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Theranostics based on MPI for brain interventions: an in vivo pilot study

O. Buchholz[a,†] · S. Bär[a,b,†,*] · J. Franke[c] · H. Wei[d] · C. Münkel[a] · K. Sajjamark[c] · U. G. Hofmann[a]

[a]Section for Neuroelectronic Systems, Department of Neurosurgery, University Medical Center Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany
[b]Division of Medical Physics, Department of Diagnostic and Interventional Radiology, University Medical Center Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany
[c]Bruker BioSpin MRI GmbH, Preclinical Imaging Division, Ettlingen, Germany
[d]Fraunhofer Research Institution for Individualized and Cell-Based Medical Engineering IMTE, Lübeck, Germany
[†]These authors contributed equally to this work
[*]Corresponding author, email: sebastien.baer@uniklinik-freiburg.de

Abstract

Magnetic particle imaging (MPI)- based magnetic fluid hyperthermia (MFH) enables localized and non-invasive application in conjunction with image guided therapeutic control which represents a significant advantage to established methods of curative heat delivery. Although phantom experiments have shown promising results with adequate MFH performance, transition into clinical and pre-clinical practice, faces several challenges. First and foremost, non-invasive, i.e., systemic administration of nanoparticle tracers, results in steadily moving MFH targets that transport the generated heat away from the targetted region. In this pilot study we investigate localized MFH efficiency in the rat brain, during systemic administration of commercial superparamagnetic iron oxide nanoparticles (SPION). For that we used an experimental set up consisting of a custom heating insert integrated into a commercial MPI-scanner. We observed a slight local temperature increase (∼0.3-0.5 K) in the brain following simoultanous SPION administration and localized MFH application.

I. Introduction

Hyperthermia serves as a potent tool, primarily employed for direct tumor ablation [1] or as an adjuvant therapy to enhance the effectiveness of chemo- or radiotherapy [2]. However, its application often faces challenges such as a lack of therapeutic control and reliance on highly invasive techniques [3]. Achieving localized hyperthermia is therefore a crucial goal in most conceivable applications to minimize off-target effects. Magnetic particle imaging (MPI) guided magnetic fluid hyperthermia (MFH) represents a promising alternative to conventional hyperthermia methods because it offers localized and non-invasive application. The theranostic synergy of MPI and MFH, facilitated by the bimodal utilization of superparamagnetic iron oxide nanoparticles (SPION), presents an ideal solution for the mentioned challenges during hyperthermia treatment. Combination of MPI and MFH seamlessly integrates tomographic imaging and therapeutic procedures, enhancing its potential for clinical applications. MPI-based MFH can be achieved by superimposing an additional high-frequency alternating magnetic field through the use of a heating insert. This leads to heat dissipation of SPION located in the field free region (FFR) of the MPI system. Previously we were able to show the feasibility of an integrated MPI-MFH-based theranostic platform in 3D by demonstrating high spatial control of the therapeutic target, adequate MPI-

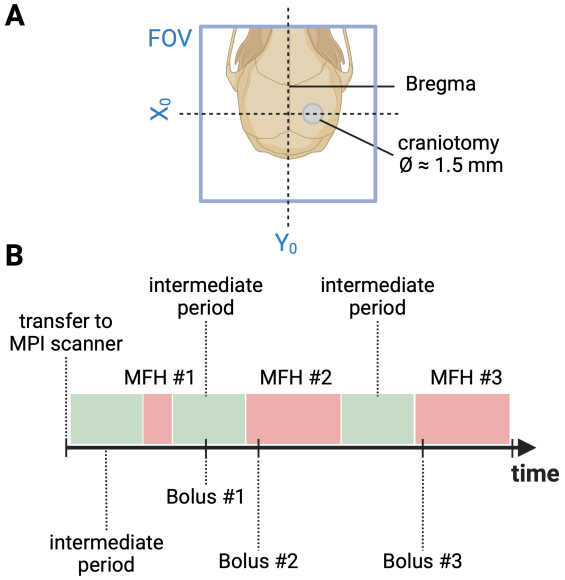

Figure 1: Experimental procedure. A fiber optic temperature probe was introduced through a craniotomy over the right hemisphere of a rat (***A***).Subsequently, the rat's head was positioned at the relative center of the MPI-MFH system used in this study. The localized MFH target was selected corresponding to the suspected location of the FOTEMP termination. Experiment protocol shows the 2 MFH cycles and the 3 boli applied during this investigation (***B***).

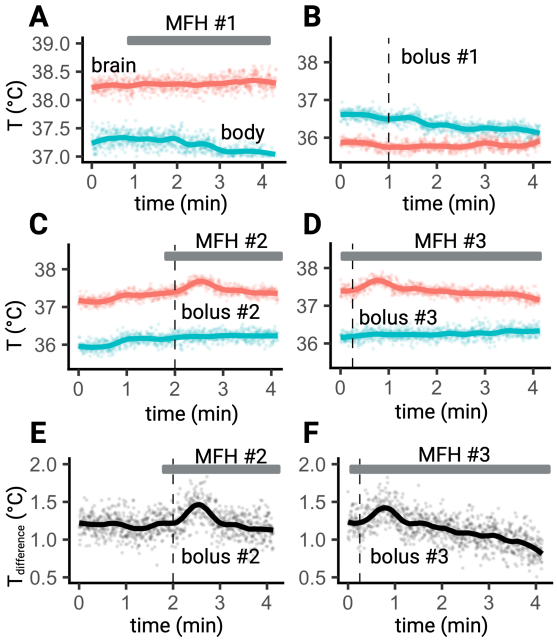

Figure 2: In vivo MFH. Brain (red) and body core temperatures (blue) of a rat were monitored during a consecutive set of MPI-based localized MFH (600W, selection field gradient = 1.25 T/m, 1.25 T/m, 2.5 T/m (X, Y, Z)) sequences and systemic SPION injections. A regression line was fitted to the individual data points in each subplot, for enhanced trend visualization.The first MFH sequence (grey rectangle, duration = 3 min) was applied without prior SPION administration (***A***). The first SPION bolus (dashed vertical line, synomag-D-70, Micromod Germany, 10 mg(Fe)/ml, 600 µl) was injected without simultaneous MFH application (***B***). The second (***C***) and third (***D***) SPION boli were both administered shortly following the second and third MFH sequences respectively. ***E*** and ***F*** show the difference between brain and body temperature of ***C*** and ***D*** respectively.

based thermometry, and successful in situ interleaved MPI-MFH application [4]. The transition into (pre-) clinical application will be essential to further validate their potential. However, significant challenges have to be overcome to enable this transition. Non- or minimally-invasive MFH application necessitates systemic administration of SPION. This in turn results in constant heat drainage from the intended therapeutic target. The here presented in vivo pilot study aims to investigate localized MPI-based MFH in the rat brain using the same theranostic platform described in [4].

II. Material and methods

II.I. Animal surgery

Prior to MFH application, one rat (Sprague Dawley, female 300 g) was anesthetized (isoflurane, 4%) and mounted onto a stereotactic frame. Body temperature was maintained using a heating pad. The intensity of isoflurane narcosis was subsequently decreased (2.5 - 3.5%). The head was shaved, and the skull was exposed through a central skin incision. Subsequently, a craniotomy (Ø ≈ 1.5 mm) was performed over the right hemisphere through which a fiber optic temperature probe (FOTEMP) was implanted into the brain tissue (see figure 1A). The FOTEMP was secured to the skull using a mixture of adhesives and dental cement. An additional FOTEMP was placed in the rectum of the animal to monitor the core temperature throught the experimental procedures. The venous tail vein was accessed using an indwelling catheter to enable SPION injection during MFH application. Subsequently, the animal was transferred to an animal cassette fitting the experimental set up used in this study (see below).

II.II. Experimental set up

The experimental set up consisted of a commercial MPI scanner (MPI 25/20FF, Bruker BioSpin MRI GmbH, Ettlingen) and an integrated custom heating insert [5]. The resulting theranostic platform, enabling interleaved MPI-MFH application, incorporates an MFH-FFP with dimensions of approximately 5 mm x 5 mm x 3 mm (X,Y,Z), representing the target volume for localized MFH application [4]. The animal bed was positioned such, that animals' head was located at the relative center of the

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MPI-MFH system. This was followed by a sequence of SPION bolus administrations (synomag-D-70, Micromod, Germany, 10 mg(Fe)/ml, 600 µl) and localized MFH sequences (600 W, selection field gradient = 1.25 T/m, 1.25 T/m, 2.5 T/m (X, Y, Z)). Brain and body temperature was measured with FOTEMPs at the respective locations connected to an oscilloscope. The MFH target which was applied to all of the MFH sequences, was selected according to the suspected location of the working end of the brain implanted FOTEMP (see figure 1 A) by adjusting the FFR offset.

In figure 1B, the experimental timeline following animal preparation and positioning is shown. The individual MFH application sequences were interspersed with intermediate phases to facilitate animal acclimatization. During these phases both core and brain temperature monitoring was maintained. The initial MFH sequence was applied for 3 minutes. This aimed to confirm that the MFH sequence does not influence temperature evolution when no SPIONs are present. Subsequently, the first SPION bolus was administered through the tail vein over a period of a few seconds. This was followed by application of the second MFH sequence (duration = 22 min). Immediately after application onset, the second SPION bolus was administered. Finally, this MFH-bolus sequence was repeated.

III. Results and discussion

The first MFH sequence resulted as expected in no observable temperature increase of the brain and body temperature (see figure 2A). Similarly, both temperatures also remain relatively unchanged after the first bolus was administrated without MFH sequence running (see figure 2B). The second bolus, which was administered during ongoing MFH application, resulted in an almost immediate temperature increase in the brain while the body core temperature remained unchanged (see figure 2C). This result could be reproduce and the exact same effect could be observed after a third bolus was administrated (see figure 2D). In figure 2E and 2F, the subtraction of the body temperature from the brain temperature is shown in figure 2C and 2D respectively. The resulting curves emphasize the instantaneous heat increase after a bolus injection and simultanous MFH application. The observed effect is minor (~0.3-0.5 K). However, the observed temperature increase might not represent the full extent of the temperature in the brain. Discrepancies between the location of the FOTEMP termination and the location of the MFH target, might influence the result.

IV. Conclusions

In this proof of principle pilot study, we show the effect of non-invasive and localized MFH application following systemic administration of commercial SPION. As neither MFH without SPION administration nor SPION administration without MFH application led to a temperature change, we attribute the observed temperature increase during both (MFH and SPION bolus) unequivocally to an MFH effect (see figure 2C-F). However, the observed temperature increase is at least one order of magnitude below the threshold for effective treatment temperatures, indicating a need for significant improvements. In future studies, maximizing the SPION concentrations in situ and in particular the use of for MFH optimized particles might allow to drastically increase the MFH efficiency.

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Author's statement

Conflict of interest: KS and JF are employed by Bruker BioSpin MRI GmbH. The remaining authors state no conflict of interest. Informed consent: Informed consent has been obtained from all individuals included in this study. Ethical approval: The research related to animal use complies with all the relevant national regulations and institutional policies and has been approved by the authors' institutional review board or equivalent committee.

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