Blood Pool Contrast-enhanced Magnetic Resonance Angiography with Correlation to Digital Subtraction Angiography: A Pictorial Review

Martha-Grace Knuttinen, Jillian Karow, Winnie Mar, Margaret Golden, Karen L Xie

Department of Radiology, University of Illinois Hospital and Health Sciences System, Chicago, Illinois, United States

ABSTRACT

Magnetic resonance angiography (MRA) provides noninvasive visualization of the vascular supply of soft tissue masses and vascular pathology, without harmful radiation. This is important for planning an endovascular intervention, and helps to evaluate the efficiency and effectiveness of the treatment. MRA with conventional extracellular contrast agents relies on accurate contrast bolus timing, limiting the imaging window to first-pass arterial phase. The recently introduced blood pool contrast agent (BPCA), gadofosveset trisodium, reversibly binds to human serum albumin, resulting in increased T1 relaxivity and prolonged intravascular retention time, permitting both first-pass and steady-state phase high-resolution imaging. In our practice, high-quality MRA serves as a detailed “roadmap” for the needed endovascular intervention. Cases of aortoiliac occlusive disease, inferior vena cava thrombus, pelvic congestion syndrome, and lower extremity arteriovenous malformation are discussed in this article. MRA was acquired at 1.5 T with an 8-channel phased array coil after intravenous administration of gadofosveset (0.03 mmol/kg body weight), at the first-pass phase. In the steady-state, serial T1-weighted 3D spoiled gradient echo images were obtained with high resolution. All patients underwent digital subtraction angiography (DSA) and endovascular treatment. MRA and DSA findings of vascular anatomy and pathology are discussed and correlated. BPCA-enhanced MRA provides high-quality first-pass and steady-state vascular imaging. This could increase the diagnostic accuracy and create a detailed map for pre-intervention planning. Understanding the pharmacokinetics of BPCA and being familiar with the indications and technique of MRA are important for diagnosis and endovascular intervention.

INTRODUCTION

Over the past decade, magnetic resonance angiography (MRA) has dramatically changed the imaging of blood
vessels. However, catheter-based digital subtraction angiography (DSA) is still widely accepted as the Gold Standard for the diagnosis of several vascular pathologies with high levels of sensitivity and specificity. DSA is invasive and comes with increased procedural risks including hemorrhage and pain at the catheter site, infection, thrombosis, and possible embolization. In addition, the patient and the provider are exposed to potentially dangerous ionizing radiation during the procedure. These limitations have led to an increased interest in exploring new MRA techniques and contrast agents. Contrast-enhanced MRA (CE-MRA) can provide reliable answers to most diagnostic questions including identifying or excluding clinically relevant arterial stenosis in adults with peripheral arterial disease symptoms with a sensitivity of 94.7% and specificity of 95.6%. MRA also is advantageous over angiography due to the concurrent visualization of surrounding tissue and the ability to reconstruct data in any plane.

**MRA and contrast agents**

Non-contrast MRA sequences are currently being developed; however, in daily practice, CE-MRA still provides a higher contrast-to-noise ratio, higher spatial resolution, more rapid speed of acquisition, less artifacts, and higher diagnostic accuracy compared to non–CE-MRA techniques. Therefore, CE-MRA is heavily favored in clinical practice. These contrast agents are formed by chelation of the gadolinium (Gd) ion to prevent cellular uptake and decrease acute toxicity. Free Gd has an ionic radius similar to calcium and acts as an inorganic blocker of many types of voltage-gated calcium channels, inhibiting many calcium-dependent physiological processes. Therefore, ligands are utilized to encapsulate the Gd ion in order to increase thermodynamic stability allowing the contrast agents to be excreted intact. Different agents contain different ligands which create compounds that have varying pharmacokinetic properties and biodistributions. These differences are the basis for the classification and target of Gd-contrast agents (Gd-CA).

The first approved agents are classified as conventional extracellular fluid (ECF) agents. After intravenous injection, these agents occupy the intravascular and interstitial space which is collectively known as the ECF. The volume of distribution ($V_d$) of these agents ranges from 0.21 l/kg to 0.28 l/kg, which is consistent with the $V_o$ of ECF agents. Blood pool contrast agents (BPCAs) which largely remain in the vasculature were recently introduced. The $V_o$ of these agents is 0.148 l/kg ± 0.016 l/kg, which is lower than that of ECF agents, but also indicates these agents are not 100% confined to the vasculature ($V_o$ of pure intravascular agents is 0.07 l/kg). BPCAs contain a lipophilic biphenylcyclohexyl group that reversibly binds human serum albumin. This bond does not allow the BPCA to rapidly extravasate from the vessel into the interstitial space, as occurs with unbounded conventional ECF agents. BPCAs exhibit a prolonged plasma half-life and, therefore, a longer imaging window unlike conventional agents which are restricted to a short imaging window during the first pass. BPCA also allows for steady-state imaging from 5 min up to 60 min post injection, if needed.

The mechanism of action for all Gd-CA can be explained by the difference in T1 relaxation times of blood and surrounding tissue when the contrast is injected intravenously. In general, these agents also shorten T1, T2, and T2* relaxation time constants of adjacent water molecules. The shortened T1 generates a high intravascular signal-to-noise ratio. The binding of albumin by BPCA further increases the relaxivity compared to conventional agents, and thus further improves the image resolution and vascular enhancement. These properties allow for a lower dose of BPCA needed for quality image acquisition. The recommended dose for gadofosveset is 0.03 mmol/kg compared to a dose of 0.1 mmol/kg for all other conventional agents. This could potentially decrease the risk of nephrogenic systemic fibrosis (NSF). There are several indications for using MRA in clinical practices, including known or suspected vascular pathology, cardiac congenital anomalies, treatment planning, and postoperative follow-up of vascular pathology or cardiac congenital anomalies. All of these indications could benefit from the improved image resolution, increased vascular enhancement, and decreased dose of contrast needed when utilizing BPCA.

**Gadofosveset trisodium**

Gadofosveset trisodium, marketed as Ablavar® (Lantheus Medical Imaging, N. Billerica, MA, USA) is the first clinically approved BPCA available in the United States for use in aortoiliac occlusive disease (AIOD). Phase III trials showed a reduced rate of non-interpretable imaging and improved diagnostic confidence compared to unenhanced two-dimensional time-of-flight MRA. The agent was proven safe with low incidence of severe and serious adverse events. Therefore, overall, gadofosveset was determined to be safe and effective for the MR evaluation of patients with AIOD. An additional phase III trial of 145 patients with known or suspected renal artery stenosis demonstrated an increased specificity (23–29%), sensitivity (25–42%), and accuracy of diagnosis (23–29%) of gadofosveset-enhanced MRA compared to non–CE-MRA. The same study demonstrated a decrease of uninterpretable images from 30% to less than 2% when utilizing gadofosveset. Gadofosveset has also
been shown to decrease the number of uninterpretable images when evaluating peripheral arterial disease affecting the pedal arteries. Bosch et al., showed a decrease in uninterpretable images from 16% to 2% when utilizing the BPCA.[10]

Interventional radiology and pre-procedural planning
The use of pre-treatment imaging is becoming increasingly important to reduce procedure time, decrease exposure to ionizing radiation, and decrease the time the patient is sedated. The Trans-Atlantic Intersociety Consensus Group (TASC) concluded that CE-MRA is the ideal imaging modality in predicting which patients require conservative management versus interventions such as angioplasty or surgical revascularization,[11] leaving angioplasty for use in targeted therapy. CE-MRA has been shown to adequately demonstrate vascular anatomy and identify the lesions responsible for patient symptoms, making it sufficient for planning and therapy in many cases.[8] Pre-procedural MR images can be reconstructed in any plane and can be viewed from many angles creating a “roadmap” of potentially complicated vasculature. The use of BPCA can further enhance the detail of these roadmaps. In this article, we illustrate through case presentations the clinical and promising future applications for gadofosveset-enhanced MRA in the evaluation of peripheral vascular disease and abdominal and pelvic pathology.

CLINICAL CASES
Imaging of aortoiliac occlusive disease
Precise anatomic arterial mapping is essential for endovascular treatment of patients with peripheral arterial disease. Although DSA has been considered the Gold Standard, its invasiveness can lead to significant morbidity and mortality. The steady-state imaging that is possible with gadofosveset allows for greater spatial resolution at the cost of acquisition time; this, in turn, allows for detailed visualization of the degree of stenosis and mural abnormalities [Figure 1a–d]. Hadizeh et al., compared the accuracy of steady-state imaging with first-pass gadofosveset MRA against DSA that included a subset of patients with known peripheral arterial disease. Their results found 100% concordance of stenosis grade between the steady-state images and the DSA images. This improved accuracy was attributed to the higher spatial resolution which can be obtained because of the longer intravascular contrast time of the steady-state images.[12]

A 64-year-old woman with a 2-year history of progressive bilateral lower extremity claudication presented with bilateral leg rest pain. Gadofosveset CE-MRA was performed to confirm the diagnosis of AIOD, grade the stenosis, and determine appropriate treatment plan. First-pass MRA revealed localized atherosclerotic disease of the infrarenal abdominal aorta [Figure 1a–d].

Imaging of venous thrombosis
Gadofosveset is also effectively applied to venous imaging. Hansch et al., demonstrated an increased detection of thrombus in the pelvic region, upper leg, and lower leg when utilizing gadofosveset-enhanced MRA over Doppler ultrasound.[13] Its high signal intensity venous enhancement relative to non-vascular structures during steady-state imaging allows for a broad coverage and high contrast evaluation of deep venous structures. This difference in signal is attributed to the higher signal intensity of contrast-enhanced venous blood compared to extracellular agents.

A 44-year-old man with a history of recurrent deep venous thrombosis (DVT) and pulmonary embolisms (PEs) status post inferior vena cava (IVC) filter placement at an outside hospital presented to the emergency room (ER) with chest pain. Computed tomography (CT) scan for work-up of PE revealed two small possible chronic PEs in the right lower lobe and apical right upper lobe. Lower extremity duplex
ultrasound revealed a subacute DVT of the right distal external iliac and common femoral veins and chronic DVT of the left distal external iliac, left common femoral, left profunda femoris, bilateral femoral, right popliteal, right gastrocnemius, right posterior tibial, and right peroneal veins. Gadofosveset CE-MRA of the abdomen and pelvis was performed to further assess the venous system. The scan showed a metallic artifact secondary to IVC filter with associated thrombus. The thrombus was noted to extend superiorly to the level of the renal vein inflows [Figure 2a–c].

**Imaging of malformations**

When assessing for vascular malformations and deciding on appropriate interventional therapies, magnetic resonance imaging (MRI) is essential for differentiating between high-flow vascular malformations and low-flow venous malformations. Utilization of the time-resolved first-pass effect of gadofosveset allows for this distinction, and can effectively be a roadmap for interventional treatment. This time-resolved first-pass effect can assess arteriolar feeders, and/or venous drainage, while the steady-state high-resolution imaging can assess the surrounding vascular structures.[14]

A 37-year-old woman with history of trauma to left knee in 2000 underwent three surgeries to help with swelling and pain presented with continued left lower extremity pain and swelling which was significantly limiting her lifestyle. On examination, a bruit was appreciated over the left patellar area. Previous MR imaging in 2008 revealed arteriovenous malformation (AVM). Gadofosveset CE-MRA was performed to re-evaluate the extent of her AVM and determine appropriate treatment plan. MRA showed a large AVM with dominant arterial feeders from the left superficial femoral artery. This was confirmed by DSA [Figure 3a–g]. Endovascular treatment of AVM was performed with Onyx resulting in decreased flow through treated portions of the AVM [Figure 3h–j].

**Imaging of pelvic pathology**

Chronic pelvic pain is a common health problem that affects millions of women worldwide, but can be a difficult condition to address. Pelvic congestion syndrome (PCS) is a diagnosis that should be considered in many women after other pelvic pathologies have been ruled out. Given its vague symptomatology, PCS is often underdiagnosed. Many of these patients undergo an MRI which offers improved diagnosis and allows for more precise pre-procedural treatment planning.

The incompetent ovarian veins in this syndrome can be identified with gadofosveset imaging. Specifically, the steady-state imaging can allow a clear depiction of the ovarian veins at high resolution. Furthermore, the time-resolved first-pass images are equivalent to a Gold Standard transcatheter venogram in depicting retrograde flow within the ovarian veins.[15]

A 41-year-old woman presented with worsening intermittent pelvic pain that had persisted for several years. Gadofosveset CE-MRA of her abdomen and pelvis was performed to assess underlying pathology. MRA revealed a dilated left gonadal vein (white solid arrow) coursing inferiorly to the pelvic area. The patient was treated with coil embolization of left gonadal vein [Figure 4a–e].

**DISCUSSION**

The role of minimally invasive imaging techniques has risen in the past several years in order to aid in clinical decision-making and determine appropriate treatment strategies in patients with various diseases. MRA is less invasive than diagnostic angiography without associated complications or radiation exposure. Contrast enhanced-MRA (CE-MRA) has a higher contrast-to-noise ratio, higher spatial resolution, more rapid speed of acquisition, and less artifacts when compared to non–CE-MRA; however, conventional extracellular agents provide limited imaging window for MR angiogram and is highly dependent on the skill of the technologist/operator to scan with the right timing. Blood pool contrast agents (BPCAs) such as gadofosveset have the added advantage of prolonged intravascular time, allowing for a longer...
steady-state imaging time for higher resolution acquisition and improved overall image quality. However, since gadofosveset remains in the vascular system for up to an hour, caution must be used in rare cases where a second injection is required as there is the possibility of residual venous contamination from the initial examination. In addition, during the steady-state imaging phase, venous enhancement may be perceived as “venous contamination,” as often seen in conventional extracellular contrast agents, especially when 3D maximal intensity projection (MIP) images are generated and viewed. To overcome this issue in our practice, we routinely review the high-resolution images in sequential slices and in multiple planes as this will help delineate the venous and arterial vasculatures easily, given the higher imaging contrast and spatial resolution.

The time-resolved first-pass effect and the steady-state imaging together paint a picture useful to provide a detailed assessment and diagnosis of various pathologies. In our experience, the imaging quality and diagnostic capability of CE-MRA with gadofosveset closely correlates with DSA and decreases the amount of uninterpretable images which is a common issue with non-CE-MRA. Moreover, if CE-MRA provides sufficient explanation/diagnosis for a patient’s symptoms that do not require intervention, then traditional angiography can be avoided. However, if the findings are inconclusive, then further detailed anatomical imaging can be obtained from traditional angiography. In addition, those patients who are diagnosed with a condition treatable by intervention on the basis of MRA will be treated accordingly, and will have the pre-treatment roadmap information available from the MRA. In our institution, the interventionalists have benefited from the improved image quality for pre-procedural planning and the subsequent decreased procedure time and dose of contrast needed when performing the procedure.

**CONCLUSION**

Gadofosveset-enhanced MRA proves to be a good diagnostic tool with accurate correlation to DSA without the risks of invasive angiography. The clear and precise images generated when using gadofosveset also create a detailed roadmap for pre-procedural planning which can reduce the
procedural time. This subsequently results in a decreased radiation dose to the patient and a potential decrease in sedation time which translates into improved patient safety.

REFERENCES

1. Goyen M. Gadofosveset-enhanced magnetic resonance angiography. Vascular Health Risk Manag 2008;4:1-9.
2. Jackson J, Allison DJ, Meaney J. Angiography: Principles, Techniques, and complications. In: Grainger RC, Allison D, Adam A, Dixon AK, editors. Diagnostic Radiology: A Textbook of Medical Imaging. 5th ed. Chapter 6. New York, NY: Churchill Livingstone; 2008. p. 109-28.
3. Menke J, Larsen J. Meta-analysis: Accuracy of contrast-enhanced magnetic resonance angiography for assessing steno-occlusions in peripheral arterial disease. Ann Intern Med 2010;153:325-34.
4. Miyazaki M, Akahane M. Non-contrast enhanced MR angiography: Established techniques. J Magn Reson Imaging 2012;35:1-19.
5. Bellin MF, Van Der Molen AJ. Extracellular gadolinium-based contrast media: An overview. Eur J Radiol 2008;66:160-7.
6. Aime S, Caravan P. Biodistribution of gadolinium-based contrast agents, including gadolinium deposition. J Magn Reson Imaging 2009;30:1259-67.
7. Goyen M, Edelman M, Perreault P, O’Riordan E, Bertoni H, Taylor J, et al. MR angiography of aortoiliac occlusive disease: A phase III study of the safety and effectiveness of the blood-pool contrast agent MS-325. Radiology 2005;236:825-33.
8. Lakshminarayan R, Simpson JO, Ettles DF. Magnetic resonance angiography: Current status in the planning and follow-up of endovascular treatment in lower-limb arterial disease. Cardiovasc Intervent Radiol 2009;32:397-405.
9. McGregor R, Vymazal J, Martinez-Lopez M, Neuwirth J, Salgado B, Beregi JP, et al. A multi-center, comparative, phase 3 study to determine the efficacy of gadofosveset-enhanced magnetic resonance angiography for evaluation of renal artery disease. Eur J Radiol 2008;65:316-25.
10. Bosch E, Kretiner KE, Peirano MF, Thurnher S, Shamsi K, Parsons EC Jr. Safety and efficacy of gadofosveset-enhanced MR angiography for evaluation of pedal arterial disease: Multicenter comparative phase 3 study. AJR Am J Roentgenol 2008;190:179-86.
11. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). J Vasc Surg 2000;31:S1-296.
12. Hadizadeh DR, Gieseke J, Lohmaier SH, Wilhelm K, Boschewitz J, Verrel F, et al. Peripheral MR angiography with blood pool contrast agent: Prospective intraindividual comparative study of high-spatial-resolution steady-state MR angiography versus standard-resolution first-pass MR angiography and DSA. Radiology 2008;249:701-11.
13. Hansch A, Betge S, Poehlmann G, Neumann S, Baltzer P, Pfeil A, et al. Combined magnetic resonance imaging of deep venous thrombosis and pulmonary arteries after a single injection of a blood pool contrast agent. Eur Radiol 2011;21:318-25.
14. Sabach AS, Bruno M, Kim D, Mulholland T, Lee L, Kaura S, et al. Gadofosveset Trisodium: Abdominal and peripheral vascular applications. AJR Am J Roentgenol 2013;200:1378-86.
15. Kim CY, Miller MJ Jr, Merkle EM. Time-resolved MR angiography as a useful sequence for assessment of ovarian vein reflux. AJR Am J Roentgenol 2009;193:W458-63.

Source of Support: Nil, Conflict of Interest: None declared.