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Thermodynamic profiling during irreversible electroporation in porcine liver and pancreas: a case study series

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1st Editorial decision

16-Feb-2020

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Thermodynamic profiling during irreversible electroporation in porcine liver and pancreas: a case study series
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Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at http://www.jctres.com/en/author-guidelines/ under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by Mar 17, 2020.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Rowan van Golen
Associate Editor
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: Interesting work. Some suggestions as follows.

1. Not just stents but even metal staples implanted during surgery can cause heating; see https://www.ncbi.nlm.nih.gov/pubmed/31385006. Consider updating this in your introduction.
2. Consider getting editorial help. For example, Intratissular is not really a word.
3. Very large number of parameters with low "n" for each parameter certainly dampens enthusiasm for the study.
4. Figure preparation is unusual, are they screenshots from powerpoint? Editing the figures for readability would be helpful.
5. M&M on temperature measurement, and overall can be reduced to be concise. It's too long right now.
6. Figures can be consolidated (may be based on location?) or moved to supplement. While it is tempting to showcase all figures in a case series, for sake of reader attention perhaps best to keep the 4 that show significant temperature change and move the rest to an appendix.
7. Some histology data could have made the arguments convincing.
8. In discussion; I am not convinced heating during IRE really matters. Rather than demonstrating that heating occurs during IRE, it would be of clinical consequence to demonstrate that heating as observed during IRE can actually cause complications. I doubt that would be the case.
9. In discussion; heating during IRE is transient and steady is never reached which would explain observations involving large blood vessels.
10. In discussion; more than measurable heating, arcing at/near locations of high current density is a bigger issue.

Author’s rebuttal

We thank the reviewer for his/her useful comments that have contributed to significant improvements to the manuscript. We have addressed the comments of the reviewer in the revised manuscript using the track changes function in Word. Furthermore, the responses to the comments of the reviewer are colored in red.

1. Not just stents but even metal staples implanted during surgery can cause heating. Consider updating this in your introduction.

Reply: The reviewer is right. Therefore, we included the influence of metal staples on heating in the third paragraph of the introduction.

"Although IRE was initially introduced as a non-thermal technique, the application of repetitive high-intensity electrical pulses in the liver, pancreas, and kidney inevitably leads to heating that may result in thermal damage when a thermal threshold (50 °C - 60 °C) is reached [13-16]. In particular, this might be the case due to the presence of metal implants, such as metal clips, staples, and stents. Specifically, in the direct vicinity of the metal implants the electric field distribution can be distorted, and the deposition of thermal energy can increase due to the relative large thermal conductivity of metal with respect to the treated tissue, resulting in possible thermal damage [17, 18]."

2. Consider getting editorial help. For example, Intratissular is not really a word.

Reply: We have improved the English language.

3. Very large number of parameters with low "n" for each parameter certainly dampens enthusiasm for the study.

Reply: We understand the feedback of the reviewer. Indeed, a larger number of experiments would have elevated the robustness of the conclusions, although we feel that the data yield credence to our conclusions. This case study-structured pilot provided us with useful insights that can contribute to improvements in IRE treatments, despite the low 'n'. We added this to the discussion section "4.2 Study limitations"

"Finally, results are obtained from a case study series and a larger number of experiments would allow more robust conclusions. Nevertheless, the study provides very relevant insights that can contribute to future improvements in IRE protocols and make clinicians employing the technique aware of its limitations and factors that warrant caution."

4. Figure preparation is unusual, are they screenshots from powerpoint? Editing the figures for readability would be helpful.

Reply: We updated all the figures to improve the readability.

5. M&M on temperature measurement, and overall can be reduced to be concise. It's too long right now.

Reply: We understand the comment of the reviewer. Therefore, we reduced the Methods text, while preserving the necessary details for sake of reproducibility.

6. Figures can be consolidated (may be based on location?) or moved to supplement. While it is tempting to showcase all figures in a case series, for sake of reader attention perhaps best to keep the 4 that show significant temperature change and move the rest to an appendix.

Reply: We agree with the reviewer. Therefore, the figures in Cases 2 – 5 and Cases 10 - 12 were moved to the Online Supplemental Information.

7. Some histology data could have made the arguments convincing.

Reply: We agree with the reviewer. Some histology data could indeed have made the arguments convincing. However, histological analysis is dichotomous, semi-quantitative at best, and non-paired. Therefore, we decided to use continuous temperature measurements to quantitatively assess the risk of thermal injury.

8. In discussion; I am not convinced heating during IRE really matters. Rather than demonstrating that heating occurs during IRE, it would be of clinical consequence to demonstrate that heating as observed during IRE can actually cause complications. I doubt that would be the case.

Reply: We agree with the reviewer that it is of clinical consequence to demonstrate that heating as observed during IRE can cause complications. However, we believe that heating matters during IRE treatment for two reasons:

- Mild hyperthermic temperatures (40˚C - 50˚C) can reduce the IRE threshold in the tumor, resulting improvement of IRE treatment of the tumor as was shown in Edelblute et al. 2017 [28] and discussed in section 4.1.3.
- Performing IRE in the vicinity of a metal stent could produce large temperatures as was shown in this study with the possible consequence of damaging the bile duct.

9. In discussion; heating during IRE is transient and steady is never reached which would explain observations involving large blood vessels.

Reply: We understand the feedback of the reviewer. In general, we think that anesthesia played a significant role in the reduction of the blood flow in the large blood vessels, where the maximal temperature increase was hardly affected by convective cooling via large blood vessels. The effect of relatively short exposure to IRE could indeed contribute to the observed effect that sometimes the temperature increase was indeed limited near large vessels. We added this to the discussion section “4.1.4. Heat-sink effects are minimal in the liver and pancreas”:

“Further investigations should be performed to confirm whether the anesthesia adversely affects the heat-sink effects caused by large blood vessels, including the superior mesenteric artery and the hepatic artery. In addition, the relatively short exposure to IRE could also contribute to the observed effect that sometimes the temperature increase was limited near large vessels.”

10. In discussion; more than measurable heating, arcing at/near locations of high current density is a bigger issue.

Reply: The reviewer is right. In the discussion in the third paragraph under the heading “4.1.1. Temperature increase depends on the organ and IRE settings” we added details about the possible effects of arcing and how to prevent it.

“Another element that can cause thermal damage is electrical arcing. In this phenomenon an instantaneous increase of the electrical current density develops in between the activated electrodes, resulting in (1) possibly inadequate treatment due to the redistribution of the electric field [23], and (2) significant temperature increase that can cause e.g., white coagulation [18, 24, 25]. During the IRE treatment, the electrical arcing is experienced as audible popping with visible electrical current spikes and possible system failure [23, 25]. This phenomenon possibly occurs because of:

- high or increase in the electrical conductivity of the IRE-subjected tissue volume between the activated electrodes [25];
- ionization of gases that were formed by electrolysis of water into oxygen (O_2) and hydrogen (H_2) due to large electric field strengths [20, 26, 27].

To prevent this anomaly and reduce the probability of thermal damage, physicians are recommended to reduce the pulse voltage or the pulse width [5, 23, 25].”

2nd Editorial decision

07-March-2020

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Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Rowan van Golen
Associate Editor
Journal of Clinical and Translational Research

Comments from the editors and reviewers: