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Review

Alternans in atria: Mechanisms and clinical relevance

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ABSTRACT

Atrial fibrillation is the most common sustained arrhythmia and its prevalence is rapidly rising with the aging of the population. Cardiac alternans, defined as cyclic beat-to-beat alternations in contraction force, action potential (AP) duration and intracellular Ca^{2+} release at constant stimulation rate, has been associated with the development of ventricular arrhythmias. Recent clinical data also provide strong evidence that alternans plays a central role in arrhythmogenesis in atria. The aim of this article is to review the mechanisms that are responsible for repolarization alternans and contribute to the transition from spatially concordant alternans to the more arrhythmogenic spatially discordant alternans in atria.

1. Introduction

Atrial fibrillation (AF), the most common cardiac arrhythmia, currently affects 1–2% of the population, and over the next several decades the prevalence of AF is expected to reach unprecedented levels as the population of developed countries ages. AF is associated with increased risk of stroke, cardiomyopathies as well as heart failure, and accounts for significant morbidity and mortality [1,2].

Several mechanisms of AF have been described. Now it is well recognized that both arrhythmogenic triggers and an appropriate substrate are required for the initiation and perpetuation of AF [3–5]. It has been suggested that action potential (AP) repolarization alternans that are observed to precede AF episodes, plays a major role in generation of proarrhythmic substrate and facilitates re-entry phenomena that ultimately lead to sustained AF [3,6–14]. At the cellular level cardiac alternans is defined as cyclic, beat-to-beat alternations in contraction force, AP duration and intracellular Ca^{2+} release at constant stimulation rate.

Most of our understanding of the mechanisms and the role of alternans stems from studies of ventricular tissue. While sharing many similarities, ventricular and atrial tissues bare distinct characteristics of excitation-contraction coupling (ECC) and intracellular Ca^{2+} regulation which also suggests differences in alternans generation and regulation. This review focuses on the mechanisms of atrial alternans, its clinical relevance for the initiation of AF, and highlights differences between atrial and ventricular alternans.

2. Putative mechanisms of alternans

Initially cardiac alternans was described as mechanical [15] and electrical alternans [16] at the whole heart level. Later

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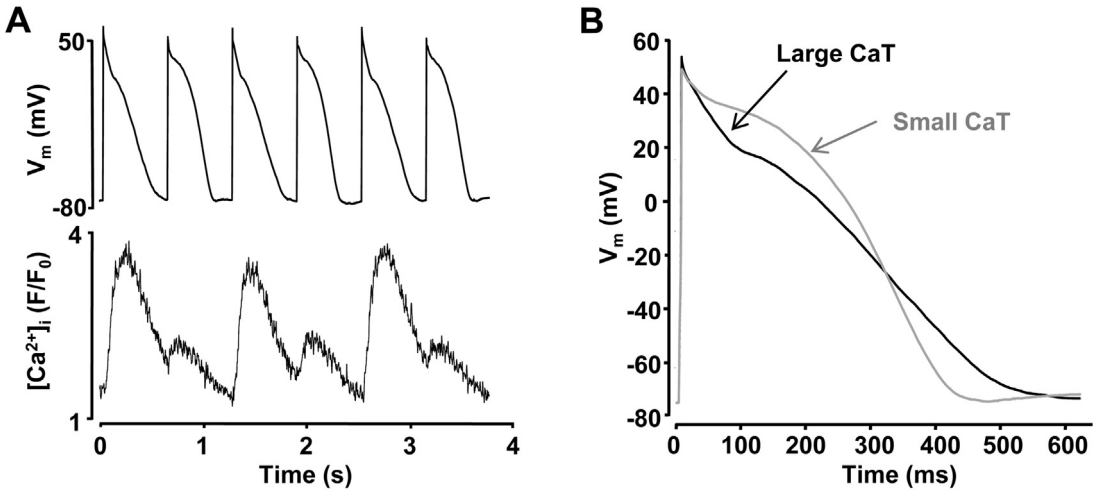

Fig. 1 – AP and Ca^{2+} alternans occur simultaneously.
(A) Simultaneously recorded APs and Ca^{2+} transients in current-clamped atrial myocytes. (B) Superimposed AP traces recorded during large (black) and small (gray) amplitude Ca^{2+} transients.
Figure modified with permission from [17].

alternans was also observed in isolated cardiomyocytes suggesting that the origin of this phenomenon resides at the cellular level. The strong spatial and temporal correlation between AP and Ca^{2+} alternans at both whole heart and single cell levels is well established (Fig. 1), [17,18] and it is generally agreed that the bi-directional relationship between cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) and membrane potential (V_m) plays a key role in the generation of alternans. Bi-directional coupling of V_m and $[Ca^{2+}]_i$ ($V_m \leftrightarrow [Ca^{2+}]_i$) is defined by the facts that (1) V_m directly determines the activity of Ca^{2+} handling mechanisms that are voltage-dependent ($V_m \rightarrow [Ca^{2+}]_i$ coupling), whereas (2) $[Ca^{2+}]_i$ dynamics affect V_m regulation through Ca^{2+}-dependent ion currents and transporters ($[Ca^{2+}]_i \rightarrow V_m$). Whether disturbances of V_m or $[Ca^{2+}]_i$ regulation is the predominant mechanism of alternans remains an ongoing matter of debate. Theoretical and computational studies have supported both hypotheses [19–24]. However, due to the complex nature of the bi-directional coupling between V_m dynamics and intracellular Ca^{2+} handling and the many feedback pathways between the two parameters, the experimental distinction between effects of Ca^{2+} and V_m is difficult and therefore the mechanisms of alternans still remains incompletely understood, especially in atrial tissue.

2.1. *V_m as key mechanism for the development of alternans*

A possible contribution of $V_m \rightarrow [Ca^{2+}]_i$ coupling to alternans is well supported by computational studies [19,21,25–29]. Nolasco and Dahlen [25] suggested that at high stimulation rates beat-to-beat V_m alternation is determined by AP duration (APD) restitution and is an underlying cause for the development of alternans. APD restitution refers to the APD dependence on the preceding diastolic interval. The slope of the APD restitution curve is determined by the recovery of ion channels from inactivation and their dependence on V_m. Computational [21,25,26,28,29] as well as several experimental studies [30,31] have suggested that self-sustaining oscillations of APD can occur if this relationship is steep enough, and that the role of V_m as a causative factor of alternans becomes more prominent with increasing pacing rates [28,32]. However, simulation results still differ and remain dependent on the computational models applied, even if they are designed to recreate processes of the same tissue [33]. Contrary to computational results, numerous experimental studies could not confirm these theoretical findings and actually show a poor relationship between experimentally determined APD restitution kinetics and inducibility of alternans [34–38]. While it was shown that in ventricular myocytes AP kinetics affect sarcoplasmic reticulum (SR) Ca^{2+} release [39,40], activity of the electrogenic Na^+/Ca^{2+} exchanger (NCX) [41–43] and L-type Ca^{2+} channels (LCC) [42,44–46], experimental evidence for the intricate details of how $V_m \rightarrow [Ca^{2+}]_i$ coupling modulates the occurrence of alternans is still lacking. Such discrepancy in theoretical and experimental findings can be explained, at least to some extent, by the fact that because of the slow recovery of ion channels and gradual change in intracellular ionic concentrations, cardiac myocytes exhibit a ''memory'' of the preceding stimulation conditions and thus APD is not determined solely by the preceding diastolic interval, and therefore constitute more complex APD dynamics than are simulated by most computational models (discussed in detail in [47,48]). Due to ''cell memory'' real cardiac tissue APD restitution curves depend greatly on the conditions under which they have been recorded such as basal pacing frequency and rate of APD adaptation to the change in pacing rate [34,48]. Also, electrical restitution is determined by inactivation and recovery thereof of different ion channels (Na^+, LCCs, slow rectifier K^+ channels and others), each of which has individual properties and kinetics and consequently experimentally measured restitution curves rarely follow a simple mathematical function [48]. Furthermore, APD restitution curves may also be poor predictors of alternans occurrence because AP morphology is strongly influenced by intracellular Ca^{2+} dynamics [18,49,50], and Ca^{2+} alternans can be initiated

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