New insights into the complex effects of KChIP2 on calcium transients

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The initial phase of cardiac repolarization (phase 1 in humans) is mediated by the transient outward K+ current ($I_{o,f}$). $I_{o,f}$ is composed of the Ca$^{2+}$-independent K+ current ($I_{o,t}$) and a Ca$^{2+}$-activated chloride current ($I_{o,t,2}$), both of which are voltage dependent (3). $I_{o,t}$ is further subdivided into fast ($I_{o,t,f}$) and slow ($I_{o,t,s}$) (3). $I_{o,t,f}$ is mediated by Kv4 channels that form complexes with K+ channel-interacting protein 2 (KChIP2) proteins in the majority of cardiomyocytes. Kv4 is the pore-forming unit, and KChIP2 is an accessory K+ channel-interacting protein residing on the cytoplasmic side (10, 12). The discovery of KChIP2 proteins in neurons (1) led to the generation of knockout mouse models of KChIP2 to study the role of this protein in cardiac electrophysiology through loss of function (9). Removal of KChIP2 in mice leads to disappearance of $I_{o,t,f}$. More recently, it was discovered that KChIP2 proteins also bind to Cav1.2, which is responsible for the L-type Ca$^{2+}$ current ($I_{Ca,L}$) (15). In KChIP2$^{-/-}$ mouse cardiomyocytes, $I_{Ca,L}$ is reduced but Cav1.2 protein levels are unchanged (15). Therefore, KChIP2 proteins are capable of modulating various ionic currents that determine the action potential plateau and regulate contractility.

Action potential duration (APD) prolongation is widely reported to occur in many forms of heart failure. A reduction in $I_{o}$ has been suggested to be a main contributing factor responsible for the prolongation of APD. KChIP2 expression has been also reported to be significantly reduced in human and animal models of cardiac hypertrophy and heart failure. Changes in KChIP2 expression have been reported to increase the trafficking of $I_{o}$ channels to the cell membrane and shift the voltage dependence of activation to more negative values. The net result of these changes indicates that KChIP2 can modulate the amplitude of $I_{o}$ more than eightfold. On the other hand, studies that have been designed to determine the ability of KChIP2 to modulate APD have been somewhat conflicting. Depending on $I_{Ca,L}$ levels, decreases in $I_{o}$ can result in either increased or decreased APD (16). While other studies have reported increases in $I_{o}$ to have little or no effect on APD (11). Changes in $I_{o}$ that occur with cardiac disease are often accompanied by changes in $I_{Ca,L}$. One potential explanation for the varied effects of $I_{o}$ on APD could be related to complex interactions of these currents where the net effect on APD can vary. It is also possible that KChIP2 interactions with the channels responsible for $I_{o}$ and $I_{Ca,L}$ contribute to the net effects on cardiac function and APD.

In a study by Grubb and colleagues (5) the role of KChIP2 in determining cardiomyocyte Ca$^{2+}$ transients and how this affects cardiac function were investigated. Specifically, the study focused on finding the mechanisms responsible for the maintenance of cardiac function in the absence of KChIP2, given that both $I_{o,t}$ and $I_{Ca,L}$ are reduced. The authors confirmed previous reports that cardiac function is unchanged in KChIP2 knockout mice (9, 13) and that absence of KChIP2 in isolated myocytes decreased the peak inward Ca$^{2+}$ current without changing the expression levels of the protein or kinetics responsible for $I_{Ca,L}$ (15). Given that reduction in $I_{Ca,L}$ might lead to decreased intracellular Ca$^{2+}$ concentration transients and decreased contraction (7), the authors turned to computational and experimental studies to determine how KChIP2 deficiency might affect Ca$^{2+}$-induced Ca$^{2+}$-release (CICR). They addressed the role CICR by measuring synchronization between Ca$^{2+}$ channels and ryanodine receptor (RyR) coupling, RyR sensitivity to Ca$^{2+}$, sarcoplasmic reticulum Ca$^{2+}$+ load, fractional Ca$^{2+}$ release, and rate of decay. Surprisingly none of those was decreased in KChIP2$^{-/-}$ myocytes; furthermore, they report increased Ca$^{2+}$ release with β-adrenergic stimulation, suggesting augmented sensitivity of the RyR. In view of these findings and on simulation data, the authors attribute preserved contractility to a prolongation in APD secondary to the loss of $I_{o,t}$. APD prolongation would provide sufficient time for intracellular Ca$^{2+}$ concentration to rise in the presence of reduced $I_{Ca,L}$.

Although this study provided new information on the effects of KChIP2 activity and Ca$^{2+}$ transients, a few important issues worth mentioning remain unresolved. In particular, APD data have been reported in the KChIP2$^{-/-}$ mice. Initially it was reported that myocytes isolated from KChIP2$^{-/-}$ mice had increased APD (9). More recently, it was shown that differences in APD between isolated wild-type and KChIP2$^{-/-}$ myocytes were only observed at room temperature but not at physiological temperatures due to an increase in $I_{o,s}$ (2, 9, 14). These results are in agreement with Thomsen et al. (14) who observed prolonged APD only in KChIP2$^{-/-}$ myocytes that had blocked $I_{o,s}$ with 4-aminopyridine. In the current study, APD was measured at physiological temperature in isolated myocytes and was longer than wild-type controls. Microelectrode measurements obtained from the epicardial left ventricular surface of intact hearts were performed by Grubb et al. (6) in a previous study and were also prolonged in KChIP2$^{-/-}$ compared with wild-type mice. It remains to be determined if differences observed in KChIP2 effects on APD are due to a heterogeneity of the cardiomyocyte population being assessed. Another important issue is related to the proteins that interact with Kv4. Many other proteins have been found in ventricular tissue that coimmunoprecipitate with Kv4 and modulate either its localization at the membrane surface and/or its channel kinetics (10). Interestingly, these include Ca$^{2+}$-/calmodulin-dependent kinase 2 (CaMKII), which has been shown to have increased activity when Kv4 or KChIP2 are reduced (8). In this study, Grubb et al. report an increase in RyR sensitivity to β-adrenergic stimulation, which remains unexplained. One possible explanation might be the increased CaMKII activity, given that it has recently been shown that CaMKII increases...
RyR sensitivity to β-adrenergic stimulation (4). Finally, another component of CICR that might be involved in Ca\(^{2+}\) handling in pathological hearts and might influence RyR Ca\(^{2+}\) release is the Na\(^{+}\)–Ca\(^{2+}\) exchanger (NCX). NCX influences [Ca\(^{2+}\)]\(_{c}\) in the dyadic cleft, and it has been proposed that at highly positive membrane potentials NCX and \(I_{Ca,L}\) might act synergistically to trigger Ca\(^{2+}\) release (7). Overall the Grubb et al. study provides us with important information on the role of KChIP2 in modulating Ca\(^{2+}\) transients. In addition, these data help to emphasize the complex interactions between electrophysiological changes and their effects on cardiac function.

REFERENCES

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

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