Magnetic Resonance–Monitored Coaxial Electrochemical Ablation—Preliminary Evaluation of Technical Feasibility

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ABSTRACT

Purpose: To evaluate the technical feasibility of a coaxial electrode configuration to rapidly create a mechanically defined electrochemical ablation zone monitored by magnetic resonance (MR) imaging in real time.

Materials and Methods: A direct current generator supplied the nitinol cathode cage and central platinum anode for coaxial electrochemical ablation. Safety and efficacy were evaluated by measuring local pH, temperature, and current scatter in saline solutions. Ablation zone diameters of 3–6 cm (n = 72) were created on ex vivo bovine liver and verified by gross pathology. Feasibility of MR monitoring was evaluated using 8 swine livers to create ablations of 3 cm (n = 12), 4 cm (n = 4), and 5 cm (n = 4) verified by histology.

Results: Local pH was 3.2 at the anode and 13.8 at the cathode. Current scatter was negligible. Ablation progress increased relative to local ion concentration, and MR signal changes corresponded to histologic findings. In the ex vivo model, the times to achieve complete ablation were 15 minutes, 20 minutes, 35 minutes, and 40 minutes for diameters of 3 cm, 4 cm, 5 cm, and 6 cm, respectively. Ablation times for the in situ model were 15 minutes, 35 minutes, and 50 minutes for 3 cm, 4 cm, and 5 cm, respectively.

Conclusions: The coaxial configuration mechanically defined the electrochemical ablation zone with times similar to comparably sized thermal ablations. MR compatibility allowed for real-time monitoring of ablation progress.

ABBREVIATIONS

DC = direct current, EChT = electrochemical treatment, NaCl = sodium chloride, PEEK = polyethylethylketone, TR/TE = repetition time/echo time, TSE = turbo spin echo, VIBE = volumetric interpolated breath-hold examination

Percutaneous ablation of malignant hepatic tumors is a widely accepted alternative in patients who are poor candidates for surgical resection. These techniques are increasingly used because of their low profile and lower cost and because they can be performed on patients who have contraindications to surgery (1). In thermal ablation, lesion size and location could result in incomplete ablation and
complications secondary to thermal injury and heat sink effects (1,2).

The use of direct current (DC) electricity for selective ablation of tissue was originally explored for treatment of tumors and thrombosis of aneurysms (3,4). Although thermal ablation superseded this technique throughout the 20th century, more recent technologic developments and the emergence of irreversible electroporation inspired further investigations into the clinical utility of electrochemical treatment (EChT). EChT is a nonthermal percutaneous ablation technique that uses DC electricity to cause tumor necrosis by generating a strongly acidic microenvironment at the anode and strongly alkaline microenvironment at the cathode (5–7). Studies showed no effect on systemic pH; necrosis was due primarily to pH-mediated protein denaturation and secondarily to disruption of cell membranes and coagulation of local capillaries (8–12). Although thermal ablation relies on heat dispersion, which is susceptible to perivascular heat sink, the acids and bases of EChT penetrate into the surrounding tissues via diffusion and electrically driven migration (13,14). This feature results in a sharp ablation margin regardless of traversing vessels (11,12). The primary considerations for ablation size and rate for EChT is the level of current and electrode distance (11,12,15–18). Additionally, magnetic resonance (MR)–compatible electrodes can be used in EChT.

EChT has been used to treat lung, gastrointestinal, and soft tissue tumors with minimal local discomfort and morbidity (19,20). Reported 5-year survival was 39% for lung, 15% for primary liver, and 50% for breast carcinomas (13). However, EChT has not gained widespread clinical use in Western countries because of the lack of standardized treatment algorithms, the paucity of published clinical trials, and because ablations are time-consuming and difficult to contour with traditional EChT (11–13,19,20). We propose a novel approach to EChT using a coaxial configuration of the electrodes consisting of a central platinum anode with a peripheral nitinol cathode cage. The purpose of this study was to test the feasibility of a coaxial electrode configuration to mechanically define the ablation zone, amplify EChT by achieving ablation times comparable to other modalities, and allow for real-time monitoring of ablation progress with MR imaging.

MATERIALS AND METHODS

Electrochemical Equipment

A B&K Precision 1901 adjustable (0–32 V) DC power supply (Yorba Linda, California) served as the electricity generator. An 18-gauge (1.024-mm-diameter) 99.9% pure platinum wire (T.B. Hagstoz, Philadelphia, Pennsylvania) was cut into 20-cm-long pieces to serve as the anode. A 16-gauge (1.291-mm-diameter) medical-grade (ASTM F2063) nitinol wire (Fort Wayne Metals, Fort Wayne, Indiana) was cut into ten 20-cm-long pieces to serve as the cathode cage.

In Vitro Model

In vitro experiments were conducted in saline solutions of 0.45%, 0.9%, 1.8%, 2.7%, and 3.6% weight/volume sodium chloride (NaCl) titrated to a pH of 7.5 to evaluate EChT ablation with respect to local ionic content. The cathode cage was constructed by arranging the ten 16-gauge nitinol electrodes into a regular 3-cm-diameter cage using a custom-designed polyethylene-tetrafluoroethylene (PEEK) needle guide. A single platinum anode was placed in the isocenter of the cage. All electrodes had a 2-cm active tip. The DC power supply was connected and set to constant voltage of 32 V with variable current (Fig 1).

Figure 1. Coaxial electrochemical ablation system. The coaxial ablation system consists of an 18-gauge platinum anode loaded into the center of a needle guide. A cage consisting of ten 16-gauge nitinol cathodes was arranged around the anode. The anode and cathodes were connected to a DC generator.
positioning of the electrodes. A coronal oblique VIBE T1 was obtained perpendicular to the long axis of the cathode cage to serve as the monitoring sequence.

The DC generator was set to constant voltage (variable current) at 32 V, and ablations were performed at each diameter. VIBE T1 monitoring sequences were performed and analyzed in real time during live ablation at 3-minute intervals for the 3-cm ablation and 5-minute intervals for the 4-cm and 5-cm ablations. There were 20 ablations performed on eight swine at 3 cm (n = 12), 4 cm (n = 4), and 5 cm (n = 4). Ablation and MR monitoring were allowed to continue for up to 60 minutes until the anode and cathode signal changes coalesced. Local specific absorption rate, the measure at which energy is deposited into the subject during MR imaging, was kept less than 10 W/kg to ensure limited heating by the MR monitoring sequences. On completion of ablation, all electrodes were removed, and TSE T2 and VIBE T1 sequences were obtained perpendicular to the ablation axis.

Subsequently, the liver was explanted and sectioned into 1-cm-thick samples for gross pathologic examination. The samples were fixed in formalin within 5 hours of euthanasia and stained with hematoxylin-eosin for histologic analysis. Complete ablation was achieved when the ablation zone extended through the entire thickness of the liver defined by the cathode cage. Histology confirmed ablation with visualization of architectural destruction, cell membrane lysis, or pyknotic nuclei indicating necrosis within the ablation zone. Correlation between gross pathology and MR signal changes was calculated.

**Statistical Analysis**

Statistical analysis was performed using Stata v13.1 (StataCorp LP, College Station, Texas). Pearson product-moment coefficient was calculated to compare ablation zone diameters measured on gross pathology and VIBE T1 and TSE T2 sequences obtained after ablation. Paired Student t tests were applied to determine the correlation in diameters between the measurement modalities.

**RESULTS**

**In Vitro Model**

Anode heating, local pH measurements, and current depended on the voltage settings and NaCl concentration. Heating was observed at the anode surface with temperatures of 49°C, 61°C, 83°C, 86°C, and 89°C by 10 minutes in 0.45%, 0.9%, 1.8%, 2.7%, and 3.6% weight/volume NaCl. No heat was produced at the cathode, and the heating effect of the system was solely the result of heat production at the anode. An increase in NaCl concentration resulted in increased anode heating (Fig 2a).
Local measurements of pH demonstrated values as low as 3.2 on the surface of the anode and values as high as 13.8 on the surface of the cathode. Current was found to be contained within the cathode cage. A marked dropoff in current was observed 1 cm beyond the cathode cage with all measurements of current scatter less than 0.05 mA regardless of saline concentration (0.45%–3.6% weight/volume NaCl) and current (3.3–10.8 A).

System current was observed at a maximum of 4.9 A at 6 minutes for 0.45%, NaCl, 5.7 A at 5 minutes for 0.9% NaCl, 7.1 A at 5 minutes for 1.8% NaCl, 8 A at 4 minutes for 2.7% NaCl, and 10.8 A at 3 minutes for 3.8% NaCl. An increase in NaCl concentration also increased the local current and rate of electrolytic reaction (Fig 2b).

MR compatibility was confirmed with the pH-sensitive gel at 32 V (0.6–2.2 A). The visual pH changes on the gel corresponded to the local pH measurements. The MR signal changes seen on TSE T1 also correlated to the pH changes seen on the gel model (Fig 3).

**Ex Vivo Model**

During tissue ablation, a zone of coagulative tissue damage was observed around the anode, and a zone of liquefaction was observed around each cathode. These ablation zones maintained a sharp border between ablated and normal tissue and increased in size relative to increasing voltage, current, and times of ablation.

**Figure 2.** (a) Anode temperature versus time. Using a 3-cm cathode cage at 32 V, temperature measurements were taken at the surface of the anode. Temperature was seen to increase with time and with increasing concentrations of saline. By comparison, no heating was produced at the cathode. (b) Current versus time. Using a 3-cm cathode cage at 32 V, system current measurements were taken within the cathode cage. System current was seen to increase with increasing concentrations of saline. For all saline concentrations, the current increased with time as ions were consumed; temperatures rose until the system reached peak ion consumption. The current subsequently decreased as fewer ions were available for electrolysis. NS = normal saline.

**Figure 3.** pH-sensitive gel. MR of a pH-sensitive phenol red 1.5% agarose/normal saline gel demonstrates MR signal changes (arrowheads) around the cathodes (thick arrow) and anode (thin arrow) during EChT using TSE-T1 (TR/TE 100/2 ms) at 1-minute ablation (32 V, 0.6–2.2 A). The corresponding gel is red in color (arrowhead) at alkaline pH around the cathodes (thick arrow) and yellow in the acidic environment about the anode (thin arrow). Normal saline has a pH of about 5.3, giving the background gel an acidic color signal.
All ablations were mechanically constrained by the cathode cage to the tissue between the cathode and the anode.

At 12 V (0.1–0.3 A), complete ablation of the desired target zone could not be achieved by 40 minutes for any cathode cage size. At 22 V (0.4–0.9 A), full ablation was achieved only for the 3-cm cage diameter at 35 minutes. The 4-, 5-, and 6-cm cage diameters lacked complete ablation by 40 minutes. At 32 V (0.8–1.4 A), complete ablation was achieved by 15 minutes for the 3-cm cage diameter, 20 minutes for the 4-cm cage diameter, 35 minutes for the 5-cm cage diameter, and 40 minutes for the 6-cm cage diameter (Fig 4b).

In Situ Model
The platinum and nitinol electrodes on the VIBE T1 and TSE T2 sequences caused minimal metallic artifact. Within the first minute of ablation, blooming artifact...
from microbubbles of gas was seen at the anode, which dissipated by 5 minutes. The ablation zone propagated circumferentially from the anode as a zone of T1 hypointense signal with a leading edge of T1 hyperintense signal. Similar signal changes were observed at each cathode with a central T1 hypointense signal and leading edge of T1 hyperintense signal (Fig 5a). The T2 sequences obtained after ablation demonstrated increased signal around the cathode cage, which correlated with liquefied tissue at gross pathology (Fig 5b). The time to achieve complete ablation was slower for each diameter compared with the ex vivo model. At 32 V (0.2–1.4 A), complete ablation was achieved by 15 minutes at the 3-cm cage diameter, 35 minutes at the 4-cm cage diameter, and 50 minutes at the 5-cm diameter as verified on histology (Fig 6a–d).

Histologic analysis demonstrated complete loss of hepatic architecture in the zones of coagulative necrosis.

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**Figure 5.** (a) Real-time MR monitoring. In situ ablation progress was monitored using T1 VIBE sequences perpendicular to the long axis of the cathode cage. Sequences were performed before, during (3-min intervals), and after ablation with the electrode wires removed. In this example of a 3-cm ablation zone, gas artifact (white arrow) was initially seen around the anode (thin black arrow) at 1 minute, which dissipated by 6 minutes. The T1 hypointense signal was seen to propagate circumferentially from the central anode toward the cathode (thick black arrow) with a leading edge of the T1 hyperintense signal (black arrowhead). A similar leading edge of the T1 hyperintense signal was seen around the cathode (white arrowhead). Complete ablation was achieved when the signal changes coalesced. (b) Gross pathology correlation. On the left, a TSE-T2 (TR/TE 5,400/96 ms) image obtained after ablation demonstrated T2 hypointense signal representing the ablation zone (arrowheads). The central T2 hyperintense signal around the anode (thin arrows) represented hemorrhagic necrosis, and the T2 hyperintense signal around the cathodes represented liquefactive necrosis (thick arrows). These MR findings correspond to the changes seen on gross pathology.
at the anode and liquefactive necrosis at each cathode. These findings included dissolution of the hepatic lobule fibrous septa, loss of hepatocyte sinusoid configuration, cell membrane lysis, and pyknotic nuclei. The liquefactive necrosis at each cathode correlated to the signal changes on MR imaging and had a sharp zone of transition with the adjacent normal hepatic parenchyma. The intervening hepatocytes located between the anode and cathode had mild loss of hepatic architecture and uniformly pyknotic nuclei also indicating necrosis.

**Statistical Analysis**

The gross pathology diameters of the 3-cm, 4-cm, and 5-cm in situ ablation zones strongly correlated to observed signal change diameters on corresponding VIBE T1 and TSE T2 sequences obtained after ablation. The VIBE T1 diameters had a Pearson correlation coefficient of $r = 0.997$ ($P < .001$); the T2 measurements also showed $r = 0.997$ ($P < .001$). The T1 measurements underestimated the ablation size by 2.1 mm ± 0.08 compared with the gross pathology ($P < .001$), whereas the T2 measurements overestimated the ablation size by 1.8 mm ± 0.08 ($P < .001$).

**DISCUSSION**

EChT is a nonthermal ablation technique that causes tissue necrosis by generating extreme pH changes at the anode and cathode resulting in protein denaturation (8,9,11). The main electrochemical reactions at the anode are decomposition of water and oxidation of chloride ions resulting in free hydrogen ions and a strongly acidic microenvironment resulting in coagulative necrosis (24):

$$2\text{H}_2\text{O} \leftrightarrow \text{O}_2 + 4\text{H}^+ + 4\text{e}^-$$

$$2\text{Cl}^- \leftrightarrow \text{Cl}_2 + 2\text{e}^-$$

At the cathode, the main reaction is the decomposition of water into hydroxyl ions and a strongly alkaline microenvironment resulting in liquefactive necrosis (24):

$$2\text{H}_2\text{O} + 2\text{e}^- \leftrightarrow \text{H}_2\text{O}_2 + 2\text{OH}^-$$

Necrosis propagates as these toxic products diffuse through tissue resulting in a sharp zone of transition between ablated and normal tissue without damage to large vessels or extension beyond an organ’s capsule (11,12,25). The rate and size of EChT ablation zones are determined by the electrode surface area, local ionic content, as well as total charge deposited and, in contrast to thermal ablation, do not depend strongly on local blood flow (11–13,16,18). As demonstrated in the in vitro experiments, increasing local ionic content increases local current and electrochemical reactions.

Historically, conventional EChT was performed by percutaneous placement of anode-cathode pairs through a target tumor and utilized currents up to 30 mA (13,19,20).
The current was limited in conventional EChT because of the concern for scatter affecting adjacent nerves and inability for conventional generators to overcome tissue resistance (12). This limited current resulted in EChT ablation times longer than 60 minutes, with some patients requiring multiple sessions over several days (11–13,19,20). In addition, the paired electrodes of conventional EChT were cumbersome and difficult to precisely contour larger targets. Platinum was the material of choice for electrodes because of its stability from dissolution by the anodic current (11–13). However, the cathode is protected from electrochemical dissolution, and metals with mild solubility, such as nitinol, can safely serve as the cathodic electrode for EChT (26).

The coaxial configuration of this study differs from conventional EChT in that it uses a single anode in the center of a cathode cage. All applied currents as well as the ablation zone are mechanically constrained within the cage, and current leakage is negligible. The proposed coaxial design and DC generator allow the current to be as high as 1.4 A at 32 V during the ex vivo and in situ experiments. In our in vitro proof-of-concept experiments, we found that current was virtually undetectable outside the cathode cage regardless of saline concentrations or DC generator current. By permitting greater local current, the coaxial design is capable of achieving 3- to 5-cm-diameter ablations in times comparable to the time needed for thermal ablation of a lesion of similar size (27,28). Gross pathology and histology confirmed a sharp zone of transition between ablated and normal liver. The cathode cage defined the periphery of the ablation zone with ablation progressing between the anode and cathodes regardless of intervening architecture. Moreover, the signal changes on MR imaging correlated to the ablation zones seen on gross pathology.

Although conventional EChT lacked an adequate method to monitor progress, coaxial electrochemical ablation progress can be monitored in real time with MR imaging. Electrodes were loaded into the needle guide through the existing cutouts on the body matrix coil, and MR sequences were performed during live ablation with minimal artifact. The VIBE T1 sequence was chosen for monitoring because of its rapid acquisition and minimization of metal-induced artifact (29). Scan times of 22 seconds were capable of demonstrating signal change during active ablation. This real-time monitoring of ablation progress allows for electrode adjustment to ensure adequate coverage of the tumor. Additionally, the sharp zone of transition between ablated and nonablated tissue without substantial image degradation from artifact allows one to visualize accurately whether EChT ablation has completely treated a target lesion using standard clinical MR sequences.

This initial feasibility study has several limitations. The presented results were derived from in vitro and ex vivo studies as well as in situ ablations in euthanized swine. No tumor models were used, and it is possible that multiple central anodes would be necessary for large or irregularly shaped tumors. Similar to other ablation techniques, the main limitations for additional electrodes in EChT are procedure time and appropriate access. For the in situ studies, a laparotomy was performed to place the PEEK needle guide on the liver surface, which is impractical in live animals. To overcome these limitations, we are developing a percutaneous approach using a collapsible compact delivery system; this will allow for survival studies and additional characterization of systemic resistance, thrombosis, and complications after ablation in a living and perfused liver. Additionally, thermal effects on the electrodes by MR pulse sequences will be monitored in real time with an MR-compatible thermometer. Lastly, the collapsible compact delivery system will allow for direct comparison with existing MR–compatible thermal ablation techniques.

In conclusion, we have described our initial experience and demonstrated technical feasibility of a coaxial electrode configuration for electrochemical ablation. The coaxial configuration improves ablation times over conventional EChT with times similar to comparably sized thermal ablations. The coaxial configuration has the added capability of mechanically defining the ablation margins, and progress can be monitored in real time using standard clinical MR sequences.

REFERENCES


