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RESEARCH

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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 20 October 2021 for human studies containing the search terms "SCN5A" and "variant" and "early repolarization" or "Brugada", with no language restrictions. Continuous variables were expressed as mean±standard deviation. PR interval, QRS duration, QTc and heart rate from the included studies were pooled to calculate a mean for each variable amongst BrS and ERS patients. A two-tailed Student's t test was then performed to for comparisons.

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. One hundred and four 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 shorter QRS duration (90.40±9.97 vs. 114.79±20.10, P = 0.0001) and shorter corrected QT intervals (QTc) with borderline significance (393.63±40.04 vs. 416.82±37.43, P = 0.052). By contrast, no significant differences in baseline heart rate (65.15±18.78 vs. 76.06±18.78, P = 0.068) or PR intervals (197.40±34.69 vs. 191.88±35.08, P = 0.621) were observed between ERS and 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

J-wave syndrome encompasses both Brugada syndrome (BrS) and early repolarization syndromes (ERS), featuring distinct abnormalities in the J-point [1]. BrS is characterized by spontaneous or drug-induced type 1 BrS pattern with a coved ST segment elevation > 2 mm in the

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right precordial leads, which can have overlapping electrocardiographic features with ERS [2]. In ERS, the ST segment is concaved upward with accompanying terminal QRS slurring or notching. Whilst ERS was assumed to be a relatively 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 sudden cardiac death [3, 4]. Patients may present with electrocardiographic features consistent with Brugada or early repolarization patterns with or without their respective syndromes [5, 6]. In both BrS and ERS, dynamic variability in ECG findings may be observed both at baseline or upon physiological challenges [7–9]. For example, in BrS, a type 1 pattern may be precipitated by drugs or stressors such as fever, which can change to a type 2 or even a normal ECG pattern, with diurnal variations [10] or altered autonomic drive [11]. Similarly, in ERS, the degree of ST-T configurations can exhibit diurnal variations [12] or change with drugs or cycle length [13].

Mutations in genes that encode for the plasmalemmal sodium, calcium and potassium channels have all been implicated in BrS and ERS [14, 15]. In particular, pathological variants in SCN5A encoding the pore-forming subunit of the sodium channel have traditionally been associated with BrS [16], with an increasing body of evidence supporting a link with ERS [17, 18]. Thus, it is reasonable to envisage overlapping electrophysiological mechanisms in both syndromes. For example, defects in SCN5A have been associated with conduction abnormalities throughout the myocardium [19, 20]. Recently, *Zhang* et al. studied the genotype–phenotype relationship between SCN5A and the ECG findings in ERS and BrS patients [21]. 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 (Additional file 1) [22]. Two databases, PubMed and Embase, were searched from their inception to 20 October 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 [23]. 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 Additional file 1: Table S1.

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; and (3) were irrelevant.

Data extraction and statistical analysis

Studies congregant with the inclusion criterion were selected for the meta-analysis. The data were 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, BrS SCN5A-positive, ERS SCN5A-positive, syncope, family history of sudden cardiac arrhythmia); (3) ECG measurements: lead II of a 12-lead ECG used to calculate PR interval, QRS duration and QT interval corrected by the Bazett formula. ECG variables were pooled and compared between BrS and ERS patients; (4) method of ECG measurements, e.g. manually performed by the original investigators or automated measurements by ECG machines, was identified. Two reviewers (SL and OC) reviewed each included the studies individually, and disputes were resolved by a third reviewer (GT).

Statistical analysis was performed using Microsoft Excel. PR interval, QRS duration, QTc and heart rate (HR) from the included studies were pooled to calculate a mean for each variable. A two-tailed Student's t test

was then performed to compare the PR interval, QRS duration, QTc and HR between BrS and ERS patients. P value < 0.05 indicated statistical significance.

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 being 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 analysed in this study were PR interval, QRS duration and QTc prolongation.

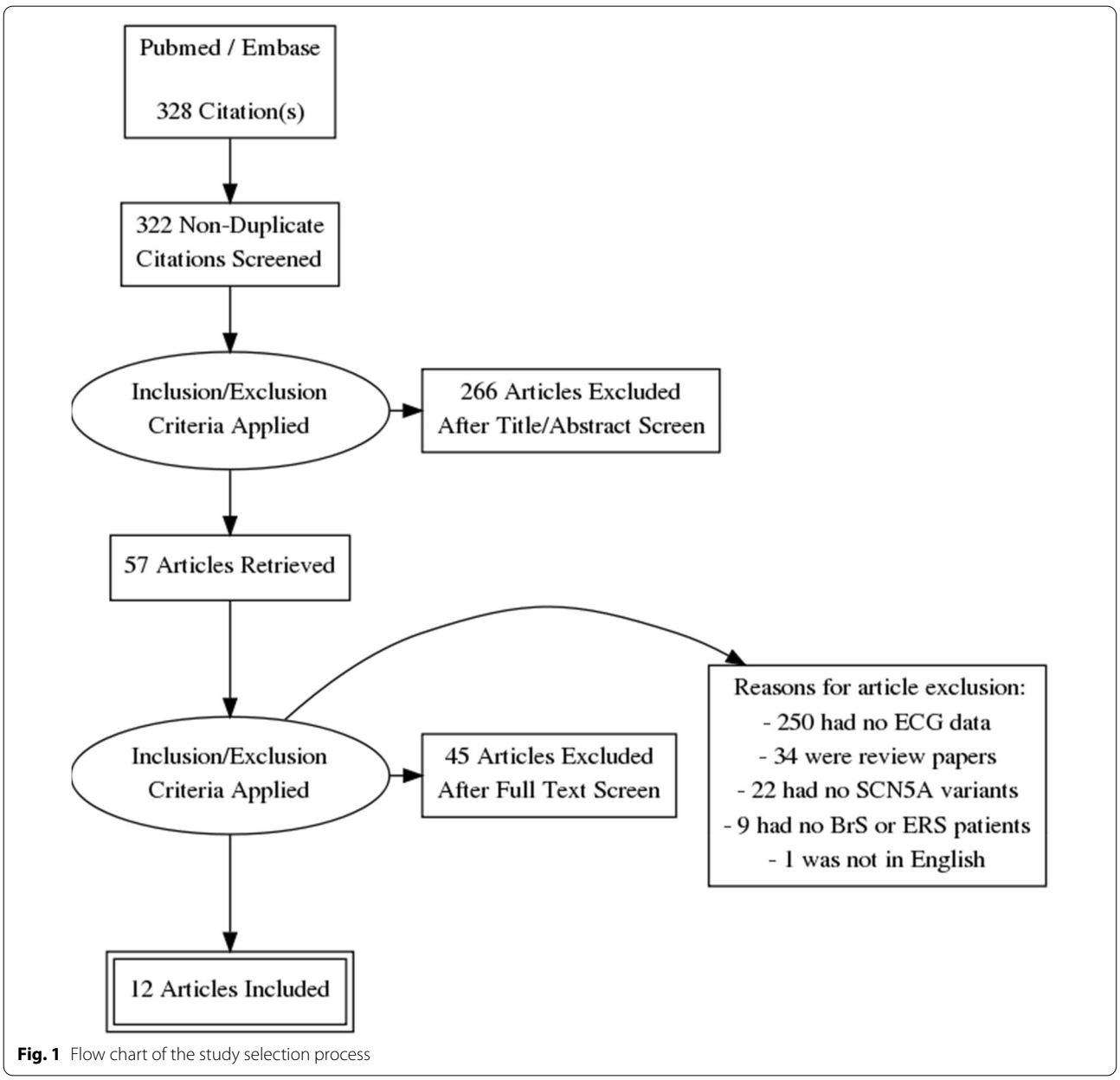

Fig. 1 Flow chart of the study selection process

Our meta-analysis found no significant differences in the PR interval between ERS and BrS patients (197.40 ± 34.69 vs. 191.88 ± 35.08, P = 0.621; Fig. 2A). By contrast, ERS patients had shorter QRS duration (90.40 ± 9.97 vs. 114.79 ± 20.10, P = 0.0001; Fig. 2B) and shorter corrected QT intervals (QTc) with borderline significance (393.63 ± 40.04 vs. 416.82 ± 37.43, P = 0.052; Fig. 2C). Finally, there was no significant difference in the heart rate between ERS and BrS patients (65.15 ± 18.78 vs. 76.06 ± 18.78, P = 0.068; Fig. 2D).

Discussion

The main findings of this systematic review and meta-analysis are that 1) BrS patients with positive SCN5A mutations exhibited prolonged QRS, indicating conduction abnormalities, whereas ERS patients with positive SCN5A mutations showed normal QRS, 2) whilst QTc intervals were longer with a borderline significance in BrS than in ERS SCN5A-positive patients, they were within normal limits, and 3) no significant differences were found in the PR interval and HR 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 [24]. 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 [25]. It has previously been described that activation recovery interval (ARI) in the right ventricular outflow tract of BrS is prolonged. In contrast, the shorter QTc interval amongst ERS patients is suggestive of extensive regions with short ARI, especially in ERS3 where SCN5A is more prevalent [17]. 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 with BrS.

Interestingly, patients with the same SCN5A variant can display different syndromic phenotypes such as BrS and ERS in the same family pedigree, with more prominent ECG features during exacerbations by fever [21]. 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 [2]. This indicates other genetic,

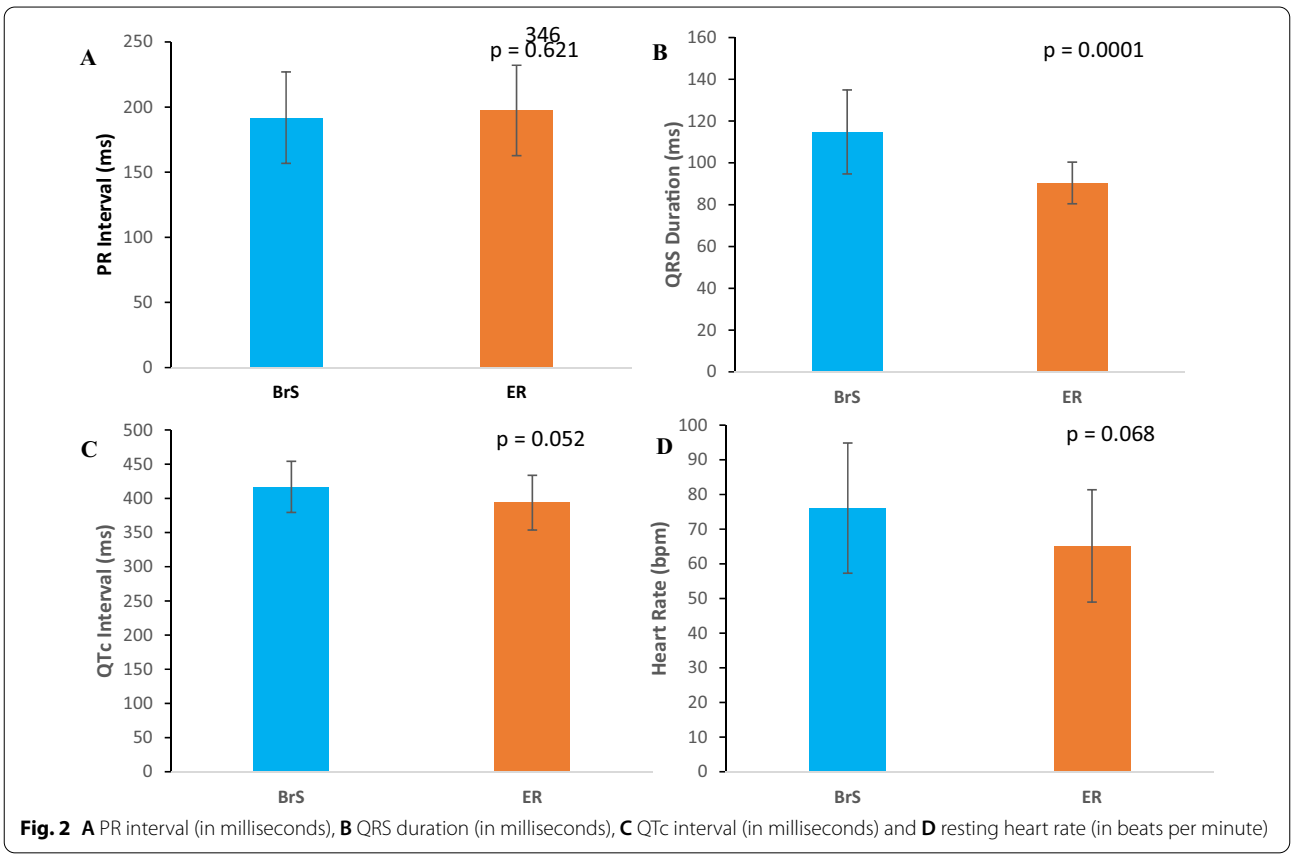

Fig. 2 **A** PR interval (in milliseconds), **B** QRS duration (in milliseconds), **C** QTc interval (in milliseconds) and **D** resting heart rate (in beats per minute)

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 ($I_{Ca\text{-}L}$) in heart failure [26, 27]. 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 [1]. This is because SCN5A is responsible for initiating the cardiac action potential [28]. In ERS, reduction in conduction reserve, the substrate for reentry and arrhythmogenesis localizes to the inferior myocardium in contrast with BrS [29]. 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 [30]. In this study, we focussed on SCN5A variants, the most commonly associated variant in ERS [31]. KCNJ8, ABCC9, KCNE5, DPP10, CACNA1C, CACNB2B, CACNA2D1, SCN5A and SCN10A are all linked with ERS [32], 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 [21].

Furthermore, no significant differences in the PR interval or HR 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 [21]. Whilst the burden of bradycardic complications such as atrioventricular block have been well-investigated in BrS [33], 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.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s42444-022-00066-y.

Additional file 1. NOS risk of bias scale for the included studies and funnel plots.

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Author contributions

DR and OHIC contributed to literature search, data extraction and analysis, drafting of the manuscript, critical revision of the manuscript; GB, KPL, and TL helped in data interpretation and critical revision of the manuscript; GT and SL performed study conception, data analysis and interpretation, drafting and critical revision of the manuscript.

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Availability of data materials

Availability of supporting data: All data are included in the tables.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent to publication

All authors consent to publication.

Competing interests

None.

Statement of disclosure

There is nothing to disclose for all authors.

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