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(Nonthermal) Tissue ablation by irreversible electroporation

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Before 2005 we all knew that if you use too high voltage, too long pulses, or too many of them, you will kill the cells. We also knew that if we use high conductive media we may "cook" them, hence low conductive media (well, not only because of that). And if the pulse repetition rate was too high, we would "cook" the cells again. At that time Boris Rubinsky and Rafael Davalos from Berkley recognized the utility of killing cells by electroporation. So: "What's new?", I got an honest question from a colleague of mine after a press release from Berkeley. Indeed, what was new? What was new was the demonstration of the possibility to kill cells by electroporation and finding conditions avoiding (too much) heating – hence the treatment was termed Nonthermal Irreversible Electroporation - NTIRE. The cells would be killed, yet the tissue architecture would remain intact to be repopulated by new/healthy cells with virtually no thermal damage.

Applying voltage and passing current through a tissue (as a conductor of finite resistance) will inevitably result in some heating. It is unavoidable, and this was exactly what authors considered and demonstrated in their inspiring paper which was published in 2005 in Annals of Biomedical Engineering [1]. This paper has been recognized as one of the two most cited papers in the 50-year history of the Journal, selected from over 6000 papers [2] and was cited more than 1300 times. Quite likely you are one of the authors citing this initial IRE paper – it is entirely a modeling paper. There are no experiments reported therein. It is simply a demonstration using numerical modeling that sufficiently high electric field in the tissue can be established to kill cells by electroporation and considerable volume of tissue could be ablated, while temperatures would remain low. In retrospect, the model is not the most accurate and was not validated by experiments, but it gave a clear answer to the question posed by the authors: can we ablate meaningful tissue volume without raising temperature to the level that would damage the same? Davalos et al. found conditions which allowed this [1]. IRE was later demonstrated *in vitro* and *in vivo* in a series of papers published in Volume 6, Number 4 issue of Technology in Cancer Research and Treatment, demonstrating the possibility to ablate tumor tissue, liver, prostate, and sparing large blood vessels. All of this laid the ground for further development and clinical use.

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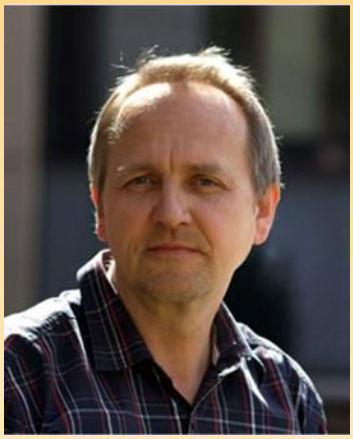

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In the hands of experimentalists and clinicians and following the linear human thinking "the more the marrier", non-thermal irreversible electroporation has soon turned into a largely thermal treatment by using and delivering too many pulses [3-7]. Thermal damage to tissue – in particular around the electrodes – has made it evident (again) that emphasizing the non-thermal nature of this ablation was not a good idea. It needs to be stressed repeatedly that tissue ablation by IRE is *not* nonthermal in its nature but can be used as such under specific conditions – and models are perfect to inform us how to avoid excessive thermal damage.

The Editorial states that "the second most cited paper in ABME history, irreversible electroporation has been implemented in the clinic as an effective approach to eradicating unresectable tumors in over 50 clinical trials and helped more than 5500 cancer patients". I would like to add: And this is just the beginning. We have witnessed an extremely fast development of cardiac ablation by irreversible electroporation in the last couple of years, and as the first clinical multicenter studies are coming close to an end, first commercial systems are already getting on the market (read more in the February 2022 newsletter written by Tomás García-Sánchez, available at https://tinyurl.com/isebtt-feb22). And I would add again: And this is only the beginning.

It all started with numerical modeling! I suggest you read that paper again. How simple and almost trivial it seems today.

List of cited references

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Forthcoming events

One-day PFA school: meet the electroporation experts
Barcelona, August 25, 2022
https://tinyurl.com/1day-PFA-school

4th World Congress on Electroporation and Pulsed Electric Fields in Biology, Medicine, and Food & Environmental Technologies
Copenhagen, October 9 – 13, 2022
https://wc2022.electroporation.net

16th interdisciplinary postgraduate course and international workshop Electroporation Based Technologies and Treatments (EBTT)
Ljubljana, November 13 – 19, 2022
http://www.ebtt.org

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The inventors: Boris Rubinsky and Rafael Davalos

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