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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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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,1.5, 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,1.5 is critical for impulse propagation [3], clinical severity should be greatest in patients who carry SCN5A mutations that disrupt Na,1.5 function the most. Accordingly, we previously showed that non-missense mutations leading to premature truncation of Nav1.5 in-transmission or missense mutations in transmembrane or pore regions of SCN5A-encoded channel protein (S) than patients with missense mutations in intrac-/extracellular channel regions (S) 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%, 63%, 70%, and 34% in S ; P < 0.001). Logistic regression indicated S and S 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, S and S are at high risk.

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extracellular regions (i.e., N-terminus, C-terminus, interdomain or intersegment linkers) (limited bNa 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-years-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, syncpe, 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 1st 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 [4].

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). Homogenous 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, homogenous 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 (no statistical difference) are indicated by an equals (=) sign. A logistic regression analysis was performed using the protocol of the BrS consensus conference [6]. Ajmaline infusion was stopped when type-1 ECG or PVCs occurred. Twelve-lead ECGs were analyzed at baseline and peak ajmaline dose (ajmalinepeak; i.e., at maximum dose of ~1 mg/kg or at the 1st 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 [4].

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 had experienced ACA or syncpe, respectively, and 89 patients (21.4%) had a FH-SCD. Ajmaline induced type-1 ECG in 171 patients (41.1%). A SCN5A mutation was identified in 88 patients (21.2%) (see Supplementary Table 1 for a list of mutations). No patient developed sustained arrhythmia or high-degree AV block during ajmaline testing. Twenty-six patients (6.3%) developed PVCs during ajmaline infusion.

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 (Ajmaline-negative; n = 425) (Supplementary Table 2). Compared to Ajmaline-negative, Ajmaline-positive were more often probands (41 [16.7%] vs. 52 [30.4%], P = 0.002), and had experienced more syncpe (23 [9.4%] vs. 29 [17.0%], P = 0.032). The proportion of patients with a SCN5A mutation (S") was higher in Ajmaline-positive than in Ajmaline-negative (59 [34.5%] vs. 29 [11.8%], P ≤ 0.001). Both at baseline and at ajmalinepeak, PR and QRs were longer in Ajmaline-positive than in Ajmaline-negative. The proportion of patients with ajmaline-induced PVCs did not differ between Ajmalinepositive and Ajmaline-negative (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 Ajmaline-positive without a SCN5A mutation (Ajmalinepositive/S-; n = 112) with Ajmaline-positive with a SCN5A mutation (Ajmalinepositive/S+; n = 59) and Ajmaline-negative with a SCN5A mutation (Ajmaline-negative/S+; n = 29) (Table 1). Ajmaline-positive/S- and Ajmaline-positive/S+ (i.e., BrS patients) were younger, and more often probands and symptomatic compared to Ajmaline-negative/S+. At baseline, PR was longer in Ajmaline-positive/S- and Ajmaline-negative/S+ (i.e., mutation carriers) than Ajmaline-positive/S-. At ajmalinepeak, PR and QRs were longer in Ajmaline-positive/S- and Ajmaline-negative/S+ (mutation carriers) than Ajmaline-negative/S-. The proportion of patients with ajmaline-induced PVCs was higher in Ajmaline-positive/S+ and Ajmaline-negative/S+ (mutation carriers) than Ajmaline-negative/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 in S- (59 [67.8%] 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 in the occurrence of ajmaline-induced PVCs, we compared patients with non-missense mutations (SNonsense-missense; n = 14), patients with missense mutations in transmembrane/pore regions (SNSense-missense-IE; n = 41), patients with missense mutations in intracellular/extracellular regions (SNSense-missense-EE; n = 33), and S- (Table 2). Except for FH-SCD, other clinical characteristics did not differ between groups.

At baseline, PR was longer in SNSsense-missense-IE and SNSsense-missense-TP than SNSsense-IE. Other baseline ECG parameters did not differ between the groups. Ajmalinepeak was lower in SNSsense-missense-IE and SNSsense-missense-TP than SNSsense-IE and S-. At ajmalinepeak, SNSsense-missense-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 SNSsense-missense-IE and SNSsense-missense-TP than SNSsense-EE and S-. Expect for baseline PR (212 ± 33 ms. in SNSsense-missense-IE vs. 223 ± 21 ms. in SNSsense-EE, 175 ± 16 ms. in SNSsense-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., $^{\text{non-missense}}$ and $^{\text{missense-TP}}$, $^{\text{missense-IE}}$, and $^{\text{S}}$).

3.4. Predictors of PVCs during ajmaline infusion

Multivariable analysis included HR, PQ, QRS, and QTc at baseline and ajmalinepeak, weight-adjusted ajmalinepeak, $^{\text{non-missense}}$, $^{\text{missense-TP}}$, and $^{\text{missense-IE}}$. Ajmaline-induced type-1 ECG was not included because it was not identified as a predictor for PVCs by logistic regression analysis. $^{\text{non-missense}}$ (OR 10.15 [CI 2.14–48.02]) and $^{\text{missense-TP}}$ (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 than without PVCs (74 ± 14 vs. 67 ± 13 beats/min, $P = 0.007$). QRS at ajmalinepeak was longer in patients 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 $^{\text{S}}$ is regardless of the occurrence of type-1 BrS ECG during ajmaline testing (i.e., the occurrence of PVCs was similar between Ajmalinepositive-$^{\text{S}}$ and Ajmalinenegative-$^{\text{S}}$ and higher than Ajmalinepositive-$^{\text{S}}$ [Table 1]). In line with earlier data [8], $^{\text{S}}$—often had PVCs with LBBB morphology and inferior axis, suggesting a right-ventricular outflow tract origin, while $^{\text{S}}$ 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 $^{\text{non-missense}}$ and $^{\text{missense-TP}}$ 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 to a level that results in QRS prolongation [4] and ultimately PVC occurrence. The peak ajmaline dose — values at baseline. $P$ values indicate results of statistical comparisons between the three groups (columns). In case of an overall statistical significant difference, homogeneous groups (with no statistical difference) are indicated by an equals ( $=$ ) sign.
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 $I_{Na}$ reduction and therefore require less $Nav_{1.5}$ 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 $I_{Na}$ 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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