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DOUBLING BIFURCATIONS**

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ELECTRICAL ALTERNANS AND PERIOD-DOUBLING BIFURCATIONS

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Abstract

Experimental studies have been performed on quiescent aggregates of ventricular cells from 7-day-old embryonic chick heart. As the frequency of large-amplitude current pulses delivered through an intracellular microelectrode is increased, a critical frequency is reached at which 1:1 entrainment is no longer observed, but rather there is an alternation in the morphology of the action potential. An explanation for this behaviour, based on the electrical restitution curve, shows that alternans arises out of a period-doubling bifurcation. Furthermore, hysteresis in the response to periodic stimulation is theoretically predicted.

Introduction

"The condition in which cardiac muscle acted upon by evenly-spaced stimuli (either natural or artificial) responds with alternate large and small contractions, has been of late the subject of much discussion."¹

G.R. Mines, 1913

Over the years a number of mechanisms have been proposed to account for cardiac alternans.¹⁻³ We have observed alternating action potential morphology in periodically stimulated space-clamped quiescent aggregates (spheroids of about 100-200 μm in diameter) composed of ventricular cells from embryonic chick heart (Fig. 1). In this note we develop a theory for alternans in space-clamped preparations. We show that as the stimulation frequency is increased, a critical frequency is reached at which a 1:1 rhythm (one action potential for each stimulus with a constant action potential morphology (upper trace of Fig. 1)) becomes unstable and is replaced by a 2:2 rhythm (one action potential for each stimulus but with alternation of the action potential morphology (lower trace of Fig. 1)). Such a phenomenon arises as a consequence of a period-doubling bifurcation (the period of a repeating cycle doubles as a parameter is varied).⁴ Period-doubling bifurcations have also been demonstrated in periodically stimulated spontaneously beating heart cell aggregates for stimulation at a frequency either higher or lower than the intrinsic frequency.⁵⁻⁷ A connection between period-doubling bifurcations and cardiac alternans has previously been hypothesized.⁸⁻¹⁰

A mathematical model for alternans

The electrical restitution curve gives the action potential duration (APD) as a function of the time from the end of the preceding action potential to the stimulus (the recovery time λ). Figure 2 shows the electrical restitution curve (measured at -60 mV) for a periodically stimulated quiescent heart cell aggregate. The data in Fig. 2a were found for stimulation periods between 160 msec and 200 msec during which alternans was observed, whereas the data in Fig. 2b extend over a wider range of stimulation frequencies. The data are fitted to either single (Fig. 2a) or double (Fig. 2b) exponentials. For a stimulus delivered at a recovery time shorter than the refractory period (which we take here at recovery time equal zero) there is no action potential. The data in Fig. 2 are in basic agreement with measurements in other cardiac preparations.¹¹⁻¹⁵

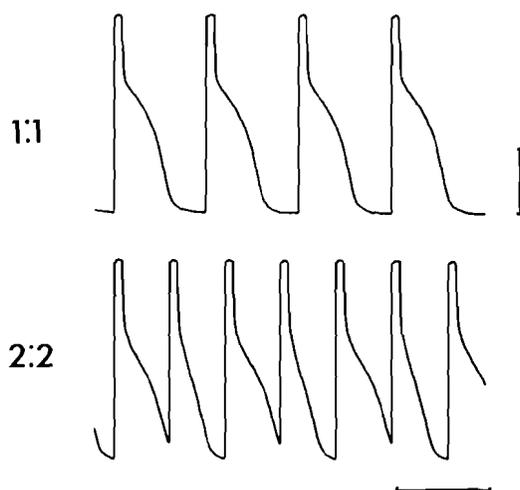


Figure 1: Intracellular recording of transmembrane potential from a periodically stimulated quiescent heart cell aggregate. Upper trace: $t_s = 300$ msec. Lower trace: $t_s = 180$ msec. Pulse duration = 20 msec; pulse amplitude = 25 nA. Aggregate diameter = 152 μm . The offscale vertical deflection is the stimulus artifact. This and all subsequent figures are taken from the same preparation. (Vertical calibration 50 mV; horizontal calibration 300 msec).

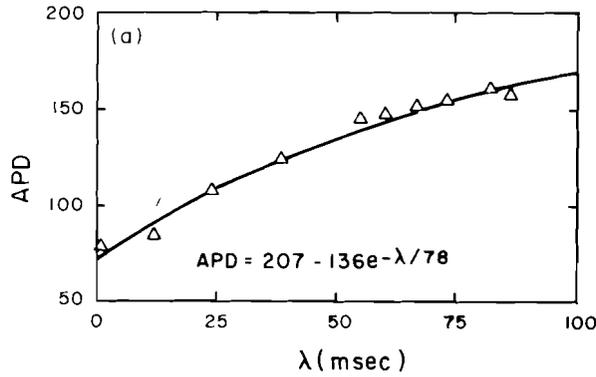


Figure 2: Electrical restitution curves showing action potential duration (APD) as a function of recovery time (λ) derived from traces such as those shown in Fig. 1. (a) Data (triangles) in

We assume that the APD following a stimulus is a function of the preceding recovery time. Referring to Fig. 3, we have

$$APD_i = g(Nt_s - APD_{i-1}), \quad (1)$$

where APD_i is the duration of the i^{th} action potential, t_s is the stimulus period, g is the electrical restitution curve and N is the smallest integer such that $(Nt_s - APD_{i-1})$ is greater than the refractory period. Equation (1) is a finite difference equation. Using a graphical method, it has been demonstrated that, for electrical restitution curves such as those shown in Fig. 2, alternans will be found as stimulation frequency increases provided the restitution curve is sufficiently steep at small recovery times.¹⁶

For the case in which the electrical restitution curve is fit by a single exponential, an explicit algebraic calculation of the frequency at which a period-doubling bifurcation occurs is possible. Assume that the electrical restitution curve is

$$g(\lambda) = APD_{\max} - \alpha e^{-\lambda/\tau}, \quad \lambda > \theta, \quad (2)$$

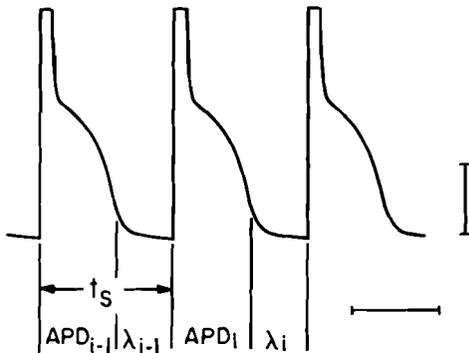
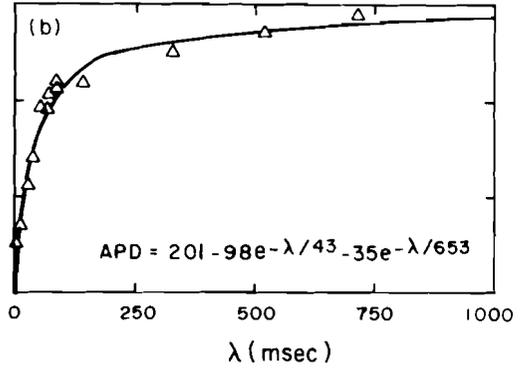


Figure 3: Diagram showing definition of terms. Calibration bars as in Fig. 1.



the alternans (2:2) zone fit to a single exponential. (b) Data in the 1:1 and 2:2 zones fit to a sum of two exponentials using nonlinear regression.

where APD_{\max} is the maximum action potential duration at long recovery times, α and τ are positive constants, and θ is the refractory period. A steady state of eq. (1) will occur if

$$APD_{i+1} = APD_i. \quad (3a)$$

If in addition

$$\left| \frac{\partial APD_{i+1}}{\partial APD_i} \right| < 1 \quad (3b)$$

at the steady state, that steady state is stable. If the derivative in eq. (3b) is equal to -1, a period-doubling bifurcation will occur. Using eqs. (1)-(3), we compute that a period-doubling bifurcation will arise if

$$\tau \ln(\alpha/\tau) > \theta \quad (4)$$

at a critical stimulation frequency, f^* , where

$$1/f^* = APD_{\max} - \tau + \tau \ln(\alpha/\tau) \quad (5)$$

Further, at the critical frequency the APD is $APD_{\max} - \tau$, and the recovery time is $\tau \ln(\alpha/\tau)$.

Numerical calculation of the dynamics as a function of stimulation frequency was carried out on a digital computer. Figure 4 shows a plot of eq. (1) for $t_s = 170$ msec using the single exponential function for the electrical restitution curve (Fig. 2a). There is a steady state at $APD_{i+1} = APD_i = 187$ msec which is stable, corresponding to a 2:1 rhythm (2 stimuli for 1 action potential) and a second steady state at 127 msec which is unstable. For an initial condition near 127 msec, there is a transient with the alternans becoming more pronounced eventually leading to the stable cycle (2:2 rhythm) with APD alternating between 94 msec and 156 msec. Finally Fig. 5 shows a plot of the theoretically computed APD as a function of stimulation frequency compared with experimental data. As stimulation frequency is increased the single stable APD decreases and the curve splits into two branches both in theory and in experiment. For the

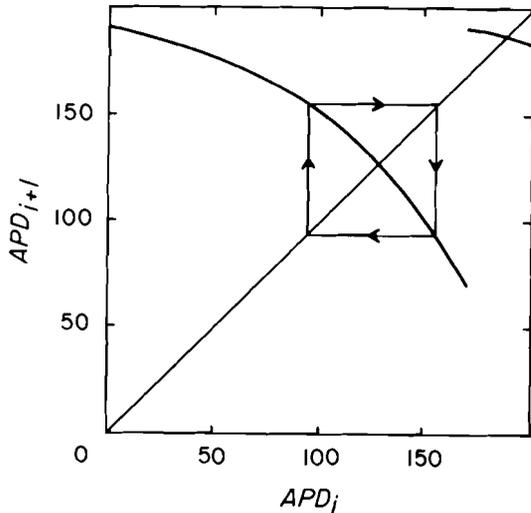


Figure 4: Graphical representation of eq. (1) for $t_s = 170$ msec with the single exponential fit in Fig. 2a assumed for the electrical restitution curve. There is a stable cycle with APD alternating between 94 msec and 156 msec (2:2 rhythm) and a stable steady state with APD = 187 msec (2:1 rhythm).

situation in which there is a 1:1 rhythm, this rhythm is approached via a transient alternans. The theory also shows the possibility for a bistability between the 1:1 (or 2:2) and 2:1 rhythms (Fig. 5). In an experiment such a bistability would produce a hysteresis phenomenon in which the particular rhythm observed would depend on the stimulation history.

Discussion

Given the electrical restitution curve of cardiac muscle, one can predict the qualitative features of the response as stimulation frequency is increased. In particular, electrical alternans may arise at a critical stimulation frequency. As well, bistability between a 1:1 (or 2:2) rhythm and a 2:1 rhythm over a range of stimulation

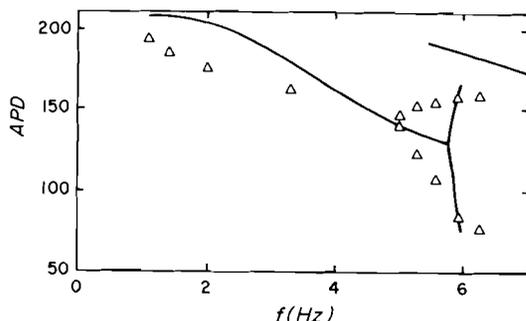


Figure 5: Bifurcation diagram showing APD as a function of stimulation frequency, f . Solid line shows theoretical results computed using the single exponential function of Fig. 2a. Triangles give data points.

frequencies is predicted. Hysteresis between 1:1 and 2:1 rhythms has been observed in frog ventricle¹ and in spontaneously beating heart cell aggregates.⁷ To the best of our knowledge, the predicted bistability between 2:2 and 2:1 rhythms has never been reported. An examination of Fig. 5 shows discrepancies between theory and experiment. Most notably, the range of frequencies over which one observes alternans is much smaller in theory than in experiment. One difficulty in applying the theory is that the APD cannot be measured accurately because of the stimulus artifact, and the point at which the APD is measured (here at -60 mV) is somewhat arbitrary. Therefore, there will be variations in the electrical restitution curve depending on exactly how it is measured. Simulations using other fits to the data points shown in Fig. 2 have shown that the bifurcation diagram (Fig. 5) is sensitive to small changes in the parameters describing the electrical restitution curve. This sensitivity, combined with the difficulty in determining the electrical restitution curve, contributes to the discrepancy between theoretical computations and experimental results. Another source of discrepancy stems from our assumption that the APD depends only on the recovery time from the preceding action potential. A more accurate treatment would necessarily include the effects of several previous action potentials, but this would complicate the theory.

The ionic mechanisms that underlie the electrical restitution curve are not fully understood. The APD depends on a delicate balance between inward and outward currents. The changes in the APD during periodic stimulation in cardiac Purkinje fibre have been related to the degree of recovery of the delayed rectifier current I_{x_1} .¹¹ However, the recovery of the plateau phase in cardiac ventricular muscle has also been related to the degree of recovery of the slow inward current I_{s_1} .¹² Embryonic heart cell aggregates have both an I_{x_1} current¹⁷ and an I_{s_1} current.¹⁸ The more rapid phase of our restitution curve is most likely attributable to these current components. However, the present study does not provide the means to separate out their relative contributions. The slower phase of the restitution curve is probably not related directly to the kinetics of I_{x_1} or I_{s_1} but to some secondary process or processes.¹⁴⁻¹⁵ During repetitive stimulation, particularly at rapid rates, the changes in APD may be due to combinations of these processes as well as changes in I_{x_1} and I_{s_1} . One of the advantages of the theoretical approach we have used is that salient features of alternans and hysteresis can be analyzed without a detailed understanding of the underlying ionic processes.

The experiments and theory reported here provide additional evidence that period-doubling bifurcations occur in cardiac physiology. We believe that nonlinear mathematics, in particular the theory of bifurcations, will play an increasingly important role in providing a framework in which other cardiac arrhythmias may be understood.

Acknowledgements

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