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The role of magnetic resonance angiography in peripheral artery disease

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Magnetic resonance angiography is an important diagnostic modality in the evaluation of peripheral artery disease. It has gained popularity within the last two decades. It is accurate, non-invasive, and avoids exposure to ionizing radiation. We are reviewing the clinical applications technique and safety issues related to this valuable tool.

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Introduction

Peripheral artery disease (PAD) is increasingly common in the general population and has been associated with increased morbidity and mortality. Population studies have revealed a significantly higher prevalence of PAD on noninvasive testing when compared to symptomatic patients [1,2]. Historically, patients had been screened for PAD with ankle-brachial index (ABI), followed by catheter-based invasive digital subtraction angiography (DSA) to confirm the diagnosis [3,4]. With advancements in technology, DSA has been replaced by non-invasive imaging to confirm diagnosis, assess severity, and guide treatment for PAD [4]. Among them, has been magnetic resonance angiography (MRA), which utilizes MRI to define the anatomy of blood vessels (Figure 1).

Clinical application of MRA in PAD

Guidelines published by the American Heart Association/American College of Cardiology (2016) currently recommend utilization of duplex ultrasonography, computed tomography angiography (CTA) or magnetic resonance angiography (MRA) in patients with symptomatic PAD in whom revascularization is planned (class I) [4]. Multiple studies have confirmed that both CTA and MRA have excellent sensitivity and specificity in confirming the diagnosis of PAD in symptomatic patients [5–7]. In a large meta-analysis, MRA was shown to have superior diagnostic accuracy when compared to duplex ultrasonography and CTA (sensitivity = 95%, specificity 97%) [8]. In addition to its high diagnostic accuracy, MRA avoids the use of ionizing radiation and potentially nephrotoxic iodinated contrast needed for CTA [9].

Multiple features of MRA unfortunately limit its applicability among the general population. Specifically, MRA requires a longer time for acquisition when compared to duplex ultrasonography and CTA. There is also an increased cost associated with MRA, which was shown in the DIPAP trial [10]. In this study, both CTA and MRA demonstrated high accuracy in diagnosing PAD, however, CTA was more cost effective than MRA. Many patients also experience claustrophobia from the confines of the MRI machine, limiting its utilization. Patients with implanted devices such as pacemakers and defibrillators that are not designated to be MRI safe or conditional cannot be evaluated by MRA. For the same reason, MRA is unsafe in patients with ferromagnetic medical implants or foreign bodies [9].

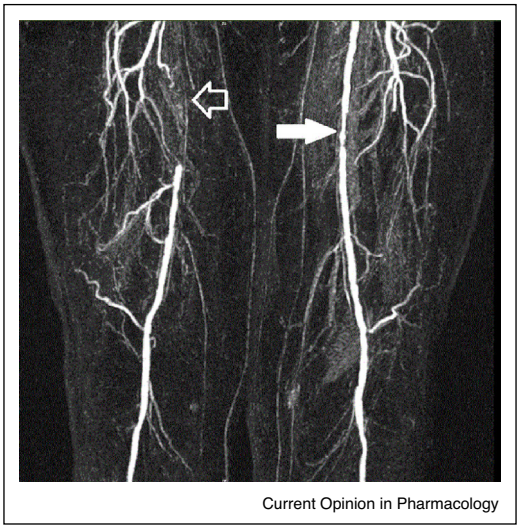
Contrast enhanced MRA

MRA emerged as a vascular imaging tool more than three decades ago [11]. Initially, scan times were long and images were fraught with artifact. MRA's clinical use took off with the introduction of contrast agent gadolinium (Gd), and the consequent development of contrast enhanced-MRA (CE-MRA) [12]. Because of its excellent image quality and speed of acquisition, CE-MRA was rapidly adopted by the medical community and has been widely used in routine clinical practice.

In CE-MRA, the injection of Gd, which has powerful paramagnetic properties, creates a high magnetic moment. This consequently enhances proton relaxation, and shortens the T1 relaxation time in the surrounding water protons and indirectly produces enhanced intravascular signal. At the clinically approved doses of gadolinium-based contrast agents (GBCAs) (0.1–0.3 mmol/kg), the T1 relaxation effect yields bright signal [13].

Recent advancements in CE-MRA for PAD include the use of multi-station serial image acquisition and higher field strength MRI (i.e., 3 T versus 1.5 T). In multi-station serial image acquisition, efficient imaging of the aorta and peripheral runoff arteries can be achieved using

Figure 1



CE-MRA of the lower extremities. The image shows severe PAD with proximal total occlusion of the right superficial femoral artery with distal reconstitution (hollow arrow). The left superficial femoral artery has mild stenosis in the mid portion (solid arrow).

the same contrast bolus [14]. Higher field strength MRI, offers several benefits. Among them, is a higher signal-to-noise ratio (SNR), which allows for higher spatial resolution and faster acquisition time [15,16]. GBCA dosage can also be reduced without compromising image quality with higher field strength MRI [17]. Ultra-high-field MRA (7 T) has been recently tested as an investigational tool for microvascular imaging and functional angiography, further studies are needed to assess feasibility and safety for this technique [18].

Properties and safety of gadolinium based contrast agents

There are nine GBCAs approved by the United States Food and Drug Administration (Table 1) [19]. In general these agents are either linear or macrocyclic chelates available as ionic or non-ionic preparations. Macrocyclic chelates are more stable and have a lower propensity to release gadolinium than linear agents. Non-ionic preparations are less stable in comparison to the ionic ones. Among, GBCAs the ionic-macrocyclic chelates are the most stable [20].

Gadofosveset trisodium is the most recently developed GBCA. Gadofosveset trisodium is unique in that it is a protein-bound blood pool contrast agent, meaning that it reversibly binds to albumin. This extends imaging windows up to 60 min or more, permitting longer scans times and high spatial resolution CE-MRA images [21,22]. Klessen *et al.* demonstrated that 10 mL of gadofosveset trisodium produced qualitatively better images with higher arterial contrast compared to 30 mL of gadopentetate dimeglumine [23]. In a prospective study using gadofosveset trisodium, there was better agreement with DSA compared to standard MRA to assess arterial stenosis [24].

Overall GBCAs have been considered extremely safe, with an incidence of adverse effect reported at 0.06–0.3% [25]. However, in 2006, Grobner described a potentially fatal condition referred to as nephrogenic systemic fibrosis (NSF) in patients with renal dysfunction who were exposed to high doses of Gd [26]. Although rare, NSF is a potentially life-threatening condition that is characterized by diffuse progressive fibrosis in various tissues. Predominantly it affects the skin, but can also affect the kidneys, lungs, heart, and striated muscle [26,27]. Since 2009, there have been no new cases of NSF reported. This may be attributable to routine screening for renal dysfunction, conservative dosing, and safer GBCAs [25].

In the last decade, multiple studies have raised further concern that repeated administration of linear GBCAs may result in Gd deposition in the brain [17–20]. Autopsy studies have validated the presence of Gd in various brain structures of patients with normal renal function and prior exposure to GBCAs [21–25]. There is no clear evidence that Gd deposition is clearly linked to clinical symptoms or organ dysfunction. However, in 2017 the European Medicine Agency released a report restricting the use of certain linear GBCAs in the European Union due to this concern [19,28]. Specifically, gadopentetic acid, gadodiamide, and gadoversetamide were suspended for intravascular use in Europe [28]. There is a definite need for systematic studies to further delineate Gd-induced symptoms in larger controlled studies [12–14].

Non-contrast enhanced magnetic resonance angiography (NCE-MRA)

Concerns regarding the safety of GBCAs sparked a renewed interest in the development of new non-contrast enhanced-MRA (NCE-MRA) techniques. These NCE-MRA techniques utilize the magnetic properties of blood and blood motion to differentiate blood from surrounding static tissues [29]. NCE-MRA was first described in the 1980s, with the development of time-of-flight (TOF) technique [11]. Because of several challenges including lengthy scan time, poor deep signal and flow related artifact, the routine use of NCE-MRA was clinically restricted. Improvements in MR hardware and software have overcome some of these challenges, making NCE-MRA clinically relevant once again [29].

In addition to TOF technique, there are multiple methods used in NCE-MRA. Specifically, there is balanced steady-state free precession (SSFP), which utilizes inherent blood characteristic with little dependence on flow to generate bright signal. Arterial spin labeling (ASL) is a technique that can be combined with SSFP to enhance image quality through improved background tissue