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Non-Contrast MR Angiography: An Update

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Abstract

Both CT angiography (CTA) and contrast-enhanced MR angiography (CEMRA) have proven to be useful and accurate cross-sectional imaging modalities over a wide range of vascular territories and vascular disorders. A key advantage of MRA is that, unlike CTA, it can be performed without the administration of a contrast agent. In this review article, we will consider the motivations for using non-contrast MRA, potential contrast mechanisms, imaging techniques, advantages and drawbacks with respect to CTA and CEMRA, and the level of evidence for using the various MRA techniques. In addition, we will explore new developments that promise to expand the reliability and range of clinical applications for non-contrast MRA, along with functional MRA capabilities not available with CTA or CEMRA.

Keywords

Magnetic resonance; Flow measurement; Non-contrast angiography; Quiescent interval slice-selective; Fast interrupted steady-state

Both CT angiography (CTA) and contrast-enhanced MR angiography (CEMRA) have proven to be useful and accurate cross-sectional imaging modalities over a wide range of vascular territories and vascular disorders (1–3). Compared with CEMRA, CTA has the benefits of lower cost, shorter scan times, higher spatial resolution, relative simplicity, and more consistent technique across scanner platforms. In many cases, CTA is more immediately available than CEMRA and is often selected primarily on that basis.

On the other hand, CEMRA provides multiple advantages as well. Unlike CTA, it does not expose the patient to ionizing radiation, while macrocyclic gadolinium-based chelates are safer to administer for contrast-enhanced exams than iodinated agents in patients with impaired renal function. For functional assessment, time-resolved CEMRA provides superior temporal resolution and is better at showing the longitudinal transit of a contrast agent than CTA (4), while phase contrast techniques allow for accurate blood flow measurements that cannot be obtained with CT.

Another drawback of CTA is that vascular calcifications, which are inapparent in MRA, can cause substantial blooming artifacts that can exaggerate the apparent severity of a stenosis or make the study uninterpretable (5). This can be especially problematic in the CTA evaluation of small vessel disease in patients with a high prevalence of vascular calcifications, such as those with diabetes (6) or chronic kidney disease (CKD) (7). Conversely, in some circumstances it might be important to detect vascular calcifications in an MR exam. For instance, dense arterial wall calcifications should be avoided when choosing a percutaneous access site, and their presence is a major determinant of failure for percutaneous endovascular aneurysm repair (8). When an MRA exam is performed and information about vascular calcifications is needed, one can acquire an additional proton density-weighted in-phase stack-of-stars pulse sequence that can identify vascular calcifications as accurately as a CT scan (Figure 1) (9).

A key advantage of MRA is that, unlike CTA, it can be performed without the administration of a contrast agent. Non-contrast MRA has been available for more than 30 years in the form of two-dimensional (2D) and three-dimensional (3D) time-of-flight (TOF) (10). Until recently, progress in the field of non-contrast MRA was relatively slow and there were few viable alternatives to legacy TOF techniques. One reason for slow progress was that the successful implementation of advanced non-contrast MRA techniques required improvements in scanner hardware, e.g. phased array coils to enable parallel acceleration techniques and increase the signal-to-noise ratio (SNR), faster and stronger magnetic field gradients to improve spatial resolution and shorten the echo spacing for balanced steady-state free precession (bSSFP) pulse sequences, precise eddy current compensation to reduce image artifacts, and so forth. Perhaps a bigger obstacle to progress was the de-motivating effect of a decades-long, widely-held belief that MRI contrast agents were entirely safe to administer, even at the double and triple doses historically used for CEMRA (11). That belief continued unchallenged until 2006, when an association was first reported between the intravenous administration of gadolinium-based contrast agents and the potentially lethal multi-system disease now known as nephrogenic systemic fibrosis (NSF) (12).

In this review article, we will consider the motivations for using non-contrast MRA, potential contrast mechanisms, imaging techniques, advantages and drawbacks with respect to CTA and CEMRA, and the level of evidence for using the various non-contrast MRA techniques. In addition, we will explore new developments that promise to expand the reliability and range of clinical applications for non-contrast MRA, along with functional MRA capabilities not available with CTA or CEMRA.

Motivations for Non-contrast MRA

There are several reasons why non-contrast MRA techniques may be of potential interest. First, and often overlooked, there is the basic issue of cost. Non-contrast MRA dispenses with the contrast agent, infusion paraphernalia, need for point-of-care renal function testing to measure estimated glomerular filtration rate (eGFR), and effort required for venous cannulation. At our institution, we have approximated the extra cost involved with contrast administration as \$200 per study, although an offsetting consideration is the shorter scan time of CEMRA versus non-contrast MRA.

Second, there is the concern about potential risks, especially NSF (13). The widespread implementation of preventative measures (e.g. switching to macrocyclic contrast agents that have proven to be safer than linear agents, avoiding contrast administration in patients with Stage 4 or 5 CKD and taking into account risk factors such as hepatorenal syndrome) has practically eliminated the risk for NSF. However, this current information is not always reflected in hospital guidelines for MR contrast agent usage, while some clinicians remain averse to ordering a contrast-enhanced MRI when the eGFR is < 60 ml/min. Gadolinium administration has recently been associated with other, less well understood conditions such as uptake by the brain (14), cerebrospinal fluid and bones (15). However, at this time there are no known pathologic conditions associated with gadolinium retention in any of these organs.

Ferumoxytol, an iron-based material that is FDA-approved for the treatment of iron deficiency anemia in adult patients with CKD, has been proposed as an alternative to gadolinium-based contrast agents for CEMRA (16,17). Being an iron-based rather than gadolinium-based agent, ferumoxytol incurs no risk of NSF. Moreover, it is a true blood pool agent with a prolonged plasma half-life of about 14 to 21 hours (18) vs. about 1.5 hours for standard extracellular MR contrast agents (19). Consequently, ferumoxytol allows the acquisition of high-resolution steady-state MRA over many minutes, much longer than is feasible using a standard contrast agent. While ferumoxytol shows great promise for CEMRA (20), there are serious drawbacks including: [1] high cost; [2] lack of FDA approval for use as an MRI contrast agent; and [3] a boxed warning (the FDA's strongest type of warning) because of reports of serious, potentially fatal allergic reactions (21). This warning includes a recommendation to only administer diluted ferumoxytol as an IV infusion over a minimum of 15 minutes, which is problematic for first-pass CEMRA.

There are other benefits of non-contrast MRA related to the MR scan procedure. For instance, it is not uncommon for a CEMRA acquisition to be mistimed with respect to the arrival of the contrast bolus due to technical issues or anatomical factors such as a severe stenosis or recirculating flow within an aneurysm delaying the progression of contrast agent through the vessel (Figure 2). While contrast timing issues are not a concern with non-contrast MRA, other kinds of timing issues can occasionally cause difficulties, e.g. mistiming of an electrocardiographically (ECG)-gated subtractive 3D MRA acquisition with respect to the onset of peak systolic flow causing loss of flow contrast; slow or recirculating flow in combination with a short inflow time limiting the length of vessel seen with inflow-dependent MRA.

Another benefit of non-contrast MRA is that, unlike a contrast-enhanced exam, it can be repeated as often as required. Whereas a first-pass CEMRA may be rendered non-diagnostic by patient motion, a non-contrast MRA can be reacquired to salvage the exam. One can image with additional scan orientations, higher spatial resolution, or different patient positioning to provide needed diagnostic information. For instance, in a patient with suspected popliteal entrapment syndrome (22), one can repeat a non-contrast MRA with the foot in multiple orientations (e.g. neutral, active plantar flexion, and dorsiflexion) to demonstrate position-dependent vascular obstruction. However, care must be taken not to

unduly prolong the study and disrupt the clinical workflow, given the longer scan times for some non-contrast techniques.

There are some circumstances where a contrast-enhanced study is required, for instance to show pathological soft tissue enhancement due to inflammation, tumor, or slow flow lesions such as hemangiomas. On the other hand, soft tissue enhancement in the setting of inflammatory disorders or venous stasis can sometimes obscure vascular detail on CEMRA, particularly if a time-resolved scan was not performed. Certain vascular-associated abnormalities such as intramural hematoma may be obscured due to the very short repetition time used for first-pass CEMRA; in these circumstances, the vascular pathology may be better identified with non-contrast techniques (Figure 3).

Contrast Mechanisms for Non-contrast MRA

There are several different contrast mechanisms available for non-contrast MRA (23). The optimal contrast mechanism and associated imaging technique are highly dependent on the individual clinical indication, since no single mechanism or imaging technique is yet ideal in all scenarios. A summary of currently available non-contrast enhanced MRA techniques, their applications, typical acquisition times, and vendor-specific terminology is provided in Table 1.

1. Flow-independent MRA

Arterial blood has long T1 and T2 relaxation times (≈ 1400 msec and 250 msec respectively at 1.5 Tesla) which depend on magnetic field strength, hematocrit, oxygen saturation and temperature (24,25). When imaged with a non-contrast bSSFP pulse sequence, blood, fat, and fluids typically appear bright based on the high T2/T1 ratio of these tissues. To improve the conspicuity of arterial blood, chemical shift-selective fat saturation can be applied to suppress the high signal from fat, while a T2 preparation can be applied to reduce the signal from myocardium or skeletal muscle. Flow-independent 3D bSSFP acquisitions, in conjunction with respiratory compensation techniques such as navigator gating, have been used for imaging of the coronary arteries, aorta, and pulmonary veins (26–29).

Unlike flow-dependent techniques, flow-independent techniques have the advantage of being less dependent on the rapid inflow of unsaturated spins into the imaging volume to generate contrast between vessels and surrounding tissues. This property can be particularly helpful to depict slow flow in veins and diseased arteries. One drawback of using a bSSFP readout for flow-independent (and other) non-contrast MRA techniques is its sensitivity to artifactual signal loss resulting from blood flowing through off-resonant regions (30). These artifacts can be ameliorated using higher-order shimming localized to the region of interest, by maximizing the sampling bandwidth and minimizing the echo spacing of the bSSFP readout (at the expense of lower SNR and higher specific absorption rate). The shorter echo spacing also helps to minimize flow-related artifacts.

Nonetheless, in some situations off-resonance artifacts are difficult to avoid. For instance, pulmonary veins imaged with bSSFP may show signal voids due to off-resonance effects caused by the proximity of air-containing lung tissue and bronchi (31). Image artifacts will

also commonly be seen near metallic implants. The severity of off-resonance artifacts worsens with increasing magnetic field strength, so 1.5 Tesla is preferred over 3.0 Tesla for imaging of the pulmonary veins or patients with implants.

2. Non-subtractive, Inflow-dependent MRA

Time-of-flight (TOF): Non-subtractive, inflow-dependent MRA techniques include legacy 2D and 3D TOF methods that are still in widespread use for the evaluation of the extracranial carotid arteries and circle of Willis (32–34). For the neck vessels, 2D TOF provides efficient head-to-foot coverage and adequate vessel-to-background contrast even in the setting of slow flow. By comparison, 3D TOF provides less head-to-foot coverage and suffers from saturation effects with slow flow. However, it is more resistant to signal loss from flow-related dephasing due to a hemodynamically-significant stenosis. Both techniques are prone to artifacts from flow saturation in horizontally-directed or tortuous vessel segments due to the rapid, repeated application of the excitation RF pulse along with the tracking venous saturation RF pulse, which is typically placed just downstream of the imaging region. They are also sensitive to artifacts from respiratory and swallowing motion given that scan times are much longer than with first-pass CEMRA. While ECG-gated 2D TOF MRA was used in the past for the evaluation of peripheral arteries (35), the technique has fallen out of favor due to frequent image artifacts and long scan times that can exceed one hour.

Inflow-dependent inversion recovery (IFDIR): Respiratory-gated IFDIR 3D MRA is often used for the non-contrast evaluation of the renal arteries. Fat signal is suppressed using chemical shift-selective fat saturation, while stationary background and venous signals are suppressed by placement of a thick axially-oriented inversion RF band that extends from just above to well below the renal arteries. Following a lengthy waiting interval (e.g. up to 1400 msec) to allow for the inflow of fresh arterial spins, imaging is performed with a 3D bSSFP pulse sequence.

Inflow-dependent inversion recovery reliably provides diagnostic image quality with typical scan times on the order of five minutes or less (36,37). It has been reported to have excellent accuracy (38), as well as higher technical success rates and image quality than CEMRA (39). Moreover, compared with CEMRA, it better displays the intra-renal branch vessels because there is no enhancement of the renal parenchyma. One drawback of the technique is that scan efficiency and image quality can be degraded in patients with irregular breathing patterns. Also, only limited lengths of the renal arteries may be displayed in the case of very slow flow (e.g. medical renal disease or distal to a severe stenosis).

Inversion-prepared 3D techniques are generally effective in vascular territories, such as the renal arteries, that are of limited length and have sufficiently brisk inflow that saturated arterial spins are replaced after each cardiac cycle. However, in regions such as the peripheral arteries where arterial length is longer and arterial flow is slower and discontinuous over the cardiac cycle, these techniques are generally ineffective. Much better results are obtained by using inflow-dependent 2D techniques such as quiescent-interval slice-selective (QISS) MRA (40) or cardiac-gated subtractive 3D techniques.

QISS: Non-contrast MRA techniques are a particularly useful option for patients with peripheral arterial disease (PAD), given that nearly 40% of these patients have significant renal dysfunction (41). The QISS technique was specifically developed with the aim of providing a fast, robust, user-friendly non-contrast approach for evaluating the peripheral arteries. Key features of the QISS technique include: (1) single-shot acquisition with a very short (≈ 300 msec) period of data collection, which makes the acquisition insensitive to patient motion; (2) application of an in-plane RF saturation pulse to suppress the background signal and tracking RF saturation pulse to suppress venous signal; (3) quiescent interval immediately after these RF saturation pulses that overlaps the period of rapid systolic flow and helps to ensure that saturated in-plane spins are fully replaced by unsaturated ones prior to the bSSFP readout; (4) use of fat saturation; and (5) acquisition of groups of 40 to 50 3-mm thick axial slices per QISS station, with each station imaged near the magnet isocenter to minimize off-resonance effects. A whole-leg exam typically entails the acquisition of about 400 slices (10 stations) over approximately 7 to 8 minutes (not including the time for shimming each station).

QISS has several practical advantages over other non-contrast peripheral MRA techniques. For instance, compared with legacy cardiac-gated 2D TOF, QISS provides nearly an order of magnitude reduction in scan time. With both TOF and QISS, signal saturation can occur in tortuous or horizontally-oriented arterial segments. However, with QISS, the artifacts are less severe than with TOF because the quiescent interval allows for substantial inflow of fresh arterial spins to replace saturated ones. Unlike subtractive 3D MRA (to be described in the next section), there is no need to tailor the imaging parameters to the individual patient nor is a scout scan required, which simplifies scan set-up for the technologist. In addition to arterial imaging, QISS can be used for venous imaging by flipping the traveling saturation pulse from below to above the imaging slice and lengthening the quiescent interval to allow for adequate refreshment of saturated in-plane spins given the lower velocities encountered with venous flow.

Motion during a 3D MRA can render all the images, and hence the entire exam, non-diagnostic. Since QISS is a single-shot 2D technique, patient motion can only degrade the images that are acquired while motion is occurring. Moreover, motion artifact is easily distinguished from vascular disease, since it manifests as a position shift for vessels and background tissues alike. If motion artifact is recognized during the scan, the affected QISS station can be immediately repeated at the cost of an extra minute or two of scan time. For avoidance of motion artifact in the pelvis and abdomen, QISS allows large numbers of slices (e.g. 15 to 20) to be acquired in each breath-hold, so motion-free evaluation of this region can be obtained using multiple breath-holds (typically about six). By comparison, breath-holding is impractical with TOF or subtractive 3D techniques because of the much longer scan times.

QISS also has drawbacks. Using a 2D bSSFP readout, the minimum slice thickness is on the order of 2-mm and the slice profile is sinc-shaped rather than rectangular. Additionally, the bSSFP slice profile is dependent on the time-bandwidth product, flip angle, and presence of off-resonance effects (42). Consequently, multiplanar reconstructions with QISS can be less sharp along the head-to-foot direction than is the case with 3D techniques, which allow

thinner, rectangular-shaped slices (3D partitions) to be acquired. Additionally, the use of a bSSFP readout renders the technique more sensitive to off-resonance artifacts than is the case with subtractive 3D techniques that use a fast spin-echo readout.

3 Subtractive 3D MRA: The first ECG-gated subtractive non-contrast MRA technique for evaluation of the peripheral arteries was reported in 1985 (43). Over the past decade, several subtractive approaches have been described for non-contrast MRA, each with advantages and drawbacks.

Cardiac-gated subtractive 3D fast spin-echo: Subtractive 3D fast spin-echo techniques rely on the fact that intravascular signal is suppressed in fast spin-echo images when data are acquired during rapid systolic flow, whereas this signal is relatively preserved during slow or absent diastolic flow (44–46). Unlike QISS where dozens of 2D slices are acquired in an axial plane, two 3D slabs (one acquired during peak systole and the other at end-diastole) are typically acquired in an oblique coronal plane for the subtractive approach. Subtraction of the 3D slab acquired at peak systole from the one acquired at end-diastole cancels background signal while retaining the signal from arteries. This technique can provide image quality that is competitive with peripheral CEMRA or CTA with scan times of several minutes per station (Figure 4).

A major benefit of using a fast spin-echo readout is that it avoids off-resonance artifacts that may occur with bSSFP. There are also several caveats with this approach (47). For instance, it is essential to acquire an ECG-gated timing scan for each vessel region to determine the optimal systolic and diastolic trigger delays for the two 3D slabs. If there is a unilateral arterial stenosis, the optimal timings may differ between the two legs. Whereas flow is largely absent at end-diastole in the more distal segments of the peripheral arteries, substantial flow may continue throughout diastole at the aortic bifurcation, potentially resulting in a loss of arterial contrast (Figure 5). Also, the technique is prone to misregistration artifact from patient motion, since the scan time for each 3D slab is on the order of minutes.

Flow-sensitive dephasing (FSD): Instead of a fast spin-echo readout, some investigators have explored using a bSSFP readout. As with subtractive 3D fast spin-echo, 3D slabs acquired at peak systole and end-diastole are subtracted. Dephasing gradients are applied along the vessel length to produce flow-dependent signal reductions and obtain arterial contrast between rapid systolic flow and slow diastolic flow (Figure 6) (48,49).

Arterial spin labeling (ASL): ASL is a subtraction method that is the non-contrast MRA equivalent of x-ray digital subtraction angiography (DSA). Two scans are acquired, in one of which RF pulses are applied to alter the longitudinal magnetization of inflowing arterial spins (50–54). Image subtraction eliminates the stationary background signal while enhancing the conspicuity of the labeled arterial spins. As with any subtractive technique care must be taken to avoid patient motion, which will otherwise result in misregistration artifact.

Although most commonly used for perfusion imaging in the brain, ASL-based techniques can also be used to create MR angiograms. ASL-based MRA is well suited to image vascular regions with rapid flow such as the extracranial carotid arteries (Figure 7), since the labeled spins can penetrate deeply into the imaging volume. Time-resolved cine implementations of ASL-based MRA have been used to depict collateral flow patterns in the circle of Willis as well as to tease out the blood supply and characterize the nidus of arterio-venous malformations (55).

4. Velocity-selective 3D MRA:

One of the key limitations of IFDIR and ASL-based 3D MRA techniques is their dependence on inflow. In the setting of slow flow, there will be insufficient penetration of labeled arterial spins into the imaging volume, so that only a portion of the target vessel will be visualized. Velocity-selective MRA avoids this limitation by applying a spatially non-selective magnetization preparation, consisting of a series of tailored RF and gradient pulses, in such a way as to preserve the signal from flowing arterial spins while suppressing the signal from stationary background tissue (56–58). With this approach, the entire length of a vessel can be shown so long as the velocity sensitivity is properly calibrated (Figure 8). A limitation of the method is its relatively sensitivity to B0 and B1 magnetic field inhomogeneity. For instance, the velocity profile shifts in proportion to the off-resonance frequency shift. Therefore, care must be taken to optimize both the shim and pulse sequence design to avoid image artifacts. Also, the technique may be ineffective in suppressing the signal from tissues that have a short T1 relaxation time, such as subacute hemorrhage.

5. Phase contrast

Two-dimensional cine phase contrast MRI was first described in the early days of MRI (59). It has proven invaluable for flow quantification and is particularly useful for functional evaluation in the cardiovascular system, e.g. for quantification of regurgitant volume and fraction in patients with valvular regurgitation, or of shunts in patients with congenital heart disease. With the introduction of more complex “4D” (i.e. 3D cine) phase contrast techniques (60), one can create MR angiograms that simultaneously display vessel anatomy and measure flow (Figure 9). Drawbacks of 4D phase contrast include relatively lengthy scan times and the need for complex image processing that can require hours of manual effort. Low SNR due to the use of a FLASH readout sometimes requires the infusion of a contrast agent, particularly to support small voxels or high levels of scan acceleration (61).

Level of Evidence for Non-contrast MRA

Estimates of evidence level provided in this section are based on the “Levels of Evidence” chart developed by the Center for Evidence-Based Medicine at the University of Oxford (62). In summary, conclusions of systematic reviews of high quality level 1 studies with good reference standards merit the highest evidence level of *1a*; validating cohort studies with good reference standards merit *1b*; systematic reviews of level >2 diagnostic studies merit *2a*; exploratory cohort studies with good reference standards merit *2b*; systematic reviews of level 3b or better studies *3a*; non-consecutive studies or studies without consistently applied reference standards *3b*; case control studies or studies with poor or non-

independent reference standards merit 4; and expert opinions or studies based on physiology, bench research or “first principles” merit the lowest evident level of 5. It should be noted that the level of evidence should not be interpreted as a recommendation of one diagnostic test over another.

1. Neurovascular MRA

The level of evidence for non-contrast TOF MRA in the diagnostic evaluation of neurovascular disease is high. The systematic review and meta-analysis of Debrey et al. (63) found that non-contrast TOF MRA of the extracranial carotid arteries provides an overall sensitivity of 91% and a specificity of 88% for the detection of 70% internal carotid arterial stenosis (evidence level 1a). However, the same meta-analysis reported that the sensitivity of TOF MRA for the detection of moderately severe 50–69% internal carotid artery stenosis was only 38%, with a specificity of 92% (evidence level 1a). In one large study evaluating 3D TOF at 1.5 Tesla for the diagnosis of 50% intracranial vascular stenosis, Korogi et al. (64) reported a sensitivity of 88% and specificity of 97% with respect to DSA (evidence level 1b). Another study done at 3.0 Tesla reported a sensitivity of $\approx 81\%$ and specificity of 95% (65) (evidence level 1b). In the diagnosis of intracranial aneurysms, a systematic review and meta-analysis (66) that predominantly included non-contrast TOF studies, found a pooled sensitivity of 95% and specificity of 89% (evidence level 1a). In the evaluation of 50–99% vertebral artery stenosis, a systematic review (67) encompassing two TOF studies (68,69) reported that TOF provides a sensitivity of 71% and a specificity of 95% with respect to DSA (evidence level 2a).

2. Thoracic MRA

The meta-analysis and systematic review of Di Leo et al. (70) reported that non-contrast coronary MRA using either a cardiac-gated 3D bSSFP or GRE imaging readout provides a sensitivity of 87% and specificity of 69%, with protocols providing whole-heart coverage being preferred over targeted protocols providing less spatial coverage (evidence level 1a). In two studies involving a total of 60 patients, free-breathing respiratory navigator-gated 3D bSSFP MRA provided diagnostic display of the pulmonary veins and ostial diameter measurements that were in good agreement with CEMRA (evidence level 2b) (28,71). In the detection of pulmonary emboli, Kluge et al. (72) reported that real-time 2D bSSFP-based MRA provides a sensitivity of 85% and specificity of 98% with respect to CTA (evidence level 1b). Cardiac-triggered navigator-gated 3D bSSFP MRA provides for diagnostic evaluation of the aorta, supra-aortic vessels, and cardiac chambers with diagnostic image quality (evidence level 1b) and provides measurements of aortic diameter that agree well with CEMRA (evidence level 1b) (29,73).

3. Abdominal MRA

The main application of IFDIR has been for the evaluation of the renal arteries. For the detection of 50% renal artery stenosis, 11 studies applying IFDIR at 1.5 Tesla in a total of 527 patients have reported a median sensitivity of $\approx 88\%$ and a median specificity of $\approx 95\%$ with respect to either CEMRA, DSA or CTA as the reference standard examination (evidence level 1b) (37–39,74–81). Other applications of IFDIR include the evaluation of celiac trunk stenosis, for which Braidly et al. (77) found a sensitivity of 100% and specificity

of 97% (evidence level 1b) with respect to CEMRA. Using CTA as the reference standard, Cardia et al. (82) reported that IFDIR provides accuracies of 89% and 95% for the diagnosis of celiac trunk stenosis and superior mesenteric artery stenosis, respectively (evidence level 1b). IFDIR has also been applied for portraying the portal veins (83–85) and hepatic arteries (86,87). In portraying the portal veins, further work is needed to validate IFDIR against reference standard examinations (evidence level 5). Tsuge et al. (87) evaluated IFDIR in a cohort of hepatocellular carcinoma patients undergoing transcatheter arterial chemoembolization and found anatomical agreement with DSA for the visualization of hepatic arterial branches; however, the approach was not evaluated for the diagnosis of steno-occlusive disease (evidence level 1b).

4. Lower Extremity MRA

QISS MRA has primarily been used to detect 50% arterial stenosis in the lower extremities (infrarenal aorta through ankle). In nine studies that included a total of 254 patients and used CEMRA as the reference standard examination, QISS provided a median sensitivity of $\approx 89\%$ and a median specificity of $\approx 96\%$ (evidence level 1b) (40,88–95). In eight studies with reference to DSA as the gold standard (154 total patients), median values for the sensitivity and specificity of QISS have been $\approx 91\%$ and $\approx 96\%$, respectively (evidence level 1b) (40,88,93,96–99). Using either CEMRA or DSA as the reference standard, the median diagnostic sensitivity and specificity values of QISS at 1.5 Tesla (174 total patients) are 89% and 96%, respectively (88,89,94,95,97,99); corresponding values at 3.0 Tesla (193 total patients) are 92% and 96%, respectively (40,90–93,96,98) (evidence level 1b).

In eight studies of the lower extremities (four of which limited to the calf or foot) involving a total of 238 patients using either CEMRA (7 studies) or CTA (1 study) as the reference standard exam, cardiac-gated subtractive non-contrast MRA using a fast spin-echo based readout provided a median sensitivity of $\approx 86\%$, and a median specificity of $\approx 86\%$ for the detection of 50% stenosis (evidence level 1b) (45,47,92,94,100–103). However, three other studies involving a total of 75 patients have reported poor image quality and a high rate of non-diagnostic vessel segments (97,104,105).

FSD MRA has primarily been applied for imaging arterial disease of the calf and foot. Across eight studies involving a total of 224 patients, the FSD technique provided a median sensitivity of 87% and a median specificity of 93% for the diagnosis of 50% arterial stenosis in the calf and foot (evidence level 1b) (49,103,106–111).

New Developments

1. Radial QISS:

Both CEMRA and non-contrast MRA are routinely acquired using a Cartesian k-space trajectory. Compared with Cartesian, radial k-space trajectories oversample the center of k-space, which has the benefit of reducing flow and motion artifacts (112). Unlike the case with Cartesian sampling, where acquiring fewer views (phase-encoding steps) to accelerate the scan reduces spatial resolution in a linear manner along the phase-encoding direction, spatial resolution is largely maintained with radial sampling when fewer views are acquired

(113). The preservation of spatial resolution despite the use of high radial undersampling factors provides a great deal of flexibility with respect to temporal resolution. For instance, using a radial acquisition with a view angle increment that pseudo-randomly samples k-space (e.g. with the use of a golden angle increment $\approx 111.25^\circ$), the data can be retrospectively sorted (“binned”) to create a series of undersampled images with nearly arbitrary temporal resolution for various applications such as time-resolved MRA, perfusion or cine imaging (114–117).

There are several potential drawbacks of radial imaging as well (118). High degrees of radial undersampling result in streak artifact and reduced SNR. Radial scans are more sensitive to off-resonance effects than Cartesian ones and require careful shimming. Slight gradient timing delays and eddy currents that are of no consequence for Cartesian k-space trajectories can cause blurring with radial acquisitions, which may require the use of a k-space trajectory correction (119). Advanced scan acceleration techniques are widely available for Cartesian k-space trajectories but much less so for radial ones; the latter also tend to be more computationally intensive (120).

Single-shot radial QISS acquisitions can be used for efficient breath-hold imaging of the aorta and pulmonary vessels (121). Other potential applications include the evaluation of suspected pulmonary embolism (Figure 10) and depiction of the pulmonary veins for guidance of pulmonary vein isolation procedures. Using multiple shots to improve temporal resolution, radial QISS has shown promise for breath-hold imaging of the coronary arteries (122). Additionally, one can use a multi-shot QISS sequence with a fast-low angle shot (FLASH) readout for peripheral or carotid MRA. For peripheral MRA, the FLASH readout substantially reduces off-resonance artifacts from air-containing bowel loops or hip prostheses (Figure 11), while the multi-shot radial k-space trajectory provides immunity to respiratory artifact for free-breathing acquisitions (Figure 12). For multi-shot QISS FLASH MRA of the carotid arteries (123), a radial k-space trajectory reduces sensitivity to respiratory and swallowing motion and is sufficiently resistant to flow artifacts that cardiac gating is unnecessary (Figure 13). Further improvements in carotid image quality can be obtained through the use of navigator techniques to correct for swallowing and other kinds of motion (124).

2. FISS:

Fast interrupted steady-state (FISS) is a newly-described radial bSSFP pulse sequence where the bSSFP echo train is frequently interrupted and the in-plane steady-state transverse magnetization is periodically stored along the z-axis (125). Moreover, magnetization that has accrued additional phase from various sources such as flow and off-resonance is spoiled. FISS differs from bSSFP in strongly suppressing fat signal when an appropriate echo spacing is selected. The technique also suppresses artifacts from through-plane and out-of-slice flowing spins, as well as those due to off-resonance effects. Cine FISS provides better suppression of flow artifacts in the heart than cine bSSFP, which is particularly noticeable for thin-slice acquisitions, and it greatly reduces the signal intensity of subcutaneous and pericardial fat.

A stack-of-stars implementation of FISS can be used to image a vessel along its length without the flow saturation-related artifacts encountered with TOF scans due to the FLASH readout. Moreover, it provides a high degree of background suppression because fat and muscle both have low signal intensity with this pulse sequence. Stack-of-stars FISS can be used to image the extracranial carotid bifurcation in less than 30 seconds (Figure 14), while a breath-hold implementation permits the depiction of the renal arteries (126) and other abdominal vessels with image quality that can rival or exceed that from much lengthier navigator-gated IFDIR MRA (Figure 15A-D).

Another emerging application of FISS is for the evaluation of blood flow (127), providing a potential alternative to phase contrast. For this purpose, FISS is used as the readout for a high-temporal-resolution cine ASL scan. The scan can be acquired within a single breath-hold for imaging of the chest or abdominal vessels. Viewing the images in cine mode provides a qualitative display of flow patterns (Figure 15E), while one can obtain an accurate measurement of flow velocity by dividing the frame-to-frame displacement of a labeled arterial bolus by the frame duration. Cine FISS ASL may be particularly advantageous for evaluating in-plane flow given that: (1) flow saturation is minimal due to the use of a FISS rather than FLASH readout; (2) the labeled spins remain visible over the entire duration of the cardiac cycle; and (3) the labeled spins remain conspicuous even when the slice is substantially thicker than the arterial diameter, allowing a semi-projective display of long lengths of the vessel. By comparison, 2D cine PC cannot be used to measure in-plane flow when the slice is thicker than the arterial diameter due to partial volume averaging of flow-induced phase shifts with those from stationary background tissue.

3. Ultra-Short Echo Time (UTE) MRA and Silent Scanning:

Non-contrast MRA using ultra-short echo times ($<100 \mu\text{sec}$) can be accomplished using specialized imaging techniques such as 3D radial (128) or Pointwise Encoding Time Reduction With Radial Acquisition (PETRA) (129). With 3D radial MRA, for instance, the UTE is obtained by applying a short duration, spatially non-selective hard pulse for RF excitation, simultaneous gradient ramping and data acquisition, and sampling with half radial projections. Potential benefits of UTE MRA include reduction of flow artifacts related to rapid, turbulent flow and off-resonance artifacts from metallic implants (130). Another virtue of certain UTE MRA techniques like PETRA is that the magnetic field gradients are much less active than with standard MRA techniques, which decreases acoustic noise and results in a so-called “silent” scan (131,132).

4. Compressed sensing:

Compressed sensing (CS) is a method for reconstructing images from highly undersampled data (133). A key requirement for CS is that the images are highly compressible or “sparse”. Given the high degree of background suppression and resultant sparsity intrinsic to non-contrast MRA techniques, CS facilitates the use of very high acceleration factors for faster scanning regardless of coil hardware (134,135). For example, recent work has shown that CS can provide as much as an eight-fold reduction in scan time for 3D TOF MRA of the brain (136). CS can also be combined with parallel imaging techniques for even higher acceleration factors (137).

5. Simultaneous multi-slice (SMS):

It is possible to image multiple slices simultaneously using SMS techniques, thereby reducing scan time in proportion to the number of simultaneously excited slices (138). Considerable progress has already been made for brain, spine and musculoskeletal applications. SMS could theoretically be used to obtain a two-fold or greater reduction in scan time for non-contrast MRA techniques such as 2D TOF or QISS without any significant loss of SNR. However, the use of SMS for non-contrast MRA presents some unique technical challenges. For instance, the usual approach of using tracking saturation RF pulses for venous suppression in peripheral non-contrast MRA becomes complicated when multiple slices are excited simultaneously, since the tracking sat pulse for one slice may inadvertently suppress arterial signal in a simultaneously-excited downstream slice.

6. Deep learning:

Deep learning is a form of artificial intelligence which allows computer-based neural networks, once trained with large amounts of image data, to perform certain image processing tasks much faster and potentially more accurately than would be possible using conventional computational approaches (139). For instance, deep learning can be used to accelerate MRA (140) with orders-of-magnitude shorter reconstruction times than is possible using iterative approaches such as compressed sensing. There is little doubt that deep learning techniques will eventually come into widespread use for MRA on the reconstruction and diagnostic fronts (141,142), but the need to obtain large amounts of well-curated, high-quality patient images for training purposes remains a significant obstacle.

In conclusion, non-contrast MRA has advanced greatly in the last few years. It offers several benefits over CEMRA and CTA, including the elimination of risk and cost associated with contrast administration and the ability to repeat a scan that has been rendered non-diagnostic due to patient motion or technical difficulty. Some drawbacks remain relative to CEMRA including dependence on flow directionality, sensitivity to off-resonance effects, and longer scan times. In addition, non-contrast MRA techniques are not yet as standardized across scanner platforms nor as well validated as CEMRA.

While further progress is needed, non-contrast MRA can already rival CEMRA and CTA with respect to image quality and diagnostic accuracy. As a result, there are several clinical scenarios (e.g. PAD, extracranial carotid and renal artery stenosis) where it might be reasonable to hold contrast agents in reserve, only to be used on an “as needed” basis depending on the outcome of an initial non-contrast MRA exam. Moreover, combining the structural information from “anatomical” non-contrast MRA with the hemodynamical information from cine PC or cine ASL could prove particularly helpful in determining prognosis and guiding the choice between medical therapy and revascularization.

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1.
Diabetic patient with PAD. A) CTA. B) Non-contrast MRA acquired using the quiescent interval slice-selective (QISS) technique. QISS MRA shows a lengthy left superficial femoral artery occlusion (arrows) as well as severe stenoses in the mid-portion of the right superficial femoral artery that are obscured in the CTA due to extensive vascular calcifications. C) There is excellent correspondence between the calcifications as demonstrated by proton density-weighted in-phase stack-of-stars MRI (bottom, minimum intensity projection with inverted display) and CTA (top, maximum intensity projection).

2.
Abdominal aorta aneurysm. CEMRA (left) shows poor opacification of the pelvic arteries due to hold-up of the contrast agent by recirculation within the aneurysm sac. The pelvic vessels are well demonstrated by non-contrast MRA using QISS (right).

3.

51-year-old male with history of elevated cholesterol and triglycerides presented with the new onset of right calf claudication. Right calf ankle-brachial index (ABI) was diminished (0.75). Left) Time-resolved CEMRA shows uncomplicated multi-focal stenosis (arrows) of the distal right superficial femoral artery which could be ascribed to PAD. Middle) High-resolution QISS MRA shows improved sharpness compared with the CEMRA and reveals a region of mildly increased signal intensity (arrows) adjoining the stenotic area suggestive of intramural hematoma. Right) Fat-saturated T1-weighted spin-echo confirms the presence of hemorrhage and, in conjunction with the QISS MRA, revealed the diagnosis to be cystic adventitial disease instead of PAD.

4.
70-year-old male with numbness of the left leg and ABI of 0.84. Left) Cardiac-gated subtractive 3D fast spin-echo MRA shows excellent image quality over the entire length of the lower extremities. Middle) Magnified view of the pelvic vessels as shown by the non-contrast MRA demonstrates a severe stenosis (arrow) of the distal left common iliac artery, which is confirmed by digital subtraction angiography (right). Images courtesy of Mr. Takashi Okigawa, Saiseikai Kumamoto Hospital, Japan.

5. Comparison of CEMRA (left) with cardiac-gated subtractive 3D fast spin-echo MRA (right). Both techniques demonstrate extensive vascular occlusions involving the right external iliac, common femoral and proximal superficial femoral arteries. The non-contrast MRA additionally shows artifactual signal voids in the region of the aortic bifurcation likely caused by flow-related dephasing during diastole and motion artifact from breathing; there is also blurring of the arteries in the left thigh due to leg motion.

6. CEMRA (left) and FSD MRA (right) MIP images of the calf arteries in a 63-year-old man with diabetes. On CEMRA images, left calf arterial segments are non-diagnostic due to severe venous contamination. On FSD MRA images, multiple significant stenoses (arrow) were depicted in the right anterior tibial artery, which are consistent with the findings on CEMRA images. Reprinted with permission from (107).

7.
Hybrid ASL 3D MRA of the neurovascular circulation. Left) Illustration of a hybrid ASL tagging scheme which entails a combination of a single pulsed inversion RF label (thick gray rectangle) and pseudo-continuous inversion label (consisting of multiple low-flip-angle RF pulses, narrow gray band) to invert the longitudinal magnetization of inflowing arterial spins. A radial 3D bSSFP sequence was used as the readout. Right) Subtraction of tagged from untagged images using a three-station protocol shows the carotid and vertebral arteries from their origins to the circle of Willis with nearly complete elimination of background and venous signals.

8. Comparison of velocity-selective inversion recovery (VSIR) versus IFDIR 3D MRA for imaging of the abdominal aorta. a) VSIR 3D MRA with a TI of 700 msec results in excellent arterial visualization throughout the entire field of view. b) IFDIR 3D MRA with the same TI results in limited evaluation of the abdominal aorta due to insufficient arterial inflow, while an increased TI of 1200 ms (c) moderately increases the visualized length of the aorta at the cost of decreased SNR. Reprinted with permission from (57).

9.

4D phase contrast MRI in a 60-year-old female patient after repair for aortic coarctation. A) Representative 4D flow MRI imaging data (time-resolved 3D anatomic magnitude images and phase contrast images representing three-directional velocity encoding). B) MIP of 4D flow-derived 3D phase contrast angiogram (3D PC-MRA) in sagittal oblique orientation demonstrating severe narrowing in the descending aorta at the site of the coarctation repair and onset of post-stenotic aortic dilatation. C) Systolic 3D streamlines depict the development of a flow jet with significantly elevated velocities (red color) at and distal to the site of the coarctation. Post-stenotic flow jet impingement on the aorta wall is accompanied by adjacent flow derangement (helix and vortex flow) indicating altered wall shear forces as a potential mechanism for aortic wall remodeling and development of aortic dilatation. AAo: ascending aorta, DAo: descending aorta, PA: pulmonary artery.

10. 68-year-old male, who presented with history of atrial fibrillation, mitral valve replacement, and shortness of breath, underwent cardiac MRI for suspected non-ischemic cardiomyopathy. Left) Coronal single-shot radial QISS demonstrated multiple unsuspected pulmonary emboli (arrows), which were subsequently confirmed by CTA (right).

11.
82-year-old male with PAD and multiple metallic implants. A) CT scout shows fixation pins in right hip and right total knee replacement. B) CTA is insufficiently diagnostic due to extensive calcifications of the right leg arteries. C) QISS using a bSSFP readout is non-diagnostic due to off-resonance artifacts from the implants. D) QISS using a FLASH readout better suppresses the off-resonance artifacts and unambiguously demonstrates diffuse narrowing of the right common and external iliac arteries as well as occlusive disease of the right superficial femoral artery.

12.

Impact of k-space trajectory on motion artifacts for QISS MRA. Imaging was performed at 3 Tesla. Left) QISS MRA of the abdomen and pelvis using fat saturation and a single-shot Cartesian bSSFP readout (echo spacing = 3.9 msec, flip angle ≈ 90 degrees). The upper pelvis and abdomen were imaged over six breath-holds with ≈ 14 slices acquired in each breath-hold. Middle) QISS with a three-shot Cartesian FLASH readout and free-breathing shows extensive artifacts representing ghosts from moving subcutaneous fat. Right) QISS with a three-shot radial FLASH readout (echo spacing = 10.1 msec, flip angle = 25 degrees) shows no motion artifacts and provides excellent depiction of the vessel anatomy. Note that fat saturation is less effective with a FLASH readout than with bSSFP. Therefore, an out-of-phase echo time (3.69 msec at 3 Tesla) was used to reduce the signal intensity from fat.

13. Healthy subject. Comparison of neck MRA using 2D TOF (left) and ungated QISS MRA (right, two-shot radial FLASH readout) each acquired in approximately 4 minutes. Ungated QISS FLASH provided greater head-to-foot coverage without saturation-related signal loss in the horizontal segment of the vertebral arteries or stair-step artifacts from breathing and swallowing seen with 2D TOF.

14. Comparison of MIPs from axial 2D TOF MRA of the neck (left) acquired in 3 min 53 sec and oblique sagittal stack-of-stars FISS (right) acquired in 27 sec. 2D TOF shows saturation-related recirculation artifact in the carotid bulb and motion artifacts not seen with the much shorter 3D FISS acquisition.

15.

67-year-old female with PAD and right renal artery stenosis. A) CTA. B) MIP from free-breathing IFDIR 3D MRA acquired in 2 minutes 49 seconds nicely shows the right renal artery stenosis and normal left renal artery. C) Breath-hold 2D radial QISS. D) Breath-hold stack-of-stars FISS acquired in 15 seconds shows the renal arteries comparably to the lengthier free-breathing IFDIR scan, but with increased sharpness due to the lack of respiratory motion. Compared with 2D radial QISS, stack-of-stars FISS better defines the renal artery stenosis due to the more rectangular profile of the 3D partitions compared with the sinc-shaped 2D slices. E) Breath-hold cine FISS ASL (slice thickness = 12-mm, frame rate = 12.2 msec, 12 frames shown of 64 acquired) with pulsed RF inversion labeling of the abdominal aorta. There is smooth progress of the labeled arterial spins through the stenosis without evidence of turbulence, suggesting that the lesion is only of moderate severity and not hemodynamically significant.

Table 1.

Summary of Non-Contrast MRA Techniques and Applications

Type	Generic Name	Vendor-Specific Names/Acronyms ¹	Primary MRA Applications	Acquisition Time ²	Physiologic Gating
Flow-Independent	Balanced steady-state free precession (bSSFP)	True SSFP / FFE 3D (Canon) FIESTA (GE) Balanced SARGE (Hitachi) Balanced FFE (Philips) TrueFISP (Siemens)	coronary, great vessels, renal	≈5 minutes (free-breathing)≈20 seconds (breath-hold)	cardiac gating ³ respiratory gating
	Time-of-Flight (TOF)	TOF (all vendors)	carotid, brain	≈5 minutes	–
Non-Subtractive Inflow-Dependent	Inflow-Dependent Inversion Recovery (IFDIR)	Time-SLIP (Canon) Inhance Inflow IR (GE) VASC-ASL (Hitachi) b-TRANCE (Philips) NATIVE TrueFISP (Siemens)	renal, abdominal	≈5 minutes	respiratory gating ⁴ cardiac gating
	Quiescent Interval Slice-Selective (QISS)	QISS (Siemens)	lower extremities	≈7 minutes	cardiac gating
Subtractive 3D MRA	Cardiac-Gated 3D Fast Spin-Echo	Fresh Blood Imaging (Canon) Inhance 3D Deltaflow (GE) VASC-FSE (Hitachi) TRANCE (Philips) NATIVE SPACE (Siemens)	lower extremities	≈12 minutes	cardiac gating
	Flow Sensitive Dephasing (FSD) ⁵	–	calf, feet	≈ 5 minutes	cardiac gating
	Arterial Spin Labeling (ASL) ⁶	ASL MRA / mASTAR (Canon) Silent MRA (GE) VASL-ASL (Hitachi) 4D-TRANCE (Philips)	carotid, brain	≈ 5 minutes	–
Phase Contrast (PC)	2D/3D Phase Contrast	Phase Shift (PS) (Canon) Inhance Velocity (GE) Phase Contrast (Hitachi) Phase Contrast (Philips) Phase Contrast (Siemens)	heart, great vessels, brain, renal	varies greatly depending on implementation	cardiac gating ⁷ respiratory gating ³
	4D Phase Contrast	ViosWorks (GE)	heart, great vessels	8–20 minutes	cardiac gating ³ respiratory gating
Velocity-Selective 3D MRA	Velocity Selective ⁵	–	renal, abdominal	≈ 5 minutes	cardiac gating respiratory gating

¹ contact vendor for most current information

² excludes time for shimming

³ needed for free-breathing imaging of chest or abdomen

⁴ needed for some implementations

⁵ not commercially available

⁶ for angiographic (not perfusion) applications

low pulsatile flow
for vessels with high pulsatile flow

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