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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.

Keywords

Alternans; Atria; Arrhythmias; Action potential; Calcium signaling

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.

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Conflict of interest

The authors state no conflict of interest.

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 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 independently of V_m alternans [17,51] (see discussion below). While the question whether $V_m \rightarrow [Ca^{2+}]_i$ or $[Ca^{2+}]_i \rightarrow V_m$ coupling plays a leading role in the initiation of alternans is still debatable, there is little doubts that $V_m \rightarrow [Ca^{2+}]_i$ coupling is critical for development and sustainability of atrial alternans. A recent study by Kanaporis and Blatter [52] in voltage-clamped rabbit atrial myocytes using AP waveforms observed during Ca^{2+} alternans (AP_{CaT_Large} observed during large systolic Ca^{2+} transient (CaT) and AP_{CaT_Small} observed with small CaT) demonstrated that both threshold for induction of Ca^{2+} alternans and degree of Ca^{2+} alternans are strongly modulated by the morphology of the AP (Fig. 2A) [52]. This study also demonstrated that AP morphology affected Ca alternans by two mechanisms: (1) by determining SR Ca^{2+} content (Fig. 2B) and (2) by regulating kinetics of L-type Ca^{2+} current (Fig. 2C) [52].

2.2. Intracellular Ca^{2+} cycling as an underlying mechanism of alternans

The inconsistent correlation between APD restitution properties and occurrence of alternans suggests that mechanisms other than V_m play a major role for the development of cardiac alternans. Indeed, there is growing evidence that alternans is initiated and sustained by disturbances of intracellular Ca^{2+} handling [17,50,51,53,54]. Major support for this hypothesis stems from the demonstration that Ca^{2+} alternans can be elicited in voltage-clamped ventricular myocytes where beat-to-beat V_m is kept constant. Recently we demonstrated that the same principle also holds for atrial myocytes (Fig. 3A) [17]. In addition, beat-to-beat alternation in AP morphology was abolished when intracellular Ca^{2+} release was blocked (Fig. 3B). These studies have provided strong evidence that AP alternations are not required for Ca^{2+} alternans to occur and thus instabilities of inherent Ca^{2+} handling properties of cardiac myocytes underlie cardiac alternans.

Several hypotheses on the mechanisms of Ca^{2+} alternans have been proposed. ***SR Ca^{2+} load hypothesis***. Under steady-state conditions influx of Ca^{2+} through LCCs, SR Ca^{2+} release, Ca^{2+} uptake by sarco/endoplasmic reticulum Ca^{2+} ATP-ase (SERCA) and extrusion from the cell by NCX are well balanced and therefore there is little beat-to-beat variation in diastolic $[Ca^{2+}]_{SR}$. If the balance between Ca^{2+} uptake and release is disturbed beat-to-beat

alternation in diastolic $[Ca^{2+}]_{SR}$ can occur. Consequently, due to the steep SR load – Ca^{2+} release relationship [55], a higher SR load would lead to a larger Ca^{2+} release and vice versa. In support of this hypothesis beat-to-beat alternations in diastolic SR Ca^{2+} load in conjunction with Ca^{2+} alternans have been reported by several studies [53,56]. However, contrary to these observations, cytosolic Ca^{2+} alternans occurring without significant beat-to-beat oscillations in diastolic SR load in single myocytes [57–59] and intact heart [60] was also demonstrated. These findings suggest that alternation in diastolic $[Ca^{2+}]_{SR}$ is not an obligatory condition for Ca^{2+} alternans to occur. Such observation was particularly common in atrial myocytes [57,59,61] and might be related to the higher activity of SERCA in the atrium [62–64] and therefore the higher capacity to refill the SR. ***L-type Ca^{2+} channel hypothesis***. LCCs are activated by AP-dependent membrane depolarization and serve as the trigger for SR Ca^{2+} release in a process known as Ca^{2+}-induced Ca^{2+} release (CICR). Importantly, the activity and inactivation of I_{LCC} is controlled by both voltage and $[Ca^{2+}]_i$ and these channels play a central role in the bi-directional coupling between V_m and intracellular Ca^{2+} dynamics. Therefore, incomplete recovery from inactivation of LCCs on a beat-to-beat basis has been proposed as a causative factor of Ca^{2+} alternans [56,65,66]. Partial inhibition of LCCs was indeed shown to increase susceptibility to Ca^{2+} alternans [53]. However numerous other studies have demonstrated that L-type Ca^{2+} currents can remain unchanged from beat to beat during Ca^{2+} alternans in both ventricular and atrial myocytes [17,51,53,57,59,67]. ***Refractoriness of ryanodine receptors (RyR) Ca^{2+} release hypothesis***. Finally, refractoriness of the SR Ca^{2+} release was suggested as a possible mechanism responsible for Ca^{2+} alternans [59,60]. In this case, it is hypothesized that Ca^{2+} alternans can arise due to varying beat-to-beat recovery from inactivation of RyR Ca^{2+} release channels of the SR. Since the magnitude of an intracellular Ca^{2+} release, referred as Ca^{2+} transient (CaT), is dictated by the number of activated RyRs, it is suggested that during a large CaT a larger number of RyRs is activated and therefore at high pacing rates these channels become unavailable for subsequent release resulting in a smaller CaT. The study of Shkryl et al. [54] demonstrated that in rabbit atrial myocytes a large amplitude CaT indeed prolongs RyR refractoriness and that the kinetics of RyR recovery from inactivation is a key factor in the generation of Ca^{2+} alternans. This hypothesis also found support from *in silico* simulations [68].

3. Differences between atrial and ventricular alternans

To date, the mechanisms of alternans have been investigated primarily in ventricular tissue and to a much lesser extent in atria. While it can be anticipated that mechanisms of alternans in atrial and ventricular cells share similarities, recent experimental data point towards important differences. For example, we reported subtle differences in APD alternans in atrial and ventricular rabbit myocytes where atrial myocytes exhibited a higher degree of beat-to-beat alternation in APD and a higher pacing frequency threshold to induce alternans [17].

The atria have unique structural properties that affect development of atrial alternans. The atrium has a complex geometry and regional structural features, such as the atrial appendages, the pectinate muscle network and specialized tissues like the sinus node, the Bachmann’s bundle and crista terminalis, as well as multiple orifices for veins, arteries, and valves, which play an important role in AF initiation and maintenance [69]. An important

difference between ventricular and atrial myocytes is also encountered at the single cell level. Atrial cells lack or have only a poorly or irregularly developed transversal tubule (t-tubule) system (Fig. 4A) [24,70,71], resulting in unique Ca^{2+} cycling features during ECC. T-tubules, deep invaginations of the sarcolemmal membrane, allows action potential penetration to the interior of the cell and ensures fast and uniform SR Ca^{2+} release in ventricular myocytes. In contrast, in atrial myocytes lacking t-tubules LCCs are restricted to the periphery of the cell and thus, membrane depolarization induced Ca^{2+} release first occurs in subsarcolemmal regions and subsequently propagates via CICR to the center of the cell (Fig. 4B) [72]. Computer simulations using cell models with and without t-tubules have predicted significant differences in possible alternans mechanisms [23,68,73]. The cardiac cell models lacking t-tubules exhibited higher likelihood to develop Ca^{2+} alternans and pointed towards the role of Ca^{2+} diffusion, inhomogeneity in $[Ca^{2+}]_i$ [73] and RyR refractoriness [68] in the process. This is consistent with experimental observations of intracellular gradients of the degree of Ca^{2+} alternans and that Ca^{2+} alternans can be spatially and temporally inhomogeneous even at the level of a single atrial myocyte and, in the extreme cases, subcellular regions can even alternate out-of-phase (Fig. 5) [57,61,74]. Another difference in Ca^{2+} handling between atrial and ventricular cells is the lower expression of phospholamban that leads to higher SERCA activity in the atria [62–64]. Since beat-to-beat fluctuation in SR Ca^{2+} load was proposed as a possible cause of Ca^{2+} alternans [53,75], it is conceivable that the lower SERCA activity in ventricle may contribute to Ca^{2+} alternans at increased pacing frequencies due to incomplete filling of the SR, whereas a more rapid filling is consistent with the observation that in atrial cells end-diastolic $[Ca^{2+}]_{SR}$ typically did not alternate during Ca^{2+} alternans [59,61]. This notion is also consistent with findings that upregulation of SERCA suppresses alternans in murine [76] and guinea pig [77] ventricular myocytes.

Furthermore, atrial and ventricle cells contain unique sets of ion channels [78,79] leading to distinctive AP morphologies and Ca^{2+}-dependent modulation of AP properties in these two cell types. For example, ventricle and atrium differ in activity of small-conductance Ca^{2+}-activated K^+ (SK) channels [80,81], Ca^{2+}-activated Cl^- channels [82], while acetylcholine-activated and ultrarapid rectifier K^+ channels are expressed exclusively in the atria [83–85]. Recently we demonstrated that Ca^{2+}-activated Cl^- channels play a major role in sustaining APD alternans in rabbit atrial cells [86]. Our data indicated that while these channels might be also important in ventricular alternans [87], atrial myocytes exhibit a higher density of this current that could explain in part the significantly higher degree of beat-to-beat alternation in APD in atrial myocytes [17]. In addition, atrial tissue displays substantial regional heterogeneity in conduction velocity (CV) and AP morphology, ranging from a triangular shape with no sustained plateau to ventricular like APs [88]. This phenomenon results in significant regional differences in electrical restitution and local intrinsic differences in rate-adaptation [88].

Finally, under pathological conditions such as heart failure, ischemia or during the progression of AF, the electrophysiological and structural properties of the atrium become significantly remodeled. Remodeling includes changes in CV [89,90], AP morphology and heterogeneity, intracellular Ca^{2+} signaling [91], ion channel expression [92,93] and fibrosis

[94]. All these changes are considered to be key factors that contribute to the development of sustained atrial arrhythmias.

4. Clinical relevance of cardiac alternans

To this date the majority of clinical data that relates cardiac alternans and arrhythmias was obtained in ventricle. The beat-to-beat alternations in the time course of ventricular AP repolarization are reflected in the ECG as T-wave alternans (TWA). Even subtle TWA at microvolt levels (referred to as microvolt TWA) was demonstrated as a valuable prognostic tool for ventricular arrhythmia risk stratification [95]. The clinical use of atrial AP repolarization alternans as a diagnostic tool, however, is hindered by the fact that the atrial repolarization signal is masked in the conventional ECG recordings by the ventricular QRS complex and therefore the clinical exploitation of the relationship between atrial alter-nans and the development of atrial arrhythmias for risk assessment has been limited. However, recently progress has been made in several experimental [12,90,96] and clinical studies [7,8,11,97,98] using monophasic AP electrodes to monitor atrial repolarization alternans in vivo. These and other studies involving computer simulations [99], animal models [12,90,96,100] and studies in humans [7,8,11,97,98] have provided convincing evidence that AP alternans in atria may lead directly to AF (Fig. 6) or its transition from atrial flutter. In addition, newer clinical studies have demonstrated that atrial repolarization alternans, similarly to ventricular TWA, can be used to predict vulnerability to AF [11,98]. For example, Narayan et al. [11] have demonstrated that APD alternans preceded AF episodes, while APD alternans was absent in subjects with no AF. Furthermore, in patients with persistent AF APD alternans was typically induced at relatively low pacing rates (100–120 bpm). In contrast, in control subjects alternans developed only at rapid pacing rates (>230 bpm) indicating that atrial repolarization alternans has potential as a prognostic tool to identify susceptibility to atrial arrhythmias. Similarly, Lalani et al. [98] established that AP alternans was larger and more prevalent in patients with persistent AF than in subjects with paroxysmal AF, while alternans was not observed in the control group. Taken together, evidence is accumulating that AP alternans in both ventricle and atrium precedes development of fibrillation, and thus, has prognostic value for arrhythmia prediction.

The mechanisms linking AP alternans to ventricular arrhythmias involve the development of spatially discordant alternans [101–104]. Usually AP alternans starts as concordant alternans, i.e. APD either prolongs or shortens simultaneously in all cells of a particular region of the ventricular myocardium. Concordant AP alternans itself may not exacerbate into fibrillation, i.e. its arrhythmogenic potential is relatively low. However, as development of alternans progresses, AP alternation can turn discordant where different regions of the heart alternate out-of-phase, i.e. in some regions APD is prolonged while during the same beat APD is shortened in other regions of the heart. Development of discordant alternans is believed to have major effects on the spatial organization of repolarization across the cardiac tissue and significantly contributes to arrhythmogenicity [101–104]. This notion is supported experimentally by the demonstration that ventricular fibrillation is always preceded by discordant AP alternans [102]. Similarly to findings in ventricle, discordant alternans was also observed in atria and has been directly linked to the development of atrial fibrillation [7,12,96]. The underlying mechanisms for the formation of spatially discordant alternans

remain uncertain and most likely are determined by the combination of factors that are discussed below.

5. Mechanisms of spatially discordant alternans

Several mechanisms for discordant alternans have been suggested that revolve around Ca^{2+} cycling, cell-to-cell communication and electrical tissue properties.

5.1. Calcium cycling heterogeneity

As discussed above disturbances in intracellular Ca^{2+} handling have been proposed as an underlying mechanism of alternans at the cellular level [17,32,50,51,53,54,75]. Spatial heterogeneities in electrical as well as Ca^{2+} cycling properties of cardiac tissue between the endocardium and epicardium or between the base and apex of the heart are essential for maintaining normal function of the heart [105,106], including excitation spread and coordinated contractility. However, under pathological conditions, such heterogeneity in Ca^{2+} cyclingcan lead to the development of spatially discordant Ca^{2+} alternans. Furthermore, since $[Ca^{2+}]_i$ dynamics feedback on ion conductances of myocytes and thus in turn affect APD, the heterogeneity in Ca^{2+} handling contributes to spatial differences in AP morphology as well. Additional support for Ca^{2+}-dependent development of discordant alternans comes from computational models, demonstrating that discordant APD alternans can be induced if $[Ca^{2+}]_i \rightarrow V_m$ coupling results in APD shortening [107] or, alternatively, by SR Ca^{2+} accumulation during rapid pacing [108]. Furthermore, suppression of intracellular Ca^{2+} release from SR by ryanodine significantly reduces development of spatially discordant alternans during tachypacing induced cardiomyopathy in transgenic rabbits with Long QT type-1 syndrome [49]. The aforementioned insights come from ventricular tissue, however experimental evidence that heterogeneity in Ca^{2+} cycling underlies generation of discordant alternans also in atria is still lacking.

5.2. Insufficient cell-to-cell coupling

Cardiac myocytes are electrically coupled via gap junctions that allow the flow of ionic currents between cells. In the heart, different isoforms of gap junction forming proteins connexins exhibit regional expression. While in the ventricle electrical coupling between myocytes is achieved almost exclusively by connexin 43 (Cx43), in the atria three types of connexins are expressed – Cx40, Cx43 and Cx45 (with levels of Cx45 being very low). A strong coupling between myocytes results in well-coordinated and relatively homogeneous repolarization of the cardiac tissue. However, in various pathological situations decreased gap junction expression and/or increased inhomogeneity of gap junction distribution in both ventricle and atrium occurs [109]. In humans with AF and in AF animal models altered expression and distribution of atrial Cx40 is well documented which can lead to dispersed conduction and thus formation of a substrate for atrial arrhythmias [93,109]. Furthermore, pharmacological enhancement of intercellular coupling effectively suppressed development of discordant alternans, and decreased susceptibility to ventricular arrhythmias [101] and atrial fibrillation [110]. In addition to the changes in connexin expression, cell-to-cell coupling can be disrupted also by increased fibrosis of the tissue. While insufficient coupling between cells is likely to contribute to increased susceptibility to arrhythmias in

remodeled myocardium, it can hardly explain development of discordant alternans in relatively healthy hearts with normal intercellular coupling. Also, it is noteworthy that cardiomyocytes have a large safety margin with respect to cell-to-cell coupling, i.e. the myocardium maintains near normal conduction velocities even when electrical coupling is significantly reduced [111]. Therefore, it is unlikely that moderate reduction in gap junction protein levels alone is sufficient for induction of cardiac arrhythmias. However, decreased intercellular coupling may amplify cell-to-cell differences in AP morphology, conduction velocity and Ca^{2+} cycling which in turn facilitates the development of spatially discordant alternans and arrhythmic events.

5.3. Conduction velocity and APD restitution

Computer modeling studies predict that impairment of CV or APD restitution can result in discordant alternans [22,47]. CV restitution refers to the relationship between CV and the preceding diastolic interval. In cardiac tissue CV is determined by intercellular electric coupling and the activity and kinetics of Na^+ channels which drive the upstroke of cardiac APs. Under normal conditions recovery of Na^+ channels from inactivation is fast and thus slowing of CV is observed only at very fast beating rates, however slowing of CV was demonstrated in several pathological conditions including AF [89,90]. Data addressing the relationship between CV and APD restitution heterogeneities and development of alternans in atria are scarce. Heterogeneous and slower CV together with prolongated and spatially dispersed APDs were demonstrated in atria of diabetic rats and these changes were associated with the increased inducibility of APD alternans and susceptibility to atrial tachyarrhythmias [112]. Also, the spatial dispersion of APD restitution was significantly increased in a canine vagally mediated AF model and in rapid pacing-induced AF [100]. Similarly, a greater spatial dispersion of APD restitution kinetics was reported in patients with chronic AF compared to patients with paroxysmal AF and control subjects [10].

6. Conclusions

While numerous clinical and animal research data obtained in ventricular tissue have greatly contributed to the understanding of putative mechanisms of alternans and their relation to ventricular arrhythmias, alternans in atrial tissue remains much less investigated. The availability of clinical data on atrial alternans is hindered by the fact that measurements of atrial repolarization require invasive methods as atrial repolarization is masked by electrical activity of ventricles in the conventional ECGs. The available clinical data, however, suggest that alternans plays a vital role in AF. In this review we summarized the current knowledge about mechanisms of alternans and their relevance to arrhythmogenesis in atria.

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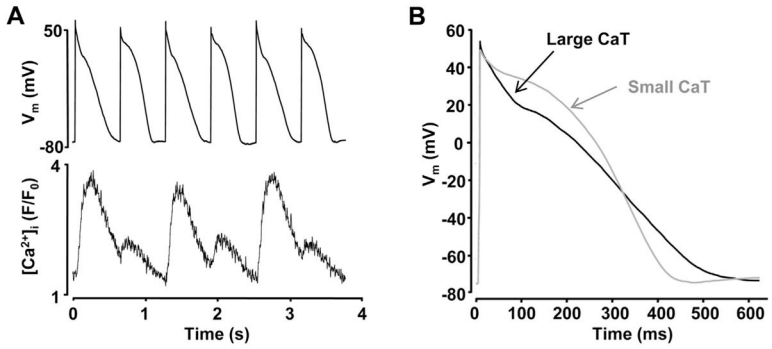

Fig. 1.

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].

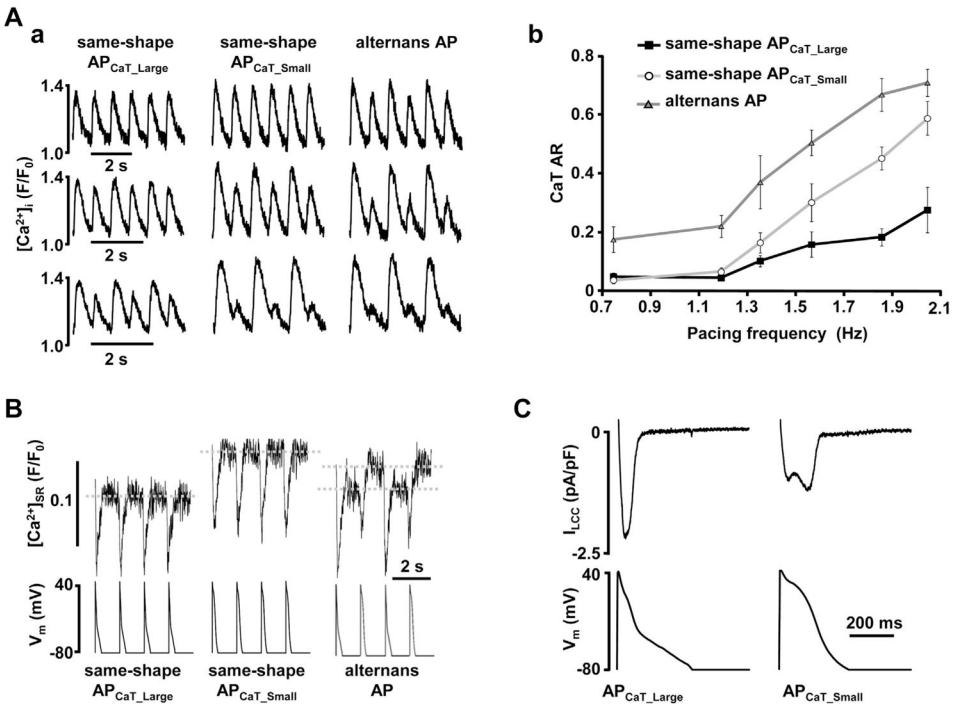

Fig. 2.

Membrane potential determines calcium alternans through modulation of sarcoplasmic reticulum Ca^{2+} load and L-type Ca^{2+} current.

Two distinct AP-like voltage commands were generated from prerecorded atrial APs observed during Ca^{2+} alternans: AP_{CaT_Large} (observed during large systolic Ca^{2+} release) and AP_{CaT_Small} (observed during small CaTs). Morphology of these voltage commands is shown on the bottom of panel C. Sequences with only AP_{CaT_Large}, only AP_{CaT_Small} or alternating AP waveforms (as shown in B bottom) were applied to rabbit atrial myocytes. (A) (a) CaTs elicited in the same voltage-clamped atrial myocyte stimulated with different sequences of AP waveforms at various pacing frequencies. (b) Pacing with same- shape AP_{CaT_Small} waveforms (open circles) enhances degree of CaT alternans compared to AP_{CaT_Large} stimuli (black squares). CaT alternans ratio (AR, where 0 indicates conditions without alternans and 1 indicates a full skipping of Ca^{2+} release on every other beat) is further increased during alternans AP voltage clamp protocol (grey triangles). (B) Sarcoplasmic reticulum Ca^{2+} load ($[Ca^{2+}]_{SR}$) measurements with Fluo-5N from the same voltage-clamped atrial myocyte exposed to three different AP clamp protocols (bottom). End-diastolic $[Ca^{2+}]_{SR}$ was higher during the same-shape AP_{CaT_Small} protocol compared to AP_{CaT_Large} and revealed $[Ca^{2+}]_{SR}$ alternans during the alternans AP clamp protocol. (C) Representative traces of L-type Ca^{2+} currents elicited with AP_{CaT_Large} and AP_{CaT_Small} voltage commands from the same atrial myocyte.

Figure modified with permission from [52].

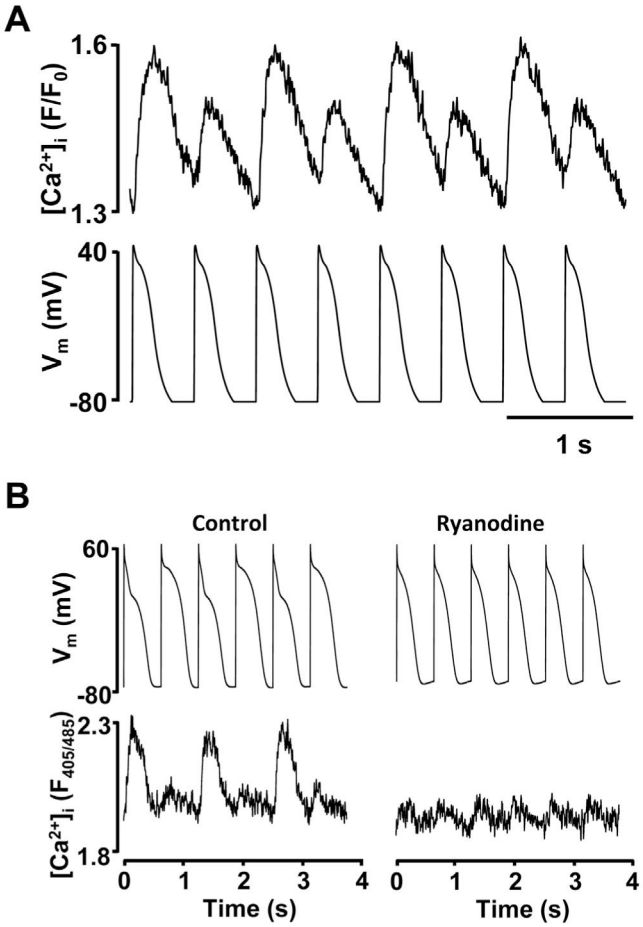

Fig. 3.

Disturbances in intracellular Ca^{2+} cycling as a key mechanism for the development of alternans.

(A) Ca^{2+} transient alternans recorded in voltage-clamped atrial myocytes under AP-clamp conditions when beat-to-beat V_m is kept constant. (B) Inhibition of cytosolic Ca^{2+} release by ryanodine abolishes AP alternans. APs and $[Ca^{2+}]_i$ recorded simultaneously from a current-clamped atrial myocyte.

Panel B is from [17].

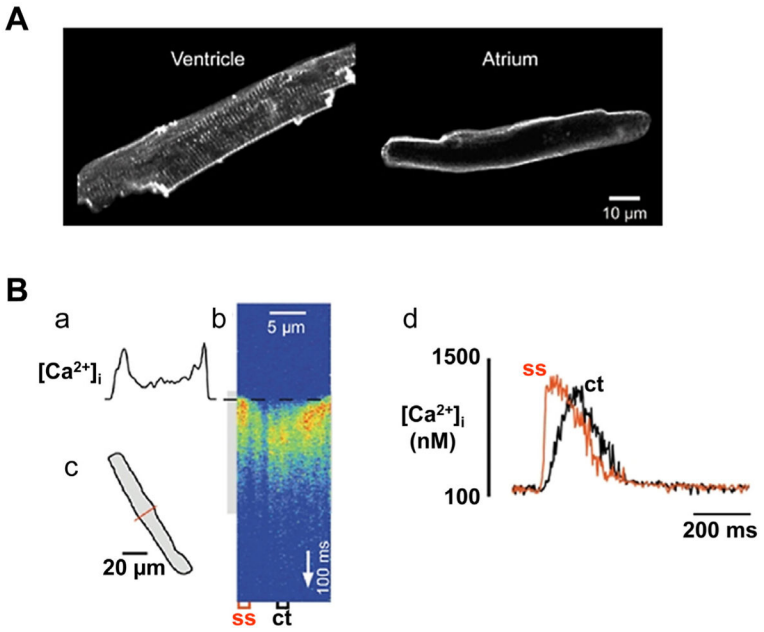

Fig. 4.

Ca^{2+} signaling during excitation-contraction coupling in atrial myocytes.

(A) Confocal images of a ventricular and an atrial myocyte from the same cat heart stained with the membrane-bound fluorescent dye Di-8-ANEPPS. The regular structures spaced in a sarcomeric pattern in the ventricular cell represent t-tubules. In contrast, the atrial myocyte is devoid of any t-tubular staining. (B) Ca^{2+} transient recorded in the confocal linescan mode. The scanned line was positioned perpendicular to the longitudinal axis of the cell (c). Electrical stimulation of the cell during acquisition of the linescan image triggered a 'U'-shaped Ca^{2+} transient (b), indicating that $[Ca^{2+}]_i$ increased first at the periphery of the cell (a) before propagating towards the center of the myocyte. Panel d shows local Ca^{2+} transients measured in the subsarcolemmal space (ss) and the center of the cell (ct).

The Figure is modified with permission from [72].

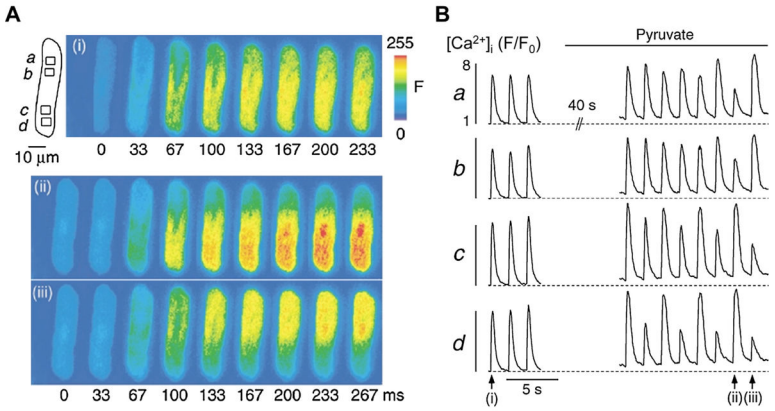

Fig. 5.

Neighboring regions within an atrial myocyte can alternate out-of-phase.

(A) Series of fluo-4 fluorescence images recorded under control conditions and during Ca^{2+} alternans. The images illustrate the rising phase of the Ca^{2+} transients marked by the arrows in (B). (B) Subcellular Ca^{2+} transients recorded from the regions marked by the boxes a–d (A). $[Ca^{2+}]_i$ images and subcellular Ca^{2+} transients reveal that the time of onset, the magnitude, and the phase of Ca^{2+} alternans exhibit large subcellular variations and that the upper and the lower half of the cell alternate out-of-phase.

The Figure is modified with permission from [74].

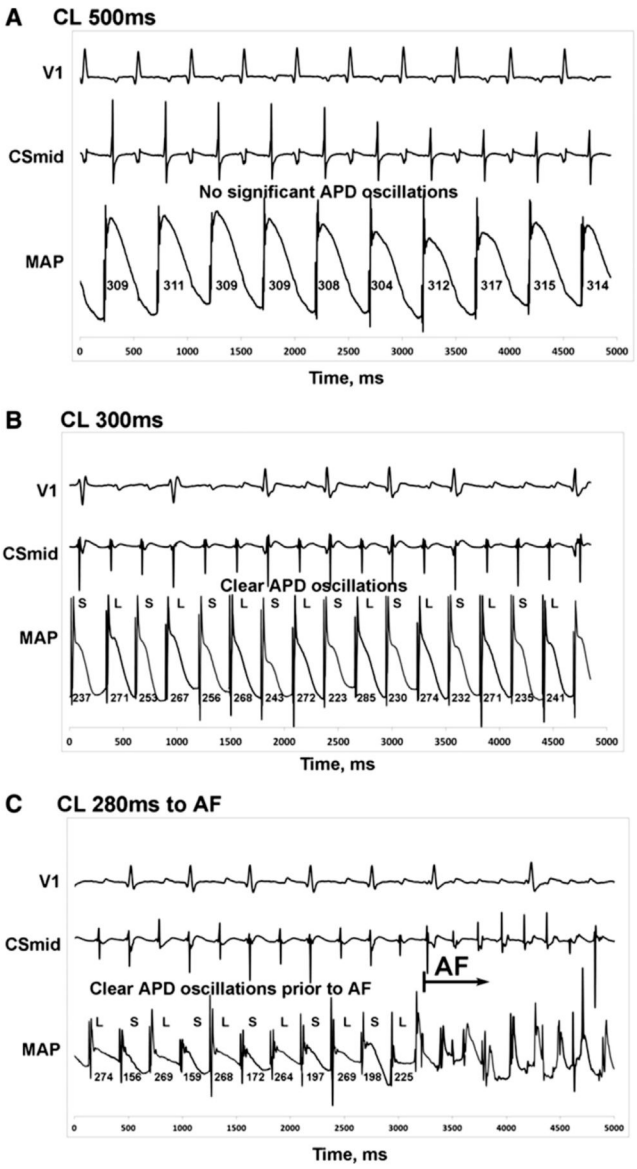

Fig. 6.

Atrial alternans precedes initiation of atrial fibrillation.

Rate dependence of AP alternans in a 61-year-old male patient with paroxysmal atrial fibrillation. (A) No significant atrial AP alternans is observed at baseline pacing with cycle length (CL) of 500 ms. (B) At CL 300 ms, APD alternans is observed. (C) APD alternans were detectable and preceded AF initiation while pacing at CL 280 ms. V1, first ECG precordial lead; CSmid, middle coronary sinus; MAP, monophasic action potential. Figure is modified with permission from [98].