Journal of Theoretical Biology 266 (2010) 408–418

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Feedback-control induced pattern formation in cardiac myocytes: A mathematical modeling study ☆

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ARTICLE INFO

Article history:
Received 12 February 2010
Received in revised form
8 June 2010
Accepted 29 June 2010
Available online 8 July 2010

Keywords:
Cardiac electrophysiology
Alternans
Subcellular alternans
Arrhythmia

ABSTRACT

Cardiac alternans is a dangerous rhythm disturbance of the heart, in which rapid stimulation elicits a beat-to-beat alternation in the action potential duration (APD) and calcium (Ca) transient amplitude of individual myocytes. Recently, "subcellular alternans", in which the Ca transients of adjacent regions within individual myocytes alternate out-of-phase, has been observed. A previous theoretical study suggested that subcellular alternans may result during static pacing from a Turing-type symmetry breaking instability, but this was only predicted in a subset of cardiac myocytes (with negative Ca to voltage ($Ca \rightarrow V_m$) coupling) and has never been directly verified experimentally. A recent experimental study, however, showed that subcellular alternans is dynamically induced in the remaining subset of myocytes during pacing with a simple feedback control algorithm ("alternans control"). Here we show that alternans control pacing changes the effective coupling between the APD and the Ca transient ($V_m \rightarrow Ca$ coupling), such that subcellular alternans is predicted to occur by a Turing instability in cells with positive $Ca \rightarrow V_m$ coupling. In addition to strengthening the understanding of the proposed mechanism for subcellular alternans formation, this work (in concert with previous theoretical and experimental results) illuminates subcellular alternans as a striking example of a biological Turing instability in which the diffusing morphogens can be clearly identified.

1. Introduction

Cardiac alternans is a disturbance in the rhythm of the diseased heart that predisposes to the formation of potentially fatal arrhythmias and serves clinically as an indicator of likelihood of sudden cardiac death. Alternans is seen clinically on the electrocardiogram (ECG) during rapid heart rates, when consecutive T-waves on the ECG alternate in amplitude (Narayan, 2006). This "T-wave alternans" is known to be a manifestation of underlying beat-to-beat alternations in the action potential durations (APDs) and peak intracellular calcium (Ca) concentrations of individual cardiac myocytes (Fig. 1A). Although alternans has been mechanistically linked to the formation of potentially fatal reentrant arrhythmias (e.g. ventricular tachycardia/fibrillation) (Pastore et al., 1999), its underlying mechanism remains unclear. Treatment or prevention of alternans may serve as a useful strategy for precluding its dangerous consequences, but no clinically practical means of doing so currently exist.

Alternans at the cellular level is understood to result from the interplay of ion channels at the cell surface and the dynamics of intracellular calcium cycling that are responsible for the rise in calcium concentration seen with each beat. Uncertainty still remains, however, regarding the primary source of instability that leads the normally period-1 rhythm (in which consecutive APDs and Ca transient amplitudes do not vary) to become a period-2, alternans rhythm at fast pacing cycle lengths (Fig. 1A). Theoretical and experimental work has identified mechanisms by which APD-alternans and Ca-alternans can result independently from one another, due only to instability in sarcolemmal ion channel and intracellular Ca-cycling dynamics, respectively. Due to bidirectional coupling between the APD and the Ca transient (described below), however, alternans in the APD will cause secondary alternans in the amplitude of intracellular Ca transients, and vice versa. This has made determination of the primary source of instability a difficult experimental challenge (Jordan and Christini, 2007; Qu and Weiss, 2007). Although Ca-cycling dynamics are now generally accepted as the primary cause of alternans (so-called "Ca-driven" alternans), both are likely to contribute to the total instability seen (Weiss et al., 2006).

Each Ca transient within a cardiac myocyte is the result of 1000s of nearly simultaneous, discrete subcellular Ca release events (Franzini-Armstrong and Peachey, 1981; Cheng and Lederer, 2008), which together result in an approximately

☆ Funded by: NIH.

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doi:10.1016/j.jtbi.2010.06.041

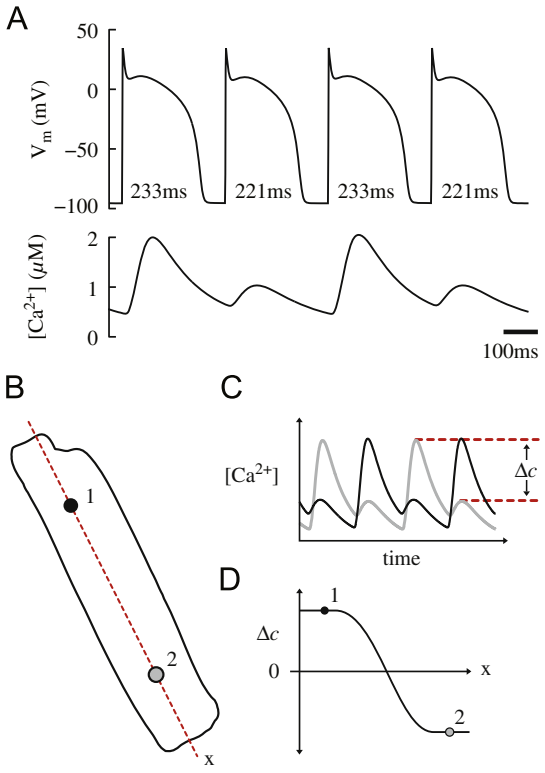

Fig. 1. (A) Alternans manifests at the cellular level as beat-to-beat alternations in the duration of subsequent action potentials (top) and the amplitude of consecutive intracellular Ca transients (bottom). Traces shown are from the detailed ionic model (see "Computational model" section for description), paced at a constant cycle length of 300 ms. The APD, defined as the time to 90% repolarization, is shown for each action potential. (B–D) Subcellular alternans occurs when distinct subcellular regions of an individual myocyte exhibit Ca-alternans of opposite phase (as diagrammed for regions 1 and 2; C). (D) This is simplified here as the formation of a gradient in Ca-alternans magnitude (Δc), where Δc is defined as the difference in peak Ca concentration between subsequent Ca transients (C; Eq. (18)). A 2-region subcellular alternans is diagrammed in this example, in which Ca transients in the two halves of the cell alternate out-of-phase, separated by a "node" with period-1 (no alternans) Ca transients where $\Delta c = 0$. B–D adapted with permission from Y. Shiferaw.

spatially synchronized change in intracellular Ca concentration. Likewise, during alternans the intracellular Ca transient normally remains spatially synchronized, with uniform alternations in Ca concentration within an individual cell. Recently, however, so-called "subcellular alternans" has been reported, in which the Ca transient desynchronizes spatially, and Ca-alternans occurs with opposite phase in adjacent subcellular regions of a single cell (as in Figs. 1B, C, and 4C) (Aistrup et al., 2006, 2009; Cordeiro et al., 2007; Díaz et al., 2002, 2004; Gaeta et al., 2009; Kapur et al., 2009; Karma and Gilmour, 2007; Kockskämper and Blatter, 2002; Xie and Weiss, 2009). This most commonly manifests as the two halves of an individual cell exhibiting beat-to-beat alternation in Ca transient amplitude, but with one half experiencing large–small–large Ca transients while the other half experiences small–large–small transients.

Although this phenomenon remains poorly characterized, several studies have shown its arrhythmogenic potential as a cause of intracellular waves of Ca-release ("Ca waves"), which are known to contribute to after depolarizations and triggered activity (Kockskämper and Blatter, 2002; Díaz et al., 2004, 2002; Xie and Weiss, 2009). Several mechanisms have been proposed to account for the formation of subcellular alternans during rapid pacing of otherwise healthy cells, invoking either anatomical (Aistrup et al., 2009) or dynamically induced (Xie and Weiss, 2009; Shiferaw and Karma, 2006) heterogeneity in subcellular Ca-cycling characteristics.

A recent theoretical study suggested that a purely dynamical mechanism—a Turing-type instability—can induce subcellular alternans in a structurally homogeneous cell (Shiferaw and Karma, 2006). A canonical Turing ("diffusion-driven") instability is a mechanism by which a concentration gradient can be established from a nearly homogenous substrate due to the interaction of only two distinct, diffusing substances ("morphogens") (Turing, 1952). This occurs when an autocatalytic substance ("activating morphogen") gives rise to its own, more quickly diffusing inhibitor ("inhibitory morphogen"). A concentration gradient arises because local increases in activator concentration will grow (autocatalysis) but will also simultaneously inhibit increases in activator concentration away from this site (due to the production of the more quickly diffusing inhibitor) (Gierer and Meinhardt, 1972). Since it was first proposed in 1952 by Turing (1952), this well-characterized, generic mechanism of pattern-formation has been invoked many times to account for patterns seen in systems as diverse as coat patterns in mammals (Murray, 2003) and shell patterns in mollusks (Meinhardt and Gierer, 2000), but the complexity of biological systems makes clear identification of the interacting morphogens difficult.

The previous study drew an elegant analogy between the amplitudes of Ca-alternans and APD-alternans and the concentrations of the activating and inhibitory morphogen in a canonical Turing instability (Shiferaw and Karma, 2006). By defining the "Ca-alternans amplitude" (Δc) as the difference in peak calcium concentration of consecutive beats at each point along the length of a cell, subcellular alternans was able to be treated as the formation of a stable gradient in Δc along the length of the cell. For example, if on two consecutive beats the left half of a myocyte experiences a small Ca-transient followed by a large transient concurrent with the right half having a large followed by a small transient (subcellular alternans), Δc will be positive on the left and negative on the right (as seen in Figs. 1D, 4B, and C).

Using a simplified coupled-map model, it was shown that such a gradient (subcellular alternans) will arise by a Turing-type instability given proper coupling between the AP and the Ca-transient. In particular, subcellular alternans was predicted to form by this mechanism during static (constant cycle length) pacing of only an uncommon subset of cardiac myocytes—those in which the Ca transient amplitude is negatively coupled to the APD ("negative $Ca \rightarrow V_m$ coupling", defined below). Here we show that this mathematical analysis also predicts that subcellular alternans will result in the remaining, more common subset of myocytes (those with positive $Ca \rightarrow V_m$ coupling, defined below) during pacing with a simple feedback control algorithm, "alternans control". Indeed, we have recently shown (in both a computational model and isolated guinea pig ventricular myocytes) that alternans control pacing robustly induces subcellular alternans in such cells (Gaeta et al., 2009). The mathematical and computational modeling work herein defines the theoretical basis for the subcellular alternans seen in those experiments, and identifies an intriguing experimental utility for alternans control pacing in the future study of alternans mechanisms.

2. Theory

2.1. Sarcomere model

To explore the effects of coupling between APD and intracellular calcium transients, Shiferaw and Karma (2006) introduced a