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Ex vivo validation of PMMA-based bone cements loaded with magnetic nanoparticles enabling hyperthermia of metastatic bone tumors

Percutaneous vertebroplasty comprises the injection of Polymethylmethacrylate (PMMA) bone cement into vertebrae and can be used for the treatment of compression fractures of vertebrae. Metastatic bone tumors can cause such compression fractures but are not treated when injecting PMMA-based bone cement. Hyperthermia of tumors can on the other hand be attained by placing magnetic nanoparticles (MNPs) in an alternating magnetic field (AMF). Loading the PMMA-based bone cement with MNPs could both serve vertebra stabilization and metastatic bone tumor hyperthermia when subjecting this PMMA-MNP to an AMF. A dedicated pancake coil is designed with a self-inductance of $10\, \mu H$ in series with a capacitance of $0.1\, \mu F$ that acts as resonant inductor-capacitor circuit to generate the AMF. The thermal rise is appraised in beef vertebra placed at 10 cm from the AMF generating circuit using optical temperatures sensors, i.e. in the center of the PMMA-MNP bone cement, which is located in the vicinity of metastatic bone tumors in clinical applications; and in the spine, which needs to be safeguarded to high temperature exposures. Results show a temperature rise of about $7\, ^\circ C$ in PMMA-MNP whereas the temperature rise in the spine remains limited to $1\, ^\circ C$. Moreover, multicycles heating of PMMA-MNP is experimentally verified, validating the technical feasibility of having PMMA-MNP as basic component for percutaneous vertebroplasty combined with hyperthermia treatment of metastatic bone tumors. © 2016 Author(s). All article content, except where otherwise noted, is licensed under a Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/). [http://dx.doi.org/10.1063/1.4973499]

I. INTRODUCTION

In spinal metastatic tumor disease, the vertebral body is invaded and weakened by pathological tissue, which can lead to the collapse of the vertebral body and a progressive compression of the spinal cord. This in turn may lead to a severe neurological function deficit. Current methods allow either stabilization or oncological treatment of the spinal column. Vertebral body augmentation by the injection of “cement” (polymethylmethacrylate, PMMA), so-called vertebroplasty (direct injection of PMMA with high pressure device) or kyphoplasty (making a cavity in the vertebral body with a balloon before filling it with PMMA at relatively low pressure) readily stabilizes the spine, but does not stop tumor progression. Current spinal metastatic disease treatments, such as the standard and most common neurosurgery, radiofrequency ablation and laser induced thermotherapy techniques are performed before the injection of the cement and can thus be performed only once. Surgical procedures are possible for 10–15% of the patients, but because of the frequent progression of spinal metastases, the surgery needs to be repeated which is costly and unwanted for the patient. The treatment should ideally be performed in a repetitive way, without additional invasive manipulations.
Magnetic nanoparticles hyperthermia (MNH) consists in locally heating cancer tissue with magnetic nanoparticles (MNPs) using an external alternating magnetic field (AMF).\textsuperscript{6,7} The heating of the tumor tissue induces a sequence of biological processes leading to tumor cells degradation.\textsuperscript{8} Traditional bone cement does not contain any magnetic materials but can be loaded with MNPs and clinically administered in a minimally invasive way as it is being done in vertebroplasty or kyphoplasty. The MNPs can then be activated through the externally generated AMF so that they heat the bone cement PMMA and thus the surrounding biological tissue. This procedure enables on the one hand the stabilization of the bone and on the other hand the hyperthermia of the spinal metastatic tumors.\textsuperscript{9} In order to achieve this, a temperature increase of 6 °C (and for 30–60 minutes of exposure) should be established in bone metastases cells to provoke cell necrosis.\textsuperscript{10} The effectiveness of hyperthermia largely depends on the precision of having temperature increase in the tumor and minimizing the heating of normal tissue elsewhere.

Technical realization of the above comes with a large number of constraints. First, when heating the tumor cells, the temperature diffusion should be controlled to not damage the healthy tissue. Particularly, in bone metastases, exposing the spine to high temperatures due to an uncontrolled heat process may subsequently cause neuronal damage.\textsuperscript{11} The effect of the MNH on the spinal cord furthermore depends on the exposure time and the maximum temperature reached. Animal experiments indicate that the maximum temperature tolerated after MNH for the spinal cord is situated in the range of 42–42.5 °C for exposure times of 40–60 min. In case temperatures in the range of 43 °C are applied, the exposure time should be reduced to 10–30 min. The use of multicycles heating, i.e. on-off switching of the AMF, enables more controlled thermal elevations.\textsuperscript{13} A second technical challenge is to engineer a device capable to produce sufficient heat at a certain distance from the AMF source. The AMF can be produced by means of a resonant inductor-capacitor (LC) circuit. The enhancement of the generated heat can be achieved in trifold manner: increasing the MNPs concentration, applying higher currents and having an inductor specifically designed to produce sufficient AMF. The increase of MNPs concentration has 2 constraints: the mechanical stability of the PMMA-MNP matrix and the MRI compatibility. The composition of the PMMA-MNP mixture has been investigated.\textsuperscript{14} The MNPs were dispersed in the cement matrix and it has been shown that the maximum MNPs content was around 60 wt.% vs. the total weight of the cement in order to keep mechanical stability.\textsuperscript{15} Unfortunately, such high concentration of MNPs has considerable artefacts on MRI images whereas the diagnosis of the bone metastases progression is done by MRI. Consequently, an appropriate concentration of the MNPs in MNH treatment should be adjusted to the limits of the MRI procedure. A second alternative to obtain a higher AMF is to increase the current flowing through the coil.\textsuperscript{16} Here again, there are limitations related to Eddy current effects and the maximum current allowed by the supply. This work provides a perspective for bone metastases MNH treatment by means of a designed pancake coil. We tested ex-vivo the heat performance of PMMA-MNPs in beef bone samples under AMF produced by this inductor.

II. MATERIAL AND METHODS

A. Dedicated AMF circuit

The AMF generator in our experimental setup comprises 3 main components: a power supply, a heating station and a closed-circulating water cooling system. The power supply is a 10 kW induction heating system able to provide an alternating current to a resonant circuit with resonance frequency $f_r = \frac{1}{2\pi\sqrt{LC}}$ between 150 kHz and 400 kHz. The minimal total capacity of the capacitors in the circuit is restricted to $C = 0.1 \mu F$. The theoretical maximum current $I$ allowed to flow through these capacitors is 450 A. In view of stability and safety, the current $I$ used in practical application is limited to 200 A. By increasing the number of turns in a pancake coil, the inductance coefficient $L$ rises while the resonance frequency decreases. Therefore, smaller capacitances $C$ should be used to keep the same value of $f_r$. A model of a pancake coil with variable number of turns $N$ and outer radius $R_{\text{max}}$ was implemented in Matlab (R2013a; Mathworks, Natick, MA, USA). The distance between 2 turns is fixed to 12 mm. The AMF amplitude of the pancake coil is calculated using the Biot-Savart law.
equation:

\[ \vec{B}(\vec{r}) = \frac{\mu_0}{4\pi} \iint_{\text{volume}} \vec{J}_{\text{coil}}(\vec{s}) \times (\vec{r} - \vec{s}) \frac{\vec{r} - \vec{s}}{||\vec{r} - \vec{s}||^3} d\vec{v} \]

This equation calculates the magnetic flux density vector \( \vec{B} \), i.e. \( B_x, B_y, B_z \), in an arbitrary point \( \vec{r} = [x, y, z] \), due to the current density \( \vec{J}_{\text{coil}} = [J_x, J_y, J_z] \) in point \( \vec{s} = [x_s, y_s, z_s] \) belonging to the coil where a total current \( I \) is enforced. The inductance \( L \) can be calculated for a given coil as \( L = \sum_{k=1}^{N} \frac{\vec{B}_k \cdot d\vec{S}_k}{I} \) with \( \vec{B}_k \) \( (k = 1, \ldots, N) \) being the magnetic induction that corresponds with the \( k \)-th turn of the coil having a surface \( A_k \) of its cross section.

B. Ex-vivo temperature assessment using PMMA-MNP matrix

PMMA cements consist of a solid phase (polymethyl methacrylate) and a liquid phase containing the methyl methacrylate monomer. The PMMA-MNP samples are made by mixing VertaPlex™ radiopaque bone cement (manufactured by Stryker®) and Ferrotec EMG (Series 1500) dry iron oxide nanoparticles. The core material of these MNPs is principally magnetite (\( \text{Fe}_3\text{O}_4 \)) with a nominal diameter of 10 nm. They are single domain and superparamagnetic nanoparticles with an initial magnetic susceptibility of 0.2. The proportions by weight are 71.8 to 79.2 of iron oxide and 28.1 to 20.8 of surfactant. Having 22 wt.% of the total amount of PMMA does not significantly alter the mechanical properties of the cement.\textsuperscript{14} The polymerization of the PMMA-MNP can be achieved directly in the core vertebra. We used the Precision Cement Delivery System (PCD) from Stryker® and created an artificial cavity in the beef vertebra to mimic the tumor area. The unipedicular approach was considered by placing a needle in the right pedicle to insert the cement in the center of the core vertebra. For having a standard measurement method that can provide reproducible results, we use instead of a randomly-shaped cavity, a cylindrical hole which is drilled in the core of the vertebra. During the polymerization, the PMMA-MNP mixtures are placed in cylindrical molds. The entire bone is placed 10 cm above the AMF generating circuit and is immersed in distilled water to mimic the biological medium, see Fig. 1. The temperature increase is measured using optical temperature sensors in two points \( T_1 \) and \( T_2 \); \( T_1 \) being the temperature increase in the PMMA-MNP and \( T_2 \) the temperature in the spine. As mentioned in the introduction, the temperature rise in \( T_2 \) needs to remain limited and if possible controlled by means of multicycles heating.

FIG. 1. (a) Beef bone immersed in distilled water with the PMMA-MNP sample placed at 10 cm above the AMF generating circuit (b) Illustration of the temperatures measurements in the vertebra (\( T_1 \)) and in the spine (\( T_2 \)) (c) Frontal view of the sample.
III. RESULTS AND DISCUSSION

A. Coil design based on inductance and AMF amplitude calculations

Fig. 2(a) shows the calculated AMF amplitudes at a distance of $z = 10\ \text{cm}$ above the center of a pancake coil as a function of the outer radius of the pancake coil $R_{\text{max}}$ for different number of turns $N = 6, 8, 10$ turns. The current peak value flowing through the coil is fixed to 200 A. The AMF amplitude increases with increasing number of turn and decreases at a certain $R_{\text{max}}$ value. The highest AMF amplitude $H_{\text{max}} = 2625\ \text{A/m}$ is obtained for an inductor with $N = 10$ turns, $R_{\text{max}} = 21\ \text{cm}$. The corresponding inductance of this coil is $L = 29.3\ \mu\text{H}$. Nevertheless, this coil cannot be used experimentally because of the high $L$ value. In fact, for a fixed capacitance $C = 0.1\ \mu\text{F}$ the condition of the resonance frequency $f_R = 160\ \text{kHz}$ requires an inductance $L = 10\ \mu\text{H}$. This is satisfied for coil radii of $11\ \text{cm}$, $13\ \text{cm}$ and $16\ \text{cm}$, see Fig. 2(b), corresponding to number of turns $N = 10, 8, 6$, respectively. The 8 turns pancake coil with an outer radius of 13 cm seems to be the best compromise with AMF amplitude $H_{\text{max}} = 1711\ \text{A/m}$. On the basis of these calculations, this coil having these specifications was made, see the insets in Fig. 3, and put in series with the $C = 0.1\ \mu\text{F}$ capacitors. Inductance measurements showed that the inductance was approximately $L = 10\ \mu\text{H}$ and our $LC$-circuit had thus a resonance frequency of about $160\ \text{kHz}$. The decrease in AMF along the center line of that specific coil is reported in Fig. 3(a) as well as the decay of AMF along the radial axis $d$ at a distance of $z = 10\ \text{cm}$ in Fig. 3(b). The gap between 2 turns is taken as $12\ \text{mm}$ for practical reasons when manufacturing the coil.

B. Heating performances of the PMMA-MNP

Temperature measurement results in Fig. 4(a) show the time dependence of the heat increase in the beef vertebra where the PMMA-MNP sample is placed at $10\ \text{cm}$ above the center of the
FIG. 4. (a) The temperature rise in the core vertebra \( (T_1) \) and in the spine \( (T_2) \) due to the heating of the PMMA-MNP sample placed at 10 cm above the center of the pancake coil \( (I = 200 \text{ A}, f_R = 160 \text{ kHz}) \). (b) The temperature rise in the core vertebra \( (T_1) \) and in the spine \( (T_2) \) due to the multicycles heating of the PMMA-MNP sample placed at 10 cm above the center of the pancake coil.

pancake coil. A temperature increase in \( T_1 \) is attained of approximately \( T_{\text{max}} = 7^\circ \text{C} \) above the initial temperature \( T_0 \) (here, \( T_0 = 20^\circ \text{C} \) approximately) when having an AMF applied during 14 min using the pancake coil with excitation current \( I = 200 \text{ A} \), whereas the increase of the temperature in the spine \( T_2 \) does not exceed 1 \( ^\circ \text{C} \). Experiments at \( T_0 = 37^\circ \text{C} \) were performed by keeping the temperature of the water container at 37 \( ^\circ \text{C} \) using a 500 Watt Titanium heater and temperature controller. Since the thermal characteristics of the materials are not significantly affected by the considered temperature ranges (20–50 \( ^\circ \text{C} \)), no significant differences in heat increase in Fig. 4(a) were observed. These ex-vivo experiments demonstrate the feasibility of heating tumor cells. Note that in our experiments there are important heat losses due to convection processes of the vertebra and PMMA-MNP in the water. One may expect higher temperature rise in-vivo because of the biological tissue surrounding the bone.

Fig. 4(b) displays the temperature variations during a multicycles heating process. The AMF is switched off when \( T_1 \) reaches a temperature of \( T_{\text{max}} = T_0 + 8^\circ \text{C} \) then switched on again after a temperature decrease of 2 \( ^\circ \text{C} \). This mimics a possible clinical procedure of MNH when having a multicycles heating process where the temperature rise is limited in the range of 6 to 8 \( ^\circ \text{C} \) during approximately half an hour (time exposure in MNH treatment) so to control the thermal elevations inflicted to healthy tissue and spine. The graph shows that after 1 hour of applying the AMF, the temperature increase in the spine \( (T_2) \) is less than 2 \( ^\circ \text{C} \). These results validate ex-vivo the technical feasibility of having PMMA-MNP material as basic component in percutaneous vertebroplasty enabling hyperthermia treatment of metastatic bone tumors.

IV. CONCLUSION

The feasibility of having hyperthermia on the basis of PMMA-MNP samples containing 22 wt.% iron oxide nanoparticles was tested ex-vivo in beef vertebra. A coil was designed so to enable future animal and clinical tests; that satisfy technological constraints, i.e. the minimally allowed capacitance of the capacitors in the resonant inductor-capacitor circuit of the AMF generator; and that generates maximum alternating magnetic fields at a distance of 10 cm above the inductor. A dedicated pancake coil of 8 turns with an outer radius of 13 cm was designed, having an inductance of \( L = 10 \mu \text{H} \) and was placed in series with \( C = 0.1 \mu \text{F} \) capacitors resulting in a resonance frequency of 160 kHz. The ex-vivo experiments show that the PMMA-MNP sample, which is in clinical application in the vicinity of the metastatic bone tumors, heats up to 7 \( ^\circ \text{C} \) with a negligible temperature increase in the spine. We moreover experimentally verified the temperate rise in the PMMA-MNP sample and in the spine when applying on-off switched AMF, mimicking a possible clinical procedure that enables the control of temperature elevations in healthy tissue as well as in the spine. The temperature rise in the spine was limited to 2 \( ^\circ \text{C} \) whereas in the PMMA-MNP a temperature rise in the range of 6–8 \( ^\circ \text{C} \) was established. In future research, we will gradually improve the efficiency of our equipment and
investigate the effect of other constraints on the technical realization towards a standard therapy for metastatic bone tumors.

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