Advances in imaging vascular inflammation

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Abstract Inflammation is central to the pathogenesis of many vascular diseases. Despite an understanding of the natural history, predicting progression and acute complications remains an important clinical challenge in both atherosclerosis and aortic aneurysms. Current means of monitoring rely mainly on structural information, such as the extent of luminal stenosis on coronary angiography or maximum aneurysm diameter on ultrasonography. Although often useful in making clinical decisions about intervention, such measures do not always correlate well with the risk of acute complications. As an example, the degree of luminal obstruction correlates poorly with the risk of future coronary plaque rupture and, similarly, aneurysm size does not account entirely for the subsequent rate of expansion and risk of rupture. It might be possible to improve risk prediction using imaging modalities that focus on the underlying disease processes rather than their consequences. This article reviews non-invasive imaging techniques that track inflammation within the arterial wall as applied to atherosclerosis and abdominal aneurysms. These all aim to improve risk prediction, to highlight the underlying pathology non-invasively and to permit the testing of new therapeutic agents against vascular disease.

Keywords Atherosclerosis · Aneurysm · Plaque rupture · Molecular imaging · Positron emission tomography · Nuclear imaging

Introduction

Atherosclerosis is a systemic lipid-driven disorder of the arterial wall that represents a principal worldwide cause of morbidity and mortality. Coronary heart disease causes 20–22 % of deaths annually across Europe [1]. Ruptured atherosclerotic plaques account for the majority of myocardial infarctions and ischaemic strokes.

The related condition of abdominal aortic aneurysm (AAA) is a further major cause of mortality, accounting for at least 15,000 deaths per year in the USA [2]. Aneurysms are often asymptomatic until rupture, after which the consequences are frequently fatal. Long-term management requires accurate detection, monitoring of expansion and, in the absence of effective medical therapies, pre-emptive surgical intervention.

Inflammation plays a pivotal role in the pathogenesis of both conditions [3, 4]. In atherosclerosis, macrophage-led inflammation contributes to plaque development and the tendency to rupture [4]. In AAA, chronic inflammation leads to a protease-mediated degradation of the extracellular matrix within the aortic media [5]. This in turn produces structural changes that predispose to dilatation and rupture.

Despite an understanding of the natural history, predicting progression and complications remains challenging. Stress testing and invasive angiography are used to identify sites and severity of stenoses in patients with angina. This information can then guide revascularisation and hence symptom relief. However, the severity of luminal stenosis correlates poorly with the risk of plaque rupture and only 18 % of acute coronary events occur in patients with pre-existing stable angina [6].

Ultrasonography and CT are used to detect and characterise AAAs. Although aneurysm size is a dominant

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factor in determining the subsequent expansion rate, it only explains about 60 % of the variability in this and is a poor predictor of aneurysm rupture [7].

Both disorders are diseases of the arterial wall, and in this respect imaging that centres around the vessel lumen will inherently be limited. This account will review non-invasive techniques that track various pathological processes within the arterial wall, focusing specifically on methods of imaging inflammation.

Atherosclerosis and plaque rupture

Pathophysiology

Atherosclerosis is a multifocal inflammatory disorder, which occurs in response to deposition of low-density lipoproteins in the vessel wall [4]. Expression of adhesion molecules by endothelial cells leads to recruitment of inflammatory cells, including monocytes and T-lymphocytes. Macrophages take up modified lipoproteins via scavenger receptors and differentiate further to become foam cells. A typical *atheroma* is composed of a soft and unstable lipid-rich cavity, with an overlying *fibrous cap* composed of smooth muscle cells separating the *necrotic core* from the arterial lumen [8].

Acute plaque rupture exposes thrombogenic material to the arterial lumen leading to vascular events such as stroke and myocardial infarction [9]. Pathogenic mechanisms underlying plaque rupture include degradation of the fibrous cap by macrophage-derived proteolytic enzymes [10] and intraplaque haemorrhage [11] due to disruption of fragile capillaries from the vasa vasorum, which form in response to hypoxia within the atheroma [12].

The rate of atherosclerotic progression and risk of rupture vary greatly and are difficult to predict. For example, coronary artery lesions may remain asymptomatic for decades and up to 40 % of the coronary wall may be involved before significant luminal narrowing occurs [13]. Coronary lesions producing stable angina are mature fibrocalcific plaques with >50–70 % luminal stenosis, which represent a different phenotype to the less stable rupture-prone plaques that lead to acute coronary events [14]. While most acute events are caused by immature lesions demonstrating <50 % luminal stenosis, the presence of severe obstructive coronary artery disease may serve as a marker for rupture-prone plaques elsewhere [14].

The thin-cap fibroatheroma (TCFA) is considered the classical rupture-prone lesion [4]. A TCFA consists of a large necrotic core, within a thin fibrous cap with a high density of macrophages and reduction in vascular smooth muscle cells [10]. These and other high-risk features (e.g. ‘spotty calcification’ and intra-plaque vasa vasorum) can

be visualised non-invasively using MR or CT. For imaging arterial wall inflammation, there has been significant progress in the development and validation of nuclear and molecular techniques.

Imaging inflammation in atherosclerotic plaques

Nuclear and molecular imaging

To complement conventional anatomical vascular imaging techniques, nuclear and molecular methods aim to detect and quantify processes implicated in plaque rupture, such as inflammation, calcification, neovascularization and apoptosis. Nuclear imaging enables new ways of identifying high-risk plaques, contributes to our understanding of pathophysiology in vivo and can be used to evaluate new therapeutic agents [15].

The principal advantage of nuclear imaging is the high sensitivity with which tracers can be detected at the site of interest compared with other methods such as MR or CT. Positron-emission tomography (PET) and single-photon emission CT can detect picomolar concentrations of radio-nuclide. Due to limited spatial resolution, the resultant images need to be co-registered with CT or MR images to allow accurate anatomical localisation of tracer uptake. The most widely validated PET tracer in vascular imaging is ^{18}F -fluorodeoxyglucose (FDG). More recently, other tracers have emerged, often with existing applications in oncology.

Imaging inflammation using FDG PET

Fluorodeoxyglucose is a glucose analogue that is taken up by cells during glucose metabolism. Upon entry to the cell, FDG is phosphorylated and becomes trapped within the cell. FDG, therefore, accumulates in proportion to metabolic activity. FDG uptake can be quantified using standardised uptake value and target-to-background ratio. Arterial FDG PET generally requires longer circulation times (>90 min) than when the technique is used for oncological imaging to allow adequate blood clearance and, therefore, a favourable arterial wall signal.

Arterial FDG uptake was first recognised in studies of patients undergoing PET cancer staging [16]. FDG uptake is thought to reflect inflammation within the arterial wall, because activated macrophages have higher metabolic activity than other cellular elements of plaques or of the healthy arterial wall [17]. More recently, in vitro studies have demonstrated that FDG uptake increases as macrophages undergo differentiation to foam cells [18].

Studies using a rabbit model of atherosclerosis reveal that FDG uptake correlates closely with macrophage

content assessed histologically ($r = 0.93$, $p < 0.002$) [19]. In rabbit models of progressive atherosclerosis, after balloon aortic injury and high-fat diet, FDG uptake has been shown to be higher in diseased regions as compared with healthy arterial wall and can be reduced with reversion to a normal diet [20]. Additionally, after pharmacological triggering of thrombosis, FDG PET is able to differentiate thrombosis-prone plaques with reasonable accuracy [21].

Whilst murine models are widely used in the study of atherosclerosis, the use of FDG PET in mice has proved challenging due to their small size and the limited spatial resolution of PET [22]. One study circumvented this issue by administering non-radioactive FDG and then using mass spectrometry to detect metabolites of FDG-6-phosphate within the plaque [23]. This approach demonstrated significant accumulation within inflamed plaque compared with control vessels, as a proof of principle experiment.

Despite these difficulties, there have been studies demonstrating increased ^{18}F -FDG uptake using PET in mice. ApoE^{-/-} mice fed a high-fat diet demonstrated increased aortic ^{18}F -FDG PET signal compared with mice fed a control diet, with this difference increasing with age [24]. Strength of FDG signal also correlated with gene expression of markers of pathological processes central to atherosclerosis [24], including CD68, lectin-like oxidised low-density lipoprotein (LDL) receptor-1 and hypoxia inducible factor-1 α .

In a prospective vascular imaging study with FDG PET, Rudd and colleagues [25] showed that FDG accumulation rate was 27 % greater in the culprit carotid artery after a recent stroke or transient ischaemic attack (TIA) than in contralateral asymptomatic lesions. As in animal models, carotid arterial FDG uptake has been shown to correlate most significantly with the macrophage content of plaques removed at endarterectomy [26], and not with wall thickness, smooth muscle cell content or degree of stenosis Fig. 1.

Uptake of FDG is increased in subjects with cardiovascular risk factors [27] and with elevated biomarkers of inflammation such as C-reactive protein [28]. It has been shown to be reproducible, with low levels of inter-observer and short-term variability [29]. In carotid imaging, high FDG uptake correlates well with features of vulnerability noted on other modalities, for example, echolucency on ultrasound [30] and lipid rich cores on MRI [31]. Vascular FDG PET is being used to investigate the excess cardiovascular risk associated with other chronic inflammatory diseases such as HIV [32], chronic obstructive pulmonary disease [33] and rheumatoid arthritis [34].

Coronary artery imaging with FDG PET is frequently complicated by intense myocardial tracer uptake that can overwhelm the signal from individual plaques. Compensation for cardiac and respiratory motion during acquisition

Fig. 1 ^{18}F -FDG PET/CT imaging after recent stroke, **a** axial CT image showing culprit left ICA lesion (green arrow); **b** co-registered PET/CT images demonstrating intense FDG uptake in culprit left ICA (blue arrow), note lesser uptake at bifurcation of right carotid (yellow arrow) (colour figure online)

of the PET dataset is possible but adds complexity. Despite this, using dietary manipulation to suppress myocardial glucose usage, Rogers and colleagues [35] have shown that culprit plaques after acute coronary syndrome have higher FDG uptake than lesions causing stable angina, though others have shown that even with such measures, around 50 % of coronary segments will not be analysable [36]. More specific PET tracers will be required for the optimal imaging of coronary plaque inflammation [15].

Serial FDG PET imaging can be used to assess the impact of anti-atherosclerotic therapy. Three months of simvastatin therapy has been shown to produce a reduction in carotid artery FDG uptake, consistent with an anti-inflammatory effect of the drug [37]. Mizoguchi and colleagues [38] used FDG to demonstrate a reduction in vascular inflammation with pioglitazone. Similarly, in an investigation of vascular inflammation in rheumatoid arthritis, 8 weeks of anti-TNF α therapy reduced aortic FDG uptake in addition to showing the expected benefits in terms of general disease activity [34].

In retrospective analyses of FDG PET studies undertaken for oncology staging, high levels of baseline vascular FDG uptake were associated with subsequent cardiovascular events in multivariate analysis [39]. Of clinical relevance, a similar analysis in a high-risk stroke population demonstrated that carotid arterial FDG uptake independently predicted recurrent cerebral events [40]. This finding is now being tested in a multi-centre international trial. If successful, arterial PET imaging after stroke and TIA in selected subjects might allow better targeting of endarterectomy.

Although histological, clinical and gene expression evidence supports the hypothesis that arterial FDG uptake

reflects vascular macrophage accumulation, controversies remain. FDG is a non-specific, non-targeted tracer and overall signal intensity may depend on other glucose-avid processes within the plaque. For example, the core of an atherosclerotic plaque constitutes an area of relative hypoxia and under these circumstances, glucose uptake is increased. Hypoxia leads to upregulation of GLUT-1 transport proteins and increased rates of glycolysis [41]. Furthermore, hypoxia produces neovascularization, which may impact on FDG delivery and signal strength [42]. Nevertheless, both hypoxia and neovascularization are hallmarks of plaque instability, and their non-invasive measurement may still provide important insights.

Novel approaches for imaging inflammation with PET

Several alternative tracers have their roots in cancer imaging, and await prospective clinical evaluation.

^{11}C and ^{18}F -choline

A choline-specific transporter exists on macrophages. This is upregulated with cellular activation [43] and can be exploited for imaging atherosclerotic plaque inflammation. Studies using radiolabelled choline in ApoE^{-/-} mice revealed that choline uptake was more sensitive in detecting carotid artery plaques than ^{18}F -FDG was [44] and showed significantly higher uptake in atherosclerotic versus normal artery wall [45].

In patients, retrospective analyses of those imaged for prostate cancer staging have confirmed arterial choline uptake [46]. Unlike FDG, choline does not demonstrate high myocardial uptake, but does accumulate in the liver, perhaps precluding assessment of the coronary arteries on the inferior surface of the heart. Definitive studies using this agent in atherosclerosis with histological verification of the image signal are still needed.

^{11}C -PK11195

^{11}C -PK11195 is a ligand for translocator protein (TSPO), heavily expressed by activated macrophages [47]. It has been used in the imaging of neuroinflammation in multiple sclerosis. Several studies have demonstrated a potential role in plaque imaging. ^{11}C -PK11195 uptake is higher in symptomatic carotid arteries compared with asymptomatic plaques [48]. Autoradiography confirmed co-localisation with CD68 immunohistochemistry, implying uptake by macrophages.

Despite these results, the short half-life of ^{11}C requires on-site facilities for tracer generation, likely limiting clinical application.

^{68}Ga -DOTATATE

^{68}Ga -DOTATATE is a gallium-based tracer, currently used in neuroendocrine tumour imaging. ^{68}Ga -DOTATATE binds somatostatin type 2 receptors, also expressed by activated macrophages. In a retrospective study, ^{68}Ga -DOTATATE uptake correlated with the presence of calcified plaques on coronary CT, history of chest pain and previous vascular events [49]. Further studies have demonstrated a correlation with cardiovascular risk factors [50]. ^{68}Ga -DOTATATE uptake often did not co-localise with FDG. It has been suggested that ^{68}Ga -DOTATATE may be more specific for activated macrophages, though differing tracer kinetics may also explain these findings.

Imaging calcification with ^{18}F -sodium fluoride (NaF)

Microcalcification within plaques is known to increase the risk of rupture, perhaps due to stress-induced microfractures around calcified areas [51]. Although mechanisms of vascular calcification are incompletely understood, it is known to be an active process contributing towards plaque progression [52]. In the initial stages, cytokines secreted by macrophages induce osteogenic transformation of vascular smooth muscle cells. Calcification, therefore, occurs as a response to inflammation. Areas of microcalcification have been shown to evolve close to areas of intense inflammation [53]. Established areas of microcalcification induce further inflammatory reaction from macrophages, therefore actively driving plaque progression [54]. When calcification progresses to such an extent that it is detectable by conventional CT (*macrocalcification*), the inflammatory component has usually subsided [52].

^{18}F -NaF has an established role in imaging areas of new bone formation in the context of cancer metastasis and in detection of osteoblastic tumours. ^{18}F -fluoride ions become bound to exposed hydroxyapatite in exchange for hydroxyl ions. Retrospective studies of patients undergoing oncological NaF PET imaging have revealed that vascular NaF uptake may identify areas of developing arterial calcification [55]. ^{18}F -NaF PET thus holds promise as means of imaging dynamic calcification in inflamed, atherosclerotic plaques [56].

In a subgroup analysis of a population recruited for assessment of calcific aortic stenosis using ^{18}F -NaF PET, Dweck and colleagues [36] demonstrated that NaF could be used to report on coronary calcification. Unlike FDG, NaF displayed no myocardial uptake and discrete areas of activity could be localised to individual plaques. ^{18}F -NaF uptake was higher in patients with atherosclerosis (calcium score >0) compared with those without. ^{18}F -NaF uptake progressively increased with increasing atherosclerotic

burden ($r^2 = 0.652$). Patients with atherosclerosis could be divided into those displaying and those not displaying elevated ^{18}F -NaF uptake. Patients who displayed increased ^{18}F -NaF uptake were more likely to have a higher Framingham risk score, previous cardiovascular events, anginal symptoms and prior revascularisation.

In addition, ^{18}F -NaF uptake was seen in coronary segments without visible calcification, implying that ^{18}F -NaF allows detection of microcalcification below the resolution of CT imaging [56] Fig. 2.

These promising findings need to be confirmed in prospective studies, preferably comparing stable and unstable presentations. Furthermore, mechanistic considerations regarding ^{18}F -NaF deposition within the arterial wall need to be confirmed histologically.

Fig. 2 PET-CT images of ^{18}F -NaF activity in coronary arteries. **a** No coronary calcium and no coronary ^{18}F -NaF uptake; **b** extensive calcification in the left anterior descending artery (LAD) but no ^{18}F -NaF uptake; **c** intense focal ^{18}F -NaF uptake in the proximal LAD overlying coronary calcium; **d** increased ^{18}F -NaF uptake in the mid-LAD near existing coronary calcification; **e** intense focal ^{18}F -NaF uptake in the proximal right coronary artery (RCA) following recent inferior myocardial infarction; **f** RCA confirmed to be the culprit with angiography (reproduced with permission from [36])

Alternative approaches for plaque imaging

Clinical non-invasive vascular imaging uses CT, ultrasound and MRI and focuses mainly on luminal stenosis. Recent developments mean that these modalities can also be used to report upon the vascular wall.

Although CT does not enable direct assessment of plaque inflammation, it can be used to characterise plaque components, and these can be used to predict acute coronary syndromes [57]. In pre-clinical models, CT can be combined with targeted nanoparticles such as N1177 (iodine-based) and gold high-density lipoprotein to track macrophage accumulation [58]. When used in combination, the signal from these agents can be discriminated using multi-energy CT, providing detailed information about plaque anatomy and cellular accumulation [59]. The relative molecular insensitivity of CT raises concerns about the toxicity of contrast agent doses required for clinical imaging.

Late-phase contrast-enhanced ultrasound using microbubbles can assess inflammation within carotid plaques [60]. Microbubbles are taken up by phagocytic cells and remain acoustically active for around 30 min. This technique has been shown to be capable of distinguishing symptomatic and asymptomatic plaques [61].

Microbubbles can be targeted towards specific pathological processes through conjugation with various ligands. For example, microbubbles can be targeted to vascular cell adhesion molecule-1 (VCAM-1). VCAM-1 is expressed by activated endothelial cells and is involved in the recruitment of leukocytes to sites of inflammation. The feasibility of such targeting has been demonstrated in preclinical studies [62].

Perhaps most promisingly, MRI has been used to characterise vascular inflammation in carotid arteries. Dynamic contrast enhancement of carotid plaque enables evaluation of plaque inflammation and neovascularization [63] and has been validated histologically. Additionally, MRI can be combined with targeted molecular probes to directly assess plaque inflammation. Ultrasmall superparamagnetic iron oxide (USPIO) particles, which have a similar diameter to LDL, accumulate within plaques under conditions of high endothelial permeability [64]. These lead to signal dropout on T2 MRI and can be used to track macrophages and assess changes in the inflammatory status of plaques [65].

Table 1 summarises the role of MRI, CT and ultrasonography in identifying vulnerable plaques.

Abdominal aortic aneurysms

Pathophysiology

Abdominal aortic aneurysms (AAAs) are defined as focal dilations of the aorta, where aortic diameter is >1.5 times

Table 1 Role of MRI, CT and ultrasonography in identifying vulnerable plaques

Modality	Newer approaches	Features of plaque vulnerability
Ultrasonography	<ul style="list-style-type: none"> • Microbubble contrast agents • Molecular targeting of bubble contrast (e.g. incorporating VCAM-1 ligand) 	<ul style="list-style-type: none"> • Quantify arterial inflammation [60] and neovascularization • Differentiate symptomatic and asymptomatic plaques [61] • Identify areas of active leukocyte recruitment [62]
Computed tomography	<ul style="list-style-type: none"> • Multidetector CT (MDCT) • Nanoparticles, e.g. N1177 (iodine-based), gold-coupled high-density lipoprotein (Au-HDL) 	<ul style="list-style-type: none"> • MDCT differentiates calcified vs non-calcified plaques [15] • MDCT revealed high-risk features, e.g. spotty calcification, large necrotic core and positive remodelling [57] • Nanoparticles can track macrophage accumulation [58, 59]
Magnetic resonance imaging	<ul style="list-style-type: none"> • Gadolinium and dynamic contrast enhancement (DCE) • Multi-contrast MRI • Ultrasmall superparamagnetic iron oxide (USPIO) particles 	<ul style="list-style-type: none"> • Visualise necrotic core, fibrous cap, neovascularization, intraplaque haemorrhage, and calcification [15] • DCE can evaluate inflammation and neovascularization [63] • USPIO particles track macrophage accumulation and plaque inflammation [65]

normal, or has an absolute value >3 cm. Most aneurysms remain asymptomatic until rupture.

Abdominal aortic aneurysms usually form below the level of the renal arteries. The volume of blood flow is lower in the infrarenal aorta, which may lead to reversed flow and consequent oscillatory shear stress, potentially causing aneurysmal dilatation [66]. Most AAAs are fusiform, with a circumferential dilatation involving all layers of the arterial wall. Turbulent flow around the aneurysm leads to deposition of laminated thrombus on the luminal surface of the aneurysm.

Dense cellular infiltration throughout the media and adventitia is a common histological finding in AAAs [67]. Inflammatory cells, including macrophages, neutrophils and lymphocytes enter the aneurysm through the vasa vasorum [68] and by infiltrating through the luminal thrombus and intima. These cells secrete destructive enzymes including matrix metalloproteases (MMPs) and reactive oxygen species, which cause degradation of the extracellular matrix [69], leading to fragmentation and destruction of structural proteins such as elastin, and consequent thinning of the arterial media. In addition, inflammation and hypoxia lead to new vessel formation and loss of vascular smooth muscle cells. These mechanisms increase the risk of AAA rupture.

Imaging abdominal aortic aneurysm progression

Maximum diameter is currently the most widely accepted method for surveillance of AAAs. A cut-off value of 5.5 cm is used to determine which patients require surgery. Aneurysms measuring 5.5 cm or more have an untreated

5-year rupture risk of 40–60 %, with rupture leading to a total mortality of more than 90 % [70]. Factors including patient co-morbidities and operative risk are balanced against risk of rupture when deciding timing of surgery.

Size is not the only determinant of rupture risk, and using vessel dimensions alone means that unexpected rupture of smaller aneurysms may be missed, whilst larger, more stable, aneurysms may be operated on unnecessarily.

The risk of rupture depends on the stresses exerted on the arterial wall and on the intrinsic strength of the arterial wall [71]. The arterial wall is destabilised through chronic inflammation and proteolysis. Using imaging to non-invasively assess the pathological processes occurring within the arterial wall may provide more accurate means of assessing rupture risk.

¹⁸F-FDG PET in abdominal aortic aneurysm imaging

In a prospective study of 15 patients undergoing ¹⁸F-FDG PET/CT and open AAA repair, Reeps and colleagues demonstrated that patients with acutely symptomatic aneurysms had significantly higher ¹⁸F-FDG uptake compared with asymptomatic individuals. Histological analysis of operative samples confirmed that areas of high FDG uptake also showed higher densities of macrophages, T-lymphocytes and increased expression of MMP enzymes [72] Fig. 3.

These findings have been corroborated by work in animal models. In rats, orthotopic implantation of decellularized guinea pig abdominal aorta leads to pathological changes comparable to AAA. Imaged with FDG PET, implanted rats displayed higher levels of aortic FDG uptake compared with controls. Histological analysis

Fig. 3 **a** Coronal ^{18}F -FDG PET/CT image of an AAA showing focal FDG uptake in the aneurysm wall and **b** axial CT, **c** ^{18}F -FDG PET and **d** fused PET/CT images of the same AAA

confirmed that this correlated closely with the quantity of macrophages and CD8 T-lymphocytes [73].

The role of FDG in AAA surveillance remains controversial, however. In a study of 40 consecutive male patients with asymptomatic AAA, FDG signal in the aneurysmal aorta was not increased compared with adjacent non-aneurysmal segments and corresponding regions in control subjects. In fact, FDG signal in the aneurysmal aorta was *lower* than in controls [74]. Further work suggested that this low uptake may reflect lower cell density in the aneurysmal wall compared with normal regions [75].

Inconsistencies in AAA FDG PET may be due to technical limitations such as the partial volume effect. The AAA wall often measures only 1–2 mm and is, therefore, smaller than the spatial resolution of many PET scanners. This limitation can lead to loss of signal (partial volume effect). Newer software tools can correct for this and improve accuracy [76].

Other PET tracers

^{11}F -choline (FCH) and ^{18}F -DPA714 (a TSPO ligand similar to PK11195) have both been used as PET tracers to assess leukocyte activity in AAA animal models. FCH signal is higher in aneurysmal aortic segments compared with controls, with the increase correlating with macrophage density. However, FCH proved to be less sensitive than FDG. There was no significant difference in ^{18}F -DPA714 uptake for AAA compared with controls [73].

Magnetic resonance imaging

As in atherosclerosis, macrophage activity can be tracked in AAA using USPIO particles. In a study of 29 individuals with asymptomatic AAA, patients with distinct regions of mural USPIO uptake had three-fold higher growth rates than those lacking distinct uptake. Histological analysis confirmed co-localisation with areas of macrophage activity [77].

Macrophage activity within aneurysms can also be imaged with agents specific to MMP enzymes. The agent P947 consists of an MMP inhibitor combined with a gadolinium chelate. In an elastase-induced rat model of AAA, P947 has shown enhanced MMP targeting in AAA compared with a scrambled control agent and un-targeted gadolinium chelate [78].

Near-infrared fluorescence and bioluminescence

These highly sensitive techniques can provide information regarding molecular processes during aneurysm progression. Near-infrared light is used because it penetrates tissues more deeply than visible light. In pre-clinical studies, optical probes sensitive to protease activity have been used

to track MMP activity in AAAs. MMPsense is activated by MMP enzymes, and in animal models there is a linear relationship between detected proteolytic activity and aneurysmal growth [79].

Bioluminescence imaging relies on cells that have been genetically modified to express luciferase, an enzyme that emits light when exposed to luciferin substrate. When luciferase-expressing macrophages are injected into animals with experimental AAAs, they demonstrate increased aortic bioluminescence compared with controls [80]. The clinical application of this technique, however, will be limited due to poor tissue penetration and the need to inject transgenic cells.

Conclusions

Recent advances in several imaging modalities indicate that significant information about pathology within the arterial wall can be obtained non-invasively, both in the context of atherosclerosis and aneurysm disease. The results can assist in understanding the underlying disease process in testing the response to new drugs and potentially in improving risk stratification in individual patients.

Future research should yield tracers with better specificity, and further hardware integration (e.g. combined PET/MRI) will allow faster imaging, lower radiation exposure and easier integration into clinical practice.

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