Brugada Syndrome physiopathology: focal epicardial arrhythmogenic cardiomyopathy responsible for "reduced RVOT conduction reserve"?

Recent expeculations about BrS physiopatology

Genetic factors underlie the variability of cardiac electrical response to Na^+-channel blockers (SCBs), polygenic risk scores PRS_{BrS} family history, and a baseline ECG can predict the development of a diagnostic drug-induced Type I BrS ECG with clinically relevant accuracy. These findings could lead to the use of polygenic risk scores (PRS) in the diagnosis of BrS and, if confirmed in population studies, to identify patients at risk for toxicity when given SCBs. **(1)**

The diversity of presentation, electrical signals, and related pathology and imaging support a complex confluence of factors in patients with BrS. The majority appear to have focal intersticial fibrous tissue and reduced gap junction expression (connexin-43 (Cx43). and consecuent dromotropic disturbance in the epicardial RVOT **(2)** with a contributory monogenic and oligogenic predisposition **(3; 4)**. This is in contrast to the understanding of hypototesis that focuses on both repolarization and genetic factors as main subjacent mechanisms. The high prevalence of symptoms and sensitivity to SCBs population highlights the adverse effect of the founder mutation on cardiac dromotropism. The large phenotypical heterogeneity, variable penetrance, and even non-segregation suggest that other genetic and **environmental** factors modify the disease expression, severity, and outcome in these families. **(5)**. This substrate is mediated at least partially by common genetic variation and apparent healthy people with a higher burden of the BrS-associated risk alleles (i.e. a high BrS-PRS) may show a positive response to ajmaline challenge. **(1)**. Further genetic susceptibility is likely to be mediated by more than rare genetic variation i.e. SCN5A variants. The role of ultra-rare genetic variants in non-SCN5A genes requires further proof and currently, evidence for a monogenic model of clinical diagnostic testing beyond SCN5A is absent.

BrS and long QT syndrome (LQTS) are inherited entities that can cause Major Adverse Cardiac Events (MACE) and SCD in youngs. Pathogenic variants in three genes account for the vast majority of genotype-positive cases for these conditions. **(6)** These three genes code for α-subunits of voltage-gated ion channels expressed in cardiomyocytes: SCN5A underlying the cardiac depolarizing Na^+ current (I_{Na}),

and KCNH2 and KCNQ1 underlying the rapid (I_{Kr}) and slow (I_{Ks}) components of the phase 3 repolarizing potassium delayed rectifier current. Rare coding variants in SCN5A cause BrS by a loss-of-function (LOF) mechanism while LQTS is caused by functional LOF variants in KCNQ1 (LQT1) and KCNH2 (LQT2) or gain-of-function variants in SCN5A (LQT3). **(7)**

"Less rare" rare variants may play an important role in susceptibility in a gene dosage model, but this remains to be elucidated as does the impact on the human substrate of genetic variation affecting repolarization. Much like the concept of reduced repolarization reserve underlying LQTS, **(8)**. Recently, Professor Arthur AA Wilde et al. propose that whether mediated by a penetrant SCN5A pathogenic variant, an increased polygenic risk scores (PRS), and/or additional genetic insults, the final common pathway**(9)**. For BrS could be viewed as a disease of **"reduced RVOT conduction reserve".** Most patients will have a primarily depolarization-mediated process, although perturbations in repolarization cannot be excluded. In this framework, the patient's intrinsic RVOT dromotropic reserve may be age- racial, and sex-dependent and marginal reserves can be exposed by the use of potent conduction slowing drugs or other acute modulators of cardiac dromotropism and repolarization, such as fever and vagal tone augmentation. Fibrosis on histopathological studies also suggest that there may be a role for superimposed inflammation on the substrate, with a potential overlap with the spectrum of arrhythmogenic cardiomyopathy. Indeed, they hypothesize that the majority of patients historically labelled with BrS may be more accurately described as **focal epicardial arrhythmogenic cardiomyopathy**.

Figure 1 shows repolarization vs. depolarization theories for the electrophysiological mechanism underlying BrS. Modified from reference **(8)**.

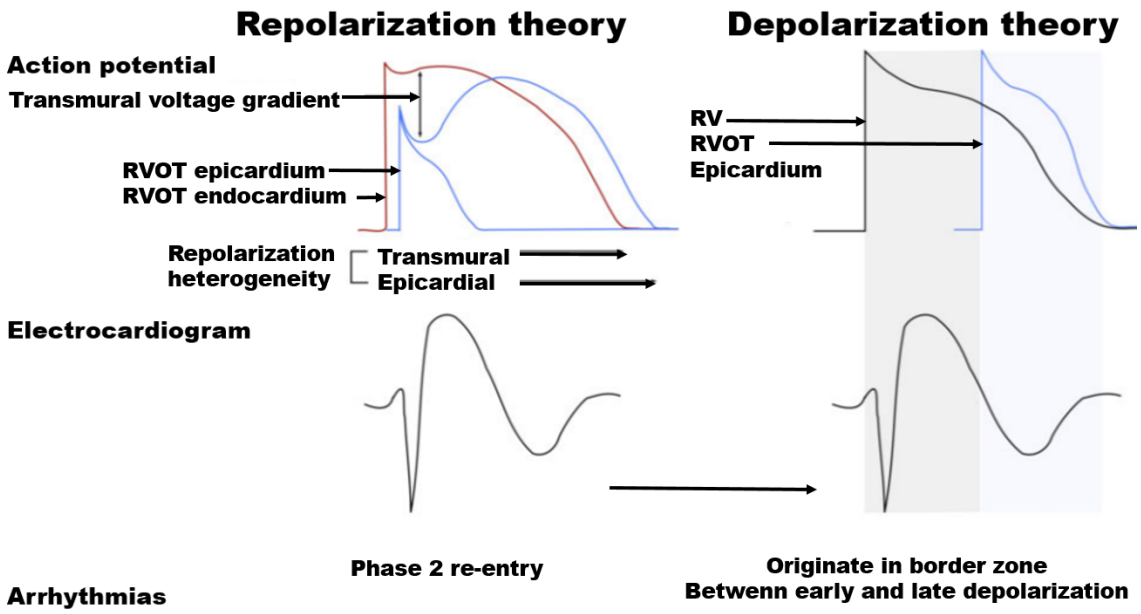

Figure 1 *Repolarization vs. depolarization theories for the electrophysiological mechanism underlying BrS. The repolarization theory suggests that reduced* INa^{+} *current causes unopposed Kv4.3-mediated* I_{to}*. This creates an epicardial–endocardial transmural voltage gradient which disrupts the normal spike and dome morphology of the AP. Due to differences in distribution of Ito and in thickness of epicardial and endocardial layers, these changes are more exaggerated in the RVOT epicardium than its endocardium and cause accentuation of the AP and therefore the J-point and right precordial ST elevation characteristic of the Brugada ECG pattern. Heterogeneity in repolarization and refractoriness in the RVOT epicardium lead to increased risk for phase 2 re-entry and VT/VF. The depolarization theory suggests that delayed conduction in the RVOT relative to the body of the RV causes the characteristic ECG pattern and arrhythmias. Dromotropic disturbance in the RVOT creates an initial gradient driving current towards the RVOT and right precordial leads. The second phase of current returning to the RV and away from the right precordial leads, leads to the characteristic symmetrical T- wave inversion (TWI). Arrhythmias are thought to originate in the border zone between early and delayed depolarization where there are mismatched potentials. RV, right ventricle; RVOT, right ventricular outflow tract; VF, ventricular fibrillation; VT, ventricular tachycardia.*

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