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Spontaneous Brugada electrocardiogram patterns are rare in the German general population: results from the KORA study

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Aims The Brugada syndrome is a rare, potentially fatal primary cardiomyopathy. Patients are identified by symptoms and typical electrocardiogram (ECG) patterns. Prevalence of spontaneous Brugada ECG patterns in the general population is unknown.

Methods and results We analysed 12-lead resting ECGs of 4149 men and women aged 25–74 years from the population-based KORA Study. Computer-assisted analysis identified ECGs with J-point elevation in leads V1–V3 and QRS duration $\leq$150 ms. Positive ECGs were re-evaluated independently by expert cardiologists. Computer-assisted analysis identified 250/4149 ECGs, predominantly from male probands (206/250) who were younger (41.0 $\pm$ 11.9 vs. 52.1 $\pm$ 13.8 years, $P < 0.0001$) than males without the ECG sign. After expert review, not a single ECG showed a Brugada ECG pattern. A high percentage of ECGs were considered abnormal, the majority (73) showing left-ventricular hypertrophy. Manual analysis of a representative, randomly selected sample of 351 ECGs without computer-assisted preanalysis revealed not a single Brugada ECG pattern. True Brugada patterns were reliably identified by screening of a control subset of patients.

Conclusion Spontaneous Brugada ECG patterns are rare in the general population and may hence constitute a relevant biological signal. Computer-aided analysis can help to identify abnormal ECGs.

Keywords Brugada Syndrome • Electrocardiogram • Computer analysis • General population • Prevalence

Introduction

The Brugada Syndrome is a primary, arrhythmogenic cardiomyopathy, which is in part genetically determined. It has first been described by Brugada and Brugada in 1992 in eight patients who presented with remarkable electrocardiogram (ECG) changes and experienced ventricular arrhythmias and aborted sudden cardiac death.[1] In the past 15 years, a number of rare mutations in the genes encoding the α-subunit of the cardiac sodium channel (SCN5A),[2,3] and some mutations in the β-subunit of the channel[4] and rare mutations in the glycerol-3-phosphate dehydrogenase 1-like gene (GPD1L)[5,6] have been identified in patients with Brugada syndrome. Another genetic abnormality associated with Brugada ECG pattern and a short QT interval has been described

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in the L-type calcium channel gene.[7] Taken together, these genetic defects account for ~18–30% of the disease, while the majority of patients carry unknown genetic defects.

The diagnosis of Brugada syndrome relies on the identification of a typical ECG pattern consisting of incomplete right bundle branch block and ST-segment elevation in the right precordial leads.[1] The diagnosis is complicated by the existence of the so-called 'benign ST segment elevation syndrome' that consists of a Brugada ECG pattern without symptoms.[8] Most commonly, a positive spontaneous ECG pattern is referred to, if the disgnostic criteria for a Brugada Type 1 ECG are fulfilled. A recent study, published in this journal, investigated individuals with a spontaneous Brugada ECG pattern and found a high rate of symptomatic subjects, although clinical presentation was the strongest predictor.[9] An ECG survey in young Finnish adults identified a substantial portion of ECGs with a spontaneous Brugada ECG pattern (0.6%).[8] Other ECG surveys in selected patients or probands from Greece (0.22%[10]), Italy (0.26%[11]), Turkey (0.48%[12]), the Filipinos (0.2%[13]), or France (6.1%[14]) found a similar or higher prevalence of a spontaneous Brugada ECG pattern. Studies in subjects of Japanese descent described prevalences between 0.146[15] and 0.7%.[16] The Finnish study did not identify arrhythmic events over a 11 year follow-up,[8] but a familial clustering of atrial fibrillation,[17] while the Japanese study demonstrated an increased mortality in probands with a Brugada ECG pattern.[15] Most of these ECG analyses were performed either in groups of patients or in selected subgroups presenting for ECG screening. Only the Japanese study attempted a population-wide estimate of spontaneous Brugada ECG pattern.

To identify the prevalence of spontaneous Brugada ECG pattern in a Caucasian population, we applied the ECG criteria described in two consensus conferences endorsed by the European Society of Cardiology and the American Heart Association[18,19] to 4149 standardized ECGs recorded in a random sample taken from the Caucasian population in the region of Augsburg (KORA). All ECGs were analysed for J-point elevation in the right precordial leads using a standardized computer-assisted algorithm; all abnormal ECG recordings were re-evaluated by expert cardiologists.

Methods

Study population

An epidemiological survey of the general population living in the city of Augsburg, Southern Germany, and two adjacent counties was conducted between 1999 and 2001 (KORA S4).[20] Individuals were identified through the registration office if they were of German nationality and were born between 1 July 1925 and 30 June 1975. An initial sample of 6640 subjects was drawn with 10 strata of equal size according to gender and age. Four thousand two hundred and sixty-one (66.8%) individuals agreed to participate in the survey, which were ethnic Germans (Caucasians) with very few exceptions (>99.5%). There was no known familial relationship between the study participants. Electrocardiogram recordings were available from 4149 subjects (97.4%), which were further analysed in our present study. Failure to ECG recording was due to physical impossibilities to record, technical obstacles or denial of the proband. All participants gave their written informed consent prior to inclusion into the study, which was approved by the responsible medical ethics committee.

Electrocardiogram recording

Twelve-lead ECG recordings were performed in a standardized manner after 10 min rest in supine position, applying detailed procedures of quality control with respect to signal quality, patient conditioning, electrode position, and proband position. All ECGs were recorded using the Hörmann Bioset 9000. To guarantee highest quality, recording technicians were specifically trained before data acquisition. Location of the chest leads has been routinely performed after marking the electrode positions using the DAL Square.[21]

Electrocardiogram analysis

Three different types of a Brugada ECG pattern are known: Type 1 shows a coved ST-segment elevation in more than one lead (V1–V3) $\geq$200 μV, followed by a negative T-wave. Type 2 is characterized by a saddle-back configuration, formed by precordial ST-elevation fading to positive T-waves. Type 3 has a right-precordial ST-segment elevation $\leq$100 μV and either Type 1 or 2 morphology.[2,18,19] Given the slight ECG changes in the Type 3 morphology and their uncertain clinical relevance, in the present investigation, we restricted analysis to Type 1 or 2 morphology.

In this study, ECG analysis was performed using a two-step approach. At first, all ECG recordings were digitally analysed using the automated Hannover ECG System (HES). To identify potential Brugada ECG patterns with high sensitivity, ECGs were considered positive in this digital analysis if they fulfilled the following criteria:

J-Point elevation in leads V1 or V2 or V3$\geq$150 μV and QRS duration $\leq$150 ms.

The ECG measurements were based on computerized analysis using the HES Version 3.22–12,[22] a validated system with good analysis performance.[23] Hannover ECG System analyses an averaged cycle computed from all normal ECG cycles of a 10 s recording period excluding ectopic beats. This procedure minimizes measurement imprecision due to possible noise effects on single ECG cycles. All 12 leads are considered simultaneously. The final interval estimates are determined from the initial deflection of a wave in any lead until the end of the latest deflection in any lead. For this study, J-point amplitudes were analysed for each individual lead.

To evaluate the computer-based screening algorithm used in this study, we selected 14 patients with diagnosed Brugada syndrome from the clinical repository of the Munich University Hospital Grosshadern, presenting with a typical type 1 ECG ($n = 11$) and a typical type 2 ECG ($n = 3$), respectively. These ECGs were processed by the computer algorithm in the same way and using the same criteria as all further ECGs. After positive evaluation of the algorithm, it was used to pre-analyse all 4149 ECG recordings from the KORA S4 study.

In a second step, all ECGs identified by digital analysis were independently analysed by three expert cardiologists for presence of a Brugada ECG pattern and other abnormalities. Manual analysis was done using standardized remeasurement of PR-, QRS-, and QT-duration as well as a quantification of J-point elevation in leads V1–V3. It was at the discretion of the cardiologist, to judge an ECG as compatible with a Brugada pattern or any other pathology.

To validate the automated analysis, a random sample of 351 ECG recordings not identified by digital pre-analysis also underwent expert analysis. Interpretation followed the same rules as the re-analysis of the ECGs filtered by digital analysis.

Results

Fourteen ECGs of patients with diagnosed Brugada syndrome (11 with type 1 ECG, 3 with type 2 ECG) were analysed using the computer-based algorithm to (i) evaluate it and then (ii) to serve as a positive control. Subjects were 12 males between 28 and 70 years of age, and two females aged 5 and 28 years, respectively. Two representative ECGs with Brugada pattern, one with more pronounced and one with more subtle changes are displayed in *Figure 1*. Using the J-point-based screening criterion, all 14 ECGs were correctly identified by our algorithm. Individual-level J-point elevation measurements are provided in *Table 1*.

The target study population consisted of 4149 individuals with an overall mean age of 50.62 $\pm$ 13.91 years, 2034 of which were of male sex. Two-hundred and fifty of 4149 computer-analysed ECGs were positive after digital evaluation using the J-point elevation-based screening criterion. Probands with J-point elevation in the right precordial leads in this digital analysis were predominantly male [(206/250 (82.4%)]. They were significantly younger ($P < 0.0001$), had longer QRS duration ($P < 0.0001$), and had a higher Sokolow–Lyon Index indicative for left-ventricular hypertrophy ($P < 0.0001$) compared with both the remaining male subjects and the entire study population (*Table 2*). PQ intervals were comparable between groups.

Based on published criteria, there was not a single ECG classified as Brugada pattern Type 1 by any of the experts. Only one ECG was considered as possibly suggestive of Brugada pattern Type 2 by one expert, where the occurrence could not entirely be ruled out, while it was considered normal by the other two experts and in a final consensus reading.

The 250 ECGs identified by the computer-based screening showed a high percentage of abnormal findings. Although we did not find a single Brugada ECG pattern in this population-based ECG survey, 87/250 ECGs (35%) with J-point elevation in the right precordial leads were considered abnormal in the expert analysis: Sixteen ECGs had abnormal atrial and AV nodal parameters: in eight patients, a first degree atrio-ventricular block was found. One subject showed atrial fibrillation, the remaining seven presented with unspecific P-wave abnormalities. The QRS complex was found to be abnormal in 33 subjects by at least one reviewer: 19 ECGs showed a complete left or right bundle branch block, 7 an incomplete left or left anterior hemi block. In seven subjects, an unspecific notching of the QRS complex was described. An inverted T-wave was described in lead V1 in 22 cases, while one subject had T-wave inversion in both leads V2 and V3 and two ECGs were suggestive of prior anterior wall myocardial infarction. Seventy-three ECGs showed signs of left-

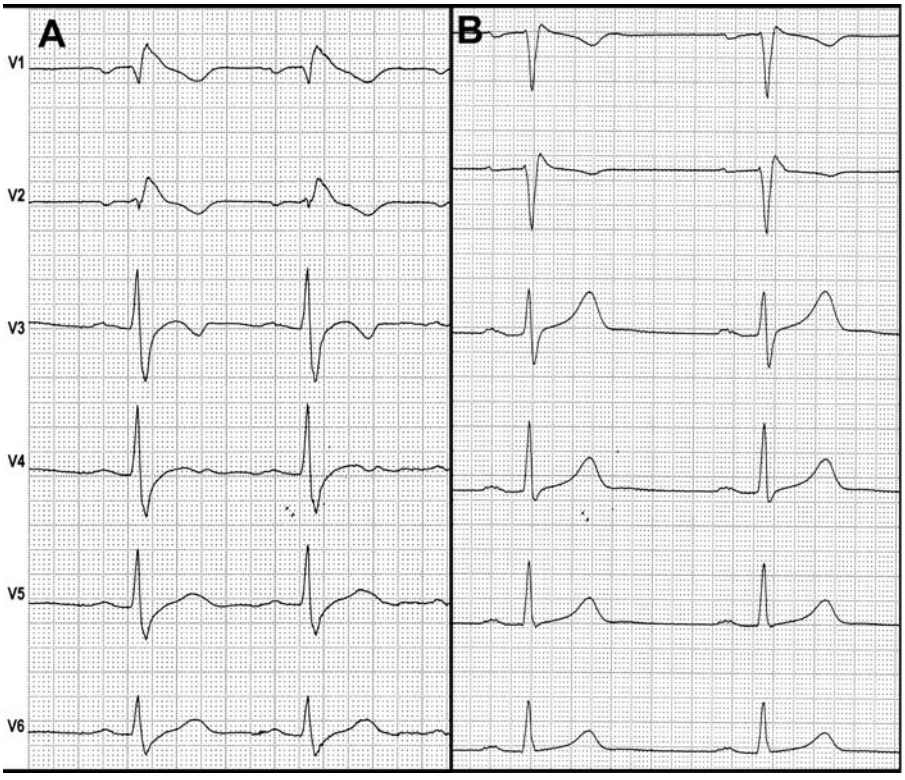

Figure 1 Examples of electrocardiograms with Brugada type 1 pattern presenting with pronounced (*A*) and subtle (*B*) electrocardiogram changes. All measurements are computer-based (*A*) 5-year-old girl, chest leads only, HR 89/min, PR 138 ms, QRS 104 ms, QTc 443 ms, J-point elevation in V1, V2, and V3 200, 100, and −80 μV, respectively. Electrocardiogram positively identified by J-point-based screening. (*B*) 55-year-old male, chest leads only, HR 52/min, PR 198 ms, QRS 96 ms, QTc 415 ms, J-point elevation in V1, V2, and V3 100, 200, and 30 μV, respectively. Electrocardiogram positively identified by J-point-based screening.

Table 1 J-point elevation in Brugada Type 1 and 2 electrocardiograms

ID	Age (years)	Sex	ECG type	J-point elevation V1 (μV)	J-point elevation V2 (μV)	J-point elevation V3 (μV)	Recognized by J-point elevation screening
1	28	Male	I	400	750	90	Yes
2	30	Male	I	230	500	70	Yes
3	34	Male	I	250	570	700	Yes
4	37	Male	I	290	410	60	Yes
5	30	Male	I	370	710	1050	Yes
6	30	Male	II	170	290	100	Yes
7	39	Male	I	130	490	10	Yes
8	55	Male	I	100	200	30	Yes
9	50	Male	I	260	310	220	Yes
10	47	Male	II	170	50	20	Yes
11	70	Male	II	230	270	60	Yes
12	23	Male	I	400	410	140	Yes
13	28	Female	I	220	390	350	Yes
14	5	Female	I	200	100	-80	Yes

Age, sex, and computer-based measurements of J-point elevation in leads V1–V3 in 14 patients with diagnosed Brugada syndrome and positive Brugada electrocardiogram pattern Type 1 or 2. The column to the right provides information whether or not these electrocardiograms were flagged abnormal using our prespecified screening criteria for J-point elevation.

Table 2 Clinical and electrocardiogram characteristics of the study population

Variable	Participants with relevant J-point elevation ($n = 250$)	Participants without relevant J-point elevation ($n = 3899$)	Male participants with relevant J-point elevation ($n = 206$)	Male participants without relevant J-point elevation ($n = 1828$)
Male gender, *n* (%)	206 (82.4)	1828 (44.1)*		
Age (years)	43.3 ± 13.1	51.1 ± 13.8*	41.0 ± 11.9	52.1 ± 13.8*
Heart rate (min^{-1})	60.6 ± 10.5	65.5 ± 10.8*	60.2 ± 10.1	64.9 ± 11.2*
PR duration >200 ms, *n* (%)	12 (4.8)	212 (5.4)	9 (4.4)	140 (7.7)
QRS duration (ms)	100.8 ± 13.2	92.6 ± 11.9*	101.3 ± 11.7	97.1 ± 12.5*
QRS duration >105 ms, *n* (%)	70 (28.0%)	369 (9.5%)*	60 (29.1%)	305 (16.7%)*
J-point amplitude in lead V1 (μV)	66.5 ± 42.7	27.0 ± 27.1*	65.1 ± 37.7	32.9 ± 30.1*
J-point amplitude in lead V2 (μV)	184.8 ± 39.9	59.6 ± 42.8*	182.9 ± 35.1	70.1 ± 46.9*
J-point amplitude in lead V3 (μV)	127.9 ± 51.7	30.8 ± 40.9*	136.1 ± 45.6	42.8 ± 44.8*
ST amplitude in lead V1 (μV)	87.9 ± 53.8	37.1 ± 35.5*	85.6 ± 46.3	45.2 ± 42.1*
ST amplitude in lead V2 (μV)	250.5 ± 65.8	91.2 ± 58.8*	256.9 ± 56.0	112.5 ± 66.2*
ST amplitude in lead V3 (μV)	196.9 ± 69.3	62.4 ± 53.9*	211.9 ± 58.8	84.5 ± 59.6*
Sokolow–Lyon Index (μV)	3668.5 ± 954.2	2576.8 ± 707.4*	3713.8 ± 951.6	2752.8 ± 766.3*
Sokolow–Lyon Index >3500 μV, *n* (%)	141 (56.4%)	379 (9.7%)*	121 (58.7%)	274 (15.0%)*

Clinical and electrocardiogram characteristics, separated for all subjects (left two columns) and male subjects only (right two columns) with and without relevant J-point elevation in the right precordial leads identified by computer-assisted analysis. Unless otherwise indicated, all values are given as mean ± standard deviation.
*$P < 0.0001$.

ventricular hypertrophy in the expert analysis. *Figure 2* shows selected examples of the observed abnormalities.

Additional analyses to verify and increase sensitivity of the digital analysis were performed. Manual evaluation by expert cardiologists of a representative sample of 351 randomly selected ECGs that did not meet the digital screening criteria did not reveal a single Brugada ECG pattern. J-point elevation was below the respective thresholds of detection of the automated analysis in the respective leads.

In summary, the prevalence of a spontaneous Brugada ECG pattern was low in this large sample representative for the general population in Germany. Computer-assisted screening for J-point elevation in right precordial leads is reliable in identifying potential Brugada ECG patterns. Interestingly, young male

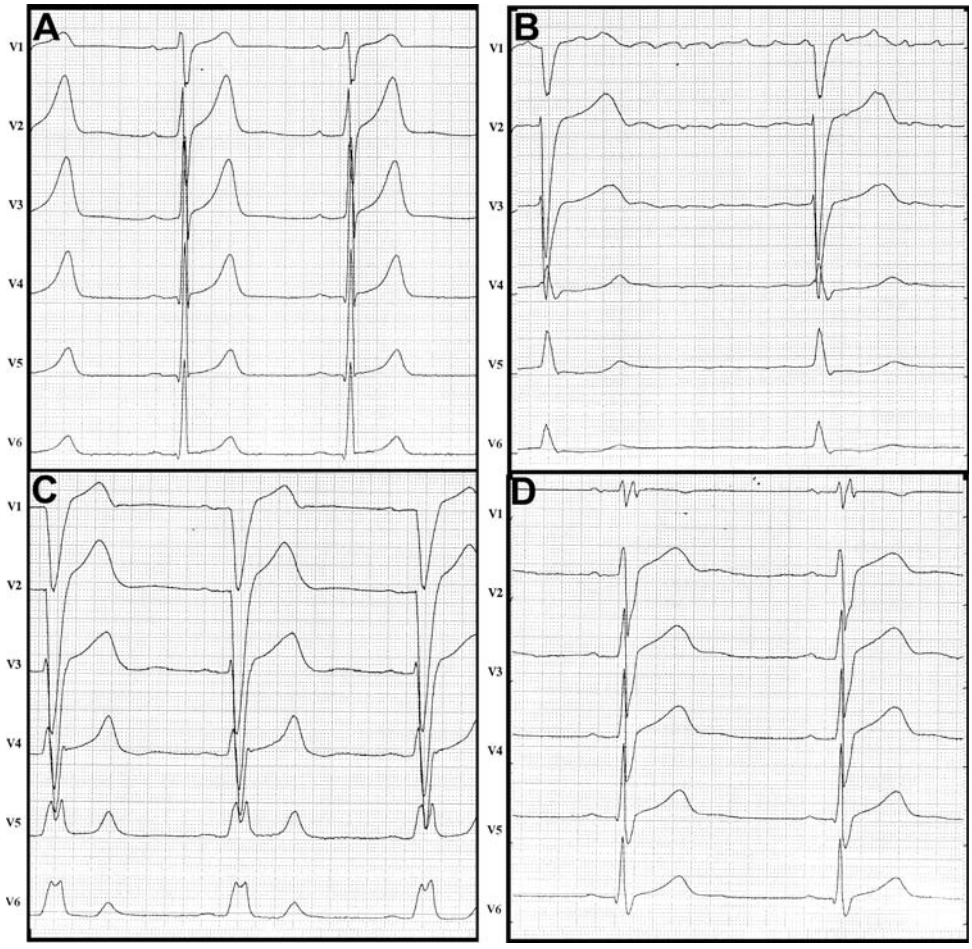

Figure 2 Examples of abnormal electrocardiograms identified by the digital analysis (all electrocardiograms at 50 mm/s and 1 mV/mm). All electrocardiograms were identified by J-point elevation in leads V1–V3, thus only chest leads are displayed. Limb leads did not show further abnormalities: (*A*) Left ventricular hypertrophy [male, 31 years, normal axis (44°), HR 67/min, PR 162 ms, QRS 102 ms, QT 394 ms]; (*B*) Atrial fibrillation [male, 67 years, left axis deviation (−63°), HR 46/min, QRS 126 ms, QT 524 ms]; (*C*) Complete left bundle branch block [male, 55 years, left axis deviation (−71°), HR 59/min, PR 156 ms, QRS 144 ms, QT 482 ms]; (*D*) Incomplete right bundle branch block [male, 45 years, normal axis (87°), HR 52/min, PR 164 ms, QRS 124 ms, QT 452 ms].

probands with 'unspecific' J-point elevations in the right precordial leads showed a high incidence of ECG abnormalities other than the Brugada ECG sign such as left-ventricular hypertrophy, left or right bundle branch block, or AV nodal block. Digital ECG analysis was valuable in identifying ECGs with abnormal J-point segments in the right precordial leads.

Discussion

This is the first study to analyse systematically the prevalence of the spontaneous Brugada ECG pattern in a European sample that was specifically recruited to epidemiologically reflect the general population of Southern Germany. Although the ECGs were of high quality and screening criteria were applied to warrant a high sensitivity, we could not identify a single ECG compatible with Brugada Type 1 or Type 2 pattern in over 4000 ECG recordings screened. Thus the prevalence of spontaneous Brugada ECG patterns in this population of Caucasian origin is low. The prevalence of the Brugada syndrome is estimated to be around 5 in 10 000 inhabitants[2] and the prevalence of the spontaneous Brugada ECG pattern is reported to be even higher.[8,10–16] Thus, in our study population one would statistically expect at least two subjects with the syndrome and accordingly more with just the ECG changes.

Low prevalence of a spontaneous Brugada electrocardiogram pattern in a Caucasian population-based sample

These findings are in contrast with those from other studies, where the prevalence ranged from 0.22 to 6.1% in European populations[10–12,14] and 0.146 to 0.7% in a Japanese population.[15,16] One explanation could be that we analysed ECGs from a strictly population-based sample of European descent. The other European studies used either subjects undergoing occupational health

examinations[11,14] or were recruited in hospitals.[10,12] This could, at least in part, explain why their prevalence was markedly higher. Occupational health examinations usually comprise the younger age-ranges of the working population, where the prevalence of the Brugada syndrome is known to be higher.[24] In our population-based sample, the youngest age groups, namely children and adolescents, were not represented due to the study design. One might argue that this subset of individuals is most affected by the Brugada syndrome, and if the Brugada ECG pattern goes along with a higher risk of sudden cardiac death, as recently described,[9] then the relevant cases could already have been deceased in our study. On the other hand, the mean age of our population is 50.62 $\pm$ 13.91 years and around 50% of the study participants are below the age of 50 years. Therefore the fraction of relatively young participants can still be assumed high enough to ensure positive Brugada ECG findings, if there were any. In hospitalized subjects, the other type of study groups investigated previously, the probability of accompanying diseases is known to be higher, even if hospitalization was not due to cardiovascular diseases. The only other strictly population-based study is one in a population of Japanese descent, were the prevalence of 0.146% is low in comparison to the European studies, but still higher than in our study. This may reflect that the Brugada syndrome and maybe as well the Brugada ECG pattern are more prevalent in Asian populations.

To the best of our knowledge, our study is the only one that applied a two-step approach using a screening stage with automated, computer-assisted analysis of a large number of ECGs, and a second stage where these identified ECGs were further investigated by expert cardiologists. This approach has been shown to effectively reduce the workload for each individual reviewer of the data and analysis of patients with known Brugada ECG pattern has proved that our screening criteria would have been capable of reliably identifying such ECG changes. One prerequisite for this, however, is a standardized protocol for data acquisition and high-quality control standards to rule out potential false positive or negative results due to poor data quality. In particular, careful and correct position of the chest-electrodes C1 and C2 is crucial, since Brugada ECG patterns can be simulated by alternative electrode positions:[25] Placement of the right precordial electrodes C1 and C2 in the second, and not the fourth, intercostal space, may increase the likelihood of right precordial J-point and ST-segment elevation.[26] There are reports, suggesting that electrode positioning in the third intercostal space as well yields relevant clinical value.[18] Within the scope of the KORA study, these needs are fulfilled.[27] To rule out potentially missed cases with Brugada ECG patterns, all 4149 ECGs were routinely analysed by a physician after data acquisition. In addition, we analysed a representative and random sample of 351 ECGs by an expert cardiologist. Both analyses revealed no Brugada ECG pattern.

J-point elevation in the right precordial leads is associated with electrocardiogram abnormalities

While the 250 ECGs with elevation of the right precordial J-point were not compatible with a Brugada ECG pattern, 87/250 were judged abnormal by expert analysis, with left-ventricular hypertrophy, first degree AV block, and bundle branch block representing the most common abnormalities. In this context, as well a more positive Sokolow–Lyon-Index—indicative of left ventricular hypertrophy—can be explained, which was found in the set of the identified 250 ECGs. The presence of such signs in an ECG should probably trigger a thorough evaluation of structural heart disease including other cardiomyopathies such as conduction disease or hypertrophic cardiomyopathy. Furthermore, digital assessment of J-point elevation in the right precordial leads may help to identify ECGs of probands with subtle ECG abnormalities.

In conclusion, Brugada-like ECG patterns are rare in the German general population. This has implications for the further diagnostic and therapeutic management of patients with a 'true positive' spontaneous Brugada ECG pattern, especially when the chest electrodes C1 and C2 are placed correctly. A two-step ECG analysis with an automated, high-sensitivity digital analysis of a high number of ECGs and subsequent expert analysis of abnormal ECGs can simplify the workflow of analysis of large ECG databases.

Limitations

This report is the first strictly population-based analysis of the prevalence of a spontaneous Brugada ECG pattern in a Caucasian population. Due to the study design, no individuals below the age of 18 and over the age of 75 are included. Thus our results are of limited interpretability for these age groups. Brugada ECG patterns partly occur only transiently.[11] Our report is based on the analysis of a single ECG recording per proband, similar to practically all published surveys. However, it is known that fluctuations between diagnostic and non-diagnostic ECG findings are common in the Brugada syndrome.[28] Thus we might have missed subjects with intermittent presence of Brugada ECG patterns. Our findings may not be transferable to populations of different ethnic background and further studies will be needed to elucidate ethnic differences in Brugada ECG pattern. We presented data on 4149 study participants. Considering reports on the estimated prevalence of the Brugada syndrome[18] and assuming that the occurrence of the Brugada ECG pattern is even more common, we considered our study sufficiently powered to determine the prevalence of the ECG pattern. However, taking into account that the real prevalence, as suggested by our data, is lower, it is possible that even our large study population was too small and further efforts will be necessary to provide a reliable estimate of the prevalence of the Brugada ECG pattern.

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References

1. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *J Am Coll Cardiol* 1992;**20**:1391–6.
2. Benito B, Brugada R, Brugada J, Brugada P. Brugada syndrome. *Progress Cardiovasc Diseases* 2008;**51**:1–22.
3. Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P *et al.* Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature* 1998;**392**:293–6.
4. Watanabe H, Koopmann TT, Le Scouarnec S, Yang T, Ingram C, Schott JJ *et al.* Sodium channel beta1 subunit mutations associated with Brugada syndrome and cardiac conduction disease in humans. *J Clin Invest* 2008;**118**:2260–8.
5. London B, Michalec M, Mehdi H, Zhu X, Kerchner L, Sanyal S *et al.* Mutation in glycerol-3-phosphate dehydrogenase 1 like gene (GPD1-L) decreases cardiac Na+ current and causes inherited arrhythmias. *Circulation* 2007;**116**:2260–8.
6. Weiss R, Barmada MM, Nguyen T, Seibel JS, Cavlovich D, Kornblit CA *et al.* Clinical and molecular heterogeneity in the Brugada syndrome: a novel gene locus on chromosome 3. *Circulation* 2002;**105**:707–13.
7. Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, Aizawa Y *et al.* Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. *Circulation* 2007;**115**:442–9.
8. Junttila MJ, Raatikainen MJ, Karjalainen J, Kauma H, Kesäniemi YA, Huikuri HV. Prevalence and prognosis of subjects with Brugada-type ECG pattern in a young and middle-aged Finnish population. *Eur Heart J* 2004;**25**:874–8.
9. Giustetto C, Drago S, Demarchi PG, Dalmasso P, Bianchi F, Masi AS *et al.* Risk stratification of the patients with Brugada type electrocardiogram: a community-based prospective study. *Europace* 2009;**11**:507–13.
10. Letsas KP, Gavrielatos G, Efremidis M, Kounas SP, Filippatos GS, Sideris A *et al.* Prevalence of Brugada sign in a Greek tertiary hospital population. *Europace* 2007;**9**:1077–80.
11. Gallagher MM, Forleo GB, Behr ER, Magliano G, De Luca L, Morgia V *et al.* Prevalence and significance of Brugada-type ECG in 12,012 apparently healthy European subjects. *Int J Cardiol* 2007;**130**:44–8.
12. Bozkurt A, Yas D, Seydaoglu G, Acartürk E. Frequency of Brugada-type ECG pattern (Brugada sign) in Southern Turkey. *Int Heart J* 2006;**47**:541–7.
13. Gervacio-Domingo G, Isidro J, Tirona J, Gabriel E, David G, Amarillo ML *et al.* The Brugada type 1 electrocardiographic pattern is common among Filipinos. *J Clin Epidemiol* 2008;**61**:1067–72.
14. Hermida JS, Lemoine JL, Aoun FB, Jarry G, Rey JL, Quiret JC. Prevalence of the brugada syndrome in an apparently healthy population. *Am J Cardiol* 2000;**86**:91–4.
15. Matsuo K, Akahoshi M, Nakashima E, Suyama A, Seto S, Hayano M *et al.* The prevalence, incidence and prognostic value of the Brugada-type electrocardiogram: a population-based study of four decades. *J Am Coll Cardiol* 2001;**38**:765–70.
16. Tsuji H, Sato T, Morisaki K, Iwasaka T. Prognosis of subjects with Brugada-type electrocardiogram in a population of middle-aged Japanese diagnosed during a health examination. *Am J Cardiol* 2008;**102**:584–7.
17. Junttila MJ, Raatikainen MJ, Perkiömäki JS, Hong K, Brugada R, Huikuri HV. Familial clustering of lone atrial fibrillation in patients with saddleback-type ST-segment elevation in right precordial leads. *Eur Heart J* 2007;**28**:463–8.
18. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D *et al.* Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation* 2005;**111**:659–70.
19. Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P *et al.* Proposed diagnostic criteria for the Brugada syndrome. *Eur Heart J* 2002;**23**:1648–54.
20. Holle R, Happich M, Löwel H, Wichmann HE. KORA–a research platform for population based health research. *Gesundheitswesen* 2005;**67**:S19–25.
21. Rautaharju PM, Wolf HK, Eifler WJ, Blackburn H. A simple procedure for positioning precordial ECG and VCG electrodes using an electrode locator. *J Electrocardiol* 1976;**9**:35–40.
22. Zywietz C, Borovsky D, Götsch G, Joseph G. Methodology of ECG interpretation in the Hannover program. *Methods Inf Med* 1990;**29**:375–85.
23. Willems JL, Abreu-Lima C, Arnaud P, van Bemmel JH, Brohet C, Degani R *et al.* The diagnostic performance of computer programs for the interpretation of electrocardiograms. *N Engl J Med* 1991;**325**:1767–73.
24. Antzelevitch C. Brugada syndrome. *PACE* 2006;**29**:1130–59.
25. Sangwatanaroj S, Prechawat S, Sunsaneewitayakul B, Sitthisook S, Tosukhowong P, Tungsanga K. New electrocardiographic leads and the procainamide test for the detection of the Brugada sign in sudden unexplained death syndrome survivors and their relatives. *Eur Heart J* 2001;**22**:2290–6.
26. Nakazawa K, Sakurai T, Takagi A, Kishi R, Osada K, Miyazu O *et al.* Clinical significance of electrocardiography recordings from a higher intercostal space for detection of the brugada sign. *Circ J* 2004;**68**:1018–22.
27. Perz S, Küfner R, Holle R. Monitoring der Qualität von EKG-Registrierungen in bevölkerungsbasierten Untersuchungen. *Proceedings Biosignalverarbeitung, PTB Braunschweig und Berlin* 2008;168–71.
28. Veltmann C, Schimpf R, Echternach C, Eckardt L, Kuschyk J, Streitner F *et al.* A prospective study on spontaneous fluctuations between diagnostic and non-diagnostic ECGs in Brugada syndrome: implications for correct phenotyping and risk stratification. *Eur Heart J* 2006;**27**:2544–52.