

# Blood pool contrast agents for venous magnetic resonance imaging

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**Abstract:** Imaging of the venous system plays a vital role in the diagnosis and management of a wide range of clinically significant disorders. There have been great advances in venous imaging techniques, culminating in the use of magnetic resonance venography (MRV). Although MRV has distinct advantages in anatomic and quantitative cross sectional imaging without ionizing radiation, there are well-known challenges in acquisition timing and contrast administration in patients with renal impairment. The latest advancement involves the addition of new contrast media agents, which have emerged as valuable alternatives in these difficult scenarios. In this review, we will focus on a group of specific contrast agents called blood pool agents and discuss their salient features and clinical applications.

**Keywords:** Contrast media; magnetic resonance imaging; venous imaging

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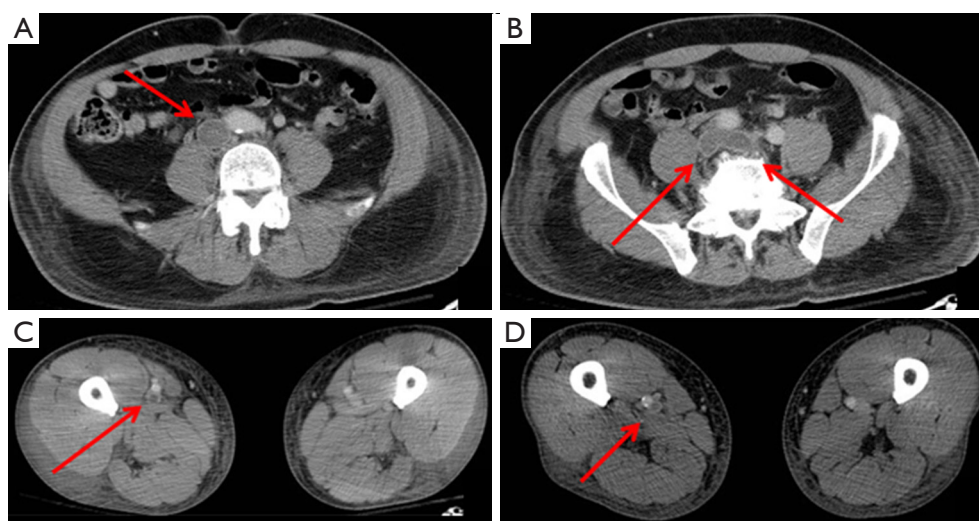
## Introduction

Despite technical imaging advances in the evaluation of the venous system, many challenges remain in the clinical application of these imaging techniques. Historically, one of the earliest imaging modalities used in venous imaging was ascending contrast venography, which is rarely used today due its invasiveness and risk of complications. Instead, ultrasound (US) has now become the modality of choice in clinical practice for the evaluation of deep vein thrombosis (DVT), with advantages in cost effectiveness, noninvasiveness, and portability in critically ill patients (1). However, key limitations of US exist, and include decreased sensitivity due to body habitus or edema, individual operator dependence (2), and difficulty in evaluation of calf veins and recurrent or chronic DVT (3). Ultrasound is also technically unable to evaluate the abdominopelvic deep venous system or the pulmonary arterial system (4),

limiting its use in the workup of patients with venous thromboembolism at other sites.

Computed tomography is another available imaging tool for venous imaging, with advantages including widespread accessibility, noninvasiveness, rapid acquisition, accuracy, high spatial and temporal resolution and the option of reconstruction and post-processing on multiple planes (5) (*Figure 1*). A key disadvantage of CT is the need for ionizing radiation, especially in young or pregnant patients. The greatest challenge of CT venography, however, is ensuring sufficient and homogenous opacification of the all lower extremity veins (6), as absence of adequate opacification leads to a non-diagnostic study.

These challenges can be overcome by the use of magnetic resonance imaging (MRI). MR venography (MRV) can be performed with or without gadolinium based contrast. Non-contrast techniques include time-of-flight (TOF), gradient recalled echo (GRE), spoiled gradient recalled (SPGR) and



**Figure 1** CT Venography in a 70-year-old man. Axial post contrast images demonstrating extensive deep vein thrombosis involving the inferior vena cava (A), both common iliac veins (B), proximal right superficial femoral vein (C) and distal right superficial femoral vein (D). Note associated superficial soft tissue edema. Note that the image acquisition is performed in late arterial phase. Adequate window width and length settings on CT can help to arrive at conclusion of presence of DVT and avoid repeat examination.

steady state free precession (SSFP) sequences. Although an exhaustive overview is beyond the scope of this discussion, each technique suffers some limitations regarding length of acquisition times, background suppression, inflow effects, motion, and image artifacts. Gadolinium-enhanced magnetic resonance angiography (MRA) of the abdomen was first introduced in 1995 (7), and has the advantages of faster acquisition times, independence from inflow effects, and decreased image artifacts. In a study with 30 patients evaluated for lower extremity or abdominopelvic deep vein thrombosis with MRV, Huang *et al.* found that contrast enhanced MRV had a higher sensitivity and specificity compared to non-contrast MRV with gradient-recalled-echo sequence (91.0% and 99.8% for contrast-enhanced *vs.* 80.8% and 95.8% for GRE MRV); this study also demonstrate the additional benefit of decreased time for image acquisition and interpretation for contrast-enhanced MRV (8).

Historically, gadolinium based MRI contrast agents were considered to have a broad safety profile until 2006, when the relationship between gadolinium based contrast agents and nephrogenic systemic fibrosis (NSF) was described in patients with renal disease (9). NSF is a debilitating disease characterized by widespread fibrosis in the skin and connective tissues that is progressive and irreversible. Although the exact pathophysiology remains unclear,

it is postulated that delayed excretion of the chelated gadolinium agent increases the risk for dissociation and subsequent proliferation of fibroblasts (10). However, with more selective contrast use and the advent of new chelated compounds, there have been no new documented cases of NSF since 2009.

More recently, serious attention has been paid to the observation made by McDonald *et al.* concerning the dose dependent association of intravenous gadolinium administration and brain deposition in patients with normal renal function (11). Deposition of gadolinium was found to be most concentrated in the dentate nucleus and globi pallidi, even in the presence of an intact blood brain barrier. This deposition occurs irrespective of renal or hepatobiliary dysfunction. The clinical consequences of gadolinium deposition are not known at this time but is currently an issue of great interest.

Gadolinium contrast agents (GCA) can be divided into extracellular, hepatobiliary and blood-pool agents according to their pharmacokinetic profile. Extracellular agents are most commonly used and share similar pharmacokinetic profile to that of iodinated contrast agents after intravenous injection (12-14). Elimination is exclusively by passive glomerular filtration in the kidneys. In patients without renal insufficiency, 98% of the administered GCA is excreted within 24 hours (12). Following the arterial first-

**Table 1** Gadolinium-based MRI contrast agents

Generic name	Commercial name	Structure	Charge	Relaxivity 1.5T/3.0T	Osmolality (mOsm/kgH <sub>2</sub> O)	Elimination (renal/hepatic)
Gadopentetate dimeglumine	Magnevist	Linear	Ionic	4.1/3.7	1,960	100/0%
Gadoterate meglumine	Dotarem	Macrocyclic	Ionic	3.6/3.5	1,350	100/0%
Gadoteridol	ProHance	Macrocyclic	Non-ionic	4.1/3.7	630	100/0%
Gadodiamide	Omniscan	Linear	Non-ionic	4.3/4.0	789	100/0%
Gadobutrol	Gadavist/Gadovist	Macrocyclic	Non-ionic	5.2/5.0	1,603	100/0%
Gadoversetamide	OptiMark	Linear	Non-ionic	4.7/4.5	1,110	100/0%
Gadobenate dimeglumine	MultiHance	Linear	Ionic	6.3/5.5	1,970	96/4%
Gadoxetate disodium	Primovist/Eovist	Linear	Ionic	6.9/6.2	688	50/50%
Gadofosveset trisodium	Vasovist/Ablavar	Linear	Ionic	19/10	825	91/9%

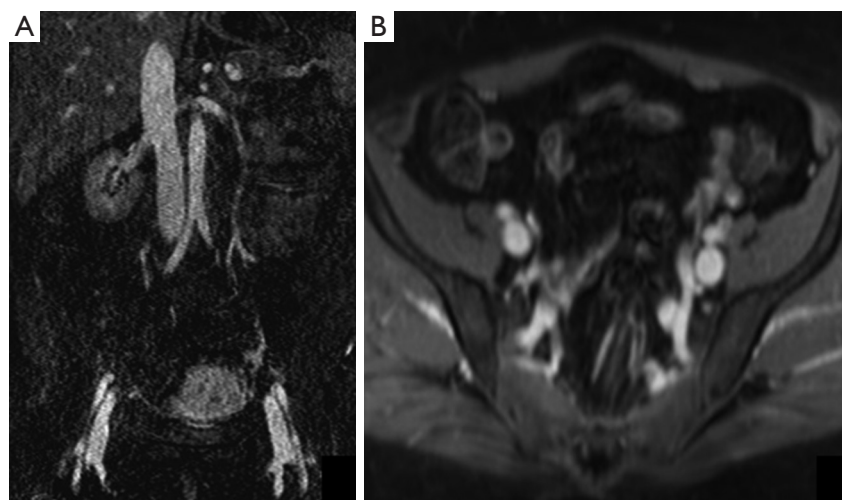
Adapted from references (12,18).

pass phase, these agents are distributed to the extracellular compartment and rapidly diffuse out of the blood pool into the interstitium which results in a decrease in vascular signal and increased background enhancement (poor contrast-to-noise ratio) and a limited acquisition window. This short intravascular retention limits the application of dynamic imaging to evaluate flow patterns and requires repeated contrast administration to evaluate multiple stations or the effect of provocative maneuvers (15). Adequate bolus timing and patient cooperation are thus essential to obtain adequate MR angiographic images with these agents (15). While non contrast imaging techniques are limited in detecting slow flow in smaller veins, contrast enhanced venous imaging with extracellular gadolinium-based agents is technically more challenging than arterial imaging due to unpredictable venous opacification as contrast bolus traverses from the blood pool to interstitial space (15). Gadolinium-based blood-pool contrast agents (BPCA) are characterized by prolonged intravascular circulation. Intuitively, MR angiographic applications of these agents include both first-pass and steady-state MRA. Due to the long plasma half-life of blood-pool agents, they are often referred to as intravascular contrast agents. The blood-pool effect of these agents is due to the large size of the macromolecules, which limits diffusion across the endothelial membrane (16), ensuring low or absent leakage into the extracellular compartment. BPCA also allows steady-state imaging from 5 min up to 60 min post injection if needed (17). The Gd-based macromolecules are high relaxivity agents because their large size leads to slow

rotational dynamics. The binding of albumin by BPCA further increases the relaxivity compared to conventional agents. These properties allow for a lower dose of BPCA needed for quality image acquisition (*Table 1*).

### Contrast agents

Gadofosveset trisodium (Ablavar<sup>®</sup>, Lantheus Medical Imaging, North Billerica, MA) is the most prominent agent in the low-molecular group of Gadolinium-based blood-pool agents. Gadofosveset is a high-relaxivity agent due to slow molecular rotational speed when bound to albumin. In human plasma, 4–20% of gadofosveset follows the same distribution as extracellular Gd-CA (12). Elimination of gadofosveset is predominantly by renal excretion and to a lesser extent by hepatobiliary excretion (9%) (12). Gadofosveset has been the first blood pool MRI contrast agent to become commercially available and received approval by the U.S. Food and Drug Administration in 2008 for imaging of aortoiliac occlusive disease in adults ( $\geq 18$  years) with known or suspected peripheral vascular disease. It was also known as Vasovist<sup>®</sup> (Bayer Schering Pharma, Berlin, Germany), which received its first marketing authorization in the European Union in 2005 (15). The large molecular size of the chelate-albumin complex results in decrease the molecular rotation rate and in significantly shorter T<sub>1</sub> relaxation times (19.0 L/mmol/sec at 37 °C, 1.5 T); approximately five times that of extracellular agents at 1.5 T. This results in greater efficacy per unit gadolinium dose so that lower injection volumes and fewer injections are sufficient for diagnostic



**Figure 2** MR Venography with Ablavar in a 40-year-old woman with left lower extremity edema. (A) Coronal subtraction images demonstrating aorta and inferior vena cava; (B) axial reconstructions showing well opacified and normal pelvic veins.

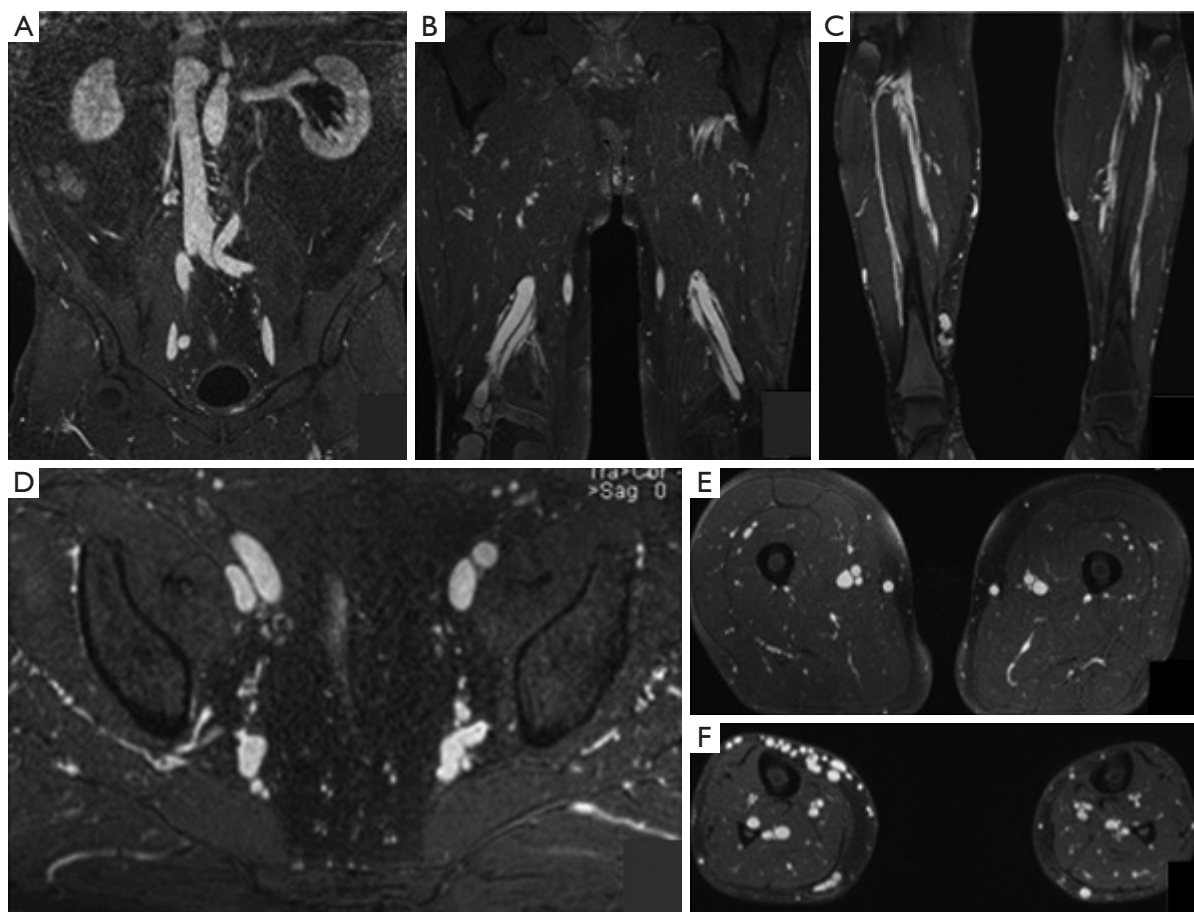
purposes (7) (Figures 2,3). The standard dose for MRA is 0.03 mmol/kg (0.12 mL/kg body weight) (2,7,9), compared to a dose of 0.1 mmol/kg for all other conventional agents (17).

Multiple studies have demonstrated its safety. In phase III trials of Ablavar performing MR angiography of the aortoiliac region in adults patients with known or suspected to have peripheral vascular disease, the most common adverse events were feeling hot (4.4%), nausea (3.6%), headache (3.3%) and burning sensation (2.9%); the incidence of severe and serious adverse events was low (19,20). Of note, QTc prolongation has been reported following gadofosveset administration, and therefore patients should be assessed for a history of underlying conditions that may predispose to arrhythmias from QTc prolongation. The most feared adverse effect of gadolinium-based contrast agents, nephrogenic systemic fibrosis (NSF), has not been reported with gadofosveset (15).

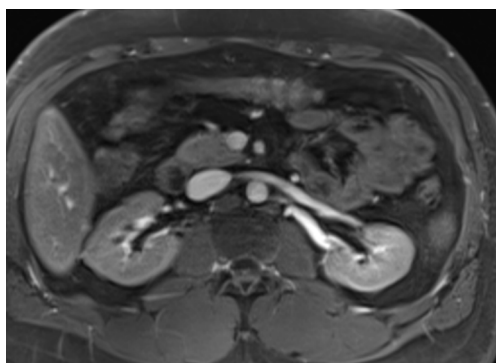
An important application of MRV and therefore BPCA is evaluating the venous system in children, who are sensitive to ionizing radiation. Rigsby *et al.* identified an adverse event rate of 0.46% following gadofosveset trisodium administration in children and young adults (21), with most reactions being mild without any adverse outcomes. Interestingly, a large number of their scans were performed under anesthesia and anesthetized patients were 5.7 times more likely to experience an adverse event than unanesthetized patients, which could be an alternative explanation for the adverse events observed.

Another agent that has been studied in the past decade is Ferumoxytol, a superparamagnetic particle of iron developed as an intravenous iron supplement for patients with anemia of renal failure (4). It is composed of an iron oxide core surrounded by a polyglucose sorbitol carboxymethyl ether envelope, with a particle size of 30 nm and a molecular weight of 750 kD (4). It has strong T1- and T2\*-shortening properties, making it an attractive agent for MRI. In addition, due to its carbohydrate coating, the agent is not filtered by the renal glomeruli, causing it to behave as a blood pool agent. Because of its size and carbohydrate coating, Ferumoxytol has a prolonged intravascular residence time (approximately 14 hours) (1) and a very long intravascular half-life, making it very attractive as an intravascular contrast agent. This extended plateau of increased vascular signal can be used for much longer imaging acquisitions than is possible with extracellular gadolinium-based agents, allowing for improved performance of navigated MRI sequences, venous imaging, and the option for repeat imaging without the need for additional contrast (22) (Figure 4). Ferumoxytol has an excellent safety profile and has been administered extensively to patients with class 1–5 chronic kidney disease (CKD). In fact, it was developed for use in this specific patient population (4) and should be considered as an alternative in vascular imaging when gadolinium-based agents are contraindicated. Its use as a contrast agent in MRI is off-label, as it is only approved by the FDA for the treatment of iron-deficiency anemia. The highest dose for





**Figure 3** MR Venography with Ablavar in a 61-year-old man with deep and superficial vein reflux. Coronal images demonstrating good opacification and normal appearance of the inferior vena cava and iliac veins (A), distal segments of superficial femoral vein and popliteal vein (B) and calf veins (C). Axial reconstructions demonstrating the respective vessels in (D,E,F), as well as superficial venous varicosities.



**Figure 4** Axial T1 weighted image in the equilibrium phase following administration of Ferumoxytol showing well opacified arterial and venous systems in this 24-year-old woman.

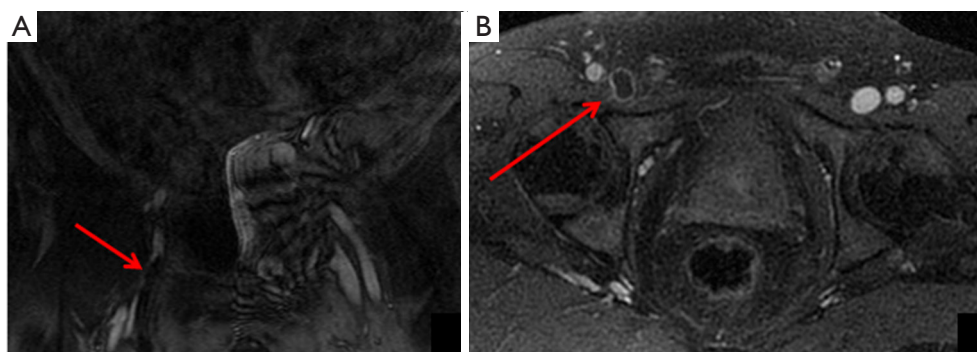
imaging is 4 mg (71.6 micromols) iron per kilogram of body weight (1).

## Applications

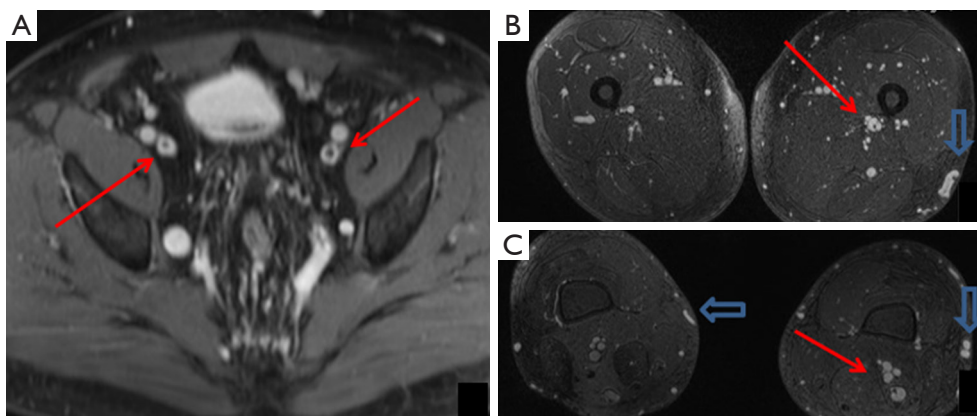
### *Deep venous thrombosis*

One of the main indications of venous MR imaging is deep vein thrombosis, with several studies demonstrating the feasibility and accuracy of MRV with BPCA (*Figures 5,6*).

Hansch *et al.* investigated the use of gadofosveset trisodium-enhanced MR in 43 patients with suspected DVT who underwent compression US. They found that MR detected 10 additional thrombi in the pelvic region and



**Figure 5** MR Venography with Ablavar in a 58-year-old man. Filling defect within the right common femoral vein (arrow) consistent with acute deep vein thrombosis demonstrated in coronal (A) and axial images (B).



**Figure 6** Axial post contrast T1W images of a MRV with Ablavar in 61-year-old man with previous episode of deep vein thrombosis. (A) Note the partial filling defects in the external iliac veins (arrows); (B) partial thrombus in the left deep femoral vein (arrow) and superficial venous varicosities in both extremities (hollow arrows); (C) partial thrombus in the left popliteal vein (arrow) and superficial venous varicosities in both extremities (hollow arrows).

inferior vena cava compared to DUS, 3 additional thrombi in the upper leg, 4 additional thrombi in the popliteal vein, and 17 additional thrombi in the lower leg. Furthermore, pulmonary emboli (PE) were detected in 16 of the 43 patients with DVT that were identically correlated with CT in location, size and shape. There were no cases with non-diagnostic image quality. Therefore, gadofosveset trisodium enhanced MR had increased sensitivity for the detection of DVT compared to US with the advantage of high accuracy detection for concurrent pulmonary embolism (23).

Pfeil *et al.* also showed the feasibility and quality of imaging of the unaffected venous system of the lower limbs using the VIBE sequence with fat saturation and blood pool contrast agent in a study with 25 individuals without clinical signs for DVT and normal Doppler US of the lower

limbs (2). Again, no nondiagnostic images were acquired and excellent inter-rater reliability was noted ( $\kappa$  value for measurement interrater reliability ranged as significant between 0.75 for the external iliac vein and 0.85 for the common iliac vein).

Enden *et al.* compared two different imaging techniques (Balanced Turbo Field Echo and Contrast-Enhanced T1 Fast Field Echo) using a blood pool agent in 15 healthy volunteers and 6 patients with verified acute proximal DVT on routine ultrasound (3). Both MR techniques produced a complete visualization of the deep venous system in the vast majority of images covering the calf, femoral, and pelvic veins. In general, all three image quality parameters analyzed were best on calf examinations and, despite the poor grading of image quality obtained in pelvic images,

both MR techniques maintained complete visualization of the pelvic veins.

In a study of MR venography of ilio caval veins with use of MS-325 (initial name for Ablavar) conducted by Sharafuddin *et al.*, it was demonstrated that MS-325 was reliable in providing consistent diagnostic visualization of the entire inferior vena cava (IVC). There was improved venous conspicuity and subjective contrast enhancement compared to gadodiamide (24). Diagnostically limiting artifacts were present in seven of 29 infrarenal IVC segments on unsubtracted Gd-MRA studies compared to none of the 12 segments on unsubtracted MS-325-MRA studies.

Ferumoxytol has also been studied as a contrast agent in the investigation of deep vein thrombosis. Bashir *et al.* compared Ferumoxytol with Gadofosveset as contrast agents and demonstrated comparable subjective and objective enhancement of the abdominopelvic and lower extremity venous systems as well as comparable visualization of venous thrombosis (4). Ferumoxytol may therefore be an attractive option for patients with renal function impairment since iron-based agents are not associated with risk of nephrogenic systemic fibrosis, and can be considered in vascular imaging when gadolinium-based agents are contraindicated. In addition, Li *et al.* evaluated extremity deep venous thrombosis with Ferumoxytol-enhanced MR and found that image quality scores for Ferumoxytol-enhanced MR were uniformly superior to those of non-contrast 2D time-of-flight images (average image quality score for Ferumoxytol was 3.6 *vs.* 1.4 for precontrast images) (1). Also, MR showed agreement with duplex US in depicting 90% of the thrombi and an increased detection of additional contralateral thrombi.

### ***May-Thurner/Cockett syndrome***

May-Thurner syndrome results from the compression of the left common iliac vein (LCIV) between the right common iliac artery (RCIA) and fifth lumbar vertebra, an anatomic relationship that was defined by May and Thurner in 1956. May-Thurner anatomy is thought to be the cause of approximately 2–3% of all lower extremity deep venous thrombosis (25,26), particularly in young to middle aged women. Symptomatic patients may present with left leg edema, pain, varicosities, venous claudication, and ulceration (27). However, it is important to note that the majority of patients with venous compression of the LCIV by the RCIA are asymptomatic. Kibbe *et al.* demonstrated

that up to 24% of patients had greater than 50% compression and 66% had greater than 25% compression (28), and thus May-Thurner variant anatomy alone is not sufficient for pathology.

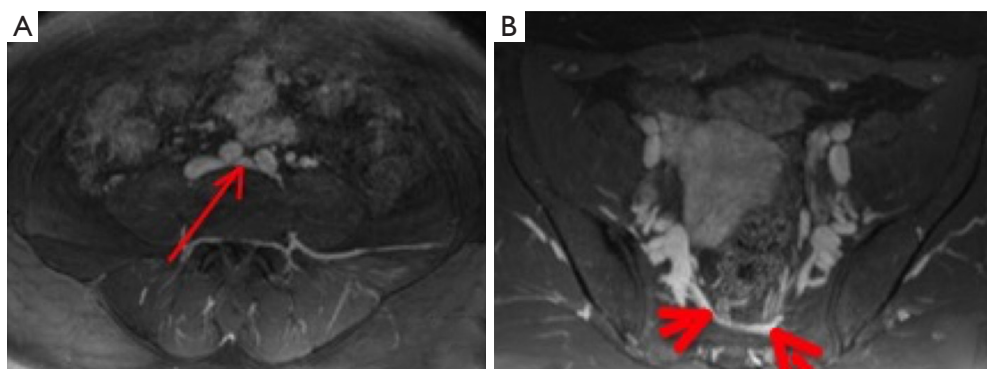
MRV is an attractive modality for the diagnosis and characterization of May-Thurner Syndrome (MTS) for several reasons. Iliac vein compression and thrombi can be directly visualized, with quantification of flow across the stenosis and accompanying reversal of flow in the internal iliac vein and collateral vessels (29). In addition, the lack of ionizing radiation is a distinct advantage over CT venography. In a case study by Wolpert *et al.*, MRV was able to confirm a diagnosis of MTS in all 9 patients while ruling out the presence of DVT and pelvic masses (27). When utilizing MRV for the evaluation of MTS, blood pool contrast agents are valuable because they both minimize the contrast dose and decrease the chance for mistimed acquisitions.

There is no consensus about specific radiologic signs that are diagnostic of MTS. However, the most useful finding is of compression of the LCIV by the RCIA (*Figure 7*). Tortuous venous collaterals crossing the pelvis to drain into the contralateral veins and thrombus formation are also suggestive features (30). A visualization of greater than 50% stenosis in the luminal diameter of the vein is considered an adequate indicator of LCIV compression related to MTS (31).

It is important to note that scanning more than once may be necessary to confirm the diagnosis since the degree of venous compression can be variable and asymptomatic. McDermott *et al.* found that the compressed LCIV on a single MRV study was not stable over time, with the mean compression of the LCIV at 62% in the index study and 39% in the comparison study in the same patients, with the mean change in the degree of compression between the two studies being 23% (32). The authors postulate that the compression in a single study may be insufficient to diagnose MTS.

### ***Nutcracker syndrome (NS)***

NS describes the compression of the left renal vein (LRV) between the aorta and superior mesenteric artery (SMA) (“anterior nutcracker”) or, if the LRV has a retroaortic or circum-aortic course, between the aorta and an underlying vertebral body (“posterior nutcracker”), predisposing to venous hypertension and the formation of intra and extrarenal hypertensive venous collaterals, gonadal vein



**Figure 7** MR venography with Ablavar in a 34-year-old woman with previous deep vein thrombosis (A). Axial reconstructions showing compression of left common iliac vein by the right common iliac artery (arrow) consistent with May Thurner anatomy; (B) opacification of pelvic veins in an axial reconstruction shows cross pelvic collaterals (arrows) in the pre sacral space suggesting the hemodynamic significance of compression of the left common iliac vein.

reflux, and periureteric varices. The most accepted hypotheses proposed to explain the compression are posterior renal ptosis, abnormal high course of the LRV or an abnormal origin of the SMA from the aorta (30,33).

It is relatively more common in females and usually presents in the 3rd or 4th decade of life. The severity of NS is variable, ranging from asymptomatic to severe pelvic congestion. The most common presenting symptom is micro- or macroscopic hematuria from the rupture of fragile varices into the collecting system (5,30), mild to severe orthostatic proteinuria, left flank pain secondary to the passage of ureteral blood clots and symptoms of pelvic venous congestion (chronic pelvic pain, dyspareunia, dysuria, and dysmenorrhea) (5).

The gold standard for diagnosis of NS is retrograde venography with a renocaval pressure gradient measurement of more than 3 mm Hg (30). However, noninvasive evaluation through CTV and MRV is far more common as they allow for evaluation of the anatomic structures and its hemodynamic consequences. Due to its pharmacokinetic profile and long intravascular stay, blood pool contrast agents have several advantages over extracellular agents in this scenario but none study so far have compared diagnostic accuracy between both class of agents. Many radiologic relationships have been studied in evaluating for possible NS. The beak sign, an abrupt narrowing of the LRV between the aorta and SMA with proximal dilatation of the LRV, can be visualized on CT and MR and has a sensitivity of 91.7% and specificity of 88.9% in the diagnosis of Nutcracker Syndrome (30). Another measure, the ratio of the LRV diameters at the hilar and

aortomesenteric regions of more than 4.9, has a sensitivity of 66.7% and specificity of 100% for this condition (30). The aortomesenteric angle (between the SMA and aorta) of less than  $41^\circ$  is considered 100% sensitive and 55.6% specific for nutcracker syndrome (34) since the normal aortomesenteric angle measures approximately  $90^\circ$  (33,35).

It is important to note however that these anatomic findings alone are not sufficient without matching clinical symptoms. For example, approximately 44% of asymptomatic patients were found to have mild narrowing of the LRV without the beak sign (35), and therefore careful correlation of symptoms is necessary before a diagnosis is made.

### *Pelvic congestion syndrome*

This syndrome is a common cause of chronic pelvic pain and it is believed to be caused by pelvic varices. Pelvic varicosities are enlarged tortuous tubular structures in the trajectory of the ovarian veins, around the uterus and the adnexa, as well as in the pelvic floor. The retrograde blood flow and the dysfunctional venous valves within the ovarian veins increase the pressure in the pelvic venous system, which cannot be compensated and generates dilation. The syndrome may also result from obstructing anatomic anomalies such as retroaortic left ovarian vein and Nutcracker syndrome or be secondary (36,37). Risk factors include pelvic surgery, retroverted uterus, hormonal influence (affects mostly premenopausal women) and multiple pregnancies (there may be a significant increase in intravascular volume at each gestation and the venous



distention can lead to valve incompetency over time). Most patients present with a noncyclical pain lasting more than 6 months, which can be worsened by movement, posture and activities that increase pelvic pressure (36,37). Interestingly, not all patients presenting with enlarged pelvic veins are symptomatic, and symptomatic patients may only have minimal or even no dilation at all. On imaging, possible causes of compression include tumors, cysts, or arterial aneurysms, and therefore renal and the iliac veins should be assessed for signs of compression.

Several criteria have been proposed for pelvic varicosities. On CT and MRI, the cut-off value for ovarian vein diameter is 8 mm. Early filling of the ovarian veins, internal iliac veins and/or left parauterine veins can be used as a sign of venous reflux (38). In nondiagnostic cases, conventional venography with direct visualization of the dilated ovarian veins can be performed, with the added advantage of simultaneous treatment if necessary.

During conventional angiographic and CT examinations, the Valsalva maneuver and table tilting have been advocated by some to induce sufficient reflux into the ovarian veins to allow visible ovarian vein engorgement. MR contrast-enhanced techniques are superior to both non-enhanced MR and CT. In a study with 10 patients diagnosed with retrograde flow through the ovarian veins, Kim *et al.* demonstrated that retrograde flow through incompetent ovarian vein valves can be easily visualized in the absence of dilation using time resolved-MRA during arterial phase, with an average time of 15 seconds after the initial aortic enhancement (39). Additional sequences can be obtained during a Valsalva maneuver, increasing the sensitivity for detecting varicose veins, especially in cases with a very slow reflux. No study has compared so far the visualization of ovarian vein reflux with blood pool and extracellular contrast agents; however the steady state imaging with gadofosveset can allow a clear depiction of the ovarian veins at high resolution (17).

### ***Thoracic venous outlet syndrome (TOS)***

TOS is a constellation of symptoms caused by the compression of the subclavian vessels and brachial plexus during their passage from the thoracic cavity to the axilla (40). The most common type is neurogenic and an arterial and venous TOS account for less than 10% of cases (41). There is no sex predilection, except for the neurogenic type, which presents a female/male ratio of 3.5/1. Some established causes for compression are the presence

of a cervical rib, long C7 transverse process, exostosis, congenital fibromuscular anomalies, repetitive movements and posttraumatic fibrosis of the scalene muscle (40). The symptoms include pain, claudication and coldness (for arterial compression) and upper extremity edema and thrombosis (venous compression). The diagnosis can be suspected with history and physical examination, although imaging is required to identify vascular abnormalities.

Contrast-enhanced MRA with provocative arm positioning has emerged as the primary tool to evaluate patients with TOS. For contrast-enhanced MRA with conventional extracellular contrast agents, a dual injection protocol is required, first during abduction and then at rest for acquiring post contrast images with good arterial and venous opacification in both positions, since arm abduction can exacerbate vascular compression (40,41). The degree of venous compression during hyperabduction is interpreted in post-contrast images and any lesion with more than 50% of subclavian vein compression should be considered significant. However, with a blood pool contrast agent, only a single-injection is necessary to achieve diagnostic image quality with high vessel contrast similar to a double-injection due to the prolonged intravascular stay. The experience of imaging of the thoracic outlet vessels with extracellular contrast agents is still poor but the feasibility for this scenario was confirmed by a study performed by Lim *et al.* with 31 patients assessed for vascular TOS using either a blood pool or an extracellular contrast agent; diagnostic quality imaging was achieved in all patients and BPS clearly demonstrated arterial and venous pathology, as well as functional changes in vessel caliber during arm position changes (41).

Other possible applications of BPCA in venous imaging include pulmonary embolism, upper extremity venous system, venous malformations and porto-splenic-mesenteric veins despite few studies demonstrating these uses. One study with 20 volunteers comparing gadofosveset trisodium and gadobenate dimeglumine during thoracic MR angiography at 3T by Frydrychowicz *et al.* did however find similar signal to noise ratio and contrast to noise ratio between both agents, suggesting that gadofosveset can depict thoracic veins and arteries with high accuracy, comparable to extracellular contrast agents (42). Also, the combination of dynamic and steady-state imaging with gadofosveset allows for evaluation of anatomical and flow characteristics of vascular malformations, allowing the differentiation between high-flow and low-flow vascular malformation. First-pass images delineate the arterial

anatomy and steady-state images facilitate assessment of the venous anatomy and enhancement pattern of the lesion (15).

## Conclusions

Contrast-enhanced MRV has emerged as an important tool for venous imaging over the last decade due to its advantages in anatomic evaluation without ionizing radiation. However, limitations in acquisition timing and administration of gadolinium-based agents in renal impairment are well known. Blood pool contrast agents are a very promising alternative in these situations and can yield quality images when compared to conventional extracellular agents.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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