Arrhythmogenic Brugada syndrome substrate: a proof of principle

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This editorial refers to ‘A transient outward potassium current activator recapitulates the electrocardiographic manifestations of Brugada syndrome’ by Calloe et al., 4 pp. 686–694, this issue.

The Brugada syndrome is an inherited, arrhythmogenic entity affecting predominantly young men without structural heart disease. 1 It is associated with a specific ECG pattern of coved-type ST-segment elevation in right precordial leads (Figure 1). Patients are at increased risk for sudden cardiac death often triggered by vagal influence and many times occurring at rest. After its description as a distinct entity in 1992, a first genetic link was identified in 1998. 2 The Brugada syndrome has a complex electrophysiological substrate, and several aspects are important for understanding its pathology. Many lines of evidence suggest a central role of $I_{to}$ in the genesis of the Brugada syndrome. First, the balance of de- and repolarizing forces during the cardiac action potential is disturbed, leading to a loss of dome in epicardial action potentials and to increased dispersion of refractoriness. Reduced depolarizing (sodium current, $I_{Na}$, or calcium current, $I_{Ca}$) or increased repolarizing ion currents (transient outward current, $I_{to}$, or rapidly activating delayed-rectifier current, $I_{Kr}$) may induce a substrate for arrhythmia in the Brugada syndrome (Figure 1). Secondly, inter- and intra-ventricular differences in ionic currents, which constitute the physiological basis of excitability, impact on the formation of the Brugada syndrome phenotype. Right ventricular myocardial cells exhibit stronger $I_{to}$ and accordingly sensitize this region to repolarization imbalance. Epicardial cells exhibit greater phase-1 of action potentials than endocardial cells and accordingly predispose these cardiomyocytes to arrhythmic changes. Thirdly, gender plays a major role in disease presentation as males apparently exhibit a greater amount of $I_{to}$ than females. Recently, a mutation in the KCNE3 $\beta$-subunit (causing increased $I_{to}$) was associated with the Brugada syndrome. 3

Calle et al. 4 report results of a study using a novel $I_{to}$ activator (NS5806) to investigate effects on canine ventricular ionic currents and cellular electrophysiology of right and left ventricular wedges. With the clarity of their results, they provide convincing evidence for a pivotal role of $I_{to}$ in generation of the electrocardiographic and arrhythmic phenotype of the Brugada syndrome. This study mechanistically proves what has previously been suggested: $I_{to}$ is central to the development of the Brugada syndrome phenotype.

The findings of this study raise interesting questions about human pathology. What is more important in man? Is it an increase in repolarizing ($I_{to}$) or a reduction in depolarizing ($I_{Na}$) forces? Calloe et al. demonstrate that an $I_{to}$ activator can (to some extent) produce a Brugada phenotype in preparations from both ventricles while application of sodium channel blockers are typically thought to induce right ventricular alterations. More extensive repolarization changes than those classically reported are rarely observed in the clinical setting, but feasibility of induction of a left ventricular Brugada phenotype highlights the importance of knowing more about regional heterogeneity of ion channel expression and function in man. Along the same lines, another question arises: if the Brugada syndrome phenotype was only inducible in 4 of 6 right and 2 of 10 left ventricular wedge preparations, what caused resistance in the remainder of the hearts? What factors modulate phenotypic clinical presentation beyond penetrance of mutated, disease-causing genes? Individual repolarization reserve owing to natural variance in ion channel current expression may turn out to be very important and it may be hard to tell if differences in $I_{Na}$, $I_{Ca}$, $I_{Ko}$, $I_{to}$ or any other candidate current are specifically responsible in an individual patient. Current limitations to genotyping patients with Brugada syndrome are reflected by this complexity. Understanding better how genotypes correlate with phenotypes is an important step on the way towards individualized therapy.

Induction of the Brugada syndrome phenotype with the help of an $I_{to}$ activator also re-emphasizes the potential therapeutic benefit from block of this respective ionic current. 5 Previous clinical studies used quinidine to inhibit $I_{to}$ in patients. 6 As this drug can have significant side effects in terms of sodium channel block, the use of...
I\textsubscript{to}/I\textsubscript{Kr} blockers that have recently been designed for ‘atrial-selective’ therapy of atrial fibrillation could represent an alternative therapeutic approach.

In summary, Calloe \textit{et al.}\textsuperscript{4} have delivered an important piece to the mosaic of cardiac repolarization abnormalities that generate an arrhythmogenic substrate in the Brugada syndrome. With their present work, the authors have characterized the role of I\textsubscript{to} in the development of the Brugada syndrome substrate and have provided incentives for future research.

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\textbf{References}