‘Leaky’ ryanodine receptors and sudden cardiac death

David A. Brown1 and Wayne E. Cascio2*

1Departments of Physiology, Brody School of Medicine and the East Carolina Heart Institute, East Carolina University, Greenville, NC, USA; and 2Cardiovascular Sciences, Brody School of Medicine and the East Carolina Heart Institute, East Carolina University, 115 Heart Drive, Mail Stop #651, Greenville NC, 27834, USA

Online publish-ahead-of-print 8 October 2009

This editorial refers to ‘Redox modification of ryanodine receptors underlies calcium alternans in a canine model of sudden cardiac death’ by A.E. Belevych et al., pp. 387–395, this issue.

Sudden cardiac death is a significant cause of mortality in the industrialized world, accounting for as much as 30% of deaths in high-risk populations. Despite the high incidence, the cellular mechanisms leading to fatal ventricular arrhythmias are not fully understood, thereby hindering the development of novel therapeutic strategies to mitigate this adverse outcome of myocardial infarction. Repolarization heterogeneities have been implicated as substrates for re-entrant arrhythmia, ultimately leading to ventricular fibrillation (VF). At the myocyte level, lability in action potential duration and beat-to-beat fluctuations in calcium (Ca\(^{2+}\)) transients (Ca\(^{2+}\) alternans) have been observed in several different models as contributing factors to altered repolarization. Although the importance of intracellular Ca\(^{2+}\) alternans in the aetiology of ventricular arrhythmia is clear, little is known about which pathways in the cellular Ca\(^{2+}\) cycle are altered in VF-prone hearts.

Belevych et al. provide compelling evidence that oxidation of the ryanodine receptor (RyR) augments the release of Ca\(^{2+}\) from the sarcoplasmic reticulum (SR) in the non-infarct zone of canine hearts made susceptible to VF by previous healed infarction. Using a variety of imaging and electrophysiological techniques, cellular Ca\(^{2+}\) influx, SR Ca\(^{2+}\) uptake/release, and luminal SR Ca\(^{2+}\) content are extensively characterized in this canine model of VF. With such a unique and comprehensive approach, the authors are able explain ‘leaky’ ryanodine receptors in VF-prone hearts as a function of receptor oxidation, which alters the SR load–release relationship. Interestingly, augmented SR Ca\(^{2+}\) leak in VF-prone myocytes occurred in the presence of decreased diastolic SR luminal Ca\(^{2+}\) content. While corroborating the previous findings where RyR leakiness increases in oxidative conditions, this study also extends previous work by showing that a reducing agent normalized differences in calcium handling between myocytes from VF-prone and control hearts.

While this study contributes new and provocative data implicating oxidative modification of RyR and the attendant SR load–release relationship as a predisposing factor contributing to the risk of VF, it is important to recognize that the wedge section and isolated myocytes were taken only from the non-infarct zone. As such, the study provides no information about the state of RyR oxidation or the SR load–release relationship in the border zone or in the surviving cells of the infarct zone. Post-infarction remodelling is known to include the infarct and border zones and involves remodelling of receptors, channels, gap junctions, and tissue architecture. Consequently, the study has a limited utility for establishing the contribution of altered SR calcium dynamics to the functional integration of active and passive electrophysiological properties, impulse formation, and conduction across the ischaemic border zone.

Of speculative interest is the mechanism accounting for the oxidation of RyR. Previous studies have shown that oxidative stress increases in the border zone and non-infarcted tissues through increased activity of intracellular NADPH oxidase, xanthine oxidase, and NO synthase, along with decreased anti-oxidant capacity. In this canine model of chronic infarction, sympathetic and parasympathetic imbalances with resulting sympathetic hyperactivity predispose to VF during ischaemic challenge. It is possible that chronic sympathetic neural activation might also contribute to oxidative modification of the RyR. A recent paper by Mercanglu et al. showed that in a chronic infarction model in rats superimposed sympathetic hyperactivity increased tissue malondialdehyde levels and decreased anti-oxidant protein activity and glutathione content. Because β-adrenergic receptor blockade is known to decrease the risk of sudden cardiac death after myocardial infarction, it would be of interest to know whether β-adrenergic receptor blockade might alter the oxidation of the RyR and the rate-dependent calcium amplitude–SR calcium content relationship and decrease the susceptibility to VF during ischaemia.

Another implication of the study is that directly targeting oxidation of the RyR might decrease the susceptibility to VF. To date, clinical trials targeting oxidative stress with anti-oxidants have been disappointing. Clearly, more investigation is needed to develop effective pharmacological strategies to modify oxidation of key membrane and intracellular proteins. Future experiments aimed at...
elucidating which sites on the RyR are oxidized in the disease state will further our understanding about how calcium release is augmented in these conditions. Additionally, confirming the protective effect of anti-oxidant agents in wedge preparations and, ultimately, the intact animal will be an important extension of this study.

Conflict of interest: none declared.

References