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ABSTRACT

Malignant cardiac tachyarrhythmias are associated with complex spatiotemporal excitation of the heart. The termination of these life-threatening arrhythmias requires high-energy electrical shocks that have significant side effects, including tissue damage, excruciating pain, and worsening prognosis. This significant medical need has motivated the search for alternative approaches that mitigate the side effects, based on a comprehensive understanding of the nonlinear dynamics of the heart. Cardiac optogenetics enables the manipulation of cellular function using light, enhancing our understanding of nonlinear cardiac function and control. Here, we investigate the efficacy of optically resonant feedback pacing (O_{RFP}) to terminate ventricular tachyarrhythmias using numerical simulations and experiments in transgenic Langendorff-perfused mouse hearts. We show that O_{RFP} outperforms the termination efficacy of the optical single-pulse (O_{SP}) approach. When using O_{RFP}, the total energy required for arrhythmia termination, i.e., the energy summed over all pulses in the sequence, is 1 mJ. With a success rate of 50%, the energy per pulse is 40 times lower than with O_{SP} with a pulse duration of 10 ms. We demonstrate that even at light intensities below the excitation threshold, O_{RFP} enables the termination of arrhythmias by spatiotemporal modulation of excitability inducing spiral wave drift.

Sudden cardiac death and arrhythmias account for about 15%–20% of annual deaths worldwide.[1] Two of its important precursors are ventricular tachycardia (VT) and ventricular fibrillation (VF). These occur when the heart begins to deliver impulses irregularly and incoherently, impairing its efficient and coordinated pumping action. Without medical intervention, survival time is limited to minutes. Therefore, patients with anti-tachycardia-pacing resistant VT or VF are treated with electroshock therapy, which can be administered externally or internally. Patients at high risk for these disorders are often advised to use implantable cardioverter defibrillators (ICDs), which continuously monitor the heart rate and deliver electrical shocks to the heart when the beating rate is outside the physiologically acceptable range. Despite a high success rate, ICD therapy is associated with significant side effects, such as tissue damage, traumatic pain, and psychological disturbances. Therefore, there is a medical need for the development of low-energy arrhythmia therapy that overcomes the common drawbacks and helps us to address the risk of cardiac arrhythmias.

I. INTRODUCTION

Self-organized pattern formation in an excitable reaction–diffusion system with nonlinear local dynamics is studied in a wide range of applications: chemical media such as the Belousov–Zhabotinsky (BZ) reaction system and biological media such as the heart.[2,3] Rotating spiral/scroll waves (a typical pattern

in excitable media) in the heart are associated with life-threatening cardiac tachyarrhythmias such as ventricular tachycardia (VT) and ventricular fibrillation (VF).[4–6] The termination of these arrhythmias requires the application of a high-voltage shock that resets all electrical activity in the heart, allowing normal cardiac rhythm to resume. However, despite its high efficiency, this electrical defibrillation entails detrimental side effects, including traumatic pain, tissue damage, and worsening of prognosis, which strongly motivates the search for alternative low-energy defibrillation techniques.[7,8]

In contrast to globally resetting high-energy shocks, low-energy defibrillation approaches aim to control the nonlinear dynamics of spiral and scroll waves underlying the arrhythmias. Theoretical and numerical studies demonstrate the potential of resonant drift induced by low-amplitude global pacing at the spiral rotation frequency to control and terminate cardiac arrhythmias. In 1987, Davydov *et al.*[9] presented the first analytical study of resonant spiral drift, a phenomenon that was demonstrated by Agladze *et al.*[10] in experiments of the BZ reaction system. Biktashev and Holden[11] proposed feedback pacing to maintain resonance when the spiral drifts in the heterogeneous cardiac muscle. It resulted in robust spiral wave drift and termination in numerical simulations. Although this concept has been extensively investigated in theory[11–15] and in some experiments,[16,17] its potential for low-energy termination of cardiac arrhythmias has not yet been fully explored.

Cardiac optogenetics is a technique that allows a normally light-insensitive cardiac tissue to become sensitive to light stimuli by genetic modification. The altered tissue then responds to light pulses by an increase or decrease of the transmembrane voltage of its cells, resulting in modulation of its excitability, affecting the propagation of excitation waves. Previous studies have demonstrated the potential of optogenetics to control electrical spiral waves in the heart with high spatiotemporal resolution.[18–20] In particular, the termination of arrhythmias was demonstrated using sub-threshold,[21–23] as well as supra-threshold optical stimulation.[24–29] Sub-threshold optical stimulation increases cell membrane voltage below the excitation threshold (minimum membrane voltage required to excite the cell) resulting only in a change in excitability and does not trigger an excitation. In contrast, supra-threshold optical stimulation raises the cell membrane voltage above the threshold, leading to the onset of an action potential and the propagating of an excitation wave.

Clinical translation of optogenetics faces major challenges, such as off-target gene expression, immune responses that lead to impairment of long-term gene expression, and light delivery to the target tissue.[30–33] Here we focus on improving pacing protocols for efficient control of cardiac function. To this end, computational studies and available optogenetically modified animal models are excellent tools.

In this study, we use cardiac optogenetics to study and control the dynamics of arrhythmia intact Langendorff-perfused transgenic mouse hearts. Using two pacing protocols: (I) optical resonant feedback pacing O_{RFP} and (II) optical single pulse O_{SP}. Our results show that, at a termination rate of 50%, O_{RFP} requires two orders of magnitude less light intensity per pulse than O_{SP}. Furthermore, we demonstrate that O_{RFP} enables the termination of arrhythmias even at sub-threshold light intensities. To elucidate the possible mechanism of arrhythmia termination, we performed two-dimensional numerical simulations on genetically modified mouse ventricular tissue. We illustrate that resonant global sub-threshold illumination leads to spatiotemporal modulation of cardiac tissue excitability, causing the spiral wave to drift and terminate by colliding with nonexcitable boundaries. Therefore, the resonant drift of the spiral wave could be the main mechanism for arrhythmia termination during O_{RFP}.

II. METHODS

The experiments were performed in accordance with the German Animal Welfare Act and declared to our animal welfare officers; the application for approval of animal experiments was authorized by the responsible animal welfare office (Lower Saxony State Office for Consumer Protection and Food Safety). Humane welfare-oriented procedures were implemented in agreement with the Guide for the Care and Use of Laboratory Animals and the recommendations of the Federation of Laboratory Animal Science Associations (FELASA).

A. Experiments

In experiments, Langendorff-perfused α-MHC-ChR2 transgenic mouse hearts with channelrhodopsin-2 (ChR2) expression restricted to cardiomyocytes were used. Tyrode solution [130 mM NaCl, 4 mM KCl, 1 mM $MgCl_2$, 24 mM $NaHCO_3$, 1.8 mM $CaCl_2$, 1.2 mM KH_2PO_4, 5.6 mM glucose, 1% albumin/BSA aerated with carbogen (95% O_2 and 5% CO_2)] was used to maintain the normal electrophysiological state of the heart during perfusion. All experiments were conducted at 37°C. To induce arrhythmias, a sequence of 30 electrical pulses (amplitude 2.3–2.5 V, pulse duration 1–3 ms) and frequencies 30–50 Hz was applied to the ventricles using a needle electrode. Sustained tachyarrhythmias were ensured by reducing the KCl concentration in the Tyrode solution from 4 to 2 mM and by adding 100 μM pinacidil (a KATP channel activator) to the Tyrode. The hearts were globally illuminated as shown in Fig. 1(a), using three LEDs ($\lambda = 470$ nm) positioned at 0°, 120°, and 240° surrounding the bath. For further details, we refer to Uribe *et al.*[28]

Pacing protocol O_{RFP} was applied to N = 5 mouse hearts to control ventricular arrhythmias. O_{RFP} consists of a series of triggered light pulses with a pulse length (PL) of 20 ms and light intensity (LI) within the range of 3.1–103.5 μW/mm^2. As it is shown in Fig. 1(b) during O_{RFP}, the optical pulses were triggered if the monophasic action potential (MAP) signal exceeds the threshold signal $V_{th} = 0$ a.u. until the arrhythmias were terminated or after reaching the maximum duration of 10 s after the first trigger event. Arrhythmia termination was detected if the dominant frequency decreased below 5 Hz.

For each heart, the optical stimulation threshold was determined. In sinus rhythm, the heart was paced with ten pulses (with a frequency two times faster than sinus rhythm's rate) with a pulse width of 20 ms duration and increasing light intensity until capture was observed in the MAP signal. We performed 5–10 arrhythmia termination attempts for each light intensity and pulse length. If unsuccessful, high-intensity global illumination was applied to terminate the arrhythmia. Between each trial, the heart was allowed to recover and rest for 60 s. Experiments were terminated if the heart rate in sinus rhythm decreased below 3 Hz. For comparison, pacing protocol O_{SP} with a LI from 4.5 to 1160 μW/mm^2 and PLs of 10 and 100 ms was applied to N = 5 mouse hearts.

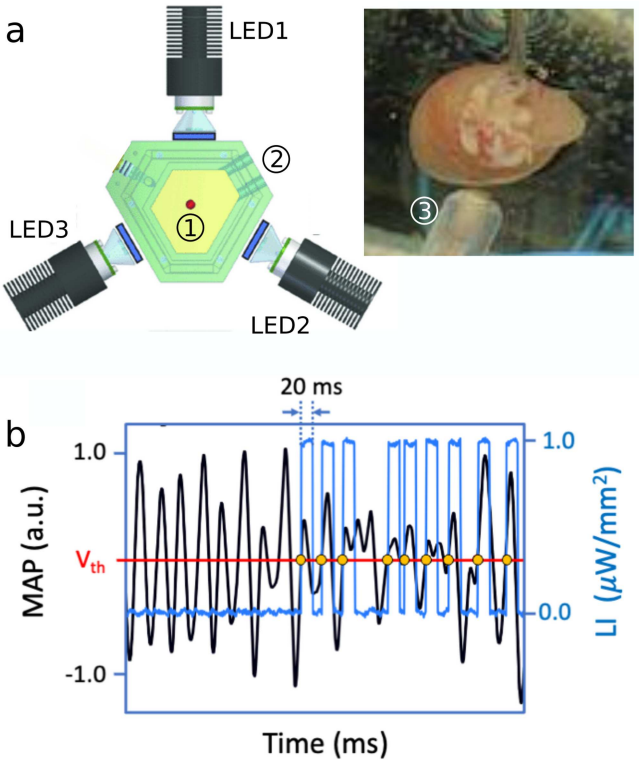

FIG. 1. Experimental setup. (a) Langendorff-perfused transgenic mouse heart (1) in temperature controlled bath (2). LED 1–3 positioned at 0°, 120°, and 240° illuminate of the entire epicardium. Monophasic action potential (MAP) electrode (3) is positioned on the left ventricle. (b) Normalized MAP signal (black) during ventricular arrhythmia. Increase of MAP signal above voltage threshold V_{th} (red) triggers a light pulse (blue) with light intensity 40 μW/mm^2, pulse length 20 ms.

B. Numerical simulations

To describe the electrical activity in the mouse heart ventricle, we used the modified Bondarenko model.[34,35] This model consists of 40 ordinary differential equations solved by Runge–Kutta (fourth order) method with a time step of 10^{-4} ms. The time evolution of the membrane voltage is as follows:

$$\frac{\partial V}{\partial t} = \nabla.\mathscr{D}\nabla V - \frac{\Sigma I_{ion} + I_{stim}}{C_m}, \tag{1}$$

$$\Sigma I_{ion} = I_{Ktof} + I_{Ktos} + I_{Kr} + I_{Kur} + I_{Kss} + I_{K1} + I_{Ks} + I_{Na^+} + I_{Ca} + I_{NaCa} + I_{Ca} + I_{NaK} + I_{CaCl} + I_{Nab} + I_{Cab}. \tag{2}$$

In Eq. (1), C_m = 1.0 μF/cm^2 is the specific capacitance of a cell membrane, $\mathscr{D}$ = 0.00014 cm^2/ms is the diffusion coefficient, which accounts for intercellular coupling, and is responsible for setting the conduction velocity (CV) of a propagating plane wave to 43.9 cm/s. I_{ion} is the total ionic current, composed of the rapidly recovering transient outward K$^+$ current (I_{Ktof}), the slowly recovering transient outward K$^+$ current (I_{Ktos}), the rapid delayed rectifier K$^+$ current (I_{Kr}), the ultrarapid activation delayed rectifier K$^+$ current (I_{Kur}), the noninactivating steady-state voltage-activated K$^+$ current (I_{Kss}), the time-independent inwardly rectifying K$^+$ current (I_{K1}), the slow delayed rectifier K$^+$ current (I_{Ks}), the fast Na$^+$ current (I_{Na}), the L-type Ca^{2+} current (I_{Ca}) , Na$^+$/Ca^{2+} exchange current (I_{NaCa}), the Ca^{2+} pump current (I_{Ca}), the Na$^+$/K$^+$ pump current (I_{NaK}), the Ca^{2+} activated Cl$^-$ current (I_{CaCl}), the background Na$^+$ current (I_{Nab}), and the background Ca^{2+} current (I_{Cab}). I_{stim} is the extra transmembrane current caused by an external stimulus.

To incorporate light sensitivity, the model was coupled with a four-state mathematical model of a light-gated protein (Channelrhodopsin-2 or ChR2),[36] which responds to blue light stimuli (wavelength 470 nm), to produce a current (I_{ChR2}) as follows:

$$I_{ChR2} = g_{ChR2}\, G(V)(O_1 + \gamma O_2)(V - E_{ChR2}), \tag{3}$$

$$G(V) = \left[(10.6408 - 14.6408 \times \exp(-V/42.7671))\right]/V, \tag{4}$$

$$dC_1/dt = G_r C_2 + G_{d1} O_1 - k_1 C_1, \tag{5}$$

$$dO_1/dt = k_1 C_1 - (G_{d1} + e_{12})O1 + e_{21} O_2, \tag{6}$$

$$dC_2/dt = G_{d2} O_2 - (k_2 + G_r)C_2, \tag{7}$$

$$dO_2/dt = k_2 C_2 - (G_{d2} + e_{21})O_2 + e_{12} O_1. \tag{8}$$

Here, g_{ChR2} is the maximum conductance, G(V) is the voltage-dependent rectification function, O_1 and O_2 are the open states of ChR2, γ = 0.1 is, probability, the ratio of contribution of the open states O_2/O_1, V is the membrane voltage, and E_{ChR2} is the reversal potential, which was taken to be 0 mV. G_1, G_{d1}, G_{d2}, e_{12}, e_{21}, k_1, and k_2 are the kinetic parameters corresponding to the transition states of ChR2 states (close: C_1, C_2; open: O_1, O_2). The model parameters are described in Ref. 36. To stimulate the cell membrane optically, I_{ChR2} is used as I_{stim} in Eq. (1).

We integrate Eqs. (1)–(8) in a 2D domain of size 25 × 25 mm^2 with dx = dy = 0.025 cm and using finite difference method with five-point stencil. Then, we induced a single spiral wave in the domain detailed in Ref. 21. To control the spiral wave dynamics, we apply the O_{SP} and O_{RFP} protocols. With O_{RFP}, we applied a sequence of pulses with a width of 33 ms (half of the spiral wave period 66 ms) each starting at V_{th} = −40 mV during depolarization. We use N = 25 initial conditions to test termination efficacy for each LI. For each initial condition, we have induced the spiral wave in such a way that the tip of the spiral wave is positioned at different points in the domain.

III. RESULTS

Figure 2(a) shows a MAP signal (black) obtained during a VT in a Langendorff-perfused optogenetic mouse heart. During O_{RFP}, the MAP signal triggers a pulsed, global illumination (shown in a blue trace) of the entire epicardium (PL = 20 ms, LI = 40 μW/mm^2) when the signal amplitude rises above the trigger level. In this example, it requires n = 27 light pulses over a period of about 1.4 s to terminate the arrhythmia allowing sinus rhythm to resume. For comparison, Fig. 2(b) shows the successful termination of an arrhythmia using the protocol O_{SP} with

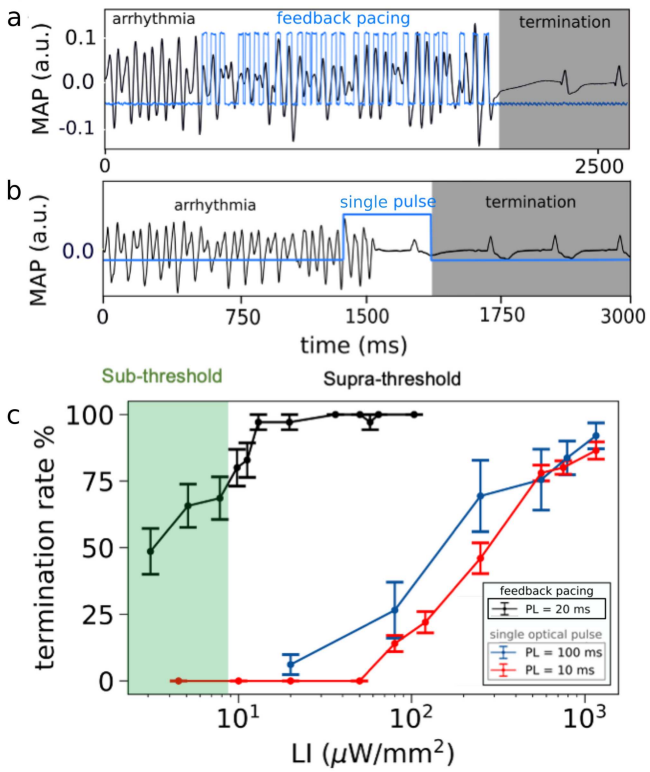

FIG. 2. Terminating efficacy of ventricular tachyarrhythmias in *ex vivo*. (a) Arrhythmia termination using optical resonant feedback pacing (O_{RFP}). Monophasic action potential (MAP, black) and light intensity (LI = 40 μW/mm^2) with pulse length (PL = 20 ms) triggered from MAP time series result in arrhythmia termination (gray). (b) Arrhythmia termination using the optical single pulse (O_{SP}) PL = 100 ms, LI = 560 μW/mm^2]. (c) Arrhythmia termination efficacy in mouse hearts (N = 5) vs LI for O_{RFP} (black line) and O_{SP} (blue line: PL 100 ms, red line: PL 10 ms). Green shaded area indicates sub-threshold LI, data given in mean ± SEM.

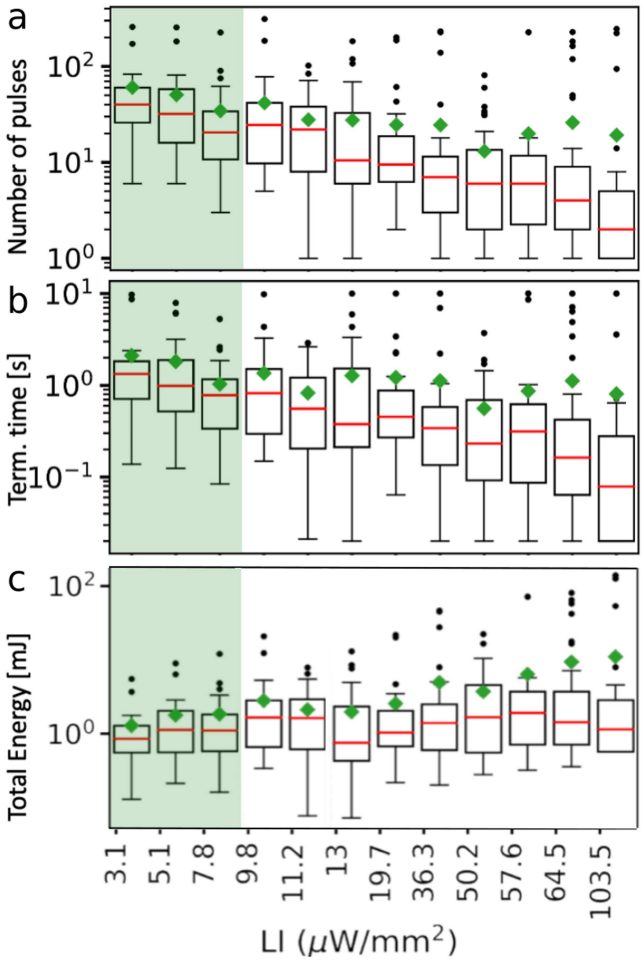

FIG. 3. Characteristics of resonant feedback pacing needed to terminate ventricular tachycardias (VT) in *ex vivo*. (a) Number of pulses with pulse length 20 ms needed to terminate VT. (b) Termination times. (c) Total energy of the pulse sequence needed to terminate VT. Boxplots indicate median (green diamond), mean (red line), and outlier (black circle), and green shaded boxes indicate the sub-threshold regime.

PL = 100 ms and LI = 560 μW/mm^2. After the onset of the light pulse, the arrhythmia is terminated following a short transient and the heart returns to sinus rhythm. The termination of arrhythmia is a stochastic process, where the success rate (SR) of each protocol depends on the LI, as shown in Fig. 2(c). For O_{SP}, the termination efficacy increases with increasing LI, with longer PL result in increased efficacy. The LIs resulting in 50% and 75% SR, LI_{50} and LI_{75}, are 150 and 560 μW/mm^2, respectively. Also, SR of the O_{RFP} method increases monotonically with LI. However, in contrast to O_{SP}, for O_{RFP}, LI_{50} is at 3.1 μW/mm^2, whereas LI_{75} is 9.8 μW/mm^2. Thus, O_{RFP} requires 50-fold less LI to obtain 50% SR, 56-fold less intensity to a 75% SR.

In the O_{RFP} method, light pulses are triggered until the arrhythmia is terminated or the maximum duration of the sequence has been reached (10*s*). Figure 3(a) shows that the number of pulses (PL = 20 ms) required to successfully terminate the arrhythmia decreases with increasing LI, from a mean of 40–50 pulses at 1.3 μW/mm^2 to 1–2 pulses at 103.5 μW/mm^2. Correspondingly, the total time to termination decreases with increasing LI from 1–2 s to 0.1 s [Fig. 3(b)]. It is also noteworthy that the termination time for O_{SP} is about 100 ms. For O_{RFP}, the total energy required for termination, i.e., the energy summed over all pulses of the sequence, remains essentially constant at 1 mJ [Fig. 3(c)] in our experiments. In comparison, the energy for O_{SP} at 50% success rate is 0.035 mJ for PL of 10 ms and 0.21 mJ for PL of 100 ms. In addition, we calculated the energy per pulse at a success rate of 50% (E_{50}) and found that 40 times more energy is required at a PL of 10 ms and 240 times more energy is required at a PL of 100 ms compared with O_{RFP}. Further details are summarized in Table I along with the number of pulses (NP) required at 50%, 75%, and 100% termination rates for the O_{SP} and O_{RFP} methods. Using numerical

TABLE I. Summary. PL—pulse length, NP—mean number of pulses, LI_{50}—mean light intensity per pulse at 50% success rate (SR), E_{50}—mean energy per pulse at 50% SR, E_{tot}—mean total energy required at 50% SR, T_{term}—average time required for termination.

		Single pulse		Res. feedback pacing		
NP		1	1	45	20	1–2
PL	ms	10	100	20	20	20
LI_{50}	$\mu W/mm^2$	250	150	3.1		
LI_{75}	$\mu W/mm^2$	560	560		9.8	
LI_{100}	$\mu W/mm^2$	<1000	<1000			103.5
E_{50}	mJ	0.035	0.21	0.87×10^{-3}		
E_{tot}	mJ	0.035	0.21	1		
T_{term}	s	≈0.1	<0.1	2	1	0.1

simulations, we investigate possible mechanisms underlying the termination of spiral waves (SWs) by O_{RFP}, especially at LIs below the excitation threshold. Figure 4(a) shows a counterclockwise rotating SW with a circular core. The time series shown in Fig. 4(e) represents the electrical activity of the domain recorded by the measuring electrode (indicated by a red dot). During O_{RFP}, the time series triggers a sequence of global light pulses with a sub-threshold LI = 20 $\mu W/mm^2$ and PL = 33 ms. As a result, O_{RFP} induces the drift of the SW, which finally collides with the boundary after NP = 9 [Figs. 4(c) and 4(d)].

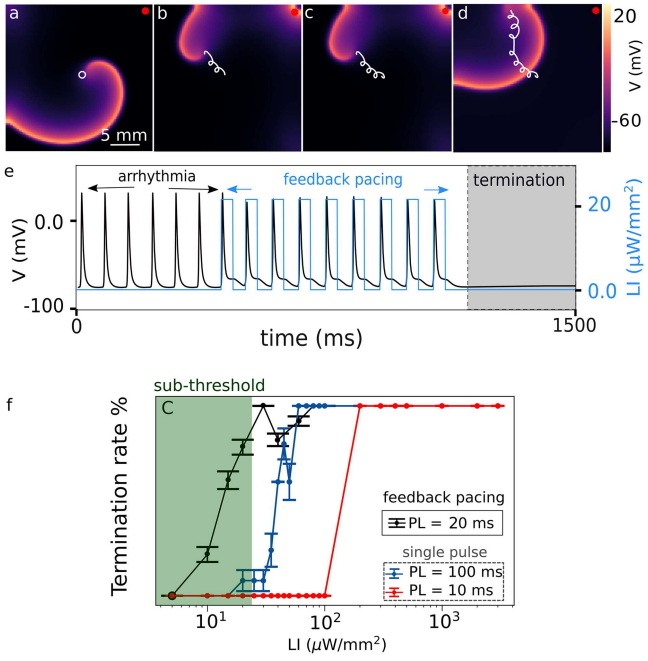

FIG. 4. Spiral wave (SW) termination *in silico*. (a) The SW rotates with an initially circular core. (b)–(d) illustrate the drift of the SW during optical resonant feedback pacing (O_{RFP}). (e) Electrical activity (black) of the domain recorded by a measuring electrode (red dot). Blue trace shows optical pulses. Gray shaded box indicates the SW termination. (f) Termination efficacy of SWs (N = 5) vs light intensity (LI) for O_{RFP} (black line) and optical single pulse (blue line: PL 100 ms, red line: PL 10 ms). Green shaded area indicates sub-threshold LI, and data given in mean ± SEM.

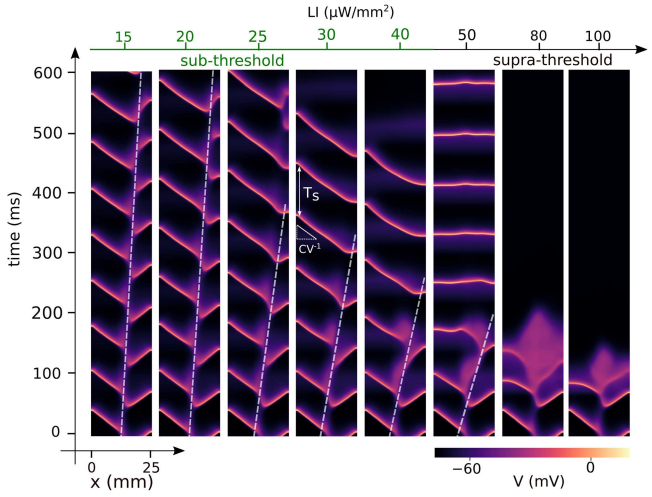

FIG. 5. Mechanisms for termination of a spiral wave during optical resonant feedback pacing (O_{RFP}). Space–time plots along a line of a two-dimensional domain containing a spiral wave paced using the O_{RFP} method. The dashed line indicates the core region of the wave.

We repeat this numerical experiment for N = 25 initial conditions and LI ranging from sub- to supra-threshold. Figure 4(e) shows the resulting numerical dose–response curve, which qualitatively reproduces the experimental observations. In particular, we observe high termination efficiency at sub-threshold LIs for O_{RFP}. The SR varies between 0% and 75% for the LIs of 5–20 $\mu W/mm^2$. For supra-threshold LIs, the SR increases toward 100%. We, therefore, hypothesize that the drift induced by O_{RFP} is a mechanism that contributes to the termination of VTs at sub-threshold LIs.

Figure 5 shows a space–time representation of the dynamics of the SWa under the effect of O_{RFP} at different LIs. The space–time diagrams show the membrane potential along a horizontal line in the 2D domain at y = 12.5 mm. We observe the termination of the waves due to drift at sub-threshold intensities, as well as supra-threshold intensities near the excitation threshold. At the supra-threshold regime with LI = 50 $\mu W/mm^2$, the termination of the SW is followed by the propagation of plane waves induced by illumination. However, at higher intensities, i.e., LI = 80 and 100 $\mu W/mm^2$, the rapid excitation of the entire region leads to phase resetting and termination of the SW. In the space–time plot, the core of the drifting SW is indicated by a dashed line. For a stationary SW, this line is vertical in the space–time representation. A drifting core is represented by an oblique line indicating the direction of motion and velocity (slope). As the LI increases, the drift velocity increases, corresponding to a decreasing slope. In addition, an increment of LI leads to a longer rotation time of the SW (Ts) and a decrease of the CV.

IV. DISCUSSION

In this study, we have experimentally investigated the control of cardiac arrhythmias by resonant feedback pacing based on theoretical and numerical work by Davidov and co-workers[9,10] and Biktashev and Holden.[11,37] The latter introduced feedback to maintain resonant pacing conditions even when the spiral drifts in the presence of heterogeneities and boundaries. In their numerical study, Biktashev and Holden applied a global electric field pulse when the membrane potential at a local electrode exceeded a predefined threshold. This approach led to robust spiral drift and improved success rate in terminating single spiral waves in simulations. Furthermore, spiral/scroll wave termination using resonant pacing with feedback has been studied in 2D models and 3D simulations with realistic heart geometry.[12,38–42] However, the experimental implementation remained elusive. The present study uses global illumination to demonstrate the efficient termination of ventricular tachyarrhythmias in intact optogenetic mouse hearts by optical resonant feedback pacing (ORFP) at subthreshold and suprathreshold light intensities.

The experiments confirm the predicted higher termination effectiveness of resonant feedback stimulation compared to single pulses in terms of energy per pulse. However, the total energy requirement for a single pulse and pacing sequence remains comparable, as stimulation sequences with low intensities require an increasing number of pulses. Depending on the light intensity, duration, number, and timing of the pulses, various mechanisms that influence the dynamics of the spiral waves and contribute to their termination were identified. When a single light pulse is applied, suprathreshold light intensities lead to tissue depolarization and wave termination with energy-dependent efficacy.[18,28] As a result of a suprathreshold light pulse, termination is often associated with complex transient spatiotemporal dynamics and energy-dependent, finite termination time (R.A. Quiñonez Uribe, Arrhythmia termination using Global Optogenetic Stimulation in ChR2 mice hearts, Dissertation, University of Goettingen, 2021 https://doi.org/10.53846/goediss-8455). Transient dissolution of the spiral wave core is observed at the transition from suprathreshold to subthreshold light intensities.[43] It should be noted that illumination with subthreshold light intensities may also lead to wave break initiation, facilitating the onset of cardiac arrhythmias.[44]

The spatial–temporal modulation of excitability, e.g., by excitability gradients and pacing, causes spiral wave drift. This effect has been investigated in several studies in the context of cardiac optogenetics and subthreshold light intensity and intensity gradients.[14,15,21,45] Spiral drift is a mechanism that may contribute to finite termination times. In three-dimensional cardiac tissue, spatial gradients of light intensity result from light absorption in the tissue[46,47] and induce spiral wave drift. Depending on the incident light intensity, wall thickness, and absorption coefficient, suprathreshold light intensities near the surface and subthreshold intensities further inside the ventricular wall are possible. In this situation, both subthreshold and suprathreshold mechanisms affect the dynamics of spiral waves in the heart.

Optogenetic mouse hearts are suitable experimental model systems to validate and advance control approaches, particularly optical feedback pacing, due to the absence of stimulation artifacts otherwise common to electrical stimulation protocols. However, the present study also has several limitations. In transgenic murine hearts, we validated the efficacy of O_{RFP} in terminating monomorphic and polymorphic ventricular tachycardia. These arrhythmias are associated with single stable or meandering scroll waves. Ventricular fibrillation, on the other hand, is associated with the complex dynamics of multiple scroll waves and their interaction with the heterogeneous substrate, resulting in wave breaks or pinning of waves at endogenous heterogeneities. While O_{RFP} may cause multiple scroll waves to terminate progressively, it may also cause the breakup and emergence of new scroll waves.[44] Thus, the effectiveness of the termination of multiple scroll waves depends on several factors, including tissue geometry and heterogeneity, the dynamics of phase singularities (2D) and singular filaments (3D), and the mechanisms underlying their drift, interaction, and stability (creation, annihilation). The application of O_{RFP} to VF is beyond the scope of this study and may be explored in future studies.

Alonso and co-workers have investigated the effect of temporal modulation of excitability on multiple phase singular filaments. Their study focuses on the impact of tissue excitability and temporal forcing on filament stability and the dynamics of scroll waves in three-dimensional excitable media.[48] They demonstrate the control of scroll waves by subthreshold non-resonant modulation of excitability and observe either the suppression or induction of scroll wave turbulence depending on forcing frequency.[49]

Progress in optogenetic control of cardiac arrhythmias may impact the advancement of concepts for efficient control of cardiac arrhythmias by electrical stimulation. Several approaches have been developed to reduce the energy requirements of arrhythmia control by local or global electrical stimulation, i.e., by using multiple local electrodes or electrical fields that recruit virtual electrodes in the tissue, using open or closed-loop control strategies.

Pak and co-workers proposed the termination of ventricular fibrillation by synchronized pacing (SyncP) from local electrodes. SyncP uses one reference and several local stimulation electrodes.[17] Local stimulation currents are triggered by the activation of a reference site and delivered when the optical potential of the stimulation site is in an excitable gap. In Langendorff-perfused rabbit hearts, a lower energy requirement but higher efficacy of SyncP compared to overdrive stimulation at 90% of the VF cycle length was observed. While controlling VF with a few local pacing electrodes is remarkable, the success rates remain too low for practical applications.

Luther and Fenton and co-workers applied suprathreshold global electric field stimulation at pacing frequencies above and below the dominant frequency.[7,50] They demonstrated termination of atrial fibrillation *ex vivo* and *in vivo* (dog) with an energy reduction of 80%–90% compared to single high-energy electric shocks. During far-field pacing, the electric field is applied globally, resulting in the formation of virtual electrodes and local tissue depolarization near heterogeneities in electrical conduction leading to local emission of excitation waves.[51–53] The efficacy of this open loop control approach depends on the ratio of pacing frequency and dominant frequency of the arrhythmia (Hornung *et al.*,[54]) and the dynamics of pinning and unpinning of single[55–59] and multiple spirals.[60] Buran *et al.* conducted a comprehensive numerical study to explore the termination mechanisms and efficacy of periodic excitation on pacing

period and number of pulses.[61] Far-field pacing has been demonstrated to effectively terminate pinned single spirals associated with tachycardia, superseding anti-tachycardia pacing.[56] Recently, further optimization led to an adaptive deceleration pacing (ADP) approach, in which a stimulation sequence is obtained from the power spectrum, slowing down the stimulation sequence from high to low pacing frequencies.[62,63] Using numerical simulations, it was shown that ADP is more robust and efficient than equidistant stimulation using overdrive or underdrive stimulation.

Uzelac and Fenton reported that low-amplitude electrical feedback stimulation may induce a transition from VF to VT and subsequently to sinus rhythm in a perfused Langendorff rabbit heart.[16] In this experiment, electric field stimulation is applied when the time since the previous stimulus exceeds a predefined time interval longer than the dominant period.

Efimov and co-workers developed a multistage algorithm combining global electric field stimulation with pacing from a local electrode. They demonstrated that this three-stage atrial defibrillation therapy terminates atrial fibrillation with significantly less energy than a single electrical shock, opening the path of low-energy defibrillation of atrial fibrillation, potentially at or below the pain threshold.[64–66]

In other studies, the response of the dynamics of nonlinear dynamical systems to weak external stimulation has been investigated.[67–69] For example, in homoclinic chaotic systems with strong fluctuations of interspike intervals, a small amount of noise has been shown to make timescales more regular by reducing the residence time in weak, unstable regions, showing phenomena including coherence resonance, noise-induced synchronization, stochastic resonance, and noise-induced phase synchronization. The response of homoclinic chaos to noise shows similarities to excitable systems, where resonance depending on signal frequency and noise intensity have been observed, motivating further research in this direction.

In summary, our results show a significant enhancement of termination efficiency at low light intensity by resonant feedback stimulation. Numerical simulations suggest that resonant drift contributes to the termination. We anticipate resonant feedback pacing, combined with advanced implantable optoelectronic devices, may open the path to efficient optogenetic control of cardiac tachyarrhythmias.

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AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

Author Contributions

S. Hussaini: Formal analysis (equal); Investigation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **A. Mamyraiym Kyzy:** Investigation (equal); Visualization (equal). **J. Schröder-Schetelig:** Investigation (equal); Visualization (equal); Writing – review & editing (equal). **S. L. Lädke:** Investigation (equal). **V. Venkatesan:** Investigation (equal). **L. Diaz-Maue:** Investigation (equal). **R. A. Quiñonez Uribe:** Investigation (equal). **C. Richter:** Investigation (equal). **V. N. Biktashev:** Conceptualization (equal); Writing – review & editing (equal). **R. Majumder:** Investigation (equal); Writing – original draft (equal); Writing – review & editing (equal). **V. Krinski:** Conceptualization (equal); Writing – review & editing (equal). **S. Luther:** Conceptualization (equal); Funding acquisition (equal); Methodology (equal); Project administration (equal); Resources (equal); Supervision (equal); Writing – original draft (equal); Writing – review & editing (equal).

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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