



Original research article

Magnetocaloric effect for inducing hypothermia as new therapeutic strategy for stroke: A physical approach



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ABSTRACT

Hypothermia is an effective neuroprotective strategy for acute stroke. However, in clinical practice, the induction of hypothermia is achieved through the systemic reduction of body temperature (using thermal covers or endovascular cooling devices) which results in a complex system associated in many cases to side effects. Therefore, the aim of this study was to test the magnetocaloric effect as a potential new therapeutic strategy for stroke by means of an adiabatic magnetic refrigerator device.

As a first approach, we have developed a simple device to evaluate *in vitro* the thermodynamic behavior of different concentrations of commercial gadolinium powder as a reference magnetocaloric material. The samples, properly thermally insulated, were cyclically magnetized and demagnetized at room temperature by 1 T permanent magnets in order to induce an adiabatic magnetic effect. Under the experimental conditions tested, results showed a maximum non-accumulative temperature variation of 0.2 °C, insufficient to carry out an effective hypothermia. This study allowed us to discuss about the use of new materials and strategies for further *in vivo* experiments.

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Introduction

It has been demonstrated that hypothermia is an effective neuroprotective strategy in the management of acute stroke (Azzimondi et al., 1995; Campos et al., 2012; Castillo et al., 1998, 1994). Minutes after the onset of ischemic stroke a cascade of molecular events and cellular processes is triggered, ending up with the destruction of the brain parenchyma hours, days or weeks later. Many of these processes are temperature dependent, so hypothermia represents an ideal neuroprotective therapy, rather than the numerous and unfruitful performed trials with neuroprotective drugs that only block one of the steps of the ischemic cascade (van der Worp et al., 2010). In clinical practice, the induction of hypothermia is achieved through the systemic

reduction of body temperature (using thermal covers, immersion in cooling fluids, or endovascular cooling devices) which results in a complex system associated in many cases to severe complications such as, pneumonia and cardiac arrhythmia for instance (Darwazeh and Yan, 2013). However, focal brain hypothermia is an effective and poorly studied therapeutic alternative to systemic hypothermia able to circumvent the harmful side effects associated with systemic cooling. Besides, a localized brain hypothermia treatment would also enable a better patient management and would open the window to design more personalized treatments depending on the patient and lesion characteristics (Castillo et al., 1999; Dong et al., 2001; Krieger et al., 2001; Millán et al., 2008; Schwab et al., 1998; Vila et al., 2000; Yanamoto et al., 1999). Recently, different methods for local brain cooling, such as Peltier chip and headset, have been reported and presented as real alternatives to use in patients (D'Ambrosio et al., 2013; Imoto et al., 2006). Sufficient miniaturization and good performance of the cooling devices were not completely demonstrated and all studies agree that further efforts to develop implantable cooling systems and improve existing ones should be continued.

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In order to find alternative strategies based on focal brain hypothermia, without the secondary side-effects associated to systemic hypothermia, the combination of magnetic nanoparticles and electromagnetic fields (EMF) could constitute a suitable candidate for it. During last decade, magnetic nanoparticles have been applied in biomedicine, such as bioseparation, molecular detection, drug delivery, contrast agents for magnetic resonance imaging and hyperthermia (Wu et al., 2015). These magnetic materials usually are comprised of an iron oxide core with a biocompatible biological polymer. Safety is an issue of constant concern emphasises on the importance of investigating the issue of toxicity, which is highly dependent on the physical, chemical and structural properties of the sample itself as well as dose and intended use. Few *in vitro* studies have reported adverse effects of nanoparticles on cells at *in vitro* in therapeutic doses (Markides et al., 2012). In this line, magnetic and electromagnetic fields are nowadays recognized by medicine as real physical entities that promise the healing of various health problems, especially when conventional medicine has failed (Ross and Harrison, 2015). Magnetotherapy provides a non-invasive, safe and easy approach to directly treat the site of injury and/or the source of pain and inflammation in several diseases (Markov, 2007). It is now commonly accepted that weak electromagnetic fields are capable of initiating various healing processes including delayed fractures, pain relief, multiple sclerosis, and Parkinson's disease (André-Obadia et al., 2006; Fang et al., 2013; VonLoh et al., 2013).

In the present study, magnetic refrigeration, based on the magnetocaloric effect (MCE), is explored as procedure for the generation of focal hypothermia in the brain. MCE is an intrinsic property of magnetic materials. Near the Curie temperature, changes in the magnetization with the applied magnetic field are maximized and induce large variation in the entropy of the magnetic material. In adiabatic conditions, this leads to temperature variations (Clot et al., 2003; Gedik et al., 2009; Gschneidner et al., 2005; Kuhn et al., 2011; Li et al., 2012b; Pecharsky and Gschneidner, 1999, 2001; Tegus et al., 2002). Fig. 1(a) illustrates these behavior represented by adiabatic temperature change, ΔT_{ad} ; and isothermal magnetic entropy change, ΔS_M .

In recent years, magnetic refrigeration based on MCE has been greatly developed within the room temperature range for different technological applications (Gedik et al., 2009; Tušek et al., 2009; Yu et al., 2003). However, to the best of our knowledge, this is the first study using the MCE to induce a focal hypothermia for the treatment of stroke. As a first approach, we have developed a simple device to evaluate *in vitro* and *in vivo* the thermodynamic behavior of different concentrations of commercial lanthanide metal gadolinium (Gd) powder as a reference magnetocaloric material. The choice of Gd was based on its second-order paramagnetic–ferromagnetic phase transition at the Curie temperature of 294 K, where the MCE and heat capacity of Gd are maximized as consequence of a large variation of the anisotropy. The fact that this occurs at room temperature in Gd has been the reason by which it has been widely studied in many different applications (Yu et al., 2003). However, during the last decade materials such as $Gd_5(Si_{1-x}Ge_x)_4$, $MnFe(P_{1-x}As_x)$, $La(FeSi)_{13}$ and $Ni_{52}Mn_{34}Sn_{14}$ have been reported to have a large concomitant MCE at the magnetic phase transition, which could be considered in future experiments (Li et al., 2012a,b; Zeng et al., 2011; Zverev et al., 2010).

Materials and methods

Gadolinium

Commercial gadolinium powder (Gadolinium 99%) (Sigma-Aldrich, MO, USA) with the following properties: formula weight =

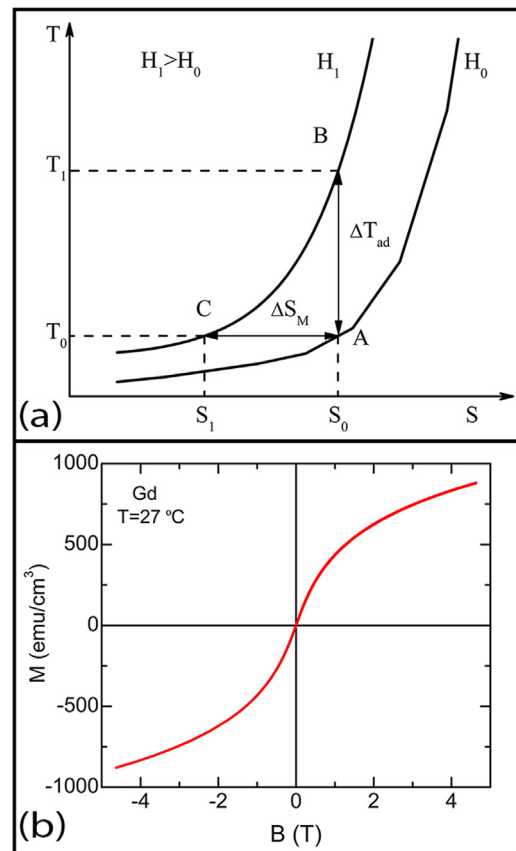


Fig. 1. (a) Temperature-entropy diagram illustrating the magnetocaloric effect (adiabatic temperature change, ΔT_{ad} , and isothermal magnetic entropy, ΔS_M). (b) Hysteresis loop of the Gd powder used in our experiments from -4 to $+4$ T at room temperature.

157.25 g/mol, purity 99% (Based On Rare Earth Analysis) and particle size about $420 \mu m$ was chosen for MCE experiments. In order to study the magnetic field dependence of the magnetization for the Gd used, Fig. 1(b) shows the hysteresis curve of this magnetocaloric material as a function of the external applied magnetic field measured in a SQUID magnetometer at room temperature.

Animals

Experimental procedures were approved by the Animal Care Committee of the University Clinical Hospital of Santiago de Compostela according to the Spanish and European Union (EU) rules (86/609/CEE, 2003/65/CE, 2010/63/EU, RD 1201/2005 and RD53/2013). Male *Sprague-Dawley* (SD) rats (Harlan Laboratories, Udine, Italy) with a weight of 380 ± 30 g were used. Rats were watered and fed *ad libitum* with tap water with commercial pellets. The sacrifice was induced by overdose of anesthetic (8% sevoflurane) in a nitrous oxide/oxygen mixture (70/30). After sacrificing the animal, brains were removed and isolated without prior washing. Manipulation of brain tissue was performed using surgical material and PBS (Sigma-Aldrich, MO, USA).

Agar gel phantom and ex vivo rat brain: thermal behavior comparison

The thermal behavior of an agar phantom was compared with that from a rat brain in order to use it as *in vitro* model ($n=3$). Phantoms were prepared following the method described by Trekker et al. (2014). Briefly, 50–25 ml of liquid 1.6% agar gel (Sigma-Aldrich, MO, USA) was added into falcon tubes of 50 ml, in

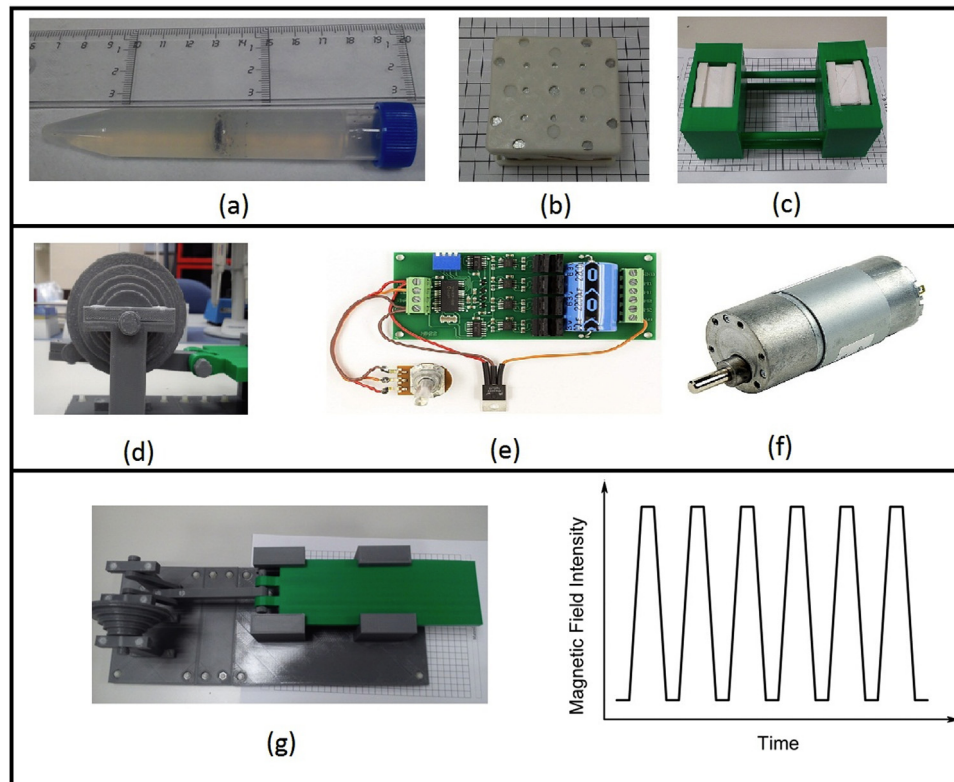


Fig. 2. (a) Example of 1.6% agar phantom with Gd inside, in which the magnetic refrigerator device is capable of generating cycles of magnetization/demagnetization. Experimental refrigerator device setup: (b) example of a 1 T block magnet; (c) space between magnets; (d) wheel; (e) electronic circuit to control the magnetization/demagnetization frequency; (f) direct current motor; and (g) global plastic movable platform. The graph presents an example of magnetic field profile provided by the device.

which we carefully placed the rat brain to obtain the second type of phantoms ($n = 3$). Then, we measured the temperature inside both types of agar phantoms (with and without rat brain) under different external conditions: (1) in a water bath at 36.8°C , measuring the temperature inside during 60 min; (2) once they were removed from the bath and until they reached room temperature (25°C).

Temperature measurements were performed by immersing in the agar phantoms the temperature probes (thermocouple wires) of a Bat 10 thermometer (Physitemp Instruments INC, Clifton, USA). Room temperature was also measured to evaluate its influence on the experiments.

Cooling system based on the adiabatic magnetic effect

There are two different ways to apply magnetic field on a magnetic refrigerant: (1) both magnetic refrigerant and magnet are static. Pulsed magnetic field (Bézaguet et al., 1994) or alternate on-off magnetic field is applied. There is no driving device and the power consumption may be great; (2) there is relative movement between magnet and magnetic refrigerant. The movement fashion may be reciprocating (Rowe et al., 1991) or rotatory (Trueblood et al., 1991). In this way, the strength of magnetic field is stable and an extra mechanical power is needed. In our experimental setup, this last model with a reciprocating movement was used.

Fig. 2(a) shows an example of 1.6% agar phantom with Gd inside, in which our magnetic refrigerator device is capable of generating cycles of magnetization/demagnetization. The experimental setup is described in Fig. 2(b–g); the magnetic system is composed by two permanent magnets (block magnets $50.8 \times 50.8 \times 25.4$ mm of Neodymium Iron Boron (NdFeB) about 1.2 T from Webcraft, Gottmadingen, Germany) spaced about 2 cm, creating a magnetic field inside of approximately 1 T and a plastic mobile platform. The

platform is driven by a direct current (dc) motor connected to a wheel, which was built for introducing and removing the phantoms inside the magnetic field at different frequencies controlled by an electronic circuit.

The magnetic field profile generated by the system is a trapezoid signal, which consists of single pulses separated by signal-off intervals (see graph of Fig. 2). This device allows modification not only of the amplitude of the signal (changing the distance between magnets), but also the duty cycle. In these controlled conditions, the magnetic material is heated (and cooled) when entering (and leaving) the magnetic field region under adiabatic conditions and controlled frequency (cycles/minute).

To determinate the temperature variations through the cycles of magnetization/demagnetization in the phantom with Gd, we introduce the probes of the Bat 10 thermometer in direct contact with the Gd. Likewise, to avoid thermal losses, phantoms were isolated with an foam material in the area of temperature probes insertion. Measurements were initiated once the whole system was perfectly stable at room temperature. In order to get large and stable temperature variations, we fabricated several agar phantoms with different amounts of Gd inside, from 30 to 90 mg ($n = 3$ for Gd mass). In order to induce magnetization and demagnetization processes, samples were exposed to a magnetic field about 0.6–1 T at 10–60 cycles/minute (0.17–1 Hz), without different pulse trains to modulate the signal and during a total period 60 minutes. All the parameters used in the experiments are presented in Table 1. Data are expressed as mean \pm SD.

Results

In Fig. 3, the similar thermal behavior of the agar phantom and the phantom with the *ex vivo* rat brain is reported. The inset of this figure displays an image of both types of phantoms: one only with

Table 1

Parameters used in the study and the corresponding temperature variations obtained (total experimental time in each case was 60 minutes and $n=3$ for Gd mass). Data are expressed as mean \pm SD.

Gd mass (mg)	Magnetization cycles (cycles/minute)	Δ Temperature ($^{\circ}\text{C}$)
95.5 \pm 0.2	20 \pm 3	0.2 \pm 0.1
	40 \pm 4	
	60 \pm 6	
87.1 \pm 0.2	20 \pm 2	0.2 \pm 0.1
	30 \pm 3	
	50 \pm 4	
71.1 \pm 0.3	20 \pm 2	0.2 \pm 0.1
	30 \pm 2	
	40 \pm 4	
31.4 \pm 0.2	18 \pm 2	0.2 \pm 0.1
	40 \pm 3	
	60 \pm 3	

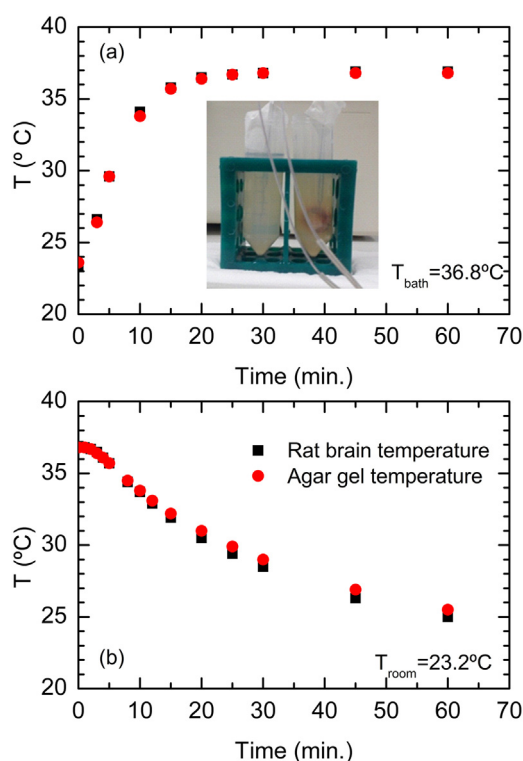


Fig. 3. Comparison between the thermal behavior of an 1.6% agar gel phantom and an identical agar phantom containing a rat brain inside. (a) Both phantoms were included in a water bath at 36.8°C and the temperature inside was measured during 60 min. (b) Phantoms were removed from the bath and temperature was measured inside the phantoms until they reached room temperature (25°C). Inset shows an image for both types of phantoms with temperature probes inside.

agar gel and the other with a rat brain inside. No significant difference in temperature was seen between both groups of phantoms (less than 5%). Taking into account this result, our experimental protocol was made using an agar phantom (without rat brain) as *in vitro* model.

Fig. 4 shows the temperature variations in two agar phantoms, as function of the time, for different cycles of magnetization/demagnetization obtained in our magnetic refrigerator system. Specifically, in Fig. 4(a–c) the sample containing 31.4 mg of Gd was subjected to 18, 40 and 60 cycles/minute of magnetization/demagnetization. As we can appreciate, the sample is heated when

it is introduced into the magnetic field and cooled back to the original temperature when it is moved out. It is clear from the figure that the temperature variations were not accumulative and fluctuated about 0.2°C over the whole 60 min time range measured. Fig. 4(d–f) shows similar results for the sample containing a higher amount of Gd (87.1 mg), in which magnetization/demagnetization frequencies of 20, 30 and 50 cycles/minute, respectively, were applied.

Table 1 presents the temperature variations obtained in our experiments with the corresponding parameters used. Under these experimental conditions, we confirmed an induced thermal effect caused by the MCE, even though the observed temperature changes resulted to be insufficient ($\Delta T = 0.2^{\circ}\text{C}$) to guarantee an efficient hypothermia. The observed temperature variation was non-accumulative and independent of the magnetization/demagnetization cycles or the Gd amount used in the range 30–90 mg. It is important to notice that temperature was measured by using probes directly in touch with Gd, and that temperature changes were imperceptible if we turn away about 5 mm from the Gd material.

Discussion

Our work studied for the first time the magnetocaloric effect as a strategy to induce a non-invasive focal hypothermia in the brain as a potential therapeutic treatment for stroke. Only a few methods have been studied as potential ways to create local brain cooling with results not very satisfactory due to their low implementability in patients (D'Ambrosio et al., 2013; Imoto et al., 2006). We reported an *in vitro* simple magnetic refrigerator device capable of generating cycles of magnetization/demagnetization, in which different parameters could be changed easily, such as the nature of the magnetocaloric material, the dimensions of the magnetocaloric material, the nature of the exchange fluid and the intensity or frequency of the magnetic field. In this regard, the magnetization processes are not totally comparable with the parameters that control the spatial and temporal characteristics of the generated magnetic field during repetitive transcranial magnetic stimulation (rTMS) techniques (Rossi et al., 2009). The main differences are the use of a constant frequency, without different pulse trains to modulate the total signal applied, and the application of higher magnetic field due to the magnetic field decay rapidly over distance and the MCE depends on the amplitude of the field. With our present system, results showed that it is not effective to apply directly the magnetocaloric effect as cooling method because specialized refrigeration cycles with a circulate fluid are required. We considered that the *in vitro* system was completely isolated from the thermal influences, but results have showed important thermal losses that avoid the system to cool down efficiently even when small temperature variations were observed. However, we confirmed a measurable MCE that could be further exploited for the search of a more efficient alternative to the systemic hypothermia in stroke diseases.

To make the method implantable in future, two fundamental aspects should be taken into account: first, a circulating refrigerant fluid for *in vivo* use able to dissipate the heat generated from the magnetic material caused by the adiabatic effect. And second, the creation of different hypothermic areas around the peri-infarct region of the ischemic brain in order to improve the cooling effective area. For these purpose, we also expect to use the cerebrospinal fluid as possible refrigerant fluid because it would keep the temperature approximately at 37°C . For a clinical application of this technique, it is important to note that currently, advances in the field of nanotechnology have enabled development of a generation of multifunctional molecular platforms that are capable of transporting drugs and substances across the blood–

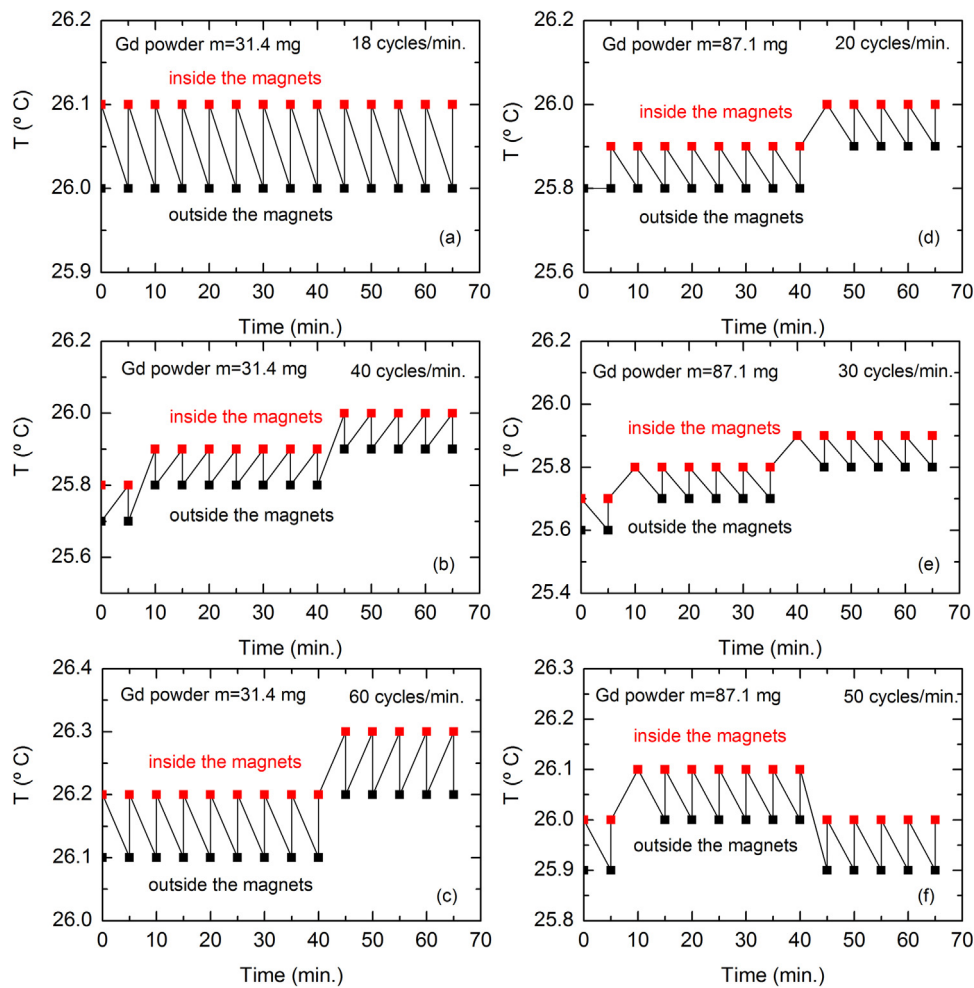


Fig. 4. Temperature evolution, as a function of the time, for different cycles of magnetization/demagnetization obtained in our magnetic refrigerator device: (a–c) phantom with 34.1 mg of Gd; (d–f) phantom with 87.1 mg of Gd. Temperatures of the samples inside and outside the space between magnets are detailed.

brain barrier, targeting specific cell types or functional states within the brain, releasing drugs in a controlled manner, and enabling visualization of processes *in vivo* using conventional imaging systems. The marriage between drug delivery and molecular imaging disciplines has resulted in a relatively new discipline, known as theranostics, which represents the basis of the concept of personalized medicine (Guenoun et al., 2012; Ramos-Cabrera and Campos, 2013). Theranostic agents are molecular platforms, such as liposomes, micelles, dendrimers, and nanospheres, that can be used as substance carriers to solubilize stabilize, protect, and ultimately deliver therapeutic drugs in a controlled manner. Thus, these carriers may include iron oxide particles or gadolinium, and “molecular antennae” such as antibodies and aptamers on their surface which may allow them to interact specifically with target cells via molecular recognition mechanisms for the induction of the focal brain hypothermia. In this regard, it is necessary to note that recent published research works showed the remarkable influence of the nanostructure on the Gd magnetocaloric effect due to the finite size effect and grain boundary properties (Pal et al., 2014; Zeng et al., 2011). Therefore, the grain sizes on magnetocaloric effect should be considered for the magnetic refrigeration practice applications. The use of inverse magnetocaloric materials could be an appropriate alternative to apply in these types of magnetic refrigerator devices thanks to their minor loop of hysteresis with the adiabatically applied

external magnetic field. As opposed to cooling by conventional adiabatic demagnetization, cooling by adiabatic magnetization (inverse MCE) requires an increase of configurational entropy after applying a magnetic field. Both, conventional and inverse MCE could be applicable for magnetic refrigeration, but future studies are needed in order to make them work together in the same magnetic refrigeration device (Pal et al., 2014; Rostamnejadi et al., 2011; Titov et al., 2012).

Conclusion

Results showed that temperature variations of the tested magnetic material (Gd), observed in our experimental device, were not accumulative and a stationary regime was not achieved by cycles of magnetization/demagnetization. Furthermore, these temperature variations were independent to the cycles and were not sufficient for inducing *in vitro* hypothermia. Despite to the results obtained, the simple device implemented for a coarse approximation of the thermodynamic behavior can be useful in the design of the forthcoming improved devices and to evaluate the potential of different MCE materials, particle sizes and geometries. Future studies may include newer cooling strategies in combination with magnetic nanoparticles and circulating refrigerant fluids in order to create a more efficient alternative for the treatment of stroke by focal hypothermia.

Conflict of interest

All the authors of this paper have no direct financial relation that might lead to a conflict of interest.

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References

- André-Obadia, N., Peyron, R., Mertens, P., Mauguière, F., Laurent, B., Garcia-Larrea, L., 2006. Transcranial magnetic stimulation for pain control. Double-blind study of different frequencies against placebo, and correlation with motor cortex stimulation efficacy. *Clin. Neurophysiol.* 117, 1536–1544.
- Azzimondi, G., Bassein, L., Nonino, F., Fiorani, L., Vignatelli, L., Re, G., D'Alessandro, R., 1995. Fever in acute stroke worsens prognosis. *Stroke* 26, 2040–2043.
- Bézaquet, A., Casas-Cubillos, J., Cyvoct, A., Lebrun, P., Losserand-Madoux, R., Marquet, M., Schmidt, M., 1994. A pulsed superconducting magnet for a static magnetic refrigerator operating between 1.8 K and 4.5 K. *IEEE Trans. Magn.* 30, 2138–2141.
- Campos, F., Blanco, M., Barral, D., Agulla, J., Ramos-Cabrer, P., Castillo, J., 2012. Influence of temperature on ischemic brain: basic and clinical principles. *Neurochem. Int.* 60, 495–505.
- Castillo, J., Martinez, F., Leira, R., Prieto, J.M.M., Lema, M., Noya, M., 1994. Mortality and morbidity of acute cerebral infarction related to temperature and basal analytic parameters. *Cerebrovasc. Dis.* 4, 66–71.
- Castillo, J., Dávalos, A., Marrugat, J., Noya, M., 1998. Timing for fever-related brain damage in acute ischemic stroke. *Stroke* 29, 2455–2460.
- Castillo, J., Dávalos, A., Noya, M., 1999. Aggravation of acute ischemic stroke by hyperthermia is related to an excitotoxic mechanism. *Cerebrovasc. Dis.* 9, 22–27.
- Clot, P., Viallet, D., Allab, F., Kedous-Lebouc, A., Fournier, J.M., Yonnet, J.P., 2003. A magnet-based device for active magnetic regenerative refrigeration. *IEEE Trans. Magn.* 39, 3349–3351.
- D'Ambrosio, R., Eastman, C.L., Darvas, F., Fender, J.S., Verley, D.R., Farin, F.M., Wilkerson, H.W., Temkin, N.R., Miller, J.W., Ojemann, J., Rothman, S.M., Smyth, M.D., 2013. Mild passive focal cooling prevents epileptic seizures after head injury in rats. *Ann. Neurol.* 73, 199–209.
- Darwazeh, R., Yan, Y., 2013. Mild hypothermia as a treatment for central nervous system injuries: positive or negative effects. *Neural. Regen. Res.* 8, 2677–2686.
- Dong, H., Moody-Corbett, F., Colbourne, F., Pittman, Q., Corbett, D., 2001. Electrophysiological properties of CA1 neurons protected by postischemic hypothermia in gerbils. *Stroke* 32, 788–795.
- Fang, J., Zhou, M., Yang, M., Zhu, C., He, L., 2013. Repetitive transcranial magnetic stimulation for the treatment of amyotrophic lateral sclerosis or motor neuron disease (review). *Cochrane Database Syst. Rev.* 5, 1–30.
- Gedik, E., Kayfec, M., Kecebas, A., Kurt, H., 2009. Magnetic refrigeration technology applications on near room temperature. 5th International Advanced Technologies Symposium (IATS'09), Turkey.
- Gschneidner Jr., K.A., Pecharsky, V.K., Tsokol, A.O., 2005. Recent developments in magnetocaloric materials. *Rep. Prog. Phys.* 68, 1479–1539.
- Guenoun, J., Koning, G.A., Doeswijk, G., Bosman, L., Wielopolski, P.A., Krestin, G.P., Bernsen, M.R., 2012. Cationic Gd-DTPA liposomes for highly efficient labeling of mesenchymal stem cells and cell tracking with MRI. *Cell Transplant.* 21, 191–205.
- Imoto, H., Fujii, M., Uchiyama, J., Fujisawa, H., Nakano, K., Kunitsugu, I., Nomura, S., Saito, T., Suzuki, M., 2006. Use of a Peltier chip with a newly devised local brain-cooling system for neocortical seizures in the rat. *J. Neurosurg.* 104, 150–156.
- Krieger, D.W., De Georgia, M.A., Abou-Chebl, A., Andrefsky, J.C., Sila, C.A., Katzan, I.L., Mayberg, M.R., Furlan, A.J., 2001. Cooling for acute ischemic brain damage (Cool Aid). *Stroke* 32, 1847–1854.
- Kuhn, L.T., Pryds, N., Bahl, C.R.H., Smith, A., 2011. Magnetic refrigeration at room temperature – from magnetocaloric materials to a prototype. *J. Phys. Conf. Ser.* 303, 012082–012092.
- Li, B., Liang, W., Ren, W., Hu, W., Li, J., Jin, Ch., Zhang, Z., 2012a. Normal or inverse magnetocaloric effects at the transition between antiferromagnetism and ferromagnetism. *Appl. Phys. Lett.* 100, 242408–242412.
- Li, J., Qu, Y., Ren, J., Yuan, W., Shi, D., 2012b. Magnetocaloric effect in magnetothermally-responsive nanocarriers for hyperthermia-triggered drug release. *Nanotechnology* 23, 505706–505716.
- Markov, M.S., 2007. Expanding use of pulsed electromagnetic field therapies. *Electromagn. Biol. Med.* 26, 257–274.
- Markides, H., Rotherham, M., ElHaj, A.J., 2012. Biocompatibility and toxicity of magnetic nanoparticles in regenerative medicine. *J. Nanomater.* 2012, 1–11 Article ID 614094.
- Millán, M., Grau, L., Castellanos, M., Rodríguez-Yáñez, M., Arenillas, J.F., Nombela, F., Pérez de la Ossa, N., López-Manzanares, L., Serena, J., Castillo, J., Dávalos, A., 2008. Body temperature and response to thrombolytic therapy in acute ischaemic stroke. *Eur. J. Neurol.* 15, 1384–1389.
- Pal, D., Ghosh, A., Mandal, K., 2014. Large inverse magnetocaloric effect and magneto resistance in nickel rich $\text{Ni}_{52}\text{Mn}_{34}\text{Sn}_{14}$ Heusler alloy. *J. Magn. Magn. Mater.* 360, 183–187.
- Pecharsky, V.K., Gschneidner Jr., K.A., 1999. Magnetocaloric effect and magnetic refrigeration. *J. Magn. Magn. Mater.* 200, 44–56.
- Pecharsky, V.K., Gschneidner Jr., K.A., 2001. Some common misconceptions concerning magnetic refrigerant materials. *J. Appl. Phys.* 90, 4614–4622.
- Ramos-Cabrer, P., Campos, F., 2013. Liposomes and nanotechnology in drug development: focus on neurological targets. *Int. J. Nanomed.* 8, 951–960.
- Ross, Ch.L., Harrison, B.S., 2015. An introduction to electromagnetic field therapy and immune function: a brief history and current status. *J. Sci. Appl. Biomed.* 3, 18–29.
- Rossi, S., Hallett, M., Rossini, P.M., Pascual-Leone, A., The Safety of TMS Consensus Group, 2009. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin. Neurophysiol.* 120, 2008–2039.
- Rostamnejadi, A., Venkatesan, M., Alaria, J., Boese, M., Kameli, P., Salamati, H., Coey, J.M.D., 2011. Conventional and inverse magnetocaloric effects in $\text{La}_{0.45}\text{Sr}_{0.55}\text{MnO}_3$ nanoparticles. *J. Appl. Phys.* 110, 043905–043912.
- Rowe, J.R., Hertel, J.A., Barclay, J.A., Cross, C.R., Trueblood, J.R., Hill, D.D., 1991. Conductively cooled Nb_3Sn magnet system for a magnetic refrigerator. *IEEE Trans. Magn.* 27, 2377–2380.
- Schwab, S., Schwarz, S., Spranger, M., Keller, E., Bertram, M., Hacke, W., 1998. Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction. *Stroke* 29, 2461–2466.
- Tegus, O., Brück, E., Buschow, K.H.J., de Boer, F.R., 2002. Transition-metal-based magnetic refrigerants for room-temperature applications. *Nature* 415, 150–152.
- Titov, I., Acet, M., Farle, M., González-Alonso, D., Mañosa, L., Planes, A., Krenke, T., 2012. Hysteresis effects in the inverse magnetocaloric effect in martensitic Ni-Mn-In and Ni-Mn-Sn. *J. Appl. Phys.* 112, 073914–073919.
- Trekker, J., Leten, C., Struys, T., Lazenka, V.V., Argibay, B., Micholt, L., Lambrichts, I., Van Roy, W., Lagae, L., Himmelreich, U., 2014. Sensitive in vivo cell detection using size-optimized superparamagnetic nanoparticles. *Biomaterials* 35, 1627–1635.
- Trueblood, J.R., Claybaker, P.J., Johnson, J.W., Stankey, T.M., 1991. A vertically reciprocating NbTi solenoid used in a regenerative magnetic refrigerator. *IEEE Trans. Magn.* 27, 2384–2386.
- Tušek, J., Zupan, S., Prebil, I., Poredoš, A., 2009. Magnetic cooling development of magnetic refrigerator. *J. Mech. Eng.* 55, 1–10.
- van der Worp, H.B., Macleod, M.R., Kollmar, R., 2010. Therapeutic hypothermia for acute ischemic stroke: ready to start large randomized trials? *J. Cereb. Blood Flow Metab.* 30, 1079–1093.
- Vila, N., Castillo, J., Dávalos, A., Chamorro, A., 2000. Proinflammatory cytokines and early neurological worsening in ischemic stroke. *Stroke* 31, 2325–2329.
- VonLoh, M., Chen, R., Kluger, B., 2013. Safety of transcranial magnetic stimulation in Parkinson's disease: a review of the literature. *Parkinsonism Relat. Disord.* 19, 573–585.
- Wu, Y., Yang, X., Yi, X., Liu, Y., Chen, Y., Liu, G., Li, R.W., 2015. Magnetic nanoparticle for biomedical applications. *J. Nanotechnol. Nanomed. Nanobiotechnol.* 2, 1–7.
- Yanamoto, H., Nagata, I., Nakahara, I., Tohnai, N., Zhang, Z., Kikuchi, H., 1999. Combination of intraischemic and postischemic hypothermia provides potent and persistent neuroprotection against temporary focal ischemia in rats. *Stroke* 30, 2720–2726.
- Yu, B.F., Gao, Q., Zhang, B., Meng, X.Z., Chen, Z., 2003. Review on research of room temperature magnetic refrigeration. *Int. J. Refrig.* 26, 622–636.
- Zeng, H., Zhang, J., Kuang, C., Yue, M., 2011. Magnetic entropy change in bulk nanocrystalline Gd metals. *Appl. Nanosci.* 1, 51–57.
- Zverev, V.I., Tishin, A.M., Kuzmin, M.D., 2010. The maximum possible magnetocaloric ΔT effect. *J. Appl. Phys.* 107, 043907–043910.