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Contrast Agents: Innovations and Potential Applications for Body MR Angiography

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In 1985, Wedeen et al [1,2] described the ability of MR imaging to illustrate blood vessels by using flow-dependent techniques, methods now well known as time-of-flight MR angiography. It was not until the 1990s, however, with numerous innovations for the more reliable and robust method of contrast-enhanced (CE) MR angiography, that the use of MR imaging has become routine clinically for vascular diagnosis. Today a variety of gadolinium (Gd)-chelate contrast agents are commercially available in the United States for neurologic and body imaging applications, although none is approved yet by the Food and Drug Administration specifically for MR angiography. Although off-label, the use of contrast media for MR angiography [3,4] has been shown to be reliable, safe, and accurate in clinical practice [5–11] and in many centers has replaced more invasive x-ray catheter angiography as a primary standard for vascular diagnosis [12].

In its current implementation, CE MR angiography typically is performed using one of the commercially available extracellular Gd-chelate contrast agents with a three-dimensional (3D) fast spoiled gradient echo pulse sequence timed for contrast bolus filling of the target vasculature (Fig. 1). Vascular illustration on CE MR angiography is provided by the T1 shortening effects of Gd on blood. The preferential timing of 3D MR angiography data acquisition can be used to illustrate selectively the various arterial or venous phases of the contrast bolus. Arterial illustration is optimal during peak arterial enhancement, and venous illustration is optimal later during venous filling. Timing often can be difficult in patients with underlying cardiovascular diseases because their circulatory times (and contrast arrival times) may be variable. More recently, time-resolved imaging has afforded continuous dynamic viewing of arterial and venous bolus progression, which may be crucial for proper recognition of certain lesions [13]. The benefit of time-resolved MR angiography is the fact that dynamic imaging can be performed without the concerns of ionizing radiation exposure that are associated with x-ray-based studies, such as CT angiography and conventional x-ray angiography. Paralleling technologic improvements in MR angiography, numerous innovations in contrast agent development have occurred. These new investigational agents are in various phases of clinical development, but offer a variety of new opportunities for MR angiography. This article reviews some promising contrast agents and potential benefits for vascular imaging.

Contrast agents

As with other radiologic applications, a contrast agent not only must be safe, but also efficacious and cost-effective [14]. The key to the efficacy of an MR contrast agent is its ability to generate contrast-to-noise ratio (CNR), which, in the case of vascular imaging, is its ability to generate vessel-to-background CNR. One must not lose sight of the importance of tissue perfusion

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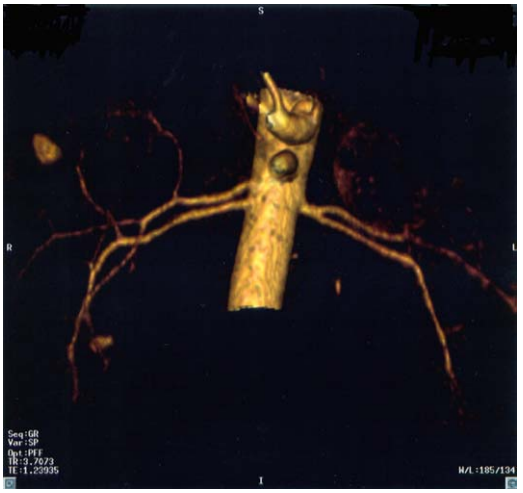

Fig. 1. High spatial resolution 3D CE MR angiography using 30 mL of Gd-DTPA. Arterial phase 3D CE MR angiography was optimized using MR fluoroscopic triggering and parallel imaging. The resulting volume-rendered view shows the accessory right renal artery and early bifurcation of the left renal artery in this otherwise normal individual. (Courtesy of William R. Corse, MD, Department of Radiology, Doylestown Hospital, Doylestown, PA.)

or tissue morphology, however, which in patients with vascular diseases may provide potentially complementary information. The additional finding of diminished end-organ perfusion may be crucial for determination of a vascular lesion's hemodynamic significance. More recently, tissue-specific contrast agents have been contemplated. These contrast agents target specific morphologic aspects of cardiovascular pathology, such as thrombus or atherosclerotic plaque. When considering potential contrast agents for MR angiography, one not only must consider the improvements in vascular signal, but also the benefits for various tissue-to-background CNR. This consideration is particularly important for the development of MR contrast agents, which often may be eclipsed by improvements in MR technology and changes in clinical therapeutic paradigms, which may make certain contrast applications obsolete. The efficacy of a contrast agent is highly dependent on the MR technique. The complexity of many cardiovascular diseases provides additional opportunities for novel implementations of various contrast agents into clinical practice.

The presence of contrast agents can provide improved CNR via two main mechanisms: proton density and molecular dipolar interactions of the ion complexes with water [15,16]. In general, contrast agents can affect T1 and T2, and these effects vary based on a variety of conditions, such as contrast dose, injection rates, vascular concentration, and field strength. CE MR angiography using conventional Gd-chelate contrast agents typically relies on the shortened T1 relaxation time of blood by the arrival of contrast media into the vascular bed [17].

The MR imaging pulse sequences used should be optimized for the specific contrast agent and its specific application. Paramagnetic contrast agents, such as the currently commercially available Gd-chelate contrast agents, are the most widely used contrast agents for CE MR angiography. Paramagnetic contrast agents have a relaxivity that predominately causes a shortened T1, or longitudinal relaxation effect [18]. The Gd ion has a high relaxivity owing to its magnetic dipolar interactions with water; however, its toxicity requires the Gd ion to be highly complexed to ensure elimination from the body [16,19]. Chelating the Gd ion makes it safer for humans, but may lower its potential relaxivity. Gd-chelate contrast agents must be designed carefully for patient safety, while maintaining the relaxivity benefits of the agent. Currently the extracellular Gd-chelates that tumble slowly have been showing a higher relaxivity than chelates that have a faster tumbling speed [19]. Size of the molecule also can be a factor in relaxivity of an agent. Rigid macromolecular paramagnetic complexes have a long 1/T1 time and result in high relaxivity [15,19].

The relaxivity of a compound depends on the compound's magnetic moment, electron spin relaxation time, and molecular interaction [15]. Gd-chelate contrast agents shorten T1 relaxation of blood, resulting in bright vascular signal on T1-weighted pulse sequences. Bright or positive enhancing agents have unpaired electrons that can be 18,000 times stronger than the hydrogen nucleus [15]. At low concentrations, paramagnetic agents are positive enhancers; however, at high concentrations, paramagnetic agents can cause significant T2* shortening effects, which can overpower the T1 contributions such that an actual decrease in vascular signal may be seen. Clinically, this T2* effect is seen most commonly as a result of a fast contrast injection rate (eg, >3 mL/sec), urinary concentration of Gd in the renal collecting system and bladder, or concentration of Gd in the central veins during the arterial phase imaging of a left antecubital venous injection [20].