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Review paper

Contemporary follow-up imaging after endovascular repair of lower extremity atherosclerotic lesions

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Abstract

Atherosclerotic disease is currently one of the most important problems of modern medicine because it is a leading cause of increased morbidity, morbidity and mortality, and disability in the Western World. Atherosclerosis of the lower limbs (peripheral arterial disease – PAD) significantly affects the quality of life and in a considerable proportion of patients is a cause of disability. Radical treatment of PAD, both surgical and endovascular, aims at revascularisation of ischaemic tissues distal to obstructed arteries. Surveillance imaging is an important part of patient management after endovascular repair of PAD. Apart from availability and contraindications, challenges of imaging include calcifications, flow dynamics, and stent-related artefacts. The aim of this paper was to review the current literature on imaging methods for follow-up after endovascular repair of atherosclerotic lesions, with special attention paid to novel techniques. As a non-invasive modality, ultrasound is still the first-line examination, but computed tomography angiography remains a current state-of-the art technique for follow-up. However, since current imaging recommendations seem not to adhere to contemporary imaging possibilities, more attention should be paid to recent improvements in magnetic resonance angiography technology.

Key words: atherosclerosis, peripheral arterial disease, percutaneous angioplasty, imaging.

Introduction

Atherosclerotic disease is currently one of the most important problems of modern medicine because it leads to increased morbidity, morbidity and mortality, and disability in highly industrialised countries [1]. Atherosclerosis is a chronic disease of the arteries that is thought to be a result of a chronic inflammatory process. This inflammation results in endothelial damage, which starts a cascade of lipid deposition, fibroproliferative activation, and increased clotting. An ultimate product of those processes is an atherosclerotic plaque formation that results in artery stenosis or occlusion, and finally in distal ischaemia [2-4].

Plaque formation starts as early as in childhood but clinically manifests later in life, when the sum of arterial pathologic processes becomes sufficient to be revealed clinically. Clinical symptoms may occur suddenly (myocardial infarction, stroke) or progressively develop (ischaemic heart or brain disease and atherosclerosis of the lower limbs) [3]. Atherosclerosis of the lower limbs (peripheral arterial disease – PAD) significantly affects the quality of life and in a considerable proportion of patients is a cause of disability The overall disease prevalence of PAD is in the range of 3-10%, which increases to 15-20% in subjects older than 70 years of age [5].

Radical treatment of PAD, both surgical and endovascular, aims at revascularisation of ischaemic tissues distal to obstructed arteries [6]. Recommendations summarised in the TASC II guidelines for the treatment of PAD consider a heterogeneous group of patients ranging from claudicants to critical limb ischaemia patients [7]. For a subset of lesions, surgical revascularisation is still considered a gold standard, especially when an applicable

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Authors' contribution:
A Study design · **B** Data collection · **C** Statistical analysis · **D** Data interpretation · **E** Manuscript preparation · **F** Literature search · **G** Funds collection

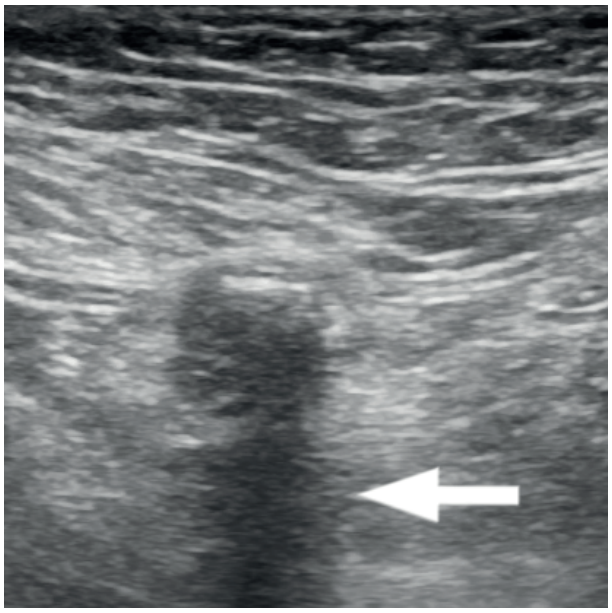

Figure 1. Ultrasonography of the right common femoral artery. Acoustic shadowing (arrow) produced by calcifications prohibit arterial lumen morphological analysis

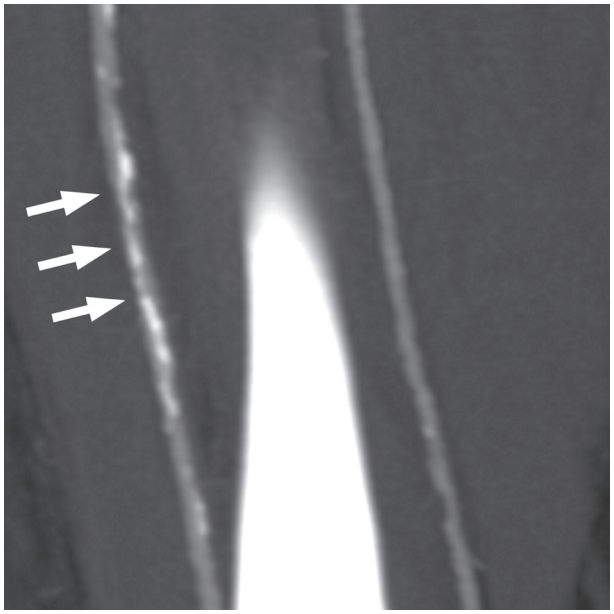

Figure 2. Computed tomography angiography of the right calf. Beam scattering (arrows) due to multiple small calcifications disallow stenosis analysis in the anterior tibial artery

venous conduit is present. Open surgery presents higher patency and limb salvage rates, even though the risk of complications is slightly higher than for endovascular strategies [8]. It is, however, more and more accepted that an endovascular first strategy is adapted in most iliac, superficial femoral, and in some infrapopliteal lesions. The latest endovascular techniques, i.e. drug-eluting stents and balloons, show promising results, especially in infrapopliteal lesions [8]. However, as much as 40% of patients undergoing vein bypass require a secondary intervention during follow-up and an average of 1.75 repeat interventions per patient for a three-year period may be estimated [9]. Moreover, after endovascular revascularisation in 35% of cases a repeat intervention is necessary within a year [10]. These numbers underline the need for a careful follow-up of patients after revascularisation. Although sustained patency of treated vessels may not always be needed to achieve limb salvage or to obtain resolution of symptoms, surveillance usually concentrates on patency monitoring [8].

Follow-up arterial imaging has to keep pace with increasingly sophisticated methods of treatment. Therefore, the aim of this paper was to review the current literature on imaging methods for follow-up after endovascular repair of atherosclerotic lesions (percutaneous angioplasty – PTA), with special attention paid to novel techniques.

Challenges of imaging

A recent review showed that conventional balloon PTA, cryoplasty, cutting balloon angioplasty, and debulking (i.e. mechanical atherectomy or laser ablation) as a standalone treatment for restenosis is not effective in the long term [11]. On the other hand, the use of covered and drug-eluting stents, the use of drug-coated balloons, and the combination of debulking and drug-coated balloon angioplasty seem to present promising results [11]. Therefore, detailed restenosis imaging becomes of special importance to perfectly suit an optimal treatment method.

Calcifications appear as one of last stages of evolution of atherosclerotic plaque. The pathomechanism of the plaque calcification still remains unclear, and currently three hypotheses are considered, including processes similar to bone formation, precipitation of calcium ions, and activation of osteoblast-like cells [12-14]. Regardless of the mechanism, calcifications were considered in the past as a passive process associated with advanced age, incurable and irreversible. Current research shows that it is an active, controlled, and organised process in which hydroxyapatite (calcium phosphate) is deposited in the walls of the vessels in a close relation to the chronic inflammation that takes place in plaques [4,15]. In general, calcifications are a source of artefacts in imaging, which reduce the quality of images. A source of those artefacts are the physical properties of calcifications that are distinct from properties of soft tissues. In ultrasound (US), calcifications present much higher acoustic impedance than that of normal arteries, which results in acoustic shadowing behind the plaque. This shadowing prohibits both morphological analysis of the vessel structure (Figure 1) and flow analysis. In computed tomography (CT) extensive calcifications, due to high X-ray scattering and beam hardening, may be a source of streak artefacts. Those artefacts may result in a completely ineffective vessel lumen analysis, especially in small arteries (Figure 2). Magnetic resonance imaging (MRI) is less sufficient for calcifications because hydroxyapatite presents just a signal void in this technique. Digital subtraction angiography (DSA) is the method least sensitive to calcification-relat-

ed artefacts, but due to its invasiveness it remains the last choice modality for follow-up after PTA.

Flow dynamics

Advanced atherosclerosis usually affects the entire organism, including coronary arteries. Therefore, the disease is commonly related to heart failure that reduces cardiac ejection fraction and stroke volume. Those parameters influence contrast material bolus shape in arteries, i.e. they flatten and elongate the bolus curve. This effect has two major consequences in CT, MRI, and CEUS examinations: (i) the vessel lumen filling with contrast medium is usually suboptimal, and (ii) there is a slight possibility that the scanning time would not fit the vessel filling. In consequence, contrast-enhanced imaging is usually of limited but reproducible quality, even when using bolus-tracking technique.

The second important influence of flow dynamics to the atherosclerosis imaging is a summarising effect of non-significant stenoses. It is seen especially in diabetic patients, who present with multiple narrowings of small-diameter arteries. In such patients it is difficult to assess the individual significance of a plaque in US when the flow is disturbed by several previous boarder-significant lesions. In such cases one may not rely on either flow curve or velocity analysis to diagnose the significance of the plaque. We "feel" the general significance of the sum of multiple small lesions rather than being able to directly measure it.

Stent-related artefacts

Stents are metal scaffolds that mechanically consolidate the effect of angioplasty due to their radial force, which helps to maintain the patency of the recanalised vessel [16]. However, the most important complication of PTA is restenosis, which limits the long-term effectiveness of endovascular treatment. Restenosis is the artery re-narrowing due to neointima proliferation, which is a mechanical and cellular response of the vessel to the injury related to the stent placement [17]. Studies show that in the first year after placement of the stent, 30-55% of patients present with restenosis [18,19]. In US and CT, stents produce artefacts in a similar way to calcifications because of comparable physical properties. However, because metals have higher atomic numbers than hydroxyapatite, in CT they produce stronger streak artefacts and also photon-starvation artefacts (Figure 3) that further hamper vessel lumen assessment and restenosis detection. Applicability of MRI to post-PTA follow-up is strongly dependent on the prosthesis composition. Nitinol stents are most suitable for magnetic resonance angiography (MRA) surveillance because Nitinol does not produce susceptibility artefacts that completely prohibit vessel assessment. Conversely nickel-alloy and stainless-steel components should not be examined using MRA [20].

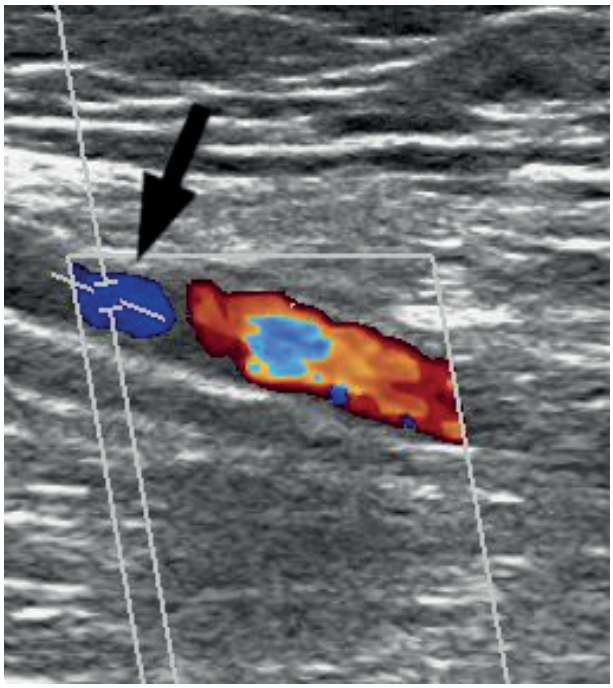

Figure 3. Color Doppler ultrasonography of the left external iliac artery. Stent-related artefacts (arrow) result in a false restenosis appearance

Follow-up methods

Surprisingly, the value of surveillance after endovascular angioplasty has not undergone the same intense testing as that after open surgery. Currently, there are no large established randomised controlled trials that could standardise diagnostic imaging in the follow-up after stent placement. Moreover, collateral vessel maintenance during PTA can further complicate the complex haemodynamic circulation analysis and can lead to an underestimation of clinical significance of restenosis [21].

Ultrasonography

The ankle-arm ultrasound Doppler index, which in most surgical centres is the basis for qualification of patients after PTA, is beyond the scope of this paper [22]. Although the technique uses ultrasound, it is not an imaging modality. Obviously, the ankle-arm index is an effective general clinical indicator of the lower leg arterial function with a specific predictive value to the foot perfusion [23]; however, it presents little specificity and sensitivity to particular lesions.

In clinical practice, US is usually the modality of choice for follow-up after PTA [16,21,24]. It is a general consensus that the criteria for haemodynamically significant stenosis (over 70%) in the stented artery include peak systolic velocity over 300 cm/s and peak velocity ratio across the stenosis over 3.0 [23]. However, in long stents these parameters may be difficult to be established. Moreover, because neointimal hyperplasia after PTA tends to be diffuse, it is recommended that additional artery im-

aging is performed before a decision for a secondary endovascular intervention, especially for iliac stents in obese patients [21]. US is a non-invasive and low-cost alternative of other arterial imaging modalities. The unquestionable advantages of US are non-invasiveness, low cost, wide availability, and lack of ionising radiation. The dynamic nature of US and Doppler US (DUS) enables identification of flow direction and flow properties in stented arteries, which is a great advantage over computed tomography angiography (CTA) and MRA, which present only a momentary image of vessels. The major disadvantages of US remain operator skill and technique dependency, equipment requirements, and the above-mentioned artefacts.

DUS in many cases has the ability to overcome its limitations related to calcium or stent-related artefacts. When the stent lumen is covered by artefacts, flow spectrum DUS analysis may reveal a significant in-stent restenosis (Figure 3). However, this technique presents limited application in stenoses below 50% and in long stents. In extremely obese patients, when ultrasound beam penetration is limited, especially when using linear probes, the diagnostic performance of US may also be inadequate [25]. In such cases, there are several solutions, including harmonic and crossed-beam imaging, that are available in modern US units as well as vendor-specific noise reduction techniques. However, in extreme cases, the use of an abdominal probe may be useful, which offers the best beam penetration but at the cost of lower resolution.

Early DUS after endovascular intervention might be the most appropriate follow-up method, as a so-called gold standard, i.e. conventional angiography can underdiagnose residual stenosis in as much as 50% of patients [26]. However, other studies have indicated that DUS may not reliably predict significant arterial occlusion because there are a high percentage of moderate and even severe stenoses that have stabilised or even resolved over time [27].

Digital subtraction angiography

DSA is still called the "gold standard" of vessel imaging methods according to TASC II [6]. However, the main drawback of this technique is its invasiveness related to the vessel puncture, the possibility of arterial dissection or distal embolisation due to atheromatous plaque fragmentation, the significant radiation dose, and the intra-arterial contrast medium application, which, especially in atherosclerotic patients, may lead to contrast-induced nephropathy [20,28]. Moreover, similarly to plain radiograph, invasive angiography can only project three-dimensional plaque to a two-dimensional image. Therefore, DSA may underestimate the real artery stenosis. Invasive angiography is also related to a number of complications, including pseudoaneurysm, arterial dissection, local haematoma, arteriovenous fistula, and distal embolism, which may additionally increase the duration of hospitalisation [3, 6].

The main advantage of DSA is its dynamic nature that enables the presentation of arterial inflow and outflow. Thus, it is especially useful in patients with a low cardiac ejection fraction and with multiple significant stenoses or occlusions. In such subjects, other large field-of-view modalities, including CTA and MRA, may be ineffective due to difficulties in establishing a proper scanning delay time. Nevertheless, DSA is not recommended as the primary imaging modality for patients with PAD and is recommended only when revascularisation is planned [29]. A history of contrast reaction should be documented before the performance of angiography, and in cases of previous serious allergic reactions the use of carbon dioxide DSA of MRA has to be considered [29].

Computed tomography angiography

Although CTA is a contemporary working horse for lower extremity peripheral arterial disease and the modality is a subject of constant technological improvement, surprisingly, the most recent evidence for its accuracy was published in 2009. In a meta-analysis by Met *et al*. it was found that compared with intra-arterial DSA, CTA was an accurate modality to assess the presence and extent of lower extremity peripheral arterial disease in patients with intermittent claudication, although definitive conclusions could not be drawn [30]. In this meta-analysis CTA correctly diagnosed occlusions in 94% of segments and detected over 50% stenoses in 87% of segments. Underestimation of occlusion was found in 6% of segments, understaging of stenoses occurred in 9% and overstaging in 4% of segments. However, it is important to understand the limitations of this meta-analysis. Firstly, although 957 patients were included, the median sample size of primary studies was only 33. Secondly, overall primary study quality was considered to be just moderate, and both publication bias and significant heterogeneity were detected. Finally, the median CTA slice thickness was as high as 2.0 mm, ranging from 0.75 mm to 5.0 mm, which does not fit contemporary protocols. Therefore, it can be concluded that the current diagnostic accuracy of CTA for diagnosing PAD in not known.

CTA is the current reference standard for the follow-up after PTA. The modality is widely available, less operator-dependent than US, and can be performed rapidly in unstable patients [20]. Because contemporary CT units offer a very good spatial resolution, CTA enables a precise measurement of arterial diameters, detection of re-stenosis, as well as detection local PTA complications. However, due to the static nature of the modality, CTA may not properly present arteries in the case of severe heart failure or multi-level occlusions [31]. Another limitation of CTA is the risk of contrast-induced acute kidney injury (CI-AKI) [28] and potentially cancerogenous cumulative radiation dose [32], especially when imaging is repeated at follow-up. Patients after PTA, due to usually generalised

atherosclerosis, are at an increased risk for CI-AKI. For instance, CI-AKI was reported in 3.5% of patients scheduled for coronary CTA, and permanent kidney injury was noted in 0.2% of them [33]. However, even higher rates of CIN-AKI were reported for subjects undergoing DSA [28]. The risk related to effects of radiation is much more difficult to assess due to the stochastic nature of carcinogenesis. One may say that because patients after PTA are usually older they do not manage to develop CTA-related cancer before death from other causes. This is of course a dilemma. Yet, the actual risk of developing cancer due to exposure to radiation in this group has not been estimated yet. Despite that, because CTA for lower extremities has to be performed using thin slices and the scan range is large, the radiation dose is significant. Therefore, it is worth considering reduction of the tube voltage to 100 or 80 kVp. Tube voltage reduction results in a mean dose lowering of up to 34% [34]. An additional advantage of low kVp scanning is an increased image contrast, which allows for iodinated contrast medium volume reduction. A disadvantage is the increased image noise, which reduces image readability. Thus, low kVp scanning requires the use of iterative or model-based image reconstructions [35]. These techniques use multiple advanced mathematical operations to optimise the image by reducing the noise. Iterative reconstructions are widely available in contemporary CT scanners and should be used as a routine [20]. Model-based reconstructions are still a work in progress because the technology is expensive and time-consuming, but they allow a dose reduction of as much as 73% as compared with low-dose conventional adaptive iterative reconstruction while maintaining diagnostic accuracy [36]. It is also obvious that native scans have to be omitted. In some cases, PAD may significantly alter blood flow, especially distally to the knee, which results in poor vessel opacification. Then an additional scan of the calf is necessary.

Another limitation of CTA used for the follow-up after PTA may be stent-related artefacts. These include beam hardening artefacts and scatter artefacts. They appear as dark and light streaks around the stent (Figure 4),

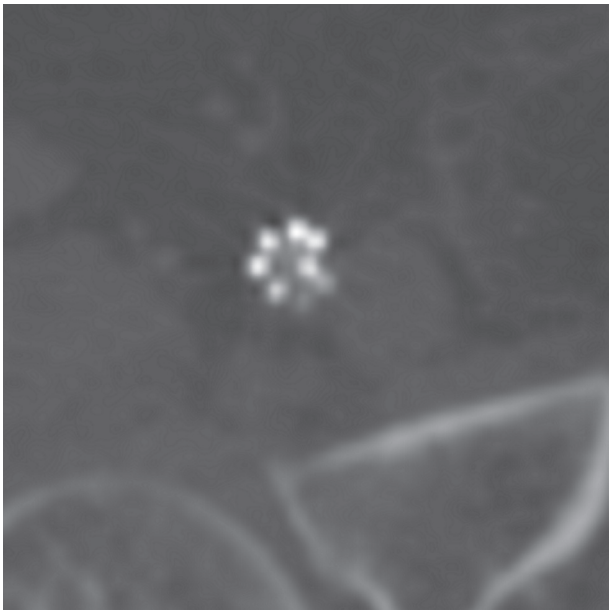

Figure 4. Computed tomography angiography of the right common femoral artery. Beam hardening artefacts at the distal stent part obstruct lumen analysis

which may make arterial lumen analysis difficult or even impossible. These artefacts are stronger when high atomic number metals (iron, platinum) are scanned, and less pronounced with low atomic number metals such as titanium. Similar artefacts may be also produced by atherosclerotic calcifications [37]. To some extent, stent-related artefacts may be reduced by specific image reconstructions and dedicated software [38]. However, the most effective approach to this problem is offered by dual-energy CT (DECT) technique. The use of two different photon energies allows for artificial image reconstruction for a number of monoenergetic images and virtual non-enhanced images, as well as for metallic artefact reduction (Figure 5). An additional advantage of DECT is the possibility of lipid core segmentation from atherosclerotic plaque [39]. Köhler *et al*. studied *in vitro* 22 different types of stents imaging using DECTA [40]. In this study the visible stent lumen diameter varied depending on

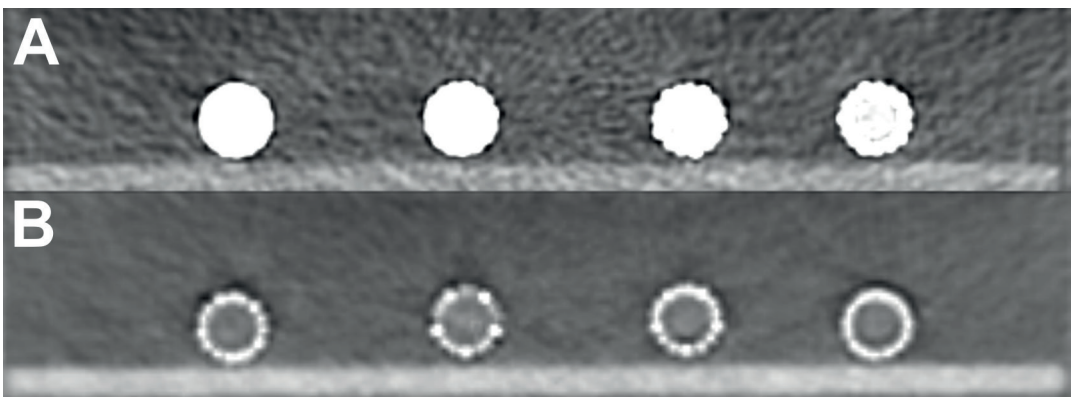

Figure 5. In vitro study using a set of stents filled with a solution of contrast medium. Stent-related artefacts in conventional polychromatic computed tomography angiography (CTA) **(A)** are much stronger than in dual-energy CTA reconstructed at 140 keV **(B)**

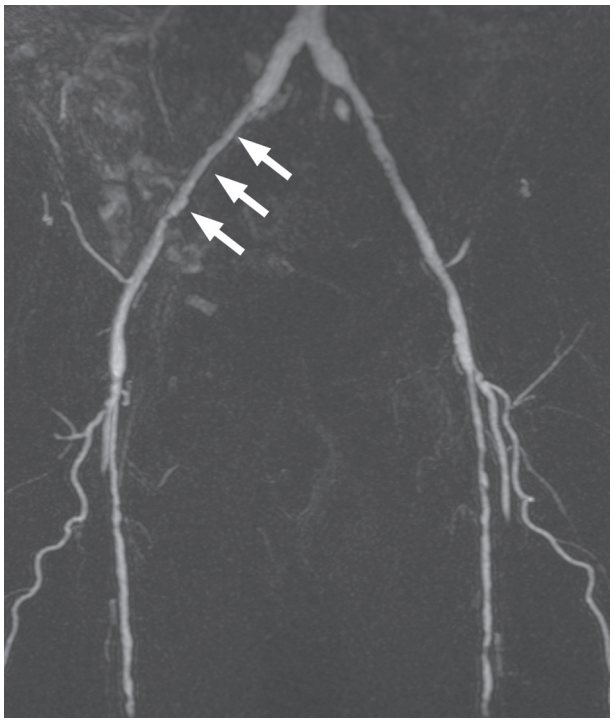

Figure 6. Magnetic resonance angiography. Susceptibility artefacts result in a false image of in-stent restenosis in the right iliac arteries (arrows)

stent type and scan parameters. Lumen diameter visibility increased with the sharpness of the reconstruction kernel, and smoother kernels provided more realistic density measurements inside the stent lumen and less image noise. Almutairi *et al.* scanned 15 stents of different sizes, materials, and designs in monochromatic spectral imaging [41]. They found that the optimal scanning protocol and energy level in the phantom study were GSI-48, pitch value 0.984, and 65 keV, which resulted in lower image noise and a low radiation dose but with acceptable diagnostic images.

Magnetic resonance angiography

MRA, in comparison with DSA and CTA, eliminates exposure to ionising radiation and the risk of CIN-AKI. Unlike US and CTA, MRA is unaffected by arterial calcifications [29]. For the purpose of lower extremity imaging, contrast-enhanced MRA is used. Contrast media generate a high intravascular SNR, which is largely unaffected by inflow [42]. CE-MRA has thus improved spatial resolution and reduced scan time compared with time-of-flight MRA and phase-contrast MRA. On the other hand, CE-MRA is limited by the largest available field of view (FOV), which is below 50 cm, and by the presence of venous signal, which increases with increasing time after contrast injection [43]. The FOV limitation is overcome by the use of a stepping-table movement, but it requires precise control of bolus timing to ensure a high concentration of contrast medium at each station during acquisition. Otherwise, image quality may be reduced because of vascular overlap resulting from venous return, especially distally to the knee [44,45]. Finally, common limitations of MRI have to be mentioned, including claustrophobia, the presence of metallic implants or foreign bodies, and the risk of nephrogenic systemic fibrosis in renal insufficiency patients.

Follow-up after stent placement using MRA is a challenge [46]. Susceptibility artefacts occurring at the ends of stents and false lumen narrowing are well-described phenomena, and therefore MRA tends to overestimate the degree of stenosis [29,47] (Figure 6). Artefacts are related to blood flow, magnetic susceptibility, and radiofrequency shielding [48,49]. Flow-related artefacts are produced by turbulent and slow flow of blood and may be more frequent at the distal end of the stent and in the case of restenosis. A solution for this kind of artefact would be the use of short TR, short TE, and flow-compensating gradients [48,49]. Differences of magnetic susceptibility between soft tissues and stents result in magnetic field inhomogeneities, which in turn lead to image distortion and regional signal loss caused by intravoxel dephasing [46]. The magnetic susceptibility thus determines MRI compatibility of stents, but there are no MRI safety issues with currently manufactured peripheral vascular stents at normal diagnostic field strengths [50]. Adams *et al.* tested 15 different stents *in vitro* and *in vivo* at 1.5 T [51]. In their material, stents made of nitinol did not give artefacts affecting the interpretation of images, while vessels with stainless steel stents were not appropriate for analysis. Similar results were reported by Lambertus *et al.*, who also found that the smallest artefacts were seen when scanning with the use of short echo times and stents aligned with the main magnetic field direction [52]. A comparative CTA and MRA phantom study by Maintz *et al.* came to the conclusion that knowledge of stent composition is essential to properly choose the imaging follow-up method after PTA. Stents made of steel, nitinol, and cobalt should be controlled using CTA, while implants composed of tantalum should be imaged with MRA [53]. However, recent evidence suggests that inversion recovery with on-resonant water suppression (IRON) sequence would allow for visualisation of nitinol stents with MRA [54].

Optimal modality selection

A fundamental difference of follow-up after endovascular treatment comes from the obvious challenge to localise the treated arterial segment precisely and not to confound restenosis or re-occlusion with progressive arterial disease elsewhere on the same artery [55]. This is reflected by the distinction between target lesion re-intervention and target extremity re-intervention as a clinically important end-point. Moreover, the preservation of collateral vessels during recanalisation may attenuate the clinical impact of restenosis or reocclusion [55]. Overall, the assessment after PTA may be similar to the protocol after open arteri-

al bypass, but particular schedules are significantly influenced by institutional bias [56]. Most reports recommend patient evaluation every three months in the first year, and every six months thereafter.

Although DSA is still considered the gold standard for arterial imaging [6], it is obvious that the invasiveness and the cost of the procedure strongly limit its application for follow-up after endovascular treatment [20]. In recent guidelines by the American College of Cardiology and American Heart Association, the strongest evidence (class of recommendation I/level of evidence C-EO) for longitudinal follow-up of patients with PAD, who have undergone lower extremity revascularisation, was given to clinical evaluation and ankle/brachial index (ABI) measurement [57]. However, lower grade evidence (IIa/C-LD) indicates that duplex US is reasonable for routine surveillance after endovascular procedures in patients with PAD. The statement says that several studies have developed duplex ultrasound diagnostic criteria for diagnosing restenosis at the site of endovascular revascularisation, but diagnostic criteria need to be customised to the location and method of revascularisation [57]. The optimal timing for surveillance after endovascular procedures is still unclear. Surprisingly, there are limited outcome data on routine duplex surveillance versus clinical surveillance plus ABI after endovascular revascularisation [57]. Some authors indicate that the value of duplex ultrasound may be greater in cases with higher rates of restenosis, such as very long lesions or occlusions [58].

European guidelines indicate that an early (six weeks to six months) colour duplex scan may be useful after endovascular revascularisation, to identify patients at risk for failure [55]. However, there is no evidence supporting routine long-term CD surveillance after endovascular revascularisation because best level evidence does not support the use of CD imaging compared to clinical follow-up with ABI every three months in patients with prosthetic bypass. However, the guidelines indicate that the role and duration of CD surveillance after endovascular treatment including use of stents, subintimal recanalisation, and endarterectomy devices should be better evaluated as compared to clinical surveillance with ABI measurements [55].

In the context of long-term follow-up, special attention has to be paid to three groups of patients, including diabetics, chronic kidney disease patients, and functionally impaired subjects. A significant proportion of revascularised patients are diabetic and therefore may be challenging to manage. Diabetes results in advanced peripheral vascular disease and in limited primary patency rates. Diabetic patients are likely to benefit from close clinical and colour duplex-scan surveillance because primary patency rates are low, and the ankle-brachial pressure index may be unreliable [59]. Therefore, an uncommon problem in diabetics comes in the form of flow disturbances that hamper the proper assessment of the significance of multiple small stenoses. Moreover, diabetics present a common kidney function impairment, which limits the application of CTA and MRA. Patients with end-stage kidney disease present a significantly increased risk of amputation after revascularisation [60]. Furthermore, significant renal function impairment remains an important limitation of contrast medium administration in CT and MRI. In elderly patients, quality of care after PTA is not solely determined by the traditional measures of patency and limb salvage but particularly by functional outcomes [55].

Conclusions

Surveillance imaging is an important part of patient management after PTA. As a non-invasive modality, US is still the first-line examination, but CTA remains a state-of-the art technique for follow-up. However, since current imaging recommendations do not adhere to contemporary imaging possibilities, more attention should be paid to recent improvements in MRA technology.

Conflict of interest

The authors report no conflict of interest.

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