Measurement 69 (2015) 109–114

Contents lists available at ScienceDirect

Measurement

journal homepage: www.elsevier.com/locate/measurement

Influence of saline and glucose molecules to contrast properties of clinically used MRI contrast agents

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ARTICLE INFO

Article history:
Received 18 August 2014
Received in revised form 15 February 2015
Accepted 20 March 2015
Available online 26 March 2015

Keywords:
Contrast agents
MRI
Contrast change
Relaxation
Saline
Glucose

ABSTRACT

Contrast agents (CA) are usually used in clinical practice for contrast enhancement during Magnetic Resonance Imaging (MRI). They are iron oxides or gadolinium-based nanoparticles in a carrier fluid. We studied whether different concentration levels of the saline and glucose molecules are able to change the relaxation properties of both types of contrast agents during MRI. The reason is that they are essential biological molecules, and their modified concentration levels are accompanied with several pathological processes. We have found that the physiological concentration of saline and glucose molecules influences the CA contrast properties selectively on the basis of CA concentration (up to 30% for iron oxide CA, and 15% for gadolinium CA). Moreover, the altered concentration levels of saline and glucose change the signal intensity (contrast), for one selected pulse sequence and CA concentration, in range of 2–17%. Although, such contrast changes are on the visibility limit to the naked eye for our system (0.178 T), they can be clearly visible with high-field system, and can have influence to the next data analysis, e.g. relaxation times calculation.

1. Introduction

Currently, Magnetic Resonance Imaging (MRI) is a technique routinely used in clinical practice. MRI provides an anatomical picture of tissue based on different intrinsic contrast. Contrast in MRI arises from the difference in signal intensity, which can be modified by intrinsic parameters (spin density, relaxation times T1 and T2) and by the pulse sequences parameters (repetition time TR, echo time TE). Modification of TR and TE results in T1, T2 or proton density weighted imaging. For contrast enhancement in clinical practice the paramagnetic contrast agents (CAs) are often used. Signal enhancement is caused by coupling of proton magnetic moments with larger magnetic moments of paramagnetic nanoparticles [1].

CAs can be either iron oxide or gadolinium based nanoparticles. Generally, iron oxide CAs have a small effect on T1, but strongly affect T2. Due to this T2 shortening they produce hypointensive artefacts in T2-weighted images. On the other hand, gadolinium CA mainly affects T1 relaxation time constant and produce hyperintensive artefacts in T1 weighted images. Iron oxide CAs are especially used in imaging of liver pathology and include two clinically approved superparamagnetic (SPIO) agents: Endorem (ferumoxides with particle size of 120–180 nm) and Resovist (ferucarbotran with particle size of about 60 nm) [2]. They are absorbed by Kupffer cells which are present only in normal reticuloendothelial system (RES) but not in lesions. This results in different visibility of normal tissue and lesions. Gadolinium-based CAs are routinely used in all other clinical MRI applications, including tumour and vascular imaging [3].

In this study we have focused on MRI contrast properties of both types of contrast agents – SPIO and gadolinium

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http://dx.doi.org/10.1016/j.measurement.2015.03.036
0263-2241/

based CA, in the presence of saline and glucose molecules. As the SPIO contrast agent model we have chosen the Resovist (Bayer Schering Pharma AG), and as the gadolinium one, the MultiHance (ALTANA Pharma AG). We have chosen saline and glucose molecules because they are essential components of the human body, and their altered concentration levels are usually accompanied with serious pathological processes, which can be studied with MRI. The modified concentration levels of the glucose are usually accompanied with different pathological processes, including diabetes, cardiovascular disease of acute stroke risk, etc. [4,5]. The saline concentration imbalance can be caused by diseases of kidney, pituitary gland, hypothalamus or by hypernatremia in critically ill patients [6,7]. Their concentration variations are also present in other types of pathology or in life stress conditions, like diet [8].

The main goal is to find out if the altered concentration of saline and glucose molecules can have an influence to the clinical agents' contrast properties, with using the low-field MRI techniques. We followed two main points: (i) if the influence is large enough to be visible to the naked eye, which would have a direct impact to the clinical practice; (ii) if there exists a "pattern of action" for the saline and glucose molecules in relation to contrast properties of CAs.

2. Material and methods

2.1. Contrast agents

As an iron oxide CA model system we chose the Resovist (Bayer Schering Pharma AG), which consists of carboxydextran coated iron oxide nanoparticles. The gadolinium CA was represented by the MultiHance (ALTANA Pharma AG), which consists of gadobenate dimeglumine molecules.

In the first series we investigated eight different concentration of CAs in various pools – distilled water, saline, glucose, and saline + glucose. Saline and glucose were in physiological concentration (saline 9 g/l, glucose 1 g/l). The concentration values of the CAs was chosen to copy the real possible concentrations in the blood stream, and simultaneously they had to fall between the experimentally determined limit values with a maximum contrast change for our system. For Resovist: 26.6, 52.7, 78.2, 103.3, 127.9, 152.1, 175.8, and 199 μg/ml. For MultiHance: 0.249, 0.494, 0.734, 0.969, 1.2, 1.426, 1.648, and 1.866 mg/ml. The aim was to find out how the physiological concentration of saline and glucose influence the contrast properties of CAs with different concentrations. It simulates the real changes of CA concentrations during in-vivo application.

Secondly, only one concentration of the CAs was chosen which was similar to recommended clinical in-vivo administration of CA: Resovist – 103.3 μg/ml of the iron oxide nanoparticles, MultiHance – 1.3 mg/ml of the gadolinium particles. Four different concentrations (around the physiological concentration) of the saline and glucose have been investigated: saline – 4.5, 9, 13.5, 18 g/l, and glucose – 0.5, 1, 1.5, 2 g/l. Here, the aim was to find out whether different concentration of saline and glucose has influence to the contrast properties of one selected concentration of CA. It simulates the use of CAs in pathological processes/diseases with altered concentrations of saline and glucose molecules [4–8].

2.2. MRI experiments

The MRI experiments were performed with the ESAOTE Opera (E-SCANTM XQ) 0.178 T system. Images were acquired using both Spin Echo (SE) and Gradient Echo (GE) pulse sequences in T1 and T2 weighted modes. In the first step we had to find the most suitable pulse sequence and its parameters for imaging the selected CAs. The selection of pulse sequence was based on three aspects: (i) artefacts formation, (ii) signal/noise ratio, and (iii) the biggest contrast change. In the last one we checked the shape of the curve of the contrast medium concentration gradient in distilled water, where we followed the difference between the reference (without particles) and the sample with the highest concentration of particles. Finally the pulse sequence with the highest change in signal intensity (and thus in contrast), without serious artefacts, and with good signal to noise ratio was chosen. On the basis of these three aspects, we selected the most suitable pulse sequence. We chose four sequences on the short-list: Spin Echo TR = 600 ms, TE = 26 ms, Spin Echo TR = 1800 ms, TE = 26 ms, Turbo Spin Echo TR = 3000 ms, TE = 80 ms, Turbo Spin Echo TR = 3000 ms, TE = 120 ms (Table 1).

Subsequently, the most appropriate protocol for contrast imaging was determined. For Resovist we found that this was a T2-weighted Turbo Spin Echo (TSE) sequence with repetition time TR = 3000 ms and echo time TE = 120 ms. For MultiHance it was a T1-weighted SE sequence with repetition time TR = 600 ms and echo time TE = 26 ms. The GE sequences showed large artefacts in both types of contrast agents and selected concentrations. This was probably caused by the high sensitivity of the GE sequences to the field inhomogeneities, caused by the magnetic particles which are present in both types of contrast media. The naked-eye visibility limit for our system is

Table 1
Intensity changes for selected CA and pulse sequence from the short-list. The maximum change indicates the best suitability of pulse sequence.

Pulse sequence	Resovist (difference in signal intensity for the reference sample – 0, and sample with the maximum CA concentration – 8)	MultiHance (difference in signal intensity for the reference sample – 0, and sample with the maximum CA concentration – 8)
SE T_1 TR600 TE26	557.3	**1068.5**
SE T_1 TR1800 TE26	5.5	604.6
TSE T_2 TR3000 TE80	1526.1	238.3
TSE T_2 TR3000 TE120	**1695.1**	634.4

The bold numbers defines the highest contrast change and thus the best suitability of a pulse sequence for imaging of selected contrast agent.