Repolarization Reserve and Action Potential Dynamics in Failing Myocytes

See Article by Hegyi et al

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Prolongation of action potential duration (APD) is typically observed in isolated myocytes from both humans and animals with heart failure (HF) and is generally thought to be an important arrhythmia substrate. Traditionally, voltage-clamp studies have found that in addition to increased Na^+/Ca^{2+} exchange and late Na^+ currents, repolarizing currents, including the inward rectifier K^+ (I_{K1}) and delayed rectifier K^+ (I_{Ks}, I_{Kr}) currents, are decreased in HF.[1,2] These changes are expected to significantly prolong repolarization; however, this is not often observed at faster beating rates in failing myocytes[3] and HF patients.[4] In this issue of the Journal, Hegyi et al[5] contend that more physiological conditions are required to understand the mechanisms of repolarization dynamics in HF myocytes. To this end, they used an elegant action potential (AP)–clamp technique to unravel the role and regulation of K^+ currents[6] under more realistic physiological conditions.

Hegyi et al[5] report that when more realistic physiological conditions are used by leaving Ca^{2+} cycling intact, APD in failing isolated myocytes is prolonged at slow beating rates but similar to control myocytes at faster, near normal rates. In contrast, APD prolongation was observed in HF versus control at all beating rates studied when 10 mmol/L 1,2-bis(o-aminophenoxy)ethane-*N,N,N′,N′*-tetraacetic acid (BAPTA) was applied to prevent $[Ca^{2+}]_i$ transients. The lack of significant APD prolongation at faster rates with Ca^{2+} cycling left intact is consistent with ECG QTc[4] intervals and ex vivo APD mapping[7] observed in humans with HF. This raises two interesting questions: (1) how does simply leaving Ca^{2+} cycling intact account for complex repolarization dynamics observed in failing myocytes and (2) does this mean that APD prolongation, an important arrhythmia substrate, is irrelevant in HF under physiological conditions (Ca^{2+} cycling intact and near normal rates)? To answer these questions, Hegyi et al[5] expertly demonstrated the contribution of K^+ currents to repolarization of the AP under more physiological conditions and explored how these currents are regulated by Ca^{2+} cycling, β-AR (β-adrenergic receptor) activation, and CaMKII (Ca^{2+}/calmodulin-dependent protein kinase II).

It is well known that $[Ca^{2+}]_i$ can regulate the function of numerous ion channels; but, how it impacts net repolarization and AP dynamics is not obvious. Hegyi et al[5] used a control AP morphology with stimulation at 2 Hz for their AP clamp, and they sequentially applied ion channel inhibitors in the same myocyte (sequential dissection) to understand how I_{Kr}, I_{Ks} and I_{K1} shape the AP in HF. With Ca^{2+} cycling left intact and at fast rates (2 Hz), I_{Ks} and I_{Kr} are actually increased in HF, which compensates for the decrease in I_{K1}, and as a result net repolarization charge and APD are unchanged compared with controls. Interestingly, this increase in I_{Kr} and I_{Ks} goes against what has been reported previously by voltage clamp when Ca^{2+} is buffered, which Hegyi et al[5] attribute to leaving Ca^{2+} cycling intact. Specifically, they demonstrated that in failing myocytes, the Ca^{2+}-induced increase in these currents is

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CaMKII dependent for I_{Ks} but CaMKII independent for I_{Kr}. Thus, at faster rates in HF, Ca^{2+} cycling causes an increase in I_{Kr} and I_{Ks}, which counteracts the decrease in I_{K1} that is unaffected by Ca^{2+} cycling. If so, then why is APD prolonged in HF compared with controls at slow rates with Ca^{2+} cycling left intact? Hegyi et al[5] did not directly test this, but less accumulation of I_{Ks} activation or less available reserve of open channels[8] may explain longer APD at slower rates. An important implication of these findings is that by buffering $[Ca^{2+}]_i$, APD prolongation in HF and related arrhythmia substrates (eg, early afterdepolarizations) may be overestimated.

Does this mean that APD prolongation, an important arrhythmia substrate, is irrelevant at fast and near normal rates in HF? The answer is no when considering the vulnerability of the failing heart to stress, such as β-AR activation. Once again, this is nicely illustrated using the AP-clamp sequential dissection method. With Ca^{2+} cycling left intact and with isoproterenol administration, the isoproterenol-induced increase in net repolarization charge was significantly smaller in HF myocytes compared with controls. This reveals the impaired repolarization reserve capacity of HF myocytes that is due to a hyporesponsive I_{Ks}. Although not shown, it is likely that APD will be prolonged (or shortened less) with isoproterenol in HF compared with control even with Ca^{2+} cycling left intact. This could be analogous to LQT1 (long-QT syndrome type 1), where under increased adrenergic tone, reduced function of I_{Ks} is unable to shorten APD as it normally would.[9] However, measurements of APD in human HF wedge preparations show that APD is shortened with β1 and β2 receptor simulation,[7] indicating more complex (eg, additional ion channel) remodeling in HF, and that further investigation is needed. Moreover, in addition to APD prolongation, spatial dispersion of APD as measured in multi-cellular or whole heart preparations would provide further information on arrhythmia substrates associated with repolarization reserve and HF.

Another very interesting observation by Hegyi et al,[5] in this issue of the Journal is that APD variability, an important cause of arrhythmia,[10] is increased in HF compared with controls. Crucially, the increase in large APD variability (>10 ms) in HF compared with controls is reduced when $[Ca^{2+}]_i$ is buffered. Hegyi et al[5] reasoned that increased APD variability in HF may be because of increased sarcoplasmic reticulum Ca^{2+} leak and delayed afterdepolarization activity that is common in their model. However, another possibility is that APD alternans, a specific type of variability, might be playing a role. APD alternans is a beat-to-beat oscillation that is associated with increased arrhythmia vulnerability[11] and HF.[12] Importantly, abnormal Ca^{2+} cycling is a mechanism of alternans,[13] especially in HF.[14] Previously, we[15] and others[16] have shown that $[Ca^{2+}]_i$ buffering with BAPTA suppresses alternans. Therefore, reduced APD alternans may explain, in part, why large variability of APD did not increase as much in HF as it did in controls when $[Ca^{2+}]_i$ was buffered. Additional studies are needed to confirm this possibility. Nevertheless, APD variability and related arrhythmia vulnerability may be underestimated unless $Ca2^{+}$ cycling is left intact.

Most experimentalists would agree that implementing realistic physiological conditions is ideal. However, if impractical, then a clear understanding of the drawbacks in not doing so is necessary. Using an innovative AP-clamp approach, Hegyi et al[5] effectively illustrate the importance of Ca^{2+} cycling, β-AR activation, and CaMKII activity on regulating key repolarization currents and AP dynamics in HF. These results have important arrhythmia implications; however, additional studies are needed to further investigate these possibilities. Furthermore, it would have been interesting to know if similar results were observed when using a failing AP clamp with a longer APD and more repolarized resting membrane potential as observed in HF myocytes. Nevertheless, it is very rewarding to learn the importance of using more physiological conditions in isolated cells and to gain meaningful physiological and pathophysiological insight at the same time.

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FOOTNOTES

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