Defibrillation success with high frequency electric fields is related to degree and location of conduction block

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BACKGROUND We recently demonstrated that high frequency alternating current (HFAC) electric fields can reversibly block propagation in the heart by inducing an oscillating, elevated transmembrane potential (V_m) that maintains myocytes in a refractory state for the field duration and can terminate arrhythmias, including ventricular fibrillation (VF).

OBJECTIVES To quantify and characterize conduction block (CB) induced by HFAC fields and to determine whether the degree of CB can be used to predict defibrillation success.

METHODS Optical mapping was performed in adult guinea pig hearts (n = 14), and simulations were performed in an anatomically accurate rabbit ventricular model. HFAC fields (50–500 Hz) were applied to the ventricles. A novel power spectrum metric of CB—the loss of spectral power in the 1–30 Hz range, termed loss of conduction power (LCP)—was assessed during the HFAC field and compared with defibrillation success and VF vulnerability.

RESULTS LCP increased with field strength and decreased with frequency. Optical mapping experiments conducted on the epicardial surface showed that LCP and the size of CB regions were significantly correlated with VF initiation and termination. In simulations, subsurface myocardial LCP and CB sizes were more closely correlated with VF termination than surface values. Multilinear regression analysis of simulation results revealed that while CB on both the surface and the subsurface myocardium was predictive, subsurface myocardial CB was the better predictor of defibrillation success.

CONCLUSIONS HFAC fields induce a field-dependent state of CB, and defibrillation success is related to the degree and location of the CB.

KEYWORDS Defibrillation; Optical mapping; Computational simulation; Conduction block; Power spectrum

ABBREVIATIONS **3D** = 3-dimensional; **CB** = conduction block; **DFT** = defibrillation threshold; **HFAC** = high frequency alternating current; **LCP** = loss of conduction power; **PVE** = proportion of variance explained; **ULV** = upper limit of vulnerability; **VF** = ventricular fibrillation; $\mathbf{V_{elev}}$ = elevated transmembrane potential level; $\mathbf{V_m}$ = transmembrane potential

(Heart Rhythm 2013;10:740–748)

Introduction

Electrical signal conduction in cardiac and nervous tissue is fundamental to their physiological function. Irregular and disorganized patterns of electrical propagation in the brain and heart can lead to life-threatening conditions, such as epileptic seizures and ventricular fibrillation (VF). Alternating current electrical fields were the first type of electrical therapy used to treat VF, dating back to the 1800s. However, the use of alternating current electric fields has, in general, been abandoned because of the high risk of inducing arrhythmias when applied in the 50–60-Hz frequency range.[1,2] Motivated by previous studies demonstrating that high frequency alternating current (HFAC) electric fields reversibly and safely block conduction in nervous tissue,[3,4] we recently demonstrated a novel biophysical mechanism in which 50 Hz–1 kHz sinusoidal HFAC electric fields reversibly block electrical conduction in cardiac tissue.[5] HFAC fields blocked conduction by maintaining myocytes in a refractory state for the field duration—findings that were recently validated independently.[6] We further showed that the same fields terminated reentrant arrhythmias, including VF, demonstrating that HFAC fields may be an effective and potentially safer approach for defibrillation compared with conventional direct current or biphasic fields.[5] Furthermore, HFAC fields may mitigate the pain of conventional defibrillation by additionally transiently blocking neural electrical conduction with the appropriate HFAC field frequency. However, while arrhythmia termination was associated with conduction block (CB) at certain locations in the ventricles, the degree of CB and the location and size of the regions

This work was supported by National Institutes of Health grants R21 HL104338 (to Dr Tung and to Dr Berger) and S10 RR025544 (to Dr Tung). Dr Weinberg, Dr Tandri, Dr Berger, Dr Trayanova, and Dr Tung are coinventors on a pending patent application for a device to treat cardiac arrhythmias using high frequency alternating current fields. **Address reprint requests and correspondence:** Dr Leslie Tung, Department of Biomedical Engineering, Johns Hopkins University, 720 Rutland Avenue, Baltimore, MD 21205. E-mail address: ltung@jhu.edu.

where CB occurred in the 3-dimensional (3D) ventricular volume have not been determined.

Previous studies have characterized electrical activity during fibrillation by quantifying the power spectrum content of the transmembrane potential (V_m) and analyzing dominant frequencies.[7] In this study, using results obtained from optical mapping experiments and realistic 3D computational simulations, we defined and used a novel measure of CB, computed from the V_m power spectrum, to assess the local degree of impeded propagation in different regions of the myocardium during HFAC field defibrillation. Quantification of CB in this manner revealed strong correlations between the degree and the location of CB with VF termination, and simulations predicted the importance of CB in the subsurface myocardium.

Methods

Experimental methods

Detailed methods are provided in the online supplement. In brief, hearts of Hartley guinea pigs (n = 14; weighing 500–800 g) were excised and connected to a Langendorff perfusion system. The epicardial surface of the hearts was optically mapped using a voltage-sensitive dye as described previously.[5,8,9] Sinusoidal HFAC field pulses (frequency 50–500 Hz, amplitude 3.1–18.4 V/cm, duration 300 milliseconds–2 seconds) were applied by platinum field electrodes. In each heart, VF termination and initiation incidence were determined for each field strength and frequency combination, and the upper limit of vulnerability (ULV), defined as the weakest voltage at and above which the HFAC field applied during sinus rhythm did not induce VF, and the defibrillation threshold (DFT), defined as the weakest voltage at and above which the applied HFAC field terminated VF, were determined for each frequency.

Computational methods

Briefly, simulations were performed using a validated[10,11] anatomical model of rabbit ventricles, as described previously.[5] VF was induced with a cross-stimulation protocol. Sinusoidal HFAC field pulses (50–500 Hz, 5–25 V/cm, 1 second) were then delivered from plate electrodes at 11 different coupling intervals following VF initiation. VF termination outcome was assessed after the HFAC field, and the VF termination rate over all coupling intervals was determined for each field strength and frequency combination.

Data analysis

Experimental recordings of optical V_m were processed as described previously.[12,13] We then defined a CB metric as follows: V_m power spectrum at each recording or simulation site was calculated before and during the HFAC field by using fast Fourier transform. V_m power spectra before and during the field were computed over time windows of equal duration (the lesser of the prefield recording duration and the applied HFAC field duration) such that the windows ended at the time of field onset and offset, respectively. V_m traces from the windows before and during the field are shown in red and blue in Figures 1C and 4, respectively. Electrical conduction during both sinus rhythm and fibrillation is typically in the range of 1–30 Hz. Therefore, the areas under the power spectrum curve in the "conduction" frequency range of 1–30 Hz were computed for time windows before and during the HFAC field (Figure 1). The loss of conduction power (LCP) at each pixel was calculated as the percentage decrease in the conduction power *during* field application, compared with that *before* application, such that

$$\mathrm{LCP} = \frac{\mathrm{Area}_{\mathrm{Before}} - \mathrm{Area}_{\mathrm{During}}}{\mathrm{Area}_{\mathrm{Before}}}$$

Further description and justification for the LCP metric are provided in the online supplement. For a given field strength and frequency, we defined 2 global values: (1) the average LCP and (2) the CB size. (1) In experiments, average LCP values were computed for a given field strength and frequency by averaging over all recording sites and then averaging over all hearts. In simulations, LCP values were calculated at each node as described above, and an average LCP value was computed for a given field strength and frequency by obtaining a weighted average over relevant nodes for each coupling interval (weighting each nodal value by the volumes of attached elements) and then averaging over all coupling intervals. (2) CB was identified as occurring at site where LCP was $>90\%$ (see the Results section). The size of CB regions was expressed as a percentage of the total optically mapped area (in experiments) or total ventricular volume (in simulations) with LCP $>90\%$.

To investigate the effect of HFAC fields on CB location and LCP distribution, we considered the fact that the majority of the V_m change induced by an external field resulting from the current entering the tissue is contained within 1 space constant.[14] Since the space constant in the direction transverse to cardiac fibers is approximately 300 μm,[15] most of the field-induced surface polarization is contained within the surface layer of elements in the model (average internodal distance of 507 μm). Thus, we considered surface nodes, defined as nodes exposed to the external bath (consisting of 24% of all nodes), separately from subsurface (interior) nodes, defined as nodes connected only to other tissue nodes (76%). In addition, we analyzed the epicardial and endocardial surface nodes separately; however, this analysis did not greatly improve prediction of defibrillation success, justifying our decision to analyze the surface LCP values collectively (see the online supplement).

Statistical methods

All summary values are expressed as mean ± standard error and were compared by using the Student *t* test. The Pearson correlation coefficient *r* was computed to assess linear correlation. The William formula was used to test for statistically significant differences between dependent correlations.[16] For all tests, $P < .05$ was considered to be significant.