

Utility of Different Electrocardiographical Leads during Diagnostic Ajmaline Test for Suspected Brugada Syndrome

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Summary: In order to compare the value of different leads and lead combinations to detect the signature Brugada type ECG pattern, we analysed digital 10-second, 15-lead ECGs (12 standard leads + leads V1 to V3 from 3rd intercostal (i.c.) space, V1h to V3h) acquired during diagnostic Ajmaline testing in 128 patients (80 men, age 37±15 years) with suspected Brugada syndrome (BS) (patient group), 15-lead resting ECGs of 108 healthy subjects (53 men, age 31.9±10.5 years) (control group A) and standard 12-lead resting ECGs of 229 healthy subjects (111 men, age 33±4 years) (control group B). Bipolar leads between V2 (positive pole) and V4 or V5 (leads V_{2,4}, V_{2,5}) were derived by subtracting leads V4 and V5 from V2 (custom-made program). The 6 peripheral, 6 right precordial leads (V1 to V3, V1h to V3h) and leads V_{2,4} and V_{2,5} of the patients group, leads V1h to V3h of control group A, and leads V_{2,4} and V_{2,5} of control group B were analysed for the presence of type 1 Brugada pattern. There were 21 (16.4%) positive and 107 (83.6%) negative Ajmaline tests. In 7 positive tests (33%), type 1 pattern appeared only in leads V1h to V3h, whereas in 14 tests (67%) it appeared in both V1 to V3 and V1h to V3h. Lead V2 displayed type 1 pattern during 10 positive tests; in all of them, plus 10 other positive tests type 1 was also noted in lead V2h (n=20, 95.2%). In all 10 cases, in which lead V2 exhibited type 1 pattern (n=10), lead V_{2,4} and/or V_{2,5} also exhibited type 1-like pattern. During 7 positive tests, in which lead V2h but not V2 exhibited type 1 pattern, lead V_{2,4} and/or V_{2,5} also demonstrated type 1 pattern. Type 1 pattern was observed in leads V3 and V3h during 1 (5%) and 5 (24%) positive tests, in 0 ECGs (0%) in control group A and in 1 ECG (0.4%) in control group B. In conclusion, the “high” V1 and V2 leads (3rd i.c. space) detect more sensitively Brugada type 1 pattern than the standard V1 and V2 leads (4th i.c. space); leads V3 and V3h are not essential for the diagnosis of BS; bipolar leads V_{2,4} and V_{2,5} are superior to lead V2 for the ECG diagnosis of BS.

Keywords: Brugada syndrome, Ajmaline test, High right precordial leads, Bipolar precordial leads.

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1. INTRODUCTION

The Brugada Syndrome (BS) is an inherited arrhythmia syndrome manifesting as syncope or sudden cardiac death (SCD) due to a polymorphic ventricular tachycardia in the absence of myocardial ischemia, structural heart disease or QT prolongation [4]. Currently the BS is diagnosed when a specific electrocardiographic (ECG) pattern characterized by J-point and ST-segment elevation with negative T wave (“coved” or type 1 Brugada ECG pattern) (Fig.1) is observed in the right precordial leads V1 to V3 in patients with personal or family history of major ventricular arrhythmic events and/or blood relatives carrying the type 1 ECG [2].

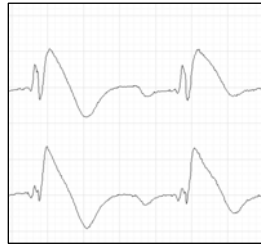


Fig. 1 Typical type 1 (coved) Brugada ECG pattern observed in lead V1 recorded from the standard position in 4th intercostal (i.c.) space (top) and from the 3rd i.c. space (bottom). All ECGs in Figures 1 to 5 are presented at 25 mm/second, 1 cm/mV.

In patients with normal or non-diagnostically changed baseline ECG, the signature type 1 Brugada ECG pattern can be provoked by intravenous administration of drugs which block the sodium channel (Ajmaline, flecainide, procainamide) [2, 21]. However, it is still not clear which are the best ECG leads or lead combinations to be monitored during the test (and for detection of Brugada ECG pattern in general). Recent studies [16, 20] have demonstrated that recording leads V1 and V2 from the 3rd or 2nd instead of the 4th intercostal (i.c.) space would increase their sensitivity for detection of type 1 Brugada pattern. However, the “high” right precordial leads should preferably be recorded in addition to, and not instead of the standard V1 to V3 leads because the latter are essential for the general interpretation of the ECG. Unfortunately, ECG recorders capable of simultaneous acquisition of more than 12 leads are not always available.

In order to assess the value of different leads and lead combinations for detection of the signature type 1 Brugada ECG pattern, we retrospectively analyzed a database of 15-lead digital ECG recordings acquired during diagnostic Ajmaline testing in patients

with suspected BS, and a database of 12- and 15-lead digital resting ECGs recorded in subjects with no apparent heart disease.

2. METHODS

Patient population and ECG data acquisition

Between August 2006 and February 2009, diagnostic Ajmaline test was performed in 128 patients (80 men, 48 women, age 37.0 ± 15.1 and 38.9 ± 14.8 years, respectively, $p=0.48$), with suspected BS as part of their standard clinical management. Indications for the test included: a) aborted cardiac arrest ($n=12$), b) syncope of unknown origin ($n=34$), c) family history of BS ($n=35$) or sudden cardiac death (SCD) ($n=53$) and d) ECG changes suspicious for but not diagnostic of BS ($n=6$) (more than one indication was present in some patients). Ajmaline was administered intravenously in dose 1 mg/kg for 5 minutes under constant ECG monitoring in hospital setting [2].

Digital 10-second ECGs with simultaneous acquisition of 15 leads (standard 12-leads plus leads V1 and V2 from the 3rd i.c. space, and lead V3 with the same cranial displacement – high V1 to V3 leads, V1h to V3h) were acquired before, at short intervals (3 – 5 ECGs per minute) during and up to 10 minutes after the end of drug infusion or until the ECG changes completely subsided using MAC 5000 recorder (GE Medical, Milwaukee, WI, USA, 500 Hz, 4.88 μ V). All ECGs were subsequently converted into XML text files to be analyzed with a custom-developed program (see below). For the purpose of this study, a test was considered positive if any two (or more) of the 6 leads (V1 to V3 plus V1h to V3h) demonstrated type 1 ECG pattern during the test, although the inclusion of the high right precordial leads in the definition of a positive test is not clearly endorsed by the Consensus Documents [2].

Healthy controls

We also analyzed digital 10-second ECGs (MAC5000, MAC55000 or CardioSoft, GE Medical 500 Hz, 4.88 μ V) recorded in 2 groups of healthy subjects participating in different research projects approved by the local Ethics Committee:

- 15-lead digital ECGs acquired in 108 subjects (53 men, age 31.9 ± 10.5 years) with the same lead configuration as in the patient group (control group A). They were used to assess the

presence of type 1 Brugada ECG pattern in leads V1h to V3h in healthy subjects.

- Standard 12-lead ECG recorded in 229 subjects (111 men, age 33.4 ± 10.6 years) (control group B). They were used for analysis of the bipolar leads V_{2-4} and V_{2-5} (see below) in healthy subjects.

All subjects in both groups had negative personal and family medical history, normal physical examination and normal standard 12-lead resting ECG.

Derivation of bipolar precordial leads

We hypothesized that a bipolar precordial lead with a positive electrode overlying a myocardial zone with expected electrophysiological changes in BS (e.g. at V2 position) and a negative electrode above a supposedly healthy myocardium (e.g. at V4 or V5) could detect more sensitively the diagnostic type 1 Brugada pattern than the standard unipolar lead with the same positive pole (lead V2). Bipolar precordial leads can be recorded directly – for example, when the right arm and left arm cables are connected to the V4 and V2 electrodes, respectively, lead I displays a bipolar lead between V2 (positive pole) and V4 (negative pole). Bipolar recordings, however, can be obtained more easily by subtracting the respective unipolar leads. For example, $\text{lead V2} = E_{V2} - E_{WCT}$, where E_{V2} is the potential at V2 and E_{WCT} is the potential of Wilson's central terminal (the average potential of the right arm, left arm and left leg). Similarly, $\text{lead V4} = E_{V4} - E_{WCT}$. Therefore, $\text{V2} - \text{V4} = E_{V2} - E_{V4}$, i.e. subtracting lead V4 from lead V2 is equivalent to recording a bipolar lead with electrodes at V2 (positive pole) and V4 (negative pole).

We used a custom developed program to obtain bipolar leads between V2 (positive pole) and V4 or V5 (lead V_{2-4} and V_{2-5} , respectively) by subtracting V4 and V5, respectively, from V2. We chose lead V2 instead of V1 or V3 because, firstly, Brugada type changes are observed much more frequently in leads V1 or V2 than in lead V3 (unpublished observations) and, secondly, because preliminary observations suggested that the shape of the QRS-T wave of bipolar lead V_{1-4} and V_{1-5} is more variable and hence more difficult to interpret than that of leads V_{2-4} or V_{2-5} .

Data analysis

For each Ajmaline test, we analyzed two 10-second ECGs recorded immediately before the beginning of Ajmaline infusion, and during each minute from the 1st to the 7th, 10th and 15th after drug infusion was started (20 ECGs per test) excluding those with visibly high noise and

arrhythmias. In the patient group, the presence or absence of Brugada type 1 pattern [2, 4] was noted in each of the 6 peripheral, 6 unipolar precordial (V1 to V3, V1h to V3h) and 2 derived bipolar leads (V_{2,4} and V_{2,5}). In the following text, however, Brugada type 1 pattern in leads V_{2,4} and V_{2,5} is referred to as “type 1-like pattern” since its origin in these leads is not clear. The prognostic value of different leads or lead combinations can only be established in relation to the occurrence of symptoms and/or arrhythmic events during follow-up. Such data were not available in the present study. Therefore we calculated the value of different lead combinations for detecting a positive test defined as type 1 pattern in any 2 of the 6 unipolar leads V1 to V3 plus V1h to V3h and their sensitivity to detect BS defined as a positive test plus relevant family history and/or relevant symptoms [2].

Leads V1h to V3h of all ECGs in all subjects of control group A, and the derived bipolar leads V_{2,4} and V_{2,5} in control group B were also examined for the presence or absence of Brugada type 1 ECG pattern. The standard 12-leads in all subjects in the 2 control groups were by definition normal.

Data are presented as mean \pm standard deviation. Nominal and categorical values were compared between study groups using paired and unpaired two-tailed student t-test and chi-square test, respectively. A two-tailed P-value of < 0.05 was considered statistically significant.

3. RESULTS

Out of 128 Ajmaline tests, 21 (16.4%) were positive and 107 (83.6%) were negative. Of those with positive tests, 18 (85.7%) were subsequently diagnosed as having BS due to family history of BS (n=9), aborted cardiac arrest (n=2), unexplained syncope (n=3), family history of SCD either alone (n=2) or in combination with syncope (n=1) or with family history of BS in a different family member (n=1) [2]. Three asymptomatic patients with positive tests and negative family history who were investigated because of the presence of ECG changes suggestive but not diagnostic of BS were considered to be asymptomatic carriers of Brugada type ECG [2, 3].

Comparison between the standard (V1 to V3) and high (V1h to V3h) right precordial leads

In accordance with previous reports, type 1 Brugada pattern was observed more frequently in leads V1h to V3h than in the standard V1 to V3 leads.

In 7 out of 21 (33%) positive tests, type 1 ECG pattern developed only in leads V1h to V3h leads, whereas in the rest (n=14, 67%) it was noted in both standard and high right precordial leads. Lead V2 displayed type 1 pattern during 10 out of 21 positive tests (47.6%). In these tests, plus in 10 other positive tests, type 1 was noted in lead V2h (20 out of 21, 95.2%). Type 1 pattern was observed in leads V3 and V3h during 1 (4.8%) and 5 (23.8%) positive tests, respectively. In none of the positive tests were leads V3 or V3h essential for the diagnosis (i.e. in each test, in which either lead V3 or V3h displayed type 1 Brugada pattern, at least 2 other of the 6 right precordial leads also displayed this pattern).

Brugada type 1 ECG pattern was not observed in leads V1h to V3h of any subject from control group A.

Comparison between leads V2, V2h and the bipolar leads V₂₋₄/V₂₋₅

In all ten cases, in which lead V2 exhibited type 1 pattern (n=10), lead V₂₋₄ and/or V₂₋₅ also exhibited type 1-like pattern. However, during 7 positive tests, in which the high V2 lead (V2h) exhibited type 1 pattern whereas lead V2 showed only non-diagnostic changes, either one or both of leads V₂₋₄ and V₂₋₅ also demonstrated Brugada type 1-like pattern.

Table 1. Value of different lead combinations for detection of BS and of asymptomatic carriers of Brugada ECG pattern

Leads	Number (%) of all positive tests (n=21)*	Number (%) of patients with BS (n=18)‡	Number (%) of carriers of Brugada ECG pattern (n=3)§
V1,V2,V3	7 (33.3%)	6 (33.3%)	1 (33.3%)
V1h,V2h,V3h	19 (90.5%)	16 (88.9%)	3 (100%)
V1,V ₂₋₄ , V ₂₋₅ , V3	9 (42.9%) †	8 (44.4%)	1 (33.3%)

* number (%) of all positive tests, in which ≥ 2 leads of the combination showed Brugada type 1 or type 1-like pattern;

† either one or both of leads V₂₋₄ and V₂₋₅ showed Brugada type 1-like pattern;

‡ number (%) of patients with positive tests who subsequently were diagnosed with Brugada syndrome according to the accepted criteria;

BS Brugada syndrome;

§ asymptomatic patients with positive tests who do not fulfil the criteria for BS

Table 1 presents the value of 3 different combinations of leads (V1 to V3, V1h to V3h, and V1, V₂₋₄/V₂₋₅, V3) for detection a positive test (i.e. the number/percentage of positive tests, in which each of these combinations displayed type 1 or type 1-like pattern in ≥ 2 leads), and for detection of BS (i.e. positive test plus relevant family history and/or relevant symptoms or

arrhythmic events). Substituting lead V2 with the bipolar leads V_{2-4}/V_{2-5} would increase the ability of the standard precordial leads to detect a positive test from 33.3% (7/21) to 42.9% (9/21), and to detect BS from 33.3% (6/18) to 44.4% (8/18).

Figures 2 to 4 present examples of ECGs recorded before and after administration of Ajmaline during positive tests to demonstrate the increased sensitivity of the bipolar leads V_{2-4} and V_{2-5} compared to that of the standard unipolar lead V2 for detection of type 1 Brugada pattern.

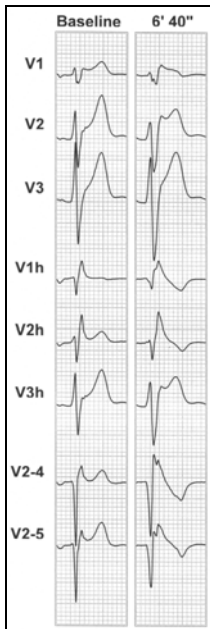


Fig. 2 ECGs recorded before (left panel) and 6'40" after the start of Ajmaline infusion (right panel) during a positive test in a 34-year-old man with a history of syncope. Note that 6' 40" after the start of drug infusion leads V_{2-4} and V_{2-5} display a clear type 1-like pattern whereas lead V2 shows a non-diagnostic type 2 pattern (right panel). In the absence of high leads the test would have been interpreted as non-positive (type 1 pattern in leads V1, V1h and V2h). All ECGs on Figures 1 to 5 are presented at 25 mm/sec and 10 mm/mV.

Leads V_{2-4} and V_{2-5} during non-positive Ajmaline tests and in healthy controls

Type 1-like pattern was observed in lead V_{2-4} and V_{2-5} in 2 patients during non-positive tests (false-positive results). However, the first patient probably had atypical (inferior) type BS (appearance of type 1 developed in III and AVF during the test), whereas in the second patient the result of the test was borderline (coved type ST elevation with J point elevation of slightly less than < 2 mm in leads V1, V1h and V2h).



Fig. 3 ECGs acquired before (left panel), 3' (middle panel) and 6' (right panel) after the beginning of Ajmaline infusion in a 15-year-old girl with a syncope and family history of BS. Note that type 1 Brugada-like pattern appears earlier in leads V₂₋₄ and V₂₋₅ than in leads V₂ and V_{2h} (middle panel).

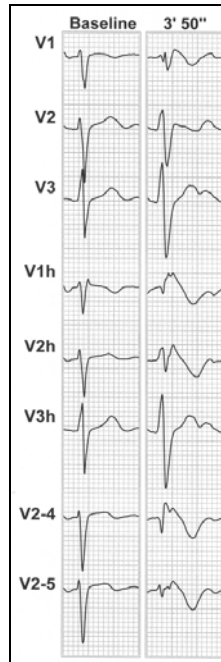


Fig. 4 ECGs recorded before (left panel) and 3'50'' after the beginning of Ajmaline test (right panel) in a 44 year old asymptomatic woman who had several family members diagnosed with BS. Note that lead V₂ displays borderline changes during the test (J elevation < 2 mm) whereas lead V₂₋₄ displays typical type 1-like pattern (right panel).

ECG changes only to some extent resembling Brugada type 1 pattern were observed in only one 24-year-old healthy man of control group B (0.4%) (Fig. 5).

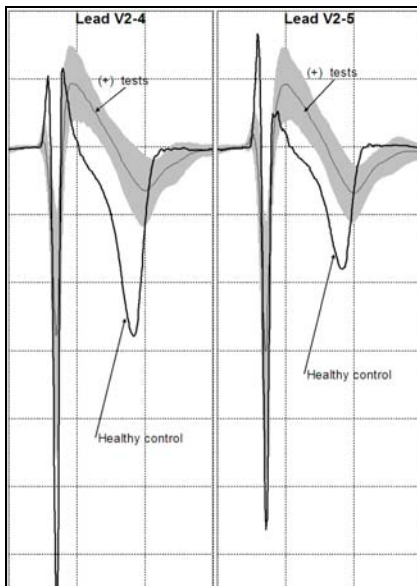


Fig. 5 Lead V_{2-4} (left panel) and V_{2-5} (right panel) derived from a resting ECG of 24-year-old healthy man (thick black lines). For comparison, the average complex (thin black line) and standard deviation (grey zone) of all positive tests in which V_{2-4} (left panel) or V_{2-5} (right panel) displayed type 1 pattern are also presented. The differences between the RSR' (RSr') complex in the healthy subject and the Brugada type 1 pattern during positive Ajmaline tests are clearly visible.

4. DISCUSSION

The main findings of this retrospective analysis can be summarized as follows:

- Leads V1 and V2 recorded from the 3rd i.c. space are more sensitive than the standard V1 and V2 leads (4th i.c. space) for detection of type 1 Brugada pattern.
- Lead V3, whether recorded from the standard position or one i.c. space higher, is of little use for the diagnosis of BS and can safely be omitted during Ajmaline test.
- A bipolar lead between V2 (positive pole) and either V4 or V5 (negative pole) is more sensitive than the standard unipolar lead V2 for detection of Brugada type 1 pattern.

Our study confirmed previous reports [10,16,20], which demonstrated increased sensitivity of the high right precordial leads recorded from one or two i.c. spaces higher (3rd or 2nd for V1 and V2) compared to the standard positions.

Meregalli et al. [10] observed type 1 pattern only in leads V1h or V2h (3rd i.c. space) in 21 of 47 positive flecainide tests (45%), whereas in the other 26 tests it was observed in both conventional and high right precordial leads. The clinical value of leads V1h to V3h seems to be similar to that of the standard V1 to V3 leads. Miyamoto et al. [12] reported that the frequency of cardiac events during follow-up of 19 patients with type 1 Brugada pattern observed spontaneously only in V1 and V2 leads from 3rd or 2nd i.c. space was not significantly different from that of 68 patients in whom type 1 pattern was spontaneously observed in both the standard (4th i.c. space) as well as the high V1 and V2 leads (2/19 (11%) vs 11/68 (16%)). Analysis of our control group A suggests that the Brugada pattern does not occur more commonly in leads V1h to V3h than in the standard V1 to V3 leads, although the group of 108 healthy subjects is quite small for more definite conclusions (in one recent European population-based study of 12-lead resting ECGs of 4149 subjects, not a single ECG displayed Brugada type 1 pattern) [19].

The diagnostic type 1 Brugada pattern is only rarely observed in lead V3 (both in the standard or higher position) during positive Ajmaline tests and this lead is not essential for the ECG diagnosis of BS. In the absence of ECG recorders with more than 12 simultaneously acquired channels, lead V3 can be used instead for monitoring leads V1h or V2h during diagnostic Ajmaline testing or therapeutic administration of drugs which can provoke Brugada ECG pattern, such as NA⁺ channel blockers (the so-called “acquired Brugada syndrome” [18]).

The bipolar precordial leads V_{2,4} and V_{2,5} detect more sensitively the appearance of type 1 Brugada pattern during Ajmaline administration than the unipolar lead V2 and this pattern in leads V_{2,4} or V_{2,5} seems to be quite specific for BS since it is rarely observed during negative tests and in healthy subjects. However, at this stage the sensitivity and specificity of the bipolar precordial leads remain unknown, because these parameters can be meaningfully established only in relation to the presence of symptoms or arrhythmic events (preferably prospectively evaluated), since at present gene mutations cannot be found in the vast majority of the patients [22]. Such data were not available in this study. Hence, the clinical value of our purely electrocardiographic observations remains to be defined.

We can only speculate about the mechanisms underlying type 1-like pattern in the bipolar precordial leads. The cellular basis of the BS and its different ECG patterns is still not clear (for a recent review see [14]). According to the “repolarization theory” [1, 8, 9, 15, 17], genetically determined or drug-induced reduction of the inward Na^+ current leads to unopposed transient outward (I_{to}) current in some epicardial regions of the right ventricular outflow tract (RVOT), which causes either delayed expression of the action potential (AP) dome and epicardial AP prolongation or loss of the dome and AP shortening. The net effect is magnification of repolarization dispersion between the RVOT endo- and epicardium, and between different RVOT epicardial regions, which is potentially arrhythmogenic.

There is also mounting evidence [1, 5, 6, 9] for the presence of conduction abnormalities in the RVOT and their importance for the genesis of ventricular arrhythmias in BS [1, 9] (“the depolarization theory”). The presence of late potentials and prolonged filtered QRS duration on signal-averaged ECG (SAECG) have also been linked to the arrhythmic risk in BS [6, 7]. Recently, increased QRS fragmentation was shown to be related to the incidence of arrhythmic events in BS [13]. A mechanism explaining the Brugada ECG type solely by RVOT conduction delay has also been proposed (see Fig. 3 in [11]).

Generally, Brugada type 1 pattern with a negative T wave results from early relative (intracellular) positivity of the unaffected zone (RVOT endocardium according to the “repolarisation theory” or normally activated myocardium outside the RVOT according to the “depolarization theory”) and late epicardial relative intracellular positivity in the affected RVOT zone due to either prolongation of the epicardial AP or its delayed activation. It seems that the type 1-like pattern in leads $V_{2,4}$ and $V_{2,5}$ reflects similar differences between the affected RVOT (predominantly epicardial) zones under the V2 electrode and the unaffected left ventricular apical epicardial zones under the V4 or V5 electrode (Fig. 6). In cases when the type 1 pattern is observed in lead V2h, but not in lead V2, the latter typically also demonstrates repolarization changes suggestive of, although not diagnostic of BS (type 2 pattern or non-specific ST elevation) (e.g. Fig. 2, right panel). It seems that in such cases the electrode at V2h directly reflects the affected myocardial zone (in the RVOT), whereas the electrode at V2 provides an “oblique view” of this zone in the form of type 2 pattern (or other kind of ST elevation) in lead V2 and type 1-like pattern in lead $V_{2,4}$ or $V_{2,5}$.

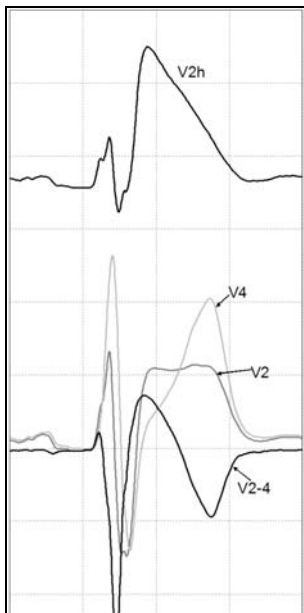


Fig. 6 The figure presents leads V2h, V2 and V4 and the subtracted bipolar lead V2-4 in order to demonstrate a possible mechanism of Brugada type 1-like pattern in a bipolar precordial lead. A median beat created from a 10-second recording has been used. The ECG has been recorded 6 minutes after the start of a positive Ajmaline test (development of type 1 ECG in leads V1h and V2h) in an asymptomatic 35-year-old man.

The bipolar precordial leads may have diagnostic value in patients with BS. In the absence of an ECG recorder capable of simultaneous acquisition of more than 12 leads, one or more derived precordial bipolar leads could considerably enhance the diagnostic power of the standard 12-lead ECG. With the advent of modern PC-based ECG recorders, one or more bipolar precordial leads can easily be derived and displayed online simultaneously with the standard precordial leads during diagnostic or therapeutic interventions with the help of a simple software upgrade. Directly recorded bipolar precordial leads V_{2-4} , V_{2-5} and possibly others may be useful during long-term ambulatory 2 or 3-lead ECG monitoring for detection of intermittently appearing Brugada ECG pattern.

5. LIMITATIONS

In some cases, Brugada type 1 pattern is detected more clearly in the lead V1 and V2 recorded from the 2nd instead of the 3rd i.c. space (unpublished observations). The subjects in both control groups were not matched for sex and age with those of the study group. However, the average age difference of several years between subjects of the study and the 2 control

groups is unlikely to account for any ECG differences. The choice of lead $V_{2,4}$ and $V_{2,5}$ was to a large extent arbitrary. Other bipolar precordial leads could possibly provide equally good or better results. A bipolar lead between two precordial electrodes does not provide, of course, any information that is not contained in the respective unipolar leads; it is merely a visually convenient presentation of the difference between the two unipolar leads. However, the same is true for the 6 peripheral leads, any 2 of which contain all available information (e.g. lead aVR is the inverted half-average of lead I and lead II, etc.). Nonetheless the 6-lead presentation format of the peripheral ECG is indispensable to clinical practice. Finally, for technical reasons the ECG measurement and analysis of this study could not be performed in a blinded fashion.

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