New electrocardiographic leads and the procainamide test for the detection of the Brugada sign in sudden unexplained death syndrome survivors and their relatives

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Aims Sudden unexplained death syndrome occurs in previously healthy South-east Asian young adults without any structural cause of death. The common electrocardiographic (ECG) change in sudden unexplained death syndrome survivors is right bundle branch block and ST elevations in leads V1 to V3, which are similar to the ECG pattern in the Brugada syndrome (Brugada sign). It is difficult to diagnose the Brugada sign with the 12-lead ECG in sudden unexplained death syndrome survivors and their family members because the ECG could be transiently normalized. We proposed using the higher intercostal space V1 to V3 lead ECG, together with procainamide to detect the Brugada sign.

Methods and Results Among 20 ventricular fibrillation cardiac arrest patients, 13 sudden unexplained death syndrome survivors and their relatives (n=88) were studied using the single standard 12-lead ECG and the new six higher intercostal space V1 to V3 lead ECG (V1 to V3 and −2V1 to −2V3). Ten sudden unexplained death syndrome survivors and relatives (n=48) who had a normalized ECG were also infused with procainamide (10 mg . kg⁻¹ i.v.) to unmask the Brugada sign and both ECG methods were recorded. Forty healthy individuals and 13 spouses served as the control group. Prior to the procainamide infusion, the Brugada sign could be detected in nine sudden unexplained death syndrome survivors (69.2%) and three (3.4%) relatives with the standard ECG and in 12 (92.3%) and nine (10.2%) with the new six-lead ECG. After the procainamide infusion, the Brugada sign could be demonstrated in seven sudden unexplained death syndrome survivors (70%) and seven (14.6%) relatives with the standard ECG and in nine (90%) (P=0.26) and 23 (47.9%) (P=0.0004) with the new six-lead ECG, respectively. All the controls were negative for the Brugada sign.

Conclusions Our data suggest that the new higher intercostal space lead ECG, with or without the procainamide test is helpful in detecting the Brugada sign in sudden unexplained death syndrome survivors and their relatives.

Key Words: Sudden unexplained death syndrome, the Brugada syndrome, the Brugada sign, electrocardiographic leads, procainamide.

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Introduction

Sudden unexplained death syndrome is one of the major causes of death in Thai young men. It has been defined (by the US-CDC in 1984) as any unexpected death in a person at least 2 years of age, born in, or with at least one parent born in Vietnam, Cambodia, Laos, Thailand, the Philippines or other South-east Asian country, and a post-mortem examination revealing no underlying
cause of death\[4\]. In probable or presumptive sudden unexplained death syndrome (PSUDS) the victim would have at least four of the following criteria for a witnessed case, and at least three for a non-witnessed case: (1) age 20–50 years; (2) event taking place during sleep or a short nap; (3) victim known to be healthy until immediately before the event; (4) agonal respiration or difficulty in breathing before death; (5) waking is difficult or unsuccessful; (6) no necropsy is performed\[2\]. Therefore a PSUDS survivor, whose cause of arrest cannot be identified after intensive investigations, is called a sudden unexplained death syndrome survivor or near sudden unexplained death syndrome (NSUDS). The majority of NSUDS had documented ventricular fibrillation, cardiac arrest and the characteristic ECG pattern of the Brugada syndrome (Brugada sign): right bundle branch block and ST-segment elevation in leads V1 to V3\[3,4\]. Transient normalization of this ECG pattern in Brugada syndrome patients may lead to under-diagnosis\[5\]. However, sodium channel blockers such as ajmaline, procainamide and flecaïnide can unmask the Brugada sign in many Brugada syndrome patients\[6\].

We hypothesized that higher intercostal space leads V1 to V3 (−V1 to V3 and −2V1 to −2V3) (Fig. 1) should be helpful in detecting the Brugada sign because (1) the Brugada sign was a reflection of conduction delay localized in the right ventricular anterior wall and the right ventricular outflow tract by isochrone mapping\[7\]. The ECG lead position could be extended to cover the sites where abnormal repolarization prevails; (2) the recent report of improved detection of coronary artery disease by exercise ECG with the use of right precordial leads along with the standard six left precordial leads\[8\] gave us the idea that the more ECG leads we utilized, the greater the chance of detecting the Brugada sign in highly suspect cases; (3) one of our patients with the Brugada syndrome who survived his second idiopathic ventricular fibrillation cardiac arrest did not have an ECG characteristic of the Brugada sign in the conventional 12-lead ECG of his immediate post-cardiac arrest tracing, but did have it in leads −V1, −2V1 and −2V2 and similar manifestations were also found in other NSUDS patients (Fig. 2) and their family members\[9\]. Shimizu et al.\[10\] also recently reported that recordings of leads V4 to V6 in the 12-lead ECG in the parasternal second or third intercostal space would be helpful in the diagnosis of the Brugada syndrome in Japanese patients, and that the sodium channel blocker (disopyramide) could accentuate ST segment elevation not associated with a shift of location of the maximum ST segment elevation in Brugada syndrome patients. Very few ECG data for NSUDS patients and none of their families are available. The purpose of this study is to determine the usefulness of the higher intercostal space V1 to V3 lead ECG, by comparing the ECG patterns of NSUDS and their relatives using the standard 12-lead and the new six higher intercostal space lead ECG (−V1 to −V3 and −2V1 to −2V3) with and without intravenous procainamide.

**Figure 1** The standard precordial positions of conventional chest leads V1 to V6 (open circles) and the higher intercostal space ECG leads: −V1 to −V3 and −2V1 to −2V3 (open squares) are shown. The lead −V1 is just to the right of the sternum in the third intercostal space; the lead −V2 to the left of the sternum in the third intercostal space; the lead −V3 is one intercostal space higher than standard lead V3; the lead −2V1 and −2V2 are just to the right and left, respectively, of the sternum in the second intercostal space; the lead −2V3 is two intercostal spaces higher than standard lead V3. MAL=mid-auxillary line; AAL=anterior auxillary line; MCL=mid-clavicular line.

**Methods**

We define an NSUDS patient as a survivor of cardiac arrest from documented/witnessed ventricular fibrillation or as a PSUDS survivor in whom polymorphic ventricular tachycardia/ventricular fibrillation could be induced by electrophysiology. The subjects were previously healthy Thais, and extensive investigations, including biochemical study, echocardiography, coronary angiography, left and right ventriculography and electrophysiology, could reveal no cause of cardiac arrest. The NSUDS patient who has not undergone extensive investigation and has no structural heart disease/conditions to explain the cause of ventricular tachycardia/ventricular fibrillation is known as a presumptive near sudden unexplained death syndrome (PNSUDS) patient. From June 1997 to November 2000, we studied ventricular tachycardia/ventricular fibrillation cardiac arrest victims who were referred, or admitted, to the Department of Medicine, King Chulalongkorn Memorial Hospital. The standard
12-lead ECG and new six higher intercostal space lead ECG (−V₁ to −V₃ and −2V₁ to −2V₃) were recorded after resuscitation. The other investigations, including complete blood count, urinary analysis, blood chemistry, electrolyte, chest X-ray, echocardiography with Doppler study, left- and right-sided cardiac catheterization with coronary angiography, left- and right-sided cardiac catheterization with coronary angiography and left/right ventriculography were also performed to exclude organic heart disease and other causes of ventricular tachycardia/ventricular fibrillation. Those who had no known causes of malignant ventricular arrhythmia were included. We performed the electrophysiological study and programmed electrical stimulation at the right ventricular apex and outflow tract in three cycle-lengths in all NSUDS and PSUDS survivors who gained consciousness and were able to sign the informed consent. The PSUDS survivors in whom ventricular tachycardia/ventricular fibrillation could not be induced with programmed electrical stimulation were excluded from the study. The NSUDS patients were treated with either beta-blocker or implantable cardioverter defibrillator.

We define the Brugada sign as an ECG with right bundle branch block and ST elevation typical of the Brugada syndrome (Brugada sign) but when the new higher intercostal space ECG leads (−V₁ to −V₃ and −2V₁ to −2V₃) were employed, the ‘coved’ types of the Brugada syndrome were revealed in lead −2V₂ and the ‘saddle-back’ type in leads −V₁ and −2V₁.

12-lead ECG and new six higher intercostal space lead ECG shown in the original publications by Brugada[3]. It is consistent with (but not a definite) Brugada sign. We define a negative Brugada sign as a normal ECG, or an ECG with minor ST-T changes dissimilar to those shown in the original publications by Brugada[3].

If the standard 12-lead ECG showed no Brugada sign or a questionable Brugada sign in leads V₁ to V₃, 10 mg·kg⁻¹ of procainamide was intravenously administered in 10 min, with the patient being continuously monitored in the intensive care unit. The procainamide test was positive when the post-procainamide ECG demonstrated a greater than 0.1 mV down-sloping ST-segment elevation in any of the leads V₁ to V₃, −V₁ to −V₃ and −2V₁ to −2V₃ in the immediate post-procainamide ECG compared with baseline ECG.

We performed the standard 12-lead and new six higher intercostal space lead ECGs in the healthy relatives of NSUDS patients, together with the procainamide test (10 mg·kg⁻¹ intravenously in 10 min) in the emergency room or intensive care unit where cardiopulmonary resuscitation facilities were available, if the ECG showed questionable or negative Brugada sign. The relatives of NSUDS with symptomatic heart disease or evidence of coronary artery disease were excluded from the procainamide test. The pedigree of sudden
unexplained death syndrome families was drawn using the Brugada sign as the phenotype and the genetic mode of transmission was determined. The protocol was approved by the Faculty of Medicine Ethical Committee and informed consent was obtained from all subjects before the study. Statistical analysis was made for the chi-squared test for the difference between the two ECG methods and a P value <0.05 was considered as statistically significant.

Results

Twenty patients with unexplained ventricular fibrillation cardiac arrest were admitted to hospital. All but one were males and the mean age was 36.8 ± 10.0 years. Seven patients were excluded because invasive cardiovascular studies to elucidate the aetiologies of ventricular fibrillation were incomplete. Thirteen patients were diagnosed as NSUDS after extensive investigations according to the protocol. These and their 88 relatives were studied, together with 53 healthy adults and spouses who served as controls. Procainamide tests were performed in 10 (out of 13) NSUDS patients who had transient normalization of the Brugada sign, in 48 relatives who had negative or questionable Brugada sign on the standard 12-lead and new six higher intercostal space lead ECG (Fig. 3), and in 13 healthy controls. The Brugada sign was detected in nine (69.2%) of the NSUDS patients by the conventional 12-lead ECG compared with 12 (92.3%) by the new six-lead ECG (P=0.13). Of the relatives, three (3.4%) were revealed to have the Brugada sign by the 12-lead ECG and nine (10.2%) by new six-lead ECG (P=0.07) (Table 1). There were similar findings in the procainamide groups: seven NSUDS patients (70%) by the 12-lead ECG compared with nine (90%) by the new six-lead ECG (P=0.26), seven (14.6%) by the 12-lead ECG and 23 (47.9%) by new six-lead ECG (P=0.0004) (Table 2). None of the controls or spouses had a positive Brugada sign by both methods with or without procainamide. No ventricular arrhythmia or serious side-effects were observed during the procainamide test.

In one eight-member NSUDS family (SSR), the 12-lead ECG alone, the 12-lead post-procainamide ECG and the six higher intercostal space lead ECG alone, showed a positive Brugada sign in one and a questionable Brugada sign in another (Fig. 4(a)). However, five positive Brugada signs were detected by the new six-lead post-procainamide ECG (Fig. 4(b)). Individuals I.1 and II.5 were healthy until they suddenly unexpectedly died in their sleep in the fourth decade of life without any obvious cause of death (PSUDS). Using presumptive sudden unexplained death and the Brugada sign as the phenotype, the pedigree of the SSR family clearly demonstrates the mode of transmission of autosomal dominance with complete penetrance, as reported in the Brugada syndrome[11].

Discussions

Table 1 Comparison of the rate of detection of the Brugada sign by the conventional 12-lead ECG with the new six higher intercostal space lead ECG (V1 to V3 and −2V1 to −2V3) in near sudden unexplained death syndrome patients, their relatives and normal controls

<table>
<thead>
<tr>
<th></th>
<th>A positive Brugada sign with the 12-lead ECG</th>
<th>A positive Brugada sign with the six higher intercostal space lead ECG</th>
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<tbody>
<tr>
<td>NSUDS, no. (%) (n=13)</td>
<td>9 (69.2)</td>
<td>12 (92.3)</td>
</tr>
<tr>
<td>Relatives, no. (%) (n=88)</td>
<td>3 (3.4)</td>
<td>9 (10.2)</td>
</tr>
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<td>Controls, no. (%) (n=53)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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Table 2 Comparison of the rate of detection of the Brugada sign by the conventional 12-lead ECG with the new six higher intercostal space lead ECG (V1 to V3 and −2V1 to −2V3) after intravenous injection of 10 mg . kg−1 of procainamide in near sudden unexplained death syndrome patients, their relatives and normal controls

<table>
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<tr>
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<th>A positive Brugada sign with the 12-lead ECG</th>
<th>A positive Brugada sign with the six higher intercostal space lead ECG</th>
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</thead>
<tbody>
<tr>
<td>NSUDS, no. (%) (n=10)</td>
<td>7 (70.0)</td>
<td>9 (90.0)</td>
</tr>
<tr>
<td>Relatives, no. (%) (n=48)</td>
<td>7 (14.6)</td>
<td>23 (47.9)*</td>
</tr>
<tr>
<td>Controls, no. (%) (n=13)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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NSUDS=near sudden unexplained death syndrome.

*P<0.001.
Brugada syndrome\cite{12}. Even through procainamide is less potent than flecainide, utilization of the higher intercostal space leads could increase the power to detect the Brugada sign. With the method of procainamide administration (10 mg intravenously in 10 min) recommended by Brugada et al.\cite{13}, no serious side-effects from procainamide have been reported in the Brugada syndrome; however, one patient developed ventricular fibrillation during ajmaline administration\cite{12}. Flecainide can be safely used to maintain sinus rhythm in patients with ventricular arrhythmia and no structural heart disease. It has recently been reported that flecainide can induce ventricular tachycardia and fibrillation in patients treated for atrial fibrillation\cite{14}. The efficacy and safety of sodium channel blockers in this condition should be elucidated in future investigations with the new six higher intercostal space ECG.

Our data confirm the recent Japanese study on the 87-lead body surface map in Brugada syndrome patients\cite{10}. The study indicated that the second and third intercostal space V1 to V3 lead ECG, alone or with sodium channel blockers, would be helpful in the detection of the Brugada sign. For the first time, we have extended the study to relatives and have found that the new six-lead ECG alone are not enough to detect the Brugada sign in healthy relatives of sudden unexplained death syndrome patients. Therefore it is mandatory to perform the procainamide test with the new six-lead ECG to identify the phenotype of the family members with the Brugada syndrome. The lack of phenotype-genotype correlation in some family members of Brugada syndrome patients\cite{15} or incomplete penetrance and variable responses to sodium channel blockade\cite{16} maybe due to inadequate efficacy of procainamide, ajmaline or the flecainide test with the conventional 12-lead ECG to unmask the Brugada sign. Moreover it is conceivable to expect a higher prevalence of the Brugada sign in an apparently healthy population by using the new six higher intercostal space lead ECG\cite{17–19} as well as in idiopathic ventricular fibrillation patients.

**Study limitations**

The diagnosis of the Brugada sign in our patients was exclusively based on an ECG only, without genotype analysis. The only gene associated with the Brugada syndrome is the cardiac sodium channel gene \((SCN5A)\)\cite{13}. At least three mutations of this gene cause Brugada syndrome and sodium channel mutation might

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**Figure 3** The pre- and post-procainamide ECGs of a relative of a near sudden unexplained death syndrome patient. (a) Baseline ECG leads V1 to V3 showed no right bundle branch block or ST elevation typical of the Brugada syndrome (Brugada sign); (b) baseline higher intercostal space ECG leads \(-V_1\) to \(-V_3\) (Fig. 1) indicate a questionable Brugada sign (arrow) in lead \(-V_2\); (c) post-procainamide ECG leads V1 to V3 showed a positive Brugada sign; (d) post-procainamide ECG leads \(-V_1\) to \(-V_3\) also showed a positive Brugada sign (arrow) at lead \(-V_2\).
be present in only a small proportion of patients with the Brugada syndrome. We still have to rely on this ECG marker (Brugada sign) for the diagnosis of the Brugada syndrome in survivors of idiopathic polymorphic ventricular tachycardia or ventricular fibrillation arrest and their healthy relatives although the specificity of the Brugada sign is questionable. In subjects without documented or suspected ventricular tachycardia/ventricular fibrillation, the specificity of ST elevation following administration of a class I drug is still not clear.

Clinical implications

The new six-lead ECG (−V₁ to −V₃ and −2V₁ to −2V₃) with procainamide is safe, easy to perform and should be helpful in the detection of the Brugada sign in sudden unexplained death syndrome survivors from polymorphic ventricular tachycardia/ventricular fibrillation cardiac arrest and their healthy relatives. It could also be used as a surrogate marker to assess therapeutic efficacy of antiarrhythmic intervention.

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References


