Myocardial Ablation and Decellularization by Irreversible Electroporation: A Novel Non- Thermal Non-Pharmacological Biophysical Approach

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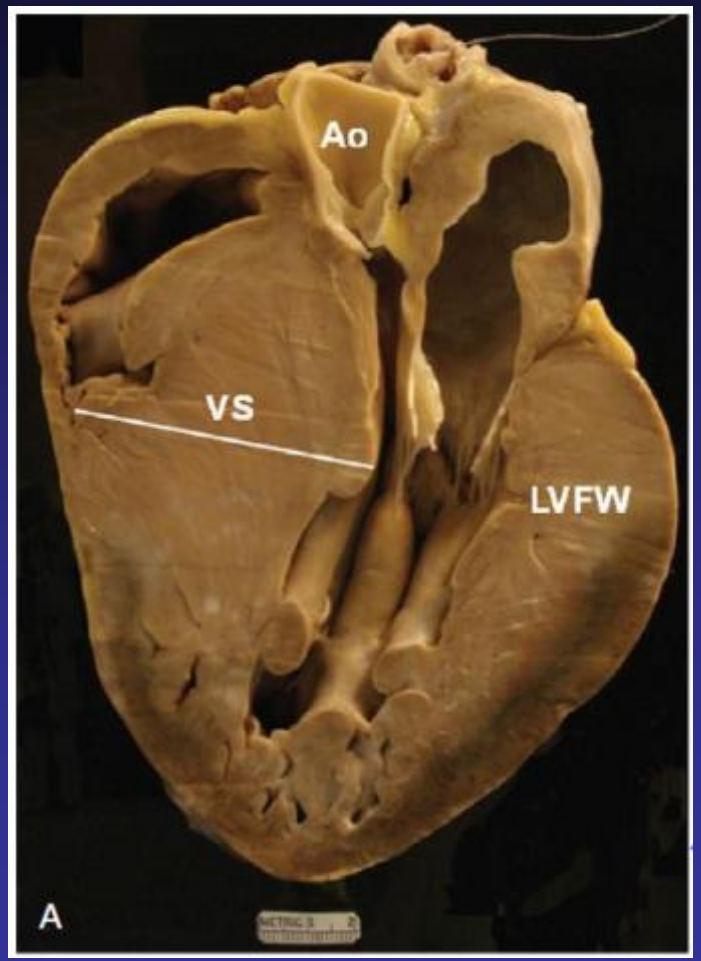
Disclosures

- None

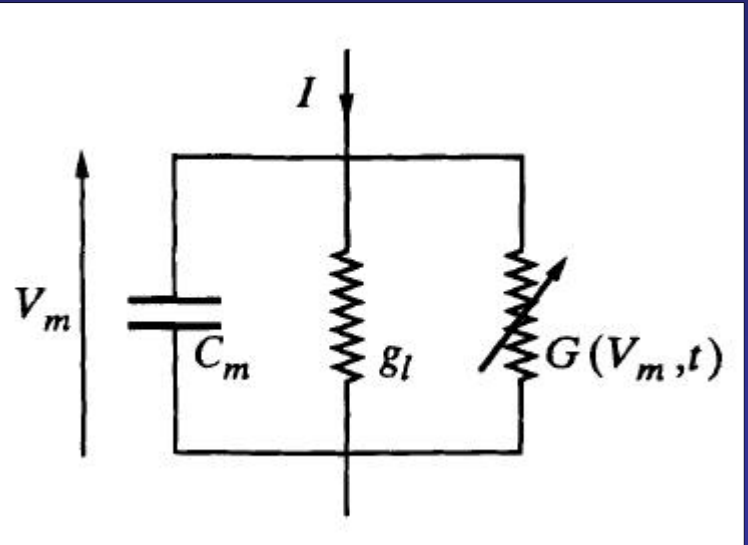
Hypertrophic obstructive cardiomyopathy can cause outflow track obstruction

- Myectomy is a major surgery
- Alcohol ablation is sub-optimal solution
- There is clinical need for minimally invasive approaches



Electroporation Increases Membrane Permeability

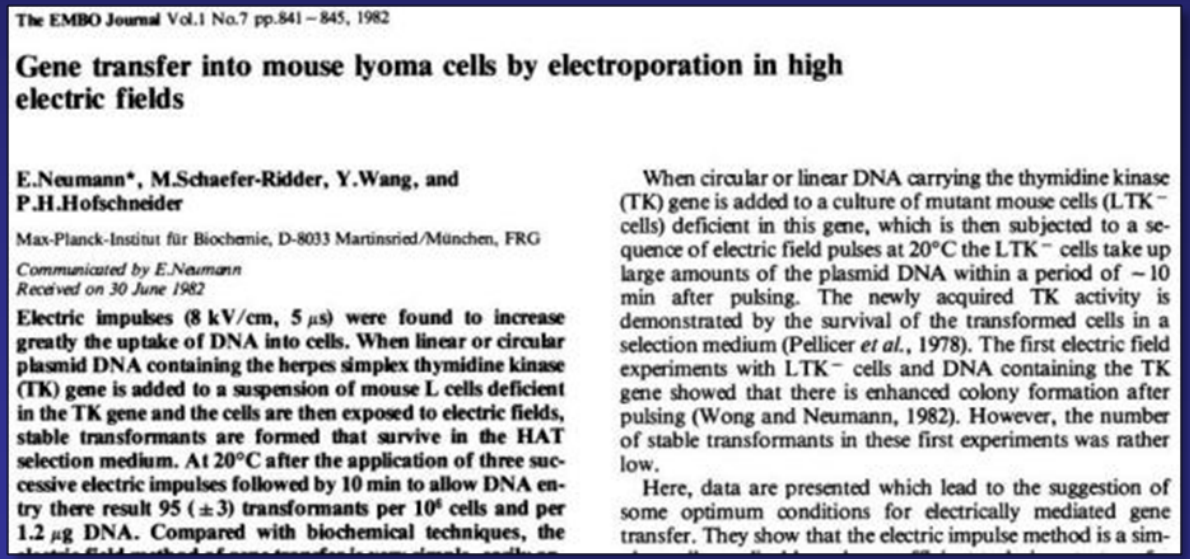
- Cell membrane permeability to ions and macromolecules is increased by exposing the cell to short high electric field pulses.



V_m	Transmembrane Potential
I	Current through the membrane
C_m	Membrane capacitance
g_l	Baseline membrane resistance
$G(V_m,t)$	Electroporation conductivity

Electroporation has proven applications

- Gene transfer
- Drug delivery
- Tissue Ablation
- Food Industry
- Environment



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Gene transfer into mouse lyoma cells by electroporation in high electric fields

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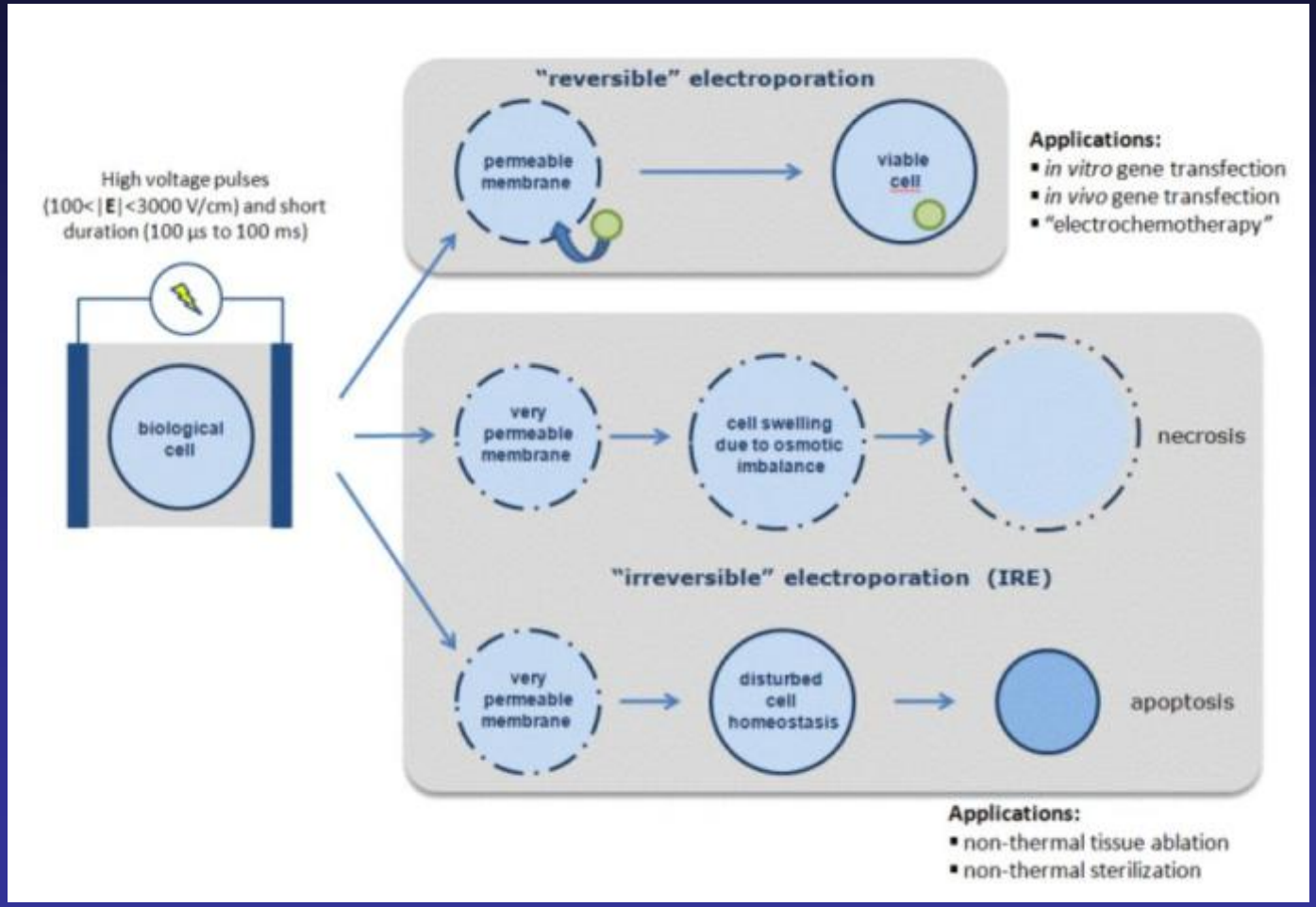
Electric impulses (8 kV/cm, 5 μs) were found to increase greatly the uptake of DNA into cells. When linear or circular plasmid DNA containing the herpes simplex thymidine kinase (TK) gene is added to a suspension of mouse L cells deficient in the TK gene and the cells are then exposed to electric fields, stable transformants are formed that survive in the HAT selection medium. At 20°C after the application of three successive electric impulses followed by 10 min to allow DNA entry there result 95 (±3) transformants per 10^6 cells and per 1.2 μg DNA. Compared with biochemical techniques, the

When circular or linear DNA carrying the thymidine kinase (TK) gene is added to a culture of mutant mouse cells (LTK^- cells) deficient in this gene, which is then subjected to a sequence of electric field pulses at 20°C the LTK^- cells take up large amounts of the plasmid DNA within a period of ~10 min after pulsing. The newly acquired TK activity is demonstrated by the survival of the transformed cells in a selection medium (Pellicer *et al.*, 1978). The first electric field experiments with LTK^- cells and DNA containing the TK gene showed that there is enhanced colony formation after pulsing (Wong and Neumann, 1982). However, the number of stable transformants in these first experiments was rather low.

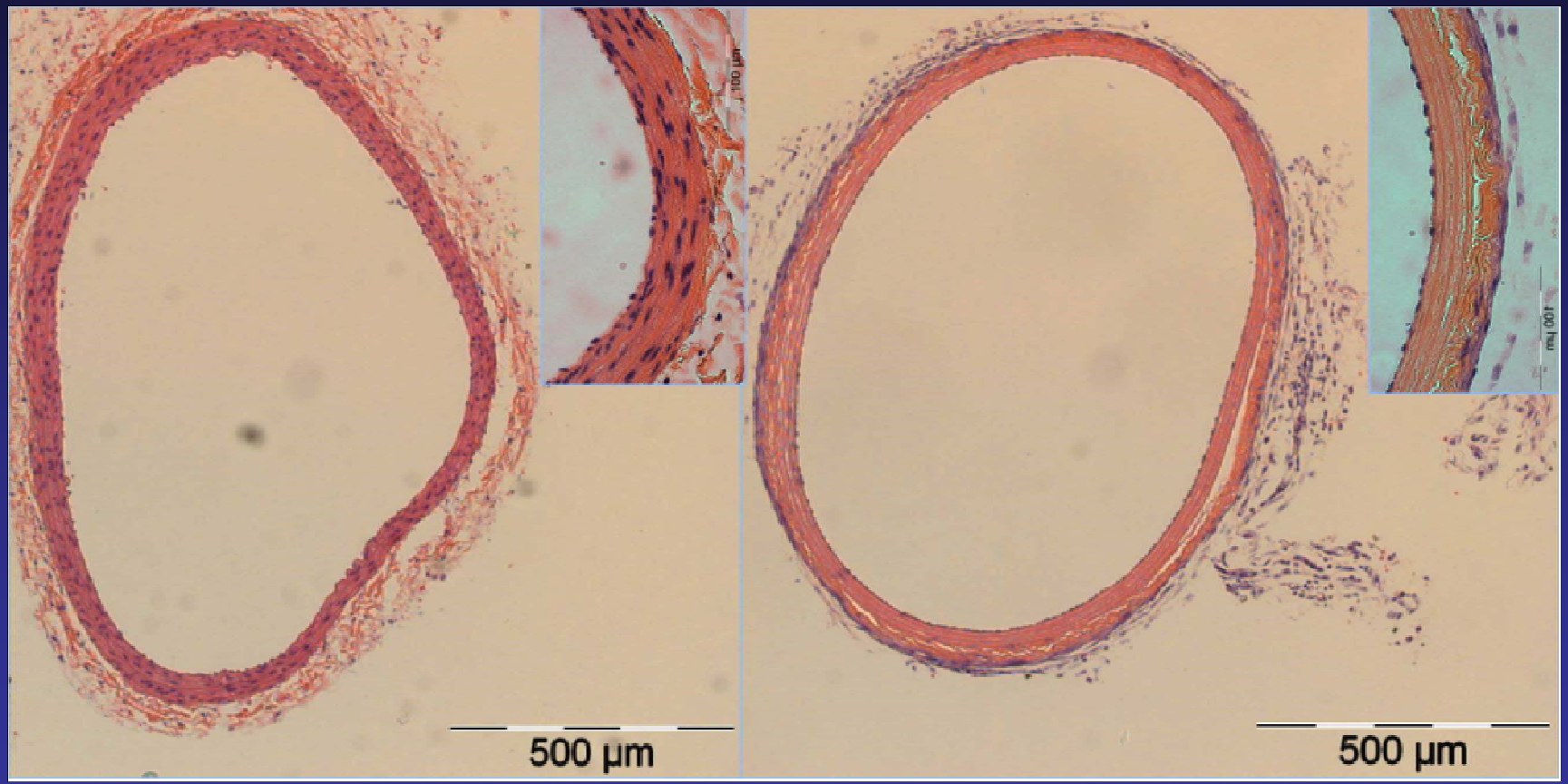
Here, data are presented which lead to the suggestion of some optimum conditions for electrically mediated gene transfer. They show that the electric impulse method is a sim-

Irreversible Electroporation (IRE) is an emerging ablation approach



Arterial wall ablation with in vivo IRE

Control Carotid Artery **Carotid Artery following IRE Ablation**



Elad Maor et al. PLoS ONE 2009

Study Hypothesis

- Irreversible electroporation can be used as a non-thermal ablation modality for in-vivo heart decellularization

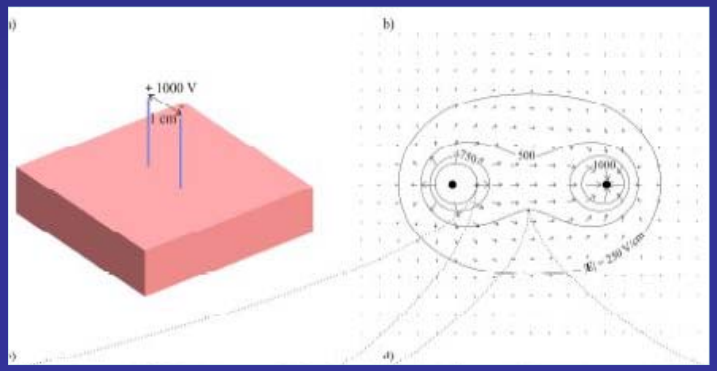
Study Aims

1. Test the feasibility of in-vivo IRE of the beating heart.
2. Evaluate different IRE protocols for myocardial ablation.
3. Evaluate the short and long term effect of IRE on the heart

Computational Finite Element Models

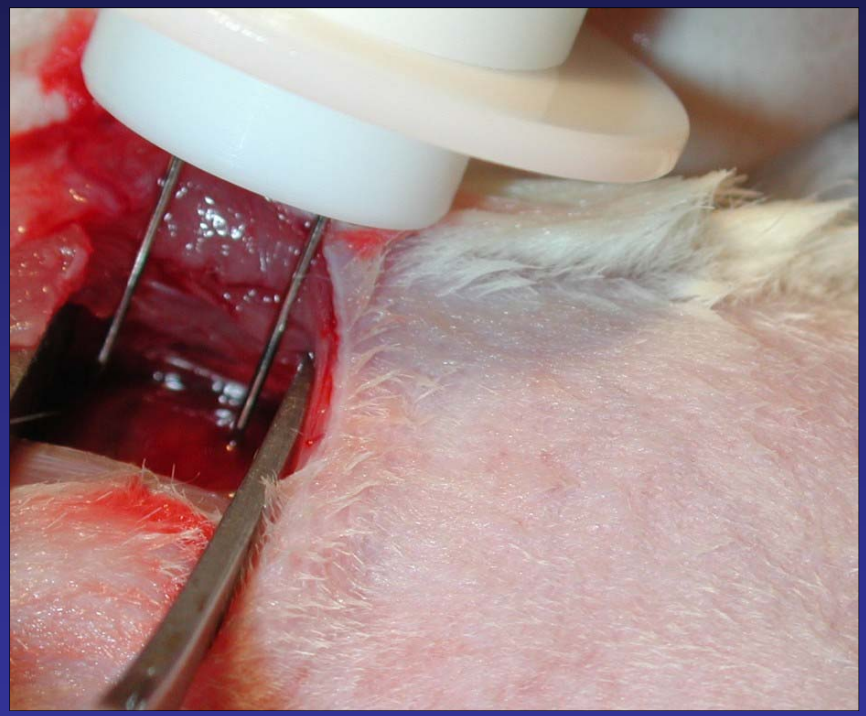
- Solve the biophysical problem
- Identify optimal IRE protocols

Potential distribution (Laplace)	$\nabla(\sigma\nabla\varphi) = 0$
Resistive heating (Joule Heating)	$p = \sigma\lvert\nabla\varphi\rvert^2$
Bio-heat (Penne's) Equation	$\nabla(k\nabla T) + \omega_b c_b(T_a - T) + q + \sigma\lvert\nabla\varphi\rvert^2 = \delta\rho c_p \frac{\partial T}{\partial t}$
Thermal damage Integral	$\Omega(t) = \int A e^{-\frac{E}{RT}} dt$

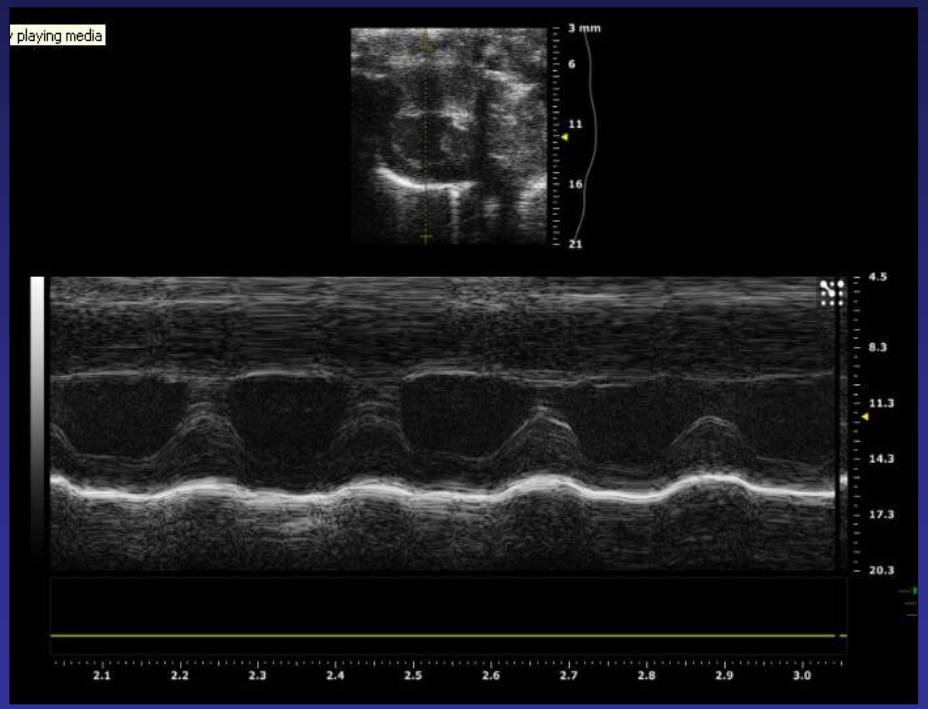


In-vivo IRE safety experiments with two needle electrodes

Open thoracotomy model



M-Mode Echocardiography

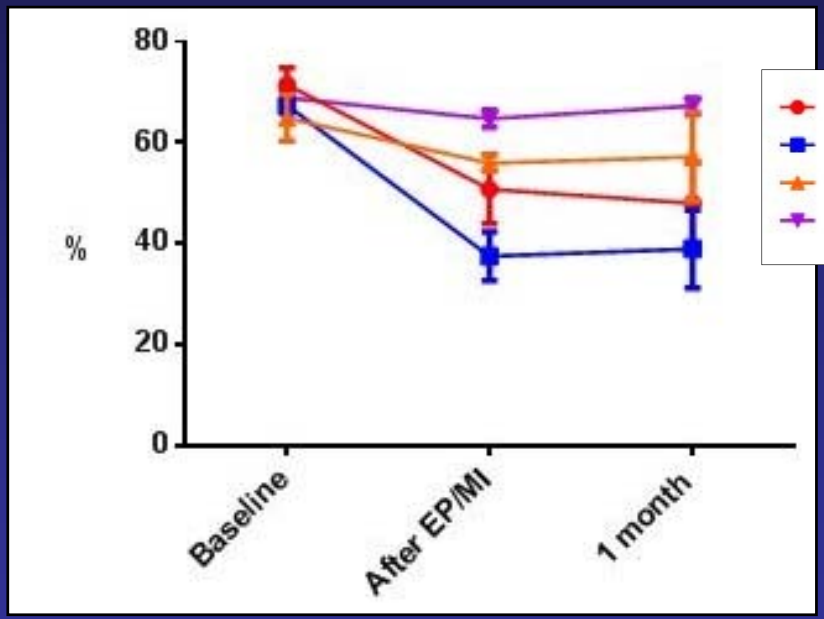


Efficacy experiment

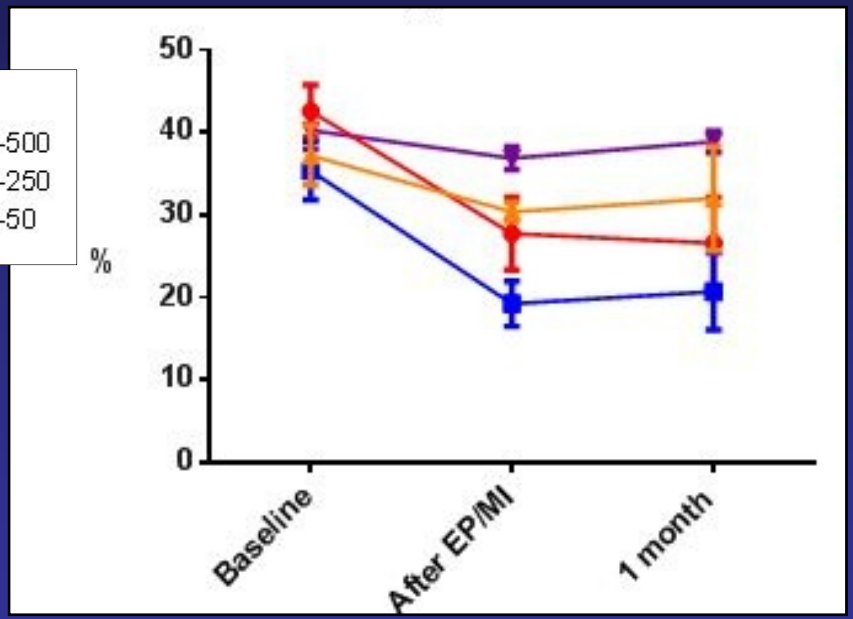
- SD Rats (N=24)
- Three different IRE protocols:
  - 500V
  - 250V
  - 50V
- Control group: Myocardial infarction
- Echocardiography: baseline, 7 days, 1 month
- Histology evaluation

IRE has a graded effect

Ejection Fraction

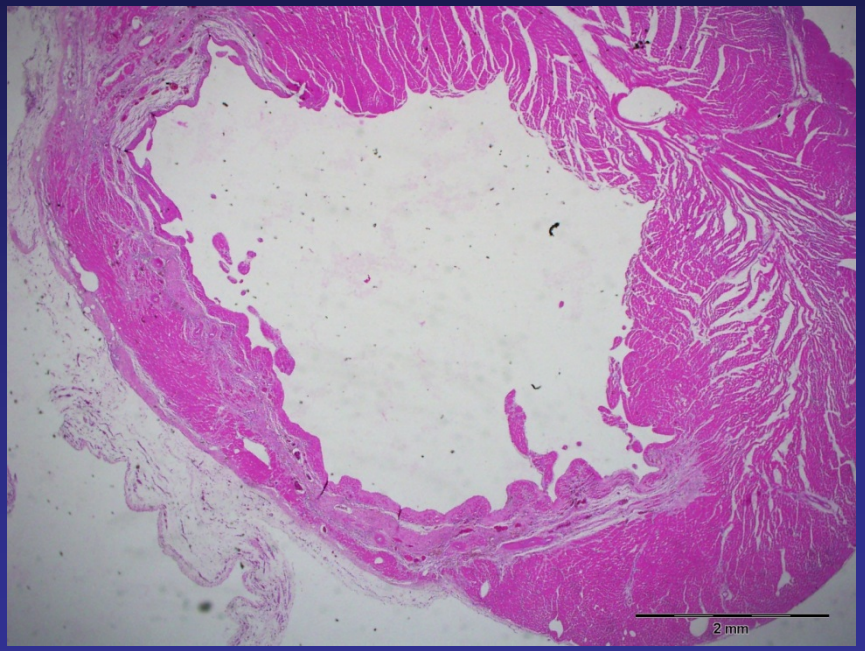


Fractional Shortening



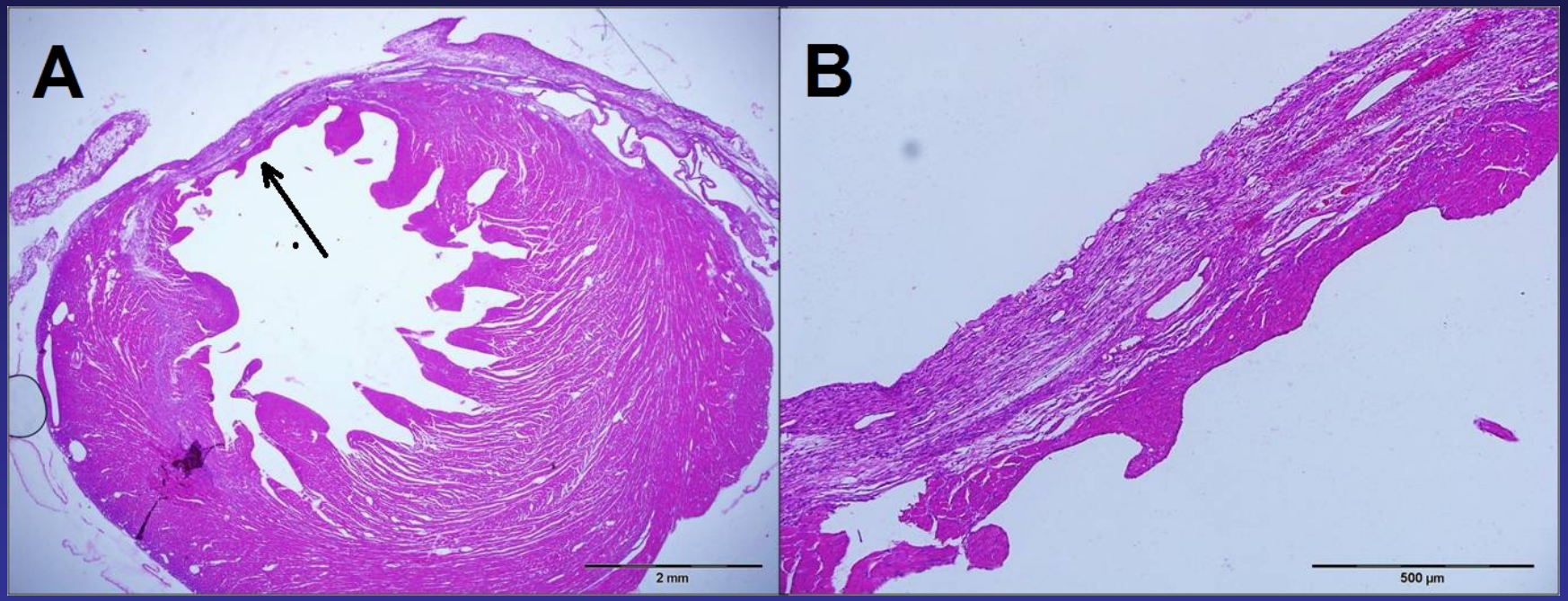
IRE vs. MI damage

MI damage

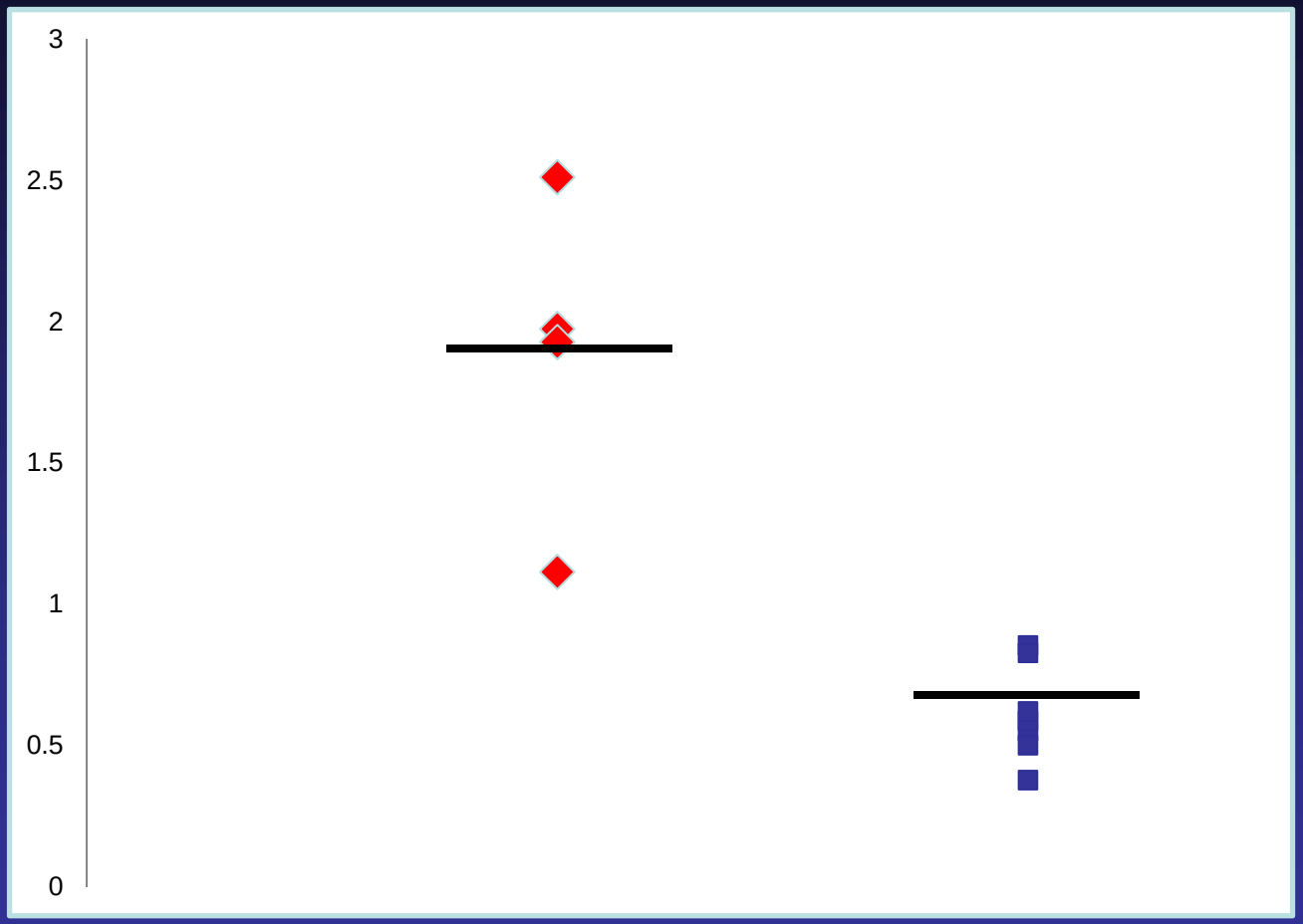


IRE damage

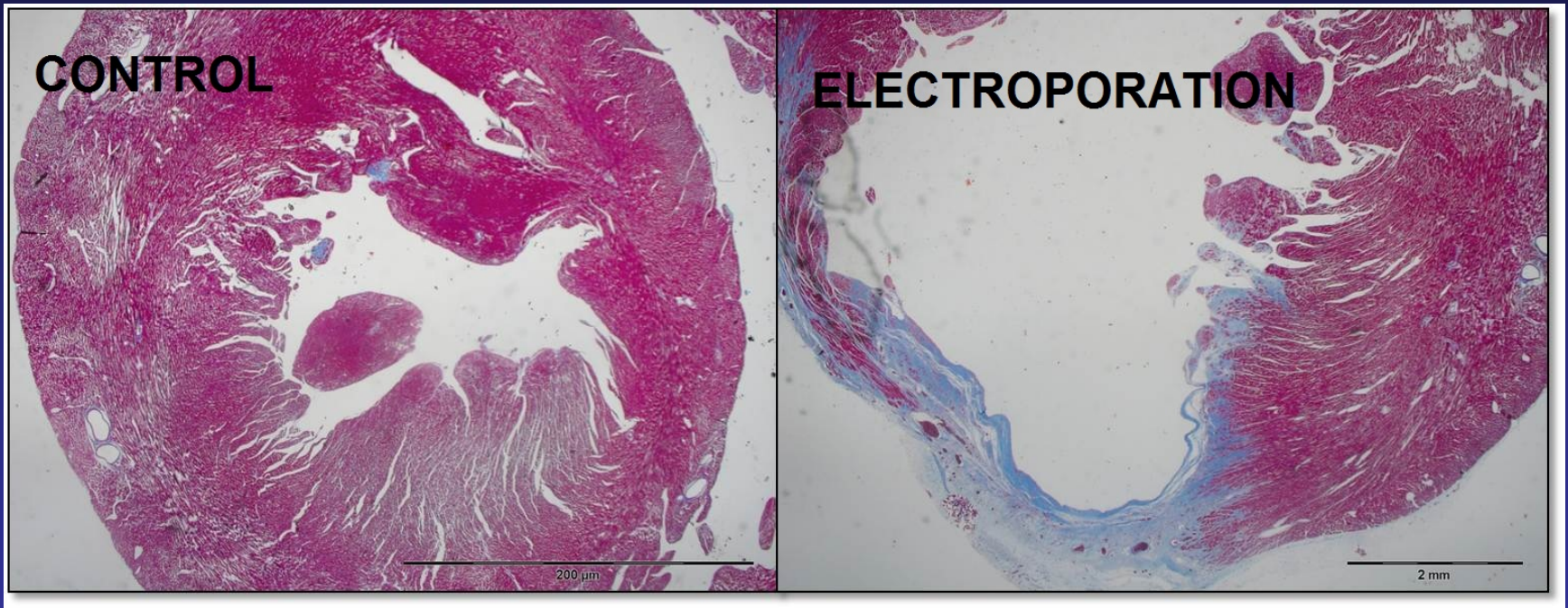
IRE damage after 7 days



IRE induces a thicker scar



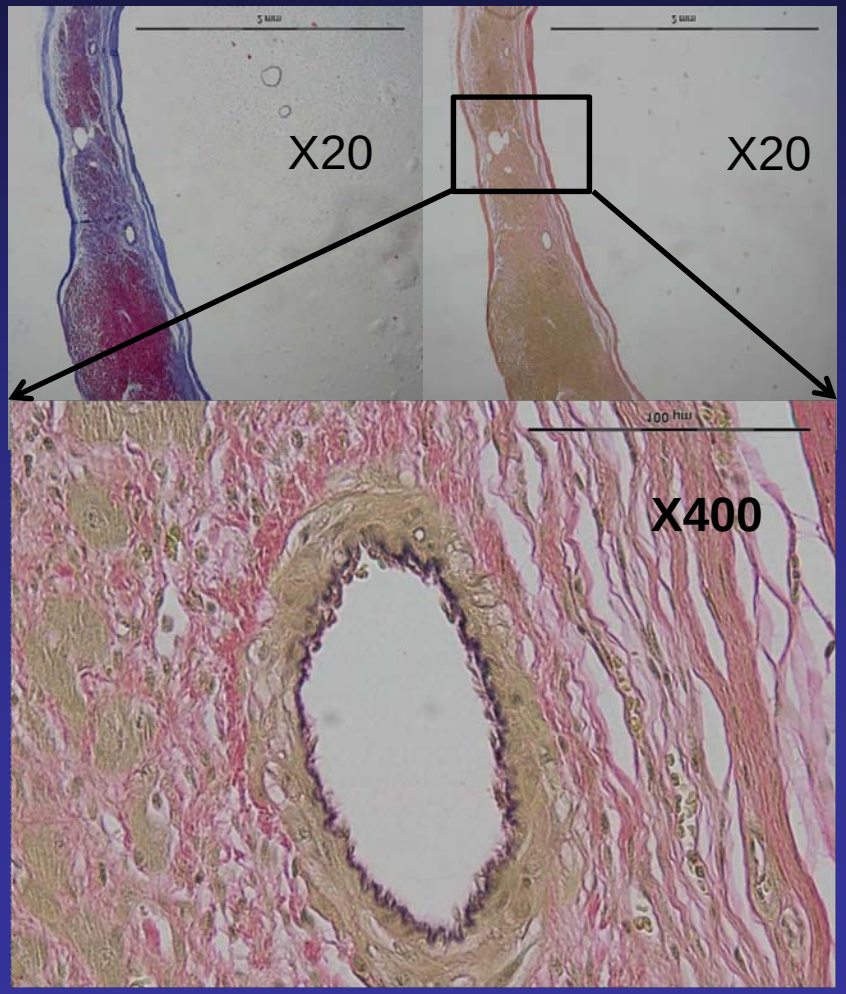
A-cellular Environment Rich in Collagen (Masson Trichrome Stain)



Electroporation 50V (no damage)

IRE (500V) ablation

Elastic stain shows sparing of blood vessels structure



Summary

- IRE protocol that selectively ablates cellular components in the beating heart with no thermal damage.

- Ten short pulses at a frequency of 1 Hz can induce significant transmural damage to the beating heart within 10 seconds !

Conclusions

1. IRE has a non thermal nature
2. IRE is directed toward cell membrane only
3. IRE shows the following advantages:
   - A trend toward a thicker scar
   - No thermal damage
   - No damage to elastic fibers and blood vessels

Clinical Implications

- Cardiac Arrhythmias
- Obstructive Hypertrophy
- Tissue Scaffolding

Thank you !