strategy. As far as we are aware, this is the first study to report on long-term effects of RyR-2 modulation and dantrolene use on cardiac activation and repolarization in humans. We see therapeutic potentials for dantrolene when arrhythmia suppression is not satisfactory with current antiarrhythmic drugs, or when their side effects profile is not tolerable. Evolving evidence suggests potential utility in ventricular arrhythmias and atrial fibrillation. An attractive, although underappreciated, aspect of dantrolene use is this novel automated antiarrhythmic paradigm, as the drug does not exert its therapeutic effect until the RyR-2s become dysfunctional, thus minimizing discernible effects on cardiac electrophysiology under basal states and providing favorable safety profile.

Our study carries the inherent limitations of a retrospective design lacking the strengths of a study that would include data before and after dantrolene therapy. Our data assessed patients with no underlying arrhythmia, that is, when RyR-2 is not dysfunctional; dantrolene has no discernible proarrhythmic features. In our previous work (2), dantrolene did not affect the QT in an in vivo ventricular arrhythmia swine mode. Although unlikely to be very different, potential proarrhythmic effects in humans cannot be ascertained from this data and further prospective studies (phase 1 and 2) are needed and underway by the authors. Despite these limitations, we believe that our observational study provides initial safety data that will help researchers designing prospective crossover studies assessing the effect of dantrolene and/or RyR-2 modulation on humans.

In conclusion, patients who had cardiac testing after 10 years of chronic dantrolene usage did not have QRS or QTc prolongation, and their left ventricular ejection fraction was normal. This observational data suggest that chronic RyR-2 modulation can now be tested in prospective crossover studies to confirm these findings.

Mahmoud M. Bokhari, MBBS, DABIM
Danna A. Spears, MD
Patrick F. Lai, MSc
Daoyuan Si, MD, PhD
Filio Billia, MD, PhD
John D. Parker, MD
Abdul O. Al-Hesayen, MD
Mohammed A. Azam, MBBS, PhD
Sheila Riazi, MSc, MD
***Kumaraswamy Nanthakumar, MD**

*The Hull Family Cardiac Fibrillation Management Laboratory
Toronto General Hospital
Cardiology
200 Elizabeth Street
Toronto M5G 2C4, Ontario
Canada
E-mail: kumar.nanthakumar@uhn.ca

https://doi.org/10.1016/j.jacep.2018.08.001

Please note: Dr. Riazi has received personal fees from Norgine Pharmaceuticals. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

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Cardiac Ablation by Electroporation

In a recent State-of-the-Art Review article, Wittkampf et al. (1) offered their view on irreversible electroporation (IRE) as a promising and potentially disruptive technology in cardiac ablation for pulmonary vein isolation. The investigators recognize advantages and disadvantages that electroporation offers over existing thermal ablation modalities. Myocardium has a lower irreversible electroporation threshold than other tissues, thus providing tissue specificity and limiting extracardiac injury. Mentioned challenges include epicardial fat, dependency on tissue-electrode contact, gas bubble formation, nerve and skeletal muscle stimulation, and technological challenge of applying high-voltage pulses.

However, some of generalizations that the investigators make based on long monophasic pulses and unipolar delivery (ground patch serving as the return electrode) should be considered with caution. Unipolar delivery produces a diffuse field gradient

JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 4, NO. 11, 2018
NOVEMBER 2018:1480–3

that can result in broad neuromuscular recruitment and diffuse lesion margins. Wittkampf et al. (1) do not recognize that bipolar delivery would confine the electric field surrounding the electrode array, minimizing skeletal muscle stimulation and resulting in well-demarcated lesion margins. They refer to a new energy source that may eliminate electrolysis and skeletal muscle contractions that is under development. There was however no insight on the device's characteristics or pulse parameters provided. Avoiding electrolysis and skeletal muscle stimulation is challenging. However, the electroporation community has already introduced delivery methods utilizing short, biphasic, high-frequency pulses with bipolar delivery methods that limit electrochemistry and extracardiac muscle contractions.

The investigators suggest that total applied current is "the parameter that most directly relates to voltage gradient, which causes electroporation" but fail to report total current throughout their review. Even though they recognize that "the local effect of the application directly depends on the strength of the local electrical field" and that "the relationship between applied voltage and local field is rather complex," I believe tissue conductivity is crucial to electric field distribution and was only partially addressed in their discussion. The local electric field (current density divided by conductivity tensor) is responsible for electroporation. Current preferentially flows through paths of higher conductivity—more longitudinally than perpendicularly in cardiac tissue due to fiber orientation. Also, electrical conductivity of infarcted myocardium is more conductive than that of a healthy myocardium. Varying conductivity influences the electric field distribution and may create inconsistent lesions. In addition, tissue heating, perfusion, and pulse delivery also change conductivity—all of which occur already during pulse delivery, hence current changes during pulse(s).

I thank Wittkampf et al. (1) for this discussion and introducing crucial questions regarding cardiac electroporation; however, there are some that were not discussed but need attention: How do electroporated cardiac cells die? What impact does intracardiac ablation have on blood cell lysis? How is "damage" inflicted to the ablated tissue resolved by the immune system? Is substantial heat generated by long monophasic pulses that could result in microbubbles and thermally generated particles? The recent clinical study demonstrating the feasibility of cardiac ablation gives extreme importance to additional preclinical cardiac irreversible electroporation work (2). The electroporation research community can support the investigation of these questions and others.

*Damijan Miklavčič, MD, PhD

*University of Ljubljana
Faculty of Electrical Engineering
Trzaska 25
1000 Ljubljana
Slovenia
E-mail: damijan.miklavcic@fe.uni-lj.si
URL: http://lbk.fe.uni-lj.si/en/

https://doi.org/10.1016/j.jacep.2018.09.014

Please note: Prof. Miklavcic has received research funding and consulting fees from Medtronic.

The author attests he is in compliance with human studies committees and animal welfare regulations of the author's institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

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REPLY: Cardiac Ablation by Electroporation

We would like to thank Prof. Miklavčič for his comments on our paper (1) and acknowledge his important contributions to the field of electroporation. As physicists and cardiologists, we know that bipolar application via 2 closely spaced electrodes results in a confined electrical field that may eliminate skeletal muscle stimulation. The steep exponential decay in current density away from the electrodes causes rather sharp lesion margins. Consequently, however, lesion depth will be limited. However, with poor tissue contact, as often happens with multielectrode catheter ablation in a moving target such as the heart, lesions may then be minimal or even absent. This is the reason why we have chosen to use a unipolar circular application. The much more gradual decay in current density facilitates deep and broad lesions, perhaps even with poor tissue contact. The gradual decay in combination with small local differences in tissue properties indeed also cause diffuse lesion margins as is shown in our publications. Skeletal muscle stimulation is another disadvantage, but with little clinical relevance given the current practice in many countries to perform catheter ablation for atrial fibrillation under general anesthesia.

Many studies have investigated the thermal effects of electroporation ablation and the general