A NOVEL MAGNETIC FIELD DEVICE FOR INDUCING HYPER-THERMIA USING MAGNETIC NANOPARTICLES

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\textbf{Abstract:} A new alternating current (AC) magnetic field applicator was designed to induce hyperthermia in an animal tumour model using superparamagnetic iron oxide nanoparticles (SPION). First experiments on phantoms including different concentrations of SPION were conducted. The results confirmed that the new AC magnetic field applicator could heat-up SPION. This proofs the capability to induce hyperthermia by SPION, dependent on the concentration.

\textbf{Keywords:} Magnetic drug targeting, nanoparticles, alternating current magnetic field, hyperthermia

\textbf{Introduction}

In cancer treatment hyperthermia is either used in combination with radio- and chemotherapy (temperature: 40-44°C) or solitarily for thermal ablation (temperature: > 60°C) \cite{1}. By the application of an alternating current (AC) magnetic field superparamagnetic iron oxide nanoparticles (SPION) can be heated and therefore be used to apply local hyperthermia. First evidence for the success of this treatment method was given by Gilchrist \textit{et al.}, in 1957 \cite{2}. Magnetic drug targeting (MDT) is a new and innovative cancer treatment based on nanoparticulate drug delivery. SPION are coated with a fatty acid and then functionalized with a chemotherapeutic agent. The solution is directly injected into the arterial vascular system supporting the tumour. The SPION and therefore the antineoplastic agent are concentrated in the tumour by an external magnetic field. To investigate MDT we established an animal tumour model: A VX-2 tumour is implanted into the left hind limb of New Zealand white rabbits and then treated by MDT \cite{3}. The combination of this local chemotherapy with hyperthermia is a very promising approach. In this work we performed first experiments employing a novel AC magnetic field applicator system to evaluate its benefit to induce hyperthermia after MDT.

\textbf{Methods}

\textbf{Nanoparticles:} The SPION were obtained after alkaline precipitation followed by self-assembling functionalization with a fatty acid \cite{4}. They were physicochemically characterised by hydrodynamic diameter (main part 75 nm), zeta potential (about -30 mV), iron content (IC=5 mg/ml) and transmission electron microscopy (TEM). Dilutions were carried out in NaCl-solution (NaCl 0.9%, Berlin-Chemie AG, Berlin), as used for infusion in the clinic. The samples (500 μl) were filled in 1.5 ml microreaction tubes.

\textbf{Alternating magnetic field system:} The magnetic field device comprises a split-coil unit for generating the magnetic field and a radio frequency (RF) amplifier ENI 1040L (Electronics & Innovation, Rochester NY, USA) to supply an alternating current to the coils (Figure 1). The split-coil is constructed from two flat pancake coils with variable distance. The coil distance can be adjusted between 40 and 100 mm to apply the magnetic field to SPION phantoms as well as animals. The amplitude of the magnetic induction $B$ in the centre between the coils reaches 8.5 mT for 50 mm coil distance (equivalent to 6.8 kA/m magnetic field strength $H$) and maximum output power of the amplifier (400 Watt). To achieve the maximum power transfer from the amplifier to the coils, the coil impedance has to match the 50 Ohm output impedance of the amplifier. This is achieved by connecting series and parallel capacitors to the coil. Doing so, the 50 Ohm matching impedance was adjusted for a parallel resonance frequency of about 200 kHz where the quality factor of the coils is at its maximum. As the resonance frequency varies slightly with coil distance due to the distance dependent coil inductance, an automatic frequency adjustment has been implemented in the control software. The control software connects via USB to an electronic data processing unit, which measures voltage and temperature of the coils and provides the input signal for the power amplifier.

\textbf{Experimental set-up:} Samples were pre-heated to 37°C (Thermomixer compact, Eppendorf AG, Hamburg) to start the experiment with physiological body temperature. After removing the samples from the incubator they were put into a heat insulated specimen mount (height: 50 mm) consisting of polystyrol. The specimen mount was attached into the novel AC magnetic field applicator. A fibre optic thermometer FOTEMP2 (Optocon AG, Dresden, Germany) was used to measure the temperature continuously over time (Figure 1). The samples were exposed to the AC magnetic field for 100 minutes.
Results

To induce hyperthermia in an animal tumour model for MDT a new AC magnetic field application system was constructed. In first experiments on phantoms we employed various SPION concentrations to evaluate the capability to generate hyperthermia by an alternating magnetic field. The following SPION concentrations were tested: IC=5 mg/ml, IC=1 mg/ml, IC=500 µg/ml, IC=100 µg/ml, IC=10 µg/ml as well as pure NaCl-solution. The temperature was recorded every 5 minutes (Figure 2).

Discussion

Today, cancer is still one of the leading causes of death worldwide. In contrast to heart and cerebrovascular diseases and despite all efforts to improve the prevention and therapy of cancer, no satisfying results have been achieved so far. Nanomedicine means the implementation of nanotechnology into diagnostics and therapy of diseases. Target specific drug delivery by nanoparticles is supposed to be the most promising approach in this area. One of these new and innovative methods is MDT. It can be applied for all solid tumours and its effectiveness has basically been demonstrated in an early experimental animal study [5]. Hyperthermia is already well established as an adjuvant to radio- and chemotherapy for the treatment of tumours. It is one of the oldest forms of cancer therapy and has been standard treatment for inoperable tumours until the middle of the twentieth century: Patients received bacterial toxins to induce high body temperatures. Hyperthermia induced by an AC magnetic field using SPION has already been successfully applied to treat glioblastoma and prostate cancer [6]. Here, in contrast to MDT, SPION have been injected directly into the tumour and not intravascular. Additionally, the SPION were not functionalized with a chemotherapeutic agent. Hyperthermia can affect the tumour by pure heat but also can improve the effect of the chemotherapeutic agent. To increase the anti-tumour effect of MDT hyperthermia seems to be an appropriate technique. The presented phantom measurements clearly proof the power of this concept.

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Bibliography