Blood Pool Contrast Agents

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Synopsis

Blood pool (BP) agents are a new class of contrast agents that are designed to enhance the imaging properties of blood, and have considerably different pharmacokinetic and imaging characteristics than currently available agents. This talk reviews the different types of BP agents, and discusses the properties that allow them to enhance blood preferentially. The initial applications of BP agents will be described, including body MR angiography (MRA) and coronary angiography. In addition, applications are emerging that exploit the biodistribution, kinetics, or imaging characteristics of BP agents. These applications include tumor and angiogenesis imaging, imaging vessel inflammation, lymphangiography, and functional imaging.

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The vast majority of contrast agents used in MRI today have remarkably similar pharmacokinetic and imaging properties. When injected, they distribute rapidly (3-6 minutes) into the accessible extracellular space (ECS), and are cleared renally over a period of a few hours. Their predominant use is for enhancing the visualization of abnormal anatomy, especially CNS pathology, and are used in 1/4 – 1/3 of all MRI cases. Immediately upon injection (~1 min), ECS agents have recently found use in MR angiography in the "dynamic", or arterial phase [1]. However, the properties of ECS agents were not specifically tailored for MRA. Dynamic imaging of more than one vascular bed is technically challenging, and subject to the well-known trade-offs of acquisition time and image-quality in MRI. Furthermore, very high resolution imaging of vascular anatomy, high resolution images of plaques and the vessel wall appears limited by the too-rapid distribution of the ECS agents.

Blood pool agents attempt to overcome these limitations by extending vascular imaging window. Multiple new products are now in late-stage clinical trials or in registration with regulatory authorities in both the US and EU. In general, these agents extend the imaging window by slowing down the distribution of the agent into the extracellular space. Early blood pool agents were constructed by covalently binding Gd to large macromolecules, such as albumin [2] and to poly-L-lysine [3]. However, such agents are not practical clinically because of safety issues. Three broad classes of agents are currently being developed either by industry or academia for clinical use. The classes are: (a) small iron oxide particulates, (b) dendritic Gd-based synthetic molecules, and (c) Gd-based agents that reversibly bind to serum proteins. (Work on other, more exotic constructs, such as hyperpolarized gas-containing spheres, or Gd-coated liposomes continues as well, but these constructs are in earlier stage research.)

Iron Oxide Particles Superparmagnetic iron oxide particles (SPIOs) are currently used as T2-based imaging agents in the liver and spleen, and are being developed as well for lymph node imaging. When SPIOs are made even smaller, these agents have longer blood circulation time, and their ability to be used as T1 agents improves (e.g., [4],[5]). These agents leak very slowly, if at all, into the extracellular space, and are primarily cleared by RES cells.

Dendritic Molecules These gadolinium dendritic constructs (e.g., [6],[7]) typically have large effective hemodynamic size, and leak more slowly into the extracellular space than molecules with comparable molecular weights (~5000 D). They remain intravascular for a longer period of time than their ECS counter-parts, but are still cleared via the same, glomerular filtration mechanisms in the kidney. Because of their larger molecule size, relaxivity is enhanced 5-10 fold for these molecules compared to ECS agents.

Albumin-binding Molecules These are small molecule (<1000 D) modifications of existing ECS agents, which reversibly bind to serum protein molecules, primarily albumin (e.g., [8],[9]) When bound to albumin, relaxivity is also enhanced 5-10 fold compared to ECS agents, and leakage into the ECS is hindered by the binding as well. By tailoring the agent, these agents can be cleared either renally or through the liver.

All three classes of molecules can, with varying degrees of success, be bolused, and thus used in the same manor as conventional ECS agents for dynamic MRA. Since the BP agents typically have higher relaxivity, smaller volumes of agents may be used, facilitating more rapid imaging in some applications. However, the primary benefit of blood pool agents for MRA will likely be their flexibility for non-dynamic MRA. By lengthening the duration of vascular contrast, higher resolution and/or larger volume coverage is possible, reducing the technical challenges of dynamic MRA, and allowing the imaging of multiple vascular beds without the need for rapid, moving-table methods. Lower and mid-field ($\leq$ 0.5 T) systems may also benefit, both from the enhanced-relaxivity and increased imaging time of these classes of agents. To benefit fully from the longer imaging time, image processing and display algorithms are under development to facilitate the separation of arterial and venous views. BP agents also appear well suited to imaging of the inflamed vessel well, and improved delineation of soft plaques within the vessels. The use of BP agents is also being explored for high resolution coronary imaging, which still lags body angiography in its broader clinical application.

In addition to angiographic applications, the kinetics of BP agents are also well-suited to tumor and angiogenesis imaging. To the extent to which macromolecular transport is specifically deranged in cancer, BP agents may provide more specific imaging than their ECS counterparts. The slower distribution and transport of BP agents also has provided dramatic imaging of lymph vessels. Finally, the slower leakage of BP agents into the ECS makes them potentially attractive as perfusion and functional imaging agents.

References: [1] Prince et al., JMRI (1993) 3: 877-881; [2] Schmiedl et al., Radiology (1987) 162: 205-10; [3] Sieving et al., Bioconjug Chem (1990) 1:65-71; [4] Frank et al, Am J Roentgenol (1994)162:209-13; [5] Stillman et al., JCAT (1996) 20:51-5; [6] Dong et al., Invest Radiol (1998) 33:699-708; [7] Port et al., Invest Radiol (2001) 36:445-54; [8] Lauffer et al., Radiology (1998) 207:529-38; [9] Cavagna et al., Acad Radiol (2002) 9 Suppl 2: S491-4.