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Diagnosis of Peripheral Vascular Disease: Current Perspectives

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Abstract

Peripheral arterial disease is a major cause of morbidity and mortality. Cardiovascular risk factors (diabetes, hypercholesterolemia, smoking, hypertension) are responsible for the development and progression of the disease.

Progressive improvement of diagnostic techniques together with clinical tools has allowed a better diagnosis and earlier referral for revascularization techniques. Duplex ultrasound, computerized tomography angiography and magnetic resonance angiography are widely used for the diagnosis of peripheral arterial disease. Digital subtraction angiography is used nowadays for revascularization procedures. This manuscript reviews the current status of the different techniques used to diagnose peripheral arterial disease.

Abbreviations

ABI: Ankle-Brachial Index; CTA: Computerized Tomography Angiography; DSA: Digital Subtraction Angiography; DU: Duplex Ultrasound; MRA: Magnetic Resonance Angiography; PAD: Peripheral Arterial Disease; PSV: Peak Systolic Velocity; SFA: Superficial Femoral Artery; TASC: Trans-Atlantic Inter-Society Consensus on Management of Peripheral Arterial Disease

Introduction

Peripheral arterial disease (PAD) is a major cause of morbidity and mortality. It affects mainly the lower limbs, reducing blood flow to the legs causing symptoms such as exertional pain, intermittent claudication, and in severe cases, pain at rest, gangrene, and eventual limb loss (known as critical limb ischaemia) (Table 1).

Category	Description	Capillary return	Muscle weakness	Sensory loss	Doppler signals	
					Arterial	Venous
Viable	Not immediately threatened	Intact	None	None	Audible (ankle pressure >30 mmHg)	Audible
Threatened	Salvageable if promptly treated	Intact, slow	Mild, partial	Mild, incomplete	Inaudible	Audible
Irreversible	Major tissue loss, amputation regardless of treatment	Absent (marbling)	Profound, paralysis	Profound, anaesthetic	Inaudible	Inaudible

Table 1: Clinical categories of acute limb ischemia.

The development and progression of peripheral arterial disease is highly associated with cardiovascular risk factors such as smoking, diabetes, hypertension and hypercholesterolemia. There is increasing evidence showing the importance of the management of cardiovascular risk factors to reduce PAD progression and symptoms [1].

The most common clinical manifestation of PAD is intermittent claudication. The Edinburgh Artery Study [2] reported an estimated prevalence of 4,5% among men and women aged between 55-74 years. 8% had major asymptomatic disease and 16.6% had minor asymptomatic disease. Five-year follow-up revealed that all new cases of symptomatic peripheral arterial disease have originally been found to have asymptomatic disease, suggesting that there may be an opportunity to prevent the progression of symptoms if an early diagnosis is made [3].

Rutherford and Fontaine classifications are widely used for describing PAD staging. Rutherford classification has seven stages:

Stage 0: asymptomatic

Stage 1: mild claudication

Stage 2: moderate claudication

Stage 3: severe claudication

Stage 4: rest pain

Stage 5: ischemic ulceration not exceeding ulcer of the digits of the foot

Stage 6: severe ischemic ulcers or frank gangrene

The Fontaine classification is useful for clinical and research purposes:

Stage I: asymptomatic. Fontaine stage I describe patients with subtle and non-specific symptoms such as paraesthesia. Physical examination may reveal cold extremities or bruits over blood vessels.

Stage II: intermittent claudication. This stage takes into account the fact that patients usually have a very constant distance at which they have pain.

Stage IIa: intermittent claudication after more than 200 meters of walking.

Stage IIb: intermittent claudication after less than 200 meters of walking.

Stage III: rest pain. Rest pain is especially troubling for patients during the night (no positive gravity effect).

Stage IV: ischemic ulcers or gangrene.

The close link between PAD and other cardiovascular diseases is well documented. Individuals with PAD are at an increased risk of cardiovascular mortality (e.g. myocardial infarction and stroke) (4) compared to those without PAD [4,5].

The prognosis of PAD in stable intermittent claudication is relatively benign. Over a five-year period, 70-80% of patients with intermittent claudication will remain symptomatically stable, 10-20% will experience worsening of their symptoms, and 5-10% will develop critical limb ischaemia. However, during this time up to 5-10% will die from their condition and a further 20% will have a non-fatal cardiovascular event such as a stroke o myocardial infarction [6].

Diagnosis

The majority of patients with PAD have limited exercise performance and walking ability. The classical symptom is intermittent claudication, which is muscle discomfort in the lower limb precipitated by exercise and relieved by rest within 10 minutes. Symptoms are most commonly localized in the calf, but may also affect to the thigh or buttocks. Typical claudication occurs in just one-third of all patients with PAD.

Physical examination should assess the circulatory system as a whole. Key components of the examination include measurement of blood pressure in both arms, assessment of cardiac murmurs, gallops or arrhythmias, and palpation for an abdominal aortic aneurysm.

The specific peripheral vascular examination requires palpation of the radial, carotid, femoral, popliteal, dorsalis pedis and posterior tibial artery pulses. The presence of a bruit may arise from turbulent flow and suggest significant arterial disease. Other features such as changes in colour or temperature of the skin of the feet, muscle atrophy, decreased hair growth and hypertrophied nails are less specific but commonly present.

Measuring the pressure in the ankle arteries has become a standard part of the initial evaluation of patients with suspected PAD. The ankle-brachial index (ABI) provides considerable information in these patients. A reduced ABI in symptomatic patients confirms the existence of haemodynamically significant occlusive disease between the heart and the ankle, with a lower ABI indicating greater severity of occlusive disease. The usefulness of ABI is based on its quantitative and objective nature, as well as its correlation between clinical symptoms and severity of the disease. Yao [7] documented this progressive reduction in ABI with increasing degrees of limb ischemia. Patients with intermittent claudication had a mean ABI of 0,59 whereas those with rest pain had less than half of this; additionally, those with tissue loss had a mean ABI of 0.05. Proximal artery occlusions will result in an ABI of less than 0.8, with higher values in those with chronic occlusions and well-developed collateral vessels. Multiple occlusions involving two or more arteries will usually result in ABI values <0.5. Thus, ABI can be helpful in the initial clinical diagnosis and provides a baseline quantitative measurement of disease severity that can be useful in measuring subsequent progression of disease or responses to treatment [8]. Limitations of the technique are quite common due to arterial wall calcification (diabetes or renal failure patients), with falsely elevated figures.

Ultrasound

The equipment that is used is an ultrasonic colour Doppler scanner that has the capabilities of operating at different frequencies. Frequencies used vary from 3, 5-5 MHz for abdominal arteries and 5-7, 5 MHz for most of infra-inguinal vessels.

Aorto-iliac segment

Doppler velocity recording with a duplex ultrasound (DU) is currently the best technique for non-invasive assessment of the severity of a lesion. Even with all the advances in probes, complete examination of the aorto-iliac segment is challenging. Despite limitations, successful evaluation is accomplished in about 95% of the patients.

The technique aims to obtain flow velocities and anatomical features from the lower aorta and the iliac branches using color-coded velocity. The increase of the peak systolic velocity (PSV) at maximal stenosis compared with that obtained in a normal adjacent segment is calculated as a normalized index. Legemate et al. [9] estimated a 150% velocity increase was an indicator of a >50% diameter reduction. An increase in PSV above 450% indicate >75% diameter reduction. Common femoral artery Doppler velocities are easily recorded. The absence of a reverse velocity component in early diastole indicates significant aorto-iliac stenosis.

Infra-inguinal occlusive disease

Visualization starts at the level of the groin with the interrogation of the common femoral-profunda femoris-superficial femoral junction. The velocity curve showing triphasic waveform in the common femoral artery with a clear window beneath the systolic peak is an indication of normal flow. The peak systolic velocity will gradually decrease downstream in the arterial system. In the aorta his value is normally 100 ± 20 cm/s. The variability in the normal range of

velocities makes it difficult to use absolute values to grade the degree of stenosis. In the normal arterial system the triphasic waveform will be present to the level of the tibial arteries at the ankle (Figures 1-3).

Figure 1: Duplex ultrasound. Normal velocity wave in the right popliteal artery.

Figure 2: Duplex ultrasound. Moderate stenosis in the superficial femoral artery.

Figure 3: Duplex ultrasound. Severe stenosis in the right superficial femoral artery.

The presence of disease is easily determined by using ABI in conjunction with DU. Determining whether disease is haemodynamically significant is much more important and deals with the issue of how much narrowing is enough to produce a pressure drop and fall in blood flow. It is generally accepted that a lesion that narrows the diameter of an artery more than 50% can be considered significant [10].

For the superficial femoral artery (SFA) the positive predictive value for detection of such a lesion is in the range of 77% for the distal SFA to 100% for the proximal SFA. Negative predictive value ranges from 88 to 91%. For the popliteal artery, the positive and negative predictive values are 100 and 93%, respectively [11].

Below the knee arteries

To complete the examination of the lower-limb arteries, the popliteal artery is scanned behind the knee. Waveform shape, peak systolic velocity and the presence of plaque are recorded. Occlusion is characterized by no-flow and rarely visible intraluminal occlusive material. The waveform usually becomes monophasic close to the occlusion. When flow is low, it can be difficult to determine the precise point at which flow ceases.

As the scan progresses down the leg, the artery becomes deeper and can be difficult to visualize. The posterior tibial artery is usually accessible just above the ankle in the medial position and can be traced up to the leg as it gets deeper. These vessels are small and close to the limit of the resolution of all but the most modern scanners, and absence of detected flow may indicate lack of sensitivity of the equipment rather than occlusion.

However, limitations of DU cannot be neglected. Ultrasound cannot provide reliable imaging if there are poor acoustic windows (eg, bowel gas attenuation, diffuse vascular calcification, or metallic stents) or poor intrinsic echogenicity of the tissues. DU is time-consuming and inconvenient post-operatively-when the region of interest is obscured by dressings-and removing these can involve infection risk [12]. In the Krnic study [13] the sensitivity of DU was found to vary widely (from 46% to 88%) for detecting significant arterial stenosis, depending on which arterial segment was being examined. DU failed to visualize up to 10% of aorto-iliac, 2% of femoro-popliteal, and 13% of tibio-peroneal arterial segments. The sensitivity of DU is as low as 72% in the pelvic region for detecting significant obstructions [13].

Clinical recommendations for treatment

Following the Trans-Atlantic Inter-Society Consensus on Management of Peripheral Arterial Disease (TASC II) [14], PAD treatment will depend on:

Arterial segments involved

Degree, extension and anatomical features of the disease (TASC II classification)

Clinical symptoms (Fontaine classification)

Comorbidities

Intermittent claudication grade IIb (Fontaine) and patients with critical limb ischemia (grades III and IV) will be offering some revascularization:

TASC A and D lesions: Endovascular therapy is the treatment of choice for type A lesions and surgery is the treatment of choice for type D lesions.

TASC B and C lesions: Endovascular treatment is the preferred treatment for type B lesions and surgery is the preferred treatment for low-risk patients with type C lesions (Figures 4 and 5). Patients co-morbidities, fully informed patient preference and the local operator long-term success rates must be considered when making treatment recommendations for type B and type C lesions.
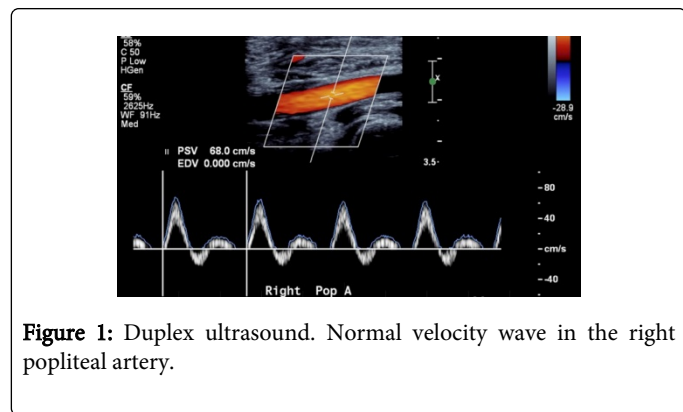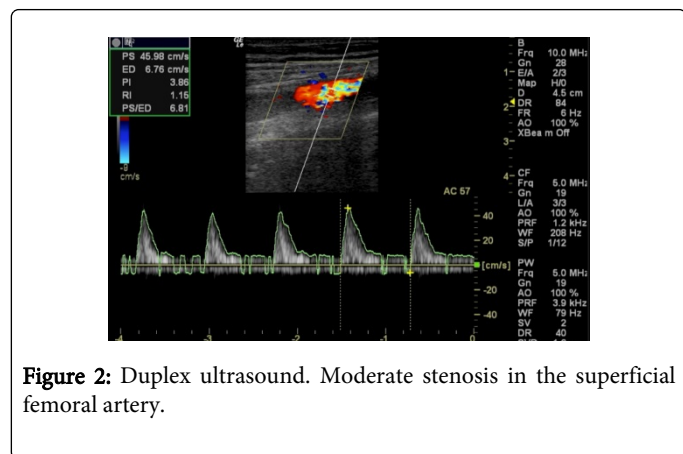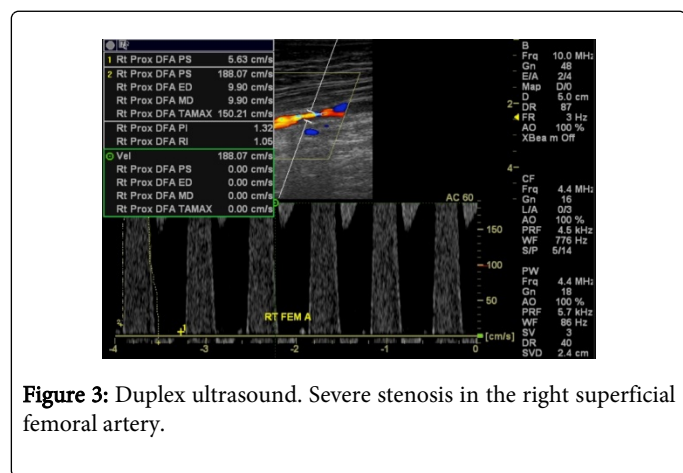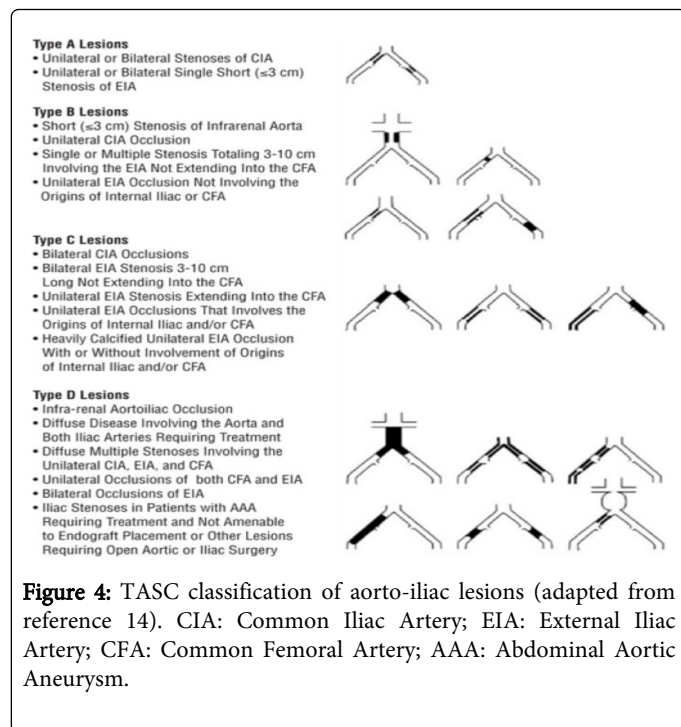
Aorto-iliac revascularization: (Figure 4)

Figure 4: TASC classification of aorto-iliac lesions (adapted from reference 14). CIA: Common Iliac Artery; EIA: External Iliac Artery; CFA: Common Femoral Artery; AAA: Abdominal Aortic Aneurysm.

Infra-inguinal revascularization: (Figure 5)

Figure 5: TASC classification of femoral popliteal lesions (adapted from reference 14). CFA: Common Femoral Artery; SFA: Superficial Femoral Artery.

Intermittent claudication (grade IIa and IIb Fontaine): the initial approach must be medical treatment, that includes:

Risk factor modification (statins)

Antiplatelet therapy (cylostazol)

Supervised and structured exercise

Smoking cessation

Those that develop critical limb ischemia or increasing symptoms will be considered for limb revascularization.

Critical limb ischemia:

TASC A and D lesions: Endovascular therapy is the treatment of choice for type A lesions and surgery is the treatment of choice for type D lesions.

TASC B and C lesions: Endovascular treatment is the preferred treatment for type B lesions and surgery is the preferred treatment for low-risk patients with type C lesions.

Computerized Tomographic Angiography and Magnetic Resonance Angiography

For many decades, invasive digital subtraction angiography (DSA) has been accepted as the gold standard technique for vascular imaging and for peripheral artery disease (PAD) evaluation. However DSA only provides a two-dimensional view of the vessels, which may underestimate the degree of stenosis for eccentric lesions and tortuous vessels. Moreover, DSA has non-negligible risks associated with arterial puncture, iodinated contrast medium and ionizing radiation. At this point, it is easy to understand that recent and rapid developments in non-invasive techniques as computed tomography angiography (CTA) and magnetic resonance angiography (MRA) are replacing DSA in the diagnostic algorithm for PAD. In fact, DSA is nowadays primarily reserved for patients undergoing therapeutic endovascular interventions rather than purely diagnostic studies [15].

Both CTA and MRA allow us to obtain high-resolution multiplanar and three-dimensional images of the peripheral arteries in a non-invasive approach. Similarly, both are accurate techniques for evaluating PAD severity, with excellent ($\approx$95%) sensitivities and specificities compared to the accepted standard DSA [16-18]. Thus, the individual use of each modality depends on local availability, medical expertise, patient's characteristics (e.g. diabetes, renal insufficiency, implanted metal devices, prior bypass grafts, etc.), costs and information required. We facilitate a brief summary of the current state of both techniques from a clinical point of view, highlighting the strengths and limitations of each modality.

Computerized Tomographic Angiography

The widespread availability of multidetector scanners has helped overcome the limitations of the older generations. Shorter acquisition times, thinner slices and higher spatial resolution reduce respiration and motion artefacts, allow visualization of smaller and distal vessels, and enable scanning of the entire vascular tree in a limited period with a decreasing (but still substantial) amount of contrast medium and radiation burden [17-19].

Opposite to DSA, CTA does not only evaluate the vessel lumen but also assesses the vessel wall. Thus, plaque morphology, calcifications, partially thrombosed aneurysms and extrinsic structures can be accurately visualized before planning any surgical or endovascular treatment (Figures 6A and 6B). In addition, CTA allows visualization of the vasculature distal to the point of occlusion while DSA only shows the patent vessel lumen. Given the advanced age and risk factors (e.g. smoking) of the population being evaluated for PAD, relevant unsuspected non-vascular findings are not uncommon (e.g. malignancies) in patients undergoing CTA, which may often lead to changes in medical decisions [19].

Multiple studies have shown that CTA has equivalent diagnostic accuracy when compared with DSA [15,17,18]. A recent systematic

review and meta-analysis of studies comparing CTA with DSA as the standard reference showed a sensitivity of 96% (95% CI, 93-98%) and a specificity of 95% (95% CI, 92-97%) without significant differences in patients with critical limb ischemia or intermittent claudication [16].

The limitation of CTA is mainly the evaluation of severely calcified lesions, where the high attenuation induces blooming artefact that results in an overestimation of stenosis. This effect becomes more relevant in small vessels (such as the infrapopliteal vessels), leading to a lower diagnostic performance of CTA in tibial disease than in aorta-iliac and femoral levels.

The two main disadvantages of CTA are the need for potentially nephrotoxic contrast agents (median 100-120 ml) and radiation exposure (average radiation dose reported 7.5 mSv) [17-19].

In comparison to MRA, CTA offers -at a significantly lower cost- better patient acceptance, a shorter time of evaluation (<5 minutes of scan time compared to 20-30 minutes of MRA), a better spatial resolution and the ability to evaluate previously stented arteries [17,18] (Table 2).

Figure 6: Computed tomographic angiography. (A) Coronal view showing diffuse aortic, iliac and femoral calcifications. An aortic aneurism is observed, measuring 5.6 × 5.1 × 7.2 cm, with asymmetrical mural thrombus (B), 3 cm below the origin of the renal arteries.

Magnetic Resonance Angiography

Rapid advances in MRA technology in the past years, as the 3D contrast enhanced MRA and the development of moving tabletops that enable whole limb examination with a single contrast injection, have led to improvement in resolution, anatomic coverage and speed of image acquisition. Current high-performance MRA provides a high signal-noise ratio and rapid data acquisition. In MRA, a bright signal that appears white within blood vessels is generated. On the contrary, the background tissues, veins, and stationary tissues appear dark. Acquiring images during first pass of extracellular gadolinium-based contrast agent is required for high-contrast images of arteries, thereby limiting contamination with contrast enhancement of veins and soft tissue [17-19]. The older gadolinium-based contrast agents provide a limited time for imaging with the maximal spatial resolution because they move quickly from the vasculature to the interstitial space. However, a new blood pool contrast agent, gadofosveset trisodium, contains the lowest dose of gadolinium of all contrast agents used in MRA, and provides an expanded imaging window of up to 1 hour for a better evaluation of the extent and severity of PAD [17]. At present, although it is also possible to perform non-contrast-enhanced MRA eliminating the complications associated with gadolinium contrast agents, the non-contrast resolution is inferior compared to contrast-enhanced techniques and it is susceptible to artefacts because slow or turbulent flow that can limit interpretation, so that technique is reserved for situations (e.g. advanced renal disease, allergy) where contrast agents could not be administered [17-19].

Undoubtedly, the lack of radiation exposure is clearly one of the main advantages of MRA. MRA requires more time to acquire and is more operator-dependent when compared with CTA, but the post processing reconstructions are more automated and faster. MRA subtracts the background structures only highlighting the enhanced vascular structures, thereby avoiding the CTA complexity of removing overlying bone from 3-D reconstructed images. Interestingly, unlike duplex ultrasound and CTA, the presence of calcium in vessels does not cause artefacts on MRA that is of great importance when examining diffusely calcified vessels, which often occurs in patients with PDA (specially in the diabetic population). Besides, MRA can provide valuable dynamic information as arterial blood flow direction and velocity [17-19].

MRA has been demonstrated to have a high sensitivity and specificity for detecting PAD when compared with DSA [15,17,18]. The recent systematic review and meta-analysis commented above, [16] found a sensitivity of 93% (95% CI, 91-95%) and a specificity of 94% (95% CI, 93-96%) for contrast-enhanced MRA in detecting haemodynamically significant arterial stenosis or occlusion in patients with critical limb ischaemia or intermittent claudication, without differences in any of both scenarios. The abdominal aorta and the superficial femoral segments are imaged reliably with MRA. However, problems still arise with imaging of the infrapopliteal arterial segments, particularly in the setting of critical limb ischemia where there is a smaller time difference between arterial and venous enhancement, and venous contamination may obscure arteries below the knee and can cause non-diagnostic images in a substantial number of patients [19].

One of the most important limitation of MRA is the evaluation of metal, and so the evaluation of in-stent restenosis. Metallic structures usually diphase the signal and can create an area of signal void, thus completely obscuring the lumen within a steel stent. Newer stents made with nitinol, cobalt and platinum are less affected by these

effects. Furthermore, all patients with implanted metal devices (pacemakers, clips, neurostimulators, etc.) should be checked before being exposed to magnetic fields as most of them may preclude the examination because of potential risks or produce significant artefacts during the scan that may make us choose a different modality. Due to the concerns about the risk of renal systemic fibrosis with the use gadolinium-based contrast agents in advance renal failure, these agents should be avoided in patients with a glomerular filtration rate <30 mL/min per 1.73 m^2. [17-19].

Disadvantages of MRA include a higher cost of equipment and thus higher costs for patient. Additionally, because of the longer acquisition times and the characteristics of the scanning, claustrophobia may also prevent MRA scanning in a considerable number of patients [17-19].

MRA offers the benefit of a non-invasive approach using neither ionizing radiation nor iodinated contrast. Given that it is unaffected by the artefacts generated in heavily calcified vessels, it may be considered the technique of choice in diabetics and patients with moderate to severe renal insufficiency (Table 2).

	CTA	MRA
Availability	+++	++
Acquisition time	≤ 5 minutes	≈ 20-30 minutes
Cost	++	+++
Operator expertise	+	++
Diagnostic accuracy Aorto-iliac Femoro-popliteal Tibial	+++ +++ +	+++ +++ ++
Ionizing radiation	Yes	No
Iodinated contrast	Yes	No
Artifact	Calcification	Metal
Contraindications	Severe renal impairment Allergy to contrast agents	Severe renal impairment (only for contrast-enhanced MRA) Allergy to contrast agents (only for contrast-enhanced MRA) Metal devices Claustrophobia
CTA : Computed Tomography Angiography; MRA : Magnetic Resonance Angiography; PDA : Peripheral Arterial Disease. Adapted from Pollak et al. [17] and Cao et al. [18]		

Table 2: Comparison between CTA and MRA for diagnosis of PAD[a]

Angiography of the Aorta And Peripheral Arteries

Aortography and peripheral angiography have experienced an increasing role in diagnostic and therapeutic interventional procedures. Non-invasive techniques accuracy has facilitated the detection of subclinical and clinical disease, leaving invasive angiography mainly for therapeutic purposes. However, catheter-based angiography remains the gold standard for diagnosis of PAD.

Catheter-based therapy is an attractive, feasible and less invasive approach than surgery for the treatment of PAD. In selected patients, lower-risk, partial revascularization by percutaneous means may thus be preferable to higher-risk attempts at complete surgical revascularization, particularly in high-risk patients with advanced age or other cardiovascular diseases.

The aim of these techniques is to maximize the benefit for the patient and minimize the associated risks. Angiographic images are essential for the design of the strategy for revascularization. Selecting the optimal access is a critical step for a safe and success of the procedure. The most common puncture sites are the femoral and brachial arteries, usually guided by fluoroscopy or Doppler ultrasound. Ipsilateral puncture is widely used to approach femoral, popliteal or infrapopliteal disease. For antegrade access, a 9-cm needle is frequently required, as compared with the standard 7-cm needle used for retrograde access, also with a less acute needle angle <45°.

Abdominal Aortography

It is typically performed using a 4-6 F pigtail catheter from a femoral approach, ideally in antero-posterior and lateral views. Assessment of a translesional pressure gradient can be used to define severity of obstructive lesions [20,21].

Lower-Extremity Arterial Occlusive Disease

Indications for arteriography of the lower extremities include ischemia (exertional or resting) owing to atherosclerosis, embolus, thrombosis, vasculitis, aneurysms, vascular tumours, trauma and extrinsic compression (radiation, collagen vascular disease, popliteal artery entrapment syndrome).

Pelvic arteriography can be performed from the femoral or brachial approach with a multi-perforated catheter. If an iliac artery occlusion is suspected, the catheter should be positioned just below the renal arteries to visualize the lumbar arteries that provide important collaterals into the pelvis.

No consensus has been reached as to which common femoral artery should be punctured - that on the side of the more symptomatic or less symptomatic leg. The advantages of accessing the less symptomatic leg are that groin complications would not interfere with surgical bypass procedures, there is less risk of iliac artery trauma (dissection or occlusion), and the option remains to then perform an antegrade puncture of the affected leg.

Lower-extremity arteriography is also easily performed using a single femoral access point. The ipsilateral lower limb can be imaged though the common femoral access sheath, while the contralateral lower limb can be imaged crossing the aorto-iliac bifurcation and selective iliac angiography. The optimal view for the common femoral bifurcation is 30 to 45° of ipsilateral oblique angulation. The superficial femoral artery can be imaged in an antero-posterior view with the addition of an oblique angle if a stenosis is suspected. The popliteal artery, tibio-peroneal trunk and trifurcation are best imaged in an ipsilateral oblique angle (30°). Infrapopliteal runoff can be performed in either an antero-posterior or an ipsilateral oblique projection. For digital subtraction angiography (DSA) [20], an image rate of four frames/second is suitable for above the knee and two frames/second for beneath the knee. To optimize the visualization of the tibial or pedal arteries, selective catheter positioning into the superficial femoral artery with the use of vasodilation agents, such as

nitroglycerin (100 to 300 µg) may enhance digital images (Figures 7 and 8).
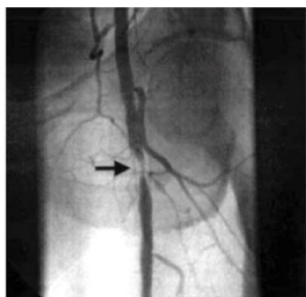

Figure 7: Angiographic view of a severe stenosis in the left superficial femoral artery.
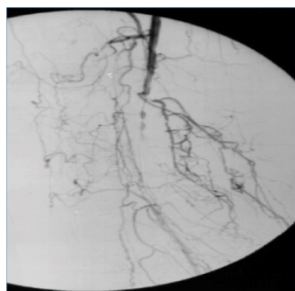

Figure 8: Angiographic appearance of an occlusion of the distal superficial femoral artery with collateral vessels.

Intra-arterial pressure monitoring may thus be more accurate than multiple angiographic images in assessing the hemodynamic significance of a vascular lesion [22]. There is no consensus as for the threshold that defines a significant gradient. However, a resting peak systolic gradient of 5 mmHg or an increase greater than 10 mmHg after augmentation with a vasodilator is considered of hemodynamic significance [10].

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