Letters to the Editor

Re: Comparisons of Monopolar Lesion Volumes with Hypertonic Saline Solution in Radiofrequency Ablation: A Randomized, Double-Blind, Ex Vivo Study

To the Editor:

We appreciate the research efforts by Dr. Paul et al (1) to evaluate the effects of low-concentration sodium chloride (NaCl) on radiofrequency ablation (RFA). However, we have concerns regarding the study's internal and external validity. In a collegial spirit we will provide insight into factors that influence the effect of fluid preinjection on RFA size.

First, the present study utilized a 1 mL mixture of 2% lidocaine with either 0.9% or 2% saline in a 1:1 ratio. Accounting for dilution, the NaCl concentrations within the 1mL injectate were low, 0.45% or 1.5%. In contrast, previous ex- and in vivo studies (2-4) demonstrating a significant effect of NaCl preinjection on ablation size involved higher concentrations of NaCl (e.g. 3%, 8%, 12%), either alone or with lidocaine. Prior trends identified suggest that a reduction in salinity would reduce the effect of preinjection.

Second, the publication recites "injectate was delivered by syringe into the center of the tissue by approximation." This contrasts previous studies and clinical practice, wherein preinjection is delivered through the RFA cannula lumen. Such injection through the cannula ensures that the injectate is placed adjacent to the active tip where is it is expected to have the greatest effect. Because that the RF electric field strength drops off rapidly with distance from the active tip (5), variable and potential distant saline injection through a separate syringe by approximation would be expected to produce an inconsistent and reduced effect.

Third, the present study does not define the relative timing of saline injection and the initiation of ablation. In a previous in vivo porcine study, lidocaine was first injected and then, 30 seconds later, the NaCl solution was injected to replicate clinical conditions wherein lidocaine is given time to anesthetize the target tissue prior to ablation (4). Dissipation of saline over a longer delay is expected to reduce enhancement.

Fourth, the study is silent on the criteria used to identify ablation boundary. This is of concern when using chicken breast to assess small ablation variations. Chicken changes color at higher temperatures so heating at the ablation periphery may be invisible (6). In vivo studies examining RFA zones under histology demonstrate three distinct ablation zones (H1-zone of complete thermal denaturation; H2-transition zone of sporadic denaturation and coagulant necrosis; and H3-outer zone of coagulant necrosis) (7). Gross visualization cannot identify these zones. The preinjection of hypertonic NaCl significantly alters the histological composition and size of the ablation in outermost zone (i.e. H3) with less effect on the innermost zone (H1, most likely zone apparent under gross visualization) (4).

Fifth, when examining the influence of a preinjected fluid, it is critical that the medium utilized is free of preservatives and not augmented with solutions prior to testing (2,3). Paul et al (1) did not provide these details. Commercially available chicken is commonly enhanced during processing with injection of saline, which would confound the influence of saline preinjection experimentally, particularly at low concentrations (8).

Sixth, the average cross-sectional ablation dimension in the study was approximately 0.5 cm in all treatment groups, whereas measurements were made to the nearest 0.1 cm, representing the possibility of a large degree of measurement noise. Furthermore, it can be difficult to dissect small ablations in multiple directions precisely.

Taken together, these elements of the study's methods seem to minimize and add uncertainty to relative ablation sizes across treatment groups. Unfortunately, the study did not contrast RF power or energy data across treatment groups; such data provide complementary information to determine if the injectate is influencing variables that correlate with ablation size changes (2-4,9). It is difficult to conclude whether the

Table 1. *Variables to consider when developing and examining RFA models.*

Research Variable	Interpretation Importance
Ex-vivo and In-vivo models (4,12,13)	- Ex-vivo models may not match in vivo ablation size - Ex-vivo models with lower baseline temperatures may reduce ablation size - Ex-vivo models lack regional blood flow, interstitial fluid, fluid dispersion patterns and active cellular physiology
Ablation Substrate (6)	**Egg White** - Ablations demonstrate substantial differences from those formed in solid animal tissue - High color-change temperature can underestimate ablation size - Fluid convection produces inconsistent and small ablation zones **Chicken** - High color-change temperature can underestimate ablation size **Beef liver & Pork** - Lower color-change temperature allow visualization of more of the ablation zone
Substrate processing (2,3,14)	- Detailed description of processing - Preservative free samples - Determination of NaCl enhancement
Inclusion of Bone-Tissue interface (15,16)	- Tissue inhomogeneity can affect ablation size and shape - The relative composition of cortical and trabecular bone (e.g. vertebra vs. diaphysis of long bone) may reduce or enhance an effect
Injection technique variable (3,4,17-19)	**Volume** - Too small, no effect - Too large, increased variability **Dilution of studied injectate** - Final concentration of injectate **Method representative of clinical practice** - Replicate time allowed for local anesthetic **Cannula injection & speed of injection** - Influence dispersion
RFA equipment selection (20)	- Active tip length and gauge - Adequate power to increase ablation size - Ability to capture electrical data -Power -Impedance -Temperature -Voltage -Current
Ablation time (3)	- Fluid preinjection increases time required to achieve maximum ablation size - Increasing ablation time beyond 90 seconds maximize ablation size and reduces ablation variability
Ablation Evaluation (7,20)	- Define the criteria by which the ablation zone is defined in terms of histological changes, temperature, or color - Histology: Zoning of ablation (H1, H2, H3) - MRI: Define method of ablation segmentation - Gross evaluation: Define color-change criteria used to segment ablation zone, e.g. by correlation to temperature/damage metrics - Dissection technique

study's particular low-concentration saline injection protocol does not actually affect ablation size, or if the study's methods confounded detection.

In contrast to the Paul et al (1) study, multiple well-designed in vivo and ex vivo studies in the fields of radiology, cardiology, and pain medicine demonstrate the ability of preinjected NaCl to increase RF ablation size, total energy delivery, and peak power (4,10,11). This study does not support the sweeping conclusion that "hypertonic saline solution does not result in a significantly increased lesion size." Rather, it underscores the fact that the details matter both in terms of the method of saline enhancement, and in the method of studying it. Important details are discussed in Table 1. The effect of saline preinjection is influenced by the saline concentration, volume, tim-

ing, and method of injection. Parameters that have shown an effect experimentally are readily achievable clinically. Ultimately, clinical study of saline preinjection protocols will be required to determine if they have a benefit in terms of pain relief.

Disclosures:

Dr. Provenzano has consulted for Avanos, Boston Scientific, Medtronic, Nevro, and Esteve. He has received research support from Avanos, Medtronic, Nevro, Stimgenics, and Abbott.

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References

1. Paul C, Suvar T, Goree J, Sanford J, Srinivasan N, Choi H. Comparisons of monopolar lesion volumes with hypertonic saline solution in radiofrequency ablation: A randomized, double-blind, ex vivo study. *Pain Physician* 2020;23:159-164.
2. Provenzano DA, Liebert MA, Somers DL. Increasing the NaCl concentration of the preinjected solution enhances monopolar radiofrequency lesion size. *Reg Anesth Pain Med* 2013;38:112-123.
3. Provenzano DA, Watson TW, Somers DL. The interaction between the composition of preinjected fluids and duration of radiofrequency on lesion size. *Reg Anesth Pain Med* 2015;40:112-124.
4. Provenzano DA, Cosman ER, Jr., Wilsey JT. Hypertonic sodium chloride preinjectate increases in vivo radiofrequency ablation size: Histological and magnetic resonance imaging findings. *Reg Anesth Pain Med* 2018;43:776-788.
5. Cosman ER, Jr., Cosman ER, Sr. Electric and thermal field effects in tissue around radiofrequency electrodes. *Pain medicine (Malden, Mass).* 2005;6:405-424.
6. Cosman ER, Jr., Gonzalez CD. Bipolar radiofrequency lesion geometry: Implications for palisade treatment of sacroiliac joint pain. *Pain practice* 2011;11:3-22.
7. Breen MS, Lazebnik RS, Nour SG, Lewin JS, Wilson DL. Three-dimensional comparison of interventional MR radiofrequency ablation images with tissue response. *Computer Aided Surgery* 2004;9:185-191.
8. https://en.wikipedia.org/wiki/Plumping. Accessed April 19, 2020.
9. Ahmed M, Brace CL, Lee FT, Jr., Goldberg SN. Principles of and advances in percutaneous ablation. *Radiology* 2011;258:351-369.
10. Goldberg SN, Ahmed M, Gazelle GS, et al. Radio-frequency thermal ablation with NaCl solution injection: Effect of electrical conductivity on tissue heating and coagulation-phantom and porcine liver study. *Radiology* 2001;219:157-165.
11. Livraghi T, Goldberg SN, Monti F, et al. Saline-enhanced radio-frequency tissue ablation in the treatment of liver metastases. *Radiology* 1997;202:205-210.
12. Kim YN, Rhim H, Choi D, et al. The effect of radiofrequency ablation on different organs: ex vivo and in vivo comparative studies. *European Journal of Radiology* 2011;80:526-532.
13. Steiner P, Botnar R, Goldberg SN, Gazelle GS, Debatin JF. Monitoring of radio frequency tissue ablation in an interventional magnetic resonance environment. Preliminary ex vivo and in vivo results. *Investigative radiology* 1997;32:671-678.
14. Provenzano DA, Lutton EM, Somers DL. The effects of fluid injection on lesion size during bipolar radiofrequency treatment. *Reg Anesth Pain Med* 2012;37:267-276.
15. Eckmann MS, Martinez MA, Lindauer S, Khan A, Ramamurthy S. Radiofrequency ablation near the bone-muscle interface alters soft tissue lesion dimensions. *Reg Anesth Pain Med* 2015;40:270-275.
16. Vallejo R, Benyamin R, Tilley DM, Kelley CA, Cedeno DL. An ex vivo comparison of cooled-radiofrequency and bipolar-radiofrequency lesion size and the effect of injected fluids. *Reg Anesth Pain Med* 2014; 39:312-321.
17. Provenzano DA, Lassila HC, Somers D. The effect of fluid injection on lesion size during radiofrequency treatment. *Red Anesth Pain Med* 2010;35:338-342.
18. Provenzano DA. Think before you inject: understanding electrophysiological radiofrequency principles and the importance of the local tissue environment. *Reg Anesth Pain Med* 2014;39:269-271.
19. Goldberg SN. Radiofrequency tumor ablation: principles and techniques. *European journal of ultrasound : official journal of the European Federation of Societies for Ultrasound in Medicine and Biology.* 2001;13(2):129-147.
20. Cosman ER, Jr., Dolensky JR, Hoffman RA. Factors that affect radiofrequency heat lesion size. *Pain Med* 2014;15:2020-2036.