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How can a single mutation cause such arrhythmic havoc?

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In most cases, sudden cardiac death (SCD) is associated with significant structural abnormalities. However, there are several instances, Brugada Syndrome (BrS) being one, where SCD occurs in an apparently normal heart. BrS is characterized by an ST segment elevation, right bundle branch block, and SCD in a structurally normal heart.¹ One aspect that makes BrS particularly intriguing is its genetic basis. Several mutations related to the function and trafficking of the sodium channel, I_{Na} , have been associated with BrS, which results in a “loss of function”.² Knowing the genetic basis and clinical phenotype, one might expect that a complete understanding of BrS is within grasp. However, this is far from being true. BrS is associated with complex electrophysiological heterogeneities that create a substrate for the initiation and maintenance of phase 2 reentry.³ Another intriguing aspect of BrS is its temperature sensitivity. For example, it is known that fever can aggravate symptoms.⁴ However, the combined influence of temperature on molecular function and arrhythmic substrates is not well known. This adds further complication to the mechanisms of arrhythmogenesis in BrS. The study by Morita et al⁵ in this issue of *Heart Rhythm* addresses this challenging problem using an experimental model of drug induced BrS and highlights the complex arrhythmic substrate that can result from a single mutation.

Effects of Temperature on Ion Channel Trafficking and Function

The mutations causing BrS that have been identified so far are found on *SCN5A*, the gene encoding the α -subunit of the voltage-gated cardiac sodium channel. A likely explanation for the fever-dependent manifestation of BrS would be the direct effect of elevated temperature on wild-type or mutated sodium channel function. It is well established that an increase in temperature significantly accelerates both the activation and inactivation kinetics of the wild-type sodium channel, causing increased peak sodium current. However, these effects on the wild-type channels do not correlate with the observed outcome on sodium currents associated with BrS. Alternatively, it is possible that the effect of temperature is rather on the mutated sodium channels found in patients with BrS. In fact, the effect of elevated temperature on mutated sodium channels alters the temperature sensitivity of fast inactivation, resulting in a “loss of function”,⁶ which can explain the BrS phenotype. However, most *SCN5A* mutations lead to a “loss-of-function” by reducing the sodium current either through a trafficking defect or by producing spliced channels. Therefore, in these cases, one can speculate that the effect of fever might be to impair trafficking of the channel, which is known to be temperature-dependent. Also, a study by Keller et al.⁷ suggests that in patients carrying a *SCN5A* mutation at the heterozygous state in whom the

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function of mutant channels is either reduced or abolished, the temperature-dependent properties of wild-type sodium current itself might also lead to the typical ECG characteristics during fever.

The other important current involved in BrS is the transient outward current, I_{to} , responsible for the notch during earlier repolarization (phase 1). Therefore, it is also important to consider the effect of temperature on this current. Increased temperature is known to modulate I_{to} by increasing current density and accelerating activation and inactivation, which is expected to increase notch depth.⁸ However, these effects of elevated temperature on the current cannot explain the reduction in the notch with elevated temperature that Morita et al⁵ reports in this issue of *The Journal*. Therefore, it is more likely that the manifestation of BrS seen with elevated temperature that they observed is mainly due to its effect on the sodium channel and/or other currents.

Another level of complexity that has recently emerged with BrS is the role of sodium channel polymorphism. We recently demonstrated that a polymorphism can restore the function of a BrS mutation and could therefore be an explanation for the low penetrance of the disease.⁹ Even though the mechanism by which this rescue occurs is still unclear, another possibility for the consequence of elevated temperature in BrS could be on these sodium channel variants. For example, if an elevated temperature interferes with the mechanism of rescue, then we might see a higher prevalence of BrS. However, this has yet to be determined.

The Arrhythmic Substrate for Brugada Syndrome

One might think that reduced sodium current would create a relatively straight forward substrate for reentrant excitation, i.e. slow conduction. This is not the case, and this study elegantly sorts out the complex arrhythmia substrate that can result from a single molecular lesion and the modulating effects of temperature. While I_{to} is not directly affected, it is a major mediator of the phenotype for several reasons. First, the effect of normal I_{to} on APD in species with long action potentials is not very significant as compared to other repolarizing currents. However, it can, when left unopposed due to reduced I_{Na} , deepen the notch during early repolarization (phase 1). This leads to the eventual loss of the plateau or “dome” and a significant reduction of APD.³ Second, the normally present heterogeneous expression of I_{to} between left and right ventricles, as well as transmurally, can significantly influence dispersion of repolarization.¹⁰ These two effects, shortening of APD and dispersion of repolarization, reduce cardiac wavelength and increase the propensity for unidirectional block, respectively, and are very potent substrates for reentrant excitation. This substrate alone, however, is not sufficient to cause reentrant excitation. A trigger that engages repolarization gradients and leads to unidirectional block is needed. In this regard, the electrophysiological substrate associated with BrS, as mentioned above, also contributes. Action potentials with a prominent spike and dome morphology juxtapose to action potentials with a significantly abbreviated duration can result in “propagation” of the dome and the initiation of phase - 2 reentry.¹¹ Therefore, not only is the substrate for reentrant excitation present (short APD and dispersion of repolarization), but so is the trigger.

In addition to the effects temperature has on the expression and function of I_{Na} and I_{to} , temperature is likely to affect other ionic processes that could have a significant effect on the substrate for reentrant activity. For example, Morita et al⁵ in this issue of *the Journal* found that an increase in temperature significantly reduced APD. This is likely due, in part, to the temperature sensitivity of ionic currents other than I_{to} , given that APD shortening was observed even when I_{to} was blocked. As a result, wavelength shortens throughout the heart and, thus, sustained reentry is more likely to occur. Indeed, Morita et al.⁵ found that an

increase in temperature significantly increased the occurrence of sustained VF/VT. It is also interesting that Morita et al.5 observed a decrease in the likelihood of PVAs (i.e. triggers) with increased temperature. This may be due to reduced notch depth associated with increased temperature that they also observed. However, it is not clear if a similar result would be observed in patients with an *SCN5A* mutation, considering the effect high temperature has on the sodium channel. This is a limitation of the drug-induced experimental model of BrS used by Morita et al.5 Nevertheless, despite this decrease in the rate of trigger occurrence, VT > 5 beats was more likely, suggesting that overall shortening of APD associated with fever may be an overriding factor in the occurrence of VT/VF lasting more than a few beats.

Conclusion

It is quite striking how a single mutation can wreak such arrhythmic havoc. In this issue of the *Journal*, Morita et al.5 demonstrate in an experimental model of drug induced BrS, significant heterogeneities of action potential morphology that creates a substrate and trigger for reentrant excitation. Add on top of this the complexity of temperature effects on ion channel function and trafficking and you get a multifaceted and potent arrhythmia substrate. This study also highlights the importance of investigating SCD due to genetic mutations at the level of the intact preparation.

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