Irreversible Electroporation

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Section Summary:

- Irreversible electroporation (IRE) affords a treatment modality for focal ablation of soft tissue while preserving vital structures such as vessels, ducts, and potentially nerves
- IRE uses electrical fields to increase the permeability of cells resulting in reversible and irreversible cell death
- IRE must be performed with muscular paralysis and cardiac gating during general anesthesia to avoid triggering motor or cardiac contractions respectively from the electrical impulses it generates
- Presently IRE is used to treat prostate and renal cell carcinoma with a range of depths and breadths of ablation zones with existing IRE platforms

1. Introduction

Irreversible electroporation (IRE) is a biophysical phenomenon by which the phospholipid bilayer of the cellular membrane develops stable "nanopores" when exposed to external electrical fields of appropriate duration.[1] This non-thermal pore creation leads to cellular instability and cell death. As early as the 19th century, electric pulses were used for water purification due to their bactericidal effect. Research by Sale and Hamilton in the 1950s and 60s determined that the bactericidal effect was unrelated to the thermal effect of the electric current but was due to irreversible loss of cell membrane function.[2] In 2005 Davalos et al discovered that IRE could be used to ablate clinically significant amounts of soft tissue.[3] There were already many other methodologies for focal ablation of soft tissue, however IRE had a significant potential advantage. IRE allows for preservation of collagen and other protein and lipid-based structures including vessels and ducts and possibly nerves.[4] Onik et al were the first to use IRE to ablate prostates in dogs and reported preservation of erectile function and continence in all the dogs undergoing IRE.[5] Neal et al first studied safety and feasibility of IRE in prostate cancer patients who subsequently underwent radical prostatectomy.

They found the treatment to be safe and observed complete ablation of the prostate cells in the treated area with preservation of neighboring structures. [6] Over the last decade, IRE has been increasingly used for tissue ablation in humans with several reported trials in prostate, kidney and advanced pancreatic cancer due to its ability to achieve non thermal tissue ablation while preserving vital structures at the same time.

2. Physics

Irreversible electroporation (IRE) is a biophysical phenomenon that occurs in cell membranes as they are exposed to an external electric field of sufficiently high intensity.[1] The electric field acts as a physical stimulus, bringing about cell alterations that result in increased permeability through formation of nanoscale pores in the cell membrane.

Electroporation can be reversible or irreversible depending upon the amplitude and duration of electric pulses with a larger strength of electric field required for irreversible electroporation. Reversible electroporation is used frequently in medicine and is becoming increasingly popular to deliver non-permeable drugs or molecules into specific tissues in the body through the generation of localized electrical fields. [3] The exact mechanism by which IRE causes cell death is unknown, however it is postulated that IRE permanently disrupts the osmotic balance of cell, resulting in the leakage of cellular contents and cellular death by apoptosis. IRE has also been shown to result in DNA fragmentation further contributing to cytotoxicity.

Typically, as external electrical fields are applied to living material, there is a loss in resistance and subsequent heat generation. Unlike thermal energy modalities, such as **cryoablation** and high intensity focused **ultrasound ablation**, IRE preserves the important structural components, such as extracellular matrices. The sparing of tissue scaffolds and vessels gives IRE a potential advantage over thermal ablative modalities in the preservation of vital structures, as IRE parameters are tissue-specific and designed to minimize the extent of thermal injury.

2. Mechanism of Delivery

For IRE treatment, patients are placed under general anesthesia with neuromuscular blocking agents which are essential to prevent muscular contractions from the IRE electric pulse generation. The electric field is typically delivered percutaneously into the treatment tissue via small 19 gauge (~1mm) monopolar needle electrodes. These electrodes are currently available in 15cm and 25cm lengths. The active region of the electrode tip can be adjusted from 0.5 to 4cm, allowing the treating physician to adjust the parameters of the focal tissue ablation to correspond to tumor size and shape. A brachytherapy grid and placement of electrodes through the perineum is utilized to deliver focal energy to the prostate in order to treat a prostate cancer lesion. The ablation zone can also be adjusted to the target by utilizing anywhere from 2 up to 6 electrodes. Once the probes are localized to the targeted tissue, typically 50-100 pulses are delivered around 100 microseconds while gated to the patient's continuous electrocardiogram (EKG). During ablation, software provides feedback regarding tissue parameters and optimal treatment metrics for ideal treatment.

After treatment for focal prostate cancer ablation, it has been the authors practice 1) to measure PSA quarterly to identify the new PSA nadir and 2) to perform an MRI/US fusion prostate biopsy at one-year post-treatment. It is important that treating clinicians document both in-field and out-of-field recurrences to better understand appropriate patient selection as well as identifying continuous process improvement for modifying treatment technique.

3. Safety

The electric pulses used to achieve IRE can interfere with electrical activity of the heart via electrical and cardiac muscular interference, therefore IRE is contraindicated in patients with a history of cardiac arrhythmias and/or recent myocardial infarction. Ablation of lesions in the thorax is contraindicated in patients with implanted pacemakers and defibrillators. The high voltage pulses can also stimulate skeletal muscle, so to prevent gross motor movement due to muscular contractions, patients must undergo complete motor blockade via anesthetic paralytics during pulse generation.

4. Devices

Presently, IRE is performed by the Nanoknife IRE system produced by Angiodynamics. The system consists of two components, monopolar needle electrodes and a direct current generator with incorporated treatment planning software. Nanoknife electrodes are 19 gauge in width and come in two lengths, 15 cm and 25 cm. The electrodes have an adjustable active electrode tip ranging from 0.5-4 cm to allow for different sizes of electric fields and associated ablation zones. The electrodes are plugged into the generator and energy is delivered through a foot pedal.

5. Clinical Indications

In urology, IRE has been used for the management of prostate and kidney cancers.

a) Prostate cancer: IRE is most commonly used for focal treatment of prostate cancer, however hemi-ablation and whole gland treatments with IRE have also been reported. In a systematic review of 10 studies on IRE for management of prostate cancer, Morozov et al reported failure rates of 10-39% in the ablation zone. [7] Guenther et al used IRE to achieve focal, sub-total, and whole-gland ablation with recurrent disease in 10 percent of the cases during the follow up. [8]

b) Kidney cancer: IRE has also been used for kidney cancer ablation. A recent systematic review included 10 studies with 83 total patients who underwent IRE for renal masses. 78% of the patients in the combined analysis were found to have a complete response as determined by imaging. [9]

6. Complications

Most adverse effects after prostatic IRE are mild. Severe or life-threatening complications are extremely rare. The most common complications after prostate IRE are urinary retention, dysuria and mild hematuria. Guenther et al reported 10% urinary retention risk in patients undergoing IRE in their experience, with another 7% reporting dysuria. [8] Urinary retention was more common in those with larger prostates and/or larger ablation zones. Other less common adverse events reported after prostate IRE are perineal pain, urinary tract infection/prostatitis and recto-prostatic fistula.

Similar to prostatic IRE, IRE of renal tumors was found to be safe with transient hematuria (13%) and asymptomatic perirenal hematomas (8%) being the most common adverse events.[9]

Presentations

Irreversible Electroporation Presentation

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