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CASE REPORTS/CASE SERIES

Anesthetic management of patients with Brugada syndrome: a case series and literature review

Prise en charge de l'anesthésie chez les patients atteints d'un syndrome de Brugada: série de cas et analyse bibliographique

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Abstract

Purpose *To review the anesthetic management and perioperative outcomes of patients diagnosed with Brugada syndrome (BrS) who were treated at a single centre and to compare those results with a comprehensive review of the existing literature.*

Clinical features *A retrospective chart review of anesthesia records from patients diagnosed with BrS at the Mayo Clinic was undertaken with the emphasis on administered drugs, ST segment changes, and occurrence of complications, including death, hemodynamic instability, and dysrhythmias. Eight patients were identified who underwent a total of 17 operative procedures from 2000 through 2010. A total of 20 significant ST segment elevations were recorded in four patients, several of which occurred in close temporal relation to anesthetic drug administration. These elevations resolved uneventfully. There were no recorded dysrhythmias, and recovery from anesthesia proceeded uneventfully. A literature review of patients with BrS yielded 52 anesthetics in 43 patients. The only recorded complications included unmasking of a Brugada ECG pattern, one episode of polymorphic ventricular tachycardia, which converted spontaneously to sinus rhythm, and one episode of postoperative ventricular fibrillation in the setting of epidural anesthesia.*

Conclusions *In this series and in the literature, BrS patients tolerated anesthesia without untoward disease-related complications. Propofol and local anesthetics carry a theoretical risk of arrhythmogenic potential in BrS patients, but clear evidence is lacking. However, awareness of their potential to induce arrhythmias warrants caution, especially with propofol infusions. Factors that might exacerbate ST segment elevations and subsequently lead to dysrhythmias (e.g., hyperthermia, bradycardia, and electrolyte imbalances, such as hyper- and hypokalemia and hypercalcemia) should be avoided or corrected.*

Résumé

Objectif *L'objectif de cette étude était de passer en revue la prise en charge de l'anesthésie et les pronostics périopératoires de patients atteints du syndrome de Brugada (BrS) traités dans un seul centre et de comparer ces pronostics à une analyse exhaustive de la littérature existante.*

Éléments cliniques *Une révision rétrospective des dossiers anesthésiques de patients porteurs d'un BrS à la Clinique Mayo a été entreprise en recherchant particulièrement les médicaments administrés, les modifications au niveau du segment ST et la survenue de complications, y compris la mort, l'instabilité hémodynamique et les dysrythmies. Huit patients ont été identifiés. Au total, ils ont subi 17 opérations entre 2000 et 2010. Un total de 20 élévations significatives du segment ST a été enregistré chez quatre patients, dont plusieurs sont survenues à un moment proche de l'administration d'un anesthésique. Ces élévations se sont résolues sans incident. Aucune dysrythmie n'a été enregistrée, et la récupération après l'anesthésie s'est faite sans incident. Une analyse de*

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la littérature portant sur des patients atteints de BrS a indiqué que 52 médicaments anesthésiques avaient été utilisés chez 43 patients. Les seules complications mentionnées sont la découverte d'un tracé typique du syndrome de Brugada à l'ECG, un épisode de tachycardie ventriculaire polymorphe, qui s'est spontanément transformée en rythme sinusal, et un épisode de fibrillation ventriculaire postopératoire dans le cadre d'une anesthésie péridurale.

Conclusion *Dans cette série et dans la littérature, les patients atteints de BrS ont toléré l'anesthésie sans complication fâcheuse liée à la maladie. Le propofol et les anesthésiques locaux comportent un risque théorique de potentiel arythmogène chez les patients atteints de BrS, mais nous ne disposons pas de données probantes claires. Toutefois, le fait d'être conscients de leur potentiel à induire des arythmies justifie que nous fassions preuve de prudence, particulièrement en ce qui touche aux perfusions de propofol. Les facteurs qui pourraient exacerber les élévations du segment ST et entraîner des dysrythmies (par ex., l'hyperthermie, la bradycardie et les déséquilibres électrolytiques tels que l'hyper- et l'hypokaliémie ainsi que l'hypercalcémie) doivent être évités ou corrigés.*

Brugada syndrome (BrS) is a rare genetic autosomal dominant disease with incomplete penetrance which affects ion channels of the cardiac conduction system and causes a coved ST segment elevation in the right precordial leads with a pseudo right bundle branch block pattern. Patients afflicted with this disease can develop malignant ventricular arrhythmias. This disorder raises specific concerns as anesthesiologists routinely administer drugs that interact with cardiac ion channels which theoretically could trigger the development of malignant arrhythmias. Propofol infusions have induced Brugada-like electrocardiogram (ECG) abnormalities.[1-6] The administration of sodium channel blockers to diagnose BrS by unmasking/provoking a type 1 Brugada ECG pattern raises safety concerns regarding the use of local anesthetics.[7] As BrS is uncommon, with an estimated prevalence of approximately 1:5,000, large prospective studies to define the risks of anesthesia are impractical. We searched the Mayo Clinic medical records database to identify patients with BrS who underwent anesthesia and reviewed their anesthetic course. The purpose of this case series was to document perioperative adverse events in BrS patients within a single institution and to determine any possible association between adverse events in patients with BrS and anesthetic drugs administered in the perioperative setting.

Methods

After obtaining Institutional Review Board approval, a computerized search of the Mayo Clinic Rochester electronic medical records (EMR) database from 2000 through 2010 was conducted to identify patients with clinically diagnosed BrS who underwent anesthetic care. We performed a keyword search using the terms "SCN5A", "Brugada", "Sudden unexpected death syndrome", and "SUDS" and refined our search by selecting terms to eliminate patients in whom BrS was excluded. Our inclusion criteria consisted of adult patients (aged $\geq$ 18 yr), procedures involving anesthesia care, and a clinical diagnosis of BrS. Since SCN5A-BrS accounts for only 20-30% of the disease, a positive genetic test result was not required for inclusion in the study. The only data included in the study were from patients who provided research authorization for the use of their medical records [Minnesota Statute 144.335 Subd. 3a. (d)].

The electronic medical and anesthesia records of eligible patients were reviewed by one of the authors (B.K.). Data were entered into a standardized data collection form, and all questionable entries were discussed with the senior authors. As BrS is a relatively heterogeneous disorder that imposes diagnostic challenges, the EMR of each subject was reviewed with a genetic cardiologist (M.J.A.) to obtain the most specific description of each patient's BrS diagnosis. The following data were collected for each anesthetic: 1) drug usage (type, amount, time point) with specific focus on medications that conceivably could increase the risk of ventricular arrhythmias in a BrS host; 2) ST segment measurement (value, time point); and 3) pre-, peri-, and postprocedural events (specifically, arrhythmias, defibrillations, and episodes of hyperthermia defined by a core body temperature $\geq$ 38°C). ST segment changes were analyzed during time increments of two minutes. A change $\geq$ 1 mm in leads II and V5 measured at J+60 during two consecutive measurements (four-minute time period) was considered significant. ST segment depressions were excluded from the analysis due to lack of association with BrS. Since ST segment changes can be prone to artifacts, we correlated significant ST segment events with the drug administration time points. We observed that ST segment monitoring data were obtained from recordings of leads II and V5, neither of which assesses the right precordium, i.e., the area of the most typical ST segment changes in BrS patients. However, these were the two leads available from the electronic medical record. Intra- and postoperative hemodynamic variables were recorded. Abnormal values were defined as hypertension (systolic BP $\geq$ 30% of preinduction baseline), hypotension (systolic BP $\leq$ 30% of preinduction

baseline), tachycardia (HR $>$ 110 beats·min^{-1}), and bradycardia (HR $<$ 50 beats·min^{-1}).

Principal findings

During the ten-year period from 2000 through 2010, there were eight adult patients (seven males) with a clinical diagnosis of BrS at the Mayo Clinic who had one or more than one anesthetic exposure. According to our definition, all patients exhibited a type 1 Brugada ECG pattern either at rest or with provocation, and four of the eight patients had SCN5A-mediated BrS (i.e., type 1 BrS, Table 1). These eight BrS patients underwent a total of 17 surgical procedures. Table 2 summarizes the demographic and clinical data of the patients, the surgeries performed, the drugs used during anesthesia, and the intraoperative and postoperative complications, including ST segment changes. Of the 17 surgical procedures, seven were performed using general anesthesia, nine procedures involved monitored anesthesia care (patients receiving sedation provided by anesthesia personal, but the patients were not unconscious), and one procedure involved combined spinal/ epidural anesthesia. The medication profiles are detailed in Table 2.

During the perioperative and recovery time periods, no arrhythmias were observed except for sinus tachycardia and isolated premature ventricular contractions (PVCs). All patients tolerated anesthesia without adverse events or complications with the exception of 20 significant ST segment elevations that occurred in four patients. Table 3 shows the specific patients and the relationships of ST segment elevation to medication administration. Patient 3 had one significant ST segment elevation which was not in close temporal relationship (within ten minutes) to bolus drug administration. Patient 5 had multiple events related to automatic implantable cardioverter defibrillator testing. Patient 4 had two significant events; one was related to applying a topical application of oxymetazoline to the nose, and the other occurred shortly after induction with propofol, lidocaine, and succinylcholine. In patient 8, two events were noted to occur in close relationship to initiation of a propofol infusion with intravenous lidocaine bolus, and another event occurred during induction with etomidate.

Discussion

Our retrospective review of anesthetics performed in eight patients with diagnosed BrS showed that all patients tolerated anesthesia well. Some anesthetic agents (propofol, etomidate, lidocaine, succinylcholine, and nasal oxymetazoline) were noted to have a temporal association to ST segment elevations, a finding that is suspected to result in an increased risk of precipitating ventricular arrhythmias.

Brugada syndrome is an uncommon autosomal dominant genetic disease with incomplete penetrance and variable expressivity stemming from various mutations of ion channels in the cardiac conduction system.[8,9] The disease is typically diagnosed during the fourth decade of life. Seven genotypes of BrS have been characterized, including mutations in cardiac sodium (types 1, 2, 5, and 7), potassium (type 6), and calcium (types 3 and 4) channels.[8] Type 1 BrS, secondary to mutations in the SCN5A-encoded Nav1.5 sodium channel α-subunit, is the most common genetic subtype accounting for about 20-30% of BrS. The type 1 Brugada ECG pattern is the most specific ECG pattern for BrS. Type 1 is characterized by a coved-type ST segment elevation of at least 2 mm in the right precordial leads associated with a complete or incomplete right bundle branch block followed by a negative T wave.[10] This ECG pattern can be either present at rest or inducible with sodium channel blockers, such as flecainide or procainamide. Patients may be asymptomatic, but they are at risk of developing ventricular tachycardia (VT) or fibrillation and sudden death.[11,12] Type 2 Brugada ECG pattern presents with a saddleback appearance and either a positive or biphasic T wave. Type 3 Brugada ECG pattern can assume a saddleback or coved appearance, but it is characterized by less pronounced ST segment elevations. An observed type 1 ECG pattern is considered diagnostic when identified in conjunction with

Table 1 Brugada syndrome study patients

Patient #	Sex	Age at first anesthetic exposure	Diagnosis
1	Male	60	Clinically diagnosed BrS with negative EP study
2	Female	26	Asymptomatic, type 1 BrS (i.e., SCN5A positive)
3	Male	58	Asymptomatic type 1 BrS
4	Male	20	Asymptomatic, genotype negative BrS
5	Male	16	Symptomatic type 1 BrS
6	Male	35	Clinically diagnosed BrS
7	Male	48	Clinically diagnosed BrS with positive EP study
8	Male	41	Asymptomatic type 1 BrS

BrS = Brugada syndrome; EP = electrophysiological

Table 2 Demographic and clinical data of patients with Brugada syndrome undergoing anesthetic care

	Patient 1	Patient 2	Patient 2	Patient 3	Patient 4	Patient 4	Patient 4	Patient 5	Patient 5
Date of birth	1947	1977	1977	1951	1983	1983	1983	1986	1986
Surgical date (yr)	2007	2003	2004	2009	2004	2008	2008	2003	2004
Sex	Male	Female	Female	Male	Male	Male	Male	Male	Male
Age at procedure	60	26	27	58	20	24	24	16	17
ASA status	3	2	1	2	3	3	2	2	3
Procedure	Inguinal herniorrhaphy	Vaginal delivery	Tooth extraction	Sinus surgery	Dental extraction	Neurofibroma resection	Neurofibroma resection	ICD follow-up testing	ICD follow-up testing
Anesthesia technique	GA	Labour Epidural	MAC	GA	GA	GA	GA	MAC	MAC
Induction agent	Prop 150 mg	None	None	Sevo	Prop 250 mg	Prop 100 mg	Prop 100 mg Scopolamine	STP 100 mg	None
Induction adjuncts	Mid Lido 100 mg, Fent	None	None	Mid Fent	Lido 100 mg	Mid Fent	Mid Fent	Mid Fent,	None
Muscle relaxants	Suc Vec	None	None	Vec	Suc	None	None	None	None
Maintenance	Des N_2O	Sufentanil 5 μg, 2-Chlorprocaine 1% 7 mL, Fentanyl-Bupivacaine 0.125% at 20 $\mu g \cdot hr^{-1}$ (total of 89 mg), Bupivacaine bolus (12.5 mg)	Mid Fent Propofol infusion	Iso N_2O Remifentanil	Sevo N_2O Prop 100 mg	Sevo N_2O	Sevo N_2O Prop 50 mg Prop infusion for 28 hr while intubated in ICU	Sevo N_2O	Sevo N_2O Fent Mid Prop 50 mg
Neuromuscular reversal	Neostigmine Glycopyrrolate	None	None	None	None	None	None	None	None
Vasoactive drugs	None	Ephedrine	None	Ephedrine	None	Ephedrine Phenylephrine	Phenylephrine Esmolol	None	None
Additional drugs	Ondansetron	None	Dexamethasone	Fentanyl Granisetron	Oxymetazoline Ondansetron	Hydromorphone Famotidine	Famotidine Dexamethasone	Ondansetron	Ondansetron
ECG changes	No	No	No	Yes	Yes	No	No	Yes	Yes
Intraoperative complications	Hypotension	Hypotension	None	Bradycardia	Hypotension, Tachycardia	Hypotension	Hypotension, Hypertension, Tachycardia	Hypotension,	Tachycardia
Bradycardia									
Postoperative complications	None	None	None	Hypertension	None	None	Hypotension, Tachycardia	None	Bradycardia
Surgical time	78 min	N/A	29 min	236 min	16 min	53 min	90 min	61 min	79 min
Postoperative level of care	PACU	Floor	PACU	PACU/ SICU	PACU	PACU	SICU	PACU	Floor
PACU time	48 min	N/A	25 min	58 min (PACU) 1,116 min (ICU)	33 min	93 min	2,817 min (ICU)	75 min	107 min

Table 2 continued

	Patient 5 Patient 5	Patient 5 Patient 5	Patient 5 Patient 5	Patient 6 Patient 6	Patient 7 Patient 7	Patient 8 Patient 8	Patient 8 Patient 8	Patient 8 Patient 8
Date of birth	1986	1986	1986	1970	1953	1967	1967	1967
Surgical date (yr)	2005	2006	2007	2005	2003	2008	2009	2010
Sex	Male	Male	Male	Male	Male	Male	Male	Male
Age at procedure	18	19	20	35	48	41	42	43
ASA status	2	2	2	2	3	3	2	3
Procedure	ICD follow-up testing	ICD follow-up testing	ICD follow-up testing	Thoracic laminectomy with cavernoma resection	Dental extraction	Prostate biopsy	Shoulder mass excision	Inguinal herniorrhaphy
Anesthesia technique	MAC	MAC	MAC	GA	MAC	MAC	MAC	GA
Induction agent	None	None	None	Prop 200 mg	None	None	None	Etomidate 30 mg
Induction adjuncts	None	None	None	Lido 80 mg, Fent Mid	None	None	None	Fent
Muscle Relaxants	None	None	None	Vec	None	None	None	Suc
Maintenance	Sevo Prop 100 mg	Sevo N_2O STP 375 mg	Sevo STP 150 mg	Iso N_2O	2% Lidocaine 3.6 ml	Prop 60 mg Prop infusion 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (total of 172.8 μg)	N_2O Prop infusion 75 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (total of 61.9 μg)	Des
Neuromuscular reversal	None	None	None	Neostigmine Glycopyrrolate	None	None	None	None
Vasoactive drugs	Ephedrine Phenylephrine	None	None	Labetalol	None	None	None	None
Additional drugs	None	None	Ondansetron Dexamethasone	Fent Famotidine Dexamethasone	None	None	Lido 40 mg Fent	Fent Ketorolac
ECG changes	No	Yes	No	No	No	No	Yes	Yes
Intraoperative complications	Hypotension, Bradycardia, Tachycardia	Hypotension, Bradycardia	Bradycardia, Tachycardia	Hypotension	None	None	None	None
Postoperative complications	Bradycardia	None	Bradycardia	Hypotension	None	None	None	Hypoxia, Hypoventilation
Surgical time	16 min	32 min	15 min	299 min	13 min	8 min	19 min	66 min
Postoperative level of care	PACU	PACU	PACU	PACU/ SICU	Floor	PACU	PACU	PACU
PACU time	45 min	51 min	30 min	50 min (PACU) 2,686 min (ICU)	N/A	66 min	78 min	255 min

ASA = American Society of Anesthesiologists; GA = general anesthesia; MAC = monitored anesthesia care; Lido = lidocaine; Suc = succinylcholine; Vec = vecuronium; Mid = midazolam; Fent = fentanyl; N_2O = nitrous oxide; Prop = propofol; STP = sodium thiopental; Sevo = sevoflurane; Iso = isoflurane; Des = desflurane; ICD = implantable cardioverter defibrillator; PACU = postanesthesia care unit; ICU = intensive care unit; SICU = surgical intensive care unit

Table 3 Significant ST segment elevations with time-relation to perioperative application of drugs

Patient #	Surgery #	Event #	ST change (mm)	Lead	Medication (application occurred number of minutes before ST segment change)
3	1	1	1.3	III	No medication given within preceding 25 minutes (granisetron and remifentanil)
4	1	1	1.1	V	oxymetazoline nasal (4 minutes)
	1	2	1.2	II	oxymetazoline nasal (8 minutes), propofol (2 minutes), lidocaine (2 minutes), succinylcholine (2 minutes)
5	1	1, 2			A total of 14 events occurred during three different surgeries which all involved monitored anesthesia care for ICD testing; due to the nature of ICD testing it is difficult to draw conclusions regarding the ST segment changes (influenced by movement and electrical stimulation). We therefore excluded the patient from this analysis.
	2	1-11			
	4	1			
8	2	1	1.4	V	propofol infusion (started 4 minutes), lidocaine (4 minutes), fentanyl (4 minutes)
	2	2	1.1	V	propofol infusion (started 7 minutes), lidocaine (7 minutes), fentanyl (7 minutes)
	3	1	1.2	V	etomidate (0 minutes), dexamethasone (2 minutes), fentanyl (4 minutes, 2 minutes), heparin (2 minutes)

ICD = implantable cardioverter defibrillator

one of the following findings[10,11] history of ventricular fibrillation or VT, family history of sudden cardiac death < 45 yr of age, coved-type ECGs in family members, inducibility of VT with programmed electrical stimulation, syncope or nocturnal agonal respiration. Type 2 and 3 ECG patterns are considered diagnostic when conversion to a type 1 ECG pattern is observed with the use of sodium channel blockers. Conversion of a type 3 ECG pattern to a type 2 ECG pattern is inconclusive.[11]

The pathophysiology behind the increased susceptibility to ventricular arrhythmias in BrS patients is beyond the scope of this article, but Morita *et al.*[9] present a comprehensive review. Physiologic stress,[13] medications, and increased vagal activity[14-16] can augment ST segment elevation. While a clear causal link between acute worsening of ST segment abnormalities and subsequent ventricular arrhythmias has not been established, multiple reports suggest such a relationship.[17-20]

It is difficult to formulate evidence-based guidelines for anesthetic management of these patients due to the absence of prospective studies combined with the low prevalence of BrS. Current guidelines are derived from theoretical models based on disease pathomechanism and observations from case reports and series.[21] We conducted a literature search to compare our observations with previous reports regarding outcomes of patients with BrS who underwent anesthetic care. PubMed (1966-present) and EMBASE (1988-present) databases were searched using the following medical subject headings (MeSH): Brugada syndrome, anesthesia, anesthetics, and bupivacaine. Text words included: Brugada, anesthesia, anesthetics, anaesthesia, anaesthetics, bupivacaine, propofol, blockade, sympathomimetic, anticholinergic, perioperative, delivery, and caesarean. The search was limited to human subjects. In our search of anesthetic management of patients with BrS, we identified 21 case reports and four case series.

Articles in languages other than English were excluded,[22-29] although an exception was made if an English abstract was provided that contained information about the surgical procedure and the medications used [30-33] or if the article was previously reviewed by another investigator (e.g., the case reports of Sugi *et al.*[34] and Lafuente *et al.*[35] were reviewed in an article by Edge *et al.*).[36]

All case reports and case series were based on review of medical records. Including the present study, a cumulative experience with 52 anesthetics involving 43 patients has been published since 1966. A comprehensive list of patients, surgical cases, anesthetic drugs, and complications is shown in Table 4.

Overall, our patients had unremarkable anesthetic courses. They exhibited normal responses to commonly used anesthetic agents, with the exception of two patients who experienced significant ST segment elevations in temporal relationship to administration of certain drugs, i.e., propofol, lidocaine, succinylcholine, oxymetazoline, or etomidate. All the documented ST segment elevations resolved spontaneously, and postanesthesia recovery times were not prolonged. The results support a small but consistent body of evidence describing relatively uneventful outcomes associated with general anesthesia and MAC sedation for patients with BrS.[31-33,35-46] Despite the generally favourable outcomes, there remain several specific concerns that merit special consideration in patients with BrS.

Regional anesthesia and sodium-channel blockers

Regional anesthesia has been associated with complications in BrS. In a report by Fujiwara *et al.*,[47] a patient with

Table 4 Previous reports of anesthesia in Brugada syndrome patients

Age	Sex	Surgery	Drugs	Complications	Ref.
7	Male	Open inguinal hernia repair	Midazolam, sevoflurane, nitrous oxide, glycopyrrolate, fentanyl and wound infiltration with bupivacaine	None	[38]
3.5	Male	Electrophysiologic study	Thiopental, vecuronium, fentanyl, sevoflurane, neostigmine	None	[42]
69	Female	Colpohysterotomy	Atenolol, lorazepam, midazolam, fentanyl, propofol (induction bolus), TIVA (propofol, fentanyl), succinylcholine, atracurium, atropine, neostigmine, buprenorphine	None	[40]
60	Male	AICD insertion	Diazepam, propofol, vecuronium, TIVA (propofol, fentanyl), atropine, ephedrine	Bradycardia, hypotension	[49]
51	Male	AICD insertion	Diazepam, propofol, vecuronium, sevoflurane, nitrous oxide	None	[49]
56	Male	AICD insertion	Diazepam, midazolam, vecuronium, sevoflurane, nitrous oxide, lidocaine, ephedrine	Hypotension	[49]
59	Male	AICD insertion	Diazepam, propofol, vecuronium, TIVA (propofol, fentanyl), atropine	Bradycardia	[49]
63	Male	AICD insertion	Diazepam, propofol, vecuronium, sevoflurane, nitrous oxide	None	[49]
63	Male	AICD insertion	Diazepam, propofol, vecuronium, sevoflurane, nitrous oxide, lidocaine, diltiazem	None	[49]
55	Male	Tooth extraction, incision and drainage of odontogenic infection	Lidocaine, propofol, succinylcholine, sevoflurane, nitrous oxide, lidocaine/ epinephrine (local infiltration), ephedrine	Hypotension	[39]
52	Male	Laparotomy for small bowel obstruction	Thiopental, succinylcholine, fentanyl, isoflurane, nitrous oxide, vecuronium, glycopyrrolate, neostigmine, thoracic epidural catheter (0.25% bupivacaine, fentanyl)	None	[36]
33	Male	Open patella fracture	Spinal anesthesia with 0.5% bupivacaine, PCA (opioids), NSAIDs	None	[37]
56	Male	Spine fusion, L1 compression fracture	Thiopental, vecuronium, fentanyl, isoflurane, ketorolac, PCA (opioids)	None	[37]
26	Male	Endoscopic sinus surgery	Midazolam, fentanyl, propofol, rocuronium, sevoflurane, nitrous oxide, neostigmine, glycopyrrolate	None	[44]
25	Male	Appendectomy	Diazepam, propofol, fentanyl, cis-atracurium, sevoflurane, ketorolac	None	[41]
36	Male	Varicocelectomy	Diazepam, propofol, fentanyl, cis-atracurium, sevoflurane, ketorolac	None	[41]
27	Male	Appendectomy	Diazepam, propofol, fentanyl, cis-atracurium, sevoflurane, ketorolac	None	[41]
43	Male	TURP	Diazepam, propofol, fentanyl, cis-atracurium, sevoflurane, ketorolac	None	[41]
51	Male	Percutaneous nephrolithotripsy	Thiamylal, vecuronium, isoflurane, nitrous oxide, atropine, neostigmine	None	[43]
56	Male	Plate fixation for mandibular fracture	Thiamylal, vecuronium, isoflurane, nitrous oxide, atropine, neostigmine	None	[43]
47	Male	Hemilaminectomy	Propofol, fentanyl, droperidol, vecuronium, sevoflurane, neostigmine, atropine	ST segment elevation	[34]
49	Male	Vocal cord polypectomy	Propofol, fentanyl, diazepam, mivacurium, glycopyrrolate, isoflurane, nitrous oxide	None	[35]
77	Male	Gastrectomy for stomach cancer	Midazolam, propofol, fentanyl, rocuronium, sevoflurane, thoracic epidural catheter (0.125% bupivacaine, fentanyl)	Postoperative unmasking of Brugada-type ECG pattern by bupivacaine continuous infusion	[7]

Table 4 continued

Age	Sex	Surgery	Drugs	Complications	Ref.
68	Male	Distal gastrectomy for stomach cancer	Propofol, fentanyl, vecuronium, sevoflurane, bilateral thoracic paravertebral block (0.5% ropivacaine), dopamine	Hypotension, polymorphic ventricular tachycardia	47
N/A	N/A	Craniotomy, clipping of middle cerebral artery aneurysm	General anesthesia but no information about anesthetic drugs used except for low-dose dopamine and glycopyrrolate	Bradycardia	75
16	Male	AICD insertion	Propofol, fentanyl, atracurium, sevoflurane, nitrous oxide, neostigmine, glycopyrrolate	Hypoxia, laryngospasm, pulmonary edema	78
40	Female	Elective Cesarean delivery	Spinal anesthesia with 0.5% bupivacaine (13.5 mg) and diamorphine (400μg), phenylephrine, oxytocin	None	79
14	Male	AICD insertion	Midazolam, TIVA (propofol, fentanyl), atracurium, neostigmine, glycopyrrolate	None	45
42	Male	Comminuted calcaneus fracture repair	Spinal anesthesia with 0.5% levobupivacaine (13.5 mg), remifentanil	None	46
40	Male	Radicular cyst excision	Midazolam, atropine, propofol, vecuronium, sevoflurane, nitrous oxide, fentanyl, lidocaine/ epinephrine (local infiltration)	None	31
70	Male	Laryngeal cancer biopsy	Propofol, tramadol, sevoflurane, nitrous oxide	None	32
23	Male	Tenotomy for lower extremity contracture	Sevoflurane, remifentanil	None	33
N/A	N/A	AICD insertion	Thiopental, sevoflurane, nitrous oxide	None	30
38	Male	Tibia/ fibula fracture, plate osteosynthesis	Propofol, remifentanil, cisatracurium, sevoflurane, morphine	None (some intra- and postoperative ST segment variations in V1-V3)	80
71	Male	Lobectomy for lung cancer	Sevoflurane, epidural anesthesia (agent and dose were not reported)	PVCs, bradycardia, postoperative ventricular fibrillation	48

AICD = automatic implantable cardioverter defibrillator; TURP = transurethral resection of the prostate; ECG = electrocardiogram; TIVA = total intravenous anesthesia; PCA = patient-controlled analgesia; NSAIDs = nonsteroidal anti-inflammatory drugs; PVCs = premature ventricular contractions

BrS developed polymorphic ventricular tachycardia 50 min following bilateral T8 paravertebral block using 40 mL of ropivacaine. However, concomitant use of a dopamine infusion to treat hypotension attributed to the block was a confounding factor which may have contributed to the development of the arrhythmia (see section "Vasoactive agents"). In a case reported by Phillips *et al.*,[7] a previously asymptomatic patient developed Brugada-like ECG changes after a 14-hr infusion of bupivacaine in a thoracic epidural catheter. The bupivacaine infusion was discontinued and the ECG normalized over the ensuing 48 hr. The patient was given a provisional diagnosis of BrS based on the inducibility of a Brugada ECG pattern with sodium channel blockers, although no further evaluation was performed. Kaneda *et al.*[48] described a case in which a patient with diagnosed BrS developed ventricular fibrillation postoperatively after undergoing general and epidural anesthesia. Unfortunately, the article does not provide details regarding the medications used in the epidural (i.e., type of local anesthetic or dose). Interestingly, Kaneda *et al.*[48] reported the successful use of intravenous lidocaine (intravenous bolus followed by continuous infusion) to control postoperative ventricular fibrillation in a BrS patient. In our series, one patient had a lumbar epidural placed for labour analgesia through which fentanyl-bupivacaine was applied by bolus and continuous infusion. No complications were noted.

Several authors reported uneventful regional or wound infiltration with local anesthetics in BrS patients.[36-39,49] Local anesthetics are class Ib antiarrhythmics and thus block sodium channels. Intravenous lidocaine was reported to induce a Brugada ECG pattern which led to the diagnosis of BrS with subsequent identification of a V232I+L1308F double-missense mutation in the SCN5A gene.[50] However, the effect of lidocaine may be dependent on specific ion channel mutation. For example, lidocaine exerted a beneficial effect in a patient with type 1 BrS secondary to a SCN5A-N406S missense mutation.[51,52] Regardless, local anesthetics should be used cautiously, and if used, the dose should be minimized and the patient

should be monitored closely. Four patients in our series received intravenous lidocaine without evidence of dysrhythmias, but an association with ST segment elevations was noted in three cases (Table 3).

Propofol and other induction agents

It has been suggested that propofol should be avoided in patients with BrS.[21] Vernooy *et al.*[1] examined the relationship of ECG changes and sudden death in propofol infusion syndrome (PRIS). The group reported an index case in which PRIS induced a Brugada ECG pattern. A subsequent chart review revealed seven additional cases of PRIS; in six of those seven patients, a Brugada ECG pattern was recorded shortly before the occurrence of an electrical storm. Roberts *et al*. defined the features of PRIS in a large prospective incidence study published in 2009.[53] The characteristics include development of metabolic acidosis and cardiac dysfunction along with at least one of rhabdomyolysis, hypertriglyceridemia, or renal failure after receiving intravenous propofol. In a report by Robinson *et al*.,[4] an infant treated with continuous propofol infusion developed wide complex tachycardia with left bundle branch block morphology. This condition was cardioverted into a slower irregular rhythm with right bundle branch block morphology and pronounced ST segment elevations in V1. In a case reported by Riezzo *et al*.,[3] a patient with long-term propofol abuse developed a Brugada ECG pattern with subsequent cardiovascular instability and death. The described presentation was reminiscent of PRIS with regard to cardiovascular instability and metabolic acidosis. An *in vitro* experiment on cardiac myocytes demonstrated that propofol exerts a dose-dependent blockade of whole cell sodium current and induces a hyperpolarizing shift in the voltage-dependence of the inactivation of sodium currents.[54] Propofol has also been found to inhibit cardiac L-type calcium channels,[55] attenuate beta-adrenergic signal transduction,[56] and augment acetylcholine receptor activity.[57]

However, these adverse outcomes have occurred only in the setting of propofol abuse[3] and PRIS.[1,5,53] More importantly, none of the observed patients carried a diagnosis of BrS. Consequently, the only association between PRIS and BrS is the implication of propofol infusions in unmasking a Brugada ECG pattern.[1-5] In a report by Weiner *et al.*,[6] they described a Brugada ECG pattern induced by propofol infusion in a healthy young male who subsequently underwent testing and was found not to have BrS. Propofol has been used during anesthesia in BrS patients without incident.[31,32,34,35,39-41,49] In our series, propofol was administered as a bolus in nine cases and as an infusion in three cases, and no dysrhythmias were observed. However, one patient who had received a propofol bolus and one patient who received a propofol infusion were noted to have significant ST segment elevations following propofol administration (within seven minutes after injection or start of infusion). The ST segments subsequently normalized spontaneously.

It is important to highlight that a type 1 Brugada ECG pattern is an electrocardiographic result which is not necessarily diagnostic of BrS in the absence of supporting findings. The differential diagnosis of a patient who exhibits a type 1 Brugada ECG pattern includes BrS, but it also encompasses various acquired diseases as well as cocaine[58]/marijuana[59] use. In addition, multiple occurrences of drug-induced Brugada ECG patterns in previously healthy patients were reported,[60-63] although those ECG changes were noted mostly in the setting of medication overdoses. Nevertheless, propofol has the potential to alter ion channel function. Despite theoretical concerns and various reports of adverse outcomes with propofol in a small subset of patients without known BrS, in our view, the clinical experience does not support the recommendation of avoiding bolus dosing for induction in BrS patients. Caution is advised for continuous infusions, however, as BrS patients may be more predisposed to cardiac arrhythmias due to their intrinsic ion channel malfunction.

Regarding other induction agents, thiopental use has been described in multiple case reports[22,28,30,31] without problems, whereas no studies reported the use of etomidate. In our series, self-limited ST segment elevations were noted following etomidate administration, while no ST segment abnormalities were noted with the administration of thiopental.

Inhalational anesthetics, muscle relaxants, acetylcholine-esterase inhibitors, anticholinergics, and antiemetics

Inhalational anesthetics have not been associated with adverse events in BrS patients either in our series or in the literature.[30-33,35-38,41-44,49] Both depolarizing and nondepolarizing neuromuscular blocking agents have been utilized clinically in our series and in previous case studies without incident.[31,36,40,42-45] In our series as well as in the literature, nondepolarizing muscle relaxants were reversed with neostigmine without incident.[36,40,42-45]

Atropine[31,40,43,49] and glycopyrrolate[35,38,44,45] were used by other authors without problems. In our series, glycopyrrolate and scopolamine were used without adverse effects. Interestingly, in one study of patients with BrS, ST segment elevation was found in the right precordial leads after intracoronary acetylcholine (3/3 tested patients) and intravenous edrophonium administration (2/3 patients).[20] In theory, given that increased vagal tone may increase

arrhythmia susceptibility in a patient with BrS, the anticholinergic action of atropine, glycopyrrolate, and scopolamine drugs could exert a beneficial effect on ST segment changes. A variety of opioids has been used in our series and reported in the literature[31-33,35-38,41,42,44,49] without adverse events in patients with BrS.

Commonly used antiemetics, including ondansetron, granisetron, and dexamethasone, have not been associated with any reported adverse effects in BrS patients, and all these drugs were used in our series without incident. Droperidol was not used in our patients, and it has been recommended to avoid phenothiazine antipsychotics (trifluoperazine, thioridazine, perphenazine).[21] Phenothiazine overdoses have resulted in Brugada ECG patterns.[64-66] Perphenazine has produced a reversible blockade of the Nav1.5 sodium current and the Kv4.3 transient outward potassium current (Ito) in isolated rat right ventricular cardiomyocytes,[67] and trifluoperazine and chlorpromazine have reduced calcium inward current, sodium currents, and inwardly and delayed potassium currents in isolated guinea pig myocytes and bovine portal veins.[68] However, the use of prochlorperazine has not been reported in BrS patients.

Vasoactive agents

Modulation of adrenergic receptors can modify ECG tracings in BrS patients by altering the ST segments.[12] Alpha-receptor agonists[20] and β-receptor antagonists[69] can worsen ECG patterns by increasing the magnitude of ST segment elevation or unmasking a Brugada ECG pattern (change from normal ST segments to ST segment elevations), whereas α-receptor antagonists[20] and β-receptor agonists[20] improve ECG patterns by returning elevated ST segments back to baseline or decreasing the magnitude of ST segment elevations. The β_1 and β_2 receptor agonistic activity of isoproterenol increases calcium current and has been used to reduce ST segment elevation[20] and suppress arrhythmic events in patients with BrS.[70-73] Several approaches have been proven to successfully abrogate electrical storms. Joshi *et al.*[72] and Jongman *et al.*[71] reported suppression of arrhythmias with an infusion of isoproterenol 1 $\mu g \cdot min^{-1}$. Watanabe *et al.*[73] used a bolus/maintenance approach with isoproterenol with an initial bolus of 1-2 µg followed by a continuous infusion adjusted from 0.15-0.30 $\mu g \cdot min^{-1}$. Ohgo *et al.*[70] showed an effect at lower doses of 0.002 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with titration to 0.004 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Besides the use of isoproterenol, the basic life support and advanced life support protocol should be no different for patients with BrS; however, data regarding the safety of other commonly used vasopressors are almost non-existent. Theoretically, the predominant β-agonist action of dobutamine could be beneficial, while other vasopressors with dual α- and β-agonist effect may have unpredictable effects. Epinephrine in conjunction with procainamide has been used to unmask Brugada,[74] and norepinephrine can augment ST segment elevations. However, the use of dopamine[75] and ephedrine[49] has been described, and ephedrine was used in our series without complication. The selective α_1-agonist activity of phenylephrine has theoretic potential to be deleterious, but it was used in our series without incident.

An overdose of the β-antagonist, propanolol, has been reported to unmask a Brugada ECG pattern.[69] This change may have resulted from bradycardia and β-antagonism. However, propanolol at high doses binds to cardiac sodium channels inhibiting sodium uptake, and this action could have been the mechanism.[63] In our series, one patient received esmolol and one patient received labetalol without incident.

Limitations

In this small case series of BrS patients, the right precordial leads (V1-V3) were not monitored in any of our patients to assess for dynamic ST segment changes. Thus, subtle undetected changes may have occurred. However, ST segment elevations in the inferior leads[76] and the left precordial leads[77] have also been observed in Brugada-like syndromes. If the surgical field allows, monitoring the right precordial leads may enhance sensitivity to detect dynamic ST segment changes in BrS patients, and this might enable the anesthesiologist to notice a possible unmasking of a Brugada-type ECG pattern in patients with normal resting ECGs. Furthermore, the ST segment changes were recorded only as numerical values without the possibility to assess morphology, thus precluding the potential to identify "coved" ST segments (Figure).

Another limitation of this retrospective case series is the small number of patients, which precluded a definitive proof of safety of any anesthetic agent or technique.

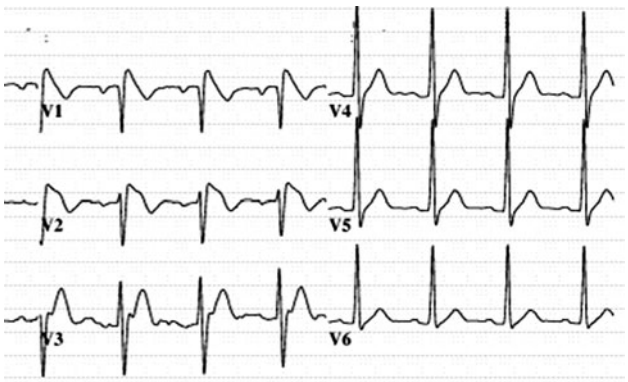

Figure Precordial lead tracing (Patient 3). Typical right precordial lead tracings (V1-V3) showing T wave abnormalities typically observed in patients with Brugada syndrome

Conclusions

Patients with BrS in our series tolerated anesthesia without any untoward events other than episodes of spontaneously resolving ST segment elevation. However, with the exception of sodium channel blockers, clear data is clearly limited regarding the drugs that can exacerbate ST segment elevations and/or facilitate the development of ventricular arrhythmias in BrS patients. For a comprehensive review, we refer the reader to the current consensus statement published in 2009[21] or to the website, http://www.brugadadrugs.org. Our case series and a limited body of existing evidence report safe anesthetics using agents that theoretically are associated with possible problems when used in BrS patients, e.g. propofol (especially when given as a continuous infusion) and local anesthetics. In multiple studies, the β-agonist, isoproterenol, has been shown to be effective in normalizing ST segment elevations and in preventing electrical storm in BrS patients.

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Conflicts of interest None declared.

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