Phase Entrainment of Induced Ventricular Fibrillation: A Human Feasibility and Proof of Concept Study.

Arun V Holden[1], Gordon A Begg[2], Katrina Bounford[2], Berthold Stegemann[3], Muzahir H Tayebjee[2].

[1]School of Biomedical Sciences, University of Leeds, Leeds, LS2 9JT; UK.
[2]West Yorkshire Arrhythmia Service, Leeds General Infirmary, Great George Street, Leeds, LS1 3EX, UK .
[3]Medtronic Plc, Bakken Research Center, Endepolsdomein 5, 6229 GW Maastricht, The Netherlands.

Abstract

Cardioversion and defibrillation by a single high energy shock applied by myocardial or body surface electrodes is painful, causes long term tissue damage, and is associated with worsening long term outcomes, but is almost always required for treatment of ventricular fibrillation .

As a initial step towards developing methods that can terminate ventricular arrhythmias painlessly, we aim to determine if pacing stimuli at a rate of 5/s applied via an implantable cardiac defibrillator (ICD) can modify human ventricular fibrillation.

In 8 patients undergoing defibrillation testing of a new/exchanged intracardiac defibrillator, five seconds of pacing at five stimuli per second was applied during the 10-20 seconds of induced ventricular fibrillation before the defibrillation shock was automatically applied, and the cardiac electrograms recorded and analyzed.

The high frequency pacing did not entrain the ventricular fibrillation, but altered the dominant frequency in all 8 patients, and modulated the phase computed via the Hilbert Transform, in four of the patients.

In this pilot study we demonstrate that high frequency pacing applied via ICD electrodes during VF can alter the dominant frequency and modulate the probability density of the phase of the electrogram of the ventricular fibrillation.

Introduction

Ventricular fibrillation (VF) is a result of high frequency (dominant frequency from 4.0-5.5 Hz, cycle length < 250 ms), irregular, interacting, re-entrant propagation of electrical excitation waves within the ventricular myocardium. This leads to cardiac arrest and death if not treated urgently with defibrillation. The electrical activity of VF may self-terminate [1] or be terminated by a short, large amplitude (5-40 J) electrical shock delivered by an implanted cardioverter defibrillator (ICD) or 120-360 J applied externally. Defibrillation needs to be prompt: in animal studies the threshold for defibrillation increases, and the probability of a successful defibrillation decreases as VF persists [2]. Clinically, between the first 5 and 15 seconds of VF the probablility that a defibrillation shock is successful halves [3]. Defibrillation shocks can produce cell and tissue damage [4]. They are painful, and some patients find the subjective effects of an ICD intolerable. Repeated defibrillation shocks, even when appropriate and successful, are associated with increased morbidity and mortality [5]. Although life style changes and pharmacological agents can reduce the risk of VF, electrical defibrillation is the most effective means of treating VF [6]. There is therefore great interest clinically in the concept of achieving painless defibrillation by using a repetitive sequence of high frequency, low energy, antifibrillation pacing stimuli, rather than a single large defibrillation shock. Defibrillation by high frequency pacing has been achieved in isolated perfusd atrial [7] and ventricular [8] preparations.

Clinically, anti-tachycardia pacing (ATP) is a short sequence of high frequency pacing stimuli, where the pacing interval may be constant (typically 88% of the tachycardia cycle length), or determined by a decreasing fraction of the preceeding cycle length [9]. Implantable cardioverter defibrillators may be routinely programmed to deliver a sequence of ATP once a tachycardia is detected. Atrial ATP is not effective in terminating persistent episodes of atrial fibrillation [10], but can terminate the slower atrial flutter or tachycardia [11]. This has been exploited in reactive ATP, where ATP is applied whenever atrial fibrillation spontaneously transitions to flutter or tachycardia [12]. Terminating these more organised episodes slows the disease progression and leads to a reduced atrial fibrillation burden [13].

ATP is well established for the control of "slow" ventricular tachycardia, with cycle length more than 250 ms [14]. A defibrillation shock may then be applied if the ATP sequence had failed. A role for ATP in VF , however, has not been established.

Downloads from implantable cardiac devices, and intra cardiac recordings during clinical electrophysiological testing in humans, can provide time series data for characterising idiopathic and induced

Key Words

Ventricular Fibrillation, Implantable Cardioverter Defibrillator, High Frequency Pacing, Anti-Tachycardia Pacing.

Corresponding Author
Professor Arun V Holden
School of Biomedical Sciences, University of Leeds, Leeds, LS2 9JT, UK.

VT and VF in humans [15]. During clinical defibrillator testing in the cardiac catheterization laboratory, the 10-30 s of induced VF provides a narrow window for examining any effects of applied perturbations on the recorded VF.

In this percutaneous human pilot study using standard clinical intracardiac defibrillation hardware, within the confines of a hospital cardiac electrophysiology catheter intervention laboratory, the objective was to determine whether the delivery of high frequency pacing at 5/s via intra-myocardial defibrillator leads during VF can alter the quantitative characteristics of the cardiac electrograms (EGMs) during VF.

Methods

This study was registered on ClinicalTrials.gov on 14th December 2015 with the ClinicalTrials.gov registration number: NCT02629445, and received ethics approval from the North West - Greater Manchester West Research Ethics Committee (15/NW/0722). The study protocol was carried out in accordance with the relevant guideslines and regulations of the Leeds General Infirmary, and conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from each patient.

Consecutive patients undergoing de novo implant, revision, or generator change of trans-venous implantable cardiac defibrillator (ICD) or cardiac resynchronisation defibrillator (CRT-D) devices at the West Yorkshire Arrhythmia Service, Leeds General Infirmary, and who were to undergo planned defibrillation testing as part of their routine medical care, were included in this study [Table 1]. The ICD or CRT-D device and trans-venous leads were implanted according to standard of care. The device pocket was prepared at the left pectoral region. After the pocket was closed, VF was induced from the implanted device using either 2 s of pacing at a rate of 50/s by 8.0 V and 1.5 ms rectangular pulses, or a by delivery of a 5J shock on the T wave. Prior to 50/s pacing VF inductions, the ICD capacitors were charged to intended defibrillation energy to reduce time to the defibrillation shock. VF was induced only once in any one patient.

All patients were implanted with ICD or CRT-D. A programmer was used for programming and interrogation of the implanted device and to induce VF using the electrophysiological testing capabilities

Table 1: Patient Characteristics.

Patient Number	Age	Gender	LV Function	Ischaemia	Device Type	DFT Performed	Induction Type	CS Lead Configuration
1	67	Male	Severe	Y	ICD	N	na	na
2	80	Male	Severe	Y	CRT-D	N	na	LV2-LV3
3	51	Male	Severe	N	ICD	Y	50/s	na
4	73	Male	Severe	Y	CRT-D	Y	50/s	LV1 - Coil
5	54	Female	Moderate	N	CRT-D	Y	T wave shock	LV tip - RVC
6	74	Male	Severe	Y	CRT-D	Y	50/s	LV3-LV4
7	83	Male	Severe	Y	CRT-D	Y	T wave shock	Unknown
8	69	Male	Severe	N	CRT-D	N	50/s	Bipolar
9	73	Male	Moderate	N	CRT-D	Y	50/s	LV3-LV4
10	47	Male	Severe	N	ICD	N	T wave shock	na
11	57	Female	Normal	N	ICD	Y	50/s	na
12	30	Male	Severe	N	ICD	Y	50/s	na
13	29	Female	Severe	N	ICD	N	na	na

The study protocol could not be carried out in patients highlighted in gray. Fibrillation was induced either by 2 s of pacing at a rate of 50/s by 8.0 V and 1.5 ms rectangular pulses, or a by delivery of a 5 J shock on the T wave.

Table 2: Quantitative characteristics of ventricular fibrillation during testing.

Patient	Phase modulation pre-pacing	Phase modulation during pacing	Phase modulation post-pacing	DF pre-pace	DF during pace	DF post-pace
3	0.0241 ± 0.0120	0.0135 ± 0.0103	0.0156 ± 0.0035	5.10 ± 0.14	5.39 ± 0.21	5.28 ± 0.28
4	0.0066 ± 0.0075	0.0082 ± 0.0026	0.0053 ± 0.0030	3.71	4.11	4.09
5	0.0354 ± 0.0208	0.0405 ± 0.0378	0.0474 ± 0.0383	4.35 ± 0.98	4.42 ± 0.21	4.43 ± 0.03
6	0.0148 ± 0.0080	0.0191 ± 0.1175	0.0079 ± 0.0029	5.13 ± 0.58	5.37 ± 0.06	5.50 ± 0.13
8	0.0148 ± 0.0135	0.0133 ± 0.0079	0.0082 ± 0.0020	4.66 ± 0.17	4.91 ± 0.16	4.87 ± 0.46
9	0.0222 ± 0.0179	0.0081 ± 0.0043	0.0087 ± 0.0054	4.87	5.12	4.73 ± 0.20
10	0.0308 ± 0.0221	0.0381 ± 0.0279	0.0200 ± 0.0106	4.95 ± 0.13	5.0	5.80 ± 0.35
12	0.0113 ± 0.0091	0.0631 ± 0.0216	0.0086 ± 0.0063	4.16	4.94 ± 0.04	4.59 ± 0.06
All	0.0200 ± 0.0156	0.0255 ± 0.0249	0.0152 ± 0.0178	4.62 ± 0.49	4.91 ± 0.43	4.91 ± 0.58

Phase modulation = modulation amplitude of probability densities (as in figure 4). DF = Dominant Frequency (Hz)
Data are mean ± standard deviation across all EGM/pseudoECG channels. Where no standard deviation is presented, the same DF value across all channels was obtained.
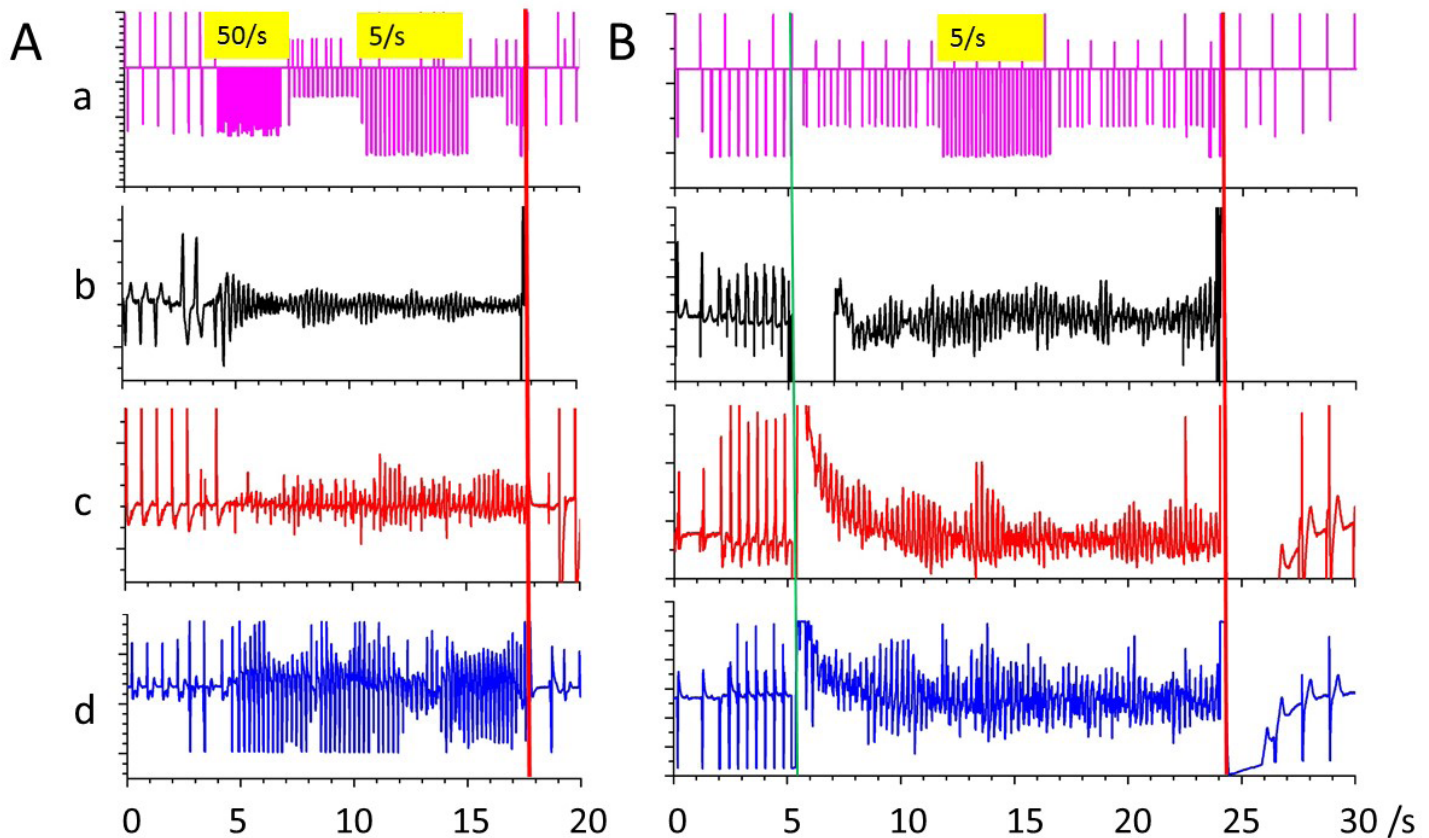
Figure 1:

Sample raw recordings from CRTD/ICD. During a defibrillation test ventricular fibrillation is induced by (A) manually controlled 50/s repetitive stimulation, and, if this fails on the second attempt, by (B) 9 stimuli (8.4 V, 1.5 ms, cycle length 410 ms) followed by a 5 J shock after 400 ms. The 5/s pacing burst is switched on manually after VF has been established for about 5 s. The red lines in A and B mark the defibrillation shock controlled by the ICD algorithm, the green line in B the shock on the T-wave, controlled by the device. (a) is the marker channel (upward stroke atrial signal, downward stroke ventricular signal), (b) the far field EGM - pseudo ECG, (c) EGM1 and (d) EGM2. A is from patient 8, B from patient 5.

of the implanted defibrillator. A breakout box was connected to the programmer and provided access to analogue signals that were continuously telemetered from the device. The breakout box provided analogue signals for the device marker information, the far field ECG was derived from the implant, and two EGM channels were derived from the right and/or left ventricular lead system. The EGM source and source sensitivity were selected on the programmer, depending on the lead system and EGM signal amplitude. Analog signals were digitized at 22 bit amplitude resolution and 500 samples/s using standard data recording equipment.

Once VF was induced, repetitive 5/s pacing was delivered from the RV tip or an LV electrode for approximately 4-5 s at a cycle length of 200 ms, at maximum output of 1.5 ms pulse width and 8.0 V. The pacing frequency was selected as it was within the range of dominant frequencies characteristic of human ventricular fibrillation and faster than the frequencies used in anti-tachycardia pacing [15]. EGMs were recorded from the RV coil and the atrial electrode for the right ventricle, and between the two LV electrodes adjacent to the LV stimulation electrodes for the left ventricle. Each patient only underwent one defibrillation test.

Data were converted from its proprietary poly5 (TMSI Porti) format and exported as .csv files, which were analysed (Short Term Fourier Transform, Hilbert Transform for phase) and plotted. Prior to analysis, the signals were low pass filtered with a 45Hz cut off and high pass filtered with a 1Hz cut off. We performed a Hilbert transformation analysis [16]. If v(t) and p(t), both of the same duration, are the recorded EGM and a 5Hz cosine phase locked to the repetitive pacing signal, and $\tilde{v}(t)$ and $\tilde{p}(t)$ are their Hilbert transforms, the phase was calculated from equation 1:

$$\text{phase} \quad = \quad \arctan\{(v\bullet \tilde{p} - \tilde{v}\bullet p)/(v\bullet p + \tilde{v}\bullet \tilde{p})(t)\} \cdot \text{(1)}$$

Dominant frequency and phase values were calculated during VF before, during and after the pacing intervention. The differences in dominant frequency and phase were quantified.

The phase, computed using the Hilbert transform from equation 1 as demonstrated in [Figure 2D], is bounded and distributed between, -90˚ and +90˚. If there is no relation between the EGM and the reference signal, the phase will be uniformly distributed, with the probability density histogram fluctuating randomly about a constant value of 1/180˚. Modulation of the probability density histogram is used as an indicator of a phase entrainment by the high frequency

pacing intervention of the EGM during ventricular fibrillation. The modulation of the probability density histogram was quantified using the amplitude of a single cycle of a cosine fitted to the histogram.

Data is represented as mean ± standard deviation unless otherwise stated.

All data generated or analysed during this study are included in this published article (and its Supplementary Information files).

Thirteen patients were enrolled. Eight patients underwent the pacing protocol with defibrillation testing . Defibrillation testing could not be performed for clinical reasons in the five excluded patients. The baseline characteristics of the patients studied and the devices which were implanted are shown in [Table 1].

50/s stimulation induced sustained VF in 6 of the 8 patients. In the remaining 2 patients, sustained VF was initiated by a low energy shock synchronised to the T wave. The interval between initiation of VF until defibrillation shock delivery from the implanted device was < 20.4 s (18.03 ±2.3s) , giving 6.79±1.03 s of VF before pacing, 4.87±0.834 s of VF during 5 /s pacing and 6.38±2.13 s of VF after pacing (see Supplementary data).

The magnitude of the EGMs during ventricular fibrillation, either as the peak-peak amplitude of the three EGM signals, as in [Figure 1B,C,D] and [Figure 2B], or as the root-mean-square amplitude/ Hz of their frequency spectra, did not change during high rate high output ventricular pacing intervention . A clear reduction in amplitude was only observed in one patient (see Supplementary Figures).
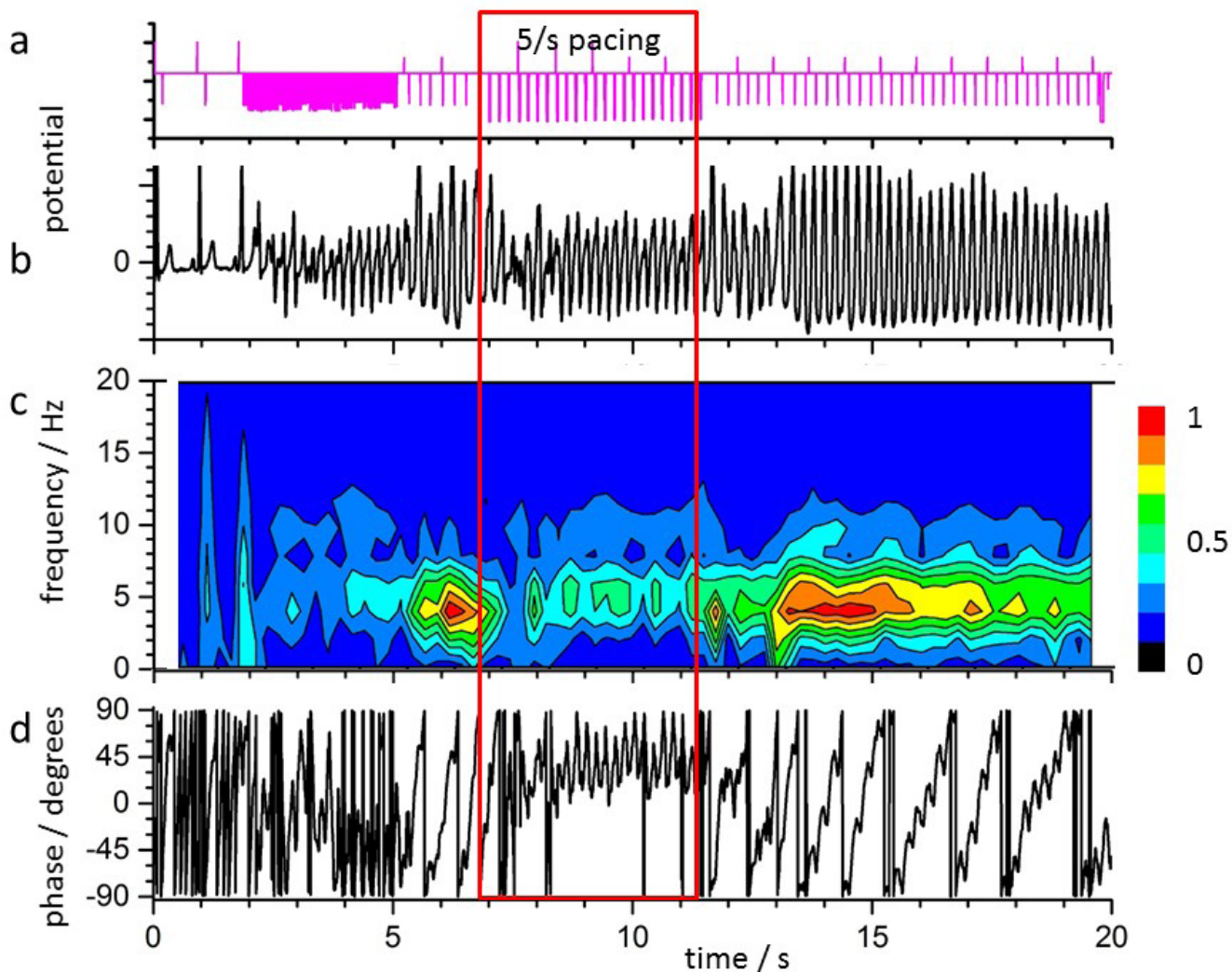

Figure 2: Characterization of ECG surrogate during ventricular fibrillation induced by 50/s pacing: (a) marker channel; (b) the far field EGM - pseudo ECG (low-pass filtered to 45 Hz, zero-meaned and normalised); (c) Chrono-spectrum of pseudo ECG, the normalized root mean square amplitude of the spectrum is colour coded with a linearly mapped colour look-up table. (d) Phase angle of ECG surrogate, estimated by equation (1). The red box outlines the period of pacing at 5/s Data from patient 12.
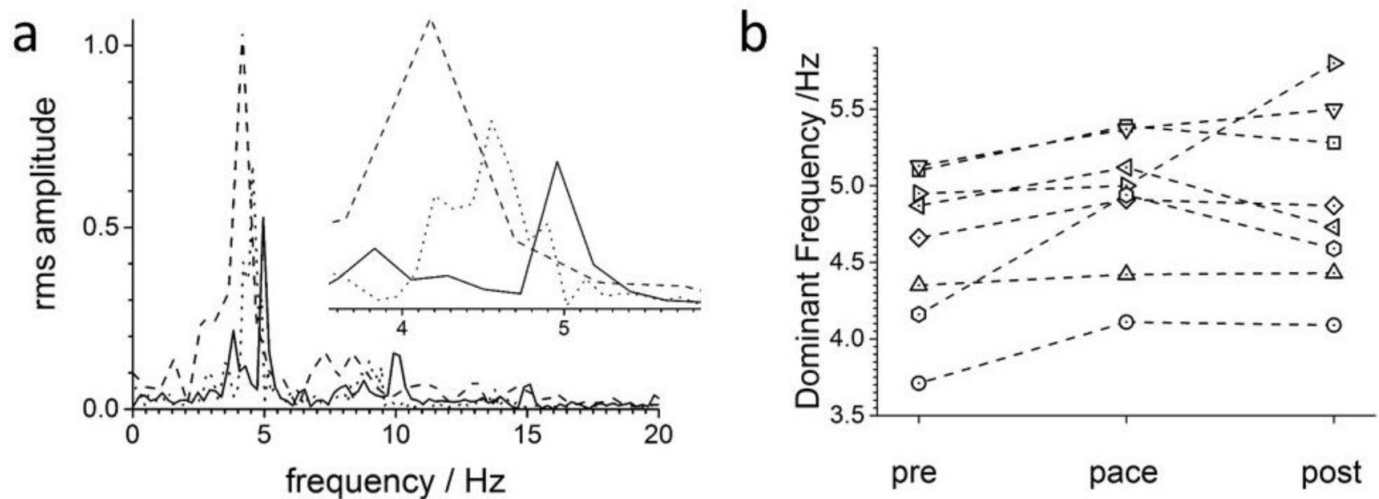
Figure 3: Dominant frequencies of cardiac electrograms during induced ventricular fibrillation: (a) normalised rms amplitude spectra of initial VF (black) that is followed by 5 s of 5 /s pacing (red) then VF (blue) before automated defibrillation. Patient 12. Frequency scale expanded in inset. (b) dominant frequencies of VF electrogram before (pre), during (pace) and after (post) pacing at 5 /s. Numbers adjacent to each plot correspond to patient number as in table 1.

The amplitude Fourier spectra of the EGMs during the VF before, during and after pacing have the harmonic structure characteristic of a repetitive waveform, with a single, large, dominant frequency (DF) component and smaller peaks at integer multiples of this DF [Figure 3A]. In all eight patients the high frequency pacing increased the DF of the ventricular fibrillation EGM, from from 4.6 ± 0.47 to 4.9 ± 0.41 - see data in [Table 2]. The increase of the dominant frequency was maintained throughout the rest of the episode until the VF was defibrillated [Figure 3B]. The DF change from 4.6 ± 0.48 to 4.9 ± 0.58 Hz from the pre- to post-pacing intervals.

Estimated probability density histograms are illustrated in [Figure 4A-4D]. During pacing [Figure 4C] there is clear modulation of the probability density. [Figure 4E] shows an increase in the amplitude of the modulation of the probability density histogram in 4 of the 8 patients.

The quantitative characteristics of the dominant frequency and phase are presented in [Table 2].

Discussion

VF is sustained by irregular, multiple re-entrant wave trains that are propagating in the excitable myocardial tissue, with a velocity of 0.2-0.7 m/s and have a rate of ~5/s [17]. During clinical VF there can be about 10 re-entrant sources [18] that generate propagating wavefronts The waves are composed of irregular action potentials, that spread into tissue that has recovered its excitability, by local circuit currents.

The tissue into which the depolarising wavefronts of the action potential propagate at any instant in time will be smoothly crumpled, curved sheets, of variable width, each ahead of a propagating wavefront, and behind the repolarisation waveback of the preceeding

propagating wave, or a boundary of the tissue. These irregular, moving, writhing narrow sheets form the recovered excitable tissue that can be influenced by electrical stimuli or shocks. The electrical stimulation alters the spatio-temporal pattern of propagation, by altering the cell membrane potentials, tissue excitability , or exciting new action potentials, If the excited cells form a compact, sufficiently large volume of tissue, activity can propagate and capture surrounding myocardium.

The theory of nonlinear waves in excitable media provides an understanding of the spatio-temporal structures and dynamics of the electrical activity driving VF, and how they are modified by anisotropic propagation and heterogeneities [19]. Optical mapping in vitro experiments can give a two dimensional, surface view of re-entrant arrhythmia, and when combined with simultaneous high resolution ultrasound imaging the associated three dimensional scroll wave mechanical filament has been recorded in animal hearts [20]. Bidomain theory [21] provides an approach to how stimulation from electrodes in or near the heart can excite and pace the myocardium, or defibrillate via the induction of virtual electrodes [22]. These theories have been used to design [23] and test methods to produce defibrillation by repetitive trains of small amplitude electrical stimuli, numerically [24, 25], in vitro, on cell cultured preparations and isolated perfused hearts, and in acute animal preparations [8, 26 -27].

The physical rationale for defibrillation by low amplitude repetitive pacing is that if VF is driven by interacting, multiple re-entrant waves, then progressive elimination of these re-entrant waves or rotors will terminate fibrillation [21,25]. If an isolated rotor is idealized as a pinned or a meandering free stable spiral or scroll wave in a two and three-dimensional excitable medium [28], then repetitive perturbations can unpin it and also produce a drift in the position of the core, or filament, of the wave. Repetitive, appropriately timed stimulation would act to gently push the core out of the medium [23].
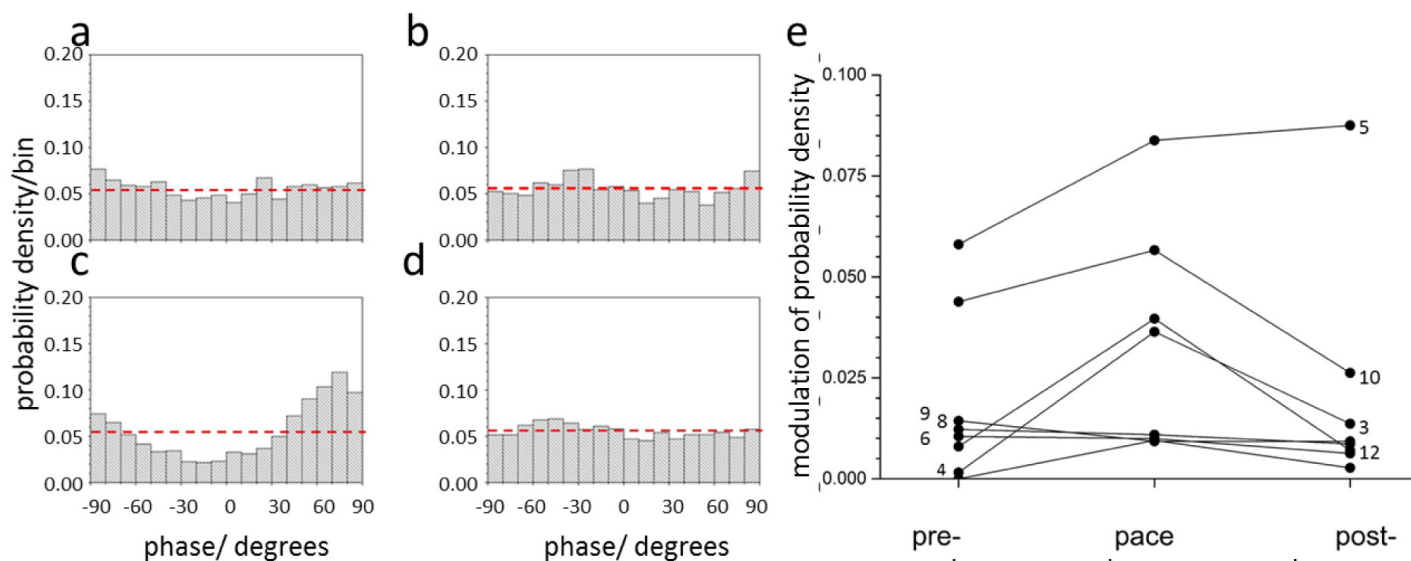
Figure 4: Estimated probability density histograms for phase relative to 5Hz cosine, calculated by equation (1), during induced fibrillation (a) during 50/s pacing induction (b) before 5/s pacing (c) during 5/s pacing (d) and after 5/s pacing and before defibrillation shock. The red dashed line is the density predicted on the assumption that there is no relation between the cardiac electrogram during fibrillation and the 5/s pacing signal (it is 1/18 as the bins are 10° wide). Patient 12 channel b. (e) Modulation amplitude of the probability densities (pre) before pacing, (pace) during 5/s pacing and (post) after 5/s pacing and before defibrillation shock. Numbers adjacent to each plot correspond to patient number as in table 1.

A few bursts of far field repetitive stimulation of ~10% defibrillation single shock amplitude have been shown to be able to terminate re-entry in an isolated canine heart [26].

Although the possible mathematical, physical and biophysical mechanisms of defibrillation can be dissected in isolation in animal and tissue model systems, and the isolated perfused human heart [29] mechanisms for clinical defibrillation need to be studied and tested in human hearts, as the quantitative details of propagation phenomena are species specific, and in vivo, as cardiac excitability and propagation are influenced by sympathetic activity .

In this first in human study, we have demonstrated that 5/s high frequency high output pacing intervention applied via ICD electrodes during VF can alter the quantitative characteristics of the VF electrograms. These changes with time, of frequency, phase and amplitudes imply that the spatio-temporal pattern of activity, or the propagating activity, that produces ventricular fibrillation have been modified by the pacing stimuli. In these experiments the VF before and after the pacing act as the controls, and the VF during the pacing as the test.

There is an apparent increase in the DF from before pacing to during pacing ([Figure 3B, [Table 2]). This higher DF can be maintained post pacing. However, the increase in DF may not be produced by the pacing itself, but result from the evolution of the properties of VF with time since its initiation, as seen in unpertubed, induced VF [17]. Since the duration of the pre-, during and post-pacing VF recordings are short, the spectral estimates have a low resolution and consistency (few degrees of freedom). However, the values in [Figure 3B] are consistent with:

• the range of DF in optical recordings of evoked VFevoked episodes in isolated perfused human hearts , from 5.4 to 6.8 Hz [29],
• the increase in the global mean DF of the cardiac electrograms reported between 1 and 30 s during induced episodes of VF in vivo, from 3.9 ± 0.8 to 5.9 ± 1.0 Hz [30]
• and the increase in DF, at a rate of rate of 0.018 ± 0.005 Hz/s during VF induced by burst pacing reported during open chest surgery using a 256 electrode epicardial sock [30].

The modulation of the estimated probability density histograms ([Figure 4], [Table 2]) for the phase is only observed during the 5 /s pacing, and is a reversible effect of the 5 /s pacing. Modulation is observed in the far field ECG channel, and both recorded EGM channels of [Figure 1], in 4 of the 8 patients. The EGMs for each of these channels is the potential between two adjacent electrodes on the ICD leads. In a mono-domain and bi-domain models of the heart this would be modelled by a weighted integral of the spatio-temporal activity. Any change in the EGMs produced by the pacing could be produced by changes in both, or either of, the temporal and spatial activity during VF.

The 3D spatio-temporal pattern of activity during clinical VF has not been observed. In isolated, perfused hearts, the epicardial surface pattern of excitation during VF (with phase singularities identified as the intersection of a reentrant vortex filament with the surface) are consistent with VF resulting from multiple reentrant vortices [17-19]. The re-entrant waves propagate into tissue that has recovered its excitability. Numerical modelling of the evolution of VF following initiation of a single scroll wave by an S1S2 protocol shows that during the first 30 s of induced VF there are multiple, irregular re-entrant waves with fluctuations in the number of vortex filaments,

which range between 5-20 (mean~11) [31]. During VF there are thin, moving, sheet-like volumes of tissue that have recovered excitability, and are ahead of and about to be invaded by the propagating wave-front surfaces. Parts of this spatio-temporal excitable gap that are close to the active electrodes may be excited by the pacing stimuli, either sub-threshold, or initiating action potentials that propagate and capture a surrounding volume. A changed distribution of excitability in the excitable gap and/or partial capture would account for the modulation of phase probability density and increase in DF shown in [Figure 3-4].

The high frequency pacing burst did not terminate the VF in any of the subjects, but phase entrainment of the cardiac electrograms was produced. The phase entrainment reflects a decrease in the complexity, or increase in the orderliness of the VF, simplifying VF to a process closer to a high frequency VT. The ability of high frequency periodic stimuli to modify the spatio-temporal patterns of the electrical activity that produces VF raises the possibility of modifying VF to a VT that can then be terminated by an appropriately timed, repetitive sequences of pulses.

Study Limitations

The number of leads for pacing and sensing, and their positioning, is determined by the implanted device, and is not designed to be optimal for capturing myocardium. Multiple or long line elctrodes that provide wide area, surface stimulation of the ventricule would be more effective [32]. In order to minimise the duration of VF, and therefore risk to the patient, stimulation was not prolonged beyond five seconds, and there was only one test per patient, to allow the defibrillation shock to be applied within 10 seconds. The effects of repeated and prolonged stimulation could be investigated in animal or in vitro experiments.

The principal limitation of this proof of concept study is the small number of participants, hence the paucity of statistical analysis. Defibrillation testing is now no longer routinely undertaken, and therefore it would be difficult to increase patient numbers.

Disclosure of Financial upport and Conflicts of Interest

MHT has received research grants from Medtronic, Abbott, Biosense Webster and Boehringer Ingelheim. GAB received research fellowship funding from St. Jude Medical (now Abbott). BS is a Senior Research Scientist at Medtronic Bakken Research Centre. AVH, KB declare no competing interests.

Conclusion

In this first in human study, we have demonstrated that a high frequency (5/s) high pacing intervention can modify VF, presumably by exciting or possibly by capturing parts of the myocardium in the excitable gap of VF. Harnessing this has potentially useful implications in extending the delivery of painless pacing from slow and fast VT to VF. Such development could be approached by incorporating data acquired during invasive clinical ventricular electrophysiological investigation and mapping (illustrative examples) with computational simulations (repeated experiments within the same ventricular geometry, or over populations of geometries) [33].

Supplementary Materials

Table 1:	Duration of VF pre-pacing, during pacing and after pacing before automatic defibrillation					
patient	50/s pacing	pre-test control	test 5/s pacing	post-test control	total VF duration before defibrillation shock	comments
3	4.238	4.054	5.45	6.62	20.362	
4	2.742	3.588	3.646	8.872	18.848	
5	N/A	6.804	4.722	7.346	18.872	Shock on T
6	3.132	3.274	4.642	5.152	16.2	
8	2.652	3.778	4.432	2.48	13.342	
9	3.352	3.288	6.434	5.06	18.134	First 2 VF inductions self-terminated
10	N/A	8.196	5.238	6.674	20.108	Shock on T
12	3.216	1.916	4.44	8.826	18.398	

Patients 5 and 10 : two episodes of 50/s stimulation failed to induce VF, and the data is from the shock on T initiation that precedes the defibrillation. For patient 10, the 8.2 s of VF preceding the test 5/s pacing includes a short period of pacing.
The data sets, from the last cycles of normal sinus rhythm, through VF induction and pacing, to the defibrillation shock, are illustrated in the following figures. A,B,C and D are the channels of a,b,c and d of Figure 1.
These data are attached in a .csv file as Holdenetal Supplementary Data.csv in the format:
Link for Patient_ID.csv File:
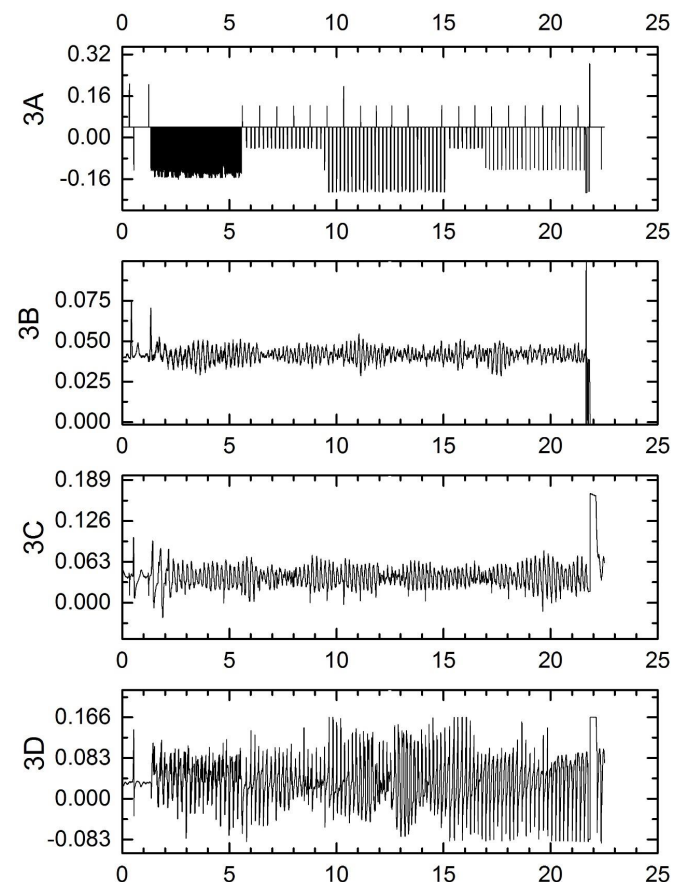http://jafib.com/PMC/XML/Inprogress/2217/Patient_ID.csv
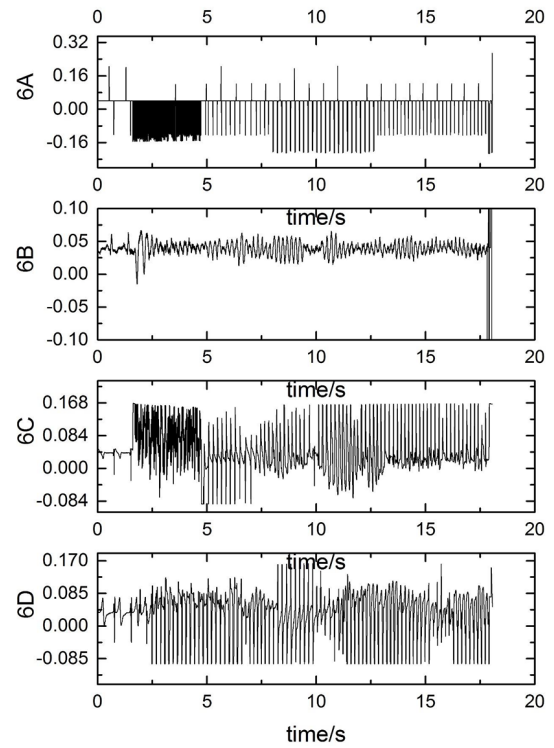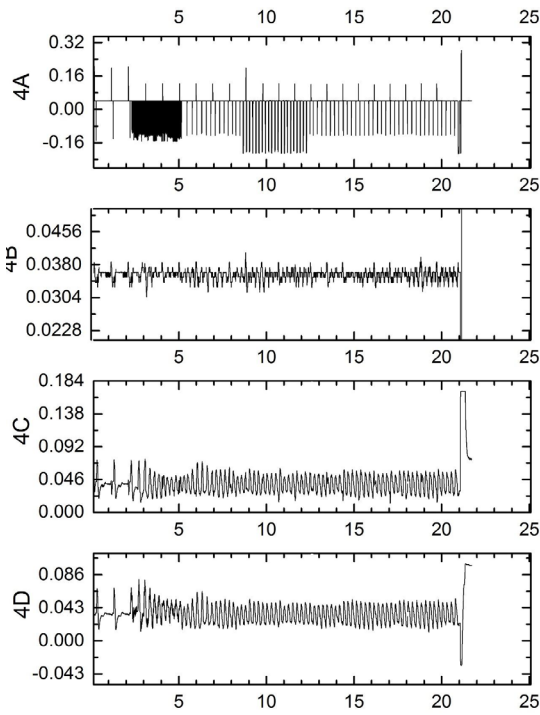

Figure S1:   **Supplementary Figure 1**

Figure S2:   Supplementary Figure 2

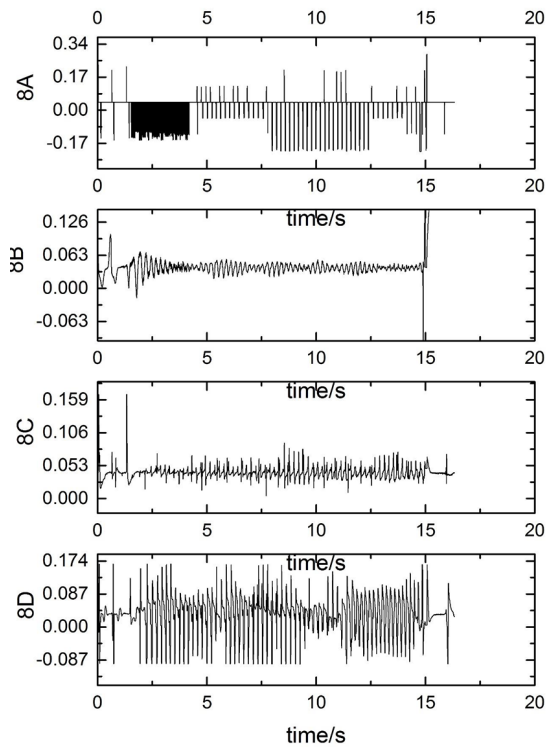**Figure S4:**   Supplementary Figure 4
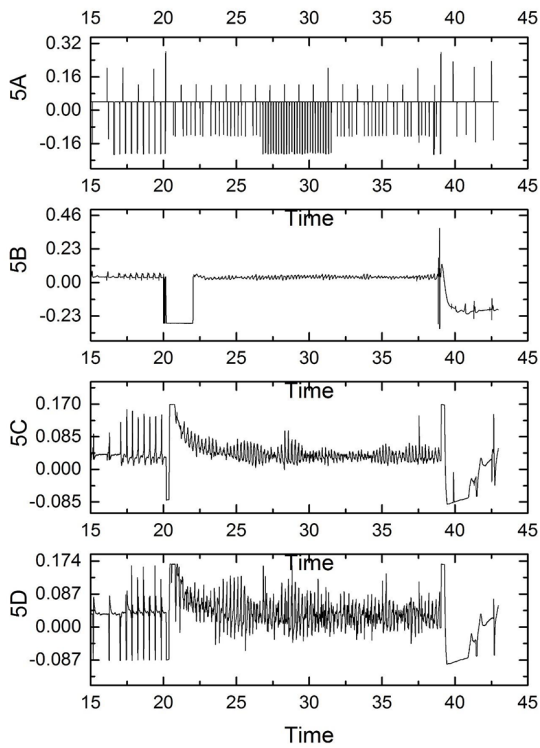

Figure S3:   Supplementary Figure 3

Figure S5:   Supplementary Figure 5
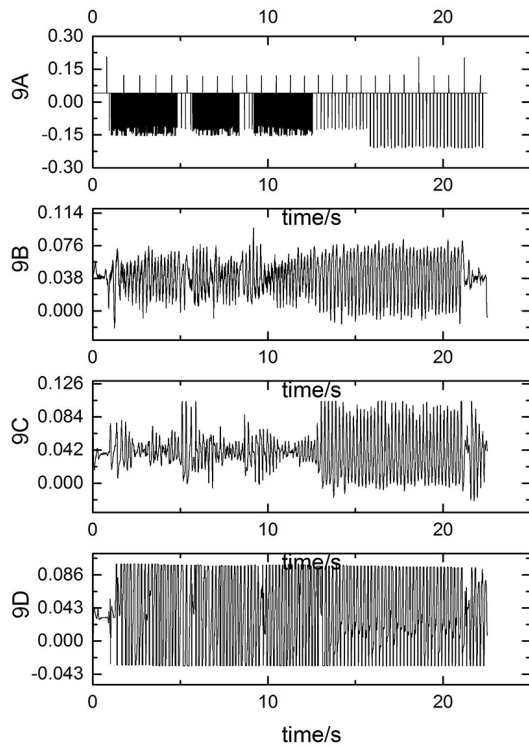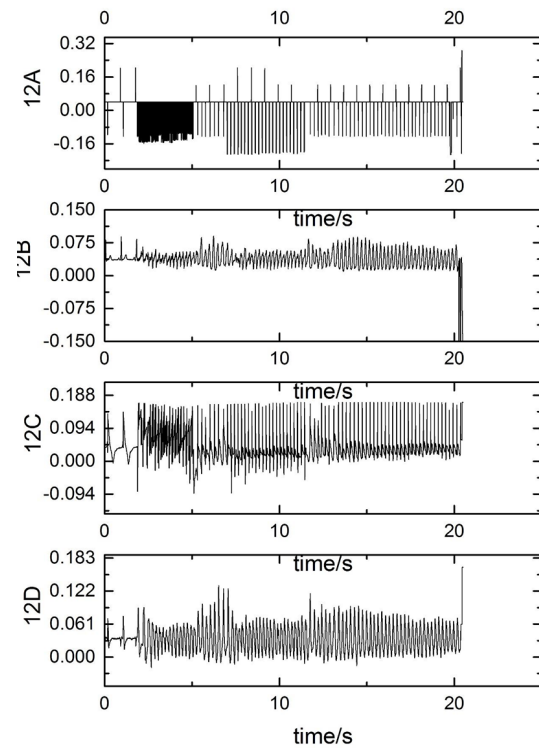
Figure S6: Supplementary Figure 6

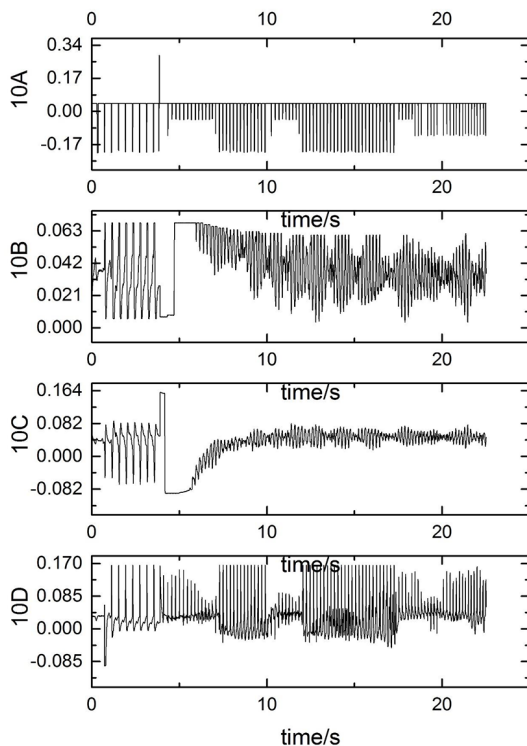**Figure S8:** Supplementary Figure 8

Figure S7: Supplementary Figure 7

References

1. Krummen DE, Hayase J, Morris DJ, Ho J, Smetak MR, Clopton P, Rappel WJ, Narayan SM. Rotor stability separates sustained ventricular fibrillation from self-terminating episodes in humans. JACC 104; 24: 2712-21.

2. Jin Q, Zhou J, Zhang N, Lin C, Pang Y, Xin Y, Pan J, Shen W, Wu L. Defibrillation threshold varies during different stages of ventricular fibrillation in canine hearts Heart Lung Circ 2013; 22:133-40.

3. Winkle RA. Effect of duration of ventricular fibrillation on defibrillation efficacy in humans Circulation 1990; 81: 1477-81.

4. Wang YT, Efimov IR, Cheng Y. Electroporation induced by internal defibrillation shock with and without recovery in intact rabbit hearts. Am J Physiol Heart Circ Physiol 2012; 303: H439-49.

5. Walcott GP, Killingsworth CR, Ideker RE. Do clinically relevant transthoracic defibrillation energies cause myocardial damage and dysfunction? Resuscitation 2001;59:59-70.

6. Dresen WF, Ferguson JD. Ventricular Arrhythmias Cardiol Clin 2018 36 129-139.

7. Fenton FH, Luther S, Cherry EM, Otani NF, Krinsky V, Pumir A, Bodenschatz E, Gilmour RF Jr. Termination of atrial fibrillation using pulsed low-energy far-field stimulation. Circulation. 2009;120:467–476.

8. Luther S, Fenton FH, Kornreich BG, Squires A, Bittihn P, Hornung D, Zabel M, Flanders J, Gladuli A, Campoy L, Cherry EM, Luther G, Hasenfuss G, Krinsky VI, Pumir A, Gilmour RF Jr, Bodenschatz E. Low energy control of electrical turbulence in the heart. Nature. 2011;475:235– 239.

9. Duncker D, Veltmann C. Optimizing Antitachycardia Pacing: Back to the Roots. Circ Arrhythm Electrophysiol. 2017 Sep;10(9).

10. Mitchell AR1, Spurrell PA, Cheatle L, Sulke N. Effect of atrial antitachycardia

pacing treatments in patients with an atrial defibrillator: randomised study comparing subthreshold and nominal pacing outputs. Heart. 2002 May;87(5):433-7.

11. Peters, R. W., Shorofsky, S. R., Pelini, M., Olsovsky, M. & Gold, M. R. Overdrive atrial pacing for reversion of atrial flutter: comparison of postoperative with nonpostoperative patients. Am. Heart J. 137, 100–103 (1999).

12. Boriani G, Tukkie R, Manolis AS, et al. Atrial antitachycardia pacing and managed ventricular pacing in bradycardia patients with paroxysmal or persistent atrial tachyarrhythmias: The MINERVA randomized multicentre international trial. Eur Heart J. 2014;35:2352-236

13. Crossley GH, Padeletti L, Zweibel S, Hudnall JH, Zhang Y, Boriani G. Reactive atrial-based antitachycardia pacing therapy reduces atrial tachyarrhythmias. Pacing Clin Electrophysiol. 2019 Jul;42(7):970-979. doi: 10.1111/pace.13696. Epub 2019 Apr 29.

14. Wathen MS, DeGroot PJ, Sweeney MO, Stark AJ, Otterness MF, Adkisson WO, Canby RC, Khalight K, Machado C, Tubenstein DS, Volosin KJ, PainFREE Rx II Investigators. Prospective randomized multicenter trial of empirical antitachycardia pacing versus shocks for spontaneous rapid ventricular tachycardia in patients with implantable cardioverter-defibrillators: Pacing Fast Ventricular Tachycardia Reduces Shock Therapies (PainFREE Rx II) trial results Circulation 2004; 110: 2591-2596.

15. Panfilov, I, Lever, NA, Smaill, BH, Larsen, PD. Ventricular fibrillation frequency from implanted cardioverter defibrillator devices Europace 2009;11: 1052–1056.

16. Rosenblum M, Pikovsky A, Jürgen Kurths J, Schäfer C, Tass PA , Phase synchronization:from theory to data analysis In: Handbook of Biological Physics, Elsevier Science, Series Editor AJ Hoff, Vol 4, Neuro-informatics, Editors: F Moss and S Gielen, 2001 Chapter 9, pp 279-321.

17. Jalife J. ,Dynamics and Molecular Mechanisms of Ventricular Fibrillation in Structurally Normal Hearts. Card Electrophysiol Clin 2016; 8::601-12

18. ten Tusscher KH, Mourad A, Nash MP, Clayton RH, Bradley CP, Paterson DJ, Hren R, Haywood M, Panfilov AC, Taggart P. Organization of ventricular fibrillation in the human heart: experiments and models Exp Physiol 2009; 94: 553-62.

19. Pandit SV, Jalife J. Rotors and the dynamics of cardiac fibrillation Circ Res 2013;112: 849-62.

20. Christoph J, Chebbok M, Richter C, Schröder-Schetelig J, Bittihn P, Stein S, Uzelac I, Fenton FH, Hasenfub G, Gilmour RF Jr, Luther S. Electromechanical vortex filaments during cardiac fibrillation Nature 2018; 555: 667–672.

21. Basser PJ, Roth BJ. New currents in electrical stimulation of excitable tissues Annual Rev Biomed Eng 2000; 2: 377-97.

22. Trayanova NA, Rantner LJ. New insights into defibrillation of the heart from realistic simulation studies Europace 2014; 16: 705-13.

23. Biktashev VN, Holden AV. Design principles of a low voltage cardiac defibrillator based on the effect of feedback resonant drift J Theor Biol 1994; 169: 101-112.

24. Morgan SW, Plank G, Biktasheva IV, Biktashev VN. Low energy defibrillation in human cardiac tissue: a simulation study Biophys J   2009; 96, 1364-1373.

25. Buran P, Bär M, Alonso S, Niedermayer T. Control of electrical turbulence by periodic excitation of cardiac tissue Chaos 2017; 27: 113110.

26. Ji YC, Uzelac I, Otani N, Luther S, Gilmour RF Jr, Cherry EM, Fenton FH Synchronization as a mechanism for low-energy anti-fibrillation pacing Heart Rhythm 2017; 14: 1254-1262.

27. Hornung D Biktashev VN, Otani NF, Shajahan TK, Baig, T, Berg S, HanS, Krinsky VI, Luther S. Mechanisms of vortices termination in the cardiac muscle R Soc Open Sci 2017;4: 170024.

28. Cherry EM, Fenton FH, Gilmour RF Jr. Mechanisms of ventricular arrhythmias: a dynamical systems-based perspective Am J Physiol Heart Circ Physiol 2012; 302: H2451-63.

29. Nanthakumar K, Jalife J, Massé S, Downar E, Pop M,, Asta J, Ross H, Rao V, Mironov S, Sevaptsidis E, Rogers J, Wright G , and Dhopeshwarkar R. Optical mapping of Langendorff-perfused human hearts: establishing a model for the study of ventricular fibrillation in humans. Am J Physiol Heart Circ Physiol 2007; 293: H875-880.

30. Nash MP, Mourad A, Clayton RH, Sutton, PM, Bradley CO, Haywayd M, Paterson DJ, Taggart P. Evidence for multiple mechanisms in human ventricular fibrillation Circulation 2006;114:536-542.

31. Kazbanov IV, Clayton RH, Nash MP, Bradley CP, Paterson DJ, Hayward MP, Taggart P, Panfilov AV. Effect of global cardiac ischemia on human ventricular fibrillation: insights from a multi-scale mechanistic model of the human heart PLoS Comput Biol 2014;10: e1003891.

32. Moreno A, Walton RD1, Constantin M, Bernus O, Vigmond EJ, Bayer JD. Wide-area low-energy surface stimulation of large mammalian ventricular tissue. Sci Rep. 2019 Nov 1;9(1):15863.

33. Niederer DA, Lumens J, Trayanova NA. Computational models in cardiology. Nat Rev Cardiol 2018; 16: 100-111.