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ORIGINAL ARTICLE

Induction of rapid, reproducible hepatic ablations using next-generation, high frequency irreversible electroporation (H-FIRE) *in vivo*

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Abstract

Introduction: Irreversible electroporation (IRE) offers an alternative to thermal tissue ablation *in situ*. High-frequency IRE (H-FIRE), employing ultra-short bipolar electrical pulses, may overcome limitations associated with existing IRE technology to create rapid, reproducible liver ablations *in vivo*.

Methods: IRE electrodes (1.5 cm spacing) were inserted into the hepatic parenchyma of swine (n = 3) under surgical anesthesia. In the absence of paralytics or cardiac synchronization five independent H-FIRE ablations were performed per liver using 100, 200, or 300 pulses (2250 V, 2-5-2 μs configuration). Animals were maintained under isoflurane anesthesia for 6 h prior to analysis of ablation size, reproducibility, and apoptotic cell death.

Results: Mean ablation time was 230 ± 31 s and no EKG abnormalities occurred during H-FIRE. In 1/15 HFIRE's minor muscle twitch (rectus abdominis) was recorded. Necropsy revealed reproducible ablation areas (34 ± 4 mm^2, 88 ± 11 mm^2 and 110 ± 11 mm^2; 100-, 200- and 300-pulses respectively). Tissue damage was predominantly apoptotic at pulse delivery ≤200 pulses, after which increasing evidence of tissue necrosis was observed.

Conclusion: H-FIRE can be used to induce rapid, predictable ablations in hepatic tissue without the need for intraoperative paralytics or cardiac synchronization. These advantages may overcome limitations that restrict currently available IRE technology for hepatic ablations.

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Introduction

Thermal tissue destruction using radiofrequency or microwave ablation (RFA/MWA) is an effective treatment for primary and metastatic liver tumors.[1–3] Using RFA or MWA tissue within the ablation zone is thermally destroyed, resulting in necrotic tissue death and preservation of surrounding liver tissue.[3,4] For tumors >3 cm, a radiologic response rate of 91% following RFA is reported with rates of local recurrence, distant intrahepatic recurrence, and extrahepatic metastasis, independent of tumor size.[5] Increasing evidence suggests MWA offers superior physical properties for tumor ablation compared to RFA,[2] and reproducible large-volume hepatic ablations (3–7 cm) can be effectively performed with MWA.[6] In addition, MWA creates more predictable ablations in the (relative) absence of heat sink, while allowing real-time, intraoperative ablation visualization with color Doppler ultrasound (US).[7]

Irreversible electroporation (IRE) is an alternative to thermal ablation that employs high-voltage (1–3 kV) short (50–100 μs) monopolar pulses (Fig. 1a). Briefly, pulsatile electrical currents are discharged between 2 and 6 electrodes placed across the

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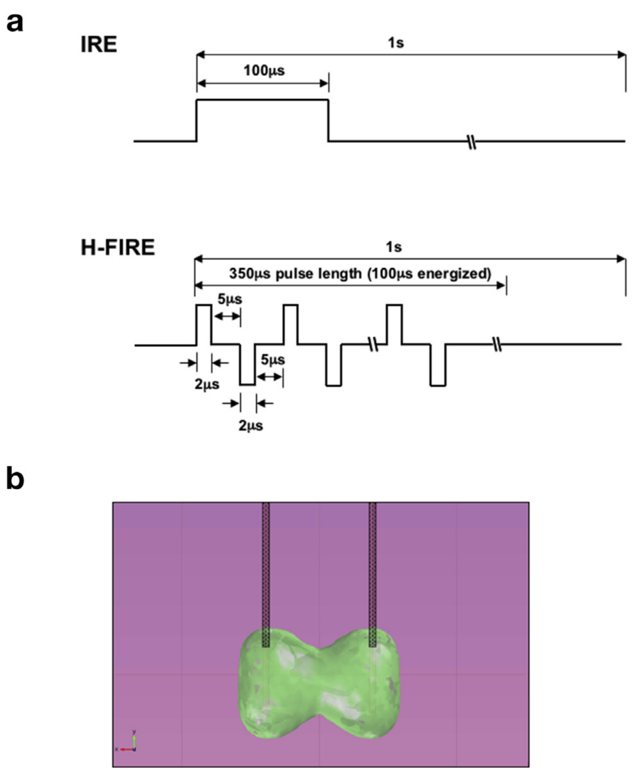

Figure 1 Comparison between conventional irreversible electroporation (IRE) and high-frequency IRE (H-FIRE). **a**). Schematic representation of electrical pulse delivery using conventional IRE (upper) and H-FIRE (lower). **b**). Theoretical, computer modeling of predicted ablation zone created using H-FIRE technology

target region, resulting in nanoscale pore formation in cell membranes located within electric fields ≥500 V/cm. Once these nanopores form, cells are unable to regulate ion and water movement leading to the induction of apoptosis.[8] Unlike thermal ablation, events following IRE occur in the absence of coagulative necrosis, and underlying organ architecture, including vascular and ductal structures, is preserved.[9,10] In addition, the (relative) absence of thermal damage using IRE means the ablation region is predominantly contained between the electrodes, the spacing of which can be varied, with spacing up to 4 cm being reported for dual electrodes.[10,11] Clinical outcomes of IRE in HPB surgery are reported, IRE being demonstrated to be a safe and effective means to ablate tissue.[10,12] With refinement of technique and improved patient selection, local complications (including bleeding, bile duct perforation, and bowel injury) can be minimized. A recent, multi-institutional series demonstrated safety and efficacy of IRE for treating pancreatic adenocarcinoma.[13]

Despite the potential advantages IRE offers over thermal ablation, other factors must be considered. For example, cardiac electrical asynchrony, with potential for arrhythmia, and severe tetanic muscle contraction[8,10] means IRE must be performed in conjunction with synchronization to cardiac activity and muscle paralysis. Similarly, the time required for electrode placement and synchronization of electrical pulses with cardiac output, means intraoperative time for IRE is typically longer than required for RFA/MWA,[2,3,8,13,14] the majority of which is performed using a laparoscopic approach.[2,6] Following IRE ablation the slower induction of apoptotic cell death, as opposed to rapid thermal necrosis using RFA/MWA, can limit post-operative imaging to determine extent of tumor destruction. Collectively, these factors have limited the use of IRE in HPB surgery to treating cancers for which resection or thermal ablation are unviable.[13]

High frequency irreversible electroporation (H-FIRE) is a novel IRE approach developed to overcome many of the challenges existing IRE faces.[15,16] Unlike the monopolar electrical pulses used in existing IRE (delivered in the 100 µs range), H-FIRE employs ultra-short (1–2 µs) bipolar electrical pulses (Fig. 1a).[15] By doing so, H-FIRE changes polarity rapidly enough to minimize nerve or muscle stimulation. Similar to IRE, changes in cellular transmembrane potential within the H-FIRE field result in nanopore formation and cellular apoptosis (Fig. 1b).[16] These properties allow H-FIRE to generate reproducible, homogenous tissue ablations in the absence of muscle contractions, so obviating the requirement of intraoperative paralytics and, potentially, cardiac synchronization.[15,17] Thus, H-FIRE should require shorter ablation times than existing IRE, while maintaining the advantage of preserving the underlying architecture.

This study sought to determine whether H-FIRE can be employed to induce reproducible, effective ablations in a swine liver model *in vivo*, and establish optimal pulse delivery parameters in the hepatic parenchyma to induce apoptotic cell death.

Methods

Assurances

Female Yorkshire pigs were used for these studies (Palmetto Research Swine, Reevesville, SC). All studies were approved by the Institutional Animal Care and Use Committee (IACUC) and conformed to the National Institutes of Health Guide for Animal Care and Use of Laboratory Animals.

Surgical procedures

In total, 15 ablations were performed in 3 separate animals with n = 5 ablations/H-FIRE pulse-setting. Prior to initiating studies animals were randomized for pulse delivery setting (100-, 200- or 300-pulses) such that no animal received more than 2 H-FIRE ablations at the same pulse setting. The number of ablations performed was selected to provide sufficient statistical power for analysis, while ensuring a sufficient distance existed between ablation sites to avoid prior ablations, and to reduce potential variability in time between completing all of the ablations in a single animal and euthanasia 6 h later.

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