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Recent Advances in ^{19}Fluorine Magnetic Resonance Imaging with Perfluorocarbon Emulsions

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ABSTRACT The research roots of ^{19}fluorine (^{19}F) magnetic resonance imaging (MRI) date back over 35 years. Over that time span, ^{1}H imaging flourished and was adopted worldwide with an endless array of applications and imaging approaches, making magnetic resonance an indispensable pillar of biomedical diagnostic imaging. For many years during this timeframe, ^{19}F imaging research continued at a slow pace as the various attributes of the technique were explored. However, over the last decade and particularly the last several years, the pace and clinical relevance of ^{19}F imaging has exploded. In part, this is due to advances in MRI instrumentation, ^{19}F/^{1}H coil designs, and ultrafast pulse sequence development for both preclinical and clinical scanners. These achievements, coupled with interest in the molecular imaging of anatomy and physiology, and combined with a cadre of innovative agents, have brought the concept of ^{19}F into early clinical evaluation. In this review, we attempt to provide a slice of this rich history of research and development, with a particular focus on liquid perfluorocarbon compound-based agents.

KEYWORDS fluorine, magnetic resonance imaging (MRI), dual-tuned coil, perfluorocarbon, angiogenesis, cell labeling

1 Introduction

Although hydrogen-based (^{1}H) magnetic resonance imaging (MRI) predominates over the cadre of magnetic resonance (MR) techniques employed clinically, renewed interest in ^{19}fluorine (^{19}F) MRI continues to increase, particularly for molecular imaging applications using perfluorocarbons (PFCs) as a fluorine source. MR fluorine spectroscopy and imaging dates back to 1977, a time when human ^{1}H MRI was in its infancy [1]. Several investigators contributed to the early technical foundation of ^{19}F imaging [2–7].

1.1 Why ^{19}fluorine?

Interest in ^{19}F nuclei imaging reflects its potential as a quantitative MRI contrast agent. ^{19}F has 100% natural abundance, a spin of 1/2, and a gyromagnetic ratio of 40.08 MHz·T^{-1} (slightly lower than the 42.58 MHz·T^{-1} of ^{1}H), resulting in 83% of the sensitivity of ^{1}H [8, 9]. With seven outer-shell electrons, ^{19}F chemical shifts (CSs) are more sensitive to the local environment than ^{1}H with its single electron. Indeed, the spectroscopic signatures of ^{19}F compounds can vary over a range more than 200 ppm [10, 11], offering the potential for definitive identification of many compounds even at lower clinical field strengths. Although soft body tissues, which contain 55%–75% water, contribute a substantial mobile ^{1}H signal, fluorine is essentially absent from soft tissues and is only found immobilized in bones or teeth, where its very short spin-spin relaxation time (T2) renders ^{19}F virtually invisible to conventional MR techniques. ^{19}F MRI of high-density exogenous fluorine compounds accumulating at target sites offers high contrast-to-noise ratios (CNRs) and improved quantification potential. Furthermore, the negligible ^{19}F background obviates the use of the serial pre-/post-contrast image comparisons that are requisite for differentiating superparamagnetic (e.g., iron oxide) or paramagnetic metal (e.g., gadolinium) contrast from the background in most molecular imaging studies.

1.2 Perfluorocarbons (PFCs)

PFC nanoparticles are 98% PFC by volume, which for perfluorooctylbromide (PFOB, 1.98 g·mL^{-1}, 498 Daltons) equates to a fluorine concentration of approximately 100 mol·L^{-1} [12]. PFC nanoparticles are distinctly different from other oil-based emulsions by virtue of the physical-chemical properties of fluorine, the most electronegative of all elements, and the unique properties of C—F bonds [13]. The fluorine-substituted hydrogen in perfluorochemicals creates bulkier, stiffer compounds that typically adopt a helical conformation with the molecules chemically distinct but often closely intertwined [13]. The C—F bond is chemically and thermally stable and its dense electron cloud creates a barrier to encroachment by other chemical reagents, rendering it virtu-

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ally non-chemically reactive [13]. The resultant large surface area combined with the low polarizability of the fluorinated chains enhances hydrophobicity. Interestingly, PFCs are both hydrophobic and lipophobic!

The biocompatibility of liquid fluorocarbons is well documented in numerous preclinical animal studies. Even at large doses, most fluorocarbons are innocuous and physiologically inactive. No toxicity, carcinogenicity, mutagenicity, or teratogenicity effects have been reported for pure fluorocarbons within the 460–520 MW range. PFCs have tissue half-life residencies ranging from 4 days for PFOB up to 65 days for perfluorotripropylamine, and are not metabolized; rather, they are slowly reintroduced to the circulation in dissolved form by lipid carriers and expelled through the lungs. However, increased pulmonary residual volumes from expired PFC, which is denser than air, and reduced pulmonary compliance, is noted with blood-transfusion-level dosages, particularly with some early-generation PFC emulsions in rabbits, swine, and macaques, although not in mice, dogs, or humans [13–15]. Similarly, PFC nanoparticles are cleared through the monocyte-phagocyte system (MPS), previously referred to as the reticulo-endothelial system (RES). Repeated high dosages of PFCs by these cells can lead to the release of macrophage cytokines, resulting in flu-like symptoms [12]. Moreover, acute engorgement of the liver with PFC nanoparticles due to a large-volume infusion or repeated high-volume dosing can result in the transient physical compression of tissue with mild hepatocellular damage, resulting in reversible elevations in serum transaminases [16].

Furthermore, it must be recognized that in rodents, nanoparticles such as PFC nanoparticles can pass rapidly and directly into the biliary system, where they flow into the small intestine [17, 18]. In non-rodent species, such as rabbits or humans, this rapid bioelimination is not present [19]. Thus, pharmacokinetics, biodistribution, and the safety of PFC nanoparticles will differ significantly between rodent and non-rodent species, affecting the dosages administered to compensate for the loss or the assessments of dose-safety margins of particles and their contrast or therapeutic payloads [18].

Early preclinical and later clinical research with PFCs involved liquid breathing, recognizing the high oxygen-dissolving capacity of PFCs and the need to address surfactant deficiencies in preterm babies [20–25]. Although it was an interesting and effective application, this use of PFCs was rapidly superseded by the development of alternative surfactant replacement technologies. However, the oxygen-dissolving capacity of PFC emulsions was not forgotten, and efforts to develop these agents as artificial blood substitutes were pursued with limited success.

Fluosol-DA (Green Cross, Japan) was the first PFC emulsion approved for blood replacement, but it was associated with significant hemodynamic compromise related mostly to the choice of surfactant [26–32]. A similar particle, Fluosol-43, was later developed, substituting an albumin surfactant to counter the unstable hemodynamic issues. Fluosol-DA was composed of a mixture of perfluorodecalin (PFD) and perfluorotributylamine, which are fluorine compounds with complicated MR spectra. From an MR cell-tracking perspective, PFD offers limited imaging or spectroscopy potential, even with today's more highly refined instruments and techniques [33, 34]. The next generation of PFCs pursued clinically for artificial blood substitutes were PFOB (Alliance Pharmaceuticals) and perfluorodichloro-octane (PFDCO, HemaGen/PFC, Inc.). These fluoro-compounds reduced pulmonary gas stacking and decreased the time for PFC bioelimination from tissues. These second-generation PFC-based blood substitutes utilized phospholipid surfactants for better biocompatibility, better oxygen-dissolving capacity, and fewer significant side effects, improved bioelimination rates, and were amenable to large-scale commercial production. The oxygen dissolved in the PFC liquid was easily extracted by oxygen-deprived tissues. However, the oxygen-loading capacity of PFCs is linearly related to the partial pressure of oxygen in equilibrium with the emulsion. PFCs demonstrate a nearly flat, linear oxygen dissociation curve in contrast to the sigmoidal dissociation curve of hemoglobin. As a result, most of the oxygen dissolved in the PFC is released in the high-pressure atmosphere of the arteries, with little oxygen being available for the capillary network where the partial pressure of oxygen is lower and the need is greatest. PFC products essentially failed clinically as blood substitutes.

During this time, Dr. Robert Mattrey, working with the Alliance PFOB emulsion platform, conducted early studies to determine whether these particles offered clinical imaging potential with ultrasound (US), computed tomography (CT), and MRI [35–44]. Although much of this work centered upon liquid PFC nanoparticles for US and CT and required large volumes of materials to provide blood pool contrast, only the use of PFOB emulsions for gastrointestinal (GI) contrast (negative contrast) with ^{1}H MRI gained traction. In this application, PFOB particles offered significant imaging and procedural advantages over standard barium contrast studies, but at a higher cost. The much lower cost of using barium for GI imaging won out.

2 MRI with PFC emulsions

The stability and significant prior human experience with PFOB offered a unique modifiable nanoparticulate theranostic platform technology that has been extensively exploited in a variety of medical applications by our laboratory, both alone and in collaboration with many others [16, 45–79]. For ^{1}H MRI, PFC nanoparticles provided a stable platform for high payloads of lipophilic gadolinium chelates to enhance targeted MR molecular imaging. However, with increasing concerns regarding gadolinium-induced nephrogenic systemic fibrosis and acute complement activation noted in clinical trials [80–82], ^{19}F imaging with targeted PFOB nanoparticles at 3 T was reconsidered in order to address these significant unmet clinical needs.

More recently, MR cell tracking with fluorocarbon labeling was pursued as an alternative to more commonly used iron oxide nanoparticles [83–90]. These investigators brought increased attention to the use of cyclic perfluoro-15-crown-5-ether (PFCE) and linear perfluoropolyether (PFPE) molecules that have repeating $-CF_2CF_2O-$ units for improved ^{19}F