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Background calcium influx in arrhythmia: lead actor or extra?

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Sequel to the seminal experiments by Ringer in 1883, Ca^{2+} has been established as the critical intermediary pairing excitation and contraction in cardiac myocytes, an integral feature for the efficient functioning of the heart (Eisner et al., 2017). Owing to this critical role of Ca^{2+} in cardiac physiology, it is no surprise that impaired Ca^{2+} homeostasis is implicated in the pathophysiology of a plethora of cardiac disorders.

In cardiac myocytes, Ca^{2+} influx mainly through the L-type Ca^{2+} channel prompts a robust increase in cytosolic Ca^{2+} by triggering the release of Ca^{2+} from the sarcoplasmic reticulum (SR) via the type 2 ryanodine receptor (RyR2). The elevated cytosolic Ca^{2+} interacts with the myofilaments to induce myocyte contraction, after which the increased level of cytosolic Ca^{2+} is depleted through active removal of Ca^{2+} by the sodium-calcium exchanger (NCX) and sarcoplasmic reticulum Ca^{2+} ATPase (SERCA) (Eisner et al., 2017). In pathophysiological conditions, SR Ca^{2+} release events may also occur independently of L-type Ca^{2+} channel flux. These spontaneous SR Ca^{2+} releases could present as abnormal Ca^{2+} waves, which facilitate arrhythmic afterdepolarizations (Voigt et al., 2012). Albeit other mechanisms including defective RyR2 and increased SERCA function, these spontaneous Ca^{2+} releases could be provoked by Ca^{2+} overload of the cardiac myocytes. This overload causes an increase in the SR Ca^{2+} content beyond the threshold for SR Ca^{2+} release, prompting the spontaneous discharge of Ca^{2+} from the SR (Eisner et al., 2017).

In this issue, Hutchings et al., (2022) provided relevant insight into mechanisms underlying the abnormal SR Ca^{2+} release mediated by Ca^{2+} overload using a sheep heart failure model, highlighting the contribution of background influx to this phenomenon. The authors adopted the often-used elevation of extracellular Ca^{2+} concentration to induce cytosolic Ca^{2+} overload in ventricular myocytes. In addition, Hutchings et al., (2022) evaluated the mechanisms by which this commonly used but poorly understood strategy causes the overload of the SR with Ca^{2+} . Interestingly, background influx of Ca^{2+} , not Ca^{2+} entry via the L-type Ca^{2+} channel nor NCX, was identified to account for the induced SR Ca^{2+} overload. Further intriguing is the observation that the myocytes from heart failure animals demonstrated higher vulnerability to arrhythmic Ca^{2+} waves, with the increased vulnerability attributed to the larger background Ca^{2+} influx and lowered SR Ca^{2+} threshold observed in these myocytes. The findings of this study are indeed fascinating and timely, suggesting a potential arrhythmic role of background Ca^{2+} influx.

Background Ca^{2+} influx denotes Ca^{2+} entry into myocytes in an unstimulated or resting state. Mechanisms mediating this background Ca^{2+} influx are still fragmentary; however, connexin hemichannels, STIM1-mediated Ca^{2+} entry and transient receptor potential canonical (TRPC) channels have been documented to contribute to this background entry of Ca^{2+}

(Hulot et al., 2011; Hutchings et al., 2022). Interestingly, in addition to the study outcomes exempting the contribution of NCX to the observed background Ca^{2+} influx via its reverse mode $\text{Na}^+/\text{Ca}^{2+}$ exchange, Hutchings et al., (2022) demonstrated that connexins and some members of the TRPC family, i.e. TRPC1/4/5, did not contribute to the background influx responsible for the SR Ca^{2+} overload in the sheep ventricular myocytes. Instead, TRPC6 was found to be a key contributor to the background Ca^{2+} entry in ventricular myocytes exposed to elevated extracellular Ca^{2+} . As rightly highlighted by the authors, the elevated extracellular Ca^{2+} limits the transferability of these findings to normal physiological conditions, including its implication *in vivo*. However, the singular fact that the heart failure myocytes exhibited a proarrhythmogenic phenotype partly potentiated by a high background influx, justifies a questioning of the contributory role of background Ca^{2+} influx to the pathomechanism of atrial fibrillation (AF), the most common arrhythmia observed in clinical practice.

As established in heart failure, AF is also associated with spontaneous SR Ca^{2+} releases. In paroxysmal AF, increased open probability of RyR2 and increased SR Ca^{2+} content were identified as the culprits driving spontaneous Ca^{2+} releases in human atrial myocytes. Although an increased SERCA activity was suggested to be the underlying molecular mechanism responsible for the culprits above (Voigt et al., 2014), possibly by increasing the SR Ca^{2+} content beyond its threshold, other mechanisms may also be involved. Furthermore, since the two Ca^{2+} influx sources, i.e. L-type Ca^{2+} channel and NCX, that could contribute to the elevated SR Ca^{2+} content are unchanged in atrial myocytes from patients with paroxysmal AF (Voigt et al., 2014), deciphering a possible role of background influx in the observed increased SR Ca^{2+} content would be an interesting prospect. Similarly, atrial myocytes from patients with long term persistent (chronic) AF (cAF) also exhibit a high incidence of spontaneous Ca^{2+} releases and its consequential delayed afterdepolarizations (Voigt et al., 2012). Increased phosphorylation of the RyR2 is a major reason for the spontaneous SR Ca^{2+} releases observed in these myocytes. However, notwithstanding the increased SR Ca^{2+} leak in myocytes from cAF patients, a known mechanism that could deplete SR Ca^{2+} levels, the SR Ca^{2+} content of these myocytes were identical in cAF patients compared to control patients. Therefore, with Hutchings et al. demonstrating the influence of background influx on SR Ca^{2+} content, it is conceivable to question if background Ca^{2+} influx could contribute to the maintenance of the comparable SR Ca^{2+} load seen in myocytes of cAF patients.

Nevertheless, although our suggestions on the possible role of background influx in the pathophysiology of AF remain highly speculative, what remains certain is that the findings of

Hutchings et al., (2022), pose an important question of whether background Ca^{2+} influx could be a "lead actor" in the "cinematic" pathophysiology of arrhythmia, or an insignificant "extra". Therefore, further research is necessary to establish the role of background Ca^{2+} influx in this "movie" called arrhythmia.

Conflict of interest: none declared.

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