Unmasking Brugada-Type Electrocardiogram on Deep Inspiration

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Background: Electrocardiogram (ECG) recorded at the upper intercostal lead positions is recommended as an additional diagnostic clue for Brugada syndrome (BrS), but similar recording conditions to unmask ECG signs have not been explored.

Methods and Results: We evaluated the diagnostic usefulness for unmasking ECG signs of BrS using recordings at the upper intercostal lead position, on deep inspiration and on standing. In 34 patients (mean age, 49±14 years; 30 male) with diagnosed and suspected BrS, ECG type and ST-elevation in leads V1–V3 recorded at a higher position by 1 rib from the standard position (3ICS), and at standard lead positions (4ICS) on deep inspiration (DI test) and on standing (Stand test) were compared with the conventional lead positions (baseline). While type 1 ECG had been documented in 17 of 34 patients on at least 1 occasion in the past, only 4 had the sign at baseline during the study. Twenty patients had type 1 on 3ICS recording, 18 on DI test, and 6 on Stand test. Among 17 patients without previous documentation of spontaneous type 1, 7 had type 1 on 3ICS recording, 6 on DI test, and 1 on Stand test.

Conclusions: ECG recording on deep inspiration is useful to unmask diagnostic signs of BrS and has similar accuracy to 3ICS recording. (Circ J 2014; 78: 360–365)

Key Words: Brugada syndrome; Deep inspiration; Standing position; Sudden cardiac death; Ventricular fibrillation

Brugada syndrome (BrS) is distinct clinical entity associated with a high risk for sudden cardiac death (SCD) due to ventricular fibrillation (VF) without major structural abnormality in the heart.1 Patients with BrS have characteristic and diagnostic waveforms on electrocardiography (ECG), showing J-wave and ST-segment elevation at the right precordial leads (V1–V3). Various reports have suggested that coved-type ST-elevation or type 1 ECG is associated with a high risk for SCD,2–9 while the magnitude and morphology of ST-elevation often fluctuate with time.6,10–14 Multiple factors have been described to influence ECG type and ST-elevation in patients with BrS. The factors include change in heart rate (HR), febrile state, autonomic imbalance, various drugs, glucose-induced insulin secretion, electrolyte abnormalities and others.10,11,14–21

Methods

BrS ECG type was classified into type 1, type 2 and type 3 according to the consensus reports by subgroups of the Heart Rhythm Society and the European Heart Rhythm Association.6,26

Thirty-four patients (mean age, 49±14 years; 30 male, 4 female) with ECG showing spontaneous type 1 (n=17) or drug-induced type 1 (n=17) (i.e. pilsicainide 1 mg/kg over 10 min)6,10 between January 2008 and March 2012 were pro-
Unmasking Brugada-Type ECG

Subjects and Methods

Twelve-lead ECG was recorded at a paper speed of 25 mm/s during sinus rhythm in a supine position in the standard lead positions V1–V3 (4ICS: baseline), and in superior positions of V1–V3 up to 1 rib above standard positions (3ICS). ECG was also recorded at 4ICS on deep inspiration (DI test) and in the standing position (Stand test) continuously. Changes in ECG type and ST-elevation at 3ICS, DI test and Stand test were assessed and compared with those at baseline. Appearance of type 1 or augmentation of ST-elevation at the J point amplitude ≥0.1 mV was evaluated. HR was also measured at each recording condition. Furthermore, we examined the difference in heart position between the deep inspiratory phase and shallow expiratory phase on chest X-ray in the supine position. We measured the distance from the superior border of the left first bow (aortic arch) to the inferior border of the 12th thoracic spine in both phases. The differences between the phases were defined as the distance of the shifted heart position. Two independent experienced observers who were unaware of the clinical data performed the measurements and analysis. Twenty-five of 34 patients underwent invasive electrophysiological study (EPS) during a fasting state, involving PVS at 2 sites (the right ventricular apex and right ventricular outflow tract; RVOT), applying up to triple extrastimuli at basic cycle lengths of 600 and 400 ms.

Table 1: Subject Clinical Characteristics

|          | n  | M/F | Spontaneous type 1 | Symptoms syncope/VF | FH SD/BrS | EPS (VF induction) |
|----------|----|-----|--------------------|---------------------|-----------|-------------------|
| Defined BrS | 19 | 15/4 | 10                 | 2/2                 | 4/2       | 19 (18)           |
| Suspected BrS | 15 | 15/0 | 7                  | 0                   | 0         | 6 (0)             |

BrS, Brugada syndrome; EPS, electrophysiological study; FH, family history; SD, sudden death; VF, ventricular fibrillation.

An additional type was defined as “non-Brugada type” including normal ECG. All 34 patients had no obvious structural heart disease on physical examination, echocardiogram, exercise stress test, coronary angiography or ventriculography. There was no evidence of electrolyte abnormalities in the study periods in any of the patients.

Results

Subject Characteristics

Among 34 patients, BrS was diagnosed in 19 patients according to the criteria proposed by the consensus reports and the remaining 15 patients had Brugada-type ECG (type 1, 2, or 3) without any clinical symptoms or FH (Table 1). Patients with spontaneous type 2 or 3 exhibited drug-induced type 1. Among 19 patients with BrS, 9 had clinical symptoms of VF, syncope and/or FH of sudden death at age <45 years old, and BrS. One patient had documented VF and BrS at sudden death. Another 10 patients had spontaneous or drug-induced type 1 with positive VF provocation on PVS. Eighteen of 25 patients who underwent EPS had inducible VT/VF on PVS and 9 asymptomatic patients did not undergo PVS.

Change in ECG Type

While spontaneous type 1 had been observed on at least 1 occasion in the past in 17 of 34 patients, only 4 showed type 1 at baseline at the time of the study. Among the total 34 patients, the number of patients with type 1 significantly increased with recordings at 3ICS and DI test compared to those at baseline, and did not increase on the Stand test (Table 2). There was no difference in the number of unmasked patients with type 1 on recording at 3ICS and DI test, although all of 18 patients who had type 1 on DI test also had type 1 at 3ICS recording. Among the 17 patients without past documented spontaneous type 1, spontaneous type 1 was seen on 3ICS, on DI test and on Stand test in 7, 6 and 1, respectively. Among 19 patients diagnosed with BrS, spontaneous type 1 had been documented in 10 in the past. During the study, type 1 was confirmed in only 3 at baseline, and the number increased to 9 at 3ICS, to 8 at DI test and to 4 at Stand test.

In 18 patients who underwent chest X-ray, the difference in heart position between the deep inspiratory phase and shallow expiratory phase was significant between 9 patients exhibiting type 1 and 9 without type 1 on DI test (6.5 [6.5]mm vs. 2.5 [11.5]mm; P<0.05).

Figure 1 shows ECG records obtained from a 34-year-old man with BrS. Spontaneous type 1 ECG was observed on the day before the study. While he had type 2 ECG at baseline during the study, type 1 was recorded at 3ICS, on DI test, and on Stand test. Figure 2 represents ECG records from an asymptomatic patient. While his ECG always exhibited non-type
Figure 1. Electrocardiogram (ECG) of a 34-year-old man with aborted sudden death due to ventricular fibrillation (VF). Type 1 was seen on ECG on the previous day. In the present study, the ECG showed ST elevation <0.2 mV (non-Brugada type ECG or type S) in V1, and type 2 in V2 at baseline. Type 1 ECG was observed at the third intercostal space (3ICS), during deep inspiration (DI) test and in the standing position (Stand test) in V2. 4ICS, fourth intercostal space.

Figure 2. Electrocardiogram (ECG) of a 46-year-old man with Brugada syndrome. The ECG showed spontaneous type 2 in V2 at baseline, while type 1 was recorded at the third intercostal space (3ICS) and during deep inspiration (DI) test but not in the standing position (Stand test).
Changes in ST Elevation and HR
Increase in amplitude of ST elevation compared to baseline was observed in 24 patients (71%) at 3ICS, 15 (44%) at DI test, and 8 (24%) at Stand test, while ST elevation in leads V2 and V3 significantly increased at 3ICS, and in V3 at DI test compared to baseline (Table 3).

HR was faster on Stand test (73 [43] beats/min) than at baseline (67 [35] beats/min), at 3ICS (67 [35] beats/min) and at DI test (67 [39] beats/min).

Table 3. Amplitude of ST Elevation

| ST level (mV) | Baseline | 3ICS | DI test | Stand test |
|--------------|----------|------|---------|------------|
| V1           | 0.1 (0.4)| 0.2 (0.5)| 0.15 (0.55)| 0.1 (0.5) |
| V2           | 0.3 (0.45)| 0.4 (0.8)*| 0.35 (0.6)| 0.3 (0.6) |
| V3           | 0.13 (0.3)| 0.2 (0.5)*| 0.2 (0.4)*| 0.2 (0.3) |

Data given as median (maximum minus minimum). *P<0.05 vs. baseline. Abbreviations as in Table 2.

Discussion
The appearance of type 1 ECG is generally considered as diagnostic for BrS, and its presence has been proposed as a prognostic marker for cardiac events. Because of diagnostic and prognostic significance, various recording procedures and provocation tests have been proposed to identify or unmask type 1 in patients with diagnosed or suspected BrS.

ECG recording at the higher lead positions of the right precordial leads (V1–V3) has a high sensitivity of diagnostic accuracy and is often recommended as a measure for unmasking BrS. Recently, Nagase et al investigated the relationship between ECG recording site and the anatomical location of RVOT on fluoroscopic images of right ventriculography, and found that type 1 ECG was recorded in leads that corresponded with RVOT.

Furthermore, Veitmann et al noted that a Brugada type 1 ECG pattern in the third intercostal space was highly matched with the corresponding RVOT location on cardiovascular magnetic resonance imaging.

In this study, ECG recording on deep inspiration was found to be a useful method to unmask Brugada-type ECG, similar to that using upper intercostal lead positions (3ICS). Furthermore, type 1 ECG could be seen without moving electrodes upwards in the DI test.

Possible Mechanism of DI and Stand Test ST-T Wave Changes
The mechanism of characteristic ST-elevation and its morphologies in BrS has been explained either by repolarization or depolarization abnormalities at RVOT. The repolarization concept proposes that decreased Na channel and/or Ca channel function in the presence of prominent transient outward K current (Ito) of epicardial myocytes at RVOT causes increased notch and loss of dome in epicardial action potentials but not in the endocardial ones. Formation of heterogeneous repolarization processes across the ventricular wall of RVOT results in the specific ST-elevation and T-wave changes. Further, disparity in repolarization among myocytes in contiguous epicardial areas leads to development of phase 2 reentry and onset of VF or polymorphic VT. The depolarization theory indicates that disturbances in depolarization at RVOT can cause inhomogeneous decreases and delay in the upstroke of action potentials, and induction of disparity of repolarizations and conduction disturbances leading to ST-elevation, T wave changes and development of tachyarrhythmias.

Among various factors that unmask Brugada-type ECG, changes in HR, various drugs, autonomic imbalance, febrile state and others are thought to influence either repolarization, depolarization or both processes through actions on responsible ionic currents, and to result in the development of ventricular arrhythmias. Recordings at 3ICS are assumed to unmask Brugada-type ECG due to a close position of the leads to RVOT, the area with assumed repolarization and/or depolarization abnormalities.

In a similar way, tumor in the mediastinum could mimic Brugada-type ECG, probably due to compression and displacement of the ventricular wall, causing the RVOT area to be closer to the recording lead position.

During deep inspiration, the heart is pulled downward as the diaphragm falls following lung expansion, leading the right precordial leads at conventional lead positions (V1–V3) to be closer to RVOT. This corresponds to the present findings that heart position, evaluated on X-ray, was lower in the deep inspiratory phase than in the expiratory phase. The previous case report indicated that deep inspiration was useful to unmask BrS because of diaphragmatic descent and possible augmentation of vagal tone. HR typically accelerates during the initial phase of inspiration, followed by deceleration toward the end of inspiration and during expiration. Thus it was suggested that inspiratory cardiac acceleration due to sympathetic tone was somewhat overcome by vagal influence at the end of deep inspiration.

Recording during deep inspiration and in a standing position could produce closer apposition of RVOT to the leads V1–V3, but the effectiveness in unmasking Brugada-type ECG was similar in the former but lower in the latter compared to that at 3ICS. The effectiveness in unmasking Brugada-type ECG between DI test and Stand test may depend on how close the electrode-lead positions can be placed to the abnormal areas of RVOT. Deep inspiration can inflate the lung with pull down of the diaphragm and displace RVOT much closer to the electrode-lead positions at 4ICS. An additional factor is the influence of autonomic tone, which affects the appearance of ECG signs in BrS. HR was increased in the Stand test compared to recordings at 3ICS and DI test, which might reflect increased sympathetic tone. Changes in autonomic tone have additional effects on the ability to unmask Brugada-type ECG, given that vagotonie augmentation and sympathetic decrease in ST elevation and appearance of type 1 have been documented. Increased HR may cause decreased availability of Ito because of its relatively slow recovery from inactivation.

Prevalence of and ST-T Morphological Change in BrS
Brugada-type ECG has been reported in 0.15–0.7% and typi-
fact that none of the control patients had type 1 ECG when the Diagnostic effectiveness of the method was supported by the detection at the standard position of V1–V3.

Clinical Implications

In asymptomatic patients, manifestation of type 1 ECG must be carefully investigated during history taking and cardiac examination, with close follow-up of clinical course. Detection of type 1 at the higher intercostal spaces alone was considered to carry similar diagnostic and prognostic value to the standard position of V1–V3. Given that DI test at fixed lead positions produced a similar detection rate to 3ICS recording, it may be diagnostically useful in unmasking Brugada-type ECG, although only a small number of patients were investigated in the present study. The Stand test should be considered as an adjunctive examination in certain circumstances such as ambulatory ECG recording, exercise stress test, or head-up tilt test.

Study Limitations

ECG recording on DI or in the standing position may be valuable to unmask Brugada-type ECG. The actual sensitivity and specificity of these methods for identifying patients with BrS and their risk for cardiac events, however, were not evaluated, due to the small number of patients without prospective follow-up for their clinical course. In addition, it was considered that fluctuation of ST-T segment morphology from day to day and during the day might influence the results. Furthermore, there was no control study with normal healthy subjects to determine whether Brugada-type ECG could be detected in these subjects or not. Thus further prospective and large-scale studies with controls should be done to evaluate the clinical utility of ECG recordings during DI and in the standing position for diagnosis and risk stratification.

Conclusions

ECG recording during deep inspiration is a useful method to unmask Brugada-type ECG, similar to that at the upper intercostal spaces.

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