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Review / Derleme

Brugada syndrome and anesthesia

Brugada sendromu ve anestezi

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Brugada syndrome is a genetic disease leading to sudden cardiac death, which is characterized by a spontaneous or induced ST-segment elevation with right bundle branch block in V1-3 leads in electrocardiography in those without any structural heart disease. As there is a limited number of experiences on anesthetizing patients with Brugada syndrome, no consensus report for clinical practice has been available yet. In this systematic review, we discussed the anesthesia techniques, and the effects and safety of anesthesia applied in this rarely seen heart disease.

Key words: Anesthesia; anesthetic drug; Brugada syndrome.

Brugada sendromu, yapısal kalp hastalığı bulunmayanlarda, elektrokardiyografide V1-3 derivasyonlarında sağ dal bloku ile spontan ya da indüklenmiş ST-segment elevasyonu ile karakterize, ani kardiyak ölüme yol açan genetik bir hastalıktır. Brugada sendromu bulunan hastalarda anestezi uygulamasına ilişkin sınırlı sayıda deneyim mevcut olduğu için, klinik uygulamaya yönelik henüz bir uzlaşı raporu bulunmamaktadır. Bu sistematik derlemede nadir görülen bu kalp hastalığında uygulanan anestezi teknikleri ve anesteziklerin etkileri ve güvenliliği irdelendi.

Anahtar sözcükler: Anestezi; anestezik ilaç; Brugada sendromu.

Advances in the fields of both surgery and anesthesia have increased the possibility of encountering patients who have rare diseases, in addition to common diseases such as diabetes mellitus, hypertension chronic obstructive pulmonary disease, and hyper/hypothyroidism in clinical practice. Hence, knowing the pathophysiological and clinical features of uncommon diseases and establishing how prescribed medications affect the progression of these diseases is important. Accomplishing this would make it possible to prevent probable adverse outcomes like mortality. Brugada syndrome (BS), a rare disease that can lead to sudden cardiac death, has special significance in the practice of anesthesia.

Brugada syndrome, which was firstly defined by Pedro and Josep Brugada[1] in 1992, is a disease that has typical electrocardiographic findings. However, it can cause polymorphic ventricular tachycardia and fibrillation along with secondary sudden cardiac death without structural heart disease.[2] In fact, BS is responsible for 4-12% of sudden cardiac deaths.[3] Furthermore, it is associated with ethnic and geographical difference as well,[4] with estimates indicating that that there are higher numbers of cases in Southeastern Asia than Europe (1-5/10,000 vs. 12/10,000, respectively).[2] In addition, BS is seen more frequently in men[5] and has a channelopathy which causes arrhythmia as a result of electrical dysfunction.[4] Arrhythmias associated with BS are mostly often found in patients between the ages of 40 and 45[5] and emerge generally during sleep, rest, or after heavy meals.[2]

Specific electrocardiographic changes also occur with BS. Three types of repolarization patterns have been defined,[6] but the J wave amplitude is ≥2 mm in all of them. Types 2 and 3 contain ST-T configuration located in the saddleback. Type 1 has the coved-type configuration. In addition, types 2 and 3 occur when the ST-segment elevation is ≥1 mm, but in type 1, it gradually descends. The T wave is negative in the type

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1 repoloarization pattern, but it is positive in type 3, and can be positive or biphasic in type 2.[6] Even if all three changes are seen, only the type 1 electrocardiogram (ECG) pattern is diagnostic for BS.[7] To meet the criteria for a major diagnosis, patients must have more than one right pericardial derivation along with having ≥2 mm type 1 ST-segment elevation. Patients with the following any of the following conditions that can lead to similar ECG changes can be ruled out as having BS: arrhythmogenic right ventricular dysplasia/cardiomyopathy, acute myocardial ischemia or infarction, acute myocarditis, acute pulmonary thromboemboli, cocaine intoxication, a dissecting aortic aneurysm, Duchenne muscular dystrophy (DMD), early repolarization syndrome, Friedreich's ataxia, a heterocyclic antidepressant overdose, hypercalcemia, hyperkalemia, long QT syndrome (LQTS), right ventricular ischemia or infarction, right or left bundle branch block, left ventricular hypertrophy, thiamine deficiency, and various central and autonomic nervous system abnormalities) that can lead to similar ECG changes.[6] A diagnosis is then made with the patient based on patients having one of the following minor criteria: documented ventricular fibrillation, (self-terminating) polymorphic ventricular tachycardia, the induction of ventricular arrhythmias with programmed arrhythmias, electrical stimulation, a family history of sudden death before the age of 45, the presence of a coved-type repolarization pattern on the ECG in family members, syncope, and nocturnal agonal respiration. In addition, type 1 ST-segment elevations are also present (elevation ≥2 mm in more than one right precordial lead), either occurring spontaneously or after sodium-blocker exposure.[5]

Electrocardiogram results are sometimes normal in patients with BS; however, diagnostic changes may appear in some cases, for example fever, alcohol, mental stress, and class 1 anti-arrhythmic drug administration.[8,9] Therefore, the antiarrhythmics ajmaline,[10] flecainide,[11] procainamide,[12] pilsicainid[13] are applied in diagnostic tests. Autosomal recessive BS has a heterogeneous genetic basis and is associated with mutation in 10 genes (SCN5A, GPD1-L, CACNA1c, CACNB2, SCN1B, KCNE3, SCN3B, MOG1, KCNE5, KCND3). Loss of function has been seen in all of these except for KCNE3, KCNE5, and KCND3. Among patients with BS, the SCN5A gene association is seen the most (11%-18%).[2]

In BS, mortality can occur with even a single cardiac event. Hence, life-threatening arrhythmias and complications can be prevented by making an early diagnosis.[14] For patients who are diagnosed with BS, drugs which trigger type 1 ECG and/or ventricular arrhythmias should be discontinued, and they should forego items such as fever, alcohol, and mental stress which promote attacks.

There are two choices for the treatment of BS patients: an implantable cardioverter defibrillator (ICD) or pharmacological agents; however, the ICD is the only method that has been proven to prevent sudden cardiac deaths.[2] On the other hand, isoproterenol,[15] quinidine,[16] dysopyramide,[17] orciprenaline,[18] tedisamil,[19] cilostazol,[20] and dimethyl lithospermate B[21] are among the pharmacological agents which have been beneficial in the hindrance of an electrical storm.

Postema et al.[22] researched BS-related drugs and divided them into four groups: *(i)* drugs which should be avoided (ajmaline, flecainide, pilsicainide, procainamide, propafenone, amitriptyline, clomipramine, desipramine, lithium, bupivacaine, and propofol), *(ii)* drugs which are recommended to be avoided (amiodarone, lidocaine, verapamil, diltiazem, and imipramine), *(iii)* potential anti-arrhythmic drugs (isoproterenol, isoprenaline, and quinidine), and *(iv)* diagnostic drugs (ajmaline, flecainide, pilsicainide, and procainamide).

The perioperative period affects all of the organ systems. Neuroendocrine and hemodynamic changes due to factors associated with both surgery and anesthesia (drugs, intubation, position, regional blocks) can directly affect the cardiovascular system. Therefore, in this systematic research, we aimed to examine the anesthetic methods used for BS and determine how these affected patients with this disease.

METHODS

In order to investigate the anesthesia techniques, two authors analyzed the effects and safety of anesthetics used in patients with BS via an electronic literature review conducted on November 1, 2012 which covered the years between 1992 and 2012. No other literature review was performed. The following research terms and word combinations were entered into the Pubmed, Ovid, Science Direct databases: brugada syndrome and anesthesia, general anesthesia, spinal anesthesia, epidural anesthesia, propofol, thiopental, ethomidate, midazolam, ketamine, desflurane, sevoflurane, isoflurane, nitrous oxide, morphine, fentanyl, remifentanil, sufentanil, alfentanil, tramadol, meperidin, sugammadex, neostigmine, atropine, thiamylal, vecuronium, rocuronium, and succinylcholine. We began the research from 1992 when BS was first identified. We limited the investigation to English (full texts and abstracts), and the detailed data

(age, gender, number of patients, procedures employed, anesthesia techniques, anesthetics, and complications) found in the articles, including the abstracts. However, case reports that focused on propofol infusion syndrome (PRIS) were not included because of controversy concerning the use of propofol. We discovered a larger number of studies which stated that the combination of propofol and intravenous anesthesia do not create PRIS,[23] but this information was based mostly on case reports.[24,25] In addition, in these case reports, instead of interpreting the effects of propofol on patients who were definitely diagnosed with BS, they focused on the fact that propofol can cause BS-like ECG changes.

Our methodology was organized according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement which provides recommendations for systematic compilation.[26] Statistical analysis was carried out with the SPSS Windows version 16.0 software program (SPSS Inc. Chicago, IL, USA), and the data was presented as mean ± standard deviation or as a proportion.

RESULTS

The literature review produced 140 pertinent articles. After duplicates were removed, 58 articles were analyzed, and 25 of these met the criteria for inclusion (Table 1). All of the reports were composed of either a case report or a series of case reports, and a total of 43 cases were evaluated in the 25 articles. After statistical analysis, it was observed that most of the patients were male (39 males and 4 females), and the average age was 41.9±20.9 (Table 2).

The following procedures were employed: ICD (n=11, 25.6%), general surgery (n=8, 18.6%), neurosurgery (n=4, 9.3%), thoracic surgery (n=4, 9.3%), and other procedures (n=16, 37.2%). In addition, general anesthesia was used with 32 of the patients (74.4%), general/regional anesthesia was utilized for six (14%), regional anesthesia alone was used for three (7%) and sedation was needed for two others (4.7%) (Table 2).

The following intravenous anesthetics were used: propofol (n=25, 58.1%), midazolam (n=13, 30.2%), diazepam (n=10, 23.3%), thiopental (n=5, 11.6%), ketamine (n=2, 4.7%), thiamylal (n=2, 4.7%), and ethomidate (n=1, 2.3%). Furthermore, the following inhalational anesthetics were utilized: sevoflurane (n=22, 53.7%), nitrous oxide (N_2O) (n=14, 32.6%), isoflurane (n=6, 14%), desflurane (n=2, 4.7%), and enflurane (n=1, 2.3%). In addition, 31 patients used fentanyl (75.1%), two required (4.7%), two needed remifentanil (4.7%), and one patient was given morphine (2.3%). Neuromuscular blocker agents (NMBAs) were also employed in the following manner: 16 were prescribed vecuronium (37.2%), five used rocuronium (11.6%), another five utilized cisatracurium (11.6%), three were given succinylcholine (7%), and two used atracurium (4.7%). Local anesthetics were also distributed, with eight being prescribed bupivacaine (18.6%), five needing lidocaine (11.6%), and one receiving ropivacaine (2.3%). Finally, the anticholinesterases neostigmine (n=9, 20.9%) and sugammadex (n=2, 4.7%) were also prescribed along with the anticholinergic drugs glycopyrrolate (n=6, 14%) and atropine (n=2, 4.7%). Propofol was the most frequently used intravenous anesthetic (58.1%), and sevoflurane was the most commonly prescribed inhalation agent (53.7%). In addition fentanyl was the opioid used most often (75.1%), and vecuronium was the NMBA that was prescribed the most (37.2%) (Table 3).

However, in 28 (65.1%) of the cases, no complications were observed. However, when a complication was present, the most frequent was bradycardia in three patients (7%) followed by hypertension in three others (7%). Additionally, there was one case of mortality (2.3%) (Table 2).

DISCUSSION

It is seen that various anesthetic techniques (general or regional anesthesia and sedation) along with anesthetic drugs (intravenous and inhalation anesthetics, opioids, etc.) were employed in the BS cases in this study. The intravenous anesthetic propofol was used for both the induction[27-38] and maintenance of anesthesia[29,37-40] while midazolam was utilized for both premedication[31,34,37,38,41] and induction.[27,29,33] Only the one case in which ketamine and diazepam were used died,[42] and this was due to sedation with high-dose ketamine, which led to cardiac arrest.[43] Propofol is different from other intravenous anesthetics because it leads to PRIS in which occur BS-like ECG changes.[24,25] In addition, we discovered a case involving thiopental that had a clinically similar picture to the propofol case which, interestingly, occurred at about the same time.[44] On the other hand, Schmidt et al.[23] concluded in a study comprised of 6,161 patients that there was no link between propofol and total intravenous anesthesia regarding PRIS. In our opinion, this study demonstrated that a causal relationship linking mortality to propofol and PRIS could be established more clearly through prospective trials.

Our research also indicated that the inhalation anesthetics isoflurane,[27,45,46] desflurane,[27,34] sevoflur ane,[27-29,31-33,35,41,43,47-49] and N_2O[27,29,31,43,45,48] were safely

Table 1. Summary of patients with Brugada syndrome

Reference	Age/gender	Number	Procedure type	Anesthesia	Drugs	Outcome
Tsutsumi et al.[30]	61/M	1	ECT, (10 times)	GA	Propofol 50 mg, rocuronium 50 mg, sugammadex 4 mg.kg^{-1}	NC; Discharged
Chan and Dob[50]	22/F	1	C/S	CS/EA	Bupivacaine 5 mg (SA), fentanyl 25 μg (SA), bupivacaine 25 mg (EA)	NC; Discharged
Cole et al.[51]	40/F	1	C/S	SA	Bupivacaine 13.5 mg	NC; Discharged
Horigome et al.[42]	13/M	1	Coarctation of the aorta	GA	Induction (diazepam, ketamine, morphine), maintenance (enflurane, fentanyl)	VF; Exitus
Candiotti and Mehta[31]	26/M	1	Endoscopic sinus surgery	GA	Premedication (midazolam 2 mg, fentanyl 50 μg), induction (propofol 150 mg, rocuromium 40 mg), maintenance (sevoflurane, nitrous oxide, fentanyl 200 μg), neostigmine 3.5 mg, glycopyrrolate 0.7 mg	NC; Discharged
Cordery et al.[48]	16/M	1	ICD insertion	GA	Induction (fentanyl 100 μg, propofol 150 mg, atracurium 30 mg), maintenance (nitrous oxide, sevoflurane), neostigmine 2.5 mg, glycopyrrolate 0.5 mg.	NC; Discharged
Fuyuta et al.[32]	72/M	1	Resection of a metastatic brain tumor	GA	Induction (remifentanil 0.3 μg.kg^{-1}.min^{-1}, lidocaine 40 mg, propofol 80 mg, 50 mg rocuronium) maintenance (sevoflurane, remifentanil)	Cardiac arrest Discharged
Baty et al.[41]	7/M	1	Repair of a right inguinal hernia	GA	Premedication (oral midazolam 0.5 mg.kg^{-1}), induction (sevoflurane, nitrous oxide), maintenance (fentanyl 1.5 μg.kg^{-1}, sevoflurane), infiltration anesthesia (11 mL of 0.25% bupivacaine)	NC; Discharged
Phillips et al.[33]	77/M	1	Gastrectomy	GA/EA	EA (bupivacaine 10 mL 0.25%, infusion of 0.125% bupivacaine and 2.5 μg.mL^{-1} fentanyl at 8 mL.h^{-1}), Induction (midazolam 2 mg, propofol 150 mg, fentanyl, 200 μg, rocuronium 50 mg), maintenance (sevoflurane)	NC; Discharged
Kapoor-Katari and Neustein[34]	19/M	1	Closure and free flap of an anterior chest wall wound	GA	Premedication (midazolam 2 mg, fentanyl 100 μg), induction (propofol 140 mg, vecuronium 8 mg), maintenance (desflurane, vecuronium 20 mg, fentanyl)	NC; Discharged
Edge et al.[45]	52/M	1	Laparotomy	GA/EA	Induction (thiopental 5 mg.kg^{-1}, succinylcholine 100 mg, fentanyl 100 μg), maintenance (nitrous oxide, isofurane, vecuronium), neostigmine 2.5 mg, glycopyrrolate 0.5 mg. EA (0.25% bupivacaine 10 mL, fentanyl 20 mg)	NC; Discharged
Santambrogio et al.[28]	25-43/M	4	Appendectomy, Varicocelectomy, TURP	GA	Premedication (diazepam oral), induction (propofol, fentanyl, cisatracurium), maintenance (sevoflurane, cisatracurium, fentanyl)	NC; Discharged
Fujiwara et al.[35]	68/M	1	Distal gastrectomy.	GA/PNB	Induction (propofol, fentanyl, vecuronium), maintenance (sevoflurane, fentanyl), PNB (40 mL of 0.5% ropivacaine)	Hypotension; Discharged
Konishi et al.[36]	60/M	1	ECT (8 times)	GA	Induction (propofol 2 mg.kg^{-1}, rocuronium 1.2 mg.kg^{-1}), sugammadex (10 mg.kg^{-1})	NC; Discharged
Inamura et al.[29]	51-63/M	6	ICD	GA	Premedication (diazepam), induction (propofol, vecuronium, fentanyl; one of six midazolam, vecuronium, fentanyl; lidocaine was used two of six), maintenance (two of six: propofol, fentanyl; four of six: sevoflurane, fentanyl, nitrous oxide) hypotension, bradycardia	Discharged
Richter and Brugada[39]	39/M	1	Catheter ablation	SA	Propofol (1%, up to 70 mL.h^{-1})	ST-elavation; Discharged;

Table 1. Continued

Reference	Age/gender/	Number	Procedure type	Anesthesia	Drugs	Outcome
Kloesel et al.[27]	16-60 8 M 8 F	7 of 1 of 8	Inguinal herniorrhaphy, vaginal delivery, tooth extraction, sinus surgery, neurofibroma resection, ICD follow up testing, thoracic laminectomy with cavernoma resection, prostate biopsy, shoulder mass excision	GA, MAC, EA	Induction (1 of 8 thiopental, 5 of 8 propofol, 1 of 8 ethomidate, 3 of 8 lidocaine, 6 of 8 fentanyl, 6 of 8 midazolam, 3 of 8 vecuronium, 3 of 8 succinylcholine), maintenance (sevoflurane, propofol, desflurane, isoflurane, midazolam, fentanyl, remifentanil, nitrous oxide), neostigmine, glycopyrrolate (2 of 8 patients) EA (bupivacaine)	Bradycardia; Hypotension; Hypoxia; Hypertension; Tachycardia; Discharged
Kaneda et al.[49]	71/M	1	Left upper lobectomy	GA/EA	Induction (sevoflurane), maintenance (sevoflurane)	VF; Discharged
Lopez-Jinemez et al.[47]	54/M	1	Release and instrumentation of L4-L5-S1	GA	Induction (fentanyl 30 μg, cisatracurium 6 mg, ethomidate 20 mg), maintenance (sevoflurane, fentanyl)	Bradycardia Discharged
Goraksha et al.[37]	14/M	1	ICD	GA	Premedication (midazolam 1 mg), induction (propofol 1.5 mg.kg^{-1}, fentanyl 1μg.kg^{-1}, atracurium 0.5 mg.kg^{-1}), maintenance (propofol, atracurium), neostigmine, glycopyrrolate	NC; Discharged
Kim et al.[46]	33, 56/M	2	Open fracture of the patella, L1 vertebral body compression fracture	SA/GA	SA (0.5% bupivacaine), induction (thiopenthal sodium, vecuronium, fentanyl), maintenance (isoflurane)	NC; Discharged
Canbay et al.[43]	3.5/M	1	ICD (twice)	Sa/GA	Sa (midazolam 0.007 mg.kg^{-1} oral, ketamine 5 mg.kg^{-1} IV), GA: induction (thiopental 5 mg.kg^{-1}, vecuronium 0.1 mg.kg^{-1}, fentanyl 1 μg.kg^{-1}), maintenance (sevoflurane, nitrous oxide)	Cardiac arrest (1st) NC (2nd), Discharged
Vernooy et al.[40]	56/M	1	Lung volume reduction surgery	GA/EA	Propofol 2.5 mg.kg^{-1}.h^{-1} EA (bupivacaine 0.25% and sufentanyl 1 μg.mL^{-1} at 7 mL.h^{-1}) Discharged	ST-segment elevation.
Vaccarella et al.[38]	69/F	1	Colpohysterotomy	GA	Premedication (midazolam), induction (propofol 1.5 mg.kg^{-1}, fentanyl 100 μg, succinylcholine 1 mg.kg^{-1}), maintenance (propofol 6-7 mg.kg^{-1}.h^{-1}, fentanyl 1 μg.kg^{-1} boluses, atracurium 0.5 mg.kg^{-1})	NC; Discharged
Hayashida and Miyauchi[54]	51, 56/M	2	Percutaneous nephrolithotripsy, Plate fixation	GA	Induction (thiamylal 4 mg.kg^{-1}, vecuronium 0.1 mg.kg^{-1}), Maintain (isoflurane, nitrous oxide) Neostigmine 0.02 mg.kg^{-1}, atropine 0.02 mg.kg^{-1}	NC; Discharged

ECT: Electroconvulsive therapy; GA: General anesthesia; NC: No complication; EA: Epidural anesthesia; C/S: Caesarian section; Sa: Sedoanalgesia; SA: Spinal anesthesia; ICD: Implantable cardioverter-defibrillator; TURP: Transurethral resection of the prostate PNB: Peripheral nerve block; ECT: Electroconvulsive therapy; MAC: Monitored anesthesia care; VF: Ventricular fibrillation.

Table 2. Analysis of demographical and perioperative data

	n	%	Mean±SD
Age (years)			41.90±20.94
Gender			
Male	39	90.7	
Female	4	9.3	
Procedures			
Others	16	37.2	
Implantable cardioverter-defibrillator	11	25.6	
General surgery	8	18.6	
Neurosurgery	4	9.3	
Thoracic surgery	4	9.3	
Anesthesia			
General anesthesia	32	74.4	
General/regional anesthesia	6	14	
Regional anesthesia	3	7	
Sedation	2	4.7	
Complications			
None	28	65.1	
Bradycardia	3	7	
Hypotension	3	7	
Ventricular fibrillation	2	4.7	
Cardiac arrest	2	4.7	
ST-segment elevation	2	4.7	
Hypoxia	1	2.3	
Hypertension	1	2.3	
Tachycardia	1	2.3	
Outcome			
Discharged	42	97.7	
Mortality	1	2.3	

SD: Standard deviation.

Table 3. Analysis of anesthetic drugs

	n	%
Intravenous anesthetics		
Propofol	25	58.1
Midazolam	13	30.2
Diazepam	10	23.3
Thiopental	5	11.6
Ketamine	2	4.7
Thiamylal	2	4.7
Ethomidate	1	2.3
Inhalation anesthetics		
Sevoflurane	22	53.7
Nitrous oxide	14	32.6
Isoflurane	6	14
Desflurane	2	4.7
Enflurane	1	2.3
Opioids		
Fentanyl	31	75.1
Sufentanil	2	4.7
Remifentanil	2	4.7
Morphine	1	2.3
Neuromuscular blocker agent		
Vecuronium	16	37.2
Rocuronium	5	11.6
Cisatracurium	5	11.6
Succinylcholine	3	7
Atracurium	2	4.7
Local anesthetics		
Bupivacaine	8	18.6
Lidocaine	5	11.6
Ropivacaine	1	2.3
Anticholinesterases		
Neostigmine	9	20.9
Sugammadex	2	4.7
Anticholinergics		
Glycopyrrolate	6	14
Atropine	2	4.7

used; however, the patient who received enflurane died.[42] The opioids fentanyl,[28,31-35,37,38,41-43,45-48,50] sufentanil,[40] morphine,[42] and remifentanil[28,32] were frequently prescribed as adjuvants to general anesthesia. Two patients were also given opioids via an epidural.[33,40] However, there have been no reports of adverse effects associated with this type of medication. Furthermore, although there have not been reported any experience of anesthesia with tramadol in patients with BS, it has been seen that tramadol has led to BS-like ECG changes.[51] All opioids except high-dose morphine, caused reversible suppression of sodium channels, but as long the patients took the prescribed dosage, they were safe.[52]

Local anesthetics like bupivacaine,[33,40,45,46,50,53] lidocaine,[27,29,32] and ropivacaine[35] are also prescribed for BS patients. Of these, lidocaine is generally given in low doses and is safe when used as an adjuvant in induction. However, the study by Vernooy et al.[40] clearly established a correlation between bupivacaine given via an epidural and impairment of the clinical picture.

Our patients also received the NMBAs vecuronium,[27,29,34,35,43,45,46,54] rocuronium,[30-33,36] cisatracurium,[28,47] succinylcholine,[27,38,45] and atracurium[37,38,48] but succinylcholine is not normally used because of its adverse effects.[29] As an anticholinesterase agent, neostigmine is also avoided because it can lead to ST-segment elevation in BS patients.[54] Nevertheless, neostigmine[27,31,37,44,45] was the most frequently chosen agent in our cases to reverse the effects of NMBAs. Hayashida et al.[54] applied as much as half of a normal dose of neostigmine with atropine for the purpose of ST-segment depression due to the effect of atropine. However, concerns about neostigmine have led some authors to prefer

sugammadex, which was used safely in two of the reported cases.[30,36] Additionally, we found that atropine was selected for use in only one case[54] and that glycopyrrolate[27,31,45,48] was more commonly applied as an anticholinergic agent.

In BS, sudden cardiac death develops secondary to polymorphic ventricular tachycardia and fibrillation. For this reason, it is necessary to take into account the possible arrhythmogenic effects of anesthetic agents. Volatile anesthetics like isoflurane, sevoflurane, and desflurane do not predispose patients to ventricular arrhythmias, and they do not sensitize the heart to the arrhythmogenic effects of epinephrine, with the exception of halothane.[55] At the same time, volatile anesthetics reduce, in a dose-dependent fashion, the arterial baroreflex modulation of the heart rate and blood pressure.[55] Moreover, propofol is especially known for causing rare cardiac events, including severe bradycardia, sinus arrest, heart block, and asystole.[56] In contrast, intravenous anesthetics cause a decrease in blood pressure and an increase in the heart rate, with ketamine being the only drug in this category that causes elevated blood pressure.[56] The recommended induction dose of ketamine is 0.5-1.0 $mg.kg^{-1}$ intravenously or 2-4 $mg.kg^{-1}$ intramuscularly.[56] Therefore, in the case report by Canbay et al.,[43] the dose of ketamine with midazolam was too high for sedation, resulting in cardiac arrest of patient.

Although bradycardia and hypertension were seen frequently in the patients with BS, anesthesia application was generally carried out without complications. In fact, there was only one case in which this might have played in role in the mortality of a patient,[42] but major surgery most likely also contributed. Although propofol was used safely in most of the cases, it was noteworthy that some patients developed complications due to this drug.

A website (http://www.brugadadrugs.org) has recommended that propofol and bupivacaine not be used as anesthetics for BS patients and that lidocaine, ketamine, and tramadole should preferably be avoided.[57] Barajas-Martínez et al.[58] stated that lidocaine creates a BS-like ECG pattern. However, no proof has been offered that shows a connection between adverse outcomes and the anesthetic application of lidocaine in BS. In addition, there were two case reports that mentioned the BS-like ECG changes that occurred with ketamine[59] and tramadol,[52] but these were related to overdose not anesthesia.

In most cases of BS, general anesthesia is preferred. Vernooy et al.[40] have tried no other local anesthetic except for bupivacaine. Therefore, it is difficult to determine whether bupivacaine or the anesthetic technique they have used was responsible for the worsening clinical conditions in the patients in their study. General anesthesia was also used for the patient who died;[42] however, it is important to reiterate that the patient also underwent major surgery. In one patient for whom an ICD had been inserted, the first application of anesthesia resulted in cardiac arrest, but general anesthesia was performed without any further complications.[43] In that case, the cardiac arrest was associated with the larger dose of ketamine (5 $mg.kg^{-1}$) and not the anesthetic technique.

Our research had two significant limitations. Not only did we evaluate only English sources, but we also excluded cases involving PRIS. Being unable to access full texts or at least abstracts of Asian case reports that met our criteria of inclusion[60-63] meant we had to ignore articles in countries where the incidence of BS is the highest. Moreover, although BS-like ECG changes occur in PRIS cases and these changes are regarded as an early indicator of death, no gene analysis was carried out for these patients.[64] Therefore, no clear connection between PRIS and BS could be established.

In conclusion, patients with family members who have experienced sudden death must be carefully evaluated for BS in the preoperative period. Prior to any surgical procedures, the patients must be monitored and a defibrillator must be made available in the operating room. However, after the necessary research has been done and the probable risk classification[65] has been determined for those who are thought to have BS, anesthetic agents can be carefully applied by taking into account their pharmacological features and potential adverse effects.

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REFERENCES

1. 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.
2. Berne P, Brugada J. Brugada syndrome 2012. Circ J 2012;76:1563-71.
3. 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.
4. Brugada P, Benito B, Brugada R, Brugada J. Brugada syndrome: update 2009. Hellenic J Cardiol 2009;50:352-72.
5. Brugada J, Brugada R, Antzelevitch C, Towbin J, Nademanee K, Brugada P. Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V1 to V3. Circulation 2002;105:73-8.
6. Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, et al. Proposed diagnostic criteria for the Brugada syndrome: consensus report. Circulation 2002;106:2514-9.
7. 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.
8. Nademanee K, Veerakul G, Nimmannit S, Chaowakul V, Bhuripanyo K, Likittanasombat K, et al. Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. Circulation 1997;96:2595-600.
9. Antzelevitch C. Brugada syndrome. Pacing Clin Electrophysiol 2006;29:1130-59.
10. Wolpert C, Echternach C, Veltmann C, Antzelevitch C, Thomas GP, Spehl S, et al. Intravenous drug challenge using flecainide and ajmaline in patients with Brugada syndrome. Heart Rhythm 2005;2:254-60.
11. Meregalli PG, Ruijter JM, Hofman N, Bezzina CR, Wilde AA, Tan HL. Diagnostic value of flecainide testing in unmasking SCN5A-related Brugada syndrome. J Cardiovasc Electrophysiol 2006;17:857-64.
12. Joshi S, Raiszadeh F, Pierce W, Steinberg JS. Antiarrhythmic induced electrical storm in Brugada syndrome: a case report. Ann Noninvasive Electrocardiol 2007;12:274-8.
13. Takagi M, Doi A, Takeuchi K, Yoshikawa J. Pilsicanide-induced marked T wave alternans and ventricular fibrillation in a patient with Brugada syndrome. J Cardiovasc Electrophysiol 2002;13:837.
14. Tatlı E, Gül Ç, Sürücü H, Özçelik F. Brugada sendromunda tanı, klinik seyir ve tedavi yaklaşımı. Turkiye Klinikleri J Med Sci 2005;25:560-4.
15. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, et al. ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation 2006;114:e385-484.
16. Schweizer PA, Becker R, Katus HA, Thomas D. Successful acute and long-term management of electrical storm in Brugada syndrome using orciprenaline and quinine/quinidine. Clin Res Cardiol 2010;99:467-70. doi: 10.1007/s00392-010-0145-7.
17. Sumi S, Maruyama S, Shiga Y, Kodama S, Miyoshi K, Tojou H, et al. High efficacy of disopyramide in the management of ventricular fibrillation storms in a patient with Brugada syndrome. Pacing Clin Electrophysiol 2010;33:e53-6. doi: 10.1111/j.1540-8159.2009.02665.x.
18. Kyriazis K, Bahlmann E, van der Schalk H, Kuck KH. Electrical storm in Brugada syndrome successfully treated with orciprenaline; effect of low-dose quinidine on the electrocardiogram. Europace 2009;11:665-6. doi: 10.1093/europace/eup070.
19. Wettwer E, Himmel HM, Amos GJ, Li Q, Metzger F, Ravens U. Mechanism of block by tedisamil of transient outward current in human ventricular subepicardial myocytes. Br J Pharmacol 1998;125:659-66.
20. Abud A, Bagattin D, Goyeneche R, Becker C. Failure of cilostazol in the prevention of ventricular fibrillation in a patient with Brugada syndrome. J Cardiovasc Electrophysiol 2006;17:210-2.
21. Fish JM, Welchons DR, Kim YS, Lee SH, Ho WK, Antzelevitch C. Dimethyl lithospermate B, an extract of Danshen, suppresses arrhythmogenesis associated with the Brugada syndrome. Circulation 2006;113:1393-400.
22. 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. doi: 10.1016/j.hrthm.2009.07.002.
23. Schmidt J, Hering W, Albrecht S. Total intravenous anesthesia with propofol and remifentanil. Results of a multicenter study of 6,161 patients. Anaesthesist 2005;54:17-28. [Abstract]
24. Kam PC, Cardone D. Propofol infusion syndrome. Anaesthesia 2007;62:690-701.
25. Fudickar A, Bein B, Tonner PH. Propofol infusion syndrome in anaesthesia and intensive care medicine. Curr Opin Anaesthesiol 2006;19:404-10.
26. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535. doi: 10.1136/bmj.b2535.
27. 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. doi: 10.1007/s12630-011-9546-y.
28. 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.
29. 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.
30. Tsutsumi YM, Tomiyama Y, Horikawa YT, Sakai Y, Ohshita N, Tanaka K, et al. General anesthesia for electroconvulsive therapy with Brugada electrocardiograph pattern. J Med Invest 2011;58:273-6.
31. Candiotti KA, Mehta V. Perioperative approach to a patient with Brugada syndrome. J Clin Anesth 2004;16:529-32.
32. Fuyuta M, Nakao S, Takai N, Shiba M, Tanaka Y, Iwamoto T, et al. Sudden Cardiac Arrest During General Anesthesia in an Undiagnosed Brugada Patient. J Cardiothorac Vasc Anesth 2012. pii: S1053-0770(12)00419-3. doi: 10.1053/j.jvca.2012.08.007. [Epub ahead of print]

33. Phillips N, Priestley M, Denniss AR, Uther JB. Brugada-type electrocardiographic pattern induced by epidural bupivacaine. Anesth Analg 2003;97:264-7.
34. Kapoor-Katari K, Neustein SM. General anesthesia for a patient with Brugada syndrome. Middle East J Anesthesiol 2012;21:743-6.
35. 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.
36. Konishi J, Suzuki T, Kondo Y, Baba M, Ogawa S. Rocuronium and sugammadex used effectively for electroconvulsive therapy in a patient with Brugada syndrome. J ECT 2012;28:e21-2. doi: 10.1097/YCT.0b013e31824b74f5.
37. 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. doi: 10.4103/0019-5049.72648.
38. Vaccarella A, Vitale P, Presti CA. General anaesthesia in a patient affected by Brugada syndrome. Minerva Anestesiol 2008;74:149-52.
39. Richter S, Brugada P. Propofol-induced coved-type electrocardiogram during catheter ablation of paroxysmal atrial fibrillation. A case of Brugada syndrome? Herzschrittmacherther Elektrophysiol 2012;23:56-8. doi: 10.1007/s00399-011-0156-8.
40. 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.
41. 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. doi: 10.1177/0885066608315823.
42. Horigome H, Shigeta O, Kuga K, Isobe T, Sakakibara Y, Yamaguchi I, et al. Ventricular fibrillation during anesthesia in association with J waves in the left precordial leads in a child with coarctation of the aorta. J Electrocardiol 2003;36:339-43.
43. 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.
44. Enting D, Ligtenberg JJ, Aarts LP, Zijlstra JG. Total suppression of cerebral activity by thiopental mimicking propofol infusion syndrome: a fatal common pathway? Anesth Analg 2005;100:1864-5.
45. Edge CJ, Blackman DJ, Gupta K, Sainsbury M. General anaesthesia in a patient with Brugada syndrome. Br J Anaesth 2002;89:788-91.
46. Kim JS, Park SY, Min SK, Kim JH, Lee SY, Moon BK, Chae YJ. Anaesthesia in patients with Brugada syndrome. Acta Anaesthesiol Scand 2004;48:1058-61.
47. Lopez-Jinemez FA, Mondragon-Villanueva ME. Brugada syndrome and anesthesia. Rev Mex Anesthesiol 2008;31:54-61.
48. Cordery R, Lambiase P, Lowe M, Ashley E. Brugada syndrome and anesthetic management. J Cardiothorac Vasc Anesth 2006;20:407-13.
49. Kaneda Y, Fujita N, Ueda K, Saeki K, Sakano H, Sudo M, et al. Surgically treated primary lung cancer associated with Brugada syndrome: report of a case. Surg Today 2001;31:817-9
50. Chan TM, Dob DP. The anaesthetic management of a parturient with polymorphic catecholamine-sensitive ventricular tachycardia. Int J Obstet Anesth 2002;11:122-4.
51. Cole JB, Sattiraju S, Bilden EF, Asinger RW, Bertog SC. Isolated tramadol overdose associated with Brugada ECG pattern. Pacing Clin Electrophysiol 2012;35:e219-21. doi: 10.1111/j.1540-8159.2010.02924.x.
52. Haeseler G, Foadi N, Ahrens J, Dengler R, Hecker H, Leuwer M. Tramadol, fentanyl and sufentanil but not morphine block voltage-operated sodium channels. Pain 2006;126:234-44.
53. Bramall J, Combeer A, Springett J, Wendler R. Caesarean section for twin pregnancy in a parturient with Brugada syndrome. Int J Obstet Anesth 2011;20:181-4. doi: 10.1016/j.ijoa.2010.10.006.
54. Hayashida H, Miyauchi Y. Anaesthetic management in patients with high-risk Brugada syndrome. Br J Anaesth 2006;97:118-9.
55. Ebert TJ, Lindenbaum L. Clinical pharmacology of inhaled anesthetics. In: Evers AS, Maze M, Kharasch ED, editors. Anesthetic pharmacology. Cambridge. Cambridge University Press; 2011. p. 317-419.
56. Sear JW. Clinical pharmacology of intravenous anesthetics. In: Evers AS, Maze M, Kharasch ED, editors. Anesthetic pharmacology. Cambridge. Cambridge University Press; 2011. p. 444-65.
57. Drugs preferably avoided by Brugada syndrome patients Avaible from: http://www.brugadadrugs.org/ [Accessed: December 10, 2012].
58. Barajas-Martínez HM, Hu D, Cordeiro JM, Wu Y, Kovacs RJ, Meltser H, et al. Lidocaine-induced Brugada syndrome phenotype linked to a novel double mutation in the cardiac sodium channel. Circ Res 2008;103:396-404. doi: 10.1161/CIRCRESAHA.108.172619.
59. Rollin A, Maury P, Guilbeau-Frugier C, Brugada J. Transient ST elevation after ketamine intoxication: a new cause of acquired brugada ECG pattern. J Cardiovasc Electrophysiol 2011;22:91-4. doi: 10.1111/j.1540-8167.2010.01766.x.
60. Kawaguchi Y, Kushikata T, Hashiba E, Kitayama M, Yoshida H, Ishihara H, et al. Anesthetic management for patients with Brugada syndrome. Masui 2006;55:142-9. [Abstract]
61. Kohda K, Sugano T, Shibama S, Harada M, Satoh Y, Ide Y, et al. Preoperative evaluation and anesthetic management of a patient with Brugada syndrome-like ECG. Masui 2007;56:1398-403. [Abstract]
62. Yatabe T, Hirohashi M, Takeuchi S, Maeda Y, Yamashita K, Yokoyama M. Case of ventricular fibrillation in patients with brugada type electrocardiogram during surgery. Masui 2011;60:728-32. [Abstract]
63. Hiuge Y, Ohta N, Hirata T, Mori T. Anesthetic management of two patients with Brugada-type ECG and of different clinical severity. Masui 2004;53:693-5. [Abstract]
64. Vernooy K, Delhaas T, Cremer OL, Di Diego JM, Oliva A, Timmermans C, et al. Electrocardiographic changes predicting sudden death in propofol-related infusion syndrome. Heart Rhythm 2006;3:131-7.
65. Priori SG, Napolitano C, Gasparini M, Pappone C, Della Bella P, Giordano U, et al. Natural history of Brugada syndrome: insights for risk stratification and management. Circulation 2002;105:1342-7.