Right Ventricular Electrocardiographic Leads for Detection of Brugada Syndrome in Sudden Unexplained Death Syndrome Survivors and Their Relatives

SOMKIAT SANGWATANAROJ, M.D., SOMCHAI PRECHAWAT, M.D., BUNCHA SUNSANEEWITAYAKUL, M.D., SURAPUN SITTHISOOK, M.D., PIYARAT TOSUKHOWONG, M.SC.,* KRIANG TUNGSANGA, M.D.†

Division of Cardiology; *Department of Biochemistry; and †Division of Nephrology, Department of Medicine; Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Summary

Background: Sudden unexplained death syndrome (SUDS) is a sudden death syndrome in previously healthy Southeast Asian young adults without any structural causes of death. Many SUDS survivors show electrocardiographic (ECG) evidence of RSR' and ST elevation in leads V₁ to V₃, which is similar to the ECG pattern in Brugada syndrome. However, in many cases transient normalization of the ECG does not make diagnosis with standard 12-lead ECG possible.

Hypothesis: To overcome this problem, we utilized the new right ventricular ECG leads to detect the Brugada syndrome in SUDS survivors.

Methods: The subject was a Thai male patient who presented with a SUDS-like syncopal attack. He had cardiac arrest due to idiopathic ventricular fibrillation.

Results: Post-resuscitation standard 12-lead ECG showed no diagnostic features of Brugada syndrome. However, ECG patterns of RSR' and ST elevations typical for Brugada syndrome could be detected at the higher intercostal space leads V₁ to V₃. We observed similar findings in 2 of the other 10 SUDS survivors and 4 of 23 healthy family members.

Conclusions: Our data suggest that these new right ventricular leads ECG may be helpful in detecting Brugada syndrome in SUDS survivors and their relatives.

Key words: Brugada syndrome, sudden unexplained death syndrome, electrocardiography, right ventricle

Introduction

Sudden unexplained death syndrome (SUDS) is characterized by sudden death in previously healthy Southeast Asian young adults during sleep or at rest, without any structural causes of death as ascertained in postmortem study. This syndrome among young male Southeast Asian refugees in the United States has been reported by the Center of Disease Control and Prevention in the last decade.¹ The native people who resided in the northeastern region of Thailand have long recognized the same pattern of death known as "Lai Tai," or dying during sleep. The survivors of SUDS are defined as patients who were apparently healthy before developing sudden cardiac arrest due to idiopathic ventricular fibrillation (VF) but were successfully resuscitated. Presumptive survivors of SUDS are patients who experienced symptoms that reflect the clinical presentation of SUDS: agonal respiration, unresponsiveness after labored respiration during sleep, transient symptoms of distress (e.g., moaning, thrashing, grimacing), and syncope or seizure-like symptoms, but did not have documented cardiac arrest or VF previously.²

Previous study in Southeast Asian refugees³ and a recent study in Thai men² showed that VF was the possible cause of cardiac arrest and death in survivors of SUDS. The electrocardiographic (ECG) patterns of RSR' and ST segment elevation in leads V₁ to V₃ are quite common in these survivors² and are similar to those found in Brugada syndrome. In 1992, Pedro and Josep Brugada described clinical characteristics of Brugada syndrome in eight otherwise healthy patients who developed sudden and aborted cardiac death due to idiopathic

This work has been supported in part by Thailand Research Fund (RTA/08/2540).

Address for reprints:

Somkiat Sangwatanaroj, M.D.
Division of Cardiology
Department of Medicine
Faculty of Medicine
Chulalongkorn University
Rama 4 Road, Patumwan,
Bangkok 10330, Thailand
e-mail: somkiat.s@chula.ac.th

Received: December 3, 1999

Accepted with revision: March 29, 2000

VF, and all patients had the ECG markers of RSR' and ST-segment elevation in leads V_1 to V_3 .⁴ Two ST-segment elevation patterns in Brugada syndrome have been described: "coved" and "saddle-back" types.⁵ The ECG manifestations in patients with Brugada syndrome could be transiently normal; thus, a diagnosis detected by standard 12-lead ECG could be missed.⁶ These dynamic ECG changes of RSR' and ST-segment elevation (Brugada sign) in leads V_1 to V_3 have also been reported in survivors of SUDS.⁷ It was proposed that the heterogeneity of repolarization across the right ventricular outflow tract (RVOT) might contribute to the pathogenesis of these ECG patterns and polymorphic ventricular arrhythmia in Brugada syndrome.⁸ We hypothesize that the RVOT repolarization heterogeneity might accordingly occur in survivors of SUDS and might lead to sudden VF. Thus, if the ECG leads for the right ventricle, especially the RVOT region, were utilized, it would be more likely that Brugada syndrome-like ECG patterns would be detected in survivors of SUDS who had transient normalization of ECG in standard ECG leads V_1 to V_3 .

Methods and Results

Case Report

A 29-year-old Thai male, a carpenter, was apparently healthy until he suddenly and unexpectedly lost consciousness while reading a newspaper. He was successfully aroused by his wife and brought to King Chulalongkorn Memorial Hospital, Bangkok. During an interview at the emergency room, he became unconscious again and was found pulseless. The ECG monitoring showed VF. He was successfully resuscitated and was transferred to the medical intensive care unit where he was determined to be clinically normal. Blood pressure was 158/72 mmHg, heart rate 76/min, and temperature 36.6°C. Physical examination was normal. The ECG showed a normal sinus rhythm, normal P waves and PR intervals, J point and ST-segment up-sloping elevation in leads V_2 and V_3 ; the corrected QT interval (QTc) was normal (408 ms)

(Fig. 1). To obtain the ECG of the right ventricle and RVOT, we recorded the leads V_1 to V_3 at the intercostal spaces (ICS) higher than standard position: the " $-V_1, -V_2, -V_3$ " represented the leads analogous to V_1, V_2, V_3 at the third ICS; the " $-2V_1, -2V_2, -2V_3$ " represented V_1 to V_3 at the second ICS; at the lower ICS, the " $+V_1, +V_2, +V_3$ " represented the leads analogous to V_1 to V_3 at the fifth ICS; and V_{3R}, V_{4R}, V_{5R} represented standard right precordial leads (Fig. 2). We arbitrarily defined the coved type of Brugada syndrome as an ECG pattern of >0.1 mV downsloping ST-segment elevation with inverted T wave and saddle-back type as a "fat" R' wave (>40 ms), a >0.1 mV of ST-segment elevation and R'/T amplitude ratio >0.75 . The RSR' and significant downsloping ST-segment elevation with negative T waves (coved type), which were not present in the initial standard ECG, were revealed in leads $-V_1, -V_2$, and $-2V_1$ to $-2V_3$ (Fig. 3). A standard 12-lead ECG taken on the next day showed saddle-back type Brugada syndrome in lead V_2 .

The laboratory test, including complete blood count, urinary analysis, blood chemistry, and electrolytes, was normal. Serum potassium was 4.0 mEq/l and magnesium 0.73 mmol/l (normal values = 0.5–1.1 mmol/l). Chest x-ray and echocardiography were normal. All pressure and oxymetry parameters during left and right-sided cardiac catheterization were within normal limits. Coronary angiography revealed normal coronary arteries. Right and left ventriculograms were normal with a ventricular ejection fraction of 68 and 61%, respectively. The electrophysiologic study showed a normal sinus node, a normal atrioventricular (AV) node, and His-Purkinje function without evidence of any accessory pathway. The Brugada sign in leads V_1 to V_3 were provoked by procainamide 10 mg/kg intravenous infusion (data not shown). No arrhythmia was induced with programmed stimulation at the right ventricular (RV) apex and RVOT at 3 cycle lengths (600, 500, 400 ms) with and without isoproterenol. Arrhythmia monitoring was negative. Because the patient refused implantation of an implantable cardioverter-defibrillator (ICD), he was discharged and treated with low-dose metoprolol. The Brugada signs in standard and new right ventricular lead ECGs (after beta

FIG. 1 Initial standard 12-lead electrocardiogram (ECG) of a Thai patient (the case report), post resuscitation from ventricular fibrillation, shows normal sinus rhythm, left ventricular hypertrophy by voltage criteria, normal QTc interval, and J point elevation with upsloping ST elevation in leads V_2 and V_3 . No "coved" or "saddle-back" type ECG of Brugada syndrome was observed.

FIG. 2 Standard precordial positions of conventional chest leads V_1 to V_6 (open circles) and the right ventricular electrocardiographic leads: $-V_1$ to $-V_3$, $+V_1$ to $+V_3$, $-2V_1$ to $-2V_3$, and V_{3R} to V_{6R} (open squares) are shown. The lead $-V_1$ is just to the right of the sternum in the third intercostal space; the lead $-V_2$ to the left of the sternum in the third intercostal space; the lead $-V_3$ is one intercostal space higher than standard lead V_3 ; the leads $+V_1$ and $+V_2$ are just to the right and left, respectively, of the sternum in the fifth intercostal space; the lead $+V_3$ is one intercostal space lower than the standard lead V_3 ; the leads $-2V_1$ and $-2V_2$ are just to the right and left, respectively, of the sternum in the second intercostal space; the lead $-2V_3$ is two intercostal spaces higher than standard lead V_3 ; the lead V_{4R} lies in the right mid-clavicular line (MCL) in the fifth intercostal space; lead V_{3R} is halfway between leads V_1 and V_{4R} ; the lead V_{5R} lies in the right anterior axillary line (AAL) in the fifth intercostal space; the lead V_{6R} lies in the mid-axillary line (MAL) in the fifth intercostal space.

blocker) were not more prominent than the predischarge ECG (without beta blocker) during 1- and 3-month follow-up.

Extended Study in Other Survivors of Sudden Unexplained Death Syndrome and Their Family Members

We employed these new 12 right ventricular ECG leads ($-V_1$ to $-V_3$, $-2V_1$ to $-2V_3$, $+V_1$ to $+V_3$, and V_{3R} to V_{5R}) and standard 12-lead ECG in cases of the other three survivors of SUDS and seven presumptive survivors of SUDS (41.5 ± 8.2 years). All but one were male. They had been apparently healthy before the syncopal attack. The three survivors of SUDS had cardiac arrest due to idiopathic VF and the other seven patients had clinical symptoms typically found in SUDS.^{9,10} Two patients (one survivor and one presumptive survivor of SUDS) had coved and/or saddle-back type of Brugada syndrome in leads V_1 to V_3 as well as in leads $-V_1$ to $-V_3$ and $-2V_1$ to $-2V_3$. The other two survivors of SUDS did not have these typical ECG markers in standard leads V_1 to V_3 , but did have when placing the recorder at the higher ICS leads (Fig. 4). We also employed these new right ventricular ECG leads together with standard 12-lead ECG to study 23 healthy family members of survivors of SUDS and 40 healthy controls. None had a history of structural heart disease and all showed normal results on physical examination. According to standard 12-lead ECG, as well as right ventricular ECG leads, two family members showed typical coved or saddle-back patterns for Brugada syndrome, and four showed them only by utilizing the higher ICS V_1 to V_3 ($-V_1$ to $-V_3$ and $-2V_1$ to $-2V_3$) ECG leads (Fig. 5), not by standard lead V_1 to V_3 (Table I). We followed up all six asymptomatic family members and did not treat them with any medication or ICD. None of the controls had typical ECG patterns of Brugada syndrome by either method. The coved or saddle-back ECG types could not be detected in lower ICS V_1 to V_3 right precordial leads ($+V_1$ to $+V_3$ and V_{3R} to V_{5R}) in either survivors of SUDS or their relatives.

FIG. 3 The initial standard leads V_1 to V_3 of the electrocardiogram (ECG) of the case report did not show the typical RSR' and ST elevation of Brugada syndrome, but when the new right ventricular ECG leads ($-V_1$ to $-V_3$, $+V_1$ to $+V_3$, $-2V_1$ to $-2V_3$, and V_{3R} to V_{5R}) were employed (see Fig. 2), the "coved" types of Brugada syndrome were revealed in leads $-V_1$, $-V_2$, and $-2V_1$ to $-2V_3$ (closed arrow).

FIG. 4 The electrocardiogram (ECG) of the survivor of sudden unexplained death syndrome (SUDS) exhibits no ECG pattern of Brugada syndrome in leads V_1 to V_3 , but reveals the "saddle-back" type in leads $-V_2$ and $-2V_3$ (open arrows) and "coved" type in lead $-2V_1$ (closed arrow).

FIG. 5 The electrocardiogram (ECG) of the father of a survivor of sudden unexplained death syndrome (SUDS). (A) Standard 12-lead ECG shows no RSR' and ST elevation of Brugada syndrome in leads V_1 to V_3 . (B) Right ventricular ECG leads (detail in text and Fig. 2) exhibit "saddle-back" type in leads $-V_2$ and $-2V_3$ (open arrow) and "coved" type in lead $-2V_2$ (closed arrow).

TABLE I Positive Brugada sign (RSR' and ST-segment elevation) in different sets of electrocardiographic leads

ECG leads	NSUDS & PNSUDS (n = 11)	Family members (n = 23)	Controls (n = 40)
Standard V ₁ to V ₃ , no. (%)	2 (18.2)	2 (8.7)	0 (0)
Higher ICS V ₁ to V ₃ , no. (%)	5 (45.5)	6 (26.1)	0 (0)
Lower ICS V ₁ to V ₃ , no. (%)	0 (0)	0 (0)	0 (0)
Standard V _{3R} to V _{5R} , no. (%)	0 (0)	0 (0)	0 (0)

Abbreviations: ECG = electrocardiographic, NSUDS = near sudden unexplained death syndrome or sudden unexplained death syndrome survivors, PNSUDS = presumptive sudden unexplained death syndrome survivors, Higher ICS V₁ to V₃ = higher intercostal space leads V₁ to V₃ or leads -V₁ to -V₃ and -2V₁ to -2V₃ (see Fig. 2), Lower ICS V₁ to V₃ = lower intercostal space leads V₁ to V₃ or leads +V₁ to +V₃ (see Fig. 2).

Discussion

The ECG pattern of RSR' with ST-segment elevation and inversion of the T wave in leads V₁ to V₃, with or without right bundle-branch block, is a diagnostic hallmark of Brugada syndrome in idiopathic patients with VF.⁴ However, this ECG pattern can be transiently normalized; thus Brugada syndrome possibly could be underdiagnosed with the standard ECG.⁶ To overcome this problem, a serial standard 12-lead ECG should be performed² because of the hourly or daily dynamic changes of this ECG manifestation,¹¹ or sodium channel-blocking agents such as procainamide can be administered intravenously to unmask the ST-segment elevation in leads V₁ to V₃.¹¹ The RSR' and ST-segment elevation in Brugada syndrome has been proposed to be a reflection of conduction delay localized in the RV anterior wall and RVOT by isochrone mapping;¹² the ECG recorder position should be extended to cover the sites where abnormal electrical impulse prevails. The more ECG leads we placed for RV and RVOT, the greater was the chance of detecting Brugada syndrome. Therefore, we selected the leads V₁ to V₃ at higher ICS (-V₁ to -V₃ and -2V₁ to -2V₃), lower ICS (+V₁ to +V₃), and right precordial leads (V_{3R} to V_{5R}) for our study.

We report the case of a survivor of SUDS with Brugada sign only in higher ICS leads V₁ to V₃ (-V₁ to -V₃ and -2V₁ to -2V₃). The patient was treated with low-dose beta blocker therapy because there is some evidence that sudden unexplained deaths among Thai workers in Singapore were related to stress and emotional problems,¹³ and beta blockers may reduce stress and the ventricular arrhythmia threshold. Beta blockers may also provoke the Brugada sign by slowing the heart rate, but this manifestation was not observed in our patient, perhaps because of the smaller dosage.

Our data have shown that the new right ventricular ECG leads could identify Brugada syndrome in 5 of 11 survivors of SUDS and 6 out of 23 of their healthy relatives, whereas the standard 12-lead ECG could do so in only 2 of 11 and 2 of

23, respectively. Thus, these right ventricular ECG leads are more sensitive than the standard 12-lead ECG for detection of Brugada syndrome.

Previous studies^{2, 6, 7} have suggested that the dynamic changes of RSR' and ST-segment elevation in Brugada syndrome might relate to the electrical heterogeneity of the right ventricle at different times, and our data demonstrate that these changes might also relate to different sites detected by different ECG leads. These findings may support the hypothesis of electrical heterogeneity at different sites leading to phase 2 reentry as a trigger for idiopathic VF, proposed by Lukas and Antzelevitch.¹⁴

The secondary R waves (R') may normally be present or increase in amplitude in the higher ICS of leads V₁ and V₂ with an inverted T wave,¹⁵ and can be differentiated from the ECG patterns of Brugada syndrome by ST-segment elevation which is absent in normal patients. The coved and saddle-back ECG patterns in Brugada syndrome look similar to right bundle-branch block and early repolarization patterns, respectively. We observed that the saddle-back type ECG in SUDS survivor had a "fat" R' wave (>40 ms) which is different from the "tall peak" R' wave in the right bundle-branch block pattern in our healthy controls. The R' wave in the saddle-back type was also as tall as or a little shorter than the T-wave amplitude (R'/T ratio >0.75), compared with the early repolarization pattern in normal controls. However, sensitivity and specificity of these criteria for Brugada syndrome need to be established in a large population study.

Conclusion

These findings have several clinical implications. First, the results demonstrate that a portion of the Thai population who suffered from acute syncopal attacks similar to SUDS probably are patients with Brugada syndrome. Second, we found that healthy family members of survivors of SUDS had an "occult" ECG pattern of Brugada syndrome as well; under certain conditions, they might develop idiopathic VF and, consequently, sudden death similar to that observed among SUDS victims. The results also support previous observations that about 30–40% of SUDS victims had a history of SUDS attacks in one or more of their family members.^{9, 13, 16} Third, to increase sensitivity for detection of subjects at high risk of developing SUDS, especially those who are family members of SUDS victims, the right ventricular ECG leads should be utilized concomitantly with a standard 12-lead ECG. When used in conjunction with the standard 12-lead ECG, the new right ventricular ECG lead method might also enhance the sensitivity for detection of Brugada syndrome. It is conceivable that utilization of this method together with sodium-channel blocker test, as well as serial ECG, will further increase the sensitivity for detecting Brugada syndrome (our unpublished data).

Our new right ventricular ECG lead method is easy to perform, inexpensive, less operator dependent, and suitable for mass screening of patients at high risk of developing SUDS.

We also propose these new right ventricular ECG leads as a screening tool for Brugada syndrome in Thai sudden death survivors.

Acknowledgments

The authors thank Mr. Tawon Supapraon for assistance with family survey and data collection.

References

1. Parish RG, Tucker M, Ing R, Encarnacion C, Eberhardt M: Sudden unexplained death syndrome in southeast Asian refugees: A review of CDC surveillance. *MMWR* 1987;36(no.1 SS):43SS–53SS
2. Nademanee K, Veerakul G, Nimmannit S, Chaowakul V, Bhuripanyo K, Likittanasombat K, Tungsanga K, Kuasirikul S, Malasit P, Tansupasawadikul S, Tatsanavivat P: Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. *Circulation* 1997;96:2595–2600
3. Otto CM, Tauxe RV, Cobb LA, Greene HL, Gross BW, Werner JA, Burroughs RW, Samson WE, Weaver WD, Trobaugh GB: Ventricular fibrillation causes sudden death in southeast Asian immigrants. *Ann Intern Med* 1984;101:45–47
4. Brugada P, Brugada J: Right bundle-branch block, persistent ST segment elevation and sudden cardiac death: A distinct clinical and electrocardiographic syndrome. A multicenter report. *J Am Coll Cardiol* 1992;20:1391–1396
5. Grace AA: Brugada syndrome. *Lancet* 1999;354:445–446
6. Bjerregaard P, Gussak I, Antzelevitch C: The enigmatic ECG manifestation of Brugada syndrome. *J Cardiovasc Electrophysiol* 1998;9:109–112
7. Veerakul G, Nademanee K: Dynamic changes in the RBBB and ST elevation in the right precordial leads observed in patients with idiopathic ventricular fibrillation: Evidence of phase 2 repolarization abnormality (abstr). *Circulation* 1996;98(suppl):I-626;3669
8. Alings M, Wilde A: “Brugada” syndrome: Clinical data and suggested pathophysiological mechanism. *Circulation* 1999;99:666–673
9. Tatsanavivat P, Chirawatkul A, Klungboonkrong V, Munger R, Chaisiri S, Charemtanyarak L, Saowakontha S: Sudden and unexplained deaths in sleep (Lai Tai) of young men in rural north-eastern Thailand. *Int J Epidemiol* 1992;21:904–910
10. Nimmannit S, Malasit P, Chaovakul V, Suseangrat W, Vasuvattakul S, Nilwarankur S: Pathogenesis of unexplained nocturnal death and endemic distal renal tubular acidosis. *Lancet* 1991;338:930–932
11. Gussak I, Antzelevitch C, Bjerregaard P, Towbin JA, Chaitman BR: The Brugada syndrome: Clinical, electrophysiologic and genetic aspects. *J Am Coll Cardiol* 1999;33:5–15
12. Kasanuki H, Ohnishi S, Ohtuka M, Matsuda N, Nirei T, Isogai R, Shoda M, Toyoshima Y, Hosoda S: Idiopathic ventricular fibrillation induced with vagal activity in patients without obvious heart disease. *Circulation* 1997;95:2277–2285
13. Goh KT, Chao TC, Chew CH: Sudden nocturnal deaths among Thai construction workers in Singapore. *Lancet* 1990;335:1154
14. Lukas A, Antzelevitch C: Phase 2 reentry as a mechanism of initiation of circus movement reentry in canine epicardium exposed to simulated ischemia. The antiarrhythmic effects of 4-aminopyridine. *Cardiovasc Res* 1996;32:593–603
15. Marriott HJ: Bundle-branch block. In *Practical Electrocardiography*, 8th ed. (Ed. Marriott HJ), p. 79. Baltimore: Williams & Wilkins, 1988
16. Tungsanga K, Sriboonlue P: Sudden unexplained death syndrome in north-east Thailand. *Int J Epidemiol* 1993;22:81–87