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Expanding role of MR angiography in clinical practice

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Abstract MRA has higher accuracy, less operator dependence, a larger field-of-view, three-dimensionality and superior contrast resolution than ultrasonography. Additionally, MRA offers a safer alternative to the patient than CTA as neither ionizing radiation nor iodinated contrast agents are used.

Contrast-enhanced MRA with extra cellular contrast agents is fast and flow-independent, offers substantially higher spatial and temporal resolution compared to non-contrast techniques and has become the standard of practice. The highly accurate but static anatomical road-map thus generated can be supplemented with time-resolved MRA and blood flow measurement techniques for a more comprehensive assessment of systemic vascular disease.

In the context of burgeoning technological advances with rapid translation into clinical MRA practice, this review explores the current position of MRA and the potential role for the new and exciting blood-pool contrast agents for diagnosing and characterizing vascular disease.

Blood-pool agents offer the potential to take MRA to the next level by combining first-pass arterial phase imaging with steady state high-resolution images that exploit the persistent high intravascular enhancement generated by blood-pool agents and which is significantly greater than with extra cellular agents. Additional benefits derive from the ability to characterize plaque and to detect internal bleeding.

These advantages place MRA in a prime position to comprehensively and non-invasively evaluate both vascular anatomy and function with anticipated further expansion into more and more clinical applications.

Keywords MRA · Gadolinium · Contrast agent · Atherosclerosis · Gadofosveset trisodium

Introduction

Diagnosis and management of vascular disease are being revolutionized by the rapid pace of technical advances in non-invasive vascular imaging, particularly MR angiography. Patients with suspected vascular disease require accurate demonstration of vessel patency and luminal contours with sufficient resolution to grade the severity of stenosis and characterize surface features including ulceration and mural irregularity. Ideally, a non-invasive modality should provide information about inflow to the organ under study in addition to haemodynamic significance of any lesions detected. This may include flow measurements or detection of turbulent flow jets with 2-D or 3-D phase contrast imaging, and determination of end organ size and perfusion with static imaging or time-resolved MRA. Imaging of the vessel wall is important in patients with vasculitis and is likely to be increasingly important for other conditions as we learn more about the biology of vascular diseases. A review of medical in-

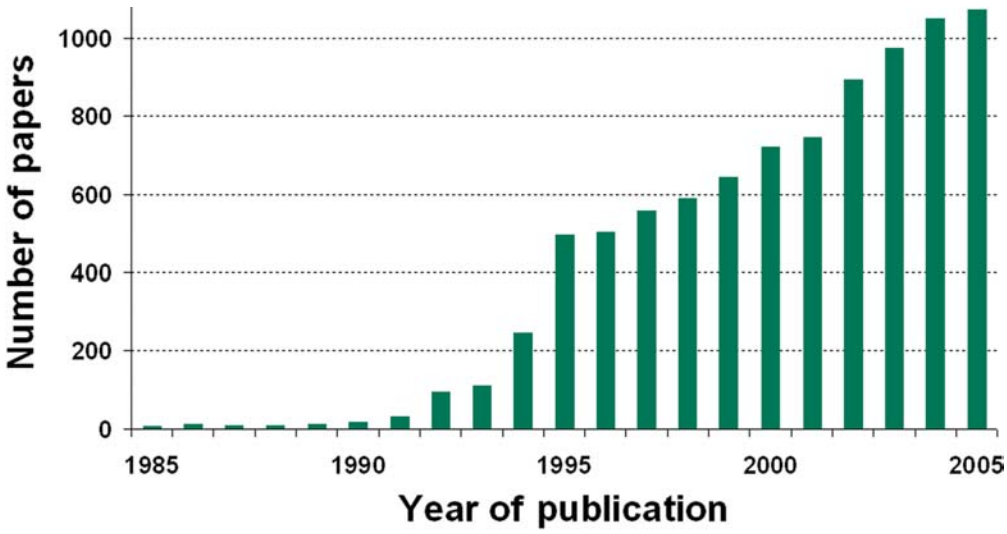

Fig. 1 Number of publications on MRA listed in index medicus each calendar year

dexes, using MRA as a keyword, reveals a continuing increase in the annual rate of publications on this topic (Fig. 1). This emphasizes the growing role of MRA in clinical practice as compared to other imaging modalities based on recognition that diagnosing vascular disease and road-mapping no longer depends upon catheter angiography, exposure to ionizing radiation or use of iodinated contrast agents.

MRA surpasses ultrasound

Compared to duplex sonography, MRA is more accurate, 3-dimensional, less operator-dependent, has a larger field-of-view and superior contrast resolution. Like ultrasound, MR can measure flow rates through vessels and additionally can evaluate the vessel wall for thrombus, plaque and plaque haemorrhage. Although MRA is more expensive and less readily available than ultrasound, the added information provided by MR has resulted in its widespread utilization as the modality of choice for a variety of vascular disorders. In fact, numerous comparative studies with DSA have established MRA as a robust, reproducible technique, the de-facto standard in most institutions where it is available for diagnosis and treatment planning of most vascular disorders. At medical centres with MRA expertise, sonography has been relegated to the role of a screening examination for many indications.

MRA is safer than CTA

MRA has three enormous advantages over CTA: elimination of ionizing radiation and iodinated contrast and more functional information with time-resolved MRA and blood-flow measurements. Although CTA offers, in many instances, anatomic information similar to MRA at higher resolution with greater ease of use, its ease of performance does not outweigh safety concerns. A growing number of reports indicate that even low doses of radiation may have associated risk .

A significant improvement in diagnostic quality of angiograms (DSA, CTA and MRA) can be achieved by elimination of "background" (bone and calcium in the case of X-ray techniques and subcutaneous and bone marrow fat in the case of MRA). For DSA, subtraction of a precontrast mask effectively eliminates interfering bony detail. Mask subtraction would also benefit CTA by addressing the issue of obscuration of vascular segments by adjacent bone and also would allow clear differentiation of the vividly enhancing vessel lumen from mural calcification. However, attempts at mask subtraction for CTA have been suboptimal and lead to doubling radiation exposure.

Table 1 Risks of ionizing radiation exposure

Journal	*Year*	*Findings*
Spine [3]	2000	Women with scoliosis have 3x risk of breast CA due to spine X-rays
AJR [10]	2001	600 000 pediatric CT scans/year will cause 500 cancer deaths
Lancet [6]	2004	700 of 124 000 cancers diagnosed annually are due to diagnostic X-rays
BMJ [4]	2004	Low-dose radiation to the brain in infancy influences cognitive abilities in adulthood
AJR [9]	2005	Increased risk of breast cancer from chest CTA for pulmonary embolism
NAS [1]	2005	BEIR VII reports indicate a dose of 10 mSv caused a 1 in 1000 risk of cancer

In the majority of vascular territories (e.g. renal, mesenteric, coronary, carotid and peripheral vasculature) mural calcification degrades CTA image quality. The signal void of calcium on all MR sequences is another advantage of MRA over CTA, as the presence of mural calcium does not impair visualization of the lumen. Occasionally, this advantage may be outweighed by the requirement to visualize calcium remote from the contrast-enhanced lumen, e.g. in patients with abdominal aortic aneurysms or densely calcified iliac arteries which may interfere with stent graft deployment.

Although the relative merits and demerits of calcium visualization within the wall on CT and MR can be disputed, there is little doubt that MR is the most likely potential imaging candidate to visualize the different components of plaque within the wall, in particular "unstable" plaque that may be at risk of intraplaque haemorrhage. Currently, multi-contrast MR at isotropic high spatial resolution (200 μm) shows promise, and both standard and targeted contrast agents can provide additional information about plaque composition.

Another method for improving the quality of angiograms is by performing multiple acquisitions in rapid succession to facilitate visualization of different vessels within the region of interest. Multiple acquisitions for time-resolved imaging (analogous to the time-resolved images produced by conventional angiography) can be acquired without penalty for MRA to maximize depiction of all segments. This also provides physiological information about the rate of blood flow through the arteries of interest and gives an indication of end-organ perfusion.

Currently, CTA may offer a speed advantage over MRA when acquiring a single dataset. However, differences in the manner in which MR data are acquired and reconstructed offer great flexibility and can be exploited to improve MRA image quality, highlight different phases and generate time-resolved images. Specifically, arterial phase images can be acquired at high resolution using a scan duration that greatly exceeds the arteriovenous transit time provided central k-space data are acquired during the arterial peak and prior to onset of venous enhancement. This feature is optimally exploited in association with fluoroscopic bolus detection (MR fluoroscopy), where visualization of contrast agents in real time allows for perfect contrast agent bolus timing. The unique features of k-space also allow updating of different portions of k-space during successive acquisitions. Using this approach, images with both high temporal and high spatial resolution can be acquired using keyhole, k-t Blast, TRICKS, radial or spiral approaches [11-21]. Improved temporal and spatial resolution utilizing a combination of improved gradient speed, novel k-space filling approaches, parallel imaging, undersampling and sliding window reconstruction is sometimes referred to as 4-D imaging.

Although 2-D fluoroscopy typically is used at low resolution to visualize contrast arrival and thus signal the requirement to initiate the 3-D scan, the same approach (usually at higher resolution) can be used to generate diagnostic quality 2-D angiograms, an approach referred to as MRDSA [22]. This approach is useful for visualization of the infrapopliteal arteries in patients with peripheral vascular disease prior to a two- or three-station peripheral MRA, and for demonstrating transit times through the different stations of a multilocation peripheral MRA. A low-dose time-resolved MRA serves as a test bolus for optimal tailoring of the 3-D scan duration and central k-space timing for each station of the bolus chase acquisition. High-speed 2-D projection MRA has also been used at very high temporal resolution to image coronary arteries [23]. Since the contrast dose required for time-resolved MRA is low (typically 6 ml), an approach similar to DSA, where the acquisition can be repeated multiple times, can be used.

Why is intravenous contrast agent injection important?

As MR angiography can be performed utilizing black blood techniques (which rely upon blood flow to eliminate intravascular signal) and bright blood techniques (time-of-flight, phase contrast and steady-state free precession), it begs the question, why use intravenous contrast? Although the physical basis of these techniques is well understood, and despite satisfactory validation for at least some clinical indications, the techniques are sensitive to flow effects, in-plane saturation and field inhomogeneity. Also, scan times are long and even when performed with meticulous technique in a co-operative patient, images are prone to artefacts and thus they have had a limited impact on clinical practice for many vascular territories. On the other hand, contrast-enhanced MRA is fast, avoids saturation effects, is flow-independent and offers substantially higher spatial and temporal resolution compared to non-contrast techniques [24]. Contrast-enhanced MRA builds on the time-honoured technique of injecting contrast in order to opacify a vessel and portrays images in a familiar format easily understood by referring physicians for clinical decision-making. Intravascular signal depends on exogenous (e.g. gadolinium-based) rather than endogenous (e.g. time-of-flight effect) contrast mechanisms. One huge advantage of contrast-enhanced MRA is that the usual loss of SNR from faster scanning with most MR pulse sequences can be compensated for by injecting the same dose of contrast faster over a shorter scan duration. In this way, faster scanning can attain higher-quality images with less motion artefact. Faster injections are becoming easier to perform with higher relaxivity contrast agents (e.g. Vasovist) and more concentrated contrast agents (e.g. 1.0 M agent, Gadovist).

With contrast MRA, the lag between arterial enhancement and onset of venous enhancement (the arteriovenous window) offers an opportunity for arterial phase imaging that shows only the arteries. When this selective arterial phase is too short, simple additional manoeuvers such as thigh compression with tourniquets inflated to a pressure intermediate between arterial and venous (e.g. 60 mm Hg) delays onset of venous enhancement in the last station of a single-injection, multistation peripheral or whole-body MRA. This can compensate for the fact that acquisition speed is still too slow to keep up with the bolus, and eliminates venous enhancement within the legs, one of the last remaining hurdles to routine implementation of peripheral and whole-body CE-MRA into clinical practice.

MR combines information from multiple sequences

A further benefit of MRA relates to the plethora of imaging approaches that can be used to supplement angiographic images. For example in renal MRA, an initial breath-hold single-shot fast spin echo T2-weighted sequence demonstrates the kidney and adrenal outlines, the size and presence of cysts or masses and the location of the aorta. In- and out-of-phase gradient echo imaging characterizes any adrenal masses that show signal drop-off on out-of-phase imaging as adenomas. Then a high-resolution contrast-enhanced 3-D MRA depicts arterial luminal anatomy, followed by venous anatomy in a subsequent acquisition and the ability to assess symmetry of renal perfusion and to infer renal function on equilibrium phase images. Alternatively, rapid repetition of the MRA or use of an interleaved sequence can yield enhancement curves for cortex, medulla and collecting system for assessment of Gd transit from glomeruli to tubules analogous to a renal scan. Finally, 3-D phase-contrast MRA can depict the significance of stenoses: complete signal drop-out in the region of the stenosis on 3-D PC MRA indicates a significant stenosis with a pressure gradient [25]. Another use of phase-contrast MRA, a 2-D cardiac-triggered cine PC MRA, can measure the blood flow to each kidney directly and also show flow waveform changes that demonstrate haemodynamic significance. In theory, the gadolinium clearance rate can be measured for each kidney [26]. All told, MR may image the kidneys with a half dozen sequences allowing assessment of both anatomical and functional aspects relevant to renal vascular disease.

An all-in-one approach within the brain offers unique information that can be gleaned only from MRI. Standard spin- and gradient-echo brain imaging, diffusion and perfusion imaging, time-of-flight MRA and contrast-enhanced MRA of the head and neck arteries are possible within an acceptable time slot (<30 min) for comprehensive evaluation of cerebrovascular disease. This will be increasingly important if thrombolytic therapy in acute stroke becomes established in widespread clinical practice.

Although MR protocols are typically organized by organ system, many diseases affect more than one organ or region of the body. Extended FOV imaging allows extension of imaging beyond the normal anatomical boundaries of individual organs and beyond the traditional constraints of a single MR scanner field of view. Ruehm et al. first reported imaging from base of skull to the pedal arch within a 72-s acquisition [27]. Schoenberg et al. reported a comprehensive evaluation in diabetic patients including intracerebral 3-D time-of-flight MRA for microvascular disease, total body Gd:MRA for large-vessel atherosclerosis, high-resolution post Gd T1 fat saturation of any ulcerating pedal lesions for osteomyelitis and finally viability imaging of the heart to detect delayed enhancement from myocardial infarction [28].

Other cardiovascular diseases that can benefit from imaging multiple organs or the whole body without concern for radiation exposure include atherosclerosis, vasculitis (e.g. Kawasaki's disease, Takayasu's arteritis or giant cell arteritis) and thrombo-embolic disease. The combination of pulmonary MRA and MR venography of the abdomen, pelvis and lower extremities is an alternative to the current pattern of pulmonary CTA and CT venography, especially for young patients and female patients who wish to avoid irradiation of breast tissue. Comprehensive evaluation of the pulmonary arteries along with evaluation of cardiac chamber morphology and function is also possible and useful in patients with pulmonary hypertension [29].

What is the role for blood-pool agents?

Considering the enormous success of extracellular contrast agents for CE-MRA, what is likely to be the role for blood pool agents? The answer probably lies in the key question: can blood-pool agents be used in first pass with equal effect? As the answer appears to be yes, this suggests that blood-pool agents can be used instead of the current extracellular agents for first-pass arterial imaging. The crucial advantage of blood-pool agents, namely the presence of persistent high intravascular enhancement significantly greater than with extracellular agents can be exploited to acquire additional high-resolution images in the steady state. It is proposed that the combination of first-pass arterial phase imaging with delayed steady-state imaging offers substantial benefit in clinical practice.

Venous mapping, e.g. in patients with recurrent venous thromboses and in patients likely to require long-term venous access, will benefit from these agents. Detection of pulmonary embolism may similarly benefit. A preferable approach might be to perform an initial evaluation of both lungs on first-pass or at equilibrium and to

supplement this information with extremely high-resolution images targeted to a particular segment during multiple repeat breath-hold acquisitions. Although both arteries and veins will enhance equally, selective arterial imaging is not a current goal of high-resolution pulmonary MRA due to the short arteriovenous transit time and regardless of whether extracellular or blood-pool contrast agent is used, arteries will be differentiated from veins by tracing them back to a central, easily identifiable proximal pulmonary artery.

Another obvious role for blood-pool agents lies in supplementing arterial phase images in patients with suspected or known vascular malformations with equilibrium phase images that will depict the full extent of all vascular anatomy to maximal effect.

Blood-pool agents also open up entirely new opportunities for investigating vascular conditions not easily studied with conventional agents. For example, Hilfiker et al. have demonstrated that surgically induced GI bleeding can be detected several hours after injection of blood-pool agents as the agent leaks into the bowel lumen [30]. This approach, similar in philosophy to a labelled red cell study, offers the advantage of higher resolution without any radiation risk. It shares the disadvantage that only the presence of bleeding, but not the exact source (which must be inferred from location of contrast agent within the bowel) can be identified. Similarly, detection of the source of bleeding in patients with haemoptysis, particularly those with bronchiectasis affecting many segments within one or both lungs, might be identified using a similar approach. Endovascular leak post-aortic aneurysm stent-graft repair can be detected by many imaging methods; however, subtle leaks will potentially be optimally detected with blood pool agent imaging [31].

Summary

MRA continues to expand rapidly and is ideally suited to imaging the growing burden of vascular disease on western society which requires improved and novel methods for non-invasive road-mapping and assessment of haemodynamic significance. Optimal MRA image quality with high temporal and spatial resolution can currently only be achieved using contrast agents. Blood-pool contrast agents are the first contrast agents targeted to a vascular indication and open up new horizons to improve image quality and answer clinical questions which cannot be addressed with conventional MR contrast agents. Safe, accurate mapping of vascular anatomy with MRA offers the opportunity to detect vascular disease rapidly and early in the course of the disease, while there is time to salvage end-organ function. It gives both anatomical and functional information and can image multiple fields of view for a more comprehensive assessment of systemic vascular disease.

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