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Magnetic resonance electrical impedance tomography for measuring electrical conductivity during electroporation

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Abstract

The electroporation effect on tissue can be assessed by measurement of electrical properties of the tissue undergoing electroporation. The most prominent techniques for measuring electrical properties of electroporated tissues have been voltage–current measurement of applied pulses and electrical impedance tomography (EIT). However, the electrical conductivity of tissue assessed by means of voltage–current measurement was lacking in information on tissue heterogeneity, while EIT requires numerous additional electrodes and produces results with low spatial resolution and high noise. Magnetic resonance EIT (MREIT) is similar to EIT, as it is also used for reconstruction of conductivity images, though voltage and current measurements are not limited to the boundaries in MREIT, hence it yields conductivity images with better spatial resolution. The aim of this study was to investigate and demonstrate the feasibility of the MREIT technique for assessment of conductivity images of tissues undergoing electroporation. Two objects were investigated: agar phantoms and in vivo liver tissue. As expected, no significant change of electrical conductivity was detected in agar phantoms exposed to pulses of all used amplitudes, while a considerable increase of conductivity was measured in liver tissue exposed to pulses of different amplitudes.

Keywords: magnetic resonance electrical impedance tomography, electrical conductivity, current density imaging, electroporation

(Some figures may appear in colour only in the online journal)
1. Introduction

Electroporation is a phenomenon caused by an electric field of adequate strength and duration externally applied to cells, that results in an increase of cell membrane permeability to various molecules, which otherwise are deprived of a transmembrane transport mechanism (Neumann et al 1982, Orłowski et al 1988, Tsong 1991, Sersa et al 1995, Mir et al 1999, Kotnik et al 2012). Cells can be exposed to an electric field by applying electric pulses generated by an electric pulse generator via electrodes. When electric parameters (number, shape, duration and repetition frequency of electric pulses and direction of electric field), electrode geometry and electrode positions are appropriately chosen and consequently cells are exposed to adequate electric field (Miklavcic et al 1998, 2006, Miklavcic and Towhidi 2010), permeabilization of the plasma membrane can be attained and the cell membrane reseals afterwards (Neumann et al 1982, Zimmermann 1982). Electroporation can thus be used to introduce various molecules into cells or to kill cells by using reversible or irreversible electroporation (Davalos et al 2005, Haberl et al 2013), respectively.

Monitoring of the electroporation process is one of the most important aspects of safe and efficient use of electroporation in clinical procedures such as electrochemotherapy (Marty et al 2006, Sersa and Miklavcic 2008, Miklavcic et al 2012) and nonthermal irreversible electroporation ablation (Garcia et al 2011, Rubinsky et al 2008, Neal et al 2013). As the membrane electroporation is a consequence of an induced transmembrane potential, which is directly proportional to the local electric field (Kotnik et al 2010), we proposed current density imaging (CDI) and magnetic resonance electrical impedance tomography (MREIT) techniques to determine the electric field distribution during electroporation (Kranjc et al 2011, 2012).

CDI is a magnetic resonance imaging (MRI) method for acquiring current density distribution inside conductive samples by measuring magnetic field changes caused by applied current (Joy et al 1989, Scott et al 1991, Sersa et al 1994, Gamba and Delpy 1998), whereas tissue conductivity can be obtained by MREIT, a technique used for reconstruction of electrical conductivity inside a tissue by means of current density (Kwon et al 2002a, Woo et al 1994, Eybolu et al 2001, Kwon et al 2002a, Seo et al 2003b, Oh et al 2003). As the measurement of current density and electrical conductivity is performed during electric pulse delivery, the electric field distribution determined also takes into account changes which occur in tissue due to electroporation (Kranjc et al 2012, Essone Mezeme et al 2012).

Measurement of electrical properties of tissues affected by electroporation has already been suggested as an approach to assessing the effects of electroporation (Ivorra and Rubinsky 2007, Granot et al 2009, Ivorra et al 2009, Grafstrm et al 2006, Edd et al 2006). It has been demonstrated by measuring changes in electrical properties of cells (Huang and Rubinsky 1999), cell cultures (Pavlin et al 2005) and also tissues (Pliquett et al 1995, Pliquett and Prausnitz 2000, Davalos et al 2002, Cukjati et al 2007, Pliquett and Schoenbach 2009) undergoing electroporation. The most prominent technique for assessment of changes in electrical properties of electroporated tissues have been voltage–current measurement of applied pulses (Cukjati et al 2007) and electrical impedance tomography (EIT) (Ivorra and Rubinsky 2007, Granot et al 2009). The method of measuring voltage and current of applied pulses was primarily established for real time electroporation control through adjusting voltage amplitude of pulses for in vivo nonviral gene therapy (Cukjati et al 2007). However, assessed electrical conductivity lacks information on tissue heterogeneity, as it depends on electrode geometry and location. EIT is based on multiple electrode placement around the tissue, through which small currents are injected while multiple measurements of voltage are carried out on the tissue boundary. The electrical conductivity of the tissue can then be reconstructed using the finite element method (Holder 2004). EIT studies showed a correlation between treatment...
outcome and changes of electrical properties of tissue, as its conductivity increased by up to 180% after the treatment (Ivorra et al. 2009). MREIT is in many aspects similar to EIT, as it is also used for reconstruction of conductivity images. The difference between the two techniques is in voltage and current measurements, which in EIT are limited to the boundaries of the measurement object, while in MREIT they cover the entire object, hence producing conductivity images with better spatial resolution.

Another benefit of measurement of electrical properties of tissues affected by electroporation would be a better characterization of numerical models of tissues in patient specific pre-treatment plans (Miklavcic et al. 2010, Zupanic et al. 2012, Neal et al. 2012, Pavliha et al. 2012). Namely, the local electric field in tissues is affected by applied electroporation pulses, which depend on local electrical conductivity, and vice versa electroporation increases the conductivity and consequently alters the electric field distribution (Sel et al. 2005, Pavselj et al. 2005). This makes it difficult to properly characterize the numerical model of the treated tissue, and therefore the pre-treatment plan cannot assure required coverage of the treated tissue with accurate electric field, as it relies mostly on the accuracy of the electrical conductivity of the treated tissue used in the numerical model (Kos et al. 2010). As there is a lack of tissue specific experimental data on tissue properties for reliable patient specific pre-treatment planning, MREIT could be of significant help in determining more accurate values of electrical conductivity for various tissues undergoing electroporation treatment.

The aim of our study was to investigate and demonstrate the feasibility of the MREIT technique for assessment of conductivity images of tissues undergoing electroporation. Two objects were investigated: an agar phantom and ex vivo liver tissue. Both were exposed to short high-voltage pulses, as are normally used in electroporation clinical applications. No alteration of electrical conductivity was expected in the agar phantom, while increased conductivity was anticipated in the ex vivo liver tissue as a result of electroporation.

2. Material and methods

2.1. Measurement setup

All experiments were done in an acrylic glass container measuring 21 mm in diameter and 2 mm in height as shown in figure 1. The measurement object, either the agar phantom or the liver tissue, was placed inside the container in which needle electrodes were inserted through four holes located on the top of the container.
The container was placed inside the horizontal bore superconducting magnet together with the radio-frequency (RF) probe. Electrodes were connected to an electric pulse generator, which was triggered by an MRI control unit and synchronized with the CDI pulse sequence. A low-pass filter was also used to avoid RF disturbances in the NMR signal. All experiments were repeated three times.

The CDI method was used for acquiring electric current density when electric pulses were delivered to the measurement object. The obtained current density was then used for reconstruction of electrical conductivity using the MREIT J-substitution algorithm.

2.2. Agar phantom and liver tissue

Measurement of electrical conductivity during electroporation was performed on two objects: an agar phantom and ex vivo liver tissue. The agar phantom was made of agar powder (Kemika, Croatia), 0.9% NaCl saline solution (Braun, Germany) and distilled deionized water (Braun, Germany) in order to decrease the electrical conductivity of the agar mixture to the range of ex vivo liver tissue. Ex vivo measurement of electrical conductivity was done on fresh chicken liver tissue, that was obtained from a slaughterhouse (Perutnina Ptuj, Ptuj, Slovenia) which operates in accordance with Slovenian law.

Both measurement objects were sliced into cylindrical shapes measuring 21 mm in diameter and 2 mm in height and placed in the acrylic glass container. They were replaced with a fresh sample after each electroporation pulse delivery to ensure identical initial conditions in all electroporation experiments.

2.3. Electroporation protocol

Electroporation was performed by applying two sequences of four high-voltage electric pulses (eight pulses altogether) with a pulse duration of 100 $\mu$s, a pulse repetition frequency of 5 kHz and an amplitude $U_e$ of either 500, 1000 or 1500 V. The electric pulses were delivered by a Cliniporator VITAE electric pulse generator (IGEA, Carpi, Italy) between two diagonal electrodes that were 14.8 mm apart. The electrodes were made of platinum–iridium, were cylindrically shaped and measured 1 mm in diameter. The voltage and current of the electric pulses were measured at the end of the last pulse with an oscilloscope (WavePro 7300A, LeCroy, USA) using a current probe (AP015, LeCroy, USA) and a high-voltage probe (PPE2KV, LeCroy, USA).

2.4. Magnetic resonance electrical impedance tomography (MREIT)

Electrical conductivity of agar phantoms and ex vivo liver tissue during electroporation was obtained by MREIT. MREIT is an MRI modality based on CDI for visualization of an electrical conductivity distribution inside a conductive sample.

CDI is an MRI method for acquiring the current density distribution inside conductive samples during the application of electric pulses (Joy et al 1989, Sersa et al 1994). The method is based on detecting magnetic field changes caused by applied electric current which is synchronized with the imaging sequence. Magnetic field changes cause a precession frequency shift that results in a precession phase shift ($\varphi$). The shift can be measured by the CDI imaging sequence (Sersa et al 1994):

$$\varphi = \gamma t_c B_z$$  \hspace{1cm} (1)

where $\gamma$ is the proton gyromagnetic ratio, $t_c$ is the total duration of the applied electric pulses and $B_z$ is the nonzero component of magnetic field in the direction of the static magnetic field and perpendicular to the direction of the imaging slice. The other two components ($B_x, B_y$)
were insignificant due to the measurement object geometry, in which currents were flowing predominantly in the direction perpendicular to the electrodes. When magnetic field changes were obtained by means of MRI, the current density distribution in measurement objects was calculated using Ampère’s law (Maxwell 1865):

$$\mathbf{J}_{\text{CDI}} = \frac{1}{\mu_0} \nabla \times \mathbf{B}. \tag{2}$$

A two-shot RARE (rapid acquisition with relaxation enhancement) current density MRI sequence was applied for mapping current density distributions during electroporation, as it allows faster magnetic field change mapping than the standard spin-echo based CDI (Sersa 2008). Parameters of the two-shot RARE imaging sequence were field of view 30 mm × 30 mm, imaging matrix 64 × 64, inter-echo delay 2.64 ms and echo time of the current encoding period 20 ms. MRI was performed on a Tecmag NMR spectrometer (Houston, TX) connected to an Oxford 2.35 T horizontal bore superconducting magnet (Abingdon, Oxfordshire, UK). The MRI system was equipped with Bruker microimaging accessories (Billerica, MA) with maximum gradients of 250 mTm⁻¹.

MREIT is a relatively new medical imaging modality based on numerical reconstruction of electrical conductivity inside a tissue by means of current density obtained by CDI (Woo et al 1994, Khang et al 2002, Seo and Woo 2011). The MREIT J-substitution algorithm was applied for reconstruction of electrical conductivity in the measurement objects (Kwon et al 2002b, Seo et al 2003a, Khang et al 2002). The algorithm is based on solving Laplace’s equation inside a mathematical model of the measurement object Ω₂ with the corresponding Neumann and Dirichlet boundary conditions on the measurement object outer boundary $\partial \Omega_{M_o}$ and on the electrode boundary $\partial \Omega_{Me+/−}$, respectively:

$$\nabla (\sigma_M \nabla u) = 0 \quad \text{in} \quad \Omega_M \tag{3}$$

$$\sigma_M \frac{\partial u}{\partial n_M} = 0 \quad \text{on} \quad \partial \Omega_M \tag{4}$$

$$u = U_e \quad \text{on} \quad \partial \Omega_{Me/+} \tag{5}$$

$$u = 0 \quad \text{on} \quad \partial \Omega_{Me/−} \tag{6}$$

where $\sigma_M$ is the electrical conductivity of the measurement object and $U_e$ is the voltage on the electrodes measured by the oscilloscope. Equations (3)–(6) are solved iteratively using the finite element method. After each iteration the solution $u$ was used in

$$\sigma^{∗}_M = \frac{|\mathbf{J}_{\text{CDI}}|}{|\nabla u|} \tag{7}$$

where $\sigma^{∗}_M$ is the new conductivity and $\mathbf{J}_{\text{CDI}}$ is the current density obtained by the CDI method. The iterative scheme lasts until the relative difference between two successive $\sigma_M$ values is negligible.

All equations were solved using the finite element method with the numerical computational environment MATLAB 2013a (MathWorks, Natick, MA) on a desktop PC (Windows 7, 2.66 GHz, 4 GB RAM).

2.5. Analysis of obtained electrical conductivity

The obtained electrical conductivity was analyzed for each applied voltage $U_e$ in region of interest $\Omega_{\text{MROI}}$ located inside the mathematical model of the measurement object $\Omega_M$ as shown in figure 2. $\Omega_{\text{MROI}}$ enclosed an area where the electric field was the highest and the largest alteration of electrical conductivity due to electroporation was expected (Miklavcic et al 2000).
Figure 2. A mathematical model of the measurement object $\Omega_M$. The electrical conductivity was analyzed inside region of interest $\Omega_{MROI}$ and along the diagonal line between the electrodes $\partial \Omega_{Mdl}$.

The electrical conductivity was also evaluated across the measurement object by determining the mean value of the conductivity $\sigma_{Mdl}$ along the diagonal line between the electrodes $\partial \Omega_{Mdl}$. The Student $t$-test was used to evaluate the statistical significance of differences between obtained electrical conductivities. All results were analyzed and statistically described using the commercial software MATLAB 2013a (MathWorks, Natick, MA) and its statistics toolbox.

3. Results

When electric pulses were delivered to the measurement object, electric current density was established inside and acquired by the CDI method. The current density distribution was then applied to the MREIT J-substitution algorithm for reconstruction of electrical conductivity. Electrical conductivities of both measurement objects exposed to electric pulses of different amplitudes ($U_e = 500, 1000, 1500$ V) within $\Omega_{MROI}$ are shown in figure 3.

No detectable changes in electrical conductivity were observed in $\Omega_{MROI}$ when agar phantoms were exposed to pulses of 500, 1000 and 1500 V except in the region close to the electrodes. Similarly, no changes were measured in $\Omega_{MROI}$ in liver tissue exposed to pulses with an amplitude of 500 V. Changes in electrical conductivity started to appear when the pulse amplitude was increased to 1000 V. Furthermore, the greatest change of conductivity was detected when liver tissue was exposed to pulses with the highest amplitude of 1500 V. Mean values of the conductivity along the diagonal line between the electrodes $\partial \Omega_{Mdl}$ for both measurement objects as a function of applied amplitude of electric pulses are shown in figure 4. Differences between mean values of electrical conductivity of agar phantoms exposed to pulses with amplitudes of 500, 1000 and 1500 V were not statistically significant ($p > 0.01$). An increase of 1.5 and 37.1 m$\text{Sm}^{-1}$ was measured when comparing mean values of electrical conductivity in liver tissue exposed to pulses with amplitudes of 500 V with mean values of electrical conductivity in liver tissue exposed to pulses with amplitudes of 1000 and 1500 V, respectively. These differences were statistically significant ($p < 0.01$).
Figure 3. Electrical conductivities of (a) agar phantom and (b) liver tissue exposed to electric pulses of different amplitudes ($U_e = 500, 1000, 1500$ V). Electric pulses were delivered between two needle electrodes (marked with + and −). Each image of the measured object is a crop of the field of view.

Figure 4. Mean values of electrical conductivity ($\sigma_{Mdl} \pm$ STD) along the diagonal line between the electrodes $\partial \Omega_{Mdl}$ for an agar phantom and liver tissue exposed to electric pulses of different amplitudes ($U_e = 500, 1000, 1500$ V). * denotes statistically significant difference ($p < 0.01$).
Table 1. Electric current at the end of the last pulse measured with the oscilloscope during pulse delivery for agar phantoms ($I_{\text{agar}}$) and liver tissue ($I_{\text{liver}}$). Results are presented as means ± standard deviations.

<table>
<thead>
<tr>
<th>$U_e$ (V)</th>
<th>500</th>
<th>1000</th>
<th>1500</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_{\text{agar}}$ (A)</td>
<td>0.07 ± 0.02</td>
<td>0.15 ± 0.03</td>
<td>0.22 ± 0.02</td>
</tr>
<tr>
<td>$I_{\text{liver}}$ (A)</td>
<td>0.16 ± 0.02</td>
<td>0.32 ± 0.08</td>
<td>0.67 ± 0.18</td>
</tr>
</tbody>
</table>

Electric currents measured with a current probe during application of electric pulses are presented in table 1 for agar phantoms and liver tissue exposed to pulses of all applied amplitudes.

4. Discussion

The aim of this study was to investigate and demonstrate the feasibility of the MREIT technique for assessment of conductivity images of tissues undergoing electroporation. The investigation was carried out on agar phantoms and ex vivo liver tissue that were subject to short high-voltage pulses, as are normally used in electroporation clinical applications. Different amplitudes of pulses were used in separate experiments to evaluate the feasibility of the proposed method to detect electrical conductivity changes of tissue.

As expected, no significant change of electrical conductivity was detected in agar phantoms exposed to pulses of all applied amplitudes. This was expected since agar lacks cell structure and therefore could not be affected by electroporation. In the region close to the electrodes there was a detectable conductivity increase as can be seen in figure 3. However, this was not a consequence of electroporation but of the electrodes, which caused distortions in the magnetic field and significant susceptibility artifacts in acquired phase images. Similar distortions in the magnetic field were also detected in liver tissue exposed to electric pulses. This presents a limitation to the MREIT approach of measuring electrical conductivity during electroporation, as it is not able to assess conductivity changes in the region close to the electrodes. Nevertheless, the region of interest of electroporation treatments is focused in the area between the electrodes and away from the electrodes, i.e. not in the immediate vicinity of the electrodes, where the highest electric field is established.

Significant differences can be observed in figure 3 when comparing changes of conductivity in agar phantoms with those in liver tissue. Furthermore, considerable differences can also be seen when comparing changes of conductivity within results of liver tissue exposed to pulses of different amplitudes. No conductivity change was, as in agar phantoms, still detected in liver tissue exposed to pulses with the amplitude of 500 V. A conductivity increase in liver tissue started to appear when the amplitude was increased to 1000 V. As they were located in regions away from the electrodes, detected conductivity changes could not be a consequence of magnetic field distortions due to the electrodes, but were rather a result of local tissue electroporation. This is even more evident in liver tissue exposed to pulses with the amplitude of 1500 V. Here, electrical conductivity increased by a factor of ~1.5 in the middle of $\Omega_{\text{MROI}}$, whereas in some regions it almost doubled. A similar nonlinear increase can be observed when comparing electric currents in liver tissue exposed to pulses with an amplitude of 1000 and 1500 V in table 1. Conductivity alterations are even more explicitly shown in figure 4, where electrical conductivity was evaluated along the diagonal line $\partial\Omega_{\text{MROI}}$, which extended through the area where the applied electric field was the highest and the...
electroporation process most efficient. Similar observations were also previously reported in studies employing EIT (Ivorra et al 2009) and voltage–current measurement of applied pulses (Cukjati et al 2007), where the conductivity of in vivo tissue increased by a factor of $\sim 1.5$ and $\sim 2.1$ when electric fields of the same magnitudes as used in this study were applied, respectively.

Different attempts to assess changes of tissue electrical properties that occur during electroporation have already been proposed, as mentioned in the introduction. Both the voltage–current measurement approach and EIT were successfully applied and showed an increase of electrical conductivity of tissue exposed to short high-voltage electric pulses. Unfortunately, there have been no reports on further development of the methods or on new results in recent times. On the other hand, new approaches to assessing the effects of electroporation have been introduced. They are all based on standard medical imaging procedures such as MRI (Hjouj et al 2012, Mahmood et al 2011, Zhang et al 2010, Rossmeisl et al 2014) and ultrasound (Lee et al 2007). The proposed methods are still focused solely on irreversible electroporation, where immediate changes of tissue properties can be detected by comparing images of different modalities acquired before and after application of pulses. Assessing changes of tissue properties during reversible electroporation is however a more demanding task, since there are no immediate visible physical changes in treated tissue. There are structural changes, which are reflected in diffusion-weighted images (Mahmood et al 2011), but they can only be detected after electric pulse delivery. Nevertheless, electrical conductivity is one of the known tissue properties which changes during reversible as well as in irreversible electroporation of tissue (Ivorra et al 2009). Therefore, different electroporation treatments could be monitored efficiently by assessing changes of conductivity in tissue during electroporation using MREIT or EIT. Furthermore, current density distribution is also obtained in addition to electrical conductivity with MREIT. This enables reconstruction of electric field distribution in tissue, the most important determinant of the electroporation process (Kotnik et al 2010).

As the measurement of electrical conductivity is performed during pulse delivery, the determined conductivity image takes into account all existing heterogeneities and changes which occur in tissue due to electroporation. Moreover, a single two-shot RARE CDI sequence takes about 20 s to acquire the current density distribution and the MREIT J-substitution algorithm an additional few seconds for reconstruction of electrical conductivity, but this could be further reduced. This makes CDI and MREIT capable of near real time monitoring of changes of electrical conductivity which occur during electroporation, as they can then be determined in a few tens of seconds after the beginning of pulse delivery. However, there is a limitation with the existing two-shot RARE CDI sequence, as it requires an application of at least two electric pulses with a delay of approximately 15 s between them in order to deliver complete current density information. This currently puts a frequency limitation on CDI, although hopefully future improvements of CDI algorithms and MRI scanners will enable us to reduce the required delay between applied pulses.

5. Conclusion

We have described and experimentally investigated the assessment of conductivity changes of tissues undergoing electroporation by means of MREIT on agar phantoms and liver tissue. The results show no significant change of electrical conductivity in agar phantoms exposed to pulses at all amplitudes used, but considerable increase of conductivity in liver tissue exposed to pulses of different amplitudes. This suggests that MREIT can indeed be used for detecting
electrical conductivity changes that occur in tissue exposed to short high-voltage pulses, and that the proposed method can be used for assessment and prediction of the electroporation effect on tissue.

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