Cardiac Sodium Channel Overlap Syndrome

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KEYWORDS

• Sodium channel • *SCN5A* • Mutation • Sudden cardiac death • Arrhythmia • Brugada syndrome • Long QT syndrome type 3 (LQT3) • Sodium channel overlap syndrome

KEY POINTS

- Cardiac sodium channels play a central role in excitability of myocardial cells and proper conduction of the electrical impulse within the heart.
- Mutations in the *SCN5A* gene encoding the cardiac sodium channel are associated with a wide range of arrhythmia syndromes that potentially lead to fatal arrhythmias in relatively young individuals.
- A single *SCN5A* mutation can result in multiple clinical phenotypes and rhythm disturbances within the same family, a phenomenon now referred to as "cardiac sodium channel overlap syndrome."
- Various clinical, environmental, and genetic modifiers modulate variable disease expressivity and severity in sodium channel overlap syndrome.

INTRODUCTION

Influx of sodium ions through cardiac voltage-gated sodium channels is responsible for the initial fast upstroke of the cardiac action potential, and consequently plays a central role in excitability of myocardial cells and proper conduction of the electrical impulse within the heart (**Fig. 1**). During common pathologic conditions, such as myocardial ischemia and heart failure, decreased sodium current function may cause conduction disturbances and potentially life-threatening arrhythmias.[1,2] In addition, sodium channel dysfunction secondary to mutations in the *SCN5A* gene, encoding the major sodium channel in heart, underlie a number of inherited arrhythmia syndromes associated with fatal arrhythmias in otherwise healthy young individuals. Over the past 20 years, an increasing number of *SCN5A* mutations have been described in patients with long QT syndrome type 3 (LQT3), Brugada syndrome (BrS), (progressive) conduction disease, sick sinus syndrome, atrial standstill, atrial fibrillation, and dilated cardiomyopathy.[3,4] Moreover, a single *SCN5A* mutation can result in multiple clinical phenotypes and rhythm disturbances within the same family (including features of LQT3, BrS, and/or conduction disease), a phenomenon now referred to as "cardiac sodium channel overlap syndrome."[5] The complexity of these overlap syndromes is further underlined by the large variability in type and severity of clinical symptoms within affected families. Multiple biophysical defects of single *SCN5A* mutations are considered instrumental to the observed overlapping clinical manifestations.[5,6] Furthermore, genetic modifiers and environmental factors are suspected to determine variable disease expressivity and severity. Here, an overview is provided of the current knowledge

This work was supported by the Netherlands Heart Institute (grant 061.02), and the Division for Earth and Life Sciences (ALW; project 836.09.003) with financial aid from the Netherlands Organization for Scientific Research (NWO).

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Card Electrophysiol Clin 6 (2014) 761–776
http://dx.doi.org/10.1016/j.ccep.2014.08.005
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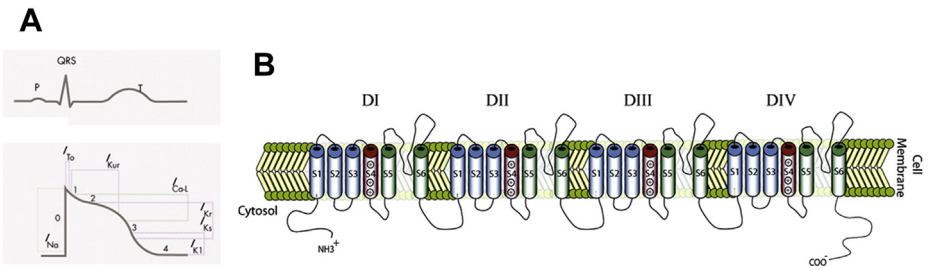

Fig. 1. (*A*) Ion currents underlying the cardiac action potential. (*B*) Structure of the cardiac sodium channel. (*From* [*A*] Remme CA, Bezzina CR. Sodium channel (dys)function and cardiac arrhythmias. Cardiovasc Ther 2010;28:288; with permission.)

on inherited sodium channelopathies and *SCN5A* mutations associated with sodium channel overlap syndromes.

CARDIAC SODIUM CHANNEL STRUCTURE, FUNCTION, DISTRIBUTION, AND REGULATION

The voltage-dependent cardiac sodium channel consists of a transmembrane pore-forming α-subunit protein associated with a small ancillary modulatory β-subunit. The α-subunit protein $Na_V1.5$ (encoded by the *SCN5A* gene) is made up of a cytoplasmic N terminus, 4 internally homologous domains (DI-DIV; each consisting of 6 transmembrane segments S1–S6) interconnected by cytoplasmic linkers, and a cytoplasmic C terminal domain (see **Fig. 1**). The positively charged fourth transmembrane segment (S4) acts as the voltage sensor responsible for increased channel permeability (channel activation) during membrane depolarization.[7] The ion-conducting pore of the channel is formed by the S5 and S6 segments of all 4 domains, and their interconnecting P-loops contain the channels' selectivity filter for sodium ions.[8] Channel inactivation is a more complicated process involving multiple parts of $Na_V1.5$, including the intracellular DIII–DIV linker, the intracellular S4–S5 linkers of both DIII and DIV, the C terminal domain, and the S5–S6 P-loops.[8,9] Secondary to mutations in *SCN5A*, sodium channel activation and/or inactivation properties may be altered, depending on the location of the mutation. Consequently, sodium channel availability and peak sodium current may be decreased, setting the stage for conduction slowing. Alternatively, the channel may not be properly inactivated, resulting in a persistent (sustained), noninactivating sodium current during the action potential plateau phase, thereby prolonging repolarization (**Fig. 2**).[10]

Cardiac sodium channels are not homogeneously distributed throughout the myocardium. Within the cardiac conduction system, low to absent $Na_V1.5$ protein expression is observed in the

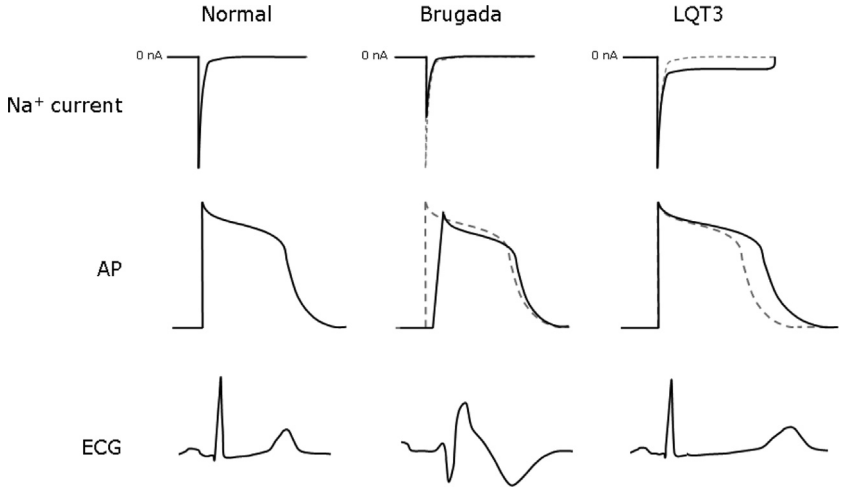

Fig. 2. Alterations in sodium current characteristics underlying action potential (AP) and ECG characteristics in LQT3 and BrS. (*From* Remme CA, Bezzina CR. Sodium channel (dys)function and cardiac arrhythmias. Cardiovasc Ther 2010;28:290; with permission.)