear, and orbit. On MRI, early granulomatous tissue shows nonspecific hypointense signal on T1-weighted images and hyperintense signal on T2-weighted images in paranasal sinuses, while chronic granulomatous inflammation appears hypointense on both T1- and T2-weighted images and shows less enhancement (Figure 10) (17, 69).

ANCA-associated vasculitis is characterized by inflammatory infiltrates that could be a good target for FDG uptake (70, 71). However, data regarding evaluation of disease extent using FDG-PET is limited. Ito et al. explored the utility of FDG-PET/CT in diagnosis and follow-up of patients with granulomatosis with polyangiitis (GPA). Authors showed feasibility of FDG-PET/CT by retrospective review of 8 patients. FDG-PET/CT improved detection of upper respiratory tract and lung lesions in comparison with non-contrast CT and provided complementary information to indicate biopsy site (72). Soussan et al. reviewed FDG-PET/CT imaging in 16 patients with ANCA-associated vasculitis, including 10 GPA, 2 eosinophilic GPA (EGPA), and 4 microscopic polyangiitis (MPA). Authors concluded that FDG-PET/CT accurately identifies organ impairments in GPA but does not bring additional value to usual screening (Figure 11). Authors did not identify any uptake in skin, joint, eye, and large vessels (71). Same group reported two cases of asymptomatic aortic arch involvement in ANCA-associated vasculitis diagnosed with FDG-PET/CT (73). Finally, a small retrospective study from Frary et al. found FDG-PET/CT to have high accuracy and predictive values for differentiating disease relapse of ANCA-associated vasculitides from infection and malignancies, two important differential diagnoses with often indistinguishable symptoms and signs (74). Role of FDG-PET in other forms of small vessel vasculitis is not well determined by means of large cohort investigations, however small studies and case reports show potentials of this
modality in providing complementary information in identifying extent of the disease and disease activity beyond usual screening (75, 76).

**CARDIOPULMONARY INFLAMMATION**

FDG-PET/CT is already used to assess inflammation in the heart and lungs, e.g. infectious endocarditis and sarcoidosis, but additional challenges arise with imaging these organs including with PET/MRI. First, with regards to the heart specific preparation is necessary to suppress physiologic activity and glucose consumption, e.g. prolonged fasting, low-carb-high-fat dietary restraints and pretreatment with heparin (10). Also, artefacts from motion or cardiac devices may interfere with image quality, and devices’ non-compliance with MRI magnetism may hamper use overall (6). In the lungs, the low tissue proton density in the lung generates less MRI signals and results in many tissue-to-air interfaces which render attenuation correction of the PET images more difficult and create more attenuation artifacts that will impact quantification (77). If these issues where to be resolved, PET/MRI might have a more promising potential for correction of respiratory motion and misalignment artifacts from simultaneous dynamic acquisition of PET and MRI signals (77, 78) which could greatly improve the quantification potential in the lung.

**Cardiac sarcoidosis**

Sarcoidosis is a systemic non-necrotizing granulomatous inflammatory disease with multiple organ involvement and heterogeneous clinical presentation (79). It primarily affects lungs and lymph nodes, but may affect every organ, and whole-body FDG-PET/CT may aid in establishing disease extent, including extra-pulmonary sarcoidosis, location of biopsy accessible lymph nodes, occult lesions, or multi-organ involvement, and some studies has found potential for
evaluation of treatment response (2, 3). With the abovementioned caveats in mind, it remains to be seen if PET/MRI adds further to the diagnostic strategy in pulmonary and systemic sarcoidosis per se, but in cardiac sarcoidosis (CS) represent an important entity, where PET/MRI may find a considerable place.

Almost 25% of deaths attributable to sarcoidosis is related to cardiac involvement; cardiac granulomas are found in about 1/4 of the patient with sarcoidosis on autopsy. The involvement of the heart is underdiagnosed, while cardiac involvement plays a very important role in the course of the disease. Sudden cardiac death may be the first sign of CS and historically, EKG has been strongly considered in all patients with suspected cardiac involvement.

There are multiple reasons for the underdiagnosing of CS. First, manifestations are very nonspecific (conductive aberrancy and/or cardiomyopathy). Second, conventional diagnosis by endomyocardial biopsy has low diagnostic yield because the technique is not optimal for the pathologic involvement, i.e. most lesions are in left ventricle while the biopsies are obtained from right ventricle and, in addition, random sampling of the patchy involvement of myocardium leads to sampling error and low yield with a high false negative rate. Finally, histological diagnosis based on Dallas criteria is disputable (80). Also, isolated cardiac sarcoidosis is not a very clear concept in the literature. The prevalence of cardiac involvement among patients with systemic sarcoidosis ranges from 25% (United States) to 60% (Japan); however, the prevalence of isolated cardiac sarcoidosis is not known (81). Reported rates of isolated cardiac sarcoidosis among patients with cardiac sarcoidosis have similar ranges from 25 to 55% (82). Considering the importance of this clinical condition and limitations of traditional diagnostic methods, FDG-PET/CT has gained extensive attention in recent years to address this unmet need (83-90).
MR imaging has been utilized to detect sequelae of chronic inflammatory changes of myocarditis by using delayed post-contrast sequences. Late gadolinium enhancement (LGE) demonstrates entrapment of extravasated contrast in the fibrous tissue representing the scar. This finding in itself is quite non-specific; however, by attention to the pattern of myocardial involvement (subepicardial versus subendocardial and transmural) as well as location of involvement (such as the junction of right and left ventricles) diagnosticians can narrow the differential diagnosis and favor sarcoidosis over other etiologies.

It is important to understand FDG-PET and delayed post-contrast MRI provide complementary information regarding sarcoidosis biology (91). PET-FDG avidity demonstrates active inflammation, whereas LGE lesions on MR show chronic sequelae. Wicks et al. investigated 51 patients suspected of CS and showed the presence of LGE and FDG uptake on PET/MRI identified patients at higher risk of adverse events (92) and suggested both PET and cardiac MRI should be considered in the assessment of disease presence, stage, and prognosis. To explore the usefulness of hybrid FDG-PET/MRI to detect cardiac sarcoidosis, Dweck and colleagues evaluated 25 suspected subjects (93). Eight subjects were MR+PET+ (Figure 12), suggestive of CS; one subject was MR+PET-, consistent with inactive cardiac sarcoidosis; and eight were MR-PET-, with no imaging evidence of cardiac sarcoidosis; and finally eight subjects were MR-PET+ with two distinctive patterns: global myocardial uptake (n=6) and focal-on-diffuse uptake (n=2).

In conclusion, the excitement about the application of PET/MR to diagnose and characterize myocarditis is profound and some clinicians believe that by this application, “cardiac PET/MRI entered the clinical arena! Finally...” (94).
**Chronic obstructive pulmonary disease (COPD)**

COPD is a major healthcare issue worldwide, and although the initial diagnoses can be obtained relatively simple through spirometric examinations, several aspects of the disease complex points towards a potential role for FDG-PET/CT to increase our basic knowledge of the disease and perhaps impact future clinical strategies. Thus, FDG-PET/CT has shown some ability to separate different phenotypes on the basis of FDG uptake patterns, to identify patients with increased used of accessory breathing muscles, and to identify patients with right heart strain – different features within the disease spectrum that may affect prognosis and treatment strategy (95). However, changes are often subtle and quantitative measures usually warranted, and the most of the scarce literature on FDG in COPD focusses on quantification.

Most studies use the Patlak-Gjede graphical analysis technique (96, 97) based on tracer kinetic modeling. By modeling the FDG uptake as an irreversible compartmental model the net influx rate of FDG, $K_i$, can be derived as a parameter for the rate of tissue FDG metabolism. Jones et al. used this method to show elevated FDG uptake in the lungs of 6 COPD patients compared to chronic asthma patients and age-matched controls (98). Subramanian et al. later reinforced these quantitative results in 10 COPD patients who displayed higher FDG uptake in the lungs compared to healthy controls and COPD patients with $\alpha_1$-antitrypsin deficiency, especially in the upper zone of the lungs (99). The reproducibility of this method was highlighted by Chen et al. in abstract form; they compared 10 COPD patients to healthy age matched controls and scanned each object 3 times during a 7 weeks period. They found significantly higher FDG uptake in COPD patients compared to controls irrespective of the examination time point (100).
The lungs give rise to multiple challenges for quantitation, especially the fact that uptake areas consist of very small regions (in terms of PET resolution) surrounded by air with no uptake. Hence, activity spill-over from partial volume effects will be a considerable problem in quantitation and blood in the lungs will lead to an increased background signal (101, 102). Also, the fraction of air and blood in the lungs changes in patients with COPD furthering the need for correction of these parameters in quantification (101). Coello et al. proposed a tracer kinetic modelling method that took into account air and blood volume in the lungs. After applying the corrections, they were not able to see a significant difference between 10 COPD patients and a healthy control group (103).

Recently Vass et al. tested the reproducibility for tracer kinetic modelling by applying the same methodology for the same reconstructed images with two different processing pipelines for 10 patients with COPD compared to COPD patients with α1-antitrypsin deficiency and a healthy control group. They found no significant differences between the groups but some variations in individual subjects between the two processing pipelines. They found blood ROI methodology, input function modeling, and time delay estimation to be key factors influencing the outcome (104).

In order to derive parameters from tracer kinetic modeling, patients need to have a dynamic PET scan, which means they will have to be injected directly on the scan bed and scanned continuously for 60-90 minutes. This limits the clinical usefulness as scanner time is in high demand with static PET scans as the routine. Static scans are often quantified using the standardized uptake value (SUV), but reproducibility has often been often discussed (105). Torigian et al. showed that PET SUV in patients with COPD correlated positively with emphysema severity from CT scans in 49 patients, but only if partial volume correction was
employed (106). In a recent study by Garpered et al., 33 patients and current smokers showed increased FDG uptake in the lungs compared to never smokers, but this was only statistically significant when the data was corrected for air fraction (107).

COPD may harbor an element of systemic inflammation with increased cardiovascular risk, and Coulsen et al. examined aortic wall uptake in 7 COPD patients compared to 5 patients with metabolic syndrome, and 7 ex-smokers without COPD (108). Aortic uptake was quantified using target-to-background ratio (TBR) where SUV of the VOI is corrected with regards to SUV of arterial blood, and the authors found aortic uptake in COPD patients lower than in metabolic syndrome but higher than the ex-smoker controls. This was further investigated by Fisk et al.; they compared 85 COPD patients with groups of 12 consisting of COPD patients with α1-antitrypsin deficiency, smokers without COPD, and never smokers. Using TBR of the aortic walls, they found significantly higher FDG uptake in both COPD with and without α1-antitrypsin deficiency compared to the groups of smokers and never smokers. These findings indicate that aortic inflammation is related to COPD in itself regardless of smoking history (109).

Recently Kothekar et al. linked increased uptake in respiratory muscles in 33 COPD patients with pulmonary function test results showing increased uptake significantly correlated with COPD severity (110), albeit mainly based on a visual grading score and with supporting SUV quantitation only to a small extent. This was previously observed in studies by Aydin et al. (111) and Osman et al. (112), and it might hold potential to stratify COPD patients according to respiratory strain.

CONCLUSION
The use of FDG-PET/CT in cardiac, vascular and pulmonary inflammation in some ways represents the extremes, i.e. from well-established indications like large-vessel vasculitis to the hitherto strictly exploratory uses like COPD. The potential for PET/CT and PET/CT/MRI is undoubtedly present in these domains, albeit probably to varying degree, but the literature is still sparse and much is still unclarified, especially with regards to PET/MRI due to the inherent challenges of imaging and quantifying the heart and lungs.

FIGURE LEGENDS

Figure 1: This diagram demonstrates (from left to right) aorta, large artery, medium artery, small artery/arteriole, capillary, venule, and vein. Vasculitides are a group of disorders with a common pathogenetic process: inflammation centered on the vessel wall. Vessels could be classified into three categories based on their luminal diameter and wall structure: large-vessels, medium-vessels, small-vessels. Distribution of vessel involvement is depicted in this figure. It is important to remember all three major categories of vasculitides can affect any size artery and there is substantial overlap with respect to arterial involvement. It is fair to say large-vessel vasculitis affects large arteries more often than other vasculitides; the same can be said for medium-vessel vasculitis. Small vessel vasculitis predominantly affects small vessels, however medium arteries and veins may be affected. A subgroup of small-vessel vasculitides, immune complex small vessel vasculitis, rarely affects arteries. Anti-GBM anti–glomerular basement membrane; ANCA antineutrophil cytoplasmic antibody. (Reproduced from Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65(1):1–11.)

Figure 2: Female with temporal headaches and elevated acute-phase reactants; clinical diagnosis of giant cell arteritis (GCA). PET/MRI showed significant FDG uptake in bilateral vertebral arteries (arrows): (A) Maximum intensity projection, and (B) fused MR-angiography/PET). There is arterial wall thickening (arrows) on: (C) MR axial T2-weighted image, and (D) fused T2-weighted/PET. (Reproduced from Laurent C, Ricard L, Fain O, Buvat I, Adedjouma A, Soussan M, et al. PET/MRI in large-vessel vasculitis: clinical value for diagnosis and assessment of disease activity. Sci Rep. 2019 Aug 27;9(1):1–7.)
Figure 3: 45-year-old female with arthralgia, and elevated acute phase reactants with diagnosis of Takayasu arteritis (TA). PET/MRI showed an increased FDG uptake in aortic arch and at the origin of supra-aortic vessels associated with arterial wall thickening on T2-weighted image (A, arrows) and wall enhancement (B, arrows). ((A) coronal PET, (B) T2-weighted image, (C) post-contrast T1-weighted image, (D) fused MR-angiography/PET, (E) fused PET/T2-weighted image). (Reproduced from Laurent C, Ricard L, Fain O, Buvat I, Adedjouma A, Soussan M, et al. PET/MRI in large-vessel vasculitis: clinical value for diagnosis and assessment of disease activity. Sci Rep. 2019 Aug 27;9(1):1–7.)

Figure 4: Four patients with various degrees of temporal artery mural enhancement on contrast-enhanced MR images (arrows). Slight enhancement is considered physiologic and normal, whereas prominent mural enhancement indicates mural inflammation (hallmark of temporal arteritis). Nitroglycerine capsule used as a fiducial marker appears as white ball in the left images. (Reproduced from Bley TA, Wieben O, Uhl M, Thiel J, Schmidt D, Langer M. High-Resolution MRI in Giant Cell Arteritis: Imaging of the Wall of the Superficial Temporal Artery. Am J Roentgenol. 2005 Jan 1;184(1):283–7.)

Figure 5: Patient with active GCA. Increased FDG uptake of the descending aorta in axial (A) and sagittal (B) planes. Mural changes in black-blood (C) and fluid-suppressed (D) sequences. High b-value diffusion-weighted images demonstrate restricted diffusion in axial (D) and sagittal (E) plans. Axial plan at the level of aortic arch demonstrates mural restricted diffusion (G) as well as increased FDG uptake (H). (Reproduced from Ironi G, Tombetti E, Napolitano A, Campolongo M, Fallanca F, Incerti E, et al. Diffusion-Weighted Magnetic Resonance Imaging Detects Vessel Wall Inflammation in Patients With Giant Cell Arteritis. JACC Cardiovasc Imaging. 2018 Dec 3;11(12):1879–82.)

Figure 6: Patient with Takayasu arteritis. Magnetic resonance images demonstrate increased aortic wall thickness. Axial (top) and longitudinal-oblique (bottom) images of the thoracic aorta reveal abnormal aortic wall thickening and ectatic changes. (Reproduced from Tso E, Flamm SD, White RD, Schwartzman PR, Mascha E, Hoffman GS. Takayasu arteritis: Utility and limitations of magnetic resonance imaging in diagnosis and treatment. Arthritis Rheum. 2002;46(6):1634–42.)

Figure 7: Seven-year-old boy with polyarteritis nodosa who presented with fever, lower leg pain, and skin lesions. T2-weighted axial image (upper, left) shows diffuse hyperintensity in soleus muscle and patchy hyperintensities in anterior compartment of lower leg. T1-weighted axial image (upper, right) reveals no specific abnormality. Coronal contrast-enhanced fat-suppressed T1-weighted image (lower, left) shows diffuse fluffy nodular enhancement in soleus muscle and patchy hyperintensities in anterior compartment of lower leg.

**Figure 8:** FDG PET scan of a 60-year-old woman with polyarteritis nodosa who presented with myalgia of the lower legs, skin ulcerations on both legs, livedo reticularis and mild polyneuropathy. *(Reproduced from Bleeker-Rovers CP, Bredie SJ, Van Der Meer JW, Corstens 0 FH, Oyen WJ. F-18-fluorodeoxyglucose positron emission tomography in diagnosis and follow-up of patients with different types of vasculitis. Neth J Med. 2003;61(10):323–9.)*

**Figure 9:** Cardiac MRI images of three patients with Kawasaki disease. Coronary artery could be normal (A; arrow shows right coronary artery), or markedly abnormal (B, arrow shows a giant aneurysm of the right coronary artery with thrombosis). Subsequent myocardial ischemic defects could be the result of coronary artery involvement (C, arrow shows basal inferoseptal-inferior myocardial infarction). *(Reproduced from Tacke Carline E., Kuipers Irene M., Groenink Maarten, Spijkerboer Anje M., Kuipers Taco W. Cardiac Magnetic Resonance Imaging for Noninvasive Assessment of Cardiovascular Disease During the Follow-Up of Patients With Kawasaki Disease. Circ Cardiovasc Imaging. 2011 Nov 1;4(6):712–20.)*

**Figure 10:** Granulomatosis with polyangiitis in an 11-year-old boy with left orbital pain and fever. Axial post-contrast MR image of the orbits shows hyperenhancement of the enlarged left medial rectus muscle with surrounding fat stranding (arrows). *(Reproduced from Khanna G, Sargar K, Baszis KW. Pediatric Vasculitis: Recognizing Multisystemic Manifestations at Body Imaging. RadioGraphics. 2015 May 1;35(3):849–65.)*

**Figure 11:** 67 year-old woman with a granulomatosis with polyangiitis. FDG-PET/CT shows increased FDG uptake in sinonasal and kidney locations (a and b, arrows). Follow up FDG-PET/CT, while the patient achieved remission, showed resolution of hypermetabolic activities in both locations (c and d). *(Reproduced from Soussan M, Abisor N, Abad S, Nunes H, Terrier B, Pop G, et al. FDG-PET/CT in patients with ANCA-associated vasculitis: Case-series and literature review. Autoimmun Rev. 2014 Feb 1;13(2):125–31.)*
Figure 12: MR+PET+ Patients With Imaging Evidence of aCS on Hybrid CMR/PET. Late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) images on the left with hybrid 18F-fluorodeoxyglucose (FDG) CMR/positron emission tomography (PET) images on the right. (A) Subepicardial (near transmural) LGE in the basal anteroseptum extending in to the right ventricular free wall with increased FDG uptake localizing to exactly the same region on fused CMR/PET (maximum standardized uptake value = 3.4; maximum tissue-to-background ratio = 2.3; maximum target-to-normal myocardium ratio = 2.0). (B) Subepicardial LGE in the basal anterolateral wall with increased FDG uptake colocalizing to exactly that region on CMR/PET. (C) Patchy midwall LGE in the anterolateral wall with matched increased FDG uptake on CMR/PET. (D) Multifocal LGE in the lateral wall with matched increased FDG uptake on CMR/PET. (Reproduced from Dweck, Marc R., Ronan Abgral, Maria Giovanna Trivieri, Philip M. Robson, Nicolas Karakatsanis, Venkatesh Mani, Anna Palmisano, et al. 2018. Hybrid Magnetic Resonance Imaging and Positron Emission Tomography With Fluorodeoxyglucose to Diagnose Active Cardiac Sarcoidosis. JACC. Cardiovascular Imaging 11 (1): 94–107.) (Permission pending)
REFERENCES


Figure 2
Figure 4
Figure 7
Figure 9
Figure 10
Figure 12