Electrocardiographic Features in SCN5A Mutation-Positive Patients with Brugada and Early Repolarization Syndromes: A Systematic Review and Meta-Analysis

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Abstract

Background*:* Early repolarization syndrome (ERS) and Brugada syndrome (BrS) are both J-wave syndromes. Both can involve mutations in the SCN5A gene but may exhibit distinct electrocardiographic (ECG) differences. The aim of this systematic review and meta-analysis is to investigate possible differences in ECG markers between SCN5A positive patients with ERS and BrS.

Methods: PubMed and Embase, were searched from their inception to October 20th, 2021 for human studies containing the search terms “SCN5A” and “variant” and “early reporlarization” or “Brugada”, with no language restrictions.

Results: A total of 328 studies were identified. After full text screening, 12 studies met our inclusion criteria and were included in this present study. 104 ERS patients (mean age: 30.86 ±14.45) and 2000 BrS patients (mean age: 36.17 ±11.39) were studied. Our meta-analysis found that ERS patients had a significantly lower heart rate (standardized mean difference [SMD]a= 14.69, 95% confidence interval [CI] = 21.43, 7.94, P = 0.0001), shorter QRS duration (SMD = 13.90, 95% CI = 17.16, 10.65, P = 0.0001) and shorter QTc [corrected QT interval] (SDM = 21.52, 95% CI = 33.77, 9.26, P = 0.0006) than BrS patients.

Conclusion: BrS patients with positive SCN5A mutations exhibited prolonged QRS, indicating conduction abnormalities, whereas ERS patients with positive SCN5A mutations showed normal QRS. By contrast, whilst QTc intervals were longer in BrS than in ERS SCN5A positive patients, they were within normal limits. Further studies are needed to examine the implications of these findings for arrhythmic risk stratification.

Introduction

Brugada Syndrome (BrS) is a cardiac ion channelopathy that predisposes patients to an increased risk of sudden cardiac death (SCD) in the absence of overt structural abnormalities [1]. The characteristic type 1 BrS electrocardiographic (ECG) presentation, a coved ST segment elevation > 2mm in the right precordial leads, is easily confused with early repolarization syndrome (ERS). J-waves on the ECG are a direct result of transient outward potassium (I_{to})-mediated action potential notch in the ventricular epicardium, causing transmural voltage gradient during early ventricular repolarization [2]. Whilst ERS was previously known as a benign syndrome observed in up to 13% of the general population, recent studies have reported that early repolarization in inferolateral leads is associated with an increased risk of SCD [3, 4]. Despite their association with the devastating outcome of SCD, little is known about the pathogenic mechanisms and the genetic basis of both syndromes.

Mutations in genes responsible for sodium channels, calcium channels and potassium channels have all been reported to have a role in the current imbalances responsible for the accelerated epicardial repolarization [5, 6]. Pathological mutations in SCN5A have been described in the literature in both BrS and ERS [7, 8]. This suggests an overlap in pathophysiological mechanisms in both J-wave syndromes. SCN5A is a gene that encodes the alpha subunit of the voltage-gated Nav1.5 cardiac sodium channel and

loss of function reduces conduction throughout the myocardium [9, 10]. Mutation in the SCN5A gene is the most common genetic mutation found amongst BrS patients [11]. *Zhang et al.* studied the genotype-phenotype relationship between SCN5A and the ECG findings in ERS and BrS patients [12]. The study reported that ERS patients had shorter QRS duration and corrected QT-interval (QTc) than patients with BrS. To validate the findings on the distinct ECG features between ERS and BrS with SCN5A mutation, we performed a meta-analysis on the ECG characteristics of ERS and BrS patients who were SCN5A mutation-positive.

Methods

Search Strategy

This study was conducted in line with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement [13]. Two databases, PubMed and Embase, were searched from their inception to October 20th, 2021 for human studies containing the search terms “SCN5A” and “variant” and “early repolarization” or “Brugada”, with no language restrictions. The title and abstract of the resultant studies are then screened for eligibility. Full text of the eligible studies was then retrieved for assessment of compliance against the inclusion criterion. Studies were excluded in the initial screening if they did not meet the inclusion criterion or on later assessment any of the exclusion criteria were met.

The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the quality of the studies included [14]. NOS evaluates the following categories: study participant selection, results comparability and outcome quality. This was broken down into representativeness of exposed cohort; selection of the non-exposed cohort; ascertainment of exposure; outcomes that were not present at the start of the study; comparability of study design/analysis; assessment of outcomes; sufficiently long follow-up periods; and adequacy of follow-up. A scale of 0-9 was used, where studies below 5 stars are graded poorly, 5-7 graded fair and >8 graded good. Only studies with 7 or above were included in this study. Details of the NOS quality assessment for the studies are shown in **Supplementary Table 1**.

Inclusion and exclusion criteria

The following inclusion criterion was applied to select eligible studies: 1) the study was an observational study on human subjects; 2) the study consists of ERS and/or BrS patients who tested positive for SCN5A mutation; 3) the study measured quantitative ECG measurements from subjects. At the initial screening studies were excluded if they: 1) were duplicated through the search process of the two databases; 2) were case reports or series, reviews or meta-analyses; 3) were irrelevant.

Data extraction and statistical analysis

Studies congregant with the inclusion criterion were selected for the meta-analysis. The data was then extracted into a standardized Microsoft Excel spreadsheet. The following data were extracted: 1) publication details (surname of the first author and publication year); 2) details of patients in the study (age, sex, sudden death, Brugada SCN5A positive, ERS SCN5A positive, syncope, family history of sudden

cardiac arrhythmia); 3) ECG parameters measured. ECG parameter measurement for each subgroup was pooled generating a combined measurement for that group, e.g. ERS SCN5A positive QRS duration. Two reviewers (SL and OC) reviewed each included the studies individually, and disputes were resolved by a third reviewer (GT).

Statistical analysis of the pooled data was delivered using the Reviewer Manager 5.3 software. Heterogeneity between studies was quantified through the I^2 statistics from the standard chi-square test. I^2 greater than 50% reflects significant statistical heterogeneity, thus the random-effects models were used for the forest plot. Otherwise, a fixed-effects model was used. Funnel plots were used to identify publication bias. Since PR interval, QRS duration, QTc and heart rate (HR) are continuous variables the standard mean difference between the two groups was calculated and supplemented by 95% confidence intervals (CI). Statistical significance was defined as a two-tailed p-value < 0.05.

Results

Search results and study characteristics

A total of 328 unique studies were identified on PubMed and Embase using our search terms. At the end of the initial title and abstract screening, 57 articles met our inclusion criteria. After the full-text screening, 12 studies met our inclusion criteria and were included in the present study. Figure 1 shows the workflow of the study selection process with the number of studies excluded by each of the exclusion criteria. Only *Zhang et al.*'s study included both BrS and ERS patients, with the remaining 11 studies were on BrS only. Overall, 2000 patients were pooled (male= 50.6%, mean age= 36.17 ± 15.06 years old), which included 719 BrS and 10 ERS SCN5A mutation-positive patients.

Differences in electrocardiographic parameters between ERS and BrS patients

The electrographic parameters analyzed in this study were PR interval, QRS duration and QTc prolongation. Our meta-analysis found no significant differences in the PR interval between BrS patients and ERS patients (SMD = 8.51, 95% CI = -0.46, 17.48, P = 0.06, I^2 = 0%; Figure 2A). By contrast, BrS patients showed longer QRS durations by 24.4 milliseconds (SMD = 13.90, 95% CI = 17.16, 10.65, P = 0.0001, I^2 = 0%; Figure 2B) and longer QTc intervals by 23.2 milliseconds (SMD = 21.52, 95% CI = 33.77, 9.26, P = 0.0006, I^2 = 26%; Figure 2C) than ERS patients. The large heterogeneity demonstrated large inter-study variation, suggesting that more studies are needed to provide enough data to make strong conclusions from the statistical analysis on PR intervals, QRS duration and QTc. Sensitivity analysis was used to remove sources of heterogeneity producing the results above. Finally, the HR is significantly higher in BrS patients than in ERS patients by 10.9 beats per minute (SMD = 14.69, 95% CI = 21.43, 7.94, P = 0.0001, I^1 = 0%; Figure 2D).

Discussion

There are several significant findings from this meta-analysis: 1) ERS patients are more likely to have a lower HR than BrS patients; 2) ERS patients are more likely to have a shorter QTc than BrS patients; 3) ERS patients are more likely to have shorter QRS duration. Insignificant differences were found in the PR interval between ERS and BrS patients.

BrS patients had longer QRS duration whilst ERS patients had shorter QTc intervals in comparison. Together, these findings suggest conduction abnormalities as a finding in BrS but not ERS, despite patients harbouring SCN5A mutations. This supports the theory that ERS and BrS have overlapping genetics and pathophysiology but are separate syndromes [15]. The difference in QTc intervals and QRS duration could be used clinically for risk stratification now that we have established the link between the early repolarization pattern on the ECG and fatal cardiac arrhythmias [16]. It has previously been described that activation recovery interval (ARI) in the right ventricular outflow tract of BrS is prolonged. In contrast, the shorter QT interval amongst ERS patients is suggestive of extensive regions with short ARI, especially in ERS3 where SCN5A is more prevalent [7]. An alternative explanation for this could be that, due to the small sample size, specific variants have caused the alteration in ERS electrophysiology in comparison to BrS.

Interestingly, patients with the same SCN5A variant can display very different phenotypes (BrS and ERS) when exacerbated by fever [12]. There has yet to be a large scale study delineating fever-induced ERS but the recent consensus statement supports the differences in the manifestation under fever in BrS and ERS [1]. This indicates other genetic, epigenetic or environmental factors that drive the pathophysiology in separate directions. Epigenetics of ERS and BrS is not very well studied. However, histone modification has been linked to dysregulation of repolarizing K^+ currents (I_{K1}, I_{to}, I_{Kr}, I_{Ks}) and depolarizing Ca^{2+} currents (I_{Ca-L}) in heart failure [17, 18]. Identification of the separate histone and DNA methylation profiles in BrS and ERS would likely help uncover further distinctions between the electrophysiological mechanisms of these two syndromes. However, it was not possible in our study to attribute differences in QRS and QTc to particular SCN5A variants nor to particular epigenetic markers.

It is postulated that reduced conduction reserve with associated fibrosis in the right ventricular outflow tract epicardium is a result of SCN5A variants in both BrS and ERS [2]. This is because SCN5A is responsible for initiating the cardiac action potential [19]. In ERS, reduction in conduction reserve, the substrate for reentry and arrhythmogenesis localizes to the inferior myocardium in contrast with BrS [20]. ERS mechanism of disease in patients without SCN5A variants requires large cohort GWAS to identify relevant loci for study to aid model development and help distinguish BrS and ERS pathophysiology.

Recent work has proposed polygenic risk scores based on the mutation type in BrS [21]. In this study we focused on SCN5A variants, the most commonly associated variant in ERS [22]. KCNJ8, ABCC9, KCNE5, DPP10, CACNA1C, CACNB2B, CACNA2D1, SCN5A, SCN10A are all linked with ERS [23] but a polygenic risk score for ERS is yet to be determined or implemented. Using this approach may be useful for the

management of ERS patients, however until such research is conducted ECG parameters are our only clinical markers. Further studies should be conducted to elucidate the distinct relationships between genotype and phenotypic severity in ERS. This should include the pathological impact of individual SCN5A variants and multiple SCN5A variants together, recent work has proposed that this propagates patients' PR intervals and QRS duration, leading to more major arrhythmia events when compared to patients carrying a single pathogenic variant [12].

Furthermore, no significant differences in the PR interval were observed, which may be attributed to small sample sizes in the ERS group. It has recently been demonstrated that ERS patients with SCN5A variants have been shown to display longer PR intervals [12]. Whilst the burden of bradycardic complications such as atrioventricular block have been well-investigated in BrS [24], this issue remains unresolved for ERS.

Limitations

There are several limitations to this meta-analysis that should be noted. The primary limitation is the population size of the ERS patients with positive mutation status for the SCN5A gene, which was 104 out of 2000 subjects, and all originating from the same cohort. Further cohort studies investigating the ECG characteristics in ERS are needed. Secondly, only a small number of studies were included. These findings should be validated in larger cohort studies.

Conclusion

BrS patients with positive SCN5A mutations exhibited prolonged QRS, indicating conduction abnormalities, whereas ERS patients with positive SCN5A mutations showed normal QRS. By contrast, whilst QTc intervals were longer in BrS than in ERS SCN5A positive patients, they were within normal limits. Further studies are needed to examine the implications of these findings for arrhythmic risk stratification.

Declarations

- Ethical Approval and Consent to participate

Not applicable.

- Consent for publication

All authors consent to publication.

- Availability of supporting data

All data are included in the tables.

- Competing interests

None.

- Funding

None.

- Authors' contributions

Danny Radford and Oscar Hou In Chou: literature search, data extraction and analysis, drafting of the manuscript, critical revision of the manuscript

George Bazoukis, Konstantinos P Letsas, Tong Liu: data interpretation, critical revision of the manuscript

Gary Tse, Sharen Lee: study conception, data analysis and interpretation, drafting and critical revision of the manuscript

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Figures

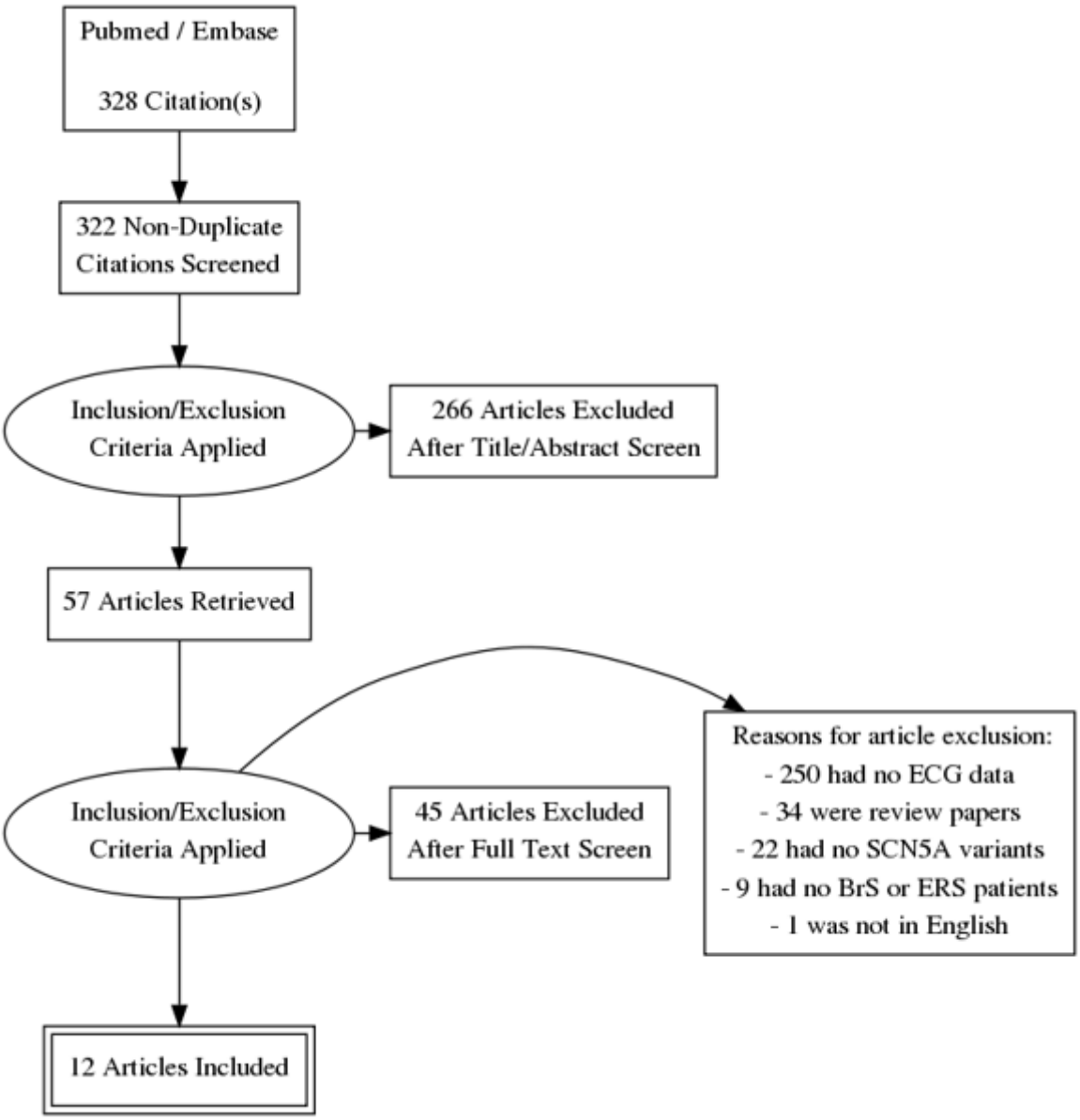

Figure 1

Flowchart of the study selection process.

Figure 2

A) PR interval (in milliseconds), **B)** QRS duration (in milliseconds), **C)** QTc interval (in milliseconds) and **D)** Resting heart rate (in beats per minute).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- ERSvsBrSPRISMA.docx
- SupplementaryMaterialsERSvsBRSSRMA.docx