Irreversible Electroporation
- from bench to bedside -

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Disclaimers

- Paid consultant for Angiodynamics
- Funding for clinical trials by Angiodynamics
- Honorarium for today’s clinical presentation provided by AngioDynamics, Inc.
- The NanoKnife System is cleared in the US, Canada and EU for surgical ablation of soft tissue. Consult your AngioDynamics representative for indications for use in specific countries. The NanoKnife System has not been cleared for the treatment or therapy of a specific disease or condition.
- This presentation provides overviews of clinical research and experiences; they are not intended to promote the use of the NanoKnife System for any specific disease or condition. The research that is the subject of this presentation was funded, in whole or in part, by grants from AngioDynamics.
Agenda

• History of IRE
• Physical principle of IRE
• Preclinical data
• Clinical applications
Thermal ablation uses electromagnetic spectrum.

Physical principle of IRE
IRE uses short intense electrical pulses to
- destabilize cell membranes by creating “nanopores”
- induce cell death through apoptosis (not necrosis!)
- kills all cells within ablation zone (exposed to ≥650V/cm)
- preserves extracellular matrix and proteins

Physical principle of IRE
Technique

• Contra-indications: ventricular arythmia
• General anesthesia + muscle relaxants
• Needle electrodes
  - 2 to 6 needles (or more!)
  - 2cm interelectrode distance
  - working length 1.5 - 2.0cm
• Approach:
  - open or percutaneous
  - US- or CT-guided
ECG-gating

- Prior to ECG-gating cardiac arrhythmias have been described
- Since ECG-gating only benign arrhythmias were documented with spontaneous recovery after IRE

• IRE-pulsing
  – Ideal distance between electrodes 2.0cm
  – Prepulse followed by 10 testpulses; total number of pulses 90 (70-100)
  – Pairs of 10 pulses
  – Voltage 1250-1500V/cm and current 20-40 Amperes
• Kort filmpje
Preclinical research

• Preclinical studies
  – **More pulses and longer exposure** to electric field cause larger and more nanopores lowering the chance of cell recovery.

  – We show through mathematical analysis that IRE can ablate substantial volumes of tissue, without causing any detrimental thermal effects and without the need of adjuvant drugs. This study suggests that IRE may become an important and innovative tool in the armamentarium of treating cancer.

  – IRE of human HCC-cells show complete non-thermal ablation
Preclinical research

**FIGURE 1.** The effect of electrode geometry on the electric field distribution (V cm⁻¹) and the amount of irreversible electroporation attainable for a two-electrode configuration. Assuming a 600 V cm⁻¹ threshold, the amount of irreversible electroporation achievable is delineated by the solid line. The effect of needle diameter using 10-mm center-to-center spacing and (A) 0.5 mm (898 V), (B) 1.0 mm (1331 V), and (C) 1.5 mm (1613 V) diameter electrodes. The effect of electrode spacing using 1-mm diameter electrodes and (D) 5 mm (891 V), (E) 7.5 mm (1143 V), and (F) 10 mm (1331 V) center-to-center spacing. The value in parentheses is the maximum applied voltage achievable with 800-μs pulse without reaching 50°C for each configuration.

**FIGURE 2.** The transient temperature distribution due to an 800-μs, 1331-V pulse for the two-electrode configuration, 1 mm in diameter with 10-mm center-to-center spacing. Surface plots illustrating the distribution at (A) 200, (B) 400, and (C) 600 μs. Contour plots detailing the temperature distribution near the rightmost electrode at (D) 200, (E) 400, and (F) 800 μs.
• Preclinical animal studies
  – IRE of rat carotid artery: histology 28 days after IRE showed:
    – connective matrix of the blood vessels remained intact
    – the number of vascular smooth muscle cells (VSMC) in the arterial wall decreased with no evidence of aneurysm, thrombus formation or necrosis

• Preclinical animal studies
  – IRE of pig portal triad:
    – Pigs survived for 2 hours, 2 days and 14 days
    – No occlusions bile ducts, portal vein and hepatic artery
    – No bile leakage or hemorrhage
    – No incomplete ablations caused by heat-sink

• Preclinical animal studies
  – IRE of pig **rectum** (11 pigs):
    – Pigs survived after 7 – 15 days
    – No perforations
    – Inflammation and fibrosis (20/39 zones)
    – Transmural inflammation (7/39 zones)
  

  – IRE of rat **jejenum & ileum** (13 rats):
    – All cells intestinal wall in apoptosis
    – After 3 days neo-epithelialisation at margin of treated area
    – After 7 days regeneration of all layers (mucosa, submucosa and muscularis) en regeneration of villi
    – No perforations
  
Preclinical animal studies

- IRE of pig renal pelvis (15 pigs (18 kidneys)):
  - Acute phase urothelium ‘complete’ necrosis & sparing extracellular matrix
  - Later phase cortical necrosis and regeneration of pelvic epithelium
  - 6 pigs follow-up: 4/6 complete resolution IRE zone on CT after 3wk

• Preclinical animal studies
  – IRE of rat sciatic nerves:
    – partial preservation and clinical recovery
    – axonal regeneration & schwann cell hyperplasia

IRE thermal or non-thermal?
- **gel phantom & pig model**
- **thermal camera**
- **schlieren camera**
  - Temperature rise 10-15° C
  - Highest at negative electrode
→ Highest temp increase at probe with **smallest** active tip length

<table>
<thead>
<tr>
<th>Tip – (mm)</th>
<th>Tip + (mm)</th>
<th>A</th>
<th>Start T – Max T –</th>
<th>Δ T –</th>
<th>Start T + Max T + Δ T +</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>5</td>
<td>15</td>
<td>14 - 21 12.4</td>
<td>32.4</td>
<td>20 12.4 27.1 14.7</td>
</tr>
</tbody>
</table>

→ Largest temperature increase with **greatest** pulse length

<table>
<thead>
<tr>
<th>A</th>
<th>Start T cross</th>
<th>MaxT cross</th>
<th>Δ T cross</th>
<th>Start T +</th>
<th>Max T + Δ T +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convergent</td>
<td>14 - 21 12.4</td>
<td>32.4</td>
<td>20</td>
<td>12.4</td>
<td>27.1 14.7</td>
</tr>
<tr>
<td>Divergent</td>
<td>21 - 25 12.7</td>
<td>24.1</td>
<td>11.4</td>
<td>12.7</td>
<td>19.4 6.7</td>
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</tbody>
</table>

→ Largest temperature increase with **highest** voltage

<table>
<thead>
<tr>
<th>A</th>
<th>Start T tip</th>
<th>MaxT tip</th>
<th>Δ T tip</th>
<th>Start T +</th>
<th>Max T + Δ T +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convergent</td>
<td>14 - 21 12.4</td>
<td>32.4</td>
<td>20</td>
<td>12.4</td>
<td>27.1 14.7</td>
</tr>
</tbody>
</table>

Δ T 90 consequent pulses: 17.3 ° C

→ Fewer heat development with **sequential pulsing**

<table>
<thead>
<tr>
<th>Pulses</th>
<th>Abort (s)</th>
<th>A</th>
<th>Start T – MaxT – Δ T –</th>
<th>Δ T 90</th>
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<tbody>
<tr>
<td>4 * 30</td>
<td>30</td>
<td>18 - 21</td>
<td>13.6 22.7 6.1</td>
<td></td>
</tr>
<tr>
<td>4 * 30</td>
<td>60</td>
<td>20 - 22</td>
<td>14.8 19.9 5.1</td>
<td></td>
</tr>
<tr>
<td>4 * 30</td>
<td>90</td>
<td>20 - 23</td>
<td>18.9 21.0 4.1</td>
<td></td>
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<tr>
<td>6 * 20</td>
<td>30</td>
<td>18 - 21</td>
<td>15.5 21.9 6.4</td>
<td></td>
</tr>
<tr>
<td>6 * 20</td>
<td>60</td>
<td>19 - 21</td>
<td>17.7 22.9 5.2</td>
<td></td>
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<tr>
<td>6 * 20</td>
<td>90</td>
<td>19 - 22</td>
<td>17.5 22.1 4.6</td>
<td></td>
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</table>
Preclinical research
<table>
<thead>
<tr>
<th>Reference</th>
<th>Target Organ</th>
<th>No. Patients</th>
<th>No. Lesions</th>
<th>Median Age (y)</th>
<th>Tumor Location</th>
<th>Approach</th>
<th>Concurrent Procedures during IRE</th>
<th>Treatment before or after IRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannon et al (28)</td>
<td>Liver</td>
<td>44</td>
<td>48</td>
<td>60</td>
<td>100% adjacent to major vascular/biliary structures or organs</td>
<td>Perc. (26)</td>
<td>7 concurrent abdominal procedures (NS)</td>
<td>Pre-IRE: 72% CT, RT, ablation, resection</td>
</tr>
<tr>
<td>Cheung et al (34)</td>
<td>Liver</td>
<td>11</td>
<td>18</td>
<td>71</td>
<td>7/18 adjacent to major vascular/biliary structures or organs</td>
<td>Perc. (2)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Kasivisvanathan et al (29)</td>
<td>Liver</td>
<td>1</td>
<td>1</td>
<td>61</td>
<td>Portal vein abutment and adjacent bowel</td>
<td>Perc.</td>
<td></td>
<td>Pre-IRE: CT, resection</td>
</tr>
<tr>
<td>Kingsham et al (35)</td>
<td>Liver</td>
<td>28</td>
<td>85</td>
<td>51</td>
<td>57% ≤ 1 cm major hepatic vein, 40% ≤ 1 cm major portal pedicle</td>
<td>Perc. (22)</td>
<td>2 perioperative pump chemotherapy</td>
<td>Pre-IRE: 86% CT</td>
</tr>
<tr>
<td>Narayanan et al (30)</td>
<td>Liver</td>
<td>21</td>
<td>29</td>
<td>61</td>
<td>62% &lt; 0.5 cm gallbladder, liver capsule, or dome of diaphragm</td>
<td>Perc. (6)</td>
<td></td>
<td>Post-IRE: 71% CT</td>
</tr>
<tr>
<td>Niessen et al (11)</td>
<td>Liver</td>
<td>1</td>
<td>1</td>
<td>61</td>
<td>Close to diaphragm and heart muscle</td>
<td>Perc.</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Niessen et al (12)</td>
<td>Liver</td>
<td>1</td>
<td>1</td>
<td>65</td>
<td>Adjacent to TIPSS stent graft</td>
<td>Perc.</td>
<td></td>
<td>Pre-IRE: RF ablation</td>
</tr>
<tr>
<td>Silk et al (20)</td>
<td>Liver</td>
<td>9</td>
<td>19</td>
<td>60</td>
<td>14% ≤ 1 cm CBD, 68% ≤ 1 cm primary bile duct</td>
<td>Perc. (1)</td>
<td></td>
<td>Pre-IRE: failed transarterial chemoembolization</td>
</tr>
<tr>
<td>Ragl and Papadouris (35)</td>
<td>Pancreas</td>
<td>1</td>
<td>1</td>
<td>78</td>
<td>Pancreatic body</td>
<td>Perc. (1)</td>
<td></td>
<td>Pre-IRE: surgery 100%, CT 91%, RT 9%, embolization 27%</td>
</tr>
<tr>
<td>Martin et al (21)*</td>
<td>Pancreas</td>
<td>27</td>
<td>27</td>
<td>61</td>
<td>15 head, 12 body/tail</td>
<td>Open (27)</td>
<td>8 partial Whipple, 13 bypass, 3 partial gastrectomy, 17 NS</td>
<td>Pre-IRE: 85% CT and CRT</td>
</tr>
<tr>
<td>Martin et al (23)*</td>
<td>Pancreas</td>
<td>64</td>
<td>54</td>
<td>61</td>
<td>35 head, 19 body/tail</td>
<td>Open (52)</td>
<td>15 partial Whipple, 35 bypass, 9 celiac plexus block, 27 NS</td>
<td>Pre-IRE: 65% CT, 45% CRT</td>
</tr>
<tr>
<td>Narayanan et al (34)</td>
<td>Pancreas</td>
<td>14</td>
<td>15</td>
<td>57</td>
<td>6 head, 7 body, 1 uncinate process</td>
<td>Perc. (2)</td>
<td></td>
<td>Post-IRE: 65%, CT, 15% CRT</td>
</tr>
<tr>
<td>Pech et al (27)</td>
<td>Kidney</td>
<td>6</td>
<td>6</td>
<td>57</td>
<td>NS</td>
<td>Open</td>
<td>All nephrectomy 15 min after IRE</td>
<td>Pre-IRE: surgery, cryoablation, RT</td>
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<tr>
<td>Usman et al (36)</td>
<td>Lung</td>
<td>2</td>
<td>2</td>
<td>33, 70</td>
<td>Close to pulmonary arteries, lobar bronchi, axillary vein, bronchus and trachea</td>
<td>Perc.</td>
<td></td>
<td>Pre-IRE: surgery, cryoablation, RT</td>
</tr>
<tr>
<td>Niessen et al (33)</td>
<td>Liver</td>
<td>13</td>
<td>46</td>
<td>NS</td>
<td>Adjacent to vital structures in most patients</td>
<td>Perc. (123)</td>
<td></td>
<td>Standard therapy impossible or unsuccessful</td>
</tr>
<tr>
<td>Thomson et al (29)</td>
<td>Liver</td>
<td>8</td>
<td>11</td>
<td>6</td>
<td>Presacral with infiltration of sacral bone and nerve plexus</td>
<td>Perc.</td>
<td></td>
<td></td>
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<tr>
<td>Lung</td>
<td>4</td>
<td>6</td>
<td></td>
<td>6</td>
<td>Adjacent to vital structures in most patients</td>
<td>Perc.</td>
<td></td>
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<tr>
<td>Presacral</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td>Perc.</td>
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<tr>
<td>Lymph node</td>
<td>2</td>
<td>2</td>
<td></td>
<td>2</td>
<td></td>
<td>Perc.</td>
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<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td>129</td>
<td>227</td>
<td></td>
<td></td>
<td>Open (94)</td>
<td>7 concurrent abdominal procedures (NS)</td>
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<tr>
<td>Liver</td>
<td>68</td>
<td>70</td>
<td></td>
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<td>Perc. (123)</td>
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<tr>
<td>Kidney</td>
<td>14</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td>Lap. (4)</td>
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<tr>
<td>Lung</td>
<td>6</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Presacral</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph node</td>
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<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Total</strong></td>
<td></td>
<td>221</td>
<td>325</td>
<td>221</td>
<td></td>
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</table>
IRE for colorectal liver metastasis

1 day pre-IRE
IRE (11 needles!)
directly post-IRE
Case 2 – Liver IRE

IRE for colorectal liver metastasis

HD shock 4-days post-IRE:
(1) hematoma & active bleeding
(2) pseudo-aneurysm
(3) arterioporal fistula

CTCAE grade IV complication
Case 2 – Liver IRE

IRE for colorectal liver metastasis

1 day pre-IRE  IRE (11 needles!)  directly post-IRE  3 mnths post-IRE
Case 3 – Pancreatic IRE

1 day pre-IRE  IRE (7 needles)  directly post-IRE  3 mnths post-IRE
VUmc center for image-guided tumor ablation: IRE research

- Lab studies
- Clinical trials
- Animal experiments
- Image-guidance, robotics, follow-up imaging
- Immunology
- Nutritional status & dietethics
Liver (n=22)
- Colorectal Liv Mets (n=22)
- Hepatic adenoma (n=1)

Biliary tumors
- Klatskin (n=1)
- ICC (n=1)

Pancreas
- Whipple recurrences (n=3)

Kidney (n=1)

Pelvic recurrences (n=5)

Liver tumors

Biliary tumors

Pancreas

Kidney

Pelvic recurrences

Thyroid cancer (n=1)

Breast

Liver (n=22)
- COLDFIRE-1 ablate & resect (n=10)
- COLDFIRE-2 efficacy (n=12/29)

Pancreas
- pre-PANFIRE (n=5)
- PANFIRE-1 phase 1/2 (n=15)
- PANFIRE-2 phase 2 (n=2)
- CROSSFIRE phase 3 (+ Univ of Miami)

Biliary tumors
- KLATSKIN phase 1?

REGISTRY

TRIALS

(total n=79)
Unstained Fresh Specimen directly after resection 60-120 minutes after IRE

At 24h after TTC staining
vital tissue turns transparent TTC into red formazan

At 3-6 weeks after TTC staining
vital tissue turns transparent TTC into red formazan

2 CRLM
1 pre-treated with IRE
1 not-pre-treated
IRE for irresect hilar cholangiocarcinoma
dr. Martijn Meijerink, interventional radiologist
dr. Petrousjka van den Tol, oncological surgeon
drs. Hester Scheffer, researcher radiology
drs. Laurien Vroomen, researcher radiology
drs. Karin Nielsen, researcher surgery
drs. Marleen Melenhorst, resident radiology
drs. Aukje van Tilborg, abdominal radiologist & researcher
mw. Mariette van der Elzen, research nurse & secretary

dr. Jan Hein van Waesbergh, abdominal radiologist
prof. dr. Cornelis van Kuijk, chair dep radiology & nucl med
drs. Bram van der Meijs, interventional radiologist
dr. Indra Pieters, abdominal radiologist
drs. Janneke van den Bergh, abdominal radiologist
prof. dr. Geert Kazemier, hepatobiliary surgeon
prof. Dr. Sybren Meijer, oncological surgeon
prof. dr. Emile Comans, nuclear physician
prof. Dr. Otto Hoekstra, nuclear physician
dr. Arthur Bouwman, anesthesiologist
drs. Jenny Vieveen, anesthesiologist
dr. Karin van Nieuwkerk, gastro-enterologist
dr. Maurice van der Vorst, medical-oncologist
prof. dr. Hans Niessen, pathologist
dr. Ed Eringa, physiologist
prof. dr. Tanja de Grujil, immunologist
ir. prof. dr. Ruud Verdaasdonk, physicist
ir. dr. John Klaessens, physicist
drs. Jill Witvliet, dietetics
drs. Karen Oussoren, dietetics
dr. Marian van der Schuuren - Bokhorst, dietetics
and many others...
‘Lichtenberg phenomenon’
• General
  – Placing needle electrodes
  – Multiple short intense electric pulses
  – Destabilizing cell membrane by creating “nanopores”
  – Inducing cell death through \textit{apoptosis} (not necrosis!)

\textit{Edward W. Lee et al. Electron Microscopic Demonstration and Evaluation of Irreversible Electroporation-Induced Nanopores on Hepatocyte Membranes. JVIR 2012(23): 107-113}