From Cell Electrophysiology to Risk of Arrhythmia

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Abstract

Arrhythmias are stochastic in vivo, organ level behaviours that can be explained by deterministic cardiac cell and tissue mechanisms that alter their risk in a person and incidence in a population. Cell population models are constructed from deterministic cell models with random fluctuations in parameters, and the probabilities of arrhythmogenic cell mechanisms estimated for different circumstances, illustrated by sex, heart failure and carbon monoxide poisoning.

Spatial heterogeneity in APD is less than rate dependent variability, but spatial heterogeneity leads to APD dispersion. This is greater in female than male models and is enhanced by the effects of CO. Dispersion is further increased by Eary After Depolarisation, which are more frequent during CO exposure, and in heart failure models. These cell level mechanisms alter the probability of arrhythmogenic triggers.

For the triggers to produce an arrhythmia the tissue needs to be vulnerable, the vulnerability of female tissue is higher than male, and the difference in vulnerability is reduced by CO effects. For the re-entrant cascade of trigger, initiate and persistence of re-entrant arrhythmia, cellular experiments and models can estimate effects of stratification and pharmacological interventions on the probabilities of arrhythmogenesis.

1. Introduction

Cardiac arrhythmia, in which the pattern of propagation of normal sinus rhythm is perturbed or lost can be quantified in an individual by the times they begin and end, and in a population by their stratified rates of occurrence/person-year. These measures can be normalized as probabilities/unit time. Arrhythmias are ~10 cm scale triggered phenomena in a structured, anisotropic, heterogeneous myocardial tissue medium. The activity of coupled myocytes can form the triggers and their properties and coupling form the medium.

Ventricular arrhythmic episodes are rare in a healthy individual but in a population are a common cause of death. Syndromes in which the QTc interval is prolonged are associated with an increased mortality, and the QT interval provides an index of ventricular APD. Increased QTc and its dispersion [1] are considered proarrhythmic. The inherited LQT syndromes can be mapped onto the mutations that produce changes in ion channel kinetics and expression that result in APD prolongation [2]

Ventricular APD varies with spatial heterogeneity, that can be modelled as differences between myocytes in membrane channel maximal conductances [3], temporal factors - basic cycle length (BCL, or RR interval of ECG) and phase in biological rhythms, and sex [4] There is variability with time within a cell, and between cells in a population.

At a BCL of 1/s left-right and base-apical epicardial differences in APD are ~30 and ~40 ms [5]; transmural epi-endocardial APD differences are ~40ms. Irregularly located patches of mid-myocardial cells have APDs ~100ms longer than epicardial cells [6].

The coefficient of variation of APDs of periodically paced ventricular myocytes and of the resting ECG QTc are less than a few %. A QTc >40% longer than the age-stratified population mean is considered pathological and is associated with a higher risk of the re-entrant arrhythmia of ventricular tachycardia and fibrillation [3]. Re-entrant arrhythmias are triggered within a heartbeat, probably after a period of discordant alternans. Once triggered, the arrhythmia needs to persist for several cardiac cycles for it to be noticeable, and for tens of minutes before simus rhythm cannot be restored by defibrillation. We consider the triggering of an arrhythmia to be an unlikely or extreme event that underpins about one arrhythmic death/thousand person-years, during which several billion heartbeats would occur. Re-entrant arrhythmia is triggered by the initiation or unidirectional block of propagating activity.

Computational modelling shows the initiation of propagating activity within the myocardium requires near synchronous activation of a compact cluster of ~10^4 – 10^5 coupled cardiomyocytes within a few cubic mm, and block of a propagating wave requires a larger volume of inexcitable or refractory tissue. Neighboring cardiomyocytes are not independent – they are electrically

coupled, resulting in a voltage diffusion coefficient of 0.1-1 cm^2s^{-1} [7] smoothing spatial differences in potential, and cell parameters modulated on the mm-cm space scale by similar perfusion [8] (pH and ischaemia) and levels of norepinephrine released from sympathetic varicosities.

We construct populations of independent cell models by randomly varying the magnitudes of their ionic conductance and permeability parameters and estimate the probability of the long extremes of APD. Such extreme long APD in a compact coupled cluster of cardiomyocytes could act as a trigger for a reentrant arrhythmia, if they occur when the tissue is vulnerable. The tissue is vulnerable to reentry if it can produce a unidirectional conduction block.

2. Methods

All cell computations used the O'Hara-Rudy model [6], with the effects on ionic current parameters of sex from [4] and CO from [9], and models excited by periodic pacing. Cell model conductance and permeability parameters were Gaussian distributed with a ±5% standard deviation and truncated at 3 standard deviations. Propagation characteristics (conduction velocity, vulnerable window) were calculated as in [2].

3. Results and Discussion

The periodically driven sub-epicardial and sub-endocardial ORd model with standard parameters produces APD_{90} at 1/s of 221.5 and 255.9 ms (Fig.1A), and the sub-epicardial APD_{90} varies smoothly from 182.7 to 225.5 ms as BCL varies from 300 to 1200 ms (Fig1.B). For base-apical and transmural (excluding mid-myocardial) cell models the range of APD_{90} produced by location at a given BCL is less than the range produced by rate: in the deterministic models APD_{90} varies more with rate than location.

For a cell population with the maximum conductance and permeability parameters all selected stochastically with a 5% coefficient of variation the resultant APD_{90} distribution, 221.5 ±5.8 ms, (Fig.1C) is similar to the endo-epicardial dispersion of Fig.1A. When the mean parameter values are weighted according to sex [4] the mean and standard deviation of the APD_{90} are larger for the female (278.4 ±11.2 ms) than the male (221.5 ±5.8 ms), with the APD90 probability density function (pdf) estimated by histogram in Fig. 1D. The coefficient of variation (CV) for the APD_{90} are both less than the CV of the conductance magnitudes producing them and are greater for the female than the male populations.

A QTc 40% more than that of the normal population is indicative of LQT syndrome and considered pathological, and long QTc, indicative of long APD, are associated with an increased risk of arrhythmia, even though APD is an index of refractory period. A simple mechanism would be that spatial differences (APD dispersion) or gradients in APD are pro-arrhythmogenic: an increase in APD would increase the dispersion [10].

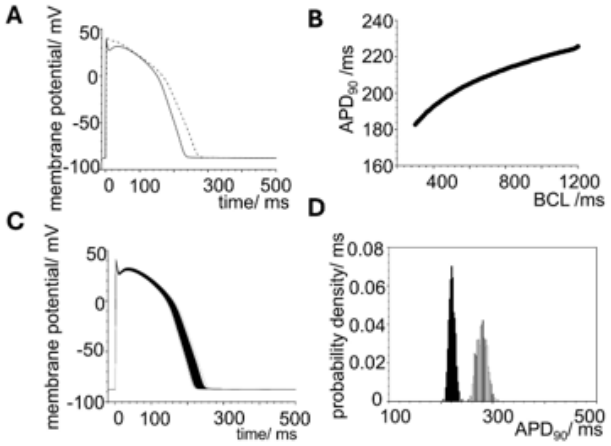

Figure 1. Diversity in computed ventricular action potential (AP) shape and duration depends on (A) cell location, sub-epicardial shorter than sub-endocardial; (B) rate, APD periodic restitution curve; (C) parametric variability, sub-epicardial ion maximal conductances with 5% coefficient of variation and (D) sex, female (grey) longer than male. ORd models, 101th AP during periodic pacing (A-C) male, (A, C, D) BCL 1000ms, (B, C, D) sub-epicardial cells. N=10,000.

The mean APD of sub-endo- and -epicardial cell model populations are distinctly different, and their pdfs overlap. For the standard female model APD_{90} are 278.4±11.2 (epi) and 316.9±12.3 (endo; Fig.2A), and these are increased to 371.7±19.7 and 434.2±23.6 (Fig.2C) by the effects of carbon monoxide (CO). The maximum transmural APD dispersions (Fig. 2C, D) are produced by sorting the APD_{90} of the independent epi- and endocardial cells in increasing and decreasing order, and taking the differences between them, are 38.5 ±16.7, and 62.5±30.7 for the standard female and female with CO population models.

The APD_{90} and dispersion pdfs are unimodal and have long tails - see inserts in Fig2C, D. These dispersion tails are rare instances when in a tissue model endocardial cells have recovered their resting potential and could be re-excited by depolarising current from the sub-epicardial cells. Most ectopic excitations occur in the sub-endocardium, and if they are sufficient to initiate a propagating wave [12] the resultant ectopic excitation

propagates towards the epicardium. Ectopic beats are usually benign.

The APs produced by the cell populations with 5% variability in conductance magnitudes have unimodal pdfs and AP shapes that repolarize monotonically. APs can be prolonged by early after-depolarisations (EADs) [13], in which dV/dt during the repolarizing phase of the AP reverses sign twice (Fig. 3). The APD_{90} is extended dramatically by a few hundred ms, giving a bi- or multi-modal pdf. Prolonged APDs and EADs are both considered pro-arrhythmogenic, and occurrence probability can be considered as a cellular index of their arrhythmogenicity. The probability that an EAD is produced in a population of cells under certain conditions *e.g.* periodic pacing can be estimated by simply counting. The probability that an AP dispersion is long enough to be considered pro-arrhythmogenic needs an arbitrary choice of duration above which it is. sufficiently pro-arrhythmo-genic. The assumption is that the greater the APD dispersion in cells, the greater the risk of an arrhythmia in a heart, and the greater the incidence of arrhythmia within in a clinical population. For the trigger to initiate a re-entrant arrhythmia it needs to occur during the vulnerable window of unidirectional conduction block that allows the initiation of re-entrant arrhythmic activity. The vulnerable window for standard female epicardial tissue models is less than that of the male, and this difference is largely abolished by the effects of CO (Fig.4), which acts by increasing in the prolonged late Na^+, and decreasing in the maximal T- and L-type Ca^{2+}. peak and late Na^+, ultra-rapid delayed, delayed rectifier, and the inward rectifier K^+ currents [3]

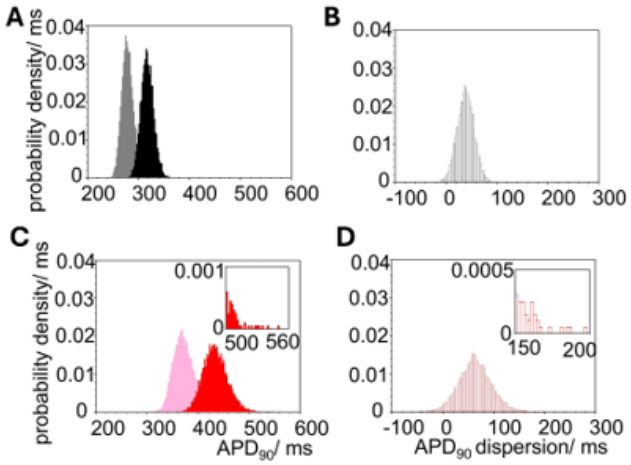

Figure 2. APD_{90} variability (A,C) and maximal dispersion (B, D) between sub-endo- (solid) and sub-epicardial cells. (A, B) standard female (C, D) female with CO models. ORd models, 101th AP after periodic pacing BCL 1/s.

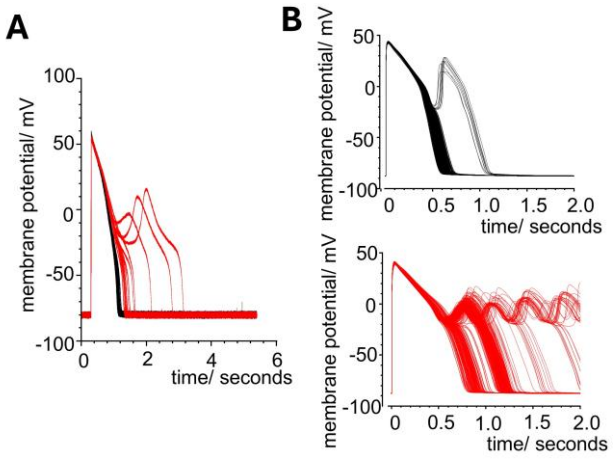

Figure 3. Extreme propagation of AP by EADs. A. Experimental recordings paced guinea pig single cardiomyocyte, BCL 6/s, room temperature. B. Paced population of ORd models, mean parameters for heart failure [11]. BCL 2/s. Black standard, red with effects of CO [9].

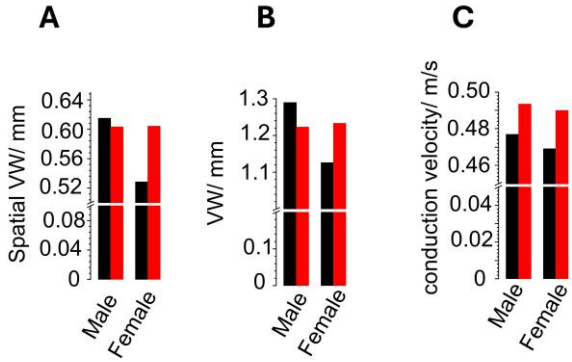

Figure 4. Sex differences in initiation and propagation characteristics of 1-D. 18mm homogenous ORd sub-epicardial tissue model A. width and B. duration of vulnerable window. the narrow time interval following a propagating AP during which a suprathreshold stimulus produces unidirectional propagation: C. conduction velocity computed for the initial AP produced by the test stimulus. Black standard, red with modelled ionic channel effects of CO. Note breaks in ordinate axes.

3. Conclusions

For a fatal episode of ventricular fibrillation to occur it must have been triggered, the trigger initiates re-entrant and fibrillatory propagation, and the fibrillatory propagation persist long enough for death to occur. Arrhythmias occur stochastically, and their probabilities

can be estimated from data from stratified populations. In vitro and computational experiments can quantify the rates and magnitudes at which putative triggers occur, and circumstances that increase these rates are expected to increase the risk of an arrhythmia.

In experiments measurement values that are outliers, more than several standard deviations away from the mean, are usually excluded from the analysis. We consider arrhythmia to be rare extreme events, produced by these outliers.

We show that APD dispersion (the main contributor to QTc dispersion) is greater in female than male cell models and is enhanced by the effects of CO. Dispersion is further increased by Eary After Depolarisation, which are more frequent during CO exposure, and in heart failure models. These cell level mechanisms alter the probability of arrhythmogenic triggers. The vulnerability of female tissue is higher than male, and the difference in vulnerability is reduced by CO effects.

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