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Mitochondrial dysfunction: a new frontier in the search for elusive arrhythmia mechanisms

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A commentary on

The role of mitochondria for the regulation of cardiac alternans.
by Florea, S. M., and Blatter, L. A. (2010). Front. Physio. 1:141. doi:10.3389/fphys.2010.00141.

Mitochondria have long been recognized for their importance in energy production and apoptosis. More recently, seminal work in various laboratories has extended the role of cardiac mitochondria from relatively static arbitrators of cell death and survival pathways to highly dynamic organelles that formed interactive networks across cardiomyocytes. These coupled networks were shown to strongly affect cardiomyocyte responses to oxidative stress by modulating key cell signaling pathways that strongly impacted physiological properties (Dedkova and Blatter, 2008; Aon, 2010; O'Rourke, 2010). Of particular importance is the role of mitochondria in storing and releasing intracellular calcium, which in turn, modulates excitation–contraction coupling and electrophysiological properties either directly or indirectly by affecting cell signaling cascades and ATP levels (Dedkova and Blatter, 2008). This important recognition has ushered a renewed interest in understanding, at a more fundamental level, the exact role that cardiac metabolism, in general and mitochondria, in particular, play in both health and disease. As a result, the journal "*Frontiers in Mitochondrial Physiology*" was born (Aon, 2010; O'Rourke, 2010).

O'Rourke and colleagues demonstrated that mitochondria formed networks of weakly coupled oscillators that spanned the entire cardiomyocyte (Aon et al., 2003). Upon reaching a critical level of oxidative stress, these networks exhibited emergent behavior that rapidly led to synchronized cell wide oscillations of the mitochondrial membrane potential, a key metric of mitochondrial function, and ATP production (Aon et al., 2003). This, in turn, resulted in cyclical oscillations of the cellular action potential via activation of the surface K-ATP current. Furthermore, spatially heterogeneous areas in tissue excitability during conditions that promoted mitochondrial membrane potential collapse led to the formation of conduction block via a mechanism which was termed metabolic sink (Akar et al., 2005; Aon, 2010). This form of conduction failure caused the genesis of sustained arrhythmias upon reperfusion (Akar et al., 2005; Aon, 2010).

In this issue of the *Journal*, Florea and Blatter demonstrate yet another mechanism by which mitochondrial membrane potential depolarization may lead to the genesis of arrhythmias, this time through a completely distinct mechanism that involves the formation of a beat-to-beat oscillatory behavior of the intracellular calcium transient. Using a highly systematic approach, these authors nicely demonstrated how disruption of mitochondrial energetics at various levels within the electron transport chain always led to a predictable increase in calcium transient alternans during steady state pacing of atrial myocytes. As such, these findings assigned another important role for cardiac mitochondria as mediators of a pathophysiological parameter (alternans) known to foreshadow the genesis of sudden death.

A MITOCHONDRIAL BASIS FOR ALTERNANS

T-wave alternans is defined as a beat-to-beat fluctuation in the polarity and/or amplitude of the T-wave, a global marker of ventricular repolarization on the surface electrocardiogram (Rosenbaum et al., 1994). The importance of this electrocardiographic feature stems from its strong association with vulnerability to sudden cardiac death (Rosenbaum et al., 1994). During the past decade, Rosenbaum and colleagues identified a mechanistic link between repolarization alternans and the genesis of ventricular fibrillation at the tissue level (Pastore et al., 1999). Specifically, they showed that conversion of concordant alternans to spatially discordant alternans markedly enhanced repolarization gradients across the heart, providing a suitable substrate for the initiation of ventricular fibrillation (Pastore et al., 1999).

Cellular mechanisms that promote the formation of repolarization alternans, include spatially heterogeneous ion channel and restitution properties, reduced cell-to-cell coupling, and abnormal intracellular calcium cycling (Wilson and Rosenbaum, 2007). The latter was identified as being especially important considering its prevalence in structural heart diseases that are strongly associated with alternans and sudden death. Also, because calcium transient alternans typically occurs before repolarization alternans, a dependence of the latter upon the former is implied. In this issue of the *Journal*, Florea and Blatter (2010) enhance our mechanistic understanding of calcium transient alternans by demonstrating their strong dependence on the state of mitochondrial energetics through a series of elegant experiments in which calcium transients were imaged while the authors systematically altered mitochondrial function.

Mitochondrial dysfunction can lead to calcium transient alternans either by depleting ATP levels and therefore adversely affecting the function of energy consuming calcium pumps, transporters, and exchangers or by altering the capacity of the mitochondrial network to uptake and store calcium on a beat-by-beat basis. Mitochondria are localized in close physical proximity to the main sites of excitation–contraction coupling (Dorn and Scorrano, 2010). This close physical interaction has recently been suggested to play an important functional role in modulating calcium cycling and contractility within the myocyte (Maack and O'Rourke, 2007). Indeed, various groups have elegantly demonstrated the ability of mitochondria to uptake relatively large amounts of calcium (Maack and

O'Rourke, 2007). While the exact magnitude and kinetics of mitochondrial calcium transients remain a subject of debate and active investigation (O'Rourke and Blatter, 2009), it is becoming clear that the mitochondrial network can compete with the sarcoplasmic reticulum (SR) for calcium uptake, potentially on a beat by beat basis.

A major finding of the present report by Florea and Blatter (2010) is that the presence of calcium alternans was independent of beat-to-beat changes in SR calcium load. This argues in favor of disrupted mitochondrial energy production and not competing uptake of calcium by mitochondria on a beat-by-beat basis in the promotion of alternans. Surprisingly, the kinetics of intracellular calcium transient decay were not altered indicating that the activity of SERCA2a, which mediates the reuptake of calcium into the SR following each heart beat, was not adversely affected by reduced ATP levels. This highlights the potential importance of other calcium fluxes, such as those through the Ryanodine receptor or the L-type calcium channel, in mitochondrially driven calcium alternans. A comprehensive investigation into mechanisms by which altered energy production affects a wide spectrum of cellular calcium fluxes is warranted in light of these exciting findings.

Finally, simultaneous measurements of intracellular and mitochondrial calcium transients under conditions the promote alternans would go a long way in improving our understanding of the mitochondrial basis of this pathophysiological phenomenon by testing the nature and extent of functional interactions between the SR and mitochondrial networks. For example, do mitochondrial calcium transients exhibit alternans behavior under the same conditions of mitochondrial energy depletion that lead to intracellular calcium transient alternans? And if so, are mitochondrial calcium alternans discordant with intracellular calcium alternans? It is important to note that these fundamental relationships may be markedly altered in chronic disease states that alter the subcellular architecture of the mitochondrial network.

THERAPEUTIC IMPLICATIONS

The strategic subcellular localization of the mitochondrial network in close spatial proximity to the SR network strongly suggests a close functional interaction between these main sites of energy production and calcium cycling (Dorn and Scorrano, 2010). Despite this knowledge, the importance of this physical interaction to the pathogenesis of calcium mediated arrhythmias has remained speculative. In this issue of the *Journal*, Florea and Blatter (2010) present highly compelling evidence that this physical interaction indeed translates into a tight functional interaction which can promote arrhythmogenic calcium transient alternans. A growing appreciation of the role of defective mitochondrial energetics in arrhythmogenesis will hopefully allow for the development of novel therapeutic strategies that target upstream pathways rather than downstream effectors of electrical dysfunction.

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