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When the clock strikes: Modeling the relation between circadian rhythms and cardiac arrhythmias

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Abstract. It has recently been observed that the occurrence of sudden cardiac death has a close statistical relationship with the time of day, viz., ventricular fibrillation is most likely to occur between 12am−6am, with 6pm−12am being the next most likely period. Consequently there has been significant interest in understanding how cardiac activity is influenced by the circadian clock, i.e., temporal oscillations in physiological activity with a period close to 24 hours and synchronized with the day-night cycle. Although studies have identified the genetic basis of circadian rhythm at the intracellular level, the mechanisms by which they influence cardiac pathologies are not yet fully understood. Evidence has suggested that diurnal variations in the conductance properties of ion channel proteins that govern the excitation dynamics of cardiac cells may provide the crucial link. In this paper, we investigate the relationship between the circadian rhythm as manifested in modulations of ion channel properties and the susceptibility to cardiac arrhythmias by using a mathematical model that describes the electrical activity in ventricular tissue. We show that changes in the channel conductance that lead to extreme values for the duration of action potentials in cardiac cells can result either in abnormally high-frequency reentrant activity or spontaneous conduction block of excitation waves. Both phenomena increase the likelihood of wavebreaks that are known to initiate potentially life-threatening arrhythmias. Thus, disruptive cardiac excitation dynamics are most likely to occur in time-intervals of the day-night cycle during which the channel properties are closest to these extreme values, providing an intriguing relation between circadian rhythms and cardiac pathologies.

> "And now it is almost midnight, the moment when the page of the night turns over into day. Almost midnight, the hour when the figure of Death strikes the golden bell of the clock. And what will happen when the clock strikes ?"
>
> *When the Clock Strikes* by Tanith Lee (1981)

1. Introduction

Heart disease constitutes a significant public health burden worldwide, being the leading cause of death in most developed countries - for instance, being responsible for about 25% of all deaths in the United States [1, 2]. A large fraction of these can be classified as *sudden cardiac death* occurring as a result of certain types of *cardiac arrhythmia*, i.e., disturbances in the normal

rhythmic activity of the heart that severely impair the normal functioning of the organ. There are many factors that determine the occurrence of cardiac pathologies. While ageing results in a progressive decline in the functioning of cardiovascular systems in general [3], genetics [4] and lifestyle choices [5] can result in a higher predisposition to arrhythmias. Apart from these, the role of circadian rhythms - which refer to temporal variations in physiological processes having a period of approximately 24 hours - in initiating cardiac dysfunction has become the focus of recent clinical interest. Circadian rhythms help in coordinating the behavior of organisms with the terrestrial day-night cycle. Such biological clocks in the body are realized by a set of proteins that enable the generation of rhythmic activation through self-sustained, transcriptional positive and negative feedback loops [6, 7]. Experimentally, it has been observed that the circadian rhythm is not driven by the environment but rather is an intrinsic property of the organism [7]. This is supported by the observation that these rhythms persist even in systems maintained in vitro [8, 9]. It has been postulated that an internal clock mechanism enables the organisms to anticipate temporal changes in their environment, thereby allowing biological processes to occur at a favorable time in the day [10, 11, 12]. Circadian clocks are entrained to the external day-night cycle by environmental factors (*zeitgebers*) that influence the timing of the molecular mechanism [13].

In this paper, we have used computational modeling to investigate the relation between onset of arrhythmias in the heart and the circadian rhythm that have been revealed by recent experimental studies. Over the last few decades, sophisticated models of electrical activity in cardiac cells (that lead to mechanical contraction and hence the pumping action of the heart) have been developed with the aim of reproducing experimentally observed phenomenon. The focus of such modelling efforts has been to capture relevant details from the level of the cell to that of the whole heart. Increased availability of experimental data and vastly improved computational power has enabled the development of these detailed models of cardiac activity in order to study the normal and pathological functioning of the heart. We use such a biologically realistic model to simulate the dynamics of cardiac tissue in order to understand the higher propensity for the onset of arrhythmias at certain times of the day-night cycle. In particular we show that the diurnal variations that cause ion channel conductances to take extreme values can result in significant changes in the repolarization properties of the excitation waves. This can lead to either abnormally rapid high-frequency activity or spontaneous conduction block of propagating excitation - both of which increase the likelihood of wavebreaks that can initiate potentially life-threatening arrhythmia. In the following section we describe the biological phenomena underlying circadian rhythm and its possible relation to onset of arrhythmia. Following this we describe the mathematical model we have used for our computational investigation of excitation dynamics in simulated cardiac tissue. In the subsequent section we describe the results of our investigation linking circadian rhythms and genesis of cardiac arrhythmias. We conclude with a brief summary of our results.

2. Circadian Rhythms

The mammalian circadian clock involves an interaction between three negative loops and one positive loop, executing a series of transcriptional, translational and post-translational events [14]. The *clock* and *bmal1* genes, which form the preliminary units of the clock system, encode the proteins CLOCK and BMAL1. These proteins, on hetero-dimerization, recognize the promoter regions of the genes, *per* and *cry*, and transcribe them in the nucleus [15, 16]. The *per* and *cry* messenger RNAs get translated in the cytosol to form proteins, PER and CRY. These proteins, on hetero-dimerization [17], translocate back into the nucleus and inhibit the activation of CLOCK/BMAL1. This, in turn, inhibits CLOCK/BMAL1-mediated transcription, thereby decreasing the expression of *per* and *cry* genes, ultimately relieving the inhibition on CLOCK/BMAL1 [18, 19, 14]. This mechanism constitutes the dominant negative transcriptional

loop of the mammalian circadian clock at the molecular level. On the other hand, the positive transcriptional loop of the circadian clock results from CLOCK/BMAL1 and/or PER2-mediated induction of *bmal1* expression [20].

Depending on the cell type, mammalian circadian clocks are divided into two major classes: the central clock located within the suprachiasmatic nucleus (SCN) of the brain, and peripheral clocks located in all non-SCN cells of the organism [21, 22]. *Zeitgebers*, the factors that reset or entrain circadian clocks, are different for the two classes of clocks. The SCN is reset by light (through electrical signals transmitted along the retino-hypothalamic tract) from the environment, whereas peripheral clocks are reset by various neuro-humoral factors, specific to it [23, 24]. For example, Norepinephrine [9] and Vasoactive intestinal peptide (VIP) [25] have been identified to be the neuro-humoral factors that entrain the cardiomyocyte peripheral clock to the SCN.

2.1. Sudden cardiac death and the circadian clock

The incidence of sudden cardiac death has been observed to exhibit a diurnal variation with peaks occurring in the early morning and late evening hours [26]. The circadian expression of clock genes and clock-controlled genes (genes that are transcribed by the clock genes) in the heart have been recently studied with the aim of understanding this variation [27, 28]. One such clock controlled gene observed to exhibit endogenous circadian rhythmicity in the heart is *klf15* [27]. KChIP2, the regulatory β subunit for the repolarizing transient outward K^+ current was identified to be the transcriptional target of *klf15*. That is, *klf15* transcribes the gene *kcnip2* that encodes the potassium ion channel protein, KChIP2. Experimentally, it has been observed that myocardial repolarization and the expression of ion channels exhibit endogenous circadian rhythmicity. In *klf15*-null mice, the QTc interval (an index of myocardial repolarization) is prolonged and the I_{to} (outward transient K^+ current density) reduced. In contrast, the QTc interval shortens and I_{to} increases in the case of transgenic mice with overexpressed *klf15*. This implies that *klf15*-dependent transcriptional regulation of rhythmic KChIP2 expression plays a key role in the rhythmic variation of myocardial repolarization. A similar observation has been made with respect to the sodium ion channel proteins [28]. The clock gene *bmal1* has been found to directly regulate the circadian oscillation of *scn5α* gene that encodes Nav1.5, the principal voltage-gated Na^+ ion channel. Ventricular myocytes isolated from *bmal1*-deleted mutants have less Na^+ current compared to the ones isolated from *bmal1*-expressed mice. This suggests that the expression of *scn5α* is a significant factor that influences the susceptibility to cardiac arrhythmias. To summarize, the susceptibility to cardiac arrhythmias is increased when the temporal variation (circadian variation) in myocardial repolarization and ion channel expression is impaired. This is reflected in the observation of lengthened/shortened QT interval downstream of a disruption to the circadian genes.

3. The computational model

Electrical activity in cardiac muscle is typically described mathematically by a generic class of models known as excitable systems. An excitable medium is characterized by a stable resting state, a metastable excited state, and a threshold which needs to be exceeded for the system to be excited. A supra-threshold stimulus gives rise to an excitation which is followed by a period of slow recovery (referred to as the refractory period) during which the system cannot be re-excited. This refractory property results in the annihilation of waves when they collide with each other. This implies that a wavefront, on encountering a region that has not yet completely recovered, develops wave breaks that can give rise to spatial patterns such as spiral waves of excitation [29].

In this paper, we have used a modified version of the Luo-Rudy I (LRI) model describing the electrical activity of cardiac myocytes in the guinea pig ventricle [30]. The model is based

on the Hodgkin-Huxley formalism [31] developed for describing the action potential of a squid giant axon. The generic form of such models are described by a partial differential equation for the transmembrane potential V:

$$\frac{\partial V}{\partial t} + \frac{I_{\rm ion}}{C} = D\,\nabla^2 V,$$

where C is the membrane capacitance, D is the diffusion constant and $I_{\rm ion}$ is the total ionic current density. In the Luo-Rudy I model, the total ionic current density is the sum of six components:

$$I_{\rm ion} = I_{\rm Na} + I_{\rm K} + I_{\rm K1} + I_{\rm Kp} + I_{\rm Ca} + I_{\rm b}\,,$$

where $I_{\rm Na} = G_{\rm Na}\,m^3\,h\,j\,(V - 54.4)$ is the fast inward Na^+ current, $I_{\rm K} = G_{\rm K}\,x\,x1\,(V + 77.62)$, $I_{\rm K1} = G_{\rm K1}\,K1_\infty\,(V + 87.95)$, and $I_{\rm Kp} = 0.0183\,K_{\rm p}\,(V + 87.95)$ are respectively the time-varying, the time-invariant and the plateau K^+ currents $I_{\rm Ca} = G_{\rm Ca}\,d\,f\,(V - E_{\rm Ca})$ is the slow inward Ca^{2+} current where $E_{\rm Ca} = 7.7 - 13.0287\,\ln([Ca^{2+}]_i)$ is the reversal potential, dependent on the intracellular ion concentration $[Ca^{2+}]$, and $I_{\rm b} = 0.03921\,(V + 59.87)$ is the background current (leakage current). The currents are determined by ion channel gating variables m, h, d, f and x, whose time evolution is governed by ordinary differential equations of the form:

$$\frac{\partial \varepsilon}{\partial t} = \frac{\varepsilon_\infty - \varepsilon}{\tau_\varepsilon},$$

where $\varepsilon_\infty = \frac{\alpha\,\varepsilon}{\alpha\,\varepsilon + \beta\,\varepsilon}$ is the steady state of ε, $\tau_\varepsilon = \frac{1}{\alpha\,\varepsilon + \beta\,\varepsilon}$ is the corresponding time constant and $\alpha\,\varepsilon$ and $\beta\,\varepsilon$ are voltage dependent rate constants, all obtained by fitting experimental data. The parameter values used are identical to those in Ref. [30], except $G_{\rm Ca}$ which is chosen to be 0.07 mS cm^{-2} [32].

The model equations are solved using the forward Euler method for time evolution on a one dimensional fiber, discretized over a spatial grid of size L, using a finite difference scheme for the spatial (Laplacian) term. The values of space step Δx and time step Δt used for integrating the equations are 0.0225 cm and 0.01 ms respectively. The diffusion coefficient D is chosen to be 0.01 cm^2/msec.

4. Results

The key experimental results that motivate our modeling study relate to the observation that knocking out *klf15* results in a marked reduction of $I_{\rm to}$ and that an over-expression of *klf15* leads to large increase of $I_{\rm to}$ compared to the normal range of variation seen over the course of a day, both increasing the susceptibility to cardiac arrhythmia. While the former mutation showed a marked increase in the susceptibility of ventricular arrhythmia on being subjected to programmed electrical stimulation of the heart, the latter mutation exhibited spontaneous occurrence of ventricular arrhythmia and resulted in a high mortality rate. In our model, we use the closest analog of $I_{\rm to}$, viz., the time-dependent potassium current $I_{\rm K}$ and study the effect of increasing or decreasing the corresponding channel conductance $G_{\rm K}$.

Fig. 1 shows the role of $G_{\rm K}$ in setting up a stable reentrant circuit. Typically, such circuits can be organized around a zone of inexcitable or partially excitable region of cardiac tissue (anatomical reentry) or even a transiently inactive zone which prevents the passage of excitation wavefront across it (functional reentry). As the wavefront of excitation goes around it, stable reentry can occur if the circuit is long enough such that the tissue recovers by the time the front completes the circuit. Such circuits act as sources for persistent high-frequency stimulation that compete with the normal rhythmic activity initiated by the sinus node. Note that the period of the waves generated around this circuit is governed by the circuit length which is determined by obstacle size (for anatomical reentry) or refractory period of tissue (for functional reentry). Focusing on the region immediately surrounding the circuit, we study the simplified system

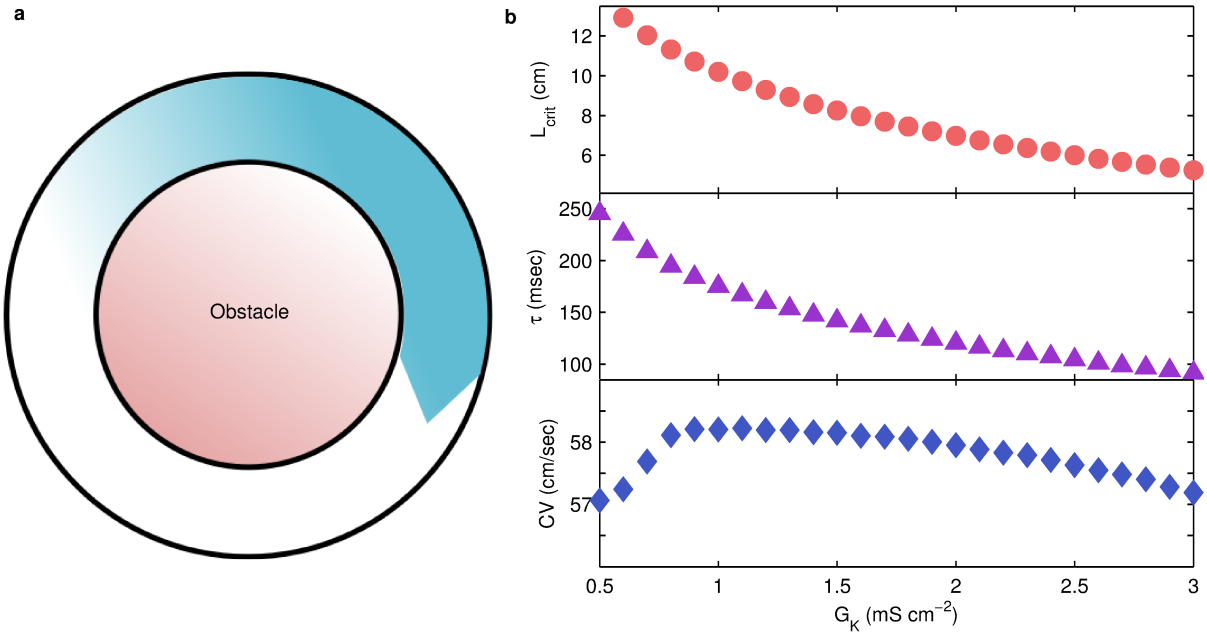

Figure 1. Potential mechanism for genesis of pathological situations in cardiac tissue with a high potassium ion channel conductance G_{K}. (a) Schematic diagram showing the ring topology of a reentry circuit which describes the motion of the spiral wave around an obstacle. The wavefront of the excitation propagating around the ring is indicated by the arrowhead. The color intensity represents the level of refractoriness with white regions indicating completely recovered tissue. (b) Variation in dynamical properties of reentrant wave propagation as a function of G_{K} in a ring of critical size, i.e., the minimum perimeter length required for sustained wave activity. The electrical activity of each cell is described by the LRI model. Unidirectional wave propagation is set up using a special initial condition. The critical ring size L_{crit} decreases monotonically on increasing G_{K} [top], as does the period of reentry τ, i.e., the time required by the wave to complete one circuit [center]. The conduction velocity CV of the wavefront [bottom] remains approximately constant, varying over a very narrow range of values, as G_{K} is changed. These results show that for high G_{K} the critical ring size reduces, allowing reentry to occur at higher frequency (i.e., smaller τ), which could potentially lead to wave breakup away from the reentry circuit.

of a one-dimensional reentrant circuit [Fig. 1 (a)]. We observe that increasing G_{K} results in stable reentry being possible for circuits of smaller lengths, and hence of much higher frequency. As more rapid stimulation of the tissue surrounding the circuit will result in waves that are more likely to result in front breakup as they travel to other regions of the tissue [33, 34, 35], we suggest that the propensity of life-threatening arrhythmia will be enhanced for higher G_{K}. Note that this is analogous to the situation corresponding to enhanced I_{to} resulting from an over-expression of *klf15*.

Fig. 2 shows an alternative scenario where the role of decreasing G_{K} in promoting arrhythmia is examined. This comes about through the mechanism of *alternans*, where periodic stimulation of excitable media at a sufficiently high frequency results in an alternating succession of strong and weak responses. In cardiac tissue, this can be observed as variations in the action potential duration (APD), such that long and short APD pulses alternate. Such alternans can appear even at the scale of a single cell as an outcome of the nonlinear restitution property (functional

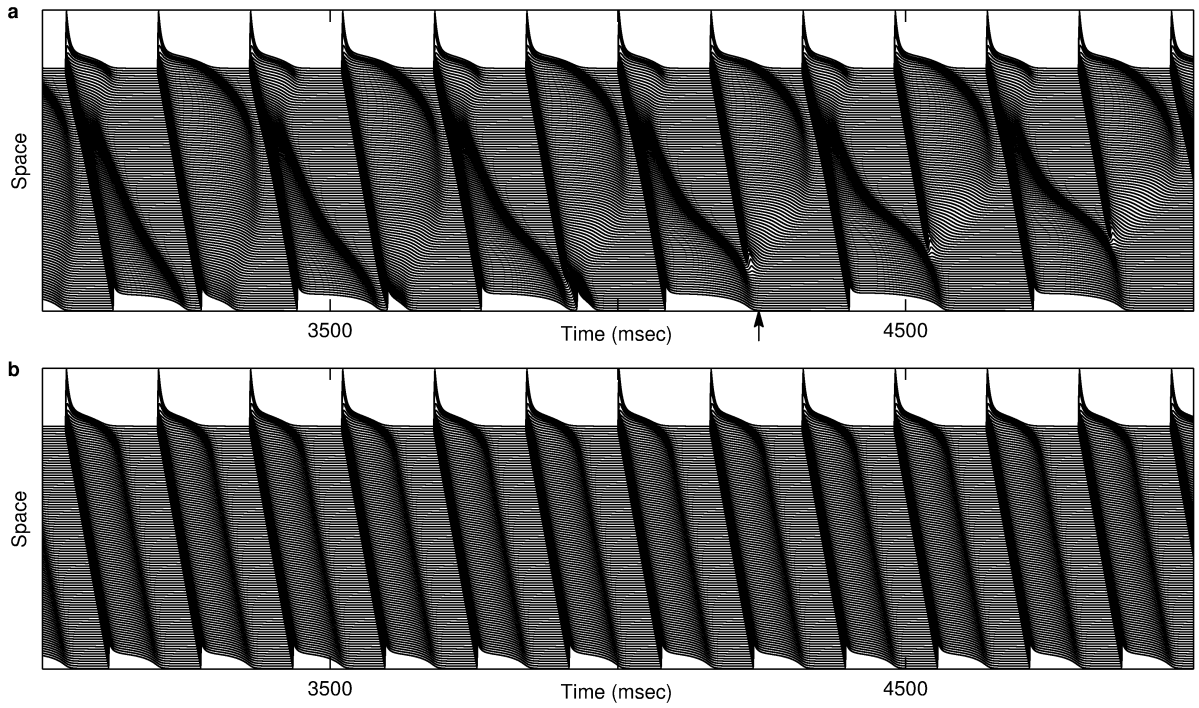

Figure 2. Potential mechanism for genesis of pathological situations in cardiac tissue with a low potassium ion channel conductance G_{K}. The dynamical response of a one-dimensional chain of cells subjected to external periodic stimulation (pacing) with a period of $T = 160$ ms at the top end is shown for two different values of (a) $G_{\mathrm{K}} = 0.7$ and (b) 0.9 mS cm^{-2}. The electrical activity of each cell is described by the LRI model. For the higher value of G_{K} (b), we observe a 1:1 periodic response, resulting in a train of identical action potentials. However, for the lower value of G_{K} (a), pacing at the same frequency results in alternating action potentials varying in duration (alternans). Moreover the pattern of alternans varies across space (discordant). The degree of variation in the action potential duration continues to increase over time, until a wavefront encounters a refractory region behind the preceding wave resulting in a conduction block (see arrow). These results show that for low G_{K}, periodic activation of cardiac tissue can occasionally cause propagating fronts to be spontaneously blocked, which may then lead to the formation of spiral waves and their breakup.

relation between APD and the interval between successive stimuli), while in combination with conduction velocity dispersion (i.e., dependence of the front propagation speed on the extent of recovery of the medium) an additional spatial variation can be seen in the alternans [36]. Such a variation is manifested in terms of long-short APD alternans in certain regions co-occurring with short-long alternans in other regions, a phenomenon termed as *discordant alternans*.

We study the pacing of a one-dimensional fiber as a simple approximation of cardiac tissue subjected to periodic electrical stimulation. We note that at lower values of G_{K} the system is much more likely to show enhanced discordant alternans that eventually results in conduction block far from the pacing site. Note that in a higher-dimensional system this will result in wave-break as a block occurs in a section of the wavefront. The broken front can then form a reentrant circuit, resulting in arrhythmia.

5. Discussion

In this paper we have computationally investigated the possible mechanism underlying the recently discovered close statistical relationship between occurrence of sudden cardiac death with the time of day. Essentially this involves understanding how cardiac activity is influenced by the circadian clock, i.e., temporal oscillations in physiological activity with a period close to 24 hours and synchronized with the day-night cycle. As noted in our paper, although studies have identified the genetic basis of circadian rhythm at the intracellular level, the mechanisms by which they influence cardiac pathologies are yet to be fully understood. We focus on evidence suggesting that the key to the circadian-cardiac relation may be provided by the diurnal variations in the conductance properties of ion channel proteins that govern the excitation dynamics of cardiac cells. Thus, we investigate the relationship between the circadian rhythm as manifested in modulations of ion channel properties and the susceptibility to cardiac arrhythmias by using a mathematical model describing the electrical activity in ventricular tissue. We show that changes in the channel conductance that lead to extreme values for the duration of action potentials in cardiac cells can result either in abnormally high-frequency reentrant activity or spontaneous conduction block of excitation waves. Both phenomena increase the likelihood of wavebreaks that are known to initiate potentially life-threatening arrhythmias. Thus, disruptive cardiac excitation dynamics are most likely to occur in time-intervals of the day-night cycle during which the channel properties are closest to these extreme values, providing an intriguing relation between circadian rhythms and cardiac pathologies. For simplicity, here we have examined the spatially homogeneous situation where every element in an excitable medium undergoes similar temporal variation in the parameter controlling repolarization. In real physiological situations, however, there may be considerable heterogeneity in the system - e.g., in terms of the repolarization dynamics of different regions as reflected in potassium channel properties. Spatial variations in the recovery characteristics are known to modulate the propagation speed of excitation wavebacks, which can result in wavebreaks [37, 38]. Furthermore, we have used one-dimensional models that consider rings or chains of cardiac cells. However, even such simple models can capture the essential properties of excitation dynamics that we investigate here. In future studies, we plan to show that the results obtained here under simplifying setting can be reproduced even for heterogeneous systems in two- or three-dimensional spatial geometries.

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