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Short communication

SCN5A mutation type and topology are associated with the risk of ventricular arrhythmia by sodium channel blockers

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A B S T R A C T

Background: Ventricular fibrillation in patients with Brugada syndrome (BrS) is often initiated by premature ventricular contractions (PVCs). Presence of SCN5A mutation increases the risk of PVCs upon exposure to sodium channel blockers (SCB) in patients with baseline type-1 ECG. In patients without baseline type-1 ECG, however, the effect of SCN5A mutation on the risk of SCB-induced arrhythmia is unknown. We aimed to establish whether presence/absence, type, and topology of SCN5A mutation correlates with PVC occurrence during ajmaline infusion.

Methods and results: We investigated 416 patients without baseline type-1 ECG who underwent ajmaline testing and SCN5A mutation analysis. A SCN5A mutation was identified in 88 patients (S+). Ajmaline-induced PVCs occurred more often in patients with non-missense mutations (Snon-missense) or missense mutations in transmembrane or pore regions of SCN5A-encoded channel protein (Smissense−TP) than patients with missense mutations in intra-/extracellular channel regions (Smissense−IP) and patients without SCN5A mutation (S−) (29%, 24%, 9%, and 3%, respectively; P < 0.001). The proportion of patients with ajmaline-induced BrS was similar in different mutation groups but lower in S− (71% Smissense−IP, 63% Smissense−TP, 70% Snon-missense, and 34% S−; P < 0.001). Logistic regression indicated Snon-missense and Smissense−TP as predictors of ajmaline-induced PVCs.

Conclusions: SCN5A mutation is associated with an increased risk of drug-induced ventricular arrhythmia in patients without baseline type-1 ECG. In particular, Snon-missense and Smissense−TP are at high risk.

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1. Introduction

Ventricular fibrillation in patients with Brugada syndrome (BrS) is often initiated by premature ventricular contractions (PVCs) [1]. Mutations in SCN5A, the gene encoding the cardiac sodium channel protein Na+, are an important cause of BrS, and BrS patients with baseline type-1 ECG who carry such mutations have increased risk of PVCs after exposure to sodium channel blockers (SCB) [2]. However, the impact of SCN5A mutations on the risk of drug-induced ventricular arrhythmia in BrS patients without baseline type-1 ECG (BrS in these patients is diagnosed through SCB testing) is unknown. As a result, no guidelines or consensus recommendations exist regarding the use of SCB in SCN5A mutation carriers without baseline type-1 ECG.

Because conduction slowing is a key pathomechanism in BrS and Na+,5 is critical for impulse propagation [3], clinical severity should be greatest in patients who carry SCN5A mutations that disrupt Na+,5 function the most. Accordingly, we previously showed that non-missense mutations leading to premature truncation of Na+,5 increased the sensitivity of the cardiac conduction system to SCB more than missense mutations, as reflected by more PR and QRS prolongation during SCB testing [4]. Similarly, missense mutations that cause severe loss of Na+,5 current (ik) caused more conduction slowing than mutations that reduced ik less. In our study, we derived the magnitude of ik from published biophysical studies [4]. However, such studies are labor-intensive and not available for many mutations. While magnitude of ik reduction and clinical severity may be easy to predict for non-missense mutations (severe), we hypothesized that this can also be estimated for missense mutations based on their topology. In support of this hypothesis, recent evidence suggests that SCN5A missense mutations affecting the transmembrane or pore regions of Na+,5 (severe ik reduction) are more likely to be pathogenic than mutations in intracellular or...
extracellular regions (i.e., N-terminus, C-terminus, interdomain or intersegment linkers) (limited hERG reduction) [5].

In this study, we aimed to establish whether SCN5A mutation presence/absence, type and topology determine the risk of PVC occurrence during SCB (ajmaline) testing in patients without baseline type-1 ECG. Such knowledge may drive clinical management strategies.

2. Methods

2.1. Patient inclusion

In this study, we included 416 consecutive subjects (> 15-year-old) who had undergone ajmaline testing and SCN5A mutation analysis. No subject displayed type-1 ECG at baseline. Indications for the test were aborted cardiac arrest (ACA), ventricular arrhythmia, syncope, palpitations, family history of BrS and/or sudden cardiac death (FH-SCD), or an ECG suspicious but not diagnostic for BrS.

2.2. Mutation analysis, ajmaline testing and ECG analysis

Informed consent was obtained. The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Genomic DNA extraction from peripheral blood lymphocytes and SCN5A mutation analysis was performed as described previously [4]. Ajmaline testing was performed using the protocol of the BrS consensus conference [6]. Ajmaline infusion was stopped when type-1 ECG appeared or immediately after occurrence of PVCs. Twelve-lead ECGs were analyzed at baseline and peak ajmaline dose (ajmalinepeak; i.e., at maximum dose of -1 mg/kg or at the first dose when type-1 ECG or PVCs occurred). Ajmaline testing was considered positive if type-1 ST elevation ≥2-mm appeared in 1 right-precordial lead [6].

2.3. Statistical analysis

Differences between groups were compared using Fisher exact test or χ² [2] test (categorical variables), or Student t-tests or analysis of variance (continuous variables). Homogeneous subsets of groups were determined with the Standardized Residual Methods (categorical variables) and Student-Newman-Keuls post hoc multiple comparison of groups (continuous variables). For ECG parameters, since multiple tests were performed, the significance level was set at 0.001. In the Tables, homogeneous subsets (no statistical difference) are indicated by an equals (=) sign. A logistic regression analysis was performed to identify predictors for PVCs during ajmaline infusion, and variables with P < 0.05 were selected for multivariable analysis. A correction for the relatedness among individuals was applied and the linearity assumption for the numerical predictors was checked. Results of the logistic regression are expressed as odds ratio (OR) with 95% confidence interval (CI). Data are expressed as mean (percentage) or mean ± standard deviation (SD), where appropriate.

3. Results

The study population included 210 men (age 43 ± 15 years) and 206 women (age 44 ± 14 years). Twenty-eight (6.7%) and 52 (12.5%) patients with ajmaline-induced PVCs did not develop type-1 ECG. Such knowledge may drive clinical management strategies.

3.1. Comparisons between patients according to the occurrence of ajmaline-induced type-1 ECG

First we studied whether ajmaline-induced BrS was associated with the occurrence of PVCs. We therefore compared patients with ajmaline-induced type-1 ECG (Ajmalinepositive; n = 171) with those without ajmaline-induced type-1 ECG (Ajmalinenegative; n = 245) (Supplementary Table 2). Compared to Ajmalinepositive, Ajmalinepositive were more often probands (41% [16.7%] vs. 52% [30.4%], P = 0.002), and had experienced more often syncpe (23 [9.4%] vs. 29 [17.0%], P = 0.032). The proportion of patients with a SCN5A mutation (S−) was higher in Ajmalinepositive than Ajmalinenegative (59 [34.3%] vs. 29 [11.8%], P ≤ 0.001). Both at baseline and at ajmalinepeak, PR and QRS were longer in Ajmalinepositive than Ajmalinenegative. The proportion of patients with ajmaline-induced PVCs did not differ between Ajmalinepositive and Ajmalinenegative (15 [8.8%] vs. 11 [4.4%], respectively; P = 0.117).

Next, we studied the role of the SCN5A mutation in relation to the occurrence of type-1 ECG and PVCs during ajmaline testing by comparing Ajmalinepositive without a SCN5A mutation (Ajmalinepositive/S−; n = 112) with Ajmalinepositive with a SCN5A mutation (Ajmalinepositive/S+; n = 59) and Ajmalinenegative with a SCN5A mutation (Ajmalinenegative/S−; n = 29) (Table 1). Ajmalinepositive/S− and Ajmalinepositive/S+ (i.e., BrS patients) were younger, and more often probands and symptomatic compared to Ajmalinenegative/S+. At baseline, PR was longer in Ajmalinepositive/S+ and Ajmalinepositive/S+ (i.e., mutation carriers) than Ajmalinepositive/S−. At ajmalinepeak, PR and QRS were longer in Ajmalinepositive/S+ and Ajmalinepositive/S+ (mutation carriers) than Ajmalinepositive/S−. The proportion of patients with ajmaline-induced PVCs was higher in Ajmalinepositive/S+ and Ajmalinepositive/S+ (mutation carriers) than Ajmalinepositive/S− (10 [16.9%] and 7 [24.1%] vs. 5 [4.4%], respectively; P = 0.002).

3.2. Comparisons between SCN5A mutation carriers and non-carriers

We next compared SCN5A mutation carriers (S+; n = 88) vs. non-carriers (S−; n = 328); regardless of the occurrence of type-1 ECG during ajmaline testing. S− were more often probands than S+ (29 [33.0%] vs. 64 [19.5%], P = 0.011). Other clinical characteristics (age, ACA, syncpe, and FH-SCD) did not differ between S+ and S− (Supplementary Table 3).

At baseline, S+ had longer PR than S−, while baseline heart rate (HR), QRS and QTc did not differ. Ajmalinepeak was lower in S− than S+. At ajmalinepeak, S− had slower HR and longer PR and QRS than S+. Ajmaline induced type-1 ECG more often in S+ than S− (59 [87.8%] vs. 112 [34.1%], P < 0.001).

Ajmaline also induced PVCs more often in S+ than S− (17 [19.3%] vs. 9 [2.7%], P < 0.001). Except for baseline PR (212 ± 28 ms. in S+ vs. 147 ± 29 ms. in S−, P > 0.001), other ECG parameters at baseline or ajmalinepeak and clinical characteristics (age, sex, history of ACA or syncpe, and FH-SCD) did not differ between S+ and S− with PVC. PVCs occurred immediately after the appearance of type-1 ECG in 10/17 S+ (58.8%) and 5/9 S− (55.5%). The remaining patients with PVCs did not develop type-1 ECG.

Ten of 17 S+ and 8/9 S− had PVCs with left bundle branch block (LBBB) morphology: 8/17 S+ (47.1%) and 7/9 S− (77.8%) with LBBB and inferior axis, and 2/17 S+ (11.8%) and 1/9 S− (11.1%) with LBBB and superior axis. Seven S+ (41.2%) and 1 S− (11.1%) had PVCs with right bundle branch block (RBBB) morphology.

3.3. Comparisons between patients with different SCN5A mutations and non-carriers

To further study the role of the SCN5A mutation on the occurrence of ajmaline-induced PVCs, we compared patients with non-missense mutations (Gon-missense; n = 14), patients with missense mutations in transmembrane/pore regions (Smis-TP; n = 41), patients with missense mutations in intra/extracellular regions (Smis-IE; n = 33), and S− (Table 2). Except for FH-SCD, other clinical characteristics did not differ between groups.

At baseline, PR was longer in Smis-IE and Smis-TP than S− and S+. Other baseline ECG parameters did not differ between the groups. Ajmalinepeak was lower in Smis-IE and Smis-TP than Smis-IE and S−. At ajmalinepeak, Smis-IE had slower HR and longer QRS than other S− and S+. The proportion of patients with ajmaline-induced type-1 ECG did not differ between different mutation groups.

Ajmaline induced PVCs more often in Smis-IE and Smis-TP than Smis-IE and S−. Expect for baseline PR (212 ± 33 ms. in Smis-IE, 223 ± 21 in Smis-TP, 175 ± 16 ms. in Smis-IE, and 147 ± 26 ms. in S−, P > 0.001), other ECG parameters at baseline or ajmalinepeak and clinical characteristics did not differ between
patients with PVCs in different groups (i.e., $S_{\text{non-missense}}$ and $S_{\text{missense-TP}}$, $S_{\text{missense-IE}}$, and $S^-$).

### 3.4. Predictors of PVCs during ajmaline infusion

Multivariable analysis included HR, PQ, QRS, and QTc at baseline and ajmalinepeak, weight-adjusted ajmalinepeak, $S_{\text{non-missense}}$, $S_{\text{missense-TP}}$, and $S_{\text{missense-IE}}$. Ajmaline-induced type-1 ECG was not included because it was not identified as a predictor for PVCs by logistic regression analysis. $S_{\text{non-missense}}$ (OR 10.15 [CI 21.14–48.02]) and $S_{\text{missense-IE}}$ (OR 7.25 [CI 1.68–31.38]) were identified as independent predictors for ajmaline-induced PVCs. Moreover, baseline HR (OR 1.05 [CI 1.02–1.09]) and QRS at ajmalinepeak (OR 1.04 [1.01–1.06]) were found as independent predictors. Baseline HR was higher in patients with than without PVCs (74 ± 14 vs. 67 ± 13 beats/min, $P = 0.007$). QRS at ajmalinepeak was longer in patients with than without PVCs (155 ± 33 vs. 131 ± 18 ms, $P < 0.001$).

### 4. Discussion

In the last 15 years, several studies have attempted to identify predictors for drug-induced ventricular arrhythmia in patients undergoing SCB testing. However, these studies did not investigate SCN5A mutation status and/or included patients with baseline type-1 ECG (who are well-recognized to be at high risk for adverse events in the presence of SCB) [2,7]. As a result, it is still unknown whether carriers of a SCN5A mutation without baseline type-1 ECG are at higher risk of drug-induced ventricular arrhythmia.

In this study, we first systematically studied the impact of SCN5A mutation on the occurrence of PVCs during ajmaline testing in patients without baseline type-1 ECG. We found that presence of SCN5A mutation increases the likelihood that ajmaline exposes BrS and evokes PVCs, and that the risk of PVCs in $S^+$ is regardless of the occurrence of type-1 BrS ECG during ajmaline testing (i.e., the occurrence of PVCs was similar between $\text{Ajmaline}_\text{positive-}S^+$ and $\text{Ajmaline}_\text{negative-}S^+$ and higher than $\text{Ajmaline}_\text{positive-}S^-$ [Table 1]). In line with earlier data [8], $S^-$ often had PVCs with LBBB morphology and inferior axis, suggesting a right-ventricular outflow tract origin, while $S^+$ had PVCs originating from both left and right ventricle.

In addition, we found that the risk for drug-induced PVCs depends on the type and topology of the SCN5A mutation. Multivariable analysis identified $S_{\text{non-missense}}$ and $S_{\text{missense-TP}}$ mutations as strong predictors for ajmaline-induced PVCs. Moreover, although the effect was weaker, baseline heart rate and QRS after ajmaline were also identified as predictors for PVCs. Ajmaline-induced type-1 ECG was not associated with PVC occurrence and did not predict PVCs, and the proportions of patients who developed type-1 ECG did not differ between mutation groups. Based on these findings, one may speculate that the mechanism underlying ajmaline-induced PVCs is large reduction of INa and the depolarization reserve in the heart [3,4,9]. INa reduction by $S_{\text{non-missense}}$ or $S_{\text{missense-TP}}$ mutations may be significant, but depolarization reserve is large enough to ensure that QRS in $S_{\text{non-missense}}$ and $S_{\text{missense-TP}}$ at baseline is not different from $S_{\text{missense-IE}}$ or $S^-$. However, the added presence of ajmaline results in further INa reduction and decline in the depolarization reserve to a level that results in QRS prolongation [4] and ultimately PVCs [9]. Since ajmaline requires repetitive opening and closing of Nav1.5 to act as a blocker ([use-dependent block], Nav1.5 is blocked more potently at higher heart rates. Together these processes may explain why SCN5A mutation type and topology, higher baseline heart rates and longer QRS intervals after ajmaline are associated with the risk for ajmaline-induced PVC occurrence.

The concept that the magnitude of INa reduction due to a SCN5A mutation plays a crucial role in the occurrence of ajmaline-induced PVCs is in line with our finding that the peak ajmaline dose was...
lower in $S_{\text{non-missense}}$ and $S_{\text{missense-TP}}$ than $S_{\text{missense-IE}}$ or $S^-$, while the proportion of patients with PVCs was much larger in $S_{\text{non-missense}}$ and $S_{\text{missense-TP}}$. This suggests that $S_{\text{non-missense}}$ and $S_{\text{missense-TP}}$ mutations cause more IbNa reduction and therefore require less Na1.5 block by ajmaline for PVCs to occur. Interestingly, the same concept may also apply for the occurrence of ajmaline-induced type-1 ECG. While the proportion of ajmaline-induced type-1 ECG did not differ between $S_{\text{non-missense}}$, $S_{\text{missense-TP}}$, and $S_{\text{missense-IE}}$, the required peak ajmaline dose was higher in the latter, suggesting that the degree of IbNa reduction may also play an important role in the pathophysiology of BrS, and that $S_{\text{non-missense}}$ and $S_{\text{missense-TP}}$ are at higher risk of developing BrS in the presence of SCB than $S_{\text{missense-IE}}$ (or $S^-$).

The limitations of our study include its retrospective design and the small size of various SCN5A mutation groups. In addition, although type-1 ECG was absent in all patients on at least two time points, we cannot exclude the presence of transient type-1 ECG, e.g., during fever. Moreover, the study population was not screened for large genomic rearrangements or mutations in other genes that have been anecdotally linked to BrS. However, in this regard it is important to note that in an earlier genetic screening study in 38 BrS patients from our center, we have excluded large genomic rearrangements and mutations in other BrS-linked candidate genes [10].

5. Conclusions

The presence of a SCN5A mutation increases the likelihood that ajmaline exposes BrS and evokes ventricular arrhythmia in patients without baseline type-1 ECG. Moreover, the risk for drug-induced arrhythmia depends on type and topology of the SCN5A mutation, and patients with $S_{\text{non-missense}}$ or $S_{\text{missense-TP}}$ mutations may be at highest risk. We recommend SCN5A mutation analysis in individuals who experience ventricular arrhythmia while using SCB, particularly if arrhythmia is preceded by QRS prolongation, also in patients in whom type-1 ECG has not been achieved (yet). Moreover, we discourage prescription of SCB in patients with SCN5A mutation, including patients without BrS.

Statement of authorship

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2017.09.010.
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