

Fluorocarbon compounds in MRI diagnostics and medical therapy

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Abstract. The lecture describes the application of fluorocarbon compounds as blood substitutes and contrasting preparations in MRI diagnostics. A blood substitute product fluorocarbon Perfluorane® has shown effectiveness in oxygen delivery to the tissues of living organisms, and cardioprotective effect which does not depend on the patient's blood group. Inclusion of paramagnetic atoms (gadolinium, iron, etc.) to the Perfluorane® chemical formula creates a new compound with high MRI contrast efficiencies at Larmor frequencies of protons so and fluorine-19 nuclei.

1. Introduction

Magnetic resonance imaging (MRI), based on the effect of nuclear magnetic resonance (NMR), has become an integral part of the medical diagnosis. MRI scanners and NMR spectrometers are used widely in numerous biomedical applications. MRI can reveal different morphological changes of the internal organs and tissues. MRI signal in all medical imaging systems is formed on Larmor frequency of protons. It's not a coincidence that the protons as hydrogen nuclei in water molecules have a maximum concentration in most tissues of living organisms. This makes proton MRI suitable for high resolution imaging of majority of the organs.

2. Perfluorane® and its properties

There is virtually no fluorine atoms in a living organism (except for weak traces in the tooth enamel). Any injection of fluorine compounds respond to electromagnetic RF exposure of magnetic resonance scanner and can be detected when the excitation frequency of the electromagnetic wave is equal to the Larmor frequency of the fluorine nuclei. Fluorine-based MR images will have absolutely no background in normal tissues where fluorides are absent. Another reason to pursue development of NMR diagnosis on fluorine nuclei is the existence of fluorine-containing medicines, for example, blood substitute Perfluorane® [1,2]. It is critical to follow the distribution of the Perfluorane® after injection and to monitor the dynamics of its biochemical interactions with tissues.

Fluorine-based MRI can detect fluorine distribution in the body after the injection, which helps to determine concentration of the oxygen carriers, retention in tissues and subsequent removal. A number of technical and fundamental issues have to be addressed for the successful application of MRI visualization of fluorine in medical practice. First of all, the transceiver transmit path of radio frequency channel has to be modified and adjusted it to the precession frequency of fluorine nuclei. Then, the imaging protocol has to be optimized in the order to form the most intensive fluorine images



with high spatial resolution. Quantification of fluorine signal is possible with implementing localized fluorine nuclei NMR spectroscopy; this would allow determination of the metabolic profile of the specific tissue. Finally, fluorine images have to be co-localized with anatomical images obtained using proton MRI. Successful implementation of fluorine imaging and spectroscopy techniques is based primarily on the fact that the fluorine nuclei have very close characteristics of their magnetic parameters to protons, on which all known MRI techniques are built. In fact, the Larmor frequency of the fluorine nuclei is only 5% less than the respective frequencies of protons, natural content of fluorine-19 (^{19}F) is 100%, both nuclei have the same spin quantum number of $\frac{1}{2}$ and close relative sensitivity.

Table 1 demonstrates that the fluorine-19 nucleus and protons have closest NMR characteristics compare to all other clinically interesting nuclei.

Table 1. NMR properties of clinically interesting nuclei.

Nucleus	Gyromagnetic ratio (MHz/T)	Spin quantum number	Relative content	Relative sensitivity
^1H	42.6	$1\frac{1}{2}$	99	1.0
^{13}C	10.7	$1\frac{1}{2}$	1.1	0.016
^{17}O	5.8	$5\frac{1}{2}$	0.1	0.029
^{19}F	40.0	$1\frac{1}{2}$	100	0.83
^{23}Na	11.3	$3\frac{1}{2}$	100	0.093
^{31}P	17.2	$1\frac{1}{2}$	100	0.07

Another reason for developing medical NMR fluorine techniques is a desire to create non-toxic fluorocarbon-based MRI contrast materials that can drastically improve imaging of internal organs and visualization of vascular network. Finally, a structure of fluorocarbon compounds in Perfluorane® may allow the use of Perfluorane® emulsion as bio-containers for the targeted delivery of pharmaceutical products to the zones of pathology.

It is known that fluorocarbon compounds can be present long time in the body without causing toxic effects and not altering organ functionality. This is a significant advantage in comparison with gadolinium-based MRI agents, which can cause toxic reactions. Perfluorocarbons (PFCs) are completely inert, not toxic, not metabolized in the body and excreted mainly with exhaled air.

Medical applications of fluorine compounds originate after discovering for fluorocarbon as an effective gas transporter. Note that fluorocarbons do not exist in nature and can be obtained by chemical substitution of all atoms of hydrogen by fluorine in hydrocarbons, therefore they are called sometimes "fluorocarbonhydrogens", although they do not contain hydrogen atoms. The emulsion of fluorocarbons in the water effectively absorbs oxygen and carbon dioxide, for example, liquid PFCs are able to dissolve more than 50% by volume oxygen and more than 150% carbon dioxide. The scientists of Nesmeyanov Institute of Organoelement Compounds RAS (INEOS RAS) [1,2] have made a major contribution to the development of this field, they discovered an outstanding gas transmission function of the PFC.

In 1966 year, Drs. Clark and Gollan [3] found that mouse submerged in the liquid PFC could long enough (up to 10 minutes) breathe the oxygen dissolved in PFC. Lungs of mouse were filled with liquid PFC, but in spite of this her breathing functions continued. After cleaning murine lungs from fluid and restoration the normal breathing process – the mouse continued to live, despite the prolonged period of deprivation from atmospheric oxygen.

3. Development of new fluorocarbon compounds for biomedicine

Immediately after this discovery, the United States, Japan and the USSR began work to create a substitute for blood plasma on the PFC basis. The joint research team of the Institute of Biophysics and INEOS RAS has developed recipes of Perfluorane®, as well as its manufacturing technology [2].

Perfluorane® is an aqueous micro-emulsion (droplet size 80-100 nm) mixture of two perfluoroorganic compounds, stabilized by polymeric surface-active substance (PSA). It quickly dissolves large amounts of oxygen, ensures the delivery of oxygen from the alveoli to erythrocytes and from erythrocytes to tissues, improves metabolism and gas exchange at the level of tissues, and also has a distinct cardio protective effect. Ministry of Health of the Russian Federation has allowed its use as blood substitute. Perfluorane® has saved the lives of hundreds of wounded soldiers who have experienced excessive blood loss during Afghanistan war. An important advantage of this artificial blood substitute is its indifference to the blood type.

PFCs are extremely resistant chemically and thermally, biologically stable and not metabolized in the body. PFCs are removed from the body mainly through the lungs with exhaled air. Speed of removal of these compounds is determined by two factors – the elasticity of PFC steam (boiling temperature) and its solubility in lipids, i.e. the ability to penetrate through membranes of pulmonary alveoli.

Fluorocarbon drug Perfluorane® is a mixture of two PFCs – perfluorodekalin and parametilcyklogeksilpiperidin, the first of which in itself is weak stable and quickly removed from the body, while the second one provides high stability of emulsion droplets in the mixture with greater duration of excretion from the body. The combination of these two compounds ensures stability and efficacy of the resulted emulsion, which can be stored in refrigerators up to 3 weeks and frozen for up to two years. It is important to outline that detailed studies have not shown any pathological changes in organs and tissues after complete removal of perfluorocarbons in spite of the long duration of their presence in the body.

High concentrations of the Perfluorane® in living tissues open up the opportunity to use this agent for medical diagnosis by detecting fluorine-19 signal with NMR (19F-MRI). Several different research groups in Netherlands, USA, and Japan applied 19F-MRI on artificial objects (phantoms) and laboratory animals and received high-intensity 19F-NMR three-dimensional images [4-6]. However, due to the fact that none of these countries did not have the drug type Perfluorane®, passed the full cycle of clinical research and allowed for medical use, these fragmented results are still very far from clinical applications.

The Moscow State University team led by academician Alexey R. Khokhlov continues development of the Perfluorane®-based MRI contrasting compounds and new reagents for targeted delivery of medicines to the damaged tissues [7-9].

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