International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Prevalence of spontaneous Brugada ECG pattern recorded at standard intercostal leads: A meta-analysis

Shaobo Shi [a,b], Hector Barajas-Martinez [c], Tao Liu [a,b], Yaxun Sun [c,d], Bo Yang [a,b], Congxin Huang [a,b,**], Dan Hu [a,b,c,*]

[a] Department of Cardiology & Cardiovascular Research Institute, Renmin Hospital of Wuhan University, Wuhan 430060, China
[b] Hubei Key Laboratory of Cardiology, Wuhan 430060, China
[c] Masonic Medical Research Laboratory, Utica, NY 13501, USA
[d] Department of Cardiology, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou 310016, China

ARTICLE INFO

Article history:
Received 28 September 2017
Received in revised form 29 November 2017
Accepted 30 November 2017
Available online xxxx

Keywords:
Brugada ECG pattern
Brugada syndrome
Prevalence
Sudden cardiac death
Risk stratification

ABSTRACT

Objective: Typical Brugada ECG pattern is the keystone in the diagnosis of Brugada syndrome. However, the exact prevalence remains unclear, especially in Asia. The present study was designed to systematically evaluate the prevalence of spontaneous Brugada ECG pattern recorded at standard leads.
Methods: We searched the Medline, Embase and Chinese National Knowledge Infrastructure (CNKI) for studies of the prevalence of Brugada ECG pattern, published between Jan 1, 2003, and September 1, 2016. Pooled prevalence of type 1 and type 2-3 Brugada ECG pattern were estimated in a random-effects model, and group prevalence data by the characteristic of studies. Meta-regression analyses were performed to explore the potential sources of heterogeneity, and sensitivity analyses were conducted to assess the effect of each study on the overall prevalence.
Results: Thirty-nine eligible studies involving 558,689 subjects were identified. Pooled prevalence of type 1 and 2-3 Brugada ECG pattern was 0.03% (95%CI, 0.01%–0.06%), and 0.42% (95%CI, 0.28%–0.59%), respectively. Regions, sample size, year of publication were the main source of heterogeneity. The prevalence of type 1 Brugada ECG pattern was higher in male, Asia, adult, patient, and fever subjects; but the relation between fever and type 2-3 Brugada ECG pattern was not significant. Sensitivity analysis showed that each study did not lonely affect the prevalence of type 1 and type 2-3 Brugada ECG pattern.
Conclusion: Brugada ECG pattern is not rare, especially preponderant in adult Asian males, and fever subjects. Clinical screening and further examination of Brugada syndrome in potential population need to be highlighted.

1. Introduction

Brugada syndrome (BrS) is a rare inherited arrhythmogenic disease, characterized by coved ST-segment elevation in the right precordial leads and an increased risk of sudden cardiac death (SCD) in the structurally normal heart [1]. There are 20 genes associated with BrS, includes those encoding sodium, calcium and potassium channels, as well as proteins affecting ion channels. By far, *SCN5A* is still the major causative gene [2]. Diagnostic criteria of BrS have been updated several times, it requires both of type 1 electrophysiology (ECG) and clinical manifestation in the initial recommendation [3,4]. But the latest one suggests that type 1 Brugada ECG pattern occurring either spontaneous or after provocative drug test has a diagnostic significance [1]. Although there is controversy about whether the clinical symptom and family history of SCD or VT/VF is necessary to confirm the BrS, there is no doubt about the pivotal role of typical Brugada ECG pattern in its diagnosis. However, since the ECG pattern is usually intermittent and dynamic, the true prevalence of BrS remains unknown.

Brugada ECG pattern shows age- and sex-related penetrance. It is more frequent in adults and men [5]. It is well known that its prevalence seems to be higher in Southeast Asia than in elsewhere [6]. But these results are large heterogeneity, since those studies were performed among different region, population and diagnostic criteria. The prevalence of Brugada ECG pattern have been reported [5,6], however, no systematic reviews using a meta-analysis method have been done and the more details have not been pooled estimated. Accurate estimates of prevalence are important for public policy and planning

* Correspondence to: D. Hu, Masonic Medical Research Laboratory, 2150 Bleecker St, Utica, NY 13501, USA.
** Correspondence to: C. Huang, Department of Cardiology & Cardiovascular Research Institute, Renmin Hospital of Wuhan University, 238 Jiefang Road, Wuchang District, Wuhan, Hubei 430060, China.
E-mail addresses: cxhuang@whu.edu.cn (C. Huang), dianah@mmrl.edu (D. Hu).

https://doi.org/10.1016/j.ijcard.2017.11.113
0167-5273/© 2017 Elsevier B.V. All rights reserved.

of clinical services tailored to people. The present study aims to perform a meta-analysis to determine the prevalence of spontaneous Brugada ECG pattern recorded at the standard intercostal leads.

2. Methods

2.1. Search strategy and selection criteria

In accordance with the PRISMA guidelines, we searched Medline, Embase, and Chinese National Knowledge Infrastructure (CNKI) with the term "prevalence and (Brugada ECG pattern", "Brugada sign", "BrS)" for studies of the prevalence of Brugada pattern published between Jan 1, 2003, and September 1, 2016. Key articles and reviews were hand-searched to identify any additional literature. After exclusion of duplicate studies, two investigators independently reviewed titles and abstracts of the remaining articles using the eligibility criteria.

Included studies had to meet following three criteria for inclusion. Studies that were published in English or Chinese were included; a proposed diagnosis criterion for the Brugada ECG pattern was employed [7]; prevalence of Brugada pattern was reported, or sufficient data was provided to calculate the estimates.

2.2. Data collection

Two reviewers independently extracted the following information from eligible articles: name of the first author, year of publication, geographical location, demographics (age, gender), method of sample selection, sample size, diagnostic criteria for Brugada ECG pattern, diagnostic method, numbers of Brugada ECG pattern, and prevalence. The prevalence of spontaneous Brugada ECG pattern recoded at standard intercostal leads was only collected and used in this analysis. We did not collect the prevalence of Brugada ECG pattern either under drug provocation or recorded at high intercostal leads.

2.3. Quality assessment

In accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [8], the quality of studies was assessed and scored as follows: whether the study population was clearly described (yes = 1, no = 0);whether the definition of Brugada ECG pattern was according to the Brugada Consensus Conference criteria (yes = 1, no = 0); participation rate (response rate > 60% = 1, response rate ≤ 60% or not reported = 0); and sample size (≥1000 participants = 1, <1000 participants = 0). A higher score indicates higher study quality.

2.4. Statistical analysis

We calculated estimates with the variance-stabilizing double arcsine transformation, because the inverse variance weight is suboptimum when dealing with binary data with low prevalence. The estimated prevalence and 95%CI were calculated using a random-effects model, because significant heterogeneity was anticipated among studies. Sensitivity analyses were performed by omitting each reference to evaluate whether the final results could have been affected markedly by any included studies. We also performed the subgroup analysis based on gender (male *vs.* female), geographical region (Asia *vs.* other), age (juvenile *vs.* adult), subject (healthy *vs.* patient), and fever (yes *vs.* no), and the odds ratio was also calculated.

We estimated heterogeneity between studies with Cochran's test was and I^2, which indicates the proportion of total variance-explained heterogeneity. *P* values <0.10 indicate heterogeneity, and I^2 values of 25%, 50% and 75% show low, moderate, and high degrees of heterogeneity. We did the meta-analyses and prepared forest plots using R software (version 3.3.1).

Potential sources of heterogeneity were further investigated by meta-regression analysis using STATA software (version 13.1), both in individually and multiple-variable models. Related factors examined included year of publication, quality scores, gender (male *vs.* mix), geographical region (Asia *vs.* other), sample size (≥1000 *vs.* <1000), subject (healthy *vs.* patient) and score.

3. Results

3.1. Study selection

Flow diagram for the study selection process is shown in Supplemental Fig. 1. Our literature search identified 726 reports, after removal of duplicated and initial screening, we reviewed 213 papers for title and abstract. After exclusion of 177 ineligible reports, with the addition of three articles from reference lists, a total of 39 articles [9–47] were included for quality assessment and meta-analysis.

3.2. Study characteristics

The summary on characteristics of included studies is showed in Supplemental Table 1. Of the 39 studies (n = 558,689) for Brugada ECG pattern, thirty-nine studies [9–47] reported the prevalence of type 1 Brugada ECG pattern, thirty-seven reports [9–16,17–45,47] of type 2-3 Brugada ECG pattern. Twenty-five studies (64.1%) were from the Asia, including eight from China [11,20,26,27,32,36,39,44], seven from Japan [11,12,14,15,18,30,47], two each from Korea [19,40] and Thailand [45,46], and one each from Israel [43], Iran [23], Philippines [29], Pakistan [31], and Singapore [34]; one study [22] from Hawaii was also included in the Asian group, since it reported the prevalence in a population of middle-aged Japanese-American men. The other fourteen reports were from the non-Asian countries, three from the USA [9,24,33], two each from Turkey [21,42] and Denmark [37,41], and one of each from Austrian [38], Canada [17], Finland [13], France [16], Italy [28], Greece [25], and German [35] (Fig. 1). Twenty-six were conducted in the adults [10–13,16,17,19,20,22–24,27,29,30,34,35,37, 38,40–47], three studies [14,15,18] in juvenile subjects, and other ten [9,21,25,26,28,31–33,36,39] in mix-age sample. Eight [12,15,17,19,22, 40,42,45] included data for men, twenty-seven [10,11,13,14,16,18,20, 21,23–32,34–36,39,41,43,44,46,47] were mixed-sex sample, and the other four [9,33,37,38] were unknown the gender proportion. Twenty-six studies [10,12–22,26–31,35,37,40–42,44–45,47] were performed in healthy examination population, and thirteen studies [9,11,23–25, 32–34,36,38,39,43,46] in the patient population. Twelve studies [9,12, 13,19,33,34,37,38,41,42,45,46] had scores of 3, and the scores were 4 in the other twenty-seven studies [10,11,14–18,20–32,35,36,39,40, 43,44,47].

3.3. Prevalence of Brugada ECG pattern

Thirty-nine studies [9–47] assessed type 1 Brugada ECG pattern, estimated ranged from 0% to 4.85%, the random-effects pooled prevalence was 0.03% (95%CI, 0.01%- 0.06%), with substantial heterogeneity (I^2 = 90.8%; 95%CI, 88.4%–92.7%; $p < 0.001$; Fig. 2A). Region and sample size were two main sources of heterogeneity in univariate meta-regression analysis; but the effect of region did not remain significant after multivariate meta-regression (Table 1).

Thirty-seven studies [9–16,17–45,47] reported prevalence of type 2-3 Brugada ECG pattern, with range from 0% to 3.9%, the random-effects pooled prevalence was 0.42% (95%CI, 0.28%–0.59%), heterogeneity was also substantial (I^2 = 98.4%; 95%CI, 98.1%–98.6%; $p < 0.001$; Fig. 2B). In individual variable meta-regression analysis, year of publication and region were primary influence factor of heterogeneity; the relation remains significant after multivariate meta-regression (Table 1).

Most studies consisted of convenience samples of people recruited from a medical institution, either for healthy examination or treatment, and the characteristic of sample and studies varied. To explore more details of prevalence, we performed subgroup analyses based on gender, region, age, subject, fever, and sample size (Fig. 3A). The pooled prevalence of type 1 Brugada ECG pattern was significantly higher in male, Asian, adult, patient, febrile, and large sample size groups than controls; and the pooled prevalence of type 2-3 Brugada ECG pattern was also higher in the above subgroups except the fever subgroup, all with statistical significance (Fig. 3B).

A sensitivity analysis, conducted both at type 1 and 2-3 Brugada ECG pattern to investigate the influence of each individual study on the overall meta-analysis summary estimate, demonstrated that no study affected the pooled prevalence.

4. Discussion

The present study aimed to systematically evaluate the prevalence of Brugada ECG pattern in the world. Our results showed that the prevalence of spontaneous type 1 and type 2-3 Brugada ECG pattern

Please cite this article as: S. Shi, et al., Prevalence of spontaneous Brugada ECG pattern recorded at standard intercostal leads: A meta-analysis, Int J Cardiol (2017), https://doi.org/10.1016/j.ijcard.2017.11.113