Mechanisms of Cardiac Alternans in Atrial Cells
Intracellular Ca\textsuperscript{2+} Disturbances Lead the Way
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Cardiac alternans, in the form of microvolt T-wave alternans, is an important clinical sign of heart disease that frequently emerges as a diagnostic manifestation of disease severity in cardiomyopathies such as heart failure, coronary artery disease, genetic and acquired channelopathies, and even in electrolyte disturbances of the body. During cardiac alternans, there is a beat-to-beat oscillation between strong and weak contractions, and although the heart keeps a regular pace, cardiac alternans ultimately spawns lethal arrhythmias, serving as a valuable risk stratification factor for sudden cardiac death and helping guide arrhythmia treatment.

The prominence of membrane currents in the genesis of cardiac alternans was demonstrated as early as 1968 by Nolasco and Dahlen in their classical experiments of APD restitution. They observed that in electrically paced frog ventricular muscle strips, APD shortened as they accelerated the pacing rate. This phenomenon appears to logic because the cardiac cycle length decreases considerably during increased metabolic demand, and it must do so by means of shortening both, APD and diastolic interval (DI). Typically, DI has a higher dynamic range because during a 1-s cardiac cycle it lasts \textapprox 700 ms (versus \textapprox 300 ms for APD), giving the heart sufficient time to refill the ventricles with oxygenated blood before the next beat. If DI is longer than APD, then membrane currents that require transit through inactivated or refractory states, most notably L-type Ca\textsuperscript{2+} channels (LTCC) and voltage-dependent Na\textsuperscript{+} channels, have time to recover and get primed for full activation in the next cycle, effectively allowing for complete restitution of the APD. However, if DI shortens to the point of being briefer than APD, then incomplete recovery of membrane currents from inactivation can occur, providing a substrate for instabilities in AP dynamics. Thus, a linear relationship between APD and DI may be built, the slope of which (APD restitution) is lower than 1 for cells that are dynamically stable (ie, displaying uniform APD). On the contrary, if the slope steepens and is experimentally forced to be >1, as in Nolasco and Dahlen, then APD can oscillate in a short–long pattern on a beat-to-beat basis, giving rise to APD alternans. Hence, we can derive from these experiments an unequivocal participation of APD restitution in the genesis of cardiac alternans, but because APD is inextricably linked to CaT dynamics (see below), CaT alternans quickly follows APD alternans.

A strong case for CaT disorders being the primary force underlying cardiac alternans may be derived from physiological settings and the more common observation that APD alternans starts to develop before the DI becomes shorter than APD (ie, the slope of APD restitution is <1 in most cases). DI lasts longer than the time that is presumably needed to reprim all inactivated membrane currents. It follows, therefore, that the observed APD alternans must trail CaT disturbances (this is even more pronounced in pathological settings with prominent intracellular Ca\textsuperscript{2+} mishandling such as heart failure and underscores the power of cardiac alternans as an index of disease severity). Even more compelling is the fact that APD alternans quickly vanishes in ryanodine-treated cells, which have negligible sarcoplasmic reticulum (SR) Ca\textsuperscript{2+} load and thus exhibit low-amplitude CaTs, despite normal Ca\textsuperscript{2+} entry. That APD alternans disappears in the absence of intracellular Ca\textsuperscript{2+} release would be unexpected if the former originated from processes devised by, completely contained in, and inherent to, the electric properties of the membrane. However, this observation is possible in cells where the information between membrane voltage (V\textsubscript{m}), intracellular Ca\textsuperscript{2+} ([Ca\textsuperscript{2+}]) flows both ways, and both processes are intertwined so radically that modifications to one inevitably affect the other. Thus, we are back to the original question because therein, in the bidirectional coupling between V\textsubscript{m} and [Ca\textsuperscript{2+}], lies the classical conundrum of electromechanical alternans: does CaT alternans lead or lag APD alternans?

In this issue of Circulation Research, Kanaporis and Blatter performed elegant experiments in isolated rabbit atrial and ventricular myocytes to determine whether failure of...
CaT regulation or disturbance in AP modulation is the primary instigator of cardiac alternans. As discussed in the preceding sections, the question has been addressed before in several experimental and computer modeling settings, and although each study has taken the issue a step ahead, there are still nagging controversies, reflecting the complexity of the subject. Kanaporis and Blatter used a clever approach wherein they first induced alternans by pacing cells at a progressively faster frequency, captured the AP waveform during the elicited APD alternans, and then applied identical APD oscillations at various pacing rates to measure intracellular CaT dynamics. Besides determining the precise sequential order (if any) at which APD or CaT alternans first appeared, these technically demanding experiments allowed them to test whether CaT alternans was enslaved to APD alternans, as would be indicated if a low-amplitude CaT alternans dependably proceeded from a short-duration APD alternans, and vice versa, a high-amplitude CaT alternans would be followed by a long-duration APD alternans. This would hint, albeit not exclusively, that CaT amplitude CaT alternans would be followed by a long-duration APD alternans, and vice versa, a high-amplitude CaT alternans can emerge even in the absence of APD alternans (by constant shape APs), and that AP clamp protocols in the form of APD alternans do not necessarily lead to CaT alternans. Moreover, when APD alternans did elicit CaT alternans, the amplitude of the latter could be completely divorced from the duration of the leading APD alternans (ie, a high-amplitude or a low-amplitude CaT alternans could arbitrarily accompany a short APD alternans). Finally, APD alternans was shown to be dependent on CaT alternans in cells in which SR Ca2+ release was suppressed by ryanodine. Altogether, the results indicate that a CaT alternans can have a life of its own and take precedence as causative link to APD alternans.

To be real, the novelty of the experiments of Kanaporis and Blatter resides in the analysis of alternans in atrial cells, which is newer, and their systematic comparison with those in ventricular cells, which stand on a more beaten path. Determining the mechanisms of alternans in atrial cells is timely now that atrial fibrillation has emerged as a disease of epidemic proportions. Atrial cells are similar to ventricular cells in the 3 fundamental events of cardiomyocyte physiology, but finer structural and functional attributes may presage differences in the onset, intensity, and duration of alternans between these 2 cell types. T-tubules are poorly organized or conspicuously absent in atrial cells, and SERCA activity is higher because of lower expression of phospholamban. These differences are expected to decrease the coupling efficiency between Ca2+ release channels/ryanodine receptors and LTCCs and to refill the SR more rapidly, both of which should impinge profoundly on the aforementioned Vm ↔ [Ca2+]i coupling of atrial and ventricular cells. Instead, Kanaporis and Blatter found that CaT alternans can emerge even in the absence of APD alternans (by constant shape APs), and that AP clamp protocols in the form of APD alternans do not necessarily lead to CaT alternans. Moreover, when APD alternans did elicit CaT alternans, the amplitude of the latter could be completely divorced from the duration of the leading APD alternans (ie, a high-amplitude or a low-amplitude CaT alternans could arbitrarily accompany a short APD alternans). Finally, APD alternans was shown to be dependent on CaT alternans in cells in which SR Ca2+ release was suppressed by ryanodine. Altogether, the results indicate that a CaT alternans can have a life of its own and take precedence as causative link to APD alternans.
ventricular layers of intact hearts may play an equally critical role in atrial tissue.

Sources of Funding
Dr Valdivia is a recipient of National Institutes of Health grants RO1-HL055438, RO1-HL108175, and RO1-HL120108.

Disclosures
None.

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Key Words: Editorials • atrial fibrillation • calcium signaling • myocardium • ryanodine receptor calcium release channel
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Circ Res. 2015;116:778-780
doi: 10.1161/CIRCRESAHA.115.305923

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/116/5/778

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