

Use of Computed Tomography and Magnetic Resonance Imaging in Central Venous Disease

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ABSTRACT: Successful management of acute deep vein thrombosis and post-thrombotic syndrome depends on careful patient selection and detailed investigation of thrombus extent, composition, and anatomy. This article reviews the use of computerized tomography and magnetic resonance imaging in the assessment of central deep veins of the pelvis and addresses new developments within the field. Despite drawbacks of each imaging modality, when contemplating deep venous reconstruction, cross-sectional imaging should be considered for preoperative planning and to compliment intraoperative imaging tools, including intravascular ultrasound and contrast venography.

INTRODUCTION

Post-thrombotic syndrome (PTS) is the most common chronic complication of lower limb deep vein thrombosis (DVT) and occurs in up to half of patients with DVT. This condition is characterized by chronic pain, swelling, skin changes, and ulceration, with the latter developing in 5% to 10% of cases.¹ A manifestation of chronic venous insufficiency, PTS develops from persistent occlusion, chronic venous scarring, and destruction of venous valves that result in pathological venous hypertension. The risk of PTS is highest when the cavo-ilio-femoral segment is involved,² thus prompting development of interventional therapies designed to specifically treat this segment. Depending on the age and composition of the thrombus, invasive treatment options can range from lysis to venous stenting and/or open bypass; therefore, obtaining adequate detail to determine the exact location and extent of the thrombus (as well as its age and composition) is helpful in preoperative planning. In addition, compression syndromes and other abnormalities contributing to thrombus formation can be assessed to determine an optimal treatment strategy.

Ultrasound remains the modality of choice when investigating the patient upon initial presentation. It is cheap, reliable, and quick, but it can be challenging to use when assessing the deep veins of the abdomen and pelvis (segments that most frequently require intervention). Thus, accurate cross-sectional imaging may be needed when deep venous interventions are being considered. To this end, contrast-enhanced computerized tomography venography and magnetic resonance venography are important imaging modalities that can help guide clinical practice. This review provides a critical appraisal of both modalities and discusses potential advancements occurring within the field.

COMPUTED TOMOGRAPHY VENOGRAPHY

Computed tomography venography (CTV) is widely available in many centers and is a less invasive yet accurate imaging modality compared with traditional contrast venography. A meta-analysis of studies on the use of CTV between 1996 and 2004 showed a pooled estimated sensitivity and specificity of 96% and 95%, respectively, for detecting proximal DVT.³ CTV requires administration of a contrast agent, and thrombi appear as low-density filling defects within the vessel lumen. An increase in vessel diameter can also be noted in the acute stages of DVT. Unlike contrast venography, cross-sectional imaging using CTV is superior at detecting extrinsic compression syndromes; for example, in a study of 56 patients with acute thrombosis evaluated using CT, 80% were shown to have a central stenosis or obstruction.⁴ Detecting these lesions is key to managing patients with an iliofemoral DVT because maintaining adequate venous outflow after lytic therapy is essential for vessel patency.⁵ Current best practice advocates using venous stents in this setting, and with the advent of dedicated nitinol venous stents, flow-limiting stenoses can be successfully overcome.^{6,7}

Although stent patency is often assessed with duplex ultrasound, this is more difficult with stents placed in the pelvis and/or in obese patients. Likewise, these stents can often produce artifacts when assessed using MRI. In our practice, CTV is the ideal imaging modality to examine the position and structure of a stent when ultrasound is equivocal or impossible, especially when the vena cava is involved, as shown in Figure 1.

CT venography is typically done after the patient receives contrast injection through the cubital vein; this is indirect CTV.

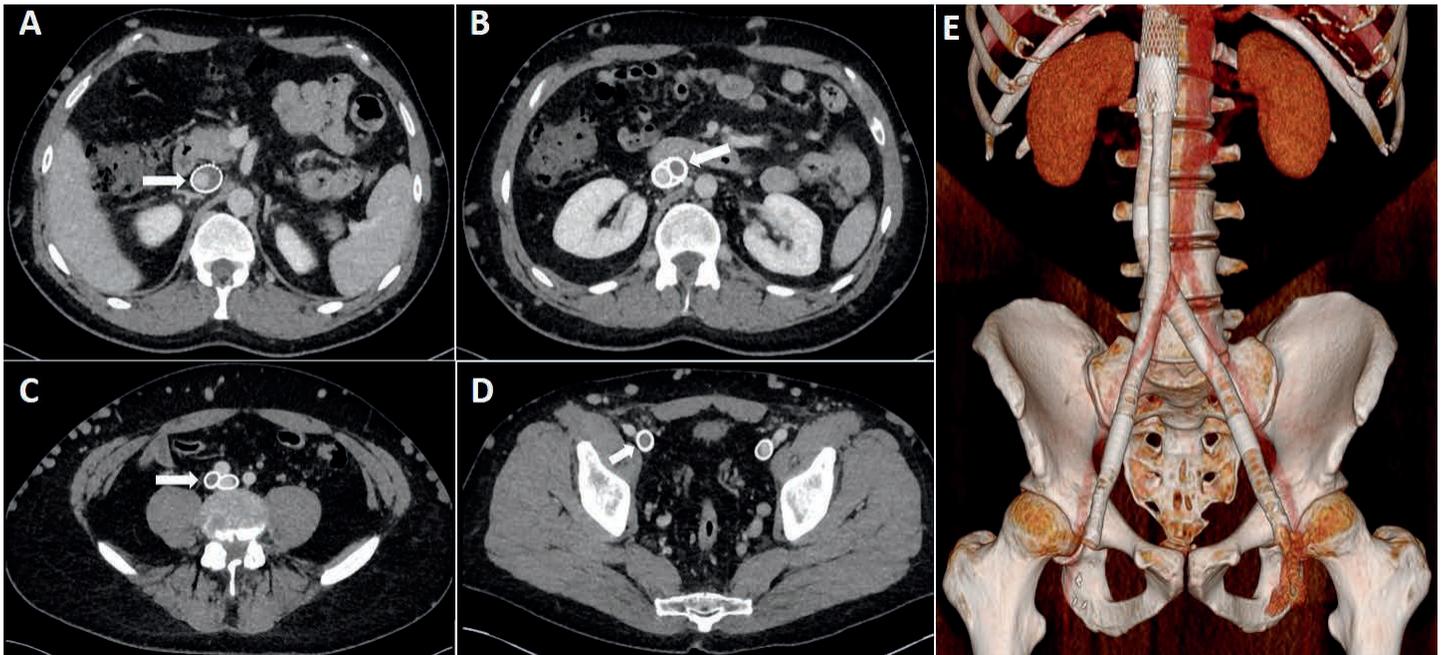


Figure 1.

Acute in-stent thrombosis. A filling defect can be seen in the inferior vena cava (IVC) stent (A), common iliac vein stent (B, C), and external iliac vein stent (D). (E) Three-dimensional reconstruction of the venous system demonstrating stenting from the IVC superiorly down to the common femoral vein inferiorly. This patient was successfully treated with catheter-directed thrombolysis.

Another option is direct CTV, wherein a contrast agent is injected in the dorsal vein of the affected foot, with a tourniquet applied to the ankle to allow preferential contrast flow into the deep veins. This allows superior visualization of the venous network and a more precise 3-dimensional reconstruction.⁸ Combined direct and indirect CTV is highly accurate but requires a larger dose of intravenous contrast; therefore, we recommend that this only be used in more complicated cases.⁹

CTV has been proposed as a method for predicting success of catheter-directed thrombolysis (CDT) in acute DVT patients. In a study by Choi et al., CTV analysis of recoiling of the external iliac vein diameter and severe rim enhancement was 93% accurate at identifying patients at risk of reocclusion within 6 months of CDT.¹⁰ CTV can also be combined with CT pulmonary angiography (CTPA) for concomitant investigation of DVT and pulmonary embolism (PE), and it is ideal for screening an occult malignancy.¹¹ However, the addition of an abdominal and pelvic CT in patients who present with their first unprovoked DVT does not seem to add diagnostic value.^{12,13}

Post-thrombotic venous disease is another area that can be assessed by CTV. A study of 51 patients scanned approximately 11 months after a DVT revealed specific features of post-thrombotic scarring, including reduced vein diameter, luminal

obliteration, residual thrombosis, development of fibrotic bands, superficial collateral veins, subcutaneous edema, and muscle enlargement.¹⁴ Such features help define the region requiring a stent and provide insight into the complexity of the intervention.

CTV Drawbacks

The main drawback of CT is exposure to high levels of radiation. The effective dose of indirect CTV is around 5.2 mSv for the pelvis and 0.6 mSv for the lower limbs.¹⁵ Although these doses do not exceed the safety recommendations and are lower than the radiation dose of a liver CT, for example,¹⁶ the risks of additional radiation should be weighed against the risks of undetected thrombosis on an individual basis. The increase in radiation exposure is substantial when combining CTV with CTPA, especially the gonadal dose, and should be carefully considered in younger patients.¹⁶

Contrast-induced nephropathy is another often-cited risk of CTV.^{7,9} However, a recent large study of emergency department patients with creatinine levels > 4 mg/dL found that contrast administration was not associated with increased frequency of renal failure.¹⁷ A number of guidelines exist for the management of patients with renal impairment, but there is still debate about the use of iso-osmolar versus low-osmolar contrast agents.

Regardless of risk, best practice is to minimize the amount of contrast agent used whenever possible and avoid repeat scans unless absolutely necessary.

Future of CTV

CTV provides excellent anatomical detail and images that most users find easy to interpret. In the near future, there will likely be further improvement in scanning time, spatial resolution, and dose efficiency that will mitigate some of the associated risks. Traditional CT imaging has long been considered a tool that provides only anatomical detail; however, coupled with nuclear medicine technology such as positron emission tomography, CT has the potential to offer molecular information regarding thrombus structure that could help guide therapy.^{18,19} A number of tracers with specific targets are available and are summarized in Table 1.

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) is an alternative imaging modality for detecting central venous disease. The main advantage over CT is the lack of ionizing radiation, which is desirable in younger patients and when serial investigations are required. Since MRI is amenable to modifications in magnetization and sampling parameters, many different sequences can be investigated. A systematic review and meta-analysis of studies involving different MRI techniques showed an estimated pooled sensitivity and specificity of 92% and 95%, respectively, when MRI was used in the diagnosis of DVT.²⁰ Despite its excellent accuracy, magnetic resonance venography (MRV) is likely underused—even in centers that have access to this technology—and could be beneficial in certain groups when the pelvic veins are affected²¹ and those in whom deep venous interventions are being considered. There are a number of sequences that can be applied to image thrombus in the veins, with the main ones summarized below.

Flow-Dependent MRI

Gradient-recalled echo (GRE) has fallen out of fashion because of slow acquisition times and artifacts. However, it has excellent sensitivity and specificity (100% and 93%, respectively) for detecting DVT.²² This technique has been shown to detect changes in appearance of the aging thrombus—with acute thrombi appearing as low-intensity homogenous structures and older thrombi appearing as higher-intensity structures with reduced vein diameter and increased vessel wall thickness.²³

Time-of-flight MRV is another method that relies on the saturation of stationary tissues with rapidly repeating radiofrequency pulses. Therefore, flowing venous blood has a high signal whereas a thrombus appears as a filling defect

within the lumen of the vein (Figure 2 A).²⁴ Although this sequence has high accuracy,²⁴ long acquisition times and flow artifacts limit its use in clinical practice.

Flow-Independent MRI

Balanced steady-state free precession MRV is a sequence in which blood has a high signal intensity irrespective of flow velocity. With a high sensitivity and specificity (95% and 100%, respectively), it is able to visualize the proximal extent of the DVT more accurately than ultrasound.²⁵ Unlike ultrasound, it is not user dependent. Acquisition time is usually less than 15 minutes and patient discomfort is minimal. In our institution, balanced steady-state free precession MRV is now routinely used for every patient with a suspected acute ilio-femoral DVT. Acute thrombosis is visualized as low signal intensity within the distended vessel lumen,²⁵ thickening of the vessel wall, and surrounding edema (Figure 3).

This sequence can also be used in patients with PTS. The characteristic features are low-intensity signals within stenosed small-caliber vessels that at times may not be visible. There is usually no surrounding edema. Post-thrombotic webs are frequently seen and reflect the chronic disease process (Figure 4). MRI performs well (99% sensitivity, 92% specificity) but tends to overdiagnose post-thrombotic webs and underdiagnose stenoses in small-caliber vessels compared with digital subtraction contrast venography.²⁶ Overall, it allows for adequate preoperative assessment of patients when planning deep venous reconstruction.

Contrast-Enhanced MRV

Blood-pool contrast agents can be used to enhance the vasculature for MRI. Albumin-binding contrast agents allow adequate visualization of the venous system, whereas gadolinium-based contrast agents provide superior vessel visualization, higher diagnostic accuracy, better differentiation of thrombi age, and significantly quicker acquisition times compared to non-contrast GRE MRV.²⁷ Nephrogenic systemic fibrosis that develops in patients with renal impairment is one of the major risks with gadolinium-based contrast agents, although the incidence is less than 0.02%.²⁸ Guidelines recommend using low-risk gadolinium-based contrast agents at the lowest possible dose with a minimum of 7 days between administrations.²⁹

Direct Thrombus Imaging

As a thrombus ages and gradually changes from a fibrin-rich to collagen-rich structure, it becomes less susceptible to lysis.³⁰ It is therefore desirable to know the structural composition of the

TARGET	TRACER	MODALITY	AUTHORS	YEAR	
Inflammatory cells	¹⁸ F-FDG	PET/CT	Rondina et al.	2012	
			Hara et al.	2014	
			Hess et al.	2015	
			Le Roux et al.	2015	
			Zhu et al.	2016	
Fibrin	Gd-EP-2104R	MRI	Stracke et al.	2007	
			Katoh et al.	2009	
			Vymazal et al.	2009	
			Andia et al.	2014	
	Gd-DTPA-PE	MRI	Winter et al.	2003	
	CLIO-GPRPP	MRI	McCarthy et al.	2009	
	⁶⁴ Cu-EP-2104R	PET/MRI	Uppal et al.	2011	
	⁶⁴ Cu-FPB8	PET/MRI	Blasi et al.		2015
	GC-AuNPs	CT	Kim et al.	2013	
fib-GC-AuNPs	CT	Kim et al.	2015		
FXIII	Gd-Bi- α_2 AP	MRI	Miserus et al.	2009	
	CLIO-FXIII	MRI	McCarthy et al.	2009	
Platelets	LIBS-MPIO	MRI	Von zur Muhlen	2008	
			Heidt et al.	2016	

Table 1.

Molecular imaging studies of venous thrombi using computed tomography (CT) and magnetic resonance imaging (MRI) techniques. FDG: fluorodeoxyglucose; PET: positron emission tomography; Gd: gadolinium; DTPA-PE: diethylene-triamine-pentaacetic acid phosphatidylethanolamine; CLIO: cross-linked iron oxide; GPRPP: Gly-Pro-Arg-Pro-Pro; ⁶⁴Cu: copper 64; FBP: fibrin binding probe; GC-AuNPs: glycol-chitosan-coated gold nanoparticles; AP: antiplasmin; LIBS: ligand-induced binding sites; MPIO: microparticles of iron oxide; FXIII: factor XIII

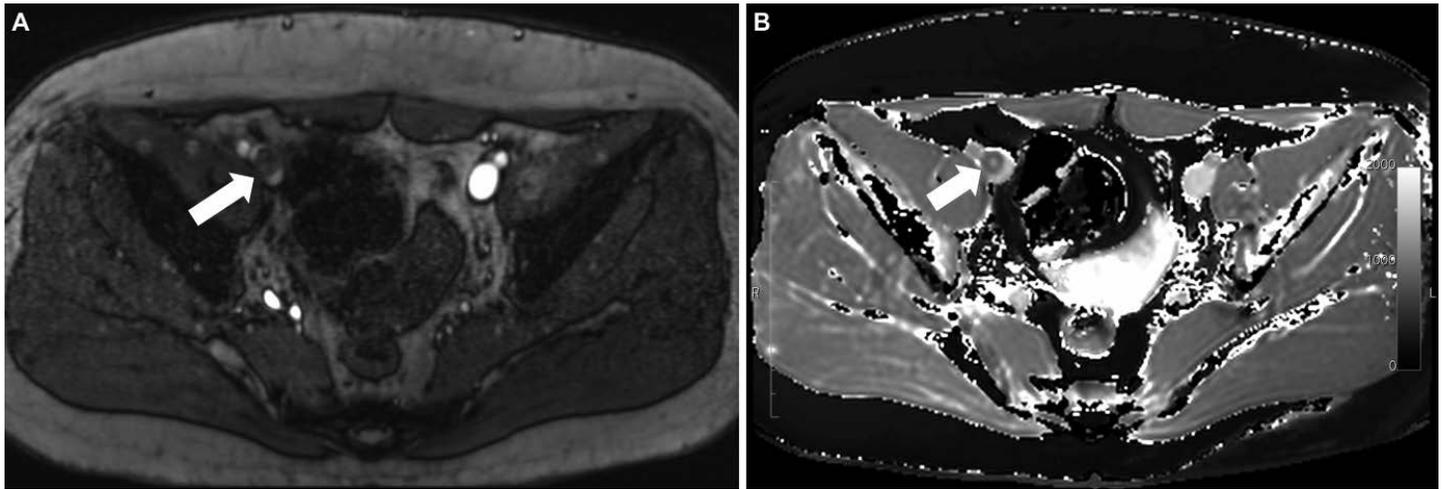


Figure 2.

(A) Time-of-flight magnetic resonance venography demonstrating right external iliac vein thrombus (white arrow) and (B) corresponding T_1 map demonstrating low T_1 relaxation time of the thrombus (white arrow).

thrombus before any intervention is considered. Indirect signs visible on MRV, such as vein distension, perivenous edema, and an enhanced vein wall, may suggest acute thrombosis. However, these signs are not always present and do not provide an objective quantitative assessment. Direct thrombus imaging has emerged as a method of assessing thrombus structure in vivo and is a blanket term used to describe a variety of sequences that reflect thrombus composition.

T_1 mapping allows measurement of the T_1 relaxation time and is both accurate and reproducible.³¹ Time is shortened by ferric iron that is present in the acute thrombus³⁰ (Figure 2 B) and returns to that of normal blood as the iron is taken up by inflammatory cells that accumulate within the resolving thrombus.³² In a murine model of DVT, T_1 relaxation time reflects thrombus structure and susceptibility to lysis.³⁰ Magnetization transfer and diffusion-weighted imaging have

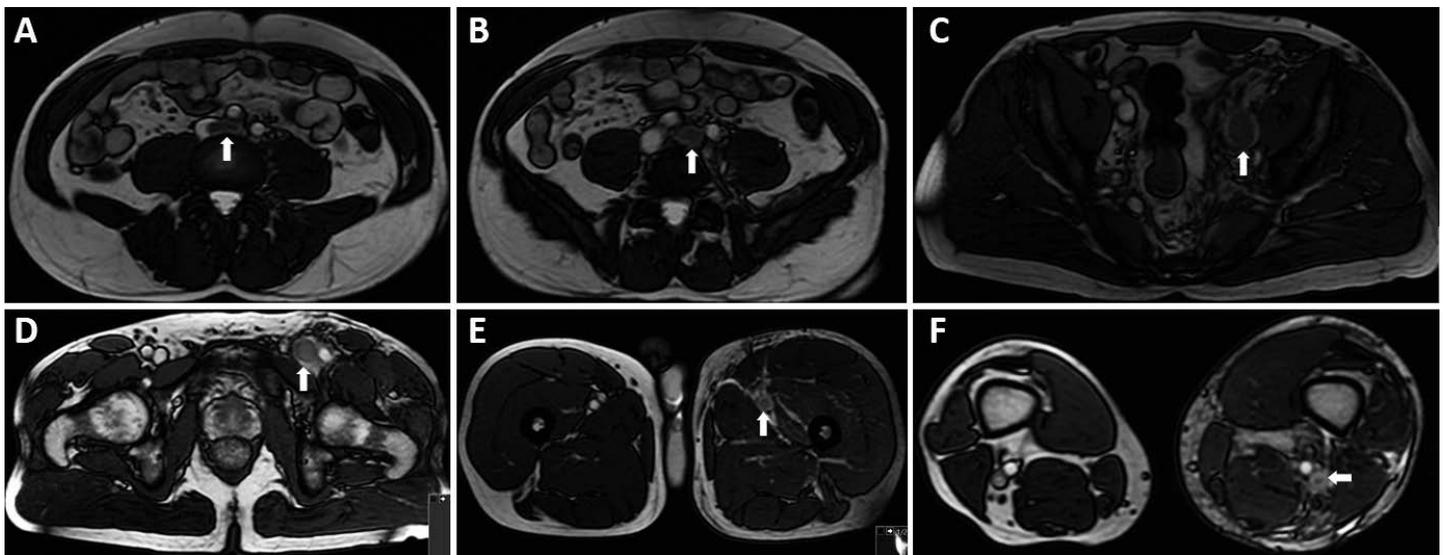


Figure 3.

Balanced steady-state free precession magnetic resonance venography of acute deep vein thrombosis. Thrombus is demonstrated by a white arrow in the inferior vena cava (A), common iliac vein (B), external iliac vein (C), common femoral vein (D), femoral vein (E), and popliteal vein (F).

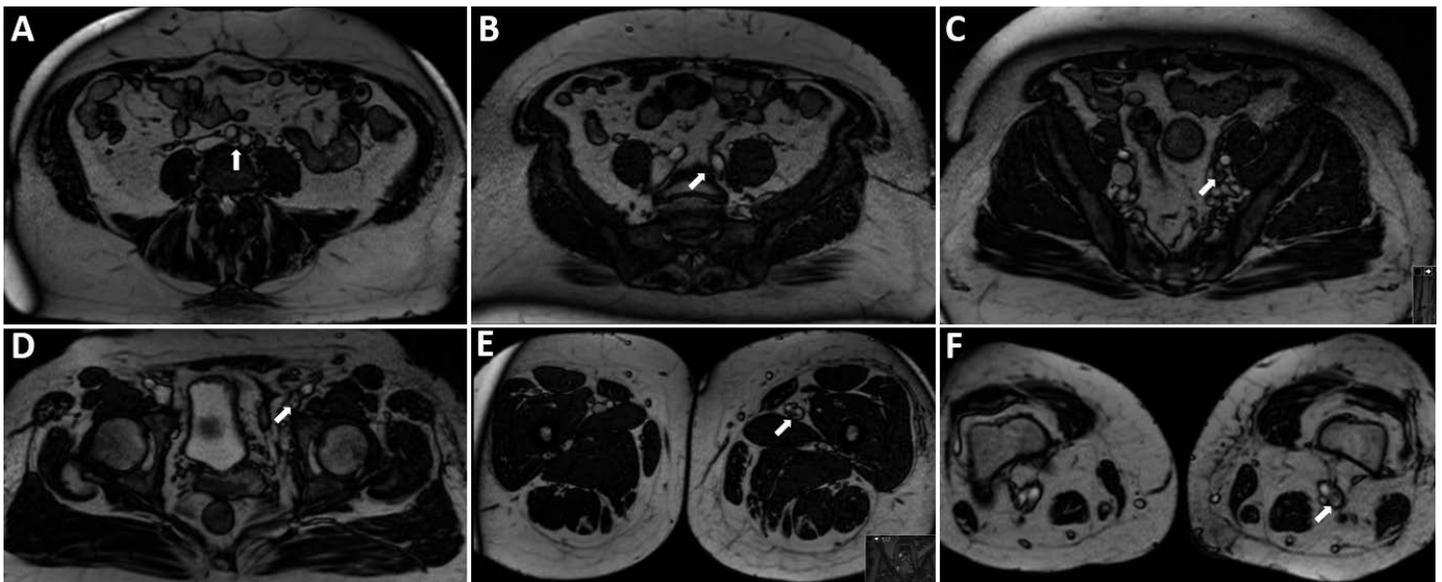


Figure 4.

Balanced steady-state free precession magnetic resonance venography of chronic deep vein thrombosis. Chronic changes (stenosed small-caliber vessels with post-thrombotic webs) are demonstrated by a white arrow in the inferior vena cava (A), common iliac vein (B), external iliac vein (C), common femoral vein (D), femoral vein (E), and popliteal vein (F).

also been investigated in the murine model and correlate with thrombus fibrin, collagen, and erythrocyte content.³³ In addition, ex-vivo investigation of human venous thrombi using apparent diffusion coefficient and T_2 mapping shows significant differences in these quantitative MRI parameters between acute and chronic thrombi.³⁴ We are currently investigating a multisequence approach combining T_1 mapping, magnetization transfer, and diffusion-weighted imaging to provide information on thrombus structure and its susceptibility to lysis in order to better identify acute DVT patients who would benefit most from lytic therapy.

MRI Drawbacks

A major disadvantage of MRI is the strong magnetic field required for imaging; this field precludes investigations in patients with MR-unsafe implants (e.g., pacemakers). Even implants that are MR-safe or MR-conditional (e.g., orthopedic implants) can produce artifacts that make the scan uninterpretable. In particular, nitinol stents, most of which are MR-conditional, produce artifacts that make it difficult to assess stent patency and thus limit the use of MRI in this setting. Developments in techniques employed by fast spin-echo sequences—such as a combination of swap phase-encode arterial double-subtraction elimination and flow refocused fresh-blood imaging—have reduced the artifact from orthopedic prostheses and enabled high diagnostic reproducibility.³⁵

Perhaps the biggest barriers to using MRI in thrombus imaging are the complexity of the MR system and its associated high costs, some of which have been negated by the increased availability of scanners to help diagnose and manage cardiac and neurological pathologies. Implementing the sequence of choice is now a matter of software configuration with optimization rather than purchasing additional hardware. Even so, a cost-benefit analysis is needed to justify the additional value MRI could bring to the management of patients with central venous disease.

The Future of MRI

Two major challenges facing the interventional field are timing and patient selection—when to intervene and in which patients interventions are likely to be most successful. Molecular imaging techniques combining MRI and nanoagents that target fibrin, FXIIIa, and platelets have been shown to detect intravascular thrombi (Table 1) and could also be used for quantitative assessment of thrombus structure.³⁶ However, it is still difficult to use MRI to detect a functional stenosis in the venous system. Advancements in tools such as 4-dimensional MRI may offer some insight into the venous return of a limb, but the problem still remains that patients are imaged in a supine or prone position without activity that would otherwise affect the hemodynamics of the venous system. Although it is still beneficial to obtain as much information as possible regarding venous anatomy, physiology, and thrombus composition, imaging during function would be more desirable.

CONCLUSION

CTV and MRV are methods of investigating acute and post-thrombotic central venous disease preoperatively, with both providing excellent anatomical detail and accurate thrombus detection. Although CTV is cheaper, quicker, and widely available, ionizing radiation and contrast-induced nephropathy are a concern. However, CTV can be easily combined with CTPA for investigating pulmonary emboli or other abdominal pathology that may predispose patients to thrombosis, and it can be used for follow-up imaging of endovenous stents when ultrasound is equivocal. MRV does not expose patients to ionizing radiation, and specific sequences can be applied that do not require a contrast agent to visualize the thrombus. Its strength lies in its highly modifiable nature and ability to provide more information about the structure of the thrombus itself. With both imaging modalities, however, there is a need for specific expertise in interpreting the data, and their cost-effectiveness remains to be shown. These tools should be used in conjunction with a careful history and examination when interventions are being considered. In our practice, CTV and MRV are complimentary to a comprehensive assessment with invasive imaging techniques such as intravascular ultrasound and contrast venography.

KEY POINTS

- Cross-sectional imaging (either computed tomography or magnetic resonance venography) should be considered before deep venous intervention.
- Computed tomography venography is accurate in the assessment of acute and chronic venous disease, although it requires contrast and ionizing radiation.
- Magnetic resonance (MR) venography can be routinely used in central venous disease in patients without MR-unsafe implants and can provide more information about thrombus structure.
- Computed tomography venography is recommended for follow-up of patients with complications after venous stenting.

Conflict of Interest Disclosure:

Dr. Black is a consultant for Cook Medical, C. L. Bard, Inc., W. L. Gore & Associates, Inc., VENITI, Inc., Phillips Healthcare, Medtronic, Boston Scientific, and OptiMed.

Keywords:

deep vein thrombosis, DVT, computerized tomography venography, CTV, magnetic resonance venography, MRV

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