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Stochastic Pacing Effect on Cardiac Alternans – Simulation Study of a 2D Human Ventricular Tissue

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Abstract— **The physiological heart rate is not deterministic but rather varies in time; those variations are termed heart rate variability (HRV). It is well known that low HRV is often seen in patients prone to arrhythmias. The ability of HRV to predict arrhythmia events is traditionally attributed to an impaired balance between the autonomic sympathetic and parasympathetic tone. However, there is no concrete model that directly relates low HRV to the electrical conduction in the cardiac tissue and to arrhythmogenic dynamic properties. We simulated stochastic cardiac pacing with Gaussian distribution using 2D human ventricular tissue model. Conduction stabilization was obtained with stochastic pacing owing to reduced propensity of the appearance of action potential duration (APD) discordant alternans and reduced APD spatial heterogeneity.**

I. Introduction

Heart rate variability (HRV) is a term used to describe the non-constant behavior of the physiological heart rate. HRV can be described in the frequency domain mainly with three typical frequency domains or in the time domain as a stochastic process [1]. Low HRV standard deviation has been found to be a good measure that may predict lethal arrhythmic events, e.g., in post myocardial infarction patients [2], or in conditions such as aging [3], smoking [4], and heart failure [5] which tend to reduce HRV.

Traditionally, the ability of HRV to predict arrhythmia events was attributed to the fact that during arrhythmias the balance between the sympathetic and parasympathetic tone is impaired, and a low HRV reflects this autonomic tone damage [6]. This explanation is sustained by the fact that HRV reflects both sympathetic and parasympathetic outflow to the heart [7]. However, there is no concrete model that directly relates low cardiac rhythm variability to the electrical conduction in the cardiac tissue and to arrhythmogenic dynamic properties.

It is well known that the potentially fatal transition from cardiac tachycardia to cardiac fibrillation is attributed to the wavebreak theory and the formation of re-entrant waves [8]. In many scenarios, wavebreaks are correlated with the appearance of preceding concordant and discordant action potential duration (APD) alternans at high activation rates, which render the cardiac substrate functionally heterogeneous [9].

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Deterministic changes of the heart rate have been previously described in the literature and their anti-arrhythmic effect was demonstrated. For example, Banville et al. [10] have demonstrated in isolated pig hearts how an abrupt shortening of the cycle length suppresses alternans by altering the action potential duration restitution (APDR). This idea has partial similarity to stochastic cardiac pacing, as an abrupt change in the basic cycle length (BCL) can be thought of as a type of variability in the heart rate, although a non-physiological one. Stochastic pacing was previously studied but not in the contest of stability. Up to now pacing stochasticity was introduced mainly as a new means for investigating cardiac memory, and the effect of stochastic pacing on stability properties of the cardiac electrical activity has not been studied [11], [12].

In the present work we aim to show how stochastic pacing (which is a type of HRV) presents a protective roll against arrhythmia. In a preliminary study, we have demonstrated that the addition of stochasticity to the pacing sequence in a 1D atrial model results in lowering the APDR curve [13]. A theoretical explanation derived from control and switched system theory was proposed. Here we further study the protective role of pacing stochasticity using a 2D ventricular model in order to assess spatial mechanisms. By employing high pacing frequencies we show that stochastic pacing works to reduce the propensity of arrhythmogenic discordant APD alternans.

II. Methods

A. Simulation of electrical activity

Transmembrane voltage was calculated by solving the following diffusion-reaction differential equation for myocytes, employing a discrete mesh, in a mono-domain formalism [14]:

$$\frac{\partial V}{\partial t} = -\frac{\left(I_{ion} + I_{stim}\right)}{C_m} + \nabla \cdot \left(D \nabla V\right) \qquad (1)$$

where V [mV] is the transmembrane voltage, Cm[pF] is the myocyte membrane capacitance, I_{stim} and I_{ion} [pA] are the external stimulation and membrane ionic currents, respectively, and D [mm^2 ms^{-1}] is the electrotonic diffusion coupling tensor, representing myocyte/myocyte gap junctional coupling. The ionic kinetics for the calculation of I_{ion} was based on the human ventricular model by ten Tusscher and Panfilov [14]. Discretization and linearization of the differential equation was done for a simplified, 10x10mm tissue model. Spatial resolution of Δh=0.1mm and a temporal resolution of Δt=7.5μsec were employed,

resulting in a 100x100 computational cells. Conduction isotropy was assumed, resulting in a constant diffusion coefficient that was adjusted to match wave propagation velocity of 0.55m/s. Pacing stimulation was delivered at coordinates (x,y)=(0,0).

B. Generating discordant alternans

Discordant alternans may be obtained in one of the following two mechanisms [15]: 1) steep APDR and conduction velocity restitution slopes, or 2) steep APDR slope in the presence of tissue heterogeneity. In both cases high heart rate must be obtained in order to facilitate discordant alternans. We chose to simulate discordant alternans via the second mechanism. Ionic kinetic parameters that obtain a high APDR slope with a maximum slope of 1.8 were employed [14]. Electrophysiological heterogeneity of the tissue was modeled following Qu et al. [9], whereby an altered spatial rapid and slow K+ channel conductance distribution was utilized as follows:

$$G_K(x,y) = \overline{G}_k \cdot \left(\alpha + \beta\sqrt{\left((x-L_x)^2 + (y-L_y)^2\right)} / \left(L_x^2 + L_y^2\right)\right) \quad (2)$$

where (x,y) are the coordinates, (Lx, Ly) are the dimensions of the tissue, $\overline{G_k}$ is the maximal potassium channel conductance, α=1.2 and β=0.8. This produces an electrophysiological heterogeneity similar to that observed in the guinea pig ventricle [9], [16].

C. Pacing

Discordant alternans were obtained during deterministic pacing with a target basic cycle length (BCL) of 190ms. In order to simulate stochastic pacing we used stochastic Gaussian pacing distributed around 190ms as follows:

$$CL = 190 + G(\sigma,0) \quad (3)$$

where CL [ms] is the cycle length and $G(\sigma,0)$ is a Gaussian distribution random variable with a standard deviation of σ ms and a mean of zero. For each σ that was simulated, a set of N=10 random stimulation pulse series was established for statistical analysis. σ=0 was considered as deterministic pacing.

D. Measuring APD spatial heterogeneity

In order to quantify the effect of stochastic pacing on APD uniformity, the degree of spatial APD homogeneity was calculated as the spatial APD standard deviation (Σ) for each of the last 14 pulses in the target BCL [9]:

$$\Sigma = \sqrt{\frac{1}{N}\sum_{i=1}^{N}\left(APD_i - \overline{APD}\right)^2} \quad (4)$$

where N is the total number of cells (N=10000), APD_i is the APD of the i'th cell and $\overline{APD}$ is the average APD of all cells. High values of Σ correspond to a high degree of APD spatial heterogeneity, and low values of Σ correspond to high spatial APD uniformity and are therefore less arrhythmogenic.

E. Statistical analysis

One sample two-tailed student's t-tests were used for comparison of means. Values are expressed as mean±SD. Statistical significance was defined for p-value<0.05.

III. RESULTS

The 2D tissue was paced with gradually decreasing cycle lengths until a mean BCL of 190ms was achieved. In the deterministic reference case, i.e., without integrated stochastic pacing, discordant alternans were clearly observed for beats 10 to 12, shortly prior to a conduction block at beat 16, as shown in figure 1a. The APDs at each beat are shown at both (x,y)=(0mm,0mm) and (x,y)=(10mm,10mm) red and blue lines, respectively. This is further demonstrated in figure 1c, where the traces of the APD values along the main diagonal connecting those two locations are shown for two consecutive beats - beat 11 (red line) and beat 12 (blue line). Those lines intersect 6mm along the diagonal demonstrating the so-called nodal line, a typical characteristic of discordant alternans.

While clear discordant alternans were observed with deterministic pacing, stochastic pacing yielded concordant alternans for the same mean BCL. Figures 1b and 1d depict the APD behavior in time (figure 1b) and in space along the diagonal line (figure 1d) in the same manner as in figures 1a and 1c, for stochastic pacing with σ=0.8ms. This chosen σ value is physiological for the low pacing BCL [17] and yields an effective BCL magnitude of ~ 3ms. Figure 1b clearly demonstrates the absence of any discordant alternans, and instead the appearance of spatially concordant APD alternans at beats 7-14. This observation is reinforced from figure 1d where the two APD profiles along the diagonal line corresponding to the two consecutive beats do not intersect.

Finally, figures 1e and 1f present the spatial distribution of APD, Σ, for pacing with σ between 0ms and 1ms (n=10 sequences for each σ). Σ values are shown for the two most heterogenic beats: beat #12 (figure 1e) and beat #14 (figure 1f). Each result is compared to σ=0 (deterministic pacing) for statistical significance. In both cases Σ was lower when stochastic pacing was employed in comparison to the deterministic case. Moreover, a general trend of a monotonic decrease in Σ was observed as σ increased.

IV. DISCUSSION

Introducing stochastic pacing to the simulated ventricular tissue transformed the discordant APD alternans into concordant alternans and obtained a more homogeneous spatial APD distribution. Furthermore, we showed that the higher the pacing stochasticity was (measured by the pacing variance), the more homogeneous APD distribution that was obtained.

Reducing the APD heterogeneity in space is an important protective mechanism against arrhythmias. A premature or ectopic beat that is formed in the presence of a sufficiently APD heterogeneous medium may result in a wavebreak and deteriorate into reentry arrhythmia [18]. Moreover, while discordant alternans are highly arrhythmogenic, concordant

alternans are much less arrhythmogenic [18]. Our study therefore suggests that by adding stochasticity to the pacing sequence per se can reduce spatial APD heterogeneity and the probability of discordant alternans, therefore exhibiting a protective role against arrhythmias.

These results go in lines with the clinical findings that patients with low HRV present higher vulnerability to arrhythmias [2], as we found that there is an inverse relationship between pacing variance and APD heterogeneity. In addition to the theoretical aspects of these findings, there may be a practical benefit regarding novel designs of artificial pacemaker. It is suggested that by adding stochastic pacing to an artificial pacemaker the probability of arrhythmias may be reduced.

A question that still remains refers to the mechanism underlying the presented phenomenon. One possible mechanism refers to our previous work [13] relating stochastic pacing and the APDR curve in the atrial tissue. Despite the differences between the two works, most importantly in the employed ionic kinetic models, we hypothesize that the ventricular APDR curve too, when subjected to stochastic pacing is more stable in comparison to deterministic pacing. Stabilizing the APDR curve may also explain the stabilizing effect on 2D conduction configurations. Our future work will address the question of which ionic mechanism is involved in the stabilizing effect of stochastic pacing on the APD. A full investigation of the currents and gating variables might point out which parameters are most affected by stochastic pacing.

Several limitations in this study should be noted. During exercise or during pathology, the action potential kinetic model parameters alter. At the current paper we used a general model behavior of healthy cells at rest and did not take into account such possible alterations. Additionally, the Gaussian stochastic pacing that was employed lacks some important physiological spectral characteristics [1]. In this paper we did not try to reproduce an accurate physiological behavior of HRV but rather focused on comprehending the isolated effect of stochasticity. Moreover, additional sources for spatial heterogeneity should be tested in the future. One such an example is the transmural heterogeneity in the human ventricular AP [14].

V. Conclusions

Spatial APD heterogeneity decreases with increased Gaussian stochastic pacing variance, rendering the tissue less arrhythmogenic and reducing the propensity of potentially fatal discordant alternans in the human ventricles.

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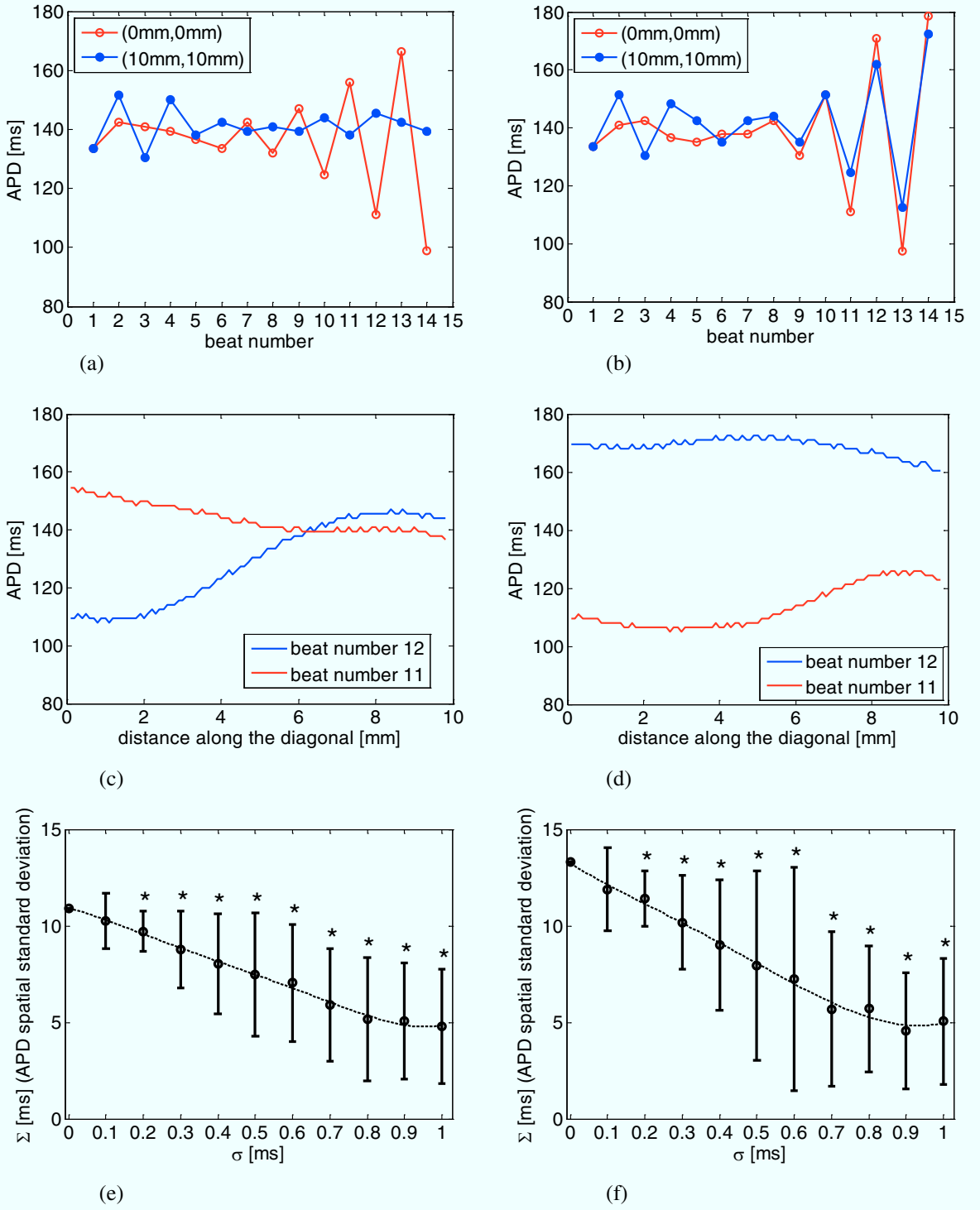

Figure 1. Effect of deterministic pacing (a,c) and stochastic pacing (b,d) with mean BCL=190ms on APD spatial heterogeneity; (a,b): temporal evolution of APD alternans for two cells located at (x,y)=(0mm,0mm) and (x,y)=(10mm,10mm) in red and blue lines, respectively. (a) Discordant alternans are present during deterministic pacing. (b) Only concordant alternans appear during stochastic pacing with σ=0.8ms. (c,d): APD profiles along the diagonal for the 11 beat (red line) and for the 12 beat (blue line), when the pacing is deterministic (c) and when the pacing is stochastic (d). (e,f): Spatial APD heterogeneity as a function of σ where σ=0 represents the deterministic case. For beat #12 (e) and for beat #14 (f). n=10, * P-value<0.05 compared to σ=0.