Body surface potential mapping in patients with Brugada syndrome: right precordial ST segment variations and reverse changes in left precordial leads

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Abstract

Objective: The aim of this study was to perform quantitative signal analysis of high-resolution body surface potential mapping (BSPM) recordings to assess its usefulness for the electrocardiographic characterization of patients with Brugada syndrome. The diagnostic value of the QRS integral and of the gradient of the ST segment have not been elucidated in Brugada syndrome. Methods: In 27 subjects (16 with Brugada syndrome and 11 healthy subjects), 120-lead BSPMs were recorded at baseline and after pharmacological provocation with intravenous administration of ajmaline (1 mg/kg). The recordings were analyzed for two regions outside the positions of the standard ECG leads: the right precordial leads (RPL) on the second and third intercostal space (high RPL) and the left precordial leads (LPL) between the fifth and seventh intercostal space (low LPL). Results: At baseline, in high RPL regions, patients with Brugada syndrome showed more positive QRS integrals (2.56 ± 2.8 vs. 2.16 ± 6 mV ms) and a steeper negative ST segment gradient (0.62 ± 0.41 vs. 0.29 ± 0.40 mV/s) compared to healthy subjects, \( P < 0.001 \). In contrast, in low LPL regions, reduced QRS integrals and positive ST segment gradients were observed. These ECG signs were even more pronounced after intravenous ajmaline and showed a better discrimination for patients with Brugada syndrome than differences in RPL or LPL during baseline, respectively. Conclusions: In the left precordial leads, patients with Brugada syndrome showed ECG changes which were reversed in relation to the ECG changes observed in right precordial leads. BSPM measurement is a useful tool to improve the understanding of the electrocardiographic changes in the Brugada syndrome. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Ventricular arrhythmias; ECG; Sudden death; Antiarrhythmic agents

1. Introduction

After previous case descriptions by Martini et al. [1], Brugada and Brugada [2] identified a rare entity of patients with survived cardiac arrest due to ventricular fibrillation who had characteristic ECG features (atypical right bundle branch block (RBBB) and right precordial ST elevation) but no structural heart disease. This entity was later referred to as ‘Brugada syndrome’. Recently, the syndrome was recognized as a genetic disorder with identification of mutations in the cardiac sodium channel SCN5A in a subset of patients [3,4].

Characteristic ECG signs of the Brugada syndrome may be mild and highly variable over time. Therefore, the identification of high-risk patients may be difficult because of borderline findings or transient ECG changes. However, family members of index patients and asymptomatic patients with Brugada syndrome are at increased risk of sudden death [5] while currently available techniques for risk stratification are unable to predict the individual risk of these patients [6].
Therefore, improvement of noninvasive electrocardiographic detection of Brugada syndrome is desirable. We hypothesized that: (1) BSPM may identify atypical ECG lead positions that might be superior to the conventional ECG in diagnosing patients with Brugada syndrome; (2) reversal of changes of the typical ECG signs should occur in an opposite area of the torso; and (3) provocation with intravenous sodium channel blockers may improve the diagnostic value of these BSPM characteristics in patients with Brugada syndrome. During the course of our study, Shimizu et al. [7] used BSPM measurements to show that the ST segment elevation 20 ms after the end of QRS was located at the parasternal second and third intercostal space which allowed a better identification of the characteristic ECG signs in Brugada syndrome.

The present study therefore assessed the presence of typical ECG signs of the Brugada syndrome in 120-channel ECG recordings (BSPM) at baseline and during intravenous ajmaline with particular focus on high right precordial (high RPL) and low left precordial lead (low LPL) areas. While Shimizu et al. [7] studied a single ST segment instantaneously potential distribution the two novel ECG parameters provide additional information: QRS integral relates to activation, whereas ST segment gradient relates to the rate of potential change during early repolarisation. These new ECG parameters were analysed from BSPM recordings with respect to their diagnostic value in patients with Brugada syndrome.

2. Methods

2.1. Patient selection

Patients with Brugada syndrome (n=16) were prospectively screened. The diagnosis of Brugada syndrome was made on the basis of typical ECG features (persistent or transient right precordial ST segment elevation with or without atypical right bundle branch block), clinical arrhythmic events (syncope, ventricular fibrillation, cardiac arrest), family history, and the absence of identifiable structural heart disease. Detailed noninvasive and invasive investigations included two-dimensional echocardiography, left and right ventricular angiography, coronary angiography, magnetic resonance imaging, and endomyocardial biopsy.

All patients underwent an invasive electrophysiological examination with programmed ventricular stimulation with up to three extrastimuli as previously reported [8]. During BSPM measurement, patients were in stable sinus rhythm. Pharmacological provocation with intravenous ajmaline (1 mg/kg, 10 mg/min) was performed to unmask or intensify ECG signs of Brugada syndrome [9]. Written informed consent was obtained from all patients who entered the study. The investigation conforms with the Declaration of Helsinki.

2.2. Body surface potential mapping

Electrodes were applied to the chest in vertical strips (Fig. 1); each electrode (Foxmed, Idstein, Germany) had a 10-mm diameter Ag/AgCl sensor embedded in an epoxy housing with a 2-mm gel cavity. In vertical direction, the inter-electrode distance on the strips were 50 mm. The 120 unipolar ECG leads referred to Wilson central terminal and were recorded simultaneously [10]. The ECG signals were amplified, bandpass-filtered (0.16–400 Hz) and A/D converted to 16-bit samples (0.5 μV least significant bit) using a sampling rate of 1 kHz (Mark-6, Biosemi, Amsterdam, The Netherlands). Leads which were excessively noisy or which contained artifacts were excluded from the data set for further off-line analysis. Measurements started at resting conditions (5 min) and continued during ajmaline infusion (1 mg/kg; 10 mg/min) and 4–8 min after infusion of ajmaline.

2.3. Drug administration

The sodium channel blocker ajmaline was administered intravenously at a constant rate of 10 mg/min until a total dose of 1 mg/kg was reached. Drug administration was stopped, if QRS duration increased more than 20% compared to baseline or in case of the occurrence of complex ventricular arrhythmias.

2.4. Genotyping

We performed SSCP analysis of the entire coding regions of the cardiac sodium channel gene SCN5A in all patients listed in Table 1 and used previously published primer for PCR [11]. SSCP analysis was improved by the use of two fluorescence-labelled primers and by optimized running and temperature conditions during electrophoresis on an ALF DNA sequencer (Amersham–Pharmacia, Freiburg, Germany). Only aberrant SSCP conformers were followed by direct sequencing (BDT kit together with ABI 3700; Perkin-Elmer, Norfolk, USA).

2.5. Signal analysis

Signal analysis was performed offline for recordings at baseline and at the maximum ajmaline dose (1 mg/kg). In a selected single beat with good signal to noise ratio and no offset variation due to respiratory motion, QRS onset, QRS offset and T onset were determined visually from the superimposed Goldberger aVR, aVL and aVF leads. For each BSPM lead the amplitude offset was corrected by the mean amplitude level of a 20-ms reference window located in the PQ interval of the ECG (Fig. 2). The mean amplitude level is the offset potential value of the differential amplifier which has to be subtracted as reference value. The interval of 20 ms is selected for the time window to avoid 50-Hz line interference in the reference potential.
value (the average is over one period, 20 ms, of the line interference interval). For each surface lead, the QRS integral was calculated. The beginning of the ST segment was defined by the latest QRS offset determined in the superimposed limb leads. The end of the ST segment was defined by the earliest T-wave onset of the limb leads, respectively. The gradient of this ‘true ST segment’ was calculated as the slope of the best linear fit of this sample.

Table 1
Clinical characteristics of the patient population (n = 16)

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex/age (years)</th>
<th>Clinical presentation</th>
<th>SCD</th>
<th>Family history</th>
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<tr>
<td>1*</td>
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<td>+</td>
<td>-</td>
<td>+ (syncope)</td>
</tr>
<tr>
<td>2</td>
<td>f/58</td>
<td>+</td>
<td>-</td>
<td>+ (syncope)</td>
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<tr>
<td>3</td>
<td>m/46</td>
<td>-</td>
<td>-</td>
<td>+ (SCD)</td>
</tr>
<tr>
<td>4</td>
<td>m/37</td>
<td>-</td>
<td>+</td>
<td>+ (syncope)</td>
</tr>
<tr>
<td>5**</td>
<td>f/36</td>
<td>-</td>
<td>-</td>
<td>+ (SCD + syncope)</td>
</tr>
<tr>
<td>6</td>
<td>m/54</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
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<td>7</td>
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<td>-</td>
<td>+</td>
<td>+ (SCD)</td>
</tr>
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<td>+</td>
<td>-</td>
<td>+ (SCD)</td>
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<tr>
<td>15</td>
<td>m/33</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>m/40</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

SCD, aborted sudden cardiac death; *patient 1 was the only patient showing a mutation in the SCN5A gene; **patient 5 is a sister of patient 4.
explained syncope ($n=4$), one patient had both. The remaining four patients were asymptomatic and presented with a family history of unexplained cardiac arrest or syncope. In the four asymptomatic patients, typical ECG abnormalities indicating Brugada syndrome were found during routine ECG examination. Eight patients had a positive family history, whereas the remaining eight patients had no family members with cardiac arrest or unexplained syncope.

3.2. Control group

The age-matched control group consisted of 11 subjects (mean age $53\pm12$, range $36–69$; $P=NS$ versus study patients) without structural heart disease, with normal cardiovascular examination results, normal resting 12-lead ECGs, and normal exercise tests. No control subject was on drug treatment.

3.3. QRS integral and the gradient of the ST segment in BSPM and V1–V6

The BSPM recordings showed the characteristic ECG pattern of Brugada syndrome. An example of a BSPM recording of a Brugada patient is given in Fig. 3a. The variations were even more pronounced after intravenous administration of ajmaline (Fig. 3b). Especially in the high right precordial leads, the typical pattern of elevated $R'$-peaks were found followed by negative gradients of the ST segment into negative T-waves; reverse changes of this pattern were observed in the low left precordial leads.

3.3.1. Measurements at baseline

Typical ECG signs of the Brugada syndrome were observed in right precordial leads and were more pronounced on the higher right torso (second and third intercostal space). Although there is a variability in the QRS integral maps of normal subjects [12], the spatial distribution of the QRS integrals showed marked changes compared to control (Fig. 4a,b). The results of the quantitative signal analyses are summarized in Table 2.

Under resting conditions, the high RPL area showed increased QRS integrals ($-5\pm8$ vs. $-16\pm8$ mV ms) and more negative ST slopes ($-0.62\pm0.41$ vs. $-0.29\pm0.40$ mV/s) compared to control ($P<0.001$ each, Fig. 5). In contrast, the QRS integrals and ST segment gradients measured in the standard ECG leads V1–V3 were not statistically different between Brugada and control patients.

In the low LPL leads, reverse changes of the signal characteristics were identified. This resulted in lower QRS integrals ($12\pm10$ vs. $23\pm15$ mV ms) and higher ST slopes ($0.75\pm0.44$ vs. $0.31\pm0.32$ mV/s) as compared to the control group ($P<0.001$ each). In the standard left precordial ECG lead V5, the ST segment gradient was increased.
Fig. 3. A typical BSPM recording of a patient with Brugada syndrome: (a) at baseline; and (b) after intravenous administration of ajmaline (1 mg/kg). For both figures each BSPM channel is visualised in a 600-ms window, amplitude range ±1 mV; (c) shows the variations of the ‘true ST segment’ at baseline. Each 122-ms window represents an amplitude range of ±0.2 mV. Waveforms outside box boundaries indicate marked ST elevation (>0.2 mV).

(0.92±0.64 vs. 0.47±0.29 mV/s in control subjects) and in V6, both a significant decrease in QRS integral (13±8 vs. 23±13 mV ms) and an increase in ST segment gradients (0.64±0.32 vs. 0.31±0.18 mV/s) were observed (P<0.05 each). Fig. 3c shows an example of the typical ST segment gradients found in Brugada patients at baseline.
3.3.2. Measurements after intravenous ajmaline

The spatial distribution of the QRS integrals after administration of ajmaline showed no apparent changes compared to measurements at baseline (Fig. 4c). However, the Brugada syndrome-typical ECG characteristics in the low LPL and high RPL areas were even more pronounced during provocation with the sodium channel blocker ajmaline (Wilcoxon test, \( P < 0.05 \)), except for the QRS integral in the low LPL area (\( P = 0.083 \)). During intravenous ajmaline, the high RPL area showed more increased QRS integrals (\( 1\pm10 \) mV ms) and more decreased ST segment gradients (\(-1.80\pm1.93 \) mV/s) compared to control subjects at baseline (\( P < 0.001 \) each). In the standard right precordial ECG leads V1–V3, only V1 showed an increase in the QRS integrals (\(-3\pm22 \) mV ms, \( P < 0.05 \)) and a decrease in ST segment gradients (\(-2.12\pm4.92 \) mV/s, \( P < 0.05 \)) (Fig. 5).

In the low LPL leads, even more decreased QRS integrals (\( 5\pm13 \) mV ms, \( P < 0.001 \)) and more positive ST slopes (\( 1.74\pm1.28 \) mV/s, \( P < 0.001 \)) were observed. For the standard left precordial ECG leads V4–V6, a significant decrease in QRS integrals (\(-3\pm21 \) vs. \( 18\pm18 \) mV ms in control subjects at baseline, \( P < 0.05 \)) and an increase in ST segment gradients (\( 2.89\pm2.54 \) vs. \( 0.98\pm0.76 \) mV/s, \( P < 0.05 \) ) were found in V4. In V5, a decrease in QRS integrals (\( 7\pm14 \) vs. \( 27\pm20 \) mV ms, \( P < 0.05 \)) and an increase in ST segment gradients (\( 2.03\pm1.69 \) vs. \( 0.47\pm0.29 \) mV/s, \( P < 0.001 \) ) were measured. In addition,

Table 2
Electrocardiographic characteristics of the Brugada patients

<table>
<thead>
<tr>
<th>Lead</th>
<th>QRS integral (mV ms)</th>
<th>ST gradient (mV/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control subjects</td>
<td>Brugada Baseline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPL</td>
<td>(-16\pm8)</td>
<td>(-5\pm8^\dagger)</td>
</tr>
<tr>
<td>LPL</td>
<td>(23\pm15)</td>
<td>(12\pm10^\dagger)</td>
</tr>
<tr>
<td>V1</td>
<td>(-20\pm9)</td>
<td>(-9\pm17)</td>
</tr>
<tr>
<td>V2</td>
<td>(-21\pm13)</td>
<td>(-15\pm22)</td>
</tr>
<tr>
<td>V3</td>
<td>(-8\pm19)</td>
<td>(-12\pm20)</td>
</tr>
<tr>
<td>V4</td>
<td>(18\pm18)</td>
<td>(6\pm14)</td>
</tr>
<tr>
<td>V5</td>
<td>(27\pm20)</td>
<td>(14\pm10)</td>
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<tr>
<td>v6</td>
<td>(23\pm13)</td>
<td>(13\pm8^*)</td>
</tr>
</tbody>
</table>

Mean±S.D., *\( P < 0.05 \) and ^\dagger\( P < 0.001 \) compared to control group. High RPL, mean of the right precordial BSPM leads on second to third intercostal space; low LPL, mean of the left precordial BSPM leads between fifth and seventh intercostal space; V1–V6, precordial leads obtained from 12-channel standard ECG.
of independent families were 13. In one (female) of 13 index patients (8%), we identified a heterozygous mutation in exon 16 of the SCN5A gene that is predicted to truncate the channel protein and most likely leads to a nonfunctional channel subunit. The mutation could be followed within the family and causes a variable ECG phenotype (unpublished data).

In the other 12 index patients, aberrant SSCP conformers were shown to result from various SNPs in SCN5A and, since present in a control population, not further considered to be causative for Brugada syndrome. Here, the genetic basis for the disease remains to be determined.

The patient with mutation in the SCN5A gene showed typical ST elevation in the right precordial leads V1–V3, which were even more pronounced after ajmaline infusion and degenerated from saddle-type to coved-type morphology. The measured novel BSPM characteristics were close to the median of the total group of patients with Brugada syndrome studied and showed no systematic differences.

4. Discussion

Body surface potential mapping (BSPM) is superior to 12-lead standard ECG in diagnosing ECG phenomena because of several reasons: first it is superior by recording 120 unipolar electrograms from the entire torso surface, thus the representation of an altered cardiac activation on the body surface is therefore not limited to the standard lead positions. In addition, the high amplitude resolution and advanced techniques for signal analysis enable a detailed assessment of ECG phenomena manifesting in the ST segment and T wave of the ECG.

In patients with Brugada syndrome, BSPM measurements with and without intravenous ajmaline and signal analysis of the QRS complex and ST segment demonstrated new ECG characteristics, which may enable improved diagnosis of Brugada syndrome.

The typical ECG signs of Brugada syndrome may be borderline, especially in asymptomatic patients and family members of patients with typical ECG changes. In addition, these typical ECG signs are frequently only transiently present as patients with a positive diagnosis may show normal ECG characteristics in follow-up registrations [6]. To improve the sensitivity of the ECG, in the present study, a quantitative signal analysis of BSPM recordings revealed additional ECG characteristics, which reflect the Brugada-like variation of the surface ECG. In accordance with the findings of Shimizu et al. [7], BSPM measurements identified more pronounced ECG variations in the right precordial leads placed on the second and third intercostal space. In addition, the high RPL region presented with a characteristic elevation of R’ waves and, therefore, resulted in more positive QRS integrals compared to control subjects. Even under baseline conditions,
steep negative gradients of the ST segment were observed in this area. By analysing the QRS integrals and ST segment gradients, the high RPL and the low LPL areas were the best separating areas to identify patients with Brugada syndrome. These areas do not include the right precordial leads conventionally used for the diagnosis of Brugada syndrome. In addition, for the most part they are outside the standard leads V1–V6. For the electrocardiographic characterization of patients with Brugada syndrome, previous studies focused on the standard right precordial leads V1–V3. In contrast, in our study additional alterations of signal characteristics were found in V4–V6 and in the low LPL area. Compared to control subjects, we identified a significant decrease of the integrals in the QRS complex and significantly increased positive ST segment, which may reflect a reversal of the typical ECG findings in the right precordial leads of patients with the Brugada syndrome. ECG changes identified by signal analysis of the QRS complex indicate an altered cardiac activation sequence in patients with Brugada syndrome. However, ECG changes found in the ST segment are more likely linked to an altered repolarization sequence of the heart. The high RPL and low LPL areas of the torso for showing the most distinct differences in both, QRS integrals and ST segment gradients compared to control subjects, may be interpreted as a spatial correlation of the underlying mechanisms, resulting in altered myocardial depolarization and repolarization. The underlying mechanisms are possibly related to altered ionic currents observed in patients with Brugada syndrome [13]. In this respect, inverse procedures may help to identify the local altered cardiac activation in these patients [14].

Antiarrhythmic agents, due to their influence on the function of myocardial ionic channels, modulate the ST segment [15]. At least in patients with transient signs of the typical ECG, they may be helpful to unmask a Brugada-like pattern [16]. The prognostic impact of ECG variations appearing only after intravenous ajmaline has not yet been reported. In combination with the diagnostic power of BSPM measurements, this test may better reflect the altered cardiac activation and repolarization found in patients with Brugada syndrome [17] and may improve risk stratification of ventricular arrhythmias.

Recently, the Brugada syndrome has been recognized to be a genetically heterogeneous disease and only a minority of patients harbour disease mutations in the sodium channel gene SCN5A [6]. In this setting, the low incidence of SCN5A mutations found in the present study, even in the absence of other known genes, is compatible with those mentioned by others. In a larger subset of Brugada syndrome patients which have meanwhile been genotype and in our center, we found a higher incidence of SCN5A mutations, especially in the presence of familial disease (29%; E. Schulze-Bahr, unpublished observations). Due to the low number of genotyped individuals, the genetic basis is unknown in the majority of patients and, thus, a genotype–phenotype correlation with BSPM parameters has not been performed yet.

The propensity to syncope or sudden cardiac death in asymptomatic patients with Brugada syndrome is difficult to estimate. During a follow-up period of 34 months, event rates between 0 [6] and 27% [18] were reported. Absence of symptoms is not a reliable predictor for freedom from future events and is therefore of limited value for risk stratification in the individual patient. Since the accuracy of programmed electrical stimulation in predicting patients at risk may also be limited, BSPM measurement is a useful tool to improve the electrocardiographic understanding of the Brugada syndrome and to improve the ECG criteria for reliable individual risk stratification.

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