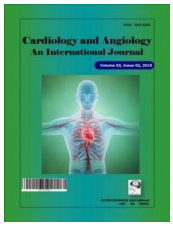

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Vectorcardiographic Investigation of Brugada ECG Unmasked by Recording at Higher Intercostal Space

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Brugada syndrome is characterised by ST segment elevation in right precordial leads and associated sometimes with idiopathic ventricular fibrillation leading to sudden cardiac death. Although ECG recording at higher intercostal space unmasks Brugada syndrome, the vectorcardiographic (VCG) mechanisms of this unmasking remain unknown.
Place and Duration of Study: Noninvasive ECG laboratory of Heart Center, Kyushu University Hospital, Fukuoka, Japan, from November 2013 to April 2015.
Methodology: Twelve-lead digital ECG was recorded at standard (4^{th}) and higher (3^{rd} and 2^{nd}) intercostal space in 5 patients with Brugada syndrome. The ECG data were transformed automatically to the VCG data based on the corrected three orthogonal Frank leads (X, Y and Z) and three vector loops of P, QRS and T waves were constructed and projected to the three (horizontal, frontal and right sagittal) orthogonal planes.
Results: ST elevation in the standard right precordial leads (V_1 to V_3) was augmented by the 12-lead ECG recorded at higher intercostal space. Saddle back ST elevation was often converted to coved type ST elevation by this invent. QRS loop was open in all 5 patients, and the maximum J-point vector showed right anterosuperior direction, whereas T loop showed left anteroinferior direction. The J-point vector faced toward and the maximum T vector faced backward the right

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precordial ECG electrodes, which was accentuated by shifting them to the higher intercostal space.
Conclusion: Unmasking of Brugada ECG was explained well even in this small-sample study by the spatial relationship between the orientations of ST-T vector and the standard right precordial ECG electrodes positioned at the higher intercostal space.

Keywords: Brugada syndrome; electrocardiogram; higher intercostal space; vectorcardiogram.

1. INTRODUCTION

Brugada syndrome was described originally in 1992 by Brugada P and Brugada J [1] as a distinct clinical and electrocardiographic (ECG) syndrome characterised by sudden cardiac death (SCD) under the baseline ECG showing strange ST elevation mimicking right bundle branch block (RBBB). To date, Brugada syndrome is a distinct genomic cardiac channelopathy associated with a high risk of SCD caused by ventricular fibrillation (VF) without structural heart diseases. ECG in patients with Brugada syndrome is characterised by specific ST elevation in the standard right precordial leads (V_1 to V_3) [1]. These findings are classified as coved type or saddle back type and unmasked or confirmed by recording the standard right precordial ECG at higher intercostal spaces [2]. This novel technique for unmasking Brugada ECG pattern is explained by that right ventricular outflow tract (RVOT) region is the area responsible for the characteristic Brugada ECG pattern [3], and that local electrogram of RVOT is reflected more in the higher (3^{rd} and 2^{nd}) intercostal space than in the standard (4^{th}) intercostal space [4]. This is confirmed actually by body surface potential mapping study, i.e., the patients with Brugada syndrome showing the maximum coved type ST elevation in body surface area equivalent to the standard (4^{th}) intercostal space was 72% of the entire patients, but the remaining (28%) patients showed the maximum ST elevation in the limited area equivalent to the higher (3^{rd} and 2^{nd}) intercostal space [5]. However, vectorcardiographic (VCG) studies to investigate the mechanisms of Brugada ECG pattern unmasked by higher intercostal space recording are scarcely performed. VCG is superior in a spatial recognition of electromotive force generated by cardiac excitation. Therefore, this study aimed to investigate such manifestation of Brugada ECG pattern by higher intercostal space recording of ECG from the viewpoint of VCG.

2. SUBJECTS AND METHODS

2.1 Subjects

This study was designed as an observational study of patients with Brugada syndrome admitted to the Kyushu University Hospital and performed from November 2013 to April 2015 according to the Declaration of Helsinki (2008). Blood examination was carried out after overnight fasting, and other routine laboratory examinations were performed in the morning. Body mass index (BMI) was calculated by body weight (BW: kg) divided by square of height (m^2). Hypertension was diagnosed by the use of antihypertensive drugs, systolic blood pressure (BP) $\geq$ 130 mmHg and/or diastolic BP $\geq$ 85 mmHg [6]. Diabetes was defined as fasting blood glucose level $\geq$ 126 mg/dl, casual blood glucose level $\geq$ 200 mg/dl, HbA1c level $\geq$ 6.5% and/or current antidiabetic medication [7]. Dyslipidemia was defined as LDL cholesterol level $\geq$ 140 mg/dl, HDL cholesterol level < 40 mg/dl and/or the prescription of lipid-lowering agents [8].

2.2 ECG and VCG Examinations

Twelve-leads digital ECG was recorded at supine position under the conditions of paper speed of 25 mm/sec and 10 mV gain, using a Fukuda Denshi HPM 7100 BPM equipment (Fukuda Denshi Inc., Tokyo, Japan). This was performed at first at the standard (4^{th}) intercostal space. Thereafter, ECG at the higher (3^{rd} and 2^{nd}) intercostal space was recorded, i.e., the standard right precordial ECG at the 4^{th} intercostal space recording (V_1-V_3) were compared with those at the 3^{rd} (V_1^*-V_3^*) and the 2^{nd} (V_1^{**}-V_3^{**}) intercostal space recordings. ECG criteria for the diagnosis of Brugada pattern was followed by the J-wave Syndromes Expert Consensus Conference Report (2016), because Brugada syndrome is considered widely as one of the J-wave syndromes (i.e. J-wave manifestation in the right precordial leads). Type I Brugada ECG was defined as coved type ST segment elevation ≥ 2 mm (0.2 mV) in ≥ 1 standard right precordial leads (V_1-V_3) positioned in the 4^{th}, 3^{rd} or 2^{nd} intercostal space. Type 2 was characterised by ST segment elevation ≥ 0.5 mm (generally ≥ 2 mm in V_2) in ≥ 1 standard right precordial leads (V_1-V_3) followed by convex ST segment. Type 3 was characterised by either coved or saddle-back appearance associated with an ST segment elevation ≥ 1 mm [3].

Scalar ECG signals were then automatically transformed to VCG signals by the corrected three orthogonal Frank lead system (X, Y and Z) using this equipment at a sampling rate of 500 Hz and an amplitude resolution of 1 μV. VCG analysis was performed using all three orthogonal (horizontal, frontal and right sagittal) planes. The maximum amplitude and the angle of all three loops (P, QRS and T) were indicated automatically. The three loops were demonstrated at the gain of 320 mm/mV in P loop, 40 mm/mV in QRS loop and 80 mm/mV in T loop, respectively. Arrow heads were inscribed to show the vector loop rotation at every 20 msec. Angles of the vector showing the maximum amplitude were indicated in horizontal plane from X to Z axis, in frontal plane from X to Y axis and in right sagittal plane from Z to Y axis, respectively. The orientation and the direction of the maximum instantaneous J-point vector were measured manually. The entire analyses of ECG and VCG were performed by the same cardiologist who was unaware of the study protocol. The two main focuses were on the ST segment alterations by recording scalar ECG at higher intercostal space and the magnitude and the direction of the J-point and T vectors in VCG analysis.

Pharmacological challenge test was performed in another day after obtaining written informed consent by using intravenous pilsicainide (1 mg/kg per 10 minutes), which is a potent sodium channel blocking agent commercialised in Japan. The pilsicainide challenge test was considered to be positive in patients showing J wave amplitude augmentation ≥ 2 mm (0.2 mV) and those showing type 2 or 3 Brugada ECG pattern converted to type 1, which was observed in ≥ 1 standard right precordial leads (V_1-V_3) by pilsicainide infusion. Finally, electrophysiological study (EPS) was conducted after obtaining written informed consent. Provocation of ventricular arrhythmias was attempted by triple extrastimuli (S_1S_2 220 msec, S_2S_3 200 msec and S_3S_4 200 msec under the basic cycle length (S_1S_1) of 400 msec) applied at the RVOT or the right ventricular (RV) apex. When EPS induced VF, polymorphic ventricular tachycardia (VT) or monomorphic VT lasting ≥ 30 sec, the provocation test was defined as positive.

2.3 Statistical Analyses

Continuous data are expressed as means ± SD. For statistical analyses, Kolmogorov-Smirnov test was used first for normality. To analyse the difference of the corresponding data, multiple comparison test was applied, i.e., Tukey-Kramer's test was used for comparison of corresponding data which were distributed normally, and Bonferroni's test was applied for corresponding data which were not distributed normally.

3. RESULTS

3.1 Baseline Characteristics

Five patients enrolled were all Japanese men (34.8 ± 5.5 years). They were hospitalised for pharmacological challenge test and EPS to stratify the risk of SCD caused by Brugada syndrome. Average BW and BMI were 71.2 ± 4.9 kg and 24.0 ± 1.3 kg/m^2, respectively. None of them had experience of syncope or night mere and documentation of VF or polymorphic VT. They had no family history of confirmed or abortive SCD. With respect to comorbidity, two of them had hypertension, none of them had diabetes, and one of them had dyslipidemia. No structural heart diseases were found by routine transthoracic echocardiogram, chest X-ray and thoracic CT imaging. Intravenous pilsicainide challenge test was positive in all five patients, and EPS was performed in three of five patients. Induction of VF was possible in only one patient by the triple extrastimuli applied at the RVOT but not at the RV apex. Therefore, implantable cardioverter defibrillator (ICD) was implanted in this patient alone.

3.2 ECG Findings

Representative ECG of the patient with Brugada syndrome was demonstrated in Fig. 1. ECG recorded at V_1 remained coved type while ST elevation was augmented by higher (V_1*, V_1**) intercostal space recordings. ECG recorded at V_2 showing saddle back type was converted to coved type in V_2*, V_2**, which was associated with ST elevation. ECG recorded at V_3 demonstrated no Brugada ECG pattern, but ECG recorded at V_3* and V_3** showed saddle back type in association with ST elevation. Table 1 summarised the results of ST elevation in all 5 patients. ST elevation observed at V_1 and V_2 at the standard (4th) intercostal space was significantly augmented by recording at higher (3rd or 2nd) intercostal space. Saddle back type observed at V_1 lead was converted to the coved type Brugada ECG pattern at V1* and V1** in one of the five patients (20%), and the same was observed in V_2 lead in two of the five patients (40%). There were 3 cases showing Brugada ECG pattern in V_3^* or V_3^{**} but not in V_3 (60%).

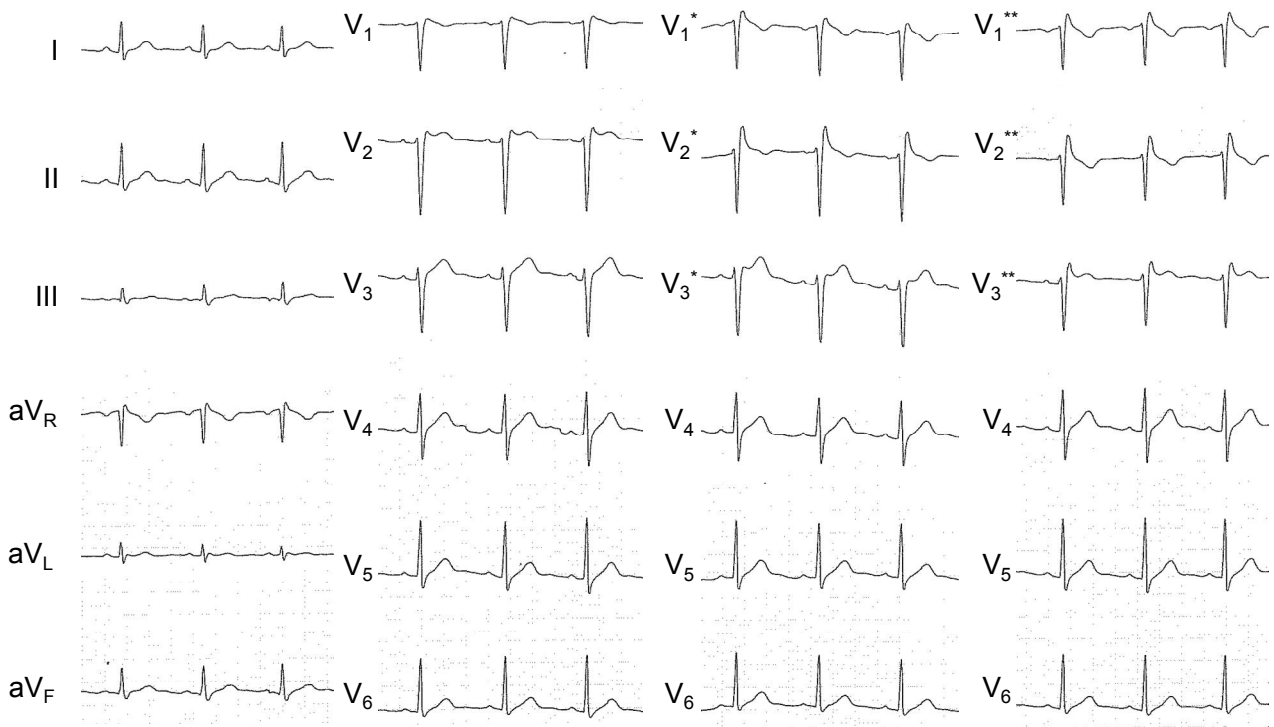

Fig. 1. A representative case of Brugada syndrome showing the electrocardiogram (ECG), where V_1 showed coved type ST elevation and V_2 showed saddle back type ST elevation at the standard (4^{th}) intercostal space. ECG recorded at the 3^{rd} intercostal space (V_1^*, V_2^* and V_3^*) showed coved type ST elevation in V_1^*-V_2^* leads and saddle back type ST elevation in V_3^* lead. ECG recorded at the 2^{nd} intercostal space (V_1^{**}, V_2^{**} and V_3^{**}) demonstrated Brugada ECG patterns similar to those recorded at the 3^{rd} intercostal space. However, ST elevation in V_1^{**} to V_3^{**} was greater than that recorded at the corresponding 3^{rd} intercostal precordial leads (V_1^* to V_3^*). Note that broad S wave characteristic for the right bundle branch block is not observed in V_6 lead.

Table 1. Amplitudes of J wave recorded in the standard right precordial leads of the three different intercostal spaces

	4th ICS	3rd ICS	2nd ICS	p
V_1 (mV)	0.18 ± 0.03	0.21 ± 0.04	0.23 ± 0.03	0.003
V_2 (mV)	0.20 ± 0.04	0.23 ± 0.04	0.25 ± 0.04	< 0.001
V_3 (mV)	0.13 ± 0.03	0.16 ± 0.03	0.19 ± 0.02	—

ICS, intercostal space. Multiple comparison among the three ICS in V_3 was not performed due to lack of data.

3.3 VCG Findings

Standard digital ECG signals were transformed to VCG signals immediately after the routine ECG recording. VCG of P, QRS and T loops of the patient presented in Fig. 1 was demonstrated in Figs. 2, 3 and 4, respectively. P loop showed no specific abnormalities suggestive of atrial overload (Fig. 2). QRS loop demonstrated an open loop configuration yielding a significant ST vector showing the right anterosuperior direction (Fig. 3). The maximum T vector showed the right anteroinferior direction (Fig. 4). Summarised data were presented in Table 2. The mean amplitude and orientation of the P, QRS and T loops in five patients were within the normal range, and the same was true with respect to the vector loop rotation (clockwise or counterclockwise) [9]. However, the QRS component showed an open loop configuration in all five patients, yielding significant J-point vector. The mean J-point vector showed right anterosuperior direction.

3.4 Unmasking of Brugada ECG

Corrected three orthogonal Frank-lead system sets the horizontal plane at the level of 5th intercostal space [9]. The spatial relationship between the right sagittal plane (Y-Z plane) of Frank-lead system and three ECG electrodes positioned at the individual intercostal space (4th, 3rd or 2nd) of the chest wall was illustrated in Fig. 5. The J-point vector projected to this plane was directed to the right anterior quadrant (bold arrow in Fig. 5A), i.e., average angle of J-point vector in the five cases was -137 ± 12° in this plane. Therefore, J-point vector faced toward the right precordial ECG electrodes, which was accentuated by putting electrodes at the higher (3rd to 2nd) intercostal space. The maximum T vector was oriented to left anteroinferior direction. i.e., the direction of the maximum T vector was 119° in right sagittal plane (Fig. 5B). The average angle of the T vector in the five cases was 99 ± 20° (Table 2) in this plane. Therefore, the maximum T vector faced backward the right precordial electrodes, which was also accentuated by shifting ECG electrodes to the higher intercostal space. These phenomena explain well that ECG recorded at higher intercostal space unmasks Brugada ECG pattern, and that this intriguing recording technique sometimes converts saddle back type to the coved type associated with inverted T wave.

4. DISCUSSION

The main findings of this study are that QRS loop shows open loop configuration, and that the instantaneous J-point vector directed right anterosuperiorly, whereas the maximum T vector directed left anteroinferiorly in patients with Brugada syndrome.

Although a few medical centers still use VCG examination routinely, VCG provides better understanding of the spatial ECG information. Recent development of computer-assisted VCG apparatus is remarkable, i.e., recording, processing and analysing digital VCG signals are automatic. Therefore, VCG is still promising to diagnose various cardiac diseases including Brugada syndrome in comparison to the scalar ECG [10]. It is important that Frank postulated a simple method to determine the correct horizontal level to represent the electrical center of the heart vector. This was realised in clinical practice to be the 5th intercostal space at the sternal border [9]. However, cross-correlation analysis of Y-axis and precordial leads indicated suitable level as 4th intercostal space [11]. Therefore, scalar ECG electrodes attached to the higher (3rd and 2nd) intercostal space are located above the horizontal plane of the three orthogonal VCG system.

The concept of J-wave syndromes includes early repolarisation pattern and Brugada ECG pattern, i.e., Brugada syndrome is considered as a J-wave manifestation especially in the standard right precordial leads (V_1 to V_3) [3]. In this sense, J-point vector is hypothesised to be recorded in VCG. Peréz-Riera et al actually investigated VCG in patients with Brugada syndrome and in those showing RBBB. They reported the clear VCG difference between the two clinical entities and the presence of J-point vector in patients with Brugada syndrome [12]. Furthermore,

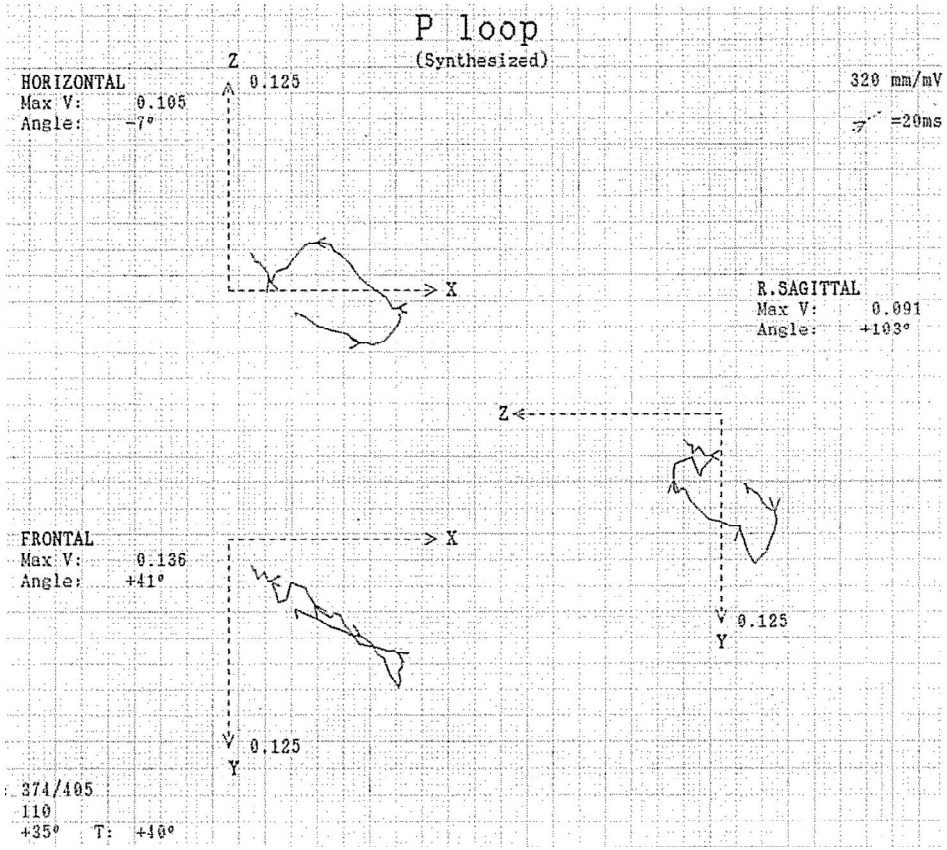

Fig. 2. Three orthogonal demonstration of P loop in the case presented in Fig. 1. No specific abnormality suggestive of atrial overload was found. Arrow heads are illustrated on the spatial P loop to indicate the rotation (clockwise or counterclockwise) of the inscription of the P loop. The same is indicated in Figs. 3-5.

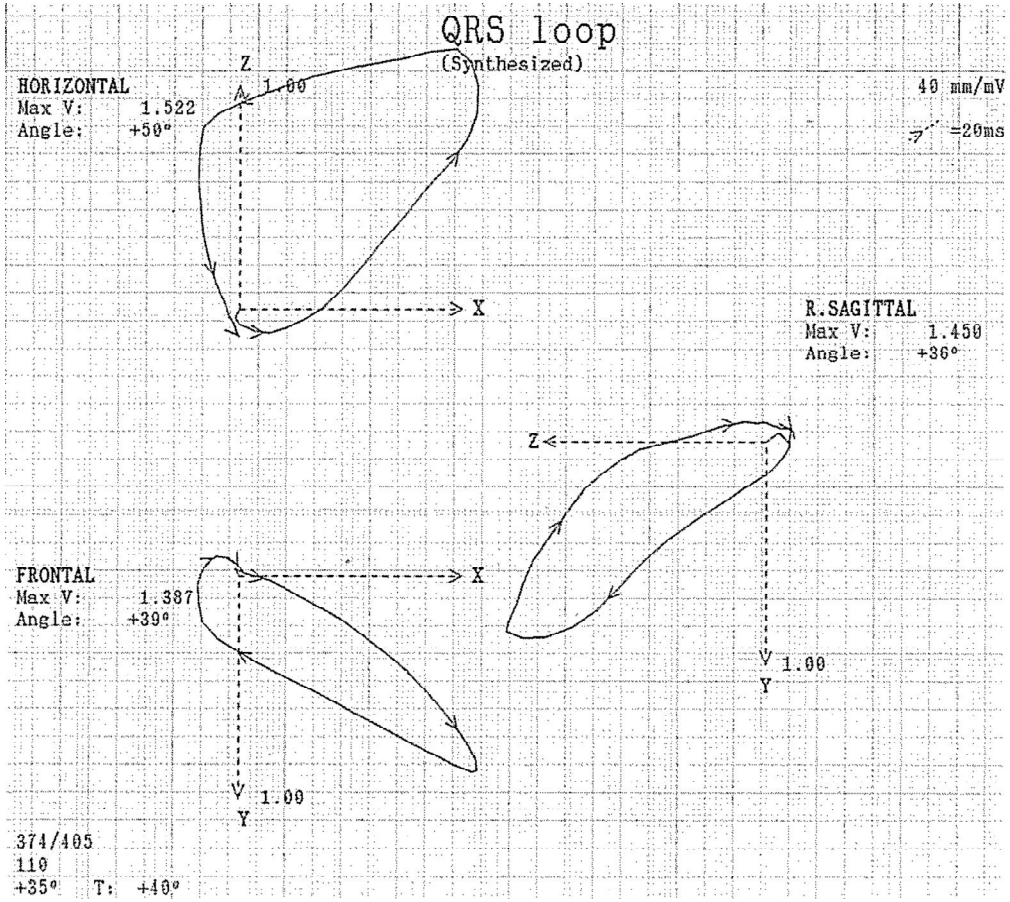

Fig. 3. Three orthogonal demonstration of QRS loop in the case presented in Fig. 1. Note that QRS configuration demonstrated open loop which indicates the significant ST vector oriented to the right anterosuperior direction

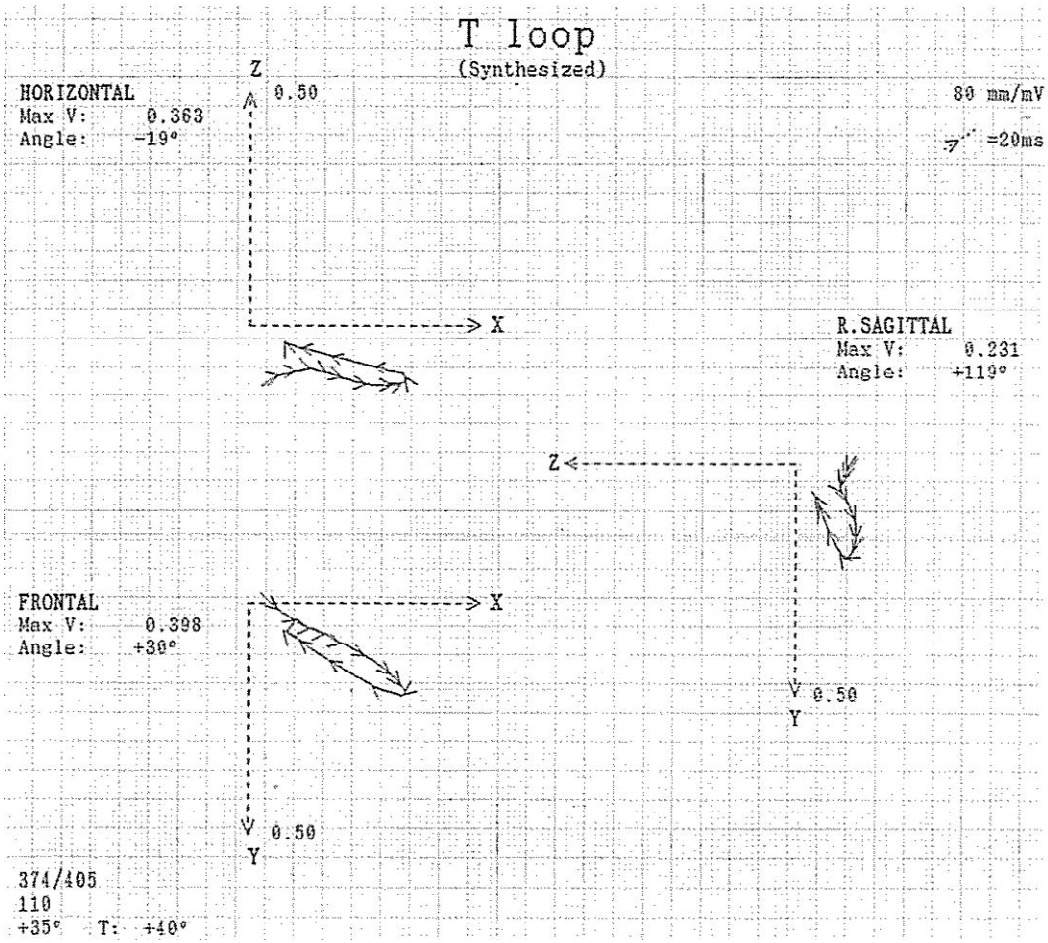

Fig. 4. Three orthogonal demonstration of T loop in the case presented in Fig. 1. The maximal T loop is oriented to the left anteroinferior direction.

Table 2. Vectorcardiographic analysis of P, QRS, T loops and instantaneous J-point vector

	P loop			QRS loop			J-point vector			T loop		
plane	**H**	**F**	**Rt. S**	**H**	**F**	**Rt. S**	**H**	**F**	**Rt. S**	**H**	**F**	**Rt. S**
amplitude (mV)	0.10± 0.02	0.14± 0.02	0.08± 0.02	1.52± 0.10	1.37± 0.12	1.23± 0.17	0.13± 0.01	0.10± 0.01	0.13± 0.01	0.41± 0.05	0.45± 0.05	0.27± 0.04
angle (degree)	-9± 3	50± 6	108± 9	47± 12	51± 9	44± 7	-116± 14	-141± 17	-137 ± 12	-16± 6	30± 4	99± 20

The maximum amplitude of each loop was automatically analyzed, and angle of the vector showing the maximum amplitude was indicated in horizontal plane from X to Z axis, in frontal plane from X to Y axis and in right sagittal plane from Z to Y axis, respectively.

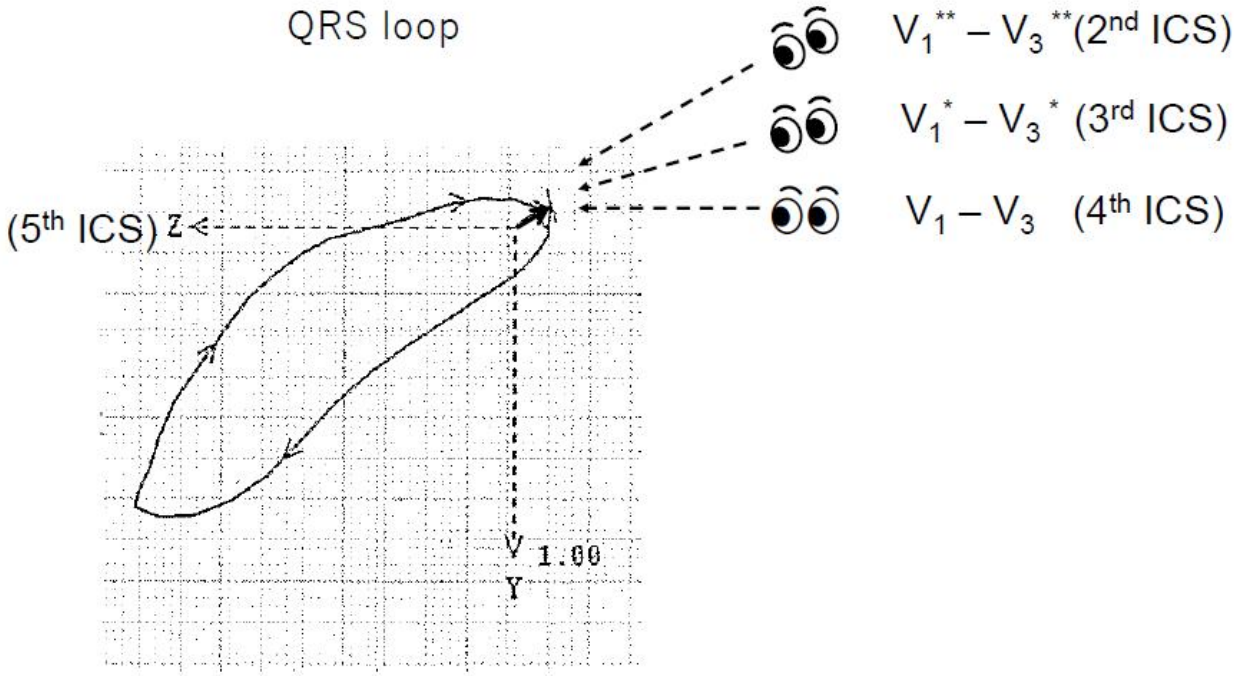

Fig. 5A.

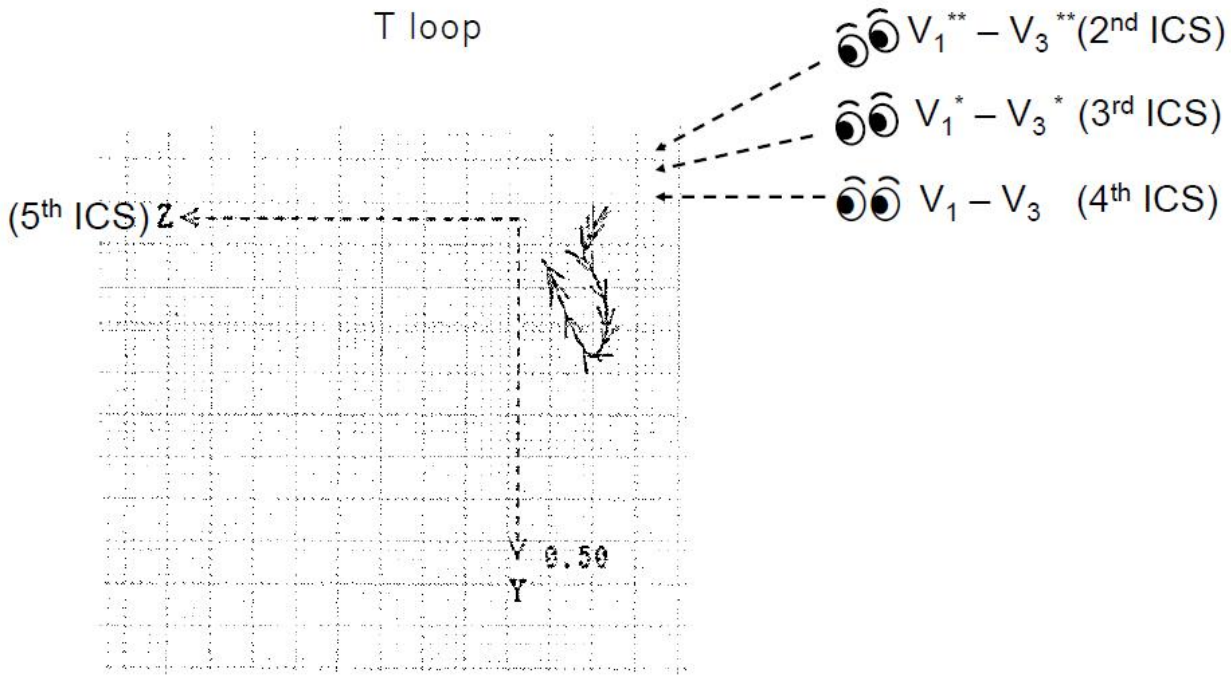

Fig. 5B.

Fig. 5. Right sagittal planes of the QRS loop (A) and T loop (B) in relation to the standard (4th) and higher (3rd and 2nd) intercostal space (ICS) recording of scalar ECG. Bold arrow oriented to anterosuperior direction (A) is the maximum instantaneous J-point vector. Note that T loop starts from the point away from the three orthogonal center, indicating the presence of ST vector (B).

Pastore et al investigated J-point vector in patients with Brugada syndrome and early repolarisation syndrome [13]. They observed open QRS loop configuration and J-point vector in both types of syndromes. However, they postulated the different J-point vector configuration pattern between the two syndromes. In patients with Brugada syndrome, they observed counterclockwise terminal rotation of the QRS loop in the right anterior quadrant in horizontal plane. On the other hand, they recognised the QRS terminal loop located in the left anterior quadrant of this plane in patients with early repolarisation syndrome. They postulated this VCG difference in the terminal portion of QRS loop and the direction of the J-point vector to distinguish the Brugada syndrome from the early repolarisation syndrome. Actually, the direction of J-point vector in all patients with Brugada syndrome enrolled in this study was right anterosuperior (Table 2).

One of the main difference between the coved type and the saddle back type ECG pattern of Brugada syndrome is the T wave polarity, i.e., T wave is inverted in the former type, and concave ST elevation associated with subsequent upright T wave are observed in the latter. This scalar ECG phenomenon has been interpreted so far by the difference of the configuration of action potentials recorded from endocardial and epicardial layers of canine myocardial wedge preparation [3]. Action potential configuration in the epicardial layer differs considerably from that in the endocardial layer. Phase 1 notch caused by the activation of transient outward ionic current (I_{to}) is evident in the epicardial but not in the endocardial layer. Therefore, transmural voltage gradient at the moment of phase 1 directs outward and forms precordial J waves. Phase 1 notch delays subsequent phase 2 (i.e., plateau phase) and phase 3 (repolarisation phase) appearance in epicardial layer, and T wave becomes inverted when the epicardial repolarisation completed later than the endocardial repolarisation [3]. However, these experimental findings are under the observation of transmural ECG, which is recorded by voltage difference among the two plate electrodes attached on the endocardial and epicardial surfaces (so-called 'transmural' ECG). Therefore, more clinically relevant explanation was expected concerning the manifestation of Brugada ECG pattern by recording ECG at higher intercostal space. The present study demonstrated the mechanisms with this respect from the viewpoint of VCG analyses, i.e., J-point vector directed right anterosuperiorly, whereas T vector directed left anteroinferiorly in patients with Brugada syndrome. Right precordial ECG electrodes confront the J-point vector and see off the maximum T vector, which is accentuated by higher intercostal ECG recordings. This is supported by the difference of the maximum J-point vector amplitude between the VCG and scalar ECG, i.e., this amplitude was ≥ 0.10 ± 0.01 mV in VCG (Table 2) and ≥ 0.13 ± 0.03 mV in 4th, ≥ 0.16 ± 0.03 in 3rd and ≥ 0.19 ± 0.02 in 2nd intercostal space (Table 1).

5. CONCLUSIONS

Although the present study is a small-sample observational study without setting control patients, this study demonstrated that significant J-point vector directed right anterosuperiorly, whereas T vector directed left anteroinferiorly in patients with Brugada syndrome. Therefore, J-point vector was oriented toward and the maximum T vector was oriented backward the right precordial ECG electrodes and these were accentuated by positioning the electrodes at the higher intercostal space. VCG analysis of Brugada ECG unmasked by challenge test using sodium channel blocking agents requires future study.

CONSENT

Medical information extraction was informed to and signed informed consent was obtained from all five patients at the enrollment.

ETHICAL APPROVAL

All the procedure performed in this study were in accordance with the ethical standards of our institutional and/or national research committee and with updated Declaration of Helsinki (2008).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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