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Review article

The link between repolarisation alternans and ventricular arrhythmia: Does the cellular phenomenon extend to the clinical problem?

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Abstract

T-wave alternans is considered a potentially useful clinical marker for the risk of ventricular arrhythmia in patients with heart disease. Cellular repolarisation alternans is thought to underlie T-wave alternans, and moreover, to cause re-entrant ventricular arrhythmia. This review examines the experimental and clinical evidence linking repolarisation alternans and T-wave alternans with the occurrence of ventricular arrhythmia. Repolarisation alternans, manifest as alternating changes in action potential duration, is observed in isolated ventricular cardiomyocytes and in multicellular preparations. Its underlying causes are discussed particularly with respect to the role of intracellular Ca^{2+}. The repolarisation alternans observed at the single cell level is compared to the alternating behaviour observed in isolated multicellular preparations including the perfused ventricular wedge and Langendorff perfused heart. The evidence concerning spatial differences in repolarisation alternans is considered, particularly the situation where adjacent regions of myocardium exhibit repolarisation alternans of different phases. This extreme behaviour, known as discordant alternans, is thought to produce marked gradients of repolarisation that can precipitate unidirectional block and re-entrant ventricular arrhythmias. Finally, the difficulties in extrapolating between experimental models of alternans and arrhythmias and the clinical manifestation are discussed. The areas where experimental evidence is weak are highlighted, and areas for future research are outlined.

Keywords: Repolarisation alternans; Ventricular arrhythmia; Intracellular calcium; Restitution; Re-entry

Contents

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1. Introduction

In recent years, the concept of repolarisation alternans has emerged as a new mechanism for the induction of re-entrant ventricular arrhythmia [1]. Repolarisation alternans describes a regular variation between two patterns of repolarisation on an every-other-beat basis, at a constant cycle length. This phenomenon, which has been demonstrated at the single cell and tissue level, has both a clinical association with ventricular arrhythmia and an experimental link to the promotion of re-entry. Repolarisation alternans is believed to underlie T-wave alternans (TWA), an electrocardiographic (ECG) finding of alternating T-wave morphology. Visually apparent TWA has been anecdotally associated with the onset of ventricular arrhythmia in different clinical situations [2]. Developments in ECG signal processing techniques have allowed the resolution of small (microvolt) changes in the T-wave amplitude [3]. Microvolt T-wave alternans (MTWA) can be commonly observed during a sub-maximal treadmill test and induction of MTWA below a threshold heart rate has been associated with an increased risk of ventricular arrhythmia [4–6]. Use of MTWA for the risk stratification of sudden cardiac death is now entering clinical practice [7]. Understanding of the cellular basis for the phenomenon may provide new insight into the causes of lethal arrhythmias in man. In animal models, at high stimulation rates, repolarisation alternans may become spatially discordant, a state which was associated with significant gradients of repolarisation and the induction of re-entry [8]. This experimental paradigm raises the possibility that repolarisation alternans causes the ventricular arrhythmias for which MTWA is a marker. Moreover, the link between alternans and fibrillation has been made in studies of human atrial electrophysiology [9]. For this reason, repolarisation alternans has become the focus of much experimental study and its presence is increasingly interpreted as a surrogate for a pro-arrhythmic substrate. However, a number of questions regarding this mechanism of arrhythmogenesis remain unanswered:

(i) What are the cellular mechanisms for repolarisation alternans?
(ii) How does discordant alternans develop?
(iii) Can discordant alternans alone lead to re-entrant arrhythmias?
(iv) What changes in ventricular electrophysiology cause MTWA in the ECG signal?
(v) Does repolarisation alternans occur with MTWA in man?
(vi) Does discordant alternans occur prior to ventricular arrhythmia in man?

This article reviews the literature in an attempt to address these questions and to establish the extent to which the link between repolarisation alternans and clinical arrhythmias has been shown.

2. Cellular mechanisms of repolarisation alternans

2.1. Primary APD alternans

The main hypothesis for the generation of repolarisation alternans is based on the action potential duration (APD) vs. diastolic interval (DI) restitution relationship. The relationship is quantified using experimental measurements of APD and DI, typically during the application of extra-stimuli at progressively shorter diastolic intervals. A steep restitution curve describes the situation where a change in DI has a larger effect on the subsequent APD. The generation of repolarisation alternans by steep APD restitution was first described in 1968 by Nolasco and Dahlen [10]. The authors constructed a cobweb diagram to illustrate the way in which the slope of the APD restitution curve dictated the presence or absence of APD alternans following a shortening in cycle length (Fig. 1). In the case of a steep restitution curve, shortening of DI produces a short APD in the next cycle and, given that cycle length is constant, a long DI. This in turn gives rise to a long APD with an associated short DI, leading to stable alternation. In contrast, a shallow APD restitution curve means that variation in APD would progressively diminish. There is both experimental [11,12] and simulation-based [13,14] evidence that an APD restitution slope > 1 promotes repolarisation alternans. Although the cobweb diagram illustrates the generation of alternans on a single restitution curve, in reality the situation is more complex. In isolated myocytes, restitution curves differ depending on whether the extrastimulus follows the beat with the long or short action potential [15]. In multicellular preparations, temporal heterogeneity of restitution may also occur [16].

2.2. Ca^{2+} transient alternans

Simultaneous measurement of intracellular Ca^{2+} and membrane voltage has shown APD alternans accompanied by alternating changes in Ca^{2+} transient amplitude [17,18]. In isolated ventricular cells and whole hearts a reduced Ca^{2+} transient amplitude generally accompanies a shorter APD (electromechanically in-phase alternans) [15,17,18]. There have been fewer reports of the opposite phenomenon: a larger Ca^{2+} transient amplitude associated with the shorter APD (electromechanically