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Heart rate variability and alternans formation in the heart: The role of feedback in cardiac dynamics

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ABSTRACT

A beat-to-beat alternation in the action potential duration (APD) of myocytes, i.e. alternans, is believed to be a direct precursor of ventricular fibrillation in the whole heart. A common approach for the prediction of alternans is to construct the restitution curve, which is the nonlinear functional relationship between the APD and the preceding diastolic interval (DI). It was proposed that alternans appears when the magnitude of the slope of the restitution curve exceeds one, known as the restitution hypothesis. However, this restitution hypothesis was derived under the assumption of periodic stimulation, when there is a dependence of the DI on the immediate preceding APD (i.e. feedback). However, under physiological conditions, the heart rate exhibits substantial variations in time, known as heart rate variability (HRV), which introduces deviations from periodic stimulation in the system. In this manuscript, we investigated the role of HRV on alternans formation in isolated cardiac myocytes using numerical simulations of an ionic model of the cardiac action potential. We used this model with two different pacing protocols: a periodic pacing protocol with feedback and a protocol without feedback. We show that when HRV is incorporated in the periodic pacing protocol, it facilitated alternans formation in the isolated cell, but did not significantly change the magnitude of alternans. On the other hand, in the case of the pacing protocol without feedback, alternans formation was prevented, even in the presence of HRV.

1. Introduction

One of the most fundamental characteristics of cardiac cells is the shortening of the action potential duration (APD) as the heart rate increases, a phenomenon known as electrical restitution. Restitution plays a vital role in heart function: for a given heart rate, a shorter APD allows for a longer diastolic interval (DI), thereby giving adequate time for the heart to refill with blood. Although important for life at moderate heart rates, at higher rates, restitution may result in life-threatening cardiac rhythms and ventricular fibrillation (VF), in particular (Zipes and Wellens, 1998; Franz, 2003).

It is generally believed that T-wave alternans, defined as an alternating change in the amplitude or shape of the T-wave in the ECG, is a precursor of cardiac electrical instability (Karma, 1994; Watanabe et al., 1995; Gilmour and Chialvo, 1999; Fox et al., 2002). T-wave alternans results from APD alternans at the cellular level. A common technique for studying the initiation and maintenance of alternans and other complex rhythms is to analyze the restitution curve, the nonlinear functional relationship between the APD and xxxthe preceding DI (Tolkacheva et al., 2003; Kalb et al., 2004; Kalb et al., 2005). While detailed ionic models were used extensively to study the response of cardiac myocytes to stimulation, mapping models were introduced to focus on restitution (Nolasco and Dahlen, 1968; Guevara et al., 1984). Specifically, it was proposed that the APD could be determined as a function of the preceding DI, essentially forming the one-dimensional mapping model

$$\mathrm{APD}_{n+1} = f(\mathrm{DI}_n). \tag{1}$$

Here, f is the restitution curve, APD_{n+1} is the APD generated by the $(n+1)$st stimulus and DI_n is the nth DI, i.e., the interval during which the tissue recovers to its resting state after the end of the previous (nth) action potential.

In 1968, Nolasco and Dahlen (Nolasco and Dahlen, 1968) developed a graphical method to analyze and predict APD alternans in a mapping model (Eq. (1)) under the assumption that pacing occurs at a constant rate, i.e. when the APD and DI are related through the pacing relation

$$\mathrm{APD}_n + \mathrm{DI}_n = \mathrm{BCL}_n, \tag{2}$$

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where the basic cycle length BCL_n=BCL (a constant) under periodic pacing. Using Eqs. (1) and (2), it was proposed that the normal cardiac rhythm, or so-called 1:1 response, becomes unstable and alternans occurs when the magnitude of the slope of the restitution curve exceeds one,

$$S_r = \left|\frac{df}{dDI}\right|_{DI = DI_n} = |f'| \geq 1, \quad (3)$$

known as the restitution hypothesis. This restitution hypothesis has been confirmed in some experiments (Koller et al., 1998) and has led to the assumption that flattening the restitution curve will help prevent VF (Koller et al., 1998; Hall and Gauthier, 1999; Gilmour, 2002; Banville and Gray, 2002; Riccio et al., 1999). However, recent experimental results have shown that this hypothesis is incorrect in many situations, where the normal cardiac rhythm is observed when the restitution curve is very steep or in which the transition to alternans occurs in the presence of a flat restitution curve (Koller et al., 1998; Hall and Gauthier, 1999; Gilmour, 2002; Banville and Gray, 2002; Narayan et al., 2008).

One of the reasons why the restitution condition fails experimentally is that Nolasco and Dahlen's approach is valid only for periodic pacing, i.e. when BCL_n=BCL is a constant in Eq. (2), and cannot be applied for complex stimulation regimes, such as those which result in physiological heart rates that exhibit heart rate variability (HRV) (Malik and Camm, 1995; Goldberger et al., 2000; Kleiger et al., 1987; La Rovere et al., 2003). It is known that the heart rate is regulated by the autonomic nervous system, baroreceptors, and other factors (Malik and Camm, 1995). The sympathetic components of the autonomic nervous system increase heart rate by releasing the neural hormones catecholamine, epinephrine, and norepinephrine; while the parasympathetic components decrease heart rate through the releasing of the neurohormone acetylcholine. HRV is affected by, but not limited to, respiration, thermoregulation, hormonal regulation, blood pressure, etc. (Malik and Camm, 1995). HRV is a temporal variation between sequences of consecutive heartbeats, which reflects the balance between sympathetic and parasympathetic mediators. HRV alters pacing relation Eq. (2), in which BCL_n is no longer a constant, and therefore, might affect the overall dynamics of cardiac rhythm. Despite these important consequences, the effect of HRV on alternans formation in the heart has never been investigated.

The purpose of this manuscript was to determine the role of HRV on alternans formation in isolated cardiac myocytes using numerical simulations of physiological ionic model of cardiac action potential. First, we analyzed ECG data from Healthy and Diseased patients, separately, to determine HRV, feedback, and several other important physiological parameters used to design pacing protocols for the numerical simulations. Specifically, we designed two pacing protocols: periodic pacing with and without feedback. We then used both protocols to investigate the influence of HRV on the formation of alternans in an ionic model of cardiac action potential.

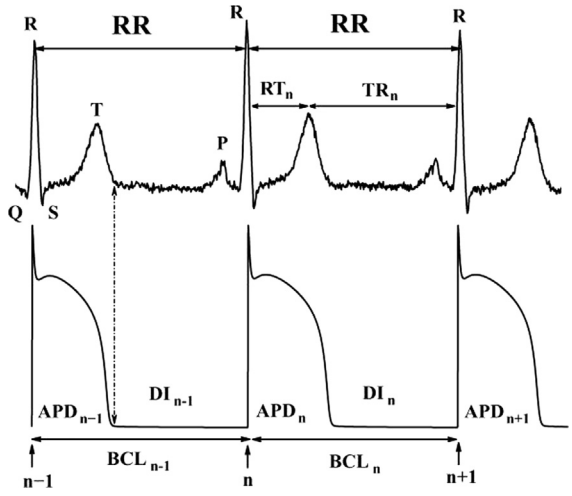

Fig. 1. The correspondence between APD, DI, and BCL values and the RT, TR, and RR intervals from the ECG, respectively.

2. Methods

2.1. HRV data analysis

ECG data analyse from 14 patients taken from Physionet database (Goldberger et al., 2000) were performed. Based on the information provided in Physionet, the data sets were divided in two different categories: Healthy (n=8), and Diseased (n=6). All Diseased patients were diagnosed with myocardial infarction.

Each ECG trace was approximately 120 s long. We applied band-pass filtering to each data set, and calculated the following parameters: RR intervals, determined as a distance between RR peaks; standard deviation (SD_{RR}) and average (AVG_{RR}) of RR intervals; TR and RT intervals, determined as a time between T and R peaks, and R and T peaks within RR intervals. Fig. 1 shows a direct correspondence between APD, DI, and BCL values and the RT, TR, and RR intervals from the ECG, respectively.

HRV for each ECG data set was determined as

$$\text{HRV} = \frac{SD_{RR}}{AVG_{RR}} * 100\%. \quad (4)$$

The sensitivity of each ECG data set, which is an indirect representation of feedback, was calculated using the following equation

$$s = \frac{SD_{TR}}{AVG_{TR}} \frac{AVG_{RT}}{SD_{RT}}, \quad (5)$$

where AVG_{TR} and AVG_{RT} are the average TR and RT values from each ECG data set, respectively. All these parameters were calculated separately for Healthy and Diseased patients and the results are presented in Tables 1 and 2, respectively.

2.2. Numerical simulations

To investigate the influences of HRV on alternans formation, we used a physiological ionic model of a canine cardiac action potential (Fox et al., 2002). This model exhibits APD alternans while being periodically paced at progressively decreased BCLs, and therefore, a distinct value of BCL for the onset of alternans, BCL_{start}, and for the end of alternans, BCL_{end}, can be defined. The system of ordinary differential equations was solved using a two-step Runge–Kutta method with a time step of Δt=0.05 ms. The APD was calculated at 80% repolarization.

Two different pacing protocols were used to model feedback and HRV in numerical simulations, based on ECG analysis: Protocol 1, a periodic pacing protocol with feedback, and Protocol 2, a pacing protocol without feedback. Specifically, the RR data from ECG data analysis was used for Protocol 1, and TR data was used for Protocol 2.

The periodic pacing protocol is described by Eq. (2), where BCL_n=BCL if HRV is absent. This pacing protocol entails a strong connection between APD_n and DI_n, and thus possesses feedback associated with periodic pacing, as described in Section 1. We started pacing at BCL=400 ms, and then decreased BCL by increments of 10 ms down to 100 ms. 120 stimuli were applied at each BCL in order to reach steady state. HRV was modeled by