Review Article

Brugada syndrome and its relevance in the perioperative period

Dan Sorajja, Harish Ramakrishna[1], A. Karl Poterack[1], Win-Kuang Shen, Farouk Mookadam

Division of Cardiovascular Diseases, Mayo Clinic Arizona, [1]Department of Anesthesiology, Mayo Clinic Arizona, AZ 85259, USA

ABSTRACT

Brugada syndrome is an autosomal dominant genetic disorder associated with an increased risk of sudden cardiac death, as well as ventricular tachyarrhythmias.The defective cardiac sodium channels result in usual electrocardiographic findings of a coved-type ST elevation in precordial leads V1 to V3. The majority of patients have uncomplicated courses with anesthesia, surgery, and invasive procedures. However there is risk of worsening ST elevation and ventricular arrhythmias due to perioperative medications, surgical insult, electrolyte abnormalities, fever, autonomic nervous system tone, as well as other perturbations. Given the increasing numbers of patients with inherited conduction disorders presenting for non-cardiac surgery that are at risk of sudden cardiac death, safe anesthetic management depends upon a detailed knowledge of these conditions.

Received: 06-05-15
Accepted: 08-06-15

Key words: Anesthesia; Arrhythmias; Brugada syndrome; Perioperative

DEFINITION OF BRUGADA SYNDROME AND BRUGADA PATTERN ELECTROCARDIOGRAM

Brugada syndrome is an autosomal dominant genetic disorder associated with an increased risk of sudden cardiac death (SCD), as well as ventricular tachyarrhythmias. In certain patient populations, the syndrome is referred to as sudden unexpected death syndrome or sudden unexpected nocturnal death syndrome.[1]

Since its initial description in 1992, patients with Brugada syndrome have no structural heart disease by echocardiography, but have distinctive electrocardiographic findings.[2] The electrocardiogram (ECG) shows a coved-type ST-segment elevation in two or more anteroseptal precordial (V1–V3) leads [Figure 1]. Infrequently, the inferior leads (limb leads II, III, and aVF) may show similar findings. The ST elevation can be variable depending on other factors such as electrolyte abnormalities, autonomic tone, and fever.[3] The configuration of the ST elevation helps differentiate between Brugada pattern type 1 and type 2 (previously, three separate configurations were described; however, recent consensus statements define only two distinct ECG patterns).[3,4] When the ECG findings are present but without symptoms or other diagnostic criteria, the term Brugada pattern is applied; whereas patients with symptoms plus the ECG findings are said to have Brugada syndrome.

The type 1 ECG pattern is coved-type, with the ST elevation being more prominent (≥2 mm or 0.2 mV) and slopes down (convex upward or concave downward) with the T-wave being inverted [Figure 1]. The type 2 ECG pattern is referred to as the "saddle back" configuration, with a less prominent ST elevation (<2 mm) followed by sloping toward the baseline before an upright T-wave, which may be

Access this article online
Website: www.annals.in
DOI: 10.4103/0971-9784.159812
Quick Response Code:

Address for correspondence: Dr. Farouk Mookadam, Division of Cardiovascular Diseases, Mayo Clinic Arizona, 13400, East Shea Boulevard, Scottsdale, AZ 85259, USA.
E-mail: mookadam.farouk@mayo.edu

Cite this article as: Sorajja D, Ramakrishna H, Poterack AK, Shen WK, Mookadam F. Brugada syndrome and its relevance in the perioperative period. Ann Card Anaesth 2015;18:403-13.

biphasic [Figure 1]. Differentiation from typical right bundle branch block is usually apparent in the lateral precordial leads, because Brugada pattern does not have the widened S-wave due to delayed terminal conduction seen in right bundle branch block. The ECG findings can be variable, with the same patient having type 1, type 2, as well as a normal ECG intermittently.[5] The type 1 ECG pattern is more diagnostic of Brugada syndrome.[3]

The diagnosis of Brugada syndrome requires the ECG pattern in at least two right precordial leads (V1–V3) and any of the following: Ventricular fibrillation (VF), polymorphic ventricular tachycardia, inducible ventricular tachycardia during electrophysiology (EP) study, unexplained syncope suggesting tachyarrhythmia, nocturnal agonal respiration, family history of SCD younger than 45 years of age, or family history of type 1 Brugada pattern ECG.[3] The diagnosis is type 1 Brugada syndrome if the ECG pattern is type 1. The diagnosis is type 2 Brugada syndrome if the ECG pattern is type 2 which converts to type 1 with drug challenge using a sodium channel blocker.

GENETICS AND PATHOPHYSIOLOGY OF BRUGADA SYNDROME

The mutations for Brugada syndrome affect the cardiac sodium channel, mainly through the SCN5A genes, which encode the subunits of these channels.[3,6] The mutation is a loss of function resulting in a reduction of sodium inflow current, thereby reducing phase 0 depolarization of the action potential. The transient

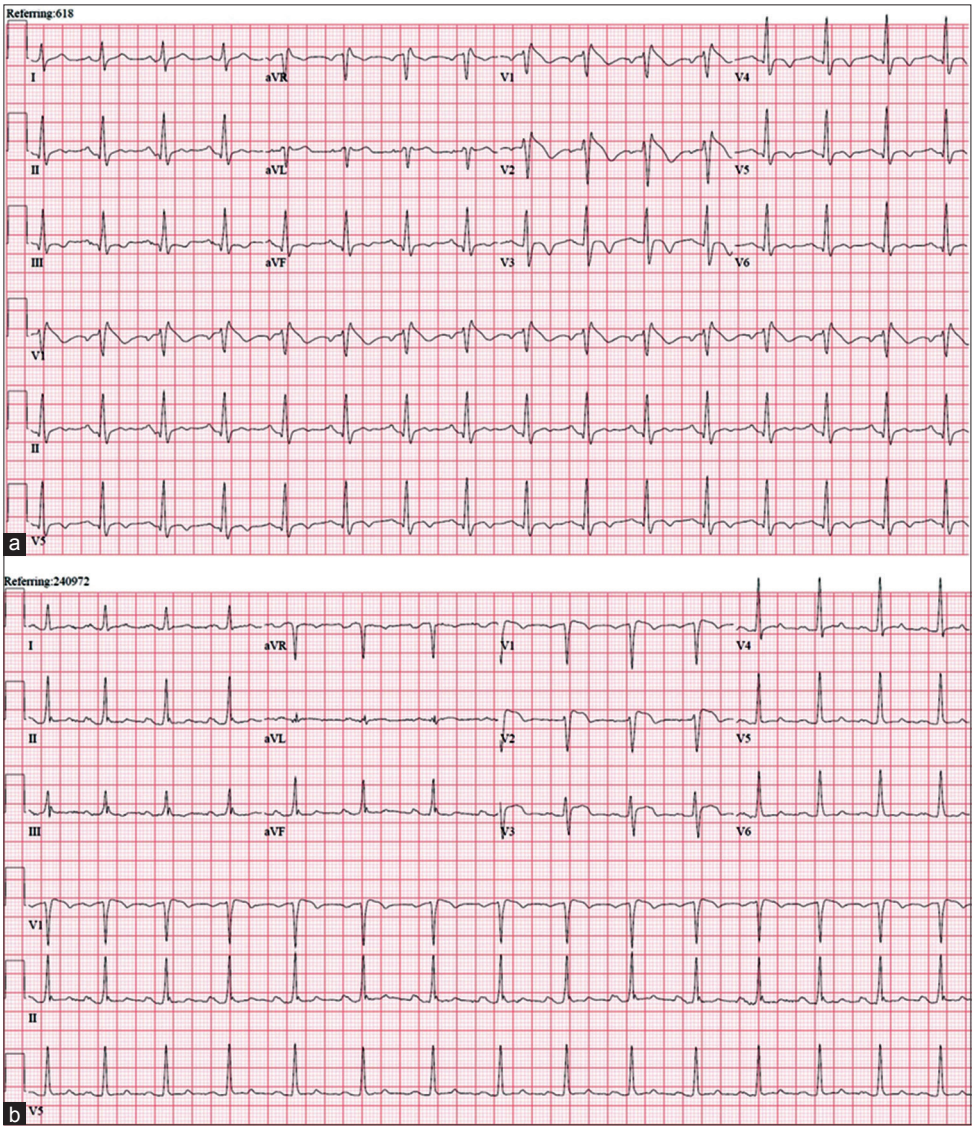

Figure 1: Twelve lead electrocardiograms showing Brugada electrocardiogram patterns. (a) Brugada electrocardiogram pattern type 1; (b) Brugada electrocardiogram pattern type 2

outward current (Ito), now opposed by a decreased inward sodium current causes an accentuated "spike and dome" morphology of the phase 1 of the action potential.[7] Most of this alteration in the action potential occurs in the epicardial portion of the myocardium where Ito has higher expression while the action potential in the endocardium remains unchanged. The result is a voltage gradient across the myocardium, with the ECG showing ST-segment elevation.

The impaired sodium channels in epicardial cells may result in localized conduction block. However, the defective sodium channels also cause a shortened plateau phase, phase 2, of the cardiac action potential due to decreased activation of calcium channels, and this results in a shorter action potential duration more so in the epicardial layer. With a shorter phase 2, a shorter refractory period results, and these epicardial cells recover the ability to propagate the action potential sooner. The combination of localized conduction block with the shortened phase 2 in the epicardium creates electrical dispersion predisposing patients to localized re-entry called phase 2 re-entry, which can precipitate ventricular arrhythmias.[8]

Other genes may be responsible for the manifestation of the Brugada syndrome suggesting the problem may be an imbalance between inflow and outflow currents during the cardiac action potential. SCN10A mutations also result in a loss of function in a subunit of the sodium channel gene.[9] Mutations in L-type calcium channel ion channels have also been described.[10] However, most patients with Brugada syndrome do not have an identifiable mutation.[3,11]

In addition to the genetic factors, microscopic abnormalities likely contribute to the genesis of arrhythmias as well. Although Brugada syndrome typically is not associated with structural heart disease, there is evidence of microscopic fibrosis and inflammation with resultant conduction delay.[12,13] The fibrosis and inflammation may cause a delay in the conduction of the action potential as well as heterogeneity in myocardial refractory periods.[14]

DIFFERENTIAL DIAGNOSIS OF BRUGADA SYNDROME

Conditions that mimic the Brugada ECG pattern should be excluded. These include early repolarization, acute pericarditis, myocardial ischemia, arrhythmogenic right ventricular cardiomyopathy, dissecting aortic aneurysm, and pulmonary embolism. Metabolic disturbances such as hypothermia, hyperkalemia, and hypercalcemia also can result in the typical ECG pattern. Also, conditions that impinge on the epicardium such as mediastinal tumors, pectus excavatum, and pericardial effusion have also been described to result in the Brugada ECG pattern [Table 1].[3,15,16]

For patients who have a structurally normal heart but with a history of ventricular tachycardia or SCD, the differential diagnosis includes long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia, right ventricular outflow tract ventricular tachycardia, idiopathic left ventricular tachycardia, idiopathic VF, and commotio cordis.

EPIDEMIOLOGY, RISK FACTORS, AND TRIGGERS OF BRUGADA ELECTROCARDIOGRAM PATTERN

Brugada syndrome is uncommon, with an estimated prevalence of 5 in 10,000 patients,[3] but occurs with greater frequency in Japan, up to 1% in some studies.[17-19] Approximately 10% of patients with the Brugada ECG pattern will subsequently develop the Brugada syndrome.[20] In patients with idiopathic VF, the prevalence is as high as 24%.[21] There is a male preponderance of the Brugada pattern, being almost

Table 1: Differential diagnosis of ST elevation resembling Brugada pattern ECG

Acute pericarditis
Arrhythmogenic right ventricular cardiomyopathy
Atypical right bundle branch block
Coronary artery anomaly with interarterial course
Direct current cardioversion
Dissecting aortic aneurysm
Duchenne muscular dystrophy
Early repolarization
Hemopericardium (compressing the right ventricular outflow tract)
Hypothermia
Hyperkalemia
Hypercalcemia
Left ventricular hypertrophy
Mediastinal tumors (compressing the right ventricular outflow tract)
Multiple myeloma
Myocardial ischemia
Pectus excavatum
Pericardial effusion
Prinzmetal angina
Pulmonary embolism
Right ventricular infarction
Thiamine deficiency

ECG: Electrocardiogram

10 times more frequent than in females.[22,23] The mean age of onset is approximately 40 years. Patients with schizophrenia are also more likely to have Brugada pattern ECG, with approximately 12% showing the ECG findings.[24]

Certain conditions and factors worsen the expression of Brugada pattern ECG. Fever is a well-described trigger, with the patients frequently being asymptomatic. With these labile ST patients, the prognosis is good in patients having no events during follow-up.[25] For patients who have Brugada pattern while normothermic and during fever, there is a risk of cardiac arrest.[26] Autonomic tone likely plays a role, as the ventricular tachyarrhythmias occur at night when vagal tone predominates.[27,28] This parasympathetic effect is also seen during the recovery from exercise.[29]

Drugs can trigger the Brugada pattern [Table 2].[30,31] with tricyclic antidepressants, lithium, diphenhydramine, alcohol, and cocaine being implicated.[32] Isolated cases of beta-blockers and calcium channel blockers causing Brugada ECG pattern are reported, and may be due to inhibition of L-type calcium channels with resultant shortening of the epicardial action potential dome.[3,32] Alpha-agonists, insulin, and glucose have also been shown to result in ST elevation.[30,33] Probably the most potent medications in unmasking Brugada ECG pattern are Vaughan Williams Class I medications. Within this class, flecainide, ajmaline, and procainamide may be used in diagnostic testing to identify at-risk patients with inducible type I pattern ECG. A comprehensive list of culprit medications and those to avoid in Brugada patients can be found at www.BrugadaDrugs.org.[31,34]

SUDDEN CARDIAC DEATH AND BRUGADA SYNDROME

The most worrisome manifestation of Brugada syndrome is SCD. The syndrome is likely the cause in 4% of all SCD and 20% of SCD patients without structural heart disease.[3] Most commonly, the occurrence of ventricular tachyarrhythmias is during sleep.[3,27,35] If a patient has a history of SCD, there is an 11-fold risk of the arrhythmic event compared to asymptomatic individuals. A history of unexplained syncope also increases the risk but to a lesser degree.[36]

Concomitant disorders appear to be associated with increased risk of SCD in Brugada syndrome as well. Atrial fibrillation manifests in approximately 10–20%

Table 2: Medications potentially causing Brugada pattern ECG and arrhythmias

	Likely mechanism
Anesthetics and analgesia	
Bupivacaine	Sodium channel blockade
Lidocaine	Sodium channel blockade
Ketamine	L-type calcium channel blockade
Procaine	Sodium channel blockade
Propofol	Sodium channel and L-type calcium channel blockade
Tramadol	Sodium channel blockade
Antiarrhythmic medications	
Ajmaline	Sodium channel blockade
Allapinin	Sodium channel blockade
Amiodarone	Sodium channel and beta blockade
Cibenzoline	Sodium channel blockade
Disopyramide	Sodium channel blockade
Ethacizin	Sodium channel blockade
Flecainide	Sodium channel blockade
Lidocaine	Sodium channel blockade
Pilsicainide	Sodium channel blockade
Procainamide	sodium channel blockade
Propanolol	Beta blockade
Propafenone	Sodium channel blockade
Verapamil	Sodium channel blockade
Vernakalant	Sodium channel blockade
Psychotropic medications	
Amitriptyline	Sodium channel blockade
Bupropion	Reduced cardiac intercellular coupling
Carbamazepine	Sodium channel blockade
Clothiapine	Sodium channel blockade, possible fever-induced
Clomipramine	Sodium channel blockade
Cyamemazine	Sodium channel blockade
Desipramine	Sodium channel blockade
Dosulepine	Sodium channel blockade
Doxepin	Sodium channel blockade
Fluoxetine	Sodium and calcium channel blockade
Fluvoxamine	Sodium channel blockade
Imipramine	Sodium channel blockade
Lamotrigine	Sodium channel blockade
Lithium	Sodium channel blockade
Loxapine	Sodium and calcium channel blockade
Maprotiline	Sodium and calcium channel blockade
Nortriptyline	Sodium channel blockade
Oxcarbazepine	Sodium channel blockade
Paroxetine	Sodium channel blockade
Perphenazine	Sodium channel blockade
Phenytoin	Sodium channel blockade

Contd...

Table 2: Contd...

	Likely mechanism
Thioridazine	Calcium channel blockade
Trifluoperazine	Sodium channel blockade
Other drugs and substances	
Acetylcholine	Cholinergic/vagotonic
Alcohol	Calcium channel blockade, possible cholinergic
Cannabis	Sodium channel blockade, possible cholinergic
Cocaine	Sodium channel blockade
Dimenhydrinate	Unknown, possible sodium channel blockade
Diphenhydramine	Sodium channel blockade
Edrophonium	Cholinergic/vagotonic
Ergonovine	Cholinergic/vagotonic
Fexofenadine	Sodium channel blockade
Glucose	Unknown
Heroin	Unknown, possibly due to alcohol intake
Indapamide	Hyponatremia
Insulin	Unknown
Methoxamine	Alpha agonist
Metoclopramide	Sodium channel blockade
Terfenadine	Sodium channel blockade

ECG: Electrocardiogram

of Brugada syndrome patients.[3] Among these patients with atrial fibrillation, there was an almost three-fold higher incidence of syncope and VF.[37] The presence of atrial and ventricular arrhythmias may suggest a more advanced disease process. Of note, not all syncope is equal to SCD. The etiology of syncope in 30% of Brugada syndrome patients is due to neurocardiogenic syncope rather than arrhythmia and carries a benign prognosis.[38]

Sleep disordered breathing is more frequently seen in Brugada syndrome as well, and nocturnal agonal respiration may represent cardiac arrhythmias such as ventricular tachycardia or fibrillation.[39] These occurrences are concerning, and when combined with Brugada ECG pattern type 1, the diagnosis of Brugada syndrome is made.

MANAGEMENT OF BRUGADA SYNDROME IN NONOPERATIVE SETTINGS

In patients with the Brugada ECG pattern (type 1 or type 2) and any high-risk feature (unexplained syncope, nocturnal agonal respiration, sustained ventricular tachyarrhythmia, or SCD), an implantable cardioverter-defibrillator (ICD) is indicated.[40] Antiarrhythmic therapy may be considered if patients experience recurrent arrhythmias resulting in appropriate ICD shocks, which occur at a rate of 2.6%/year.[41] Amiodarone generally is better tolerated than quinidine, and these medications should be considered in patients who cannot or refuse to have an ICD implanted. One special situation with Brugada syndrome is ventricular tachycardia storm. In these patients, an isoproterenol infusion in the acute setting is helpful.

For asymptomatic patients with Brugada pattern ECG, risk stratification has proven difficult due to conflicting data. In patients with a type 2 Brugada ECG pattern or a nondiagnostic ECG combined with a family history of SCD or family history of type 1 ECG pattern, a drug challenge to attempt to unmask type 1 Brugada ECG pattern is reasonable. Under the surveillance of an electrophysiologist, the drug challenge is performed with one of several sodium channel blockers (e.g. flecainide, procainamide, or ajmaline) with ECG monitoring for manifestation of the type 1 Brugada ECG pattern, ST-segment elevation greater than or equal to 2 mm, ventricular premature beats, ventricular arrhythmias, or widening of the QRS more than 30% above baseline.[42] Brugada ECG pattern patients should avoid known triggers and conditions that may further worsen the Brugada pattern, and consideration of ICD should be discussed with these patients.[31,34,40] However, these asymptomatic patients with drug-induced Brugada pattern type 1 generally have a good prognosis with low-risk of arrhythmic events. For patients with type 2 Brugada ECG pattern but no high-risk family history, drug challenge is not recommended. For patients with type 1 Brugada ECG pattern under baseline conditions, drug challenge should not be performed as the test does not provide clear prognostic value.[3]

The role of invasive EP testing in risk stratification of asymptomatic patients with Brugada ECG pattern also remains debatable. In one study of 547 asymptomatic patients with type 1 ECG pattern, inducible sustained ventricular tachyarrhythmias during EP testing predicted future events.[43] Other large registries, including the France, Italy, Netherlands, Germany Brugada registry and PRogrammed ELectrical stimUlation preDictive valuE registry which were comprised of 369 and 308 asymptomatic patients, however, have shown no predictive value of inducible ventricular tachyarrhythmias on future events.[36,44]

Genetic testing is now readily available, and usually involves gene sequencing for SCN5A. While most of the

genetic mutations responsible for Brugada syndrome result from mutations in SCN5A, the yield remains low at 15–30%.[11] Furthermore, the lack of a mutation in SCN5A does not rule out Brugada syndrome. Part of the issue is that other mutations such as SCN10A and calcium channel mutations also are becoming more frequently described and are not part of routine testing for Brugada syndrome. Referral to an electrophysiologist or genetic counselor should be considered prior to any genetic tests being performed.

PREOPERATIVE EVALUATION AND PREPARATION

While there are no prospective studies evaluating the preoperative assessment of patients with Brugada ECG or Brugada syndrome, the following recommendations are based on current understanding of the pathophysiology of Brugada syndrome and anesthetic agents. The majority of Brugada patients have an unremarkable perioperative course, but the goal of preoperative evaluation remains to reduce the potential risk of ventricular arrhythmias. An algorithm is suggested in Figure 2.

If the characteristic Brugada pattern ECG is found during the preoperative evaluation, EP consultation and evaluation should be obtained.[45] The main concern with Brugada syndrome patients is the susceptibility to ventricular tachyarrhythmias and SCD, and this risk is present even with asymptomatic patients.[3,46] A number of medications are implicated in Brugada pattern ECG, and the patient history should be reviewed for use of these [Table 2]. An up-to-date list can be found at the website, www.BrugadaDrugs.org.[31,34] Certain medications to be avoided in Brugada patients include Class IA and Class IC antiarrhythmics, tricyclic antidepressive medications, lithium, oxcarbazepine, acetylcholine, and ergonovine. Patients should also be screened for recreational drugs such as cocaine, cannabis, and heavy alcohol use. In patients with known or suspected Brugada syndrome, an electrolyte panel should be checked preoperatively, as hyperkalemia and hypercalcemia can result in the Brugada ECG pattern.[15,16]

Preoperative Evaluation
- EP consultation
- Outpatient medication screening
- Laboratory evaluation:
  - Electrolyte panel
  - Calcium
  - Magnesium
- If ICD present, turn off tachyarrhythmia therapy
- Place external defibrillator pads
- If pacemaker present or requires pacing through ICD, program device to non-tracking pacing mode (VOO or DOO)

Intraoperative Care
- Monitor with multi-lead ECG (preferably with ST trend analysis)
  - If ST elevation, give isoproterenol infusion
  - If ventricular fibrillation or tachycardia, give isoproterenol infusion
  - If bradycardia, give atropine with or without ephedrine
- Temperature probe, and maintain normothermia via appropriate warming or cooling procedures
- Preferred Medications
  - Antiemetics: Droperidol or ondansetron
  - Opioids and Analgesics: Fentanyl, hydromorphone, meperidine, ketorolac
  - Local Anesthetics: Short-acting agents preferred: lidocaine, mepivacaine, ropivacaine
  - Inhaled Anesthetics: Sevoflurane, nitrous oxide
  - Intravenous Anesthetics: Propofol, etomidate
  - Neuromuscular Blockers: Succinylcholine, vecuronium, atracurium, cisatracurium
  - Neuromuscular Blockade Reversal Agent: Neostigmine with atropine or glycopyrrolate

Postoperative Care
- Reprogram ICD or pacemaker to original settings
- Continuous ECG monitoring for up to 36 hours postoperatively

Figure 2: Checklist for perioperative care of Brugada patients

Patients who have had an ICD implanted for Brugada syndrome should be programmed with the tachyarrhythmia therapy of the device disabled.[45] Brugada syndrome patients with and without an ICD should have external defibrillator pads placed with an external defibrillator readily available.[47-49] For patients who require pacing, the ICD (or pacemaker if the patient had a device implanted for bradyarrhythmia therapy only), should be reprogrammed to a nontracking or nonsensing mode such as VOO or DOO depending on the presence of a single or dual chamber device respectively.[45,47] This programming change is to prevent the device from detecting electrical interference from electrocautery or other electronic equipment in the operating room. Such interference may result in an inappropriate shock by an ICD and inhibition of pacing by the pacemaker function.[47]

MONITORING AND INTRAOPERATIVE CONSIDERATIONS

Perioperative monitoring in patients with Brugada syndrome depends on the site and complexity of the planned surgery. Multi-lead ECG monitoring should be utilized, preferably with ST trend analysis.[45,49-51] The ability to monitor worsening ST-segment elevation may prevent hemodynamically significant arrhythmias by allowing for timely corrective treatment.[45] While there has not been a definitive correlation between ST-segment elevation and resultant ventricular arrhythmias, prior studies suggest a mechanistic link.[28,33,52] A temperature probe should also be placed, as the fever has been shown to trigger arrhythmias in Brugada patients.[25,26,47,53] Appropriate warming or cooling should be applied as necessary to maintain normothermia. For major surgery requiring general anesthesia, invasive blood pressure monitoring and central venous access may be helpful.

Autonomic tone can change intraoperatively, and increased vagal tone can result in ventricular arrhythmias.[27,28] Bradycardia, which may be a manifestation of this increased vagal tone, may be seen with the development of the Brugada ECG pattern.[45,54] A sudden rise in vagal activity immediately before the development of VF has been described in Brugada patients.[52] The intraoperative period is notable for multiple stressors, both leading to sympathetic activity (surgical incision, endotracheal intubation, anesthetic induction, and emergence) as well as sudden increases in parasympathetic tone (tracheal suctioning, peritoneal insufflation, and bowel retraction). The use of atropine and ephedrine has been advocated to reduce vagal tone in a series of patients undergoing general anesthesia for ICD insertion.[51] If the Brugada ECG pattern becomes more prominent with ST elevation, isoproterenol can be used to restore ST segments to the pretreatment level.[51,55,56] ST elevation in these patients can also be due to selective alpha-adrenergic receptor stimulation, seen with methoxamine alone or with norepinephrine in combination with propranolol. Alpha-adrenergic blockade in some patients has been shown to reduce this ST elevation in some patients.[33]

PERIOPERATIVE PHARMACOLOGY

Antiemetics

Droperidol and 5-HT_3 receptor antagonists are not contraindicated as antiemetics in Brugada syndrome, but it should be noted that there is a potential association between long QT and Brugada syndrome. Metoclopramide and dimenhydrinate are preferably avoided. Phenothiazines are also to be avoided.[31,34,57]

Opioids and analgesics

Fentanyl use has been described in multiple case reports and series without incident.[47-51,58-62] There is limited data on the use of remifentanil;[63] due to its ultra-short duration of action it may be of use in short procedures. Fentanyl, meperidine, and ketorolac have been successfully used for postoperative analgesia in patients with Brugada syndrome.[49,50,59] Ketamine has been used for sedation in combination with midazolam.[62]

OTHER MEDICATIONS

Pharmacological interactions during anesthesia and autonomic imbalance may facilitate ECG changes in Brugada syndrome. These ECG changes are usually resolved when the triggering drugs are discontinued.[47] Cholinergic drugs, such as neostigmine, can increase ST elevation.[55] Beta-adrenergic antagonists and alpha-adrenergic agonists may also exacerbate ST elevation.[33] As such, typical recommendations for beta-blockade to be used perioperatively may not be applicable in Brugada patients.[47] Conversely, beta-adrenergic agonists or alpha-adrenergic antagonists should be considered if ST-changes appear in the absence of arrhythmias due to the possible link between ST-segment elevation and associated ventricular arrhythmias.[33,47] Isoproterenol is the beta-adrenergic agonist of choice and has been reported to restore elevated ST segments to the pretreatment level in patients undergoing a challenge test with pilsicainide.[51] Atropine and ephedrine have been used for the treatment of bradycardia and hypotension, respectively, without complications.[51] Although specific data are lacking, alpha-2 adrenergic agonists, such as clonidine and dexmedetomidine, may produce sympathetic suppression and increased vagal stimulation of the heart.[64]

Other drugs such as Class IA and Class IC antiarrhythmics (disopyramide, procainamide, flecainide, and ajmaline) have a direct drug effect that may worsen ST-segment elevation.[33,47,49] Ajmaline administration, even while isoproterenol was infusing, has resulted in ventricular tachycardia and VF with cardiac arrest.[62] In contrast, Class IB antiarrhythmic drugs (mexiletine and lidocaine) likely have no effect on ST-segment elevation.[33,55]

LOCAL ANESTHETICS

The sodium channel blocking the action of local anesthetics may exacerbate Brugada ECG changes. However, neuraxial techniques have also been used in patients with Brugada syndrome.[33,59,60] Bupivacaine epidurally has been implicated in the evolution of a Brugada-type ECG possibly due to its longer duration of action.[47,59,65] It has been recommended to avoid bupivacaine in these patients, because of its effect on the rapid phase of depolarization, and because it remains bound to sodium channels longer than other local anesthetics.[34] Other authors have reported the use of bupivacaine for epidural and intrathecal anesthesia without adverse effects.[48] The total dose of bupivacaine may need to be reduced in Brugada patients if shorter-acting alternatives such as lidocaine cannot be used.[47-49] The use of lidocaine has also been described to cause ST-segment elevation on its own.[47,66] However, the ST elevation may be due to concurrent administration of medications such as propofol along

with the lidocaine.[66] Also, intravenous administration of lidocaine has been used uneventfully to attenuate intubation-related hemodynamic changes.[51] Because of this, the use of lidocaine is preferable in these patients. For Brugada patients undergoing implantation of an ICD, local anesthesia with lidocaine or bupivacaine is adequate for placement of most ICDs.[47] Additional sedation is required for defibrillation function testing and for subpectoral implants.[47-49] These situations may require general endotracheal anesthesia with the use of volatile anesthetics.

VOLATILE ANESTHETICS

The use of volatile agents in Brugada patients has no documented issues, but part of the concern comes from prolonged QT syndromes and use of volatile agents that may further prolong the QT interval.[47,67] Most genetically proven Brugada syndrome patients have a mutation in SCN5A, and this gene has also been linked to prolonged QT syndrome.[47] Isoflurane has been shown to prolong the QT interval while halothane has been shown to shorten the QT interval.[47] Sevoflurane has not been shown to have a significant effect on the QT interval. While both isoflurane[48,66,68] and sevoflurane[47,66,67] have been used successfully in these patients, sevoflurane likely should be considered the preferred volatile agent in Brugada patients.

NITROUS OXIDE

There is no laboratory data to question the use of nitrous oxide in Brugada patients. Multiple clinical reports have described its uneventful use in combination with propofol or a volatile agent in these patients.[47,51,55,58,62,68,69]

INTRAVENOUS AGENTS

The use of propofol in patients with Brugada syndrome is somewhat controversial.[31,34,70] There are several case reports that detail a Brugada-type ECG pattern in association with long-term propofol abuse and propofol infusion syndrome; however, none of these patients was shown to have Brugada syndrome.[45,59,66,70] There are numerous case reports and series in which propofol has been used without incident in these patients.[47,50,51,55,58-61,63,66,69] In one cohort of patients undergoing ICD implantation, propofol was used for induction of anesthesia, and no patients developed any malignant arrhythmias.[70] One patient received propofol to maintain anesthesia and had an unremarkable perioperative course. While there are theoretical concerns about the use of propofol in Brugada syndrome patients, there have been no documented arrhythmias, but ST-segment elevation has been described.[66]

Thiopental[48,49,62] and midazolam[51,58,59] have also been used uneventfully in Brugada patients. Self-limited ST-segment elevations were described in one patient after etomidate use.[66]

NEUROMUSCULAR BLOCKERS AND REVERSAL AGENTS

Succinylcholine,[48,58] vecuronium,[48,49,51,68] atracurium,[58] cisatracurium,[50] and mivacurium[51] have all been used without adverse effects. Parasympathetic stimulation specifically by neostigmine has been reported to increase ST changes in Brugada patients.[33,48,56,71] In another report, the administration of neostigmine coincided with the development of pulmonary edema.[47] There are concerns about the use of neostigmine for reversal of neuromuscular block because of the possibility of triggering the characteristic ECG pattern.[48,50,51,68] However, multiple case reports have documented neostigmine usage combined with atropine[58,68] or glycopyrrolate[47,48,55,66] without complications.

POSTOPERATIVE CARE

After surgery, patients with a pacemaker or ICD should have the settings restored to its preoperative mode.[45] Brugada patients may have more susceptibility to arrhythmias such as from phase 2 block, so the time spent in nontracking modes (VOO or DOO) should be minimized.[47] Due to the risk of postoperative arrhythmias, continuous ECG monitoring should continue for up to 36 h postoperatively.[45,47,49,50,54,55,68,72] Sinus tachycardia and isolated premature ventricular complexes can be seen without increasing the occurrence of other more worrisome arrhythmias.[66]

CONCLUSIONS

Brugada syndrome and Brugada ECG pattern are uncommon but carry the risk of ventricular arrhythmias and even SCD. With certain triggers, including drug exposure, this condition may pose a significant risk to the patient. The perioperative period may have fluctuations in autonomic tone, and potential exposures to triggers for patients with Brugada syndrome or the ECG pattern. While most Brugada syndrome and

Brugada ECG pattern patients have unremarkable perioperative courses, these patients will benefit from expert consultation and meticulous management of triggers and conditions thereby reducing potential morbidity and mortality.

Financial support and sponsorship

Nil.

Conflict of interest

There are no conflict of interest.

REFERENCES

1. Vatta M, Dumaine R, Varghese G, Richard TA, Shimizu W, Aihara N, *et al.* Genetic and biophysical basis of sudden unexplained nocturnal death syndrome (SUNDS), a disease allelic to Brugada syndrome. Hum Mol Genet 2002;11:337-45.
2. 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;20:1391-6.
3. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, *et al.* Brugada syndrome: Report of the second consensus conference: Endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. Circulation 2005;111:659-70.
4. Bayés de Luna A, Brugada J, Baranchuk A, Borggrefe M, Breithardt G, Goldwasser D, *et al.* Current electrocardiographic criteria for diagnosis of Brugada pattern: A consensus report. J Electrocardiol 2012;45:433-42.
5. Veltmann C, Schimpf R, Echternach C, Eckardt L, Kuschyk J, Streitner F, *et al.* A prospective study on spontaneous fluctuations between diagnostic and non-diagnostic ECGs in Brugada syndrome: Implications for correct phenotyping and risk stratification. Eur Heart J 2006;27:2544-52.
6. Cordeiro JM, Barajas-Martinez H, Hong K, Burashnikov E, Pfeiffer R, Orsino AM, *et al.* Compound heterozygous mutations P336L and I1660V in the human cardiac sodium channel associated with the Brugada syndrome. Circulation 2006;114:2026-33.
7. Antzelevitch C. The Brugada syndrome: Ionic basis and arrhythmia mechanisms. J Cardiovasc Electrophysiol 2001;12:268-72.
8. Aiba T, Shimizu W, Hidaka I, Uemura K, Noda T, Zheng C, *et al.* Cellular basis for trigger and maintenance of ventricular fibrillation in the Brugada syndrome model: High-resolution optical mapping study. J Am Coll Cardiol 2006;47:2074-85.
9. Hu D, Barajas-Martínez H, Pfeiffer R, Dezi F, Pfeiffer J, Buch T, *et al.* Mutations in SCN10A are responsible for a large fraction of cases of Brugada syndrome. J Am Coll Cardiol 2014;64:66-79.
10. Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, Aizawa Y, *et al.* Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. Circulation 2007;115:442-9.
11. Miura D, Nakamura K, Ohe T. Update on genetic analysis in Brugada syndrome. Heart Rhythm 2008;5:1495-6.
12. Coronel R, Casini S, Koopmann TT, Wilms-Schopman FJ, Verkerk AO, de Groot JR, *et al.* Right ventricular fibrosis and conduction delay in a patient with clinical signs of Brugada syndrome: A combined electrophysiological, genetic, histopathologic, and computational study. Circulation 2005;112:2769-77.
13. Frustaci A, Priori SG, Pieroni M, Chimenti C, Napolitano C, Rivolta I, *et al.* Cardiac histological substrate in patients with clinical phenotype of Brugada syndrome. Circulation 2005;112:3680-7.
14. Yan GX, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. Circulation 1999;100:1660-6.
15. Tarín N, Farré J, Rubio JM, Tuñón J, Castro-Dorticós J. Brugada-like electrocardiographic pattern in a patient with a mediastinal tumor. Pacing Clin Electrophysiol 1999;22:1264-6.
16. Tomcsányi J, Simor T, Papp L. Images in cardiology. Haemopericardium and Brugada-like ECG pattern in rheumatoid arthritis. Heart 2002;87:234.
17. Matsuo K, Akahoshi M, Nakashima E, Seto S, Yano K. Clinical characteristics of subjects with the Brugada-type electrocardiogram. J Cardiovasc Electrophysiol 2004;15:653-7.
18. Miyasaka Y, Tsuji H, Yamada K, Tokunaga S, Saito D, Imuro Y, *et al.* Prevalence and mortality of the Brugada-type electrocardiogram in one city in Japan. J Am Coll Cardiol 2001;38:771-4.
19. Patel SS, Anees S, Ferrick KJ. Prevalence of a Brugada pattern electrocardiogram in an urban population in the United States. Pacing Clin Electrophysiol 2009;32:704-8.
20. Gehi AK, Duong TD, Metz LD, Gomes JA, Mehta D. Risk stratification of individuals with the Brugada electrocardiogram: A meta-analysis. J Cardiovasc Electrophysiol 2006;17:577-83.
21. Remme CA, Wever EF, Wilde AA, Derksen R, Hauer RN. Diagnosis and long-term follow-up of the Brugada syndrome in patients with idiopathic ventricular fibrillation. Eur Heart J 2001;22:400-9.
22. Benito B, Sarkozy A, Mont L, Henkens S, Berruezo A, Tamborero D, *et al.* Gender differences in clinical manifestations of Brugada syndrome. J Am Coll Cardiol 2008;52:1567-73.
23. Matsuo K, Akahoshi M, Nakashima E, Suyama A, Seto S, Hayano M, *et al.* The prevalence, incidence and prognostic value of the Brugada-type electrocardiogram: A population-based study of four decades. J Am Coll Cardiol 2001;38:765-70.
24. Blom MT, Cohen D, Seldenrijk A, Penninx BW, Nijpels G, Stehouwer CD, *et al.* Brugada syndrome ECG is highly prevalent in schizophrenia. Circ Arrhythm Electrophysiol 2014;7:384-91.
25. Adler A, Topaz G, Heller K, Zeltser D, Ohayon T, Rozovski U, *et al.* Fever-induced Brugada pattern: How common is it and what does it mean? Heart Rhythm 2013;10:1375-82.
26. Amin AS, Meregalli PG, Bardai A, Wilde AA, Tan HL.

Fever increases the risk for cardiac arrest in the Brugada syndrome. Ann Intern Med 2008;149:216-8.
27. Matsuo K, Kurita T, Inagaki M, Kakishita M, Aihara N, Shimizu W, *et al.* The circadian pattern of the development of ventricular fibrillation in patients with Brugada syndrome. Eur Heart J 1999;20:465-70.
28. Mizumaki K, Fujiki A, Tsuneda T, Sakabe M, Nishida K, Sugao M, *et al.* Vagal activity modulates spontaneous augmentation of ST elevation in the daily life of patients with Brugada syndrome. J Cardiovasc Electrophysiol 2004;15:667-73.
29. Makimoto H, Nakagawa E, Takaki H, Yamada Y, Okamura H, Noda T, *et al.* Augmented ST-segment elevation during recovery from exercise predicts cardiac events in patients with Brugada syndrome. J Am Coll Cardiol 2010;56:1576-84.
30. Nogami A, Nakao M, Kubota S, Sugiyasu A, Doi H, Yokoyama K, *et al.* Enhancement of J-ST-segment elevation by the glucose and insulin test in Brugada syndrome. Pacing Clin Electrophysiol 2003;26:332-7.
31. Postema PG, Neville J, de Jong JS, Romero K, Wilde AA, Woosley RL. Safe drug use in long QT syndrome and Brugada syndrome: Comparison of website statistics. Europace 2013;15:1042-9.
32. Yap YG, Behr ER, Camm AJ. Drug-induced Brugada syndrome. Europace 2009;11:989-94.
33. Miyazaki T, Mitamura H, Miyoshi S, Soejima K, Aizawa Y, Ogawa S. Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. J Am Coll Cardiol 1996;27:1061-70.
34. Postema PG, Wolpert C, Amin AS, Probst V, Borggrefe M, Roden DM, *et al.* Drugs and Brugada syndrome patients: Review of the literature, recommendations, and an up-to-date website (www.brugadadrugs.org). Heart Rhythm 2009;6:1335-41.
35. Atarashi H, Ogawa S, Harumi K, Hayakawa H, Sugimoto T, Okada R, *et al.* Characteristics of patients with right bundle branch block and ST-segment elevation in right precordial leads. Idiopathic Ventricular Fibrillation Investigators. Am J Cardiol 1996;78:581-3.
36. Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, Tan HL, *et al.* Long-term prognosis of patients diagnosed with Brugada syndrome: Results from the FINGER Brugada Syndrome Registry. Circulation 2010;121:635-43.
37. Kusano KF, Taniyama M, Nakamura K, Miura D, Banba K, Nagase S, *et al.* Atrial fibrillation in patients with Brugada syndrome relationships of gene mutation, electrophysiology, and clinical backgrounds. J Am Coll Cardiol 2008;51:1169-75.
38. Sacher F, Arsac F, Wilton SB, Derval N, Denis A, de Guillebon M, *et al.* Syncope in Brugada syndrome patients: Prevalence, characteristics, and outcome. Heart Rhythm 2012;9:1272-9.
39. Macedo PG, Brugada J, Leinveber P, Benito B, Molina I, Sert-Kuniyoshi F, *et al.* Sleep-disordered breathing in patients with the Brugada syndrome. Am J Cardiol 2011;107:709-13.
40. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, *et al.* HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: Document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm 2013;10:1932-63.
41. Sacher F, Probst V, Maury P, Babuty D, Mansourati J, Komatsu Y, *et al.* Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: A multicenter study-part 2. Circulation 2013;128:1739-47.
42. Brugada R, Brugada J, Antzelevitch C, Kirsch GE, Potenza D, Towbin JA, *et al.* Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. Circulation 2000;101:510-5.
43. Brugada J, Brugada R, Brugada P. Determinants of sudden cardiac death in individuals with the electrocardiographic pattern of Brugada syndrome and no previous cardiac arrest. Circulation 2003;108:3092-6.
44. Priori SG, Gasparini M, Napolitano C, Della Bella P, Ottonelli AG, Sassone B, *et al.* Risk stratification in Brugada syndrome: Results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. J Am Coll Cardiol 2012;59:37-45.
45. Carey SM, Hocking G. Brugada syndrome – A review of the implications for the anaesthetist. Anaesth Intensive Care 2011;39:571-7.
46. Antzelevitch C. Brugada syndrome. Pacing Clin Electrophysiol 2006;29:1130-59.
47. Cordery R, Lambiase P, Lowe M, Ashley E. Brugada syndrome and anesthetic management. J Cardiothorac Vasc Anesth 2006;20:407-13.
48. Edge CJ, Blackman DJ, Gupta K, Sainsbury M. General anaesthesia in a patient with Brugada syndrome. Br J Anaesth 2002;89:788-91.
49. Kim JS, Park SY, Min SK, Kim JH, Lee SY, Moon BK, *et al.* Anaesthesia in patients with Brugada syndrome. Acta Anaesthesiol Scand 2004;48:1058-61.
50. Santambrogio LG, Mencherini S, Fuardo M, Caramella F, Braschi A. The surgical patient with Brugada syndrome: A four-case clinical experience. Anesth Analg 2005;100:1263-6.
51. Inamura M, Okamoto H, Kuroiwa M, Hoka S. General anesthesia for patients with Brugada syndrome. A report of six cases. Can J Anaesth 2005;52:409-12.
52. Kasanuki H, Ohnishi S, Ohtuka M, Matsuda N, Nirei T, Isogai R, *et al.* Idiopathic ventricular fibrillation induced with vagal activity in patients without obvious heart disease. Circulation 1997;95:2277-85.
53. Ozeke O, Aras D, Geyik B, Deveci B, Selcuk T. Brugada-type electrocardiographic pattern induced by fever. Indian Pacing Electrophysiol J 2005;5:146-8.
54. Dulu A, Pastores SM, McAleer E, Voigt L, Halpern NA. Brugada electrocardiographic pattern in a postoperative patient. Crit Care Med 2005;33:1634-7.
55. Candiotti KA, Mehta V. Perioperative approach to a patient with Brugada syndrome. J Clin Anesth 2004;16:529-32.
56. Sugi Y, Mori M, Ono M, Kurihara Y. Anesthetic management of a patient with Brugada syndrome. Masui 2000;49:884-6.
57. Sanders P, Farouque O, Cehic DA, Young GD. An unusual cause of arrhythmic syncope: The Brugada syndrome. Aust N Z J Med 1999;29:737-8.
58. Vaccarella A, Vitale P, Presti CA. General anaesthesia in a patient affected by Brugada syndrome. Minerva Anestesiol 2008;74:149-52.

59. Vernooy K, Sicouri S, Dumaine R, Hong K, Oliva A, Burashnikov E, *et al.* Genetic and biophysical basis for bupivacaine-induced ST segment elevation and VT/VF. Anesthesia unmasked Brugada syndrome. Heart Rhythm 2006;3:1074-8.
60. Fujiwara Y, Shibata Y, Kurokawa S, Satou Y, Komatsu T. Ventricular tachycardia in a patient with Brugada syndrome during general anesthesia combined with thoracic paravertebral block. Anesth Analg 2006;102:1590-1.
61. Goraksha S, Bidaye S, Gajendragadkar S, Bapat J, Butani M. General anaesthesia for insertion of an automated implantable cardioverter defibrillator in a child with Brugada and autism. Indian J Anaesth 2010;54:562-4.
62. Canbay O, Erden IA, Celebi N, Aycan IO, Karagoz AH, Aypar U. Anesthetic management of a patient with Brugada syndrome. Paediatr Anaesth 2007;17:1225-7.
63. Brunetti ND, De Gennaro L, Pellegrino PL, Ieva R, Di Nardo F, Cuculo A, *et al.* Intra day ECG variation after general anesthesia in Brugada syndrome. J Interv Card Electrophysiol 2008;21:219-22.
64. Golusinski LL Jr, Blount BW. Clonidine-induced bradycardia. J Fam Pract 1995;41:399-401.
65. Phillips N, Priestley M, Denniss AR, Uther JB. Brugada-type electrocardiographic pattern induced by epidural bupivacaine. Anesth Analg 2003;97:264-7.
66. Kloesel B, Ackerman MJ, Sprung J, Narr BJ, Weingarten TN. Anesthetic management of patients with Brugada syndrome: A case series and literature review. Can J Anaesth 2011;58:824-36.
67. Güler N, Kati I, Demirel CB, Bilge M, Eryonucu B, Topal C. The effects of volatile anesthetics on the Q-Tc interval. J Cardiothorac Vasc Anesth 2001;15:188-91.
68. Hayashida H, Miyauchi Y. Anaesthetic management in patients with high-risk Brugada syndrome. Br J Anaesth 2006;97:118-9.
69. Theodotou N, Cillo JE Jr. Brugada syndrome (sudden unexpected death syndrome): Perioperative and anesthetic management in oral and maxillofacial surgery. J Oral Maxillofac Surg 2009;67:2021-5.
70. Flamée P, De Asmundis C, Bhutia JT, Conte G, Beckers S, Umbrain V, *et al.* Safe single-dose administration of propofol in patients with established Brugada syndrome: A retrospective database analysis. Pacing Clin Electrophysiol 2013;36:1516-21.
71. 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.
72. Baty L, Hollister J, Tobias JD. Perioperative management of a 7-year-old child with Brugada syndrome. J Intensive Care Med 2008;23:210-4.