Enhanced self-termination of re-entrant arrhythmias as a pharmacological strategy for anti-arrhythmic action.

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ABSTRACT:

Ventricular tachycardia and fibrillation are potentially lethal cardiac arrhythmias generated by high frequency, irregular spatio-temporal electrical activity. Re-entrant propagation has been demonstrated as a mechanism generating these arrhythmias in computational and in vitro animal models of these arrhythmias. Re-entry can be idealised in homogenous isotropic virtual cardiac tissues as spiral and scroll wave solutions of reaction-diffusion equations. A spiral wave in a bounded medium **can** be terminated if its core reaches a boundary. Ventricular tachyarrhythmias in patients are sometimes observed to spontaneously self-terminate. One possible mechanism for self-termination of a spiral wave is meander of its core to an inexcitable boundary. We have previously proposed the hypothesis that the spatial extent of meander of a re-entrant wave in the heart can be directly related to its probability of self-termination, and so inversely related to its lethality. Meander in 2-dimensional virtual ventricular tissues based on the Oxsoft family of cell models, with membrane excitation parameters simulating the inherited long Q-T syndromes has been shown to be consistent with this hypothesis: the largest meander is seen in the syndrome with

the lowest probability of death per arrhythmic episode. Here we extend our previous results to virtual tissues based on the Luo-Rudy family of models. Consistent with our hypothesis, for both families of models, whose different ionic mechanisms produce different patterns of meander, the LQT virtual tissue with the larger meander simulates the syndrome with the lower probability of death per episode. Further, we search the parameter space of the repolarising currents to find their conductance parameter values that give increased meander of spiral waves. These parameters may provide targets for anti-arrhythmic drugs designed to act by increasing the likelihood of self-termination of re-entrant arrhythmias.

Ventricular tachycardias and fibrillation are potentially lethal arrhythmias that can result in sudden cardiac death. However, some episodes of ventricular tachycardia are observed to self-terminate; understanding of the mechanisms that produce self-termination could provide approaches to anti-arrhythmic therapies. Based on the results of computational and *in vitro* tissue and whole heart experiments , tachycardia and fibrillation are believed to be generated and maintained by the re-entrant propagation of self-sustaining waves of excitation that can propagate around a gross heterogeneity such as a scar, or in functional re-entry, be idealised as spiral and scroll waves that can drift, or be pinned to small heterogeneities. These re-entrant waves rotate around a phase singularity, called the core in thin (effectively two-dimensional), or the filament in three-dimensional tissue preparations. Re-entry is no longer sustained if these singularities are eliminated (by a defibrillating shock) or moved out of the medium (by induced drift due to spatially uniform, repetitive perturbations, parametric drift due to spatial inhomogeneities, or intrinsic meander). Increasing the spatial extent of the motion of these phase singularities could produce termination of re-entry, by moving the singularity to an inexcitable border of the heart. The spatial extent of meander of spiral waves in two-dimensional virtual cardiac tissue depends on both the kinetics and magnitudes of specific ionic conductances that differ in congenital syndromes associated with mutations in genes that are expressed as cardiac ionic channels. Larger meander is found in models of syndromes with the higher likelihood of self-termination, i.e., the lower lethality of arrhythmic episodes. The dependence of the spiral wave meander on the membrane channel parameters in virtual cardiac tissues can be used to identify membrane targets for drugs designed to increase the likelihood of self-termination of re-entrant arrhythmias.

INTRODUCTION

During ventricular fibrillation the synchronised, mechanical pumping action of the ventricles is lost, and irregular trembling of the ventricular muscle is produced by irregular excitation, which manifest as a high frequency, irregular electrocardiogram. The irregularity is believed to be produced by re-entrant propagation of a number of moving, interacting rotors within the ventricle. Computational models within an

anatomically detailed ventricular geometry [1] allow plausible simulations [2,3,4] of how an intraventricular scroll wave can break down into a fluctuating number of interacting re-entrant waves.

High resolution optical mapping of the electrical activity on the surface of the isolated mammalian heart during fibrillation induced by high frequency stimulation has shown spatio-temporal irregularity, a fluctuating number of transient phase singularities, but rarely shows spiral waves that persist for more than a few rotations [5,6] . Persistent re-entry around an obstacle has been seen in a thin preparation of the ventricular surface [7] .

However, simultaneous recordings from both endo- and epicardial surfaces of an isolated, perfused slab of ventricular wall has shown different, changing activation patterns on the two surfaces *i.e.* the process is intrinsically three-dimensional [8,9] , and produced by intramural, rather than transmural, re-entrant sources. The spatio-temporal irregularity has a strong local periodicity, with dominant frequencies that can be organised into large (about a square cm), persistent domains that have sharp boundaries [10] . The existence of these domains is controversial, but a domain structure can be produced from a single re-entrant source by intermittent conduction block [11] .

Thus experiments on isolated tissue models of ventricular tachycardia and fibrillation show that the arrhythmia is generated by one, or a modest number, of re-entrant wave sources within the ventricular wall. It is likely that at the onset of fibrillation there are a small number of re-entrant sources. The effect of fibrillation is that the ventricles are no longer activated synchronously, and so fail to act as a pulsatile pump maintaining the circulation. Ventricular tachyarrhythmias account for approximately 300,000 deaths per annum in the US, 50% of all adult deaths from cardiovascular diseases, the commonest cause of natural death [12] , and almost always occurs during the process of dying. However, every episode of ventricular tachycardia need not be lethal.

II. SELF-TERMINATING VENTRICULAR TACHYARRHYTHMIAS

Self-terminating ventricular tachyarrhythmias are occasionally observed in clinical practice, and during Holter recording of the electrocardiogram. Recordings of spontaneous ventricular tachyarrhythmias, including fibrillation, are rare even from patients in intensive or Coronary Care Units - for example, recording from 2462 patients showed 57 examples of spontaneous ventricular tachyarrhythmia, of which 12 self-terminated and 45 were terminated by prompt clinical intervention [13,14] . Idiopathic episodes of syncope are a common reason for referral for electrocardiographic investigation, as a possible cause could be a self-terminating arrhythmic episode. Self-terminating episodes of ventricular tachyarrhythmias may not be exceptional: a lethal episode may be considered as an episode that failed to self-terminate in time.

Although they are encountered most commonly during clinical electrophysiology studies, when they have been induced, spontaneously occurring self-terminating tachyarrhythmias have been recorded. Examples of two such events, recorded from

Coronary Care Unit patients, are shown in Figure 1. Until they self-terminate, the electrocardiographic signals are virtually indistinguishable from those of tachyarrhythmias that are terminated by a defibrillating shock, or are lethal. Understanding the mechanisms that terminate these episodes is important since a pharmaceutical agent capable of encouraging self-termination would be of enormous clinical value.

Although these episodes could be sustained by repetitive discharge of an ectopic focus, the rapid frequency of between 4 and 8 Hz suggests a re-entrant mechanism. Re-entry can terminate by different mechanisms. One is if the region of unidirectional conduction block at the center of the re-entrant circuit is enlarged. Oscillations of the period of re-entry in both 1-dimensional computational domains [15] and patients [16,17] have been observed, and this is a potential mechanism to explain self-termination. Another mechanism, derived from the point of view of nonlinear wave propagation in excitable media, corresponds to either movement of the re-entrant core to an inexcitable boundary or movement of the cores of a pair of re-entrant waves so that they annihilate each other. This paper explores the motion of the core of spiral waves in homogeneous virtual cardiac tissues as a route to self-termination of re-entry.

Figure 1 near here

III. RE-ENTRY, SPIRAL WAVES AND MEANDER

The electrical activity of cardiac cells is determined by nonlinear properties of the cell membrane, produced by the kinetics of ion channels, pumps and exchangers. Normal ventricular tissue is excitable; it has a stable resting state, and its response to a small localised stimulation is of small amplitude, localised and decremental. If the local stimulation is sufficiently large and long lasting (over a threshold), the response is a large amplitude action potential that propagates away from the initiation site. Following initiation of an action potential the tissue is refractory, and then slowly recovers its excitability. These are the characteristics of a spatially extended excitable system.

Originally, the mathematical models of excitation propagation in cardiac cells were cellular automata [19] where time, space and cell state were all considered discrete. All possible variants of discrete and continuous description of these three components have been considered, e.g. 'axiomatic' models (continuous time and space but discrete cell state) [20,21] , coupled map lattices, with discrete time and space [22] and coupled ordinary differential equation lattices, where only space is discrete and time and cell state are continuous [22] and partial differential equations where time, space and state are all continuous variables. The dynamics of spiral waves in one kind of models can be phenomenologically reproduced in another kind of models [23] All these different sorts of models have been considered within the single theoretical framework of synchronous concurrent algorithms, which also provides formal tools for transfer from one type of model to another and combining them in a single hierarchical structure [24] .

Cardiac cells are electrically connected by low resistance pathways, and form a complicated network, or a syncytium. The discrete structure of cardiac muscle may play an important role in pathological conditions [25] . However, due to the low intercellular resistance, current spreads through normal cardiac tissue as if it were a continuum, an excitable medium, rather than a system of connected cells.

A two dimensional, isotropic excitable medium may be modelled by a reaction-diffusion system:

$$\partial_t \mathbf{u} = \mathbf{f}(\mathbf{u}) + \mathbf{D}\,\nabla^2 \mathbf{u} \qquad (1)$$

where $\mathbf{u}(r) \in R^l$ is a column vector of membrane potential, gating variables and ionic concentrations; $r \in R^2$; $\mathbf{f} \in R^l$ is a column vector of reaction rates; $\mathbf{D} \in R^{l \times l}$ is the positively semi-definite matrix of diffusion coefficients in two dimensional media. The simplest re-entrant behaviour in such an excitable medium is a spiral wave.

A spiral wave solution of (1) appears as a circulation of excitation, in the form of an Archimedean spiral, around the core, which act as an organising centre that imposes its rhythm on the rest of the tissue by emitting propagating waves. Spiral waves have been observed experimentally in a variety of chemical, biological and physical systems that may be represented as excitable media, and as solutions of simple caricature (FitzHugh-Nagumo -like) [26,27,28], and high order biophysically detailed models of cardiac tissue [29,30,31,32,33]. In both experimental observations and in numerical investigations with homogeneous, isotropic media spiral waves need not rotate rigidly, around a circular core, but meander. In meander the tip of the spiral wave (defined in experiments by a phase singularity, or the point on a voltage isoline where the wavefront meets the waveback, and in numerical solutions by intersection of isolines of two state variables, say voltage and and a gating variable) follows a complicated trajectory. This complicated motion can be classified as biperiodic meander [26,27,28,32,34,35,36,37,38,39] n+1-periodic hypermeander [28] or deterministic Brownian hypermeander [38,40]. In this paper we use meander to describe the motion of the tip trajectory for the particular excitable medium, including both rigid rotation and biperiodic motion.

The transition from rigid rotation to biperiodic meander is by a supercritical Hopf bifurcation [26,27] with some specific features due to the symmetry of (1) with respect to Euclidean motions of the plane [35]. A method for studying meander patterns reduces (1) by the Euclidean group SE(2) to a generic (without the symmetries of (1)) ODE for tip motion, by moving over to a frame of reference attached to the tip of the spiral [34,36,37]. An equilibrium solution of the ODE generates rigid periodic rotation; transition from the equilibrium to a limit cycle *via* a Hopf bifurcation generates the transition from rigid rotation to biperiodic motion; in the biperiodic regime there are isolated codimension 1 resonant parameter sets, with unbounded linear drift of spirals. An invariant *n*-torus and a chaotic attractor for the ODE generate bounded *n+1* periodic and unbounded deterministic Brownian hypermeander.

This qualitative theory can be extended to consider motion of spiral waves produced by symmetry-breaking perturbations, such as spatial gradients in parameters corresponding to spatial tissue gradients in the expression of membrane channel proteins. For example, if there is a gradient in the parameters , the spiral wave will drift and the drift velocity in the first approximation is proportional to the gradient of parameter. The component of the drift orthogonal to the gradient depends on the chirality (direction of rotation) of the spiral whereas the component along the gradient does not. The theoretical explanation of that is based on the observation that the homogeneous and isotropic reaction-diffusion system is equivariant with respect to the group of Euclidean motions of the physical space. Since the isotropy subgroup of a rigidly rotating spiral wave is trivial, its orbit by the Euclidean group is a three-dimensional manifold of spiral waves with different rotation centres and phases. A small symmetry-breaking perturbation, such as a smooth spatial gradient of properties, then leads to a drift along this manifold with the period-averaged position and phase described by response functions that are localised around the core of the spiral[41,42,43,44].

Thus there is the outline of a theory for understanding the meander and drift of spiral wave solutions in homogenous and inhomogeneous media, that depends only on the symmetries of (1). Although mathematical analysis can account for the occurrence of meander and drift, to obtain quantitative information about its spatial extent and speed we require numerical solutions of specific models.

Figure 2 near here

Figure 2 presents illustrative spatial distributions of voltage and the tip trajectories simulated with the Luo-Rudy[45] models or normal and ischaemic[46] ventricular tissues. The latter models a consequence of ventricular tachycardia, when the cardiac muscle is inadequately perfused and becomes progressively ischaemic. The spiral waves in both tissues were initiated by the phase distribution method, in which the dynamical variables for a one-dimensional periodic wave train of high frequency are expressed as functions of phase, and are then mapped onto an Archimedean spiral with appropriate wavelength [31]. The solutions have a similar period of 90 ms, but different wavelengths, due to the shorter action potential duration for the ischaemic model. Besides, the tip trajectory is almost circular for the normal tissue, but more complex - presumably biperiodic - for the ischaemic virtual tissue.

Spiral wave solutions for virtual tissue based on the Oxsoft guinea-pig ventricular excitation models [30] , the Beeler-Reuter model [50], and the Luo-Rudy phase 1 model with faster Ca^{++} kinetics or with increased G_{si} [33] can demonstrate another kind of biperiodic meander. In these models the tip trajectory is composed of almost linear segments and sharp turns, and the local wavefront velocity close to the tip of the spiral changes, with slower velocities as the trajectory curves around in sharp turns. This slowing down, with bunching of isochronal lines, appears as a functional partial conduction block produced by accumulated Na^{+} inactivation, leaving Ca^{++} current to sustain propagation [31]. Thus the pattern of meander can be understood in terms of the balance between the kinetics of the two depolarising currents.

The excitation wavefront propagates as fast as, and wherever, it can: in re-entry this is determined not only by the spread of excitation (the depolarising currents and the effective diffusion coefficient), but also the degree of recovery in tissue ahead of the wavefront, i.e., the repolarising K^+ currents. The kinetics and magnitudes of the ionic currents underlying these excitatory and recovery processes differ in congenital syndromes that are characterised by abnormal ventricular action potentials, in different parts of the ventricle, in different species, and in different models of ventricular electrophysiology. The pattern of meander computed for these different virtual tissues can provide insight into the role of individual ionic conductances in meander, allowing the possibility of targeting conductances to change the pattern and extent of meander .

IV. THE LQT SYNDROMES

The congenital long QT (LQT) syndromes are characterised by lengthening of the ventricular action potential, resulting in a prolonged QT interval in the electrocardiogram, and are associated with an increased risk of ventricular tachyarrhythmias, and of early, sudden death. They are rare but intensively studied syndromes, and mutations at loci that give rise to the syndrome have been identified. LQT1 results from mutations in the KVLQT1 gene encoding a subunit of the I_{Ks} potassium channel; LQT2 from a mutations in the HERG gene encoding a subunit of the I_{Kr} potassium channel; and LQT3 from mutations in the SCN5A gene encoding the sodium channel [51]. Although different mutations have different effects on kinetics, the LQT1 and LQT2 mutations result in a loss of K^+ channel function and a reduction in the total maximal K^+ conductance, while LQT3 mutations result in failure to deactivate in a small fraction of Na^+ channels, giving a persistent Na^+ current.These mutations all produce similar increases in the action potential duration, but can have radically different outcomes: although the death rates for the syndromes are similar, an arrhythmic event of LQT3 is five times more likely to be lethal than an episode of LQT1 [52] . This implies that LQT1 episodes are five times more likely to self-terminate.

A possible mechanism for this difference in the probability of self-termination of arrhythmic episodes in the LQT syndromes has been proposed, based on the behaviour of deterministic cardiac virtual tissues [53] . The spatial extent of meander of stable spiral wave solutions of two-dimensional virtual cardiac tissues simulating the LQT syndromes was quantified. In a thin slab of real tissue, the minimum distance between the initiation site of a re-entrant wave and the inexcitable boundaries enclosing it has effectively a random value, and the wave moves in effectively random direction. The larger the extent of meander, the more likely it is that the core will reach a boundary within a given time, in whatever direction it is, and extinguish the re-entrant wave.

Thus, the spatial extent of meander (quantified by the radius of the smallest circle completely enclosing the tip trajectory during one second of rotation) provides a

measure of the likelihood of the spiral wave being extinguished by reaching an inexcitable boundary within some given time. For a tissue model based the Oxsoft equations for guinea-pig ventricular cells described in[54], modifications for LQT1, LQT2, and LQT3 showed that although the vulnerable window of homogeneous, isotropic, LQT virtual tissues were not greater than that of the normal tissues, the spatial extent of meander in LQT1 virtual tissue was 2-5 times greater than the spatial extent of meander in LQT2 and LQT3 [53]. In LQT1 tissue the spatial extent of meander continued to increase with time. A possible explanation for the relative non-lethality (or increased likelihood of self-termination) of LQT1 episodes is that meander of re-entry in LQT1 tissue is greater, and so more likely to reach an inexcitable boundary of the ventricular muscle. Spatial inhomogeneities also produce drift of the spiral - depending on its direction this drift could facilitate, or retard, motion towards a boundary.

However, models for ventricular cells are continuously developing [54], and phenomena that are common to all current models have firmer support than phenomena seen in only one specific model. We have therefore repeated the computations of [53] for Luo-Rudy family models for LQT1, 2 and 3. The Luo-Rudy phase 2 model [46] has been extended to a family of models that include endocardial and epicardial differences; Markovian, rather than simple gated, models for single channels; and the LQT syndromes [48,49].

The Luo-Rudy family cell models for LQT1, 2 and 3 all show the action potential prolongation characteristic of the LQT syndromes, and can show early after-depolarisations in M cells that are believed to be important in arrhythmogenesis. Figure 3 shows action potential prolongation in LQT epicardial cell models. LQT1 is modelled by a reduced magnitude of G_{Ks} , LQT2 by a reduced magnitude of G_{Ks} , in the standard Luo-Rudy epicardial model [47] and LQT3 by an increased late Na+ current described by the Markovian model of the Na+ -channel [49] .

Figure 3 near here

The tip trajectories, computed as in Figure 2, for the standard epicardial , LQT1, LQT2 and LQT3 Luo-Rudy tissue models are shown in Figure 4. The LQT3 meander in Figure 4 corresponds to the maximum prolongation of the cell solitary action potential duration, longer than APD in the normal tissue and both LQT1 and LQT2 tissues. In simple terms, one would expect the long action potential duration of the LQT3 tissue to be associated with a large extent of meander. However, as for the Oxsoft model [53] , for the Luo-Rudy models, the spatial extent of meander is greatest in LQT1 and least in LQT3. The repolarising K^+ currents in the Oxsoft and Luo-Rudy family of models for ventricular excitation have different magnitudes; in the standard Luo-Rudy model $G_{Ks} > G_{Kr}$, and so reduction of G_{Ks} has the larger effect on action potential duration. In the Oxsoft model [54] $G_{Ks} < G_{Kr}$, and so reduction of G_{Kr} has the larger effect on action potential duration. In spite of the opposite effect on action potential duration in the Oxsoft and Luo-Rudy models, changes in G_{Ks} in LQT1 always produce the largest extent of meander. The spatial extent of meander does not simply reflect the action potential duration, but depends on the detailed kinetics of the

repolarising currents. This suggests G_{Ks} as a target for producing changes in the extent of meander.

Figure 4 near here

V. TARGETTING K+ -SELECTIVE CONDUCTANCES

In principle, it would be possible to selectively and differentially block both G_{Ks} and G_{Kr} , for example, the K+ channel -blocker Chlofilium is a proarrhythmic agent that is used to produce induced LQT syndrome and torsade de pointes in an in vivo rabbit model [55] . Figure 5 presents the meander during 0-1 s after initiation by the phase distribution method in an 8 cm square, two-dimensional virtual tissue obtained with separate and combined blocks of these two separate K+ conductance systems. The largest increase in meander shown here is with 70% block of model G_{Ks} . For panels where no meander is displayed, it was not possible to initiate a sustained spiral wave in the 8 cm square medium. The spatial extent of the meander can be measured by the minimum radius of the circle that completely encloses the meander pattern: Figure 6 plots this measure for LQT1 and LQT2 Luo-Rudy virtual tissues, with different degrees of block of G_{Ks} and G_{Kr} : as in virtual tissues based on the Oxsoft model, the largest meander is produced by maximal block of G_{Ks} .

Figures 5, 6 near here

VI.LIMITATIONS

Biophysical models of cardiac cell excitation have been constructed , based on experimental data, and allow reconstruction of the electrochemical behaviour - membrane potentials, currents, and ion concentrations - of the cell. However, they are constructed from data from different experiments, using differing techniques, and perhaps even a range of animal species. They are based on data from patch, cell and tissue electrophysiological experiments that typically last from ten to several hundred ms: their incorporation into virtual tissues used to simulate re-entrant propagation over a time scale of seconds is stretching the range of their applicability, by applying them to time scales for which slow processes (concentration and biochemical changes) have not been incorporated into the model. Even if the cell excitation model is electrically neutral (all depolarising currents are exactly balanced by repolarising currents) it is generally not chemically neutral, and so repetitive activity (as in a spiral wave solution) can build up inappropriate changes in intra- and extracellular ion concentration variables. These appear as "ageing" of the meander pattern, and is seen in atrial and ventricular virtual tissues [29,31]. The slow changes in period during re-entry seen in virtual tissues do not necessarily accurately reproduce slow changes seen in real cardiac tissue; real experiments do not map the motion of the filament. Although experimental validation of cell models is well established, experimental validation of virtual tissue behaviours is not.

Spiral waves in two dimensional media need not be stable - the behaviour may be dominated by breakdown, rather than drift and meander. Numerical experiments with the Luo-Rudy phase 1 model [33] have shown that the steepness of the action potential duration and conduction velocity restitution curve is an important factor in determining the break-up of scroll waves, and agents that flatten the restitution curve can prevent ventricular fibrillation in both computational and experimental tissue models [56].

Cardiac tissue is three dimensional rather than two-dimensional, and in three-dimensional media re-entrant waves rotate around a thin, rod-like filaments. The motion of filaments even in isotropic and homogenous three dimensional media is more complex than the motion of cores in two-dimensional media. Since biophysically detailed models in three dimensions are computationally very demanding, the behaviours that occur in three dimensions have been explored using simpler, caricature models. Filament twist and local curvature influence filament motion, and closed filament rings are generally unstable, contracting or expanding [57]. In a homogeneous, isotropic simple medium it is possible for a simple untwisted scroll wave to be unstable, even though the two-dimensional spiral wave with the same medium parameters is stable [58].

Transmural rotational anisotropy can induce filament motion and breakdown. Filaments in media that has a positive "filament tension"[58] tend to shorten, and also tend to align along the fibre orientation [59]; in the ventricular wall this would tend to keep intramural filaments aligned along the muscle fibres, and so oppose meander that could take a transmural filament towards the epi- or- endocardial surface. Fenton and Karma have shown how transmural rotational anisotropy can lead to the break up of a transmural scroll wave that would be stable in a rotationally isotropic medium[59].

In media with a smooth gradient in parameters, not only is there an induced drift along the gradient, but the gradient can destabilise scroll waves. Drift and rotation of scroll rings in a parameter gradient have been quantified [60], and for parameter gradients that produce only small differences in action potential duration produce breakdown of transmural scroll waves [61]

Although these factors all lead to break-up of scroll waves, re-entrant tachyarrhythmias usually start with a single source, and so meander of filaments to an inexcitable boundary might still provide a mechanism for early self-termination of re-entry.

For this to be effective, movement of all the filaments to boundaries must occur rapidly, before the re-entry breaks down into multiple re-entrant sources [62,63,64] . The self-terminating arrhythmias observed clinically had durations of 5-50 s [13] , equivalent to up to about 500 rotations of a ventricular scroll wave. The pharmacologically induced *torsade de pointes* episodes in the rabbit heart [55] lasted less than 5 s, or less than 50 rotations. The numerical computations for the guinea-pig cardiac tissue of figures 4-6 give spatial meanders of a few mm during the first s of re-entrant propagation; this is of the right order of magnitude to account for the times to self-terminate. In the Oxsoft LQT1 virtual tissue [53], and the Luo-Rudy epicardial cell

model with 70% block of G_{Ks} (Figure 4) the extent of meander for LQT1 continued to increase with time. Increasing the spatial extent of meander should increase the probability of reaching an inexcitable boundary.

VII CONCLUSIONS

The meander of re-entrant waves provides one possible mechanism for the self-termination of tachyarrhythmias. Although the dynamics of meander are beginning to be understood in terms of the symmetries of reaction-diffusion models for excitable media representations of cardiac tissue, the nature and extent of meander is highly model dependent, and strongly influenced by model parameters. Computations of meander pattern are only as good as the models of excitation on which they are based, and all current models of mammalian ventricular excitation need improvement in terms of the kinetics of slower processes and intracellular and extracellular ion concentration dynamics [65].

However, the Luo-Rudy, as well the Oxsoft ventricular tissue models show an increase in the spatial extent of meander when G_{Ks} is reduced, as in simple models for LQT1. This increased meander could provide a partial explanation for the relative non-lethality of individual arrhythmic LQT1 episodes. The spatial extent of meander does not simply depend on the action potential duration, but on which conductances are altered to produce the prolongation of action potential duration. This raises the possibility of selectively targeting the spatial extent of meander as a means of increasing the likelihood of self-termination of a simple re-entrant source. This could be combined with the strategy suggested by Garfinkel *et al.* [43], which aims to prevent the breakdown of re-entry into fibrillation. In both these cases, the target is a tissue dynamical process, rather than a specific membrane protein.

Increased drift of spiral waves, due to resonant drift of rigidly rotating spirals produced by period or repetitive, feedback controlled, perturbations has been proposed as a means of defibrillation by low amplitude voltage shocks [29,30,66] . The aim is to move the spiral core to the medium boundaries. Pharmacologically increasing the meander of the re-entrant wave source could also lead to extinguishing the re-entry by moving its core to a boundary. This could be achieved by agents that altering the magnitudes, or kinetics, of one or more membrane conductances. Here we have used G_{Ks} and showed that a selective decrease of G_{Ks} in the Luo-Rudy family of ventricular tissue models - as well as in the Oxsoft models - produces an increases the spatial extent of meander. However, the LQT1 syndrome , where G_{Ks} is reduced, is an arrhythmogenic syndrome. G_{Ks} is not an ideal target for anti-arrhythmic interventions; it is an illustrative target that shows it is possible to target the spatial extent of meander by targeted molecular interventions.

ACKNOWLEDGMENTS

This work was supported in part by grants from the British Heart Foundation and Medical Research Council (UK) .

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FIGURE LEGENDS

Figure 1. Electrocardiograms of two episodes of self-terminating tachyarrhythmias recorded from Coronary Care Unit patients [18] using an automatic detection and acquisition system.

Figure 2. Re-entrant spiral waves in 8 cm square isotropic homogeneous virtual ventricular tissue (top), and their tip trajectories for central 4 mm square region (bottom), for standard epicardial tissue (left) and acute ischaemic tissue (right). Equations describing the virtual tissues are based on the Luo-Rudy ventricular cell model [46] as downloaded from the web-site http://www.cwru.edu/med/CBRTC/LRdOnline, with excitation parameter values adopted for the epicardial [47] and ischaemic [45] tissues. The cell model kinetics were incorporated as reaction terms into reaction-diffusion equations describing the respective tissues, the diffusion term presented by a standard Laplacian operator with the diffusion coefficien D = 0.06 mm^2/ms that corresponds to a solitary plane wave propagation velocity of 0.45 m/s. Spiral waves were initiated by phase distribution method [30], and simulated for 2 s using standard explicit methods with time step Δt = 0.1 ms and space step Δx = 0.2 mm.

Figure 3. Characteristics of the Luo-Rudy single epicardial cell [47] kinetics during LQT syndromes: simulated action potentials (top) and the membrane currents responsible for their prolongation (bottom). **A** and **B**: I_{Ks} and I_{Kr} currents are decreased from 100% to 75, 50 and 30% to simulate LQT1 and LQT2 syndrome, respectively [48] **C**: Markovian I_{Na} current [49] is introduced, with the percentage of mutant sodium channels increased from 0% to 40, 70 and 100% to simulate LQT3 syndrome.

Figure 4. Tip trajectories of spiral waves in (**A**) standard epicardial virtual tissue and (**B**) LQT1, (**C**) LQT2 and (**D**) LQT3 tissues. The tip trajectory of a spiral wave initiated by the phase distribution method in the 8 cm square isotropic medium is followed over 2 s in 2 mm square region of the respective virtual tissue. To simulate LQT1 and LQT2 tissues I_{Ks} and I_{Kr} currents are decreased to 75 and 30%, respectively, which provides similar action potential duration in both tissues. LQT3 tissue corresponds to 100% of mutant channels in all cells [49].

Figure 5. Tip trajectories of spiral waves in LQT1 and LQT2 tissues in parameter space of the conductances G_{ks} and G_{Kr}. Established rotation of a spiral wave initiated with the phase distribution method is followed over 1 s in 3 mm square region of the respective virtual tissue. Numbers at the axes indicate the percentage of the respective conductances for each row and column of the trajectories.

Figure 6. Spatial extent of the tip meander for LQT1 (filled circles) and LQT2 (open squares) virtual tissues plotted versus the percentage of block of the respective currents (I_{Ks} and I_{Kr}).