Application of imaging techniques for Takayasu arteritis

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Summary

Arterial injury with subsequent remodelling and predisposition to arterial stenosis and/or dilation are the hallmarks of Takayasu arteritis. The degree of arterial damage closely aligns with prognosis and therefore its prevention is the predominant aim of therapy. Non-invasive imaging has greatly improved our ability to identify the extent and severity of disease and to monitor its progress. However, many questions remain concerning the optimal use of individual modalities at different stages of disease. Imaging methods for the quantification of arterial damage are lacking. Likewise, no single technique can accurately determine disease activity within the arterial wall or distinguish inflammatory and non-inflammatory disease progression. The aim of this review is to outline current imaging strategies in Takayasu arteritis, their individual roles in diagnosis and disease monitoring and potential future advances.

Background

Progressive advances in radiological imaging have the potential to transform the management of Takayasu arteritis (TA). Non-invasive imaging may facilitate earlier diagnosis and identification of relapse. More accurate monitoring of disease activity and sensitive detection of arterial injury allows more precise titration of therapy [1]. Ultimately patient experience and outcomes should improve [2]. Of course, this is predicated upon physician insight into the clinical presentations of large vessel vasculitis (LVV) and requires close collaboration with imaging specialists to ensure the appropriate scans and protocols are selected for each clinical indication. A “wish list” for the optimal imaging modality in TA might comprise description of a single non-invasive scanning technique that facilitates diagnosis and assessment of disease extent; accurately quantifies disease activity in the arterial wall; demonstrates response to immunosuppressive therapy and allows precise tailoring of therapy to disease activity. While no single modality can achieve this, combination use of current techniques comes close. Indeed, it has been suggested...
that imaging may be a more sensitive means for detecting residual low-grade arteritis than currently available plasma biomarkers [3]. However, non-invasive imaging remains very expensive and access is limited in many countries. This fact is not helped by a relative lack of controlled prospective studies to demonstrate their benefit. Faced with these restraints, knowledge of the pros and cons of individual imaging modalities will help the supervising physician and radiologist select the appropriate scan at each stage of disease management. This in turn requires a detailed understanding of disease pathogenesis and the patterns of vascular involvement seen.

TA is an idiopathic inflammatory disease typically affecting young women. The majority of patients endure a relapsing-remitting disease course prior to eventually entering remission after a variable length of time. Inflammation predominantly localises to the wall of large arteries, including the aorta, the pulmonary arteries and their main branches [1,4]. Immunohistochemical analysis reveals a lymphomonoctytic infiltrate, with occasional multinucleate giant cells. Bidirectional cross-talk is thought to occur between stromal components of the arteries and invading leukocytes. The resultant pan-arteritis leads to hyperplasia, hypertrophy, fibrosis and arterial wall thickening. Mesenchymal cell proliferation is principally responsible for remodelling that results in arterial stenosis and occlusion, while more rarely local metalloprotease release leads to arterial dilatation and aneurysm formation [1,4].

TA may result in significant morbidity and mortality [5-7], with the degree of arterial injury closely correlated with prognosis [5,8,9]. Evidence of increased arterial wall thickening during active inflammatory phases of disease suggests that arterial lesions may be reversible [10,11]. In contrast, secondary arterial remodelling is believed to be irreversible and hence prevention of disease progression is the main therapeutic goal [9,12]. Current understanding of disease pathogenesis is significantly limited by the relative inaccuracy of physical examination for evaluating vasculitic involvement of large vessels and by the lack of available biopsy material [13]. Similarly, methods for the precise assessment of disease activity represents another major unmet need, with data demonstrating that laboratory markers are inaccurate in 50% of cases [14]. There is no single clinical finding that accurately reflects disease activity and therefore multi-item activity indices have been proposed. These include the National Institute of Health (NIH) activity criteria [14] and the Indian Takayasu Activity Score (ITAS) [15]. However, based on clinical and laboratory findings, their accuracy remains suboptimal. As a consequence non-invasive imaging has become an essential component in the diagnosis and follow-up of TA.

In this review we will focus on the current roles of imaging in the management of TA, concentrating upon positron emission tomography (PET), magnetic resonance imaging (MRI), computerised tomography (CT) and high-resolution ultrasound (US). The benefits and limitations of the different modalities will be addressed and novel prospects and approaches for the future will be discussed.

**Angiography**

Intra-arterial digital subtraction angiography (DSA) provides volumetric images of the arterial lumen. The spatial resolution and the detail of images obtained with DSA are superior to those acquired by computed tomography (CT) or magnetic resonance (MR), hence DSA still represents the gold standard for studying the lumen of the affected arteries [2]. This approach has shown that TA arterial lesions are of variable length, spanning a few millimetres to several centimetres. They exhibit either a smooth or irregular appearance. Typical patterns in terms of the morphology of individual lesions and their distribution throughout the vascular tree are characteristic for TA. For example, lesions are often ostial and the most commonly affected arteries are the left subclavian and left common carotid. Angiographic assessment of the distribution of arterial in TA has described six types [16]. However, important limitations of DSA are its invasive nature and failure to characterise the arterial wall. In addition, patients may need hospitalisation and there is a low but measurable risk of procedural complications. Thus, in the management of TA, the use of DSA is now confined to a few specific indications such as preparation for arterial revascularisation, or measurement of central arterial pressure when peripheral arterial involvement precludes non-invasive blood pressure recording.

**Positron emission tomography**

Although widely utilised, the precise role of 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography (18F-FDG-PET) in the management of TA remains to be determined. Accurate assessment of disease activity in the arterial wall represents an important unmet need in the management of LVV and 18F-FDG-PET currently represents the best option [1]. However legitimate concerns remain. First, these scans are very expensive, there is limited access to them outside oncology indications in many parts of the world and the typical radiation exposure during an 18F-FDG-PET/computerised tomography (CT) scan is between 10 and 15 mSv. 18F-FDG uptake by metabolically active cells, predominantly monocytes and macrophages, provides an estimate of the extent and intensity of arterial wall inflammation in TA [17-20]. Co-registration of 18F-FDG-PET images with those generated by CT allows metabolic activity to be localised anatomically, resulting in improved sensitivity for detection of arterial wall inflammation [21] (figure 1). Perhaps the predominant role for 18F-FDG-PET/CT in TA is for the diagnosis of active disease [1]. If the diagnosis of LVV is suspected early enough 18F-FDG-PET/CT can reveal pre-stenotic arterial disease and prompt immunosuppression may improve outcomes. Indeed, 18F-FDG-PET scan findings identify more affected arterial regions than MR imaging [21,22] and significantly improve diagnostic accuracy and affect...
therapeutic decisions [23]. A meta-analysis of TA studies showed that \(^{18}\)F-FDG uptake had a pooled sensitivity of 87% and specificity of 73% [24]. The role of \(^{18}\)F-FDG-PET/CT in the follow-up of patients with TA is less clear. Neither plasma biomarkers nor individual imaging modalities have proven sufficiently sensitive for detection of low-grade persistent arteritis and the physician global assessment remains a significant factor in clinical assessment [9]. Due to concern regarding undetected inflammation and the potential severity of disease complications, there is a tendency to over-treatment and prolongation of therapy. \(^{18}\)F-FDG-PET/CT has been considered as a means to monitor disease activity. However, in addition to the radiation exposure involved, questions persist regarding its sensitivity and specificity for the detection of low-grade relapsing or partially-treated arteritis. Although the \(^{18}\)F-FDG uptake observed in the untreated patient typically falls rapidly in the face of effective immunosuppression, concern remains that any residual inflammatory activity is not readily detected by \(^{18}\)F-FDG-PET/CT [23,25]. Moreover, interpretation of low-grade arterial uptake of \(^{18}\)F-FDG in a patient with normal acute-phase response markers and clinically inactive disease remains complicated [17,26]. A close relationship between \(^{18}\)F-FDG uptake and disease activity markers has been observed in some studies [27–29], while in contrast poor correlation has also been reported [30]. The causes of persistent arterial \(^{18}\)F-FDG uptake are likely multifactorial. They might include residual arterial wall inflammation or alternatively myofibroblast proliferation in response to arterial injury, vascular remodelling, progressive fibrosis or premature atherogenesis. In an ideal world arterial biopsy would help solve this conundrum but in its absence the search for novel and specific biomarkers must go on [9]. This conclusion leads on to another relative limitation of \(^{18}\)F-FDG-PET imaging in LVV and that is signal quantification and the lack of standardised PET criteria for diagnosis. Qualitative assessment is most commonly used, with visual comparison of arterial uptake and constitutive uptake in normal tissue, often the liver, using a 4-point scale [31]. A systematic review has reported that visual uptake equal to or exceeding that of the liver was seen in 84% of LVV patients and 18% of controls [22,24]. The semi- quantitative measure, standardized uptake value (SUV), is also frequently used. This is typically based upon weight and body size, with SUVmax representing the maximum SUV of all voxels within a prescribed region of interest [32]. In a recent study we employed both these methods to investigate \(^{18}\)F-FDG uptake by synthetic arterial grafts in patients with clinically inactive LVV. Qualitative and semi-quantitative analyses demonstrated increased arterial graft-associated uptake which was not associated with active arteritis, infection of the prosthesis or local disease complications [33]. Peri-prosthetic \(^{18}\)F-FDG uptake is thought to reflect a foreign body reaction.

**Magnetic resonance (MR)**

Through its ability to evaluate a wide range of vascular territories MR has become one of the most important imaging techniques for TA. A particular advantage is the lack of radiation exposure,
which allows multiple evaluations in young patients. MR-angiography (MRA) requires a relatively short acquisition time and generates images of the arterial lumen (figure 2A). Specific MRA sequences can be used to obtain angiographic images without contrast medium [34,35]. Despite important advances in recent years, individual sequences for non-contrast-enhanced MRA still have important limitations, and each sequence is usually applied to specific arterial districts (e.g., 3D time-of-flight sequences are used to study intracranial vessels). For these reasons the use of non-contrast-enhanced MRA in TA is still limited.

MR is also able to depict and characterise the thickened arterial wall (figure 2B). However, this type of analysis is more time-consuming. In general, T1-weighted imaging is used to provide anatomical depiction of arterial wall lesions, while T2-weighted imaging (to assess wall oedema) and contrast-enhanced T1-weighted imaging (to assess late contrast enhancement) are used to look for changes suggestive of active inflammation in the arterial wall.

In recent years, MR and CT have largely replaced DSA for the diagnosis of TA [36,37]. The diagnostic value of contrast-enhanced MRA is comparable to that of DSA, with impressive accuracy for detection and grading of stenosis and dilation [38,39]. Anatomical depiction of the arterial wall can be useful for those cases in which luminal analysis is inconclusive. Although not yet formally studied, the typical, circumferential or crescentic wall thickening seen in long irregular lesions can be considered pathognomonic for large vessel vasculitis [36,37,40]. Moreover, the presence of oedema or post-contrast signal enhancement is considered suggestive of arterial wall inflammation and highly characteristic for vasculitis. MR can localise fibro-inflammatory lesions and reveal whether these are limited to the arterial wall or extend to peri-adventitial tissues. MR is also useful for determining disease extent [11]. Addition of arterial wall data to lumen analysis extends the estimate of arterial disease extent [11,25,41]. When considering disease activity some authors have suggested that arterial wall thickening and more intense post-contrast enhancement may reflect active disease [10,11,40]. However, despite a moderate correlation between these findings and acute-phase reactants [10,40], an overlap between active and inactive disease remains, lessening the role of MR for differentiation of active disease [10,40]. Two of these studies [10,40] also evaluated T2-weighted imaging for the assessment of arterial oedema in clinical practice and suggested that this approach may help determine TA disease activity. However, Tso et al. evaluated electrocardiogram-gated T2-weighted MRI imaging in 24 TA patients [42]. They found that while 94% of scans obtained during periods of unequivocal disease activity revealed arterial wall oedema, this was also found in 56% of scans in those in apparent clinical remission [42]. The discrepancy might reflect low-grade grumbling disease.

Most importantly the presence of oedema did not correlate with acute-phase reactants or with appearance of new lesions in follow-up studies of 17 patients. Other reports also suggest that arterial enhancement after paramagnetic contrast medium infusion was similar in active and inactive disease [43,44]. Multiple explanations for the differing study results exist. Heterogeneity between studies is substantial due to varying definitions of active disease [9]. Concurrent medications might also have influenced results. Finally, the contrast media used can diffuse into the extracellular space and post-contrast enhancement might reflect either inflammation or increased extracellular volume, for example in the presence of fibrosis. Of note Gadofosveset trisodium, a purely intravascular contrast medium no longer available for commercial reasons, does not detect fibrosis and may increase the accuracy of MR for disease activity assessment [45].

The predominant role for MR in the follow-up of patients with TA is to provide a safe, non-invasive mean of assessing changes in
vascular anatomy over time. It is still matter of debate whether MR can add useful information to disease activity assessment with a cross sectional, single time-point assessment of arterial wall oedema or post-contrast enhancement. Some recent biomarker studies have combined analysis of novel targets with non-invasive imaging to try and address some of these issues [46–48].

**Computed tomography (CT)**

CT may also be used to image the vascular lumen and the arterial wall, allowing diagnosis to be made in the early disease phase, before significant luminal remodelling has occurred [36] (figure 3). CT studies in patients with TA are usually performed according to an angiographic protocol (angio-CT, CTA). Images are acquired in the early arterial phase following infusion of iodinated contrast medium. Delayed acquisition is needed to assess late contrast enhancement, which has the appearance of a double ring, especially in the venous phase [17,18]. The inner, poorly enhanced rim is proposed to represent the hyperplastic intima, while the outer, highly enhanced rim might represent vasa vasorum neoangiogenesis in the actively inflamed media and adventitia. Electrocardiogram-gating is required to study arterial territories affected by the heartbeat, such as the coronary arteries and the pulmonary circulation. CTA provides similar anatomic analysis of the arterial lumen and wall to MR [49,50], and may demonstrate post-contrast enhancement [51]. The clinical utility of CTA in diagnosis, assessment of disease extent and follow-up of TA patients is similar to MR, and CTA is also able to differentiate TA from atherosclerosis [52].

The advantages of CT over MR include shorter acquisition times and provision of images that are typically more intuitive than MR, with improved anatomical detail. Thus CTA is particularly useful for preoperative planning in the event that revascularisation is required. However, radiation exposure and the use of iodinated contrast medium limit the use of CTA for long-term management. Improved technology, including the latest generation of single- and dual-source CT scanners, is moving towards minimisation of radiation exposure.

The origin of arterial calcification detected by CT is multifactorial. Vascular calcification is more commonly associated with chronic renal failure and atherosclerosis than vasculitis. However, the radiological appearance of aortic calcification due to LVV seems to differ from that of atherosclerosis, with a circumferential pattern of calcification seen only in TA [53]. The clinical significance of arterial calcification in TA remains unclear.

An additional bonus of CTA is its ability to evaluate coronary artery involvement in TA. Coronary artery disease (CAD) is present in up to 55% of patients and may reflect direct vasculitic involvement or secondary atherosclerosis [54–56]. Both ostial and non-ostial stenoses have been described [54–56]. The former are believed to result from vasculitic involvement of the ascending aorta and its extension into the coronary ostia. In the case of acute coronary syndrome in TA, DSA remains an important option if angioplasty is considered, although caution should be taken in the face of active coronary arteritis. Coronary CTA is used in the non-acute setting to demonstrate the presence of coronary artery involvement. While not recommended for all patients, those with suggestive symptoms should be investigated. Likewise, patients with significant ascending aortitis should be considered for coronary CTA. The data obtained help to establish the need for intervention and to plan whether endovascular or surgical revascularisation is required.

**High-resolution ultrasound**

Of all the imaging modalities, high-resolution colour duplex US is probably the most underused in the management of TA, particularly given that it is relatively cheap, well tolerated, can...
readily distinguish the arterial wall from the lumen, measure intima-media thickness (IMT) and delineate degrees of stenosis or aneurysm [57]. Its restrictions include the need for a specialised operator and the fact that this technique is limited to the assessment of the carotid and vertebral circulation, proximal subclavian and axillary arteries. US may also be used to study the abdominal aorta in TA and the temporal and facial arteries in giant cell arteritis [58].

US studies can help to establish a diagnosis of TA, and may reveal those with pre-stenotic disease [59]. Carotid US is particularly important for young patients presenting with carotidynia, where the differential diagnosis may lie between carotid arteritis, migraine and carotid dissection [60]. In TA US reveals concentric arterial wall thickening, which may appear bright as a consequence of active arterial wall inflammation and oedema [60,61] (figure 4A). Although a precise link between active arteritis and US wall enhancement disease activity has not been established, increased IMT as a consequence of arterial wall inflammation may be reduced in response to effective treatment [62].

**Figure 4**

Ultrasound studies in Takayasu arteritis

A. High-resolution Doppler US of the common carotid artery reveals concentric homogenous thickening of the arterial wall in a patient with Takayasu arteritis. B. Doppler flow studies of the upper limbs showing a normal flow pattern in the right arm and markedly attenuated flow in the left arm in a patient with a left subclavian artery stenosis.
Doppler US studies can provide an excellent assessment of the site and degree of stenoses in the limb arteries, accurately assessing their effect on blood flow (figure 4B). Once the baseline arterial involvement is determined, changes in response to treatment can be readily monitored. Recent research interest has focused on the potential additional benefits associated with contrast-enhanced US (CE-US) (see below).

**Luminal and arterial wall assessment**

Ideally imaging in TA should assess both the arterial lumen and the arterial wall. Luminal assessment is only able to diagnose TA once stenosis or dilatation has occurred. In contrast, arterial wall data derived from PET, MRI, US or CT may reveal pre-stenotic disease. Following diagnosis, routine follow-up imaging is mandatory for the identification of progressive vascular involvement [12,63]. At present, the interpretation of arterial wall features (oedema, FDG uptake or post-contrast enhancement) remains a matter of debate. We believe that state-of-the-art follow-up requires anatomical data derived from the lumen and the arterial wall. Lumenography reflects hemodynamic derangement in the case of stenosis, while wall thickening is more directly linked to pathogenic events occurring in the arterial wall. A panoramic anatomical view including both the lumen and arterial wall can be obtained by MR or CT. Similarly, for some vascular beds high-resolution US can provide this analysis. Development of new lesions does on occasion contribute to progressive vascular disease. However, in our experience, progression is more frequently associated with remodelling in existing lesions.

**Future perspectives**

The rapid developments in the field of medical imaging include the study of LVV and a variety of exciting new approaches have been described. CE-US utilises intravenously administered gas-filled microbubbles which generate hyperechogenic signals when exposed to US. A pilot study has demonstrated improved definition of the border of the arterial lumen, with accurate assessment of carotid wall vascularisation [64]. The localisation of the enhanced signal at the arterial adventitial border led to the proposal that the microbubbles provide a contrast-enhanced signal by allowing visualisation of the vasa vasorum [64-66], a hypothesis supported by matched arterial biopsy studies [67]. The observed signal can be quantified by analysis of grey scale median and this was reduced following six months immunosuppressive treatment [65]. A subsequent prospective study of 31 LVV patients used CE-US of the carotid arteries and a graded vascularisation score as an index of disease activity and found that the data correlated closely with that obtained using 18F-FDG-PET [68]. Attempts are also being made to optimise 18F-FDG-PET image quality using novel reconstruction algorithms in conjunction with time-of-flight (TOF) corrections [69]. However, the uptake of 18F-FDG by all metabolically active cells limits its utility in LVV. Thus, different PET ligands are being investigated. [11C]-PK11195 binds to the translocator protein (TSPO) and is predominantly used in neuroscience. Although widely expressed, TSPO is significantly upregulated on activated monocytes and macrophages. In LVV [11C]-PK11195-PET-CT revealed aortitis in the 5 clinically active patients included in a proof-of-principle study of 15 patients [70]. Moreover, the [11C]-PK11195 signal was suppressed when immunosuppressive therapy was enhanced [70-72]. The importance of both mononuclear cells and changes in the vasa vasorum in active arteritis suggests that development of novel ligands targeting activated endothelium, alongside those specifically binding to pro-inflammatory mononuclear cells may offer more specific and sensitive means for the precise detection of persistent arteritis. Furthermore, a ligand able to distinguish progressive arterial remodelling due to myofibroblast proliferation from active inflammation would allow more precise therapeutic targeting, if and when therapies specific for myofibroblast proliferation are developed. The rapid advances in MR technology also suggest that this modality has more to offer in the management of LVV. Development and use of alternative contrast agents might offer improved sensitivity and specificity for the detection of arterial wall inflammation [45]. In particular, exciting preliminary studies suggest that MR-PET imaging may address some of the current imaging limitations in LVV. Comparison of whole body TOF-PET/MRI with TOF-PET/CT shows that the former offers improved image quality and shorter imaging duration [73]. A small comparative study in LVV demonstrated that while 18F-FDG-PET-CT and 18F-FDG-PET-MR generate comparable visual and quantitative results, soft tissue resolution and definition of anatomy was improved by 18F-FDG-PET-MR, and at a lower total radiation dose [74]. Prospective studies of active disease, pre- and post-changes in immunosuppressive therapy and matched to measurement of plasma biomarkers and disease activity scores are now required.

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