The Cardiac Society of Australia and New Zealand

Guidelines for the diagnosis and management of Brugada Syndrome

Development of these guidelines was co-ordinated by A/Prof Jitendra Vohra and members of the Cardiovascular Genetic Diseases Council Writing Group.

The guidelines were reviewed by the Continuing Education and Recertification Committee and ratified at the CSANZ Board meeting held on Wednesday, 10th August 2011.

1. Clinical Characteristics

1.1 Definition and prevalence

Brugada Syndrome (BS) was described as a clinical entity in 1992. The diagnosis is made by ECG and is defined by the presence of an atypical right bundle branch block pattern with a characteristic cove-shaped ST elevation in leads V_1 to V_3, in the absence of obvious structural heart disease, electrolyte disturbances or ischaemia. This condition is genetically transmitted as an autosomal dominant syndrome with incomplete penetrance. BS is reported to be responsible for 4% of all sudden deaths and 20% of sudden deaths in those without structural heart disease and is a leading cause of death in subjects under the age of 40 years. A family history is present in about 20 to 30% of patients. It is difficult to estimate the exact incidence of BS in the general population but the prevalence is quoted as 1 in 2000. The condition is particularly common in South East Asia and amongst migrants of South Asian origin and in the Japanese population the prevalence is reported to be 0.12 to 0.14%. BS has also been reported as Sudden Unexplained Death Syndrome (SUDS) or Sudden Unexplained Nocturnal Death Syndrome (SUNDS). The ECG changes of BS are dynamic and can vary spontaneously which also makes it difficult to assess its exact incidence.

1.2 Clinical presentation

The patient may present with syncope due to polymorphic ventricular tachycardia (VT) or resuscitated sudden death in the third or fourth decade of life. Symptoms typically occur at night, or at rest during the day, and are due to polymorphic VT or ventricular fibrillation (VF). Monomorphic VT is rare and is more prevalent in children and infants, among whom fever is the commonest trigger. The diagnosis of BS may also be made on family screening of patients with BS or from a routine ECG. More than 80% of adult patients are males but in children there is an equal male: female ratio. Clinical presentation is predominantly after adolescence with a peak in the third and fourth decade of life. In cases of sudden cardiac deaths BS may be under-diagnosed as ECG prior to death is generally not available and even if an ECG has been recorded ECG changes, being variable, may not be diagnostic.

1.3 Clinical diagnosis

Diagnostic ECG features of BS are shown in Fig.1. Three subtypes have been recognised, based on different ECG features:

i) *Type 1:* Cove-shaped ST elevation in right precordial leads with J wave or ST elevation of ≥ 2mm (mV) at its peak followed by a negative T wave with little or no isoelectric interval in more than one right precordial leads V1-V3.
ii) *Type 2:* The ST segments also have a high take-off but the J amplitude of ≥ 2mV gives rise to a gradually descending ST elevation remaining ≥ 1mV above the baseline followed by a positive or biphasic T wave that results in a saddle back configuration.
iii) *Type 3:* Right precordial ST elevation of <1mm of saddle-back type or coved type.

The first consensus report of 2002 proposed the diagnostic ECG criteria mentioned above. In a subsequent consensus report published in 2005, the definitions were revised and a definitive diagnosis of BS was considered when type 1 ST elevation is observed in >1 right precordial lead either spontaneously or following drug provocation, in conjunction with one of the following: documented ventricular fibrillation (VF), polymorphic VT, a family history of sudden cardiac death at <45 years, coved-type ECG in family members, inducibility of VT with programmed stimulation, syncope or nocturnal agonal respiration (attributed to self-terminating polymorphic VT or VF). While these criteria have higher specificity they have lower sensitivity.

Even in genetically-proven cases of BS, the morphology of ST segment elevation varies considerably day by day and the chances of finding typical cove-shaped elevation increases with more frequent ECG recordings and even more with placement of precordial leads V1,V2 and V3 in the 2nd and 3rd intercostal space which may bring out a typical Brugada pattern and should be routinely performed when the diagnosis is suspected but is uncertain on a standard ECG and in screening of family members of BS patients. 12-lead Holter recordings with placement of precordial leads V_1 V_2 V_3 in the 2nd and 3rd intercostal space is also helpful and a typical Brugada pattern may become apparent during nocturnal bradycardia. ECG changes of BS can also be brought out following a meal. Rarely ST changes of BS may be seen in inferior or lateral leads.

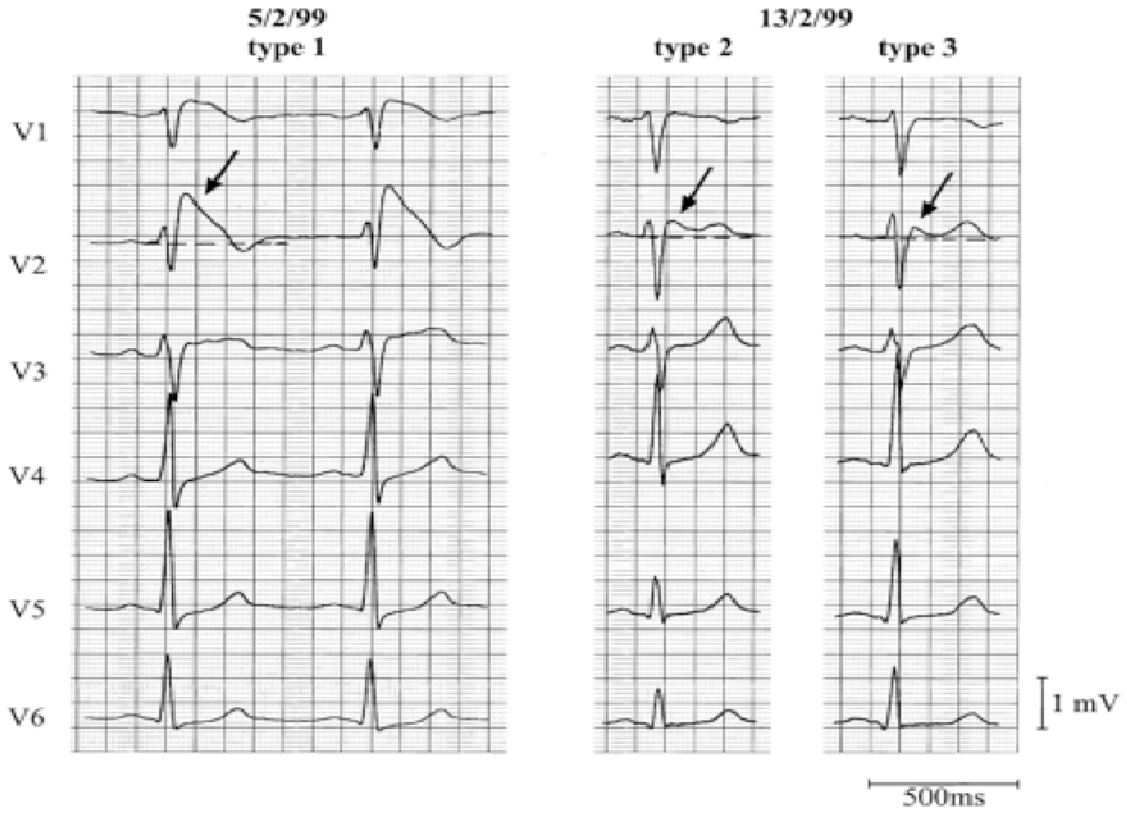

Fig. 1. Precordial leads of a resuscitated patient with BS showing all 3 ECG patterns and dynamic changes over an 8-day period. Arrows indicate J waves. Reproduced with permission from: Wilde AA et al. Proposed diagnostic criteria for the Brugada syndrome. Circulation 2002; 106:2514-19.

Spurious BS type ECG changes can be seen in patients following cardioversion and last for a few hours and may lead to an incorrect diagnosis of BS. Only Type 1 ECG pattern is diagnostic of BS, Type 2 and 3 are not diagnostic of BS and distinction from a normal variant can be difficult and pharmacological provocation test may be required if the diagnosis of BS is suspected. ECG changes of early repolarization, athlete's heart, right bundle branch block, acute pericarditis, myocardial infarction, Prinzmetal angina, arrhythmogenic RV cardiomyopathy, myocarditis, Duchenne muscular dystrophy, electrolyte disturbances, hypothermia, etc. can be misdiagnosed as BS.

ECG in BS patients may also show other changes. The PR interval is often increased (≥ 200ms) and reflects the presence of an increased HV interval. P wave abnormalities (prolonged or biphasic P waves) have also been described. Slight QT prolongation in RV leads has also been described with ST

elevation. Late potentials detected by signal-averaged ECG are common and QRS widening and fragmented QRS are present in a proportion of patients.

Atrial fibrillation occurs in about 10 to 20% of BS patients. Sick sinus syndrome and atrial standstill have also been described. Recent reports from Japanese workers have demonstrated electrophysiological changes in the atria. Increased incidence of syncope and sudden cardiac death has been reported in patients who also have atrial fibrillation. Conduction delays in the RV outflow tract have also been reported. BS appears to be a channelopathy which, besides electrophysiological changes, also produces subtle structural changes in the atria and the RV outflow tract.

1.4 Mechanism of BS

During phase 1 of the normal action potential, the inward Na^+ current and transient outward K^+ current, $I_{To,}$ cause a normal spike and dome morphology. In the presence of weak Na^+ current, the unopposed outward K^+ current I_{To} and $I_{Ca,}$ cause accentuation of the action potential notch in the RV epicardium, resulting in accentuated J wave and ST segment elevation associated with the Brugada pattern. As these changes occur in the epicardium but not in the endocardium, they create a transmural voltage gradient (Fig 2). Arrhythmias develop because of inhomogeneous repolarization in different areas of the RV epicardium leading to the so-called phase 2 re-entry and to the development of closely coupled extrasystoles leading to VT/VF. Triggering extrasystoles have left bundle branch morphology, have a close coupling interval and arise from the RV outflow tract. Successful ablation of initiating ectopics has been performed in BS patients who have arrhythmic storms. The male preponderance in adult patients is probably explained by the fact that the transient outward current I_{To} in the RV epicardium is stronger in men than women. Both androgens and oestrogens also modulate inward Na^+ and Ca^+ and outward I_{To} currents, which explains the male preponderance and the onset of symptoms after puberty.

1.5 Drug Challenge

Intravenous administration of Na^+ channel blocking drugs like ajmaline, flecainide, pilscanide and, to a variable extent, procainamide, are useful in bringing out Type 1 Brugada pattern on the ECG when ECG changes are not diagnostic. Ajmaline is an ideal drug for this purpose because of its short duration of action and higher sensitivity than flecainide but as it is not available in Australia, flecainide (2mg/kg maximum 150mg in 10 minutes) is the drug commonly used. The sensitivity and specificity of flecainide test in *SCN5A* mutation-positive probands and their families has been reported as 77% and 80%, respectively. Pharmacological provocation should only be performed when the baseline ECG is not diagnostic of BS. There is no advantage and possibly a risk of inducing VT/VF, in performing it in the presence of Type 1 BS pattern in the baseline ECG. PR prolongation in the baseline ECG is also a contraindication because of the risk of inducing AV block. Drug challenge should be performed under strict monitoring of BP and 12-lead ECG and facilities for cardioversion and resuscitation should be available. Drug administration should be stopped if a Type 1 pattern becomes apparent on the ECG, if the patient develops ventricular arrhythmias, if the QRS widens to $\geq$ 130% of the baseline, or if a total of 150mg flecainide is administered. The patient needs to be monitored until the ECG is normalized. Plasma half-life of flecainide is 20 hours. Isoprenaline infusion may be employed to counteract if serious ventricular arrhythmias develop. The incidence of serious arrhythmia is low if the drug is not administered to patients who already have Type 1 ECG at baseline. Provocative drug challenge is helpful in asymptomatic family members of BS and where the baseline ECG shows Type 2 or 3 changes. It is also performed as a part of investigations in survivors of cardiac arrest without any apparent cause.

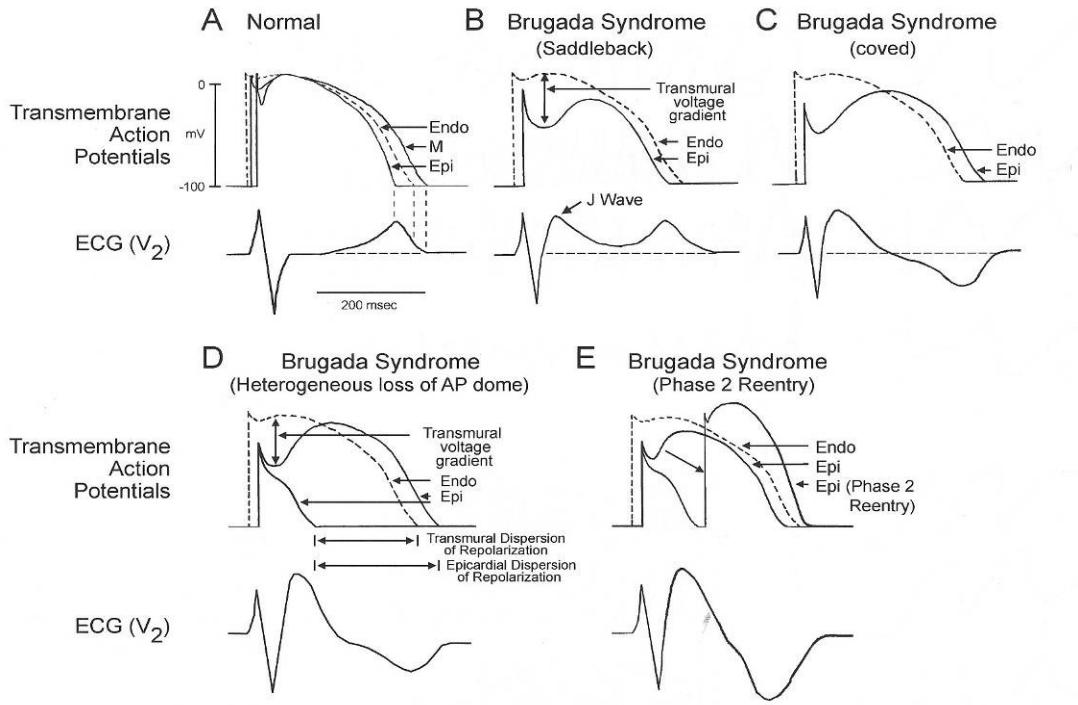

Fig. 2. Mechanisms of BS. Reproduced with permission from: Antzelevitch C. Brugada Syndrome. PACE 2006;29:1130-59.

2. Molecular Genetics

BS is a channelopathy linked to loss-of-function mutations in the *SCN5A* gene that encodes the α-subunit of the Na^+ channel, I_{Na}. A number of mechanisms such as reduced rate of recovery from inactivation, faster inactivation and protein trafficking defects have been shown to underlie the loss of function in BS. Over 100 different mutations of *SCN5A* have been identified and the list is growing. BS is not the only condition attributed to *SCN5A* mutations; LQT3 (gain-of-function), progressive cardiac conduction disease (Lenegre's disease) idiopathic VF, sick sinus syndrome, dilated cardiomyopathy and familial atrial fibrillation are other disorders linked to *SCN5A* mutation and overlapping syndromes have been described. *SCN5A* mutations can occur in approximately 18 to 30% of BS patients and a negative gene test does not rule out BS. A higher incidence has been reported in familial as opposed to sporadic cases.

Mutations in the genes encoding the cardiac L-type Ca^+ channel alpha subunit, *CACNA1c* and the β-subunit, *CACNB2b,* were reported in 2007 in BS and some of them have short QT syndrome, sudden death and Type 1 Brugada ECG. Mutations in the glycerol-3-phophatedehydrogenase 1-like gene, *GPD1-L*, in infant death syndrome and in the sodium channel $beta_1$ subunit, *SCN1B,* are also thought to be causes of BS and conduction disease.

The presence or absence of an *SCN5A* mutation does not have any effect on the incidence of sudden cardiac death in BS. Priori and Napolitano have developed a score system to express cost/benefit assessment of genetic analysis and BS scores 1.5 as opposed to 4.5 for LQTS. Genetic analysis in BS is useful in non-penetrant mutation carriers but is not useful in risk stratification. Genetic analysis is also useful in advancing research and for studying genotype-phenotype relationship.

3. Management

3.1 Affected individuals

While the diagnosis of BS is essentially made on the ECG and the heart is said to be structurally normal, recent reports have shown discrete morphological abnormalities. In addition to

echocardiography, patients should have an MRI to exclude arrhythmogenic right ventricular cardiomyopathy or myocarditis.

ICD: The second consensus report of 2005 recommends ICD implantation in BS patients who have survived cardiac arrest (Class 1) or have a history of syncope and documented ventricular arrhythmia (Class 2A). Electrophysiology Study (EPS) is only recommended for investigations if there are associated supraventricular arrhythmias.

Drugs: Quinidine, an I_{To} inhibitor, is the only drug, which is effective in BS. Unfortunately, this old drug is now difficult to get and is only available under special access scheme in Australia and New Zealand. It is used in patients who have repeated ICD shocks or have an arrhythmic storm. Isoprenaline infusion increases Ca^{+} current and is helpful in emergency treatment of arrhythmic storms in BS.

Risk stratification: Patients presenting with aborted sudden death are at the highest risk. Table 1 lists cardiac event rate per year reported in three large series in patients presenting with cardiac arrest, syncope and asymptomatic spontaneous Type 1 BS ECG. Brugada et al use programmed electrical stimulation to further risk stratify asymptomatic BS patients. In a recently published follow up of 1029 BS patients from four European centres ,France, Italy, Netherlands and Germany (FINGER study), Probst et al reported an event rate 7.7, 1.9 and 0.5% per year respectively in these three groups. There is consensus that the risk of life threatening arrhythmias in asymptomatic patients who only have spontaneous Type 1 ECG changes is moderate, between 0.24 and 1.7. Where Type 1 ST changes appear only after pharmacological provocation, the patients are at minimal risk for arrhythmic events. BS patients who have atrial fibrillation and fragmentation of QRS complexes in their ECG are reported to be at a higher risk of spontaneous VF.

There is ongoing controversy regarding the role of programmed electrical stimulation for risk stratification in BS. While Brugada et al have found induction of sustained ventricular arrhythmia a strong marker of risk (8 fold risk) other workers, including a large prospective European study in 1,029 BS patients have found it to be of poor predictive value. The protocol used for electrophysiological study used by Brugada et al included measurement of conduction intervals and programmed electrical stimulation from the RV apex with a minimum of 3 ventricular extra stimuli at 3 different pacing rates. The shortest coupling interval was limited to 200 ms the test was considered positive if sustained arrhythmia lasting >30 s or requiring intervention was induced.

Gehi et al performed a meta analysis of 30 prospective studies on 1,545 patients and concluded that a history of syncope or sudden death (SCD), the presence of spontaneous Type 1 Brugada ECG and male gender predict a more malignant natural history. Family history of SCD, the presence of *SCN5A* mutation and EPS were not predictive.

Table 1. Cardiac event rate per year in BS

Authors (Reference in brackets)	Number of Patients	Follow up (months)	Cardiac arrest survivors	Syncope	Asymptomatic Type I ECG
Brugada et al (2005)	724	54 ± 54	18%	8.8%	0.5 (non-inducible) 4.5 (inducible)
Eckardt et al (2005)	212	40 ± 50	5%	1.8%	0.81%
Probst et al (2010)	1,029	14 to 54.4, mean 31.9	7.7%	1.9%	0.5%

3.2 Asymptomatic individuals

While there is no dispute about the management of symptomatic patients of BS, the management of asymptomatic patients is a highly controversial topic. The consensus report recommends EPS in asymptomatic patients with spontaneous Type 1 ECG and ICD implantation be recommended if the EPS is positive (Class 2A) and a close follow up, if the EP is negative. If the patient is asymptomatic and BS ECG changes are brought out only after a drug challenge, it recommends EPS and ICD implantation if EPS is positive, (Class 2B indication). Several authorities have, however, questioned these recommendations and the role of EPS in risk stratification. ICD implantation in BS has been reported to have a high complication rate and most authorities do not recommend it for asymptomatic patients. A family history of sudden death does not translate into increased risk in relatives.

As the changes of BS on ECG are unmasked by a febrile state caused by loss of function of I_{Na} channel, aggressive treatment of all febrile episodes is recommended with antipyretics like aspirin and paracetamol and cold sponges. Hypokalemia, large carbohydrate meals and alcohol and very hot baths have also been incriminated and should be avoided.

Drugs that can cause Brugada-like changes on the ECG are best avoided and include: Class 1 antiarrhythmic drugs like flecainide, beta and alpha adrenergic blockers, Ca^{++} channel blockers like verapamil, diltiazem, nifedipine, nitrates, K^{+} channel openers like nicorandil, tricyclic and tetracyclic antidepressants, phenothiazines and SSRI like fluoxetine, alcohol and cocaine intoxication. A website www.brugadadrugs.org gives a list of drugs to be avoided, preferably avoided and potential antiarrhythmic drugs in BS and a letter that can be downloaded and be given to BS patients to carry. At this stage, apart from quinidine, no other oral drug therapy is available for treatment of BS. This situation may alter in future; phosphodiesterase inhibitors and tedesamil and dimethyl lithospermate B (dmLSB) a Chinese herbal medicine are drugs that are being investigated.

4. Further Information

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Fig. 3 Diagnosis of Brugada Syndrome

OHCA= out of hospital cardiac arrest, SUD= sudden unexplained death