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Review

# Cardiac dynamics: Alternans and arrhythmogenesis

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ABSTRACT

Pre-existing heterogeneities present in cardiac tissue are essential for maintaining the normal electrical and mechanical functions of the heart. Exacerbation of such heterogeneities or the emergence of dynamic factors can produce repolarization alternans, which are beat-to-beat alternations in the action potential time course. Traditionally, this was explained by restitution, but additional factors, such as cardiac memory, calcium handling dynamics, refractory period restitution, and mechano-electric feedback, are increasingly recognized as the underlying causes. The aim of this article is to review the mechanisms that generate cardiac repolarization alternans and convert spatially concordant alternans to the more arrhythmogenic spatially discordant alternans. This is followed by a discussion on how alternans generate arrhythmias in a number of clinical scenarios, and concluded by an outline of future therapeutic targets for anti-arrhythmic therapy.



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## 1. Introduction

Pre-existing heterogeneities present in cardiac tissue are essential for maintaining the normal electrical and mechanical functions of the heart. However, an increased risk of cardiac arrhythmias can result from the exacerbation of such heterogeneities, which can occur under pathological conditions or following the administration of cardiotoxic drugs. The emergence of dynamic factors, which can interact with each other as well as with pre-existing tissue heterogeneities, can produce arrhythmogenic repolarization alternans and therefore cardiac arrhythmias. The focus of this review is to illustrate the mechanisms that (i) generate cardiac alternans, (ii) convert spatially concordant alternans to the more arrhythmogenic spatially discordant alternans, and (iii) are responsible for the production of arrhythmias in a number of clinically relevant conditions. This is

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concluded by a discussion on future therapeutic targets for anti-arrhythmic therapy.

## 2. Cardiac alternans

Cardiac alternans are beat-to-beat oscillations in either arterial pulse or electrocardiographic QRS and T waves. Of these, T-wave alternans (TWAs) have been associated with re-entrant arrhythmogenesis and identified as a good predictor of sudden cardiac death [1]. They are due to alternations in repolarisation time courses (measured as action potential durations, APDs) at the cellular level, which increase in amplitude with faster heart rates. TWAs have been observed in a number of conditions, including electrolyte abnormalities, hypothermia, coronary artery disease, post-myocardial infarction, long QT and Brugada syndromes, vasospastic angina, dilated, hypertrophic, and Takotsubo cardiomyopathies, and end-stage heart failure.

### 2.1. APD restitution-dependent mechanisms

The relationships between the diastolic interval (DI), APD, and basic cycle length (BCL) are shown in Fig. 1. BCL is the sum of APD and DI. The mechanism of APD alternans was first described by using a graphical method, relating them to APD restitution [2]. This refers to the normal shortening of APD in response to faster heart rates, and is thought to be an adaptive mechanism for preserving diastole at such rates. It can be defined as the dependence of APD on the previous DI. Experimentally, this can be determined by using an S1S2 protocol, which gradually shortens the interval between the S1 and S2 stimuli, or by using a dynamic pacing protocol, which increases the heart rate by progressively reducing the BCL. While both methods can be used to measure APD restitution [3], the S1S2 restitution curve is a measure of the immediate response to a change in BCL, whereas the dynamic restitution curve is a measure of the steady-state response [4]. Fig. 2 shows a typical APD restitution curve obtained from mouse hearts, $APD_{n+1}=f(DI_n)$, where $f$ is the function relating the new APD to its previous DI. The dashed line indicates the gradient of the curve and the gray area refers to values of DIs with gradients greater than one.

The gradient of the restitution curve is a collective measure of the recovery of all the ion channels opened during the cardiac action potential. First, of these channels, sodium channels recover from inactivation rapidly, and therefore their effects on APD restitution occur mainly at short DIs, between 0 and 40 ms in human hearts. However, if the recovery of sodium channels is slowed, which can occur under ischemic conditions [5], their effects on APD restitution would be extended to longer DIs. Second, the L-type calcium channels recover more slowly than sodium channels, and their effects are therefore observed in the short and intermediate DI ranges, between 0 and 100 ms. These calcium channels provide the majority of the inward current during the plateau phase of the action potential and therefore exert major effects on APD restitution. Their inhibition leads to reduced gradients of APD restitution curves. Third, time-dependent potassium channels, such as the voltage-gated delayed rectifiers, show the slowest recovery compared to other ion channels and therefore their effects are observed over a much larger DI range beyond 100 ms. In addition, the block of potassium channels shows reverse use dependence, where there is less block with increasing use [6]. Thus, the block increases during phase 4 of the action potential (diastole) and decreases during the plateau phase. Consequently, potassium channel blockers, which prolong APDs, have greater effects at long BCLs (bradycardia) and long DIs (e.g. compensatory pause after an ectopic beat), but have much smaller effects at short BCLs (tachycardia) and DIs [6]. They generally increase the gradients of APD restitution curves. The steep portion of the APD restitution curve is relevant in sinus tachycardia, where the heart rate is increased. It is also relevant in heart failure or the congenital and acquired long QT syndromes. In these conditions, APD is prolonged and therefore the DIs can become short enough to engage the steep portion of the APD restitution curve even at normal heart rates.

Fig. 3 shows cobweb plots that can be used to determine the stability of APD alternans. As BCL decreases, APD also decreases and the relationship BCL=APD+DI can be shown graphically as a straight line with a gradient of −1. The equilibrium point of APD for each BCL is the intersection point of the restitution curve and this line, which has the coordinates [$DI_s$, $APD_s$]. The stability of APD can be determined by perturbing the DI by a small amount, $\delta$,

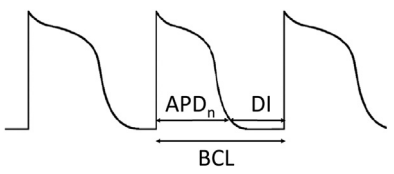


**Fig. 1.** Voltage trace showing the relationships between action potential duration (APD), diastolic interval (DI), and basic cycle length (BCL).

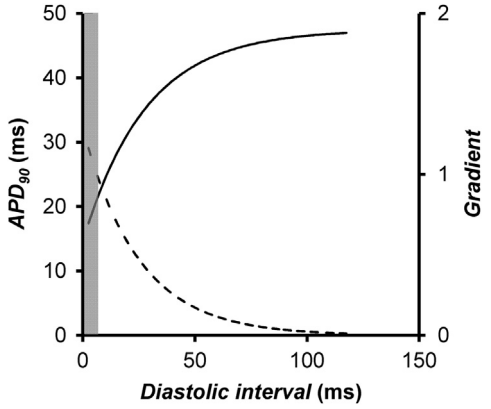


**Fig. 2.** An APD restitution curve describes the relationship between the APD and the previous diastolic interval (solid line). The gradients of the curve are represented by the broken line. The values of DIs at which such gradients are greater than one are represented by the gray box.

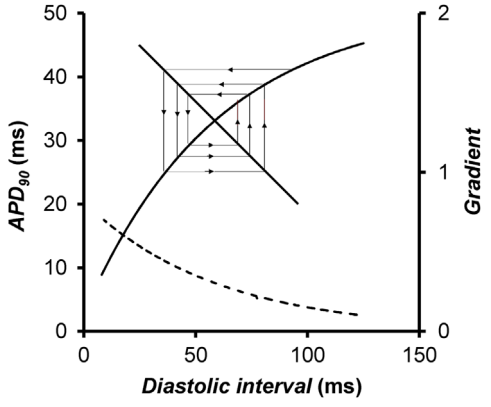


**Fig. 3.** APD restitution curve plotting APD against the previous DI (solid line) along with their gradients (broken line). The values of DIs with gradients greater than one are represented by the gray box. The cobweb plot shows that when the APD restitution gradient is less than one, a stable equilibrium point is produced on successive beats.

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