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REVIEW

Intensive care and anesthetic management of patients with Brugada syndrome and COVID-19 infection

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Abstract

Coronavirus disease 2019 (COVID-19) spreads across the world, and the intensive care unit (ICU) community must prepare for the challenges associated with this pandemic viral infection. Rapid diagnosis, isolation, and intensive clinical management are very important for all patients with COVID-19, especially for those with cardiac diseases as Brugada syndrome (BrS). BrS is an arrhythmogenic disease reported to be one among the leading causes of sudden cardiac death. In these patients, episodes of lethal arrhythmias may be induced by several factors or situations, and for this reason management during ICU permanence or anesthesia must provide some precautions, avoiding factors that are known to have the potential to worsen the probability to induce arrhythmias. For ICU practitioners, management of acute respiratory failure, hemodynamics, and cardiovascular complications certainly are the key for the best treatment of these patients but to date specific data on supportive ICU care for these patients are lacking, and current recommendations are based on existing evidence from other viral infections and general intensive care management. We want to focus on some general rules, resulted from cases series and clinical practice, to be followed during the ICU management of patients with BrS and concomitant COVID-19 infection.

KEYWORDS
anesthesia, Brugada syndrome, COVID-19 infection, drugs, ICU management

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) spreads worldwide, the number of people diagnosed is constantly increasing, and the intensive care unit (ICU) community must prepare for the challenges associated with this pandemic viral infection. The fatality rates available today should be interpreted with caution, because they vary across countries, are higher in strained health-care systems, and do not account for undiagnosed patients with mild disease.

As now known from clinical practice, COVID-19 patients may develop severe cardiac complications such as myocarditis, heart failure, and arrhythmias.[1] For this reason, a rapid diagnosis, isolation, and intensive clinical management are very important for all patients with COVID-19, especially for those with cardiac diseases as Brugada syndrome (BrS).

BrS is an arrhythmogenic disease reported to be one among the leading causes of cardiac death in subjects under the age of 40 years. Global prevalence of BrS varies from five to 20 in every 10 000 inhabitants worldwide, and it is considered endemic in Asian and Southeast Asian countries. Patients with BrS are at high arrhythmic risk and they may present with syncope due to ventricular arrhythmias as polymorphic ventricular tachycardia, ventricular fibrillation, or aborted cardiac arrest.([1,2] As far as we know, inheritance of BrS occurs via an autosomal dominant mode of transmission, and about 18 genes have been associated with BrS, and thus far genetic abnormalities are found in 30-50% of genotyped BrS patients; especially mutations in the cardiac sodium channel gene SCN5A are identified in 11-28% of patients with BrS. Since genotype remains lacking for at least half of probands, a negative genetic test does not rule out BrS.

TABLE 1 Precautions and general rules during ICU management of patients with Brugada syndrome and COVID-19 infection

Precautions and general rules during ICU management of patients with Brugada syndrome and COVID-19 infection
a. Continuous ECG recording and monitoring of temperature, arterial blood pressure, bispectral index, degree of neuromuscular block.
b. External defibrillation pads have always to be applied.
c. Fever is an element to be monitored immediately with adequate treatment of pyrexia.
d. Avoid unintentional parasympathetic stimulation, thermal variations, and periods of bradycardia.
e. Provide adequate analgesia in order to prevent potential arrhythmias that may be triggered by changes of the autonomic tone.
f. If necessary management of pacemakers and ICD should be performed under the supervision of a cardiologist/electrophysiologist.
g. Isoproterenol and quinidine ready for use in case of arrhythmic storm.

Febrile states, dysionia, and many drugs may unmask the electrocardiographic concealed electrocardiogram (ECG) manifestations of BrS and may precipitate episodes of ventricular arrhythmias in these patients.[2]

In patients with COVID-19 infection to date many questions on ICU management remain difficult to clarify, including the significance of associated myocardial dysfunction, arrhythmic risk, thromboembolic complications, the role of noninvasive ventilation, pharmacological management of fever, and various others purposed and experimental therapies. Specific and large data on supportive ICU care for these patients are lacking, and to date the recommendations are based on existing evidence from other viral respiratory infections and general intensive care management.[1–3]

1.1 | General recommendations

COVID-19 patients, in addition to known respiratory problems, may develop severe cardiac complications such as myocarditis, heart failure with hemodynamic impairment, and arrhythmias.[1,4] For these reasons, patients with structural or primarily arrhythmic heart disease are at greater risk of complications and death. Especially in BrS patients, any factor that unbalances the parasympathetic and sympathetic traffic may precipitate a lethal arrhythmia. Episodes of arrhythmias can also be induced during ICU management or anesthesia by episodes of sinus bradycardia, anesthetics, vagotonic agents, beta-adrenergic blockers, alpha-adrenergic agonists, thermal variations, hypovolemia, hyperkalemia, hypokalemia, and hypercalcemia.[3]

Patients with COVID-19 might have hypovolemia due to high fever, anorexia, vomiting, and diarrhea but fluids should be administered cautiously, with assessments for preload responsiveness such as the passive leg raise test, given the high incidence of concomitant myocardial dysfunction. A conservative fluid strategy, with early detection of myocardial involvement through the blood measurement of troponin and beta-natriuretic peptide and echocardiography, is recommended as also early use of vasopressors, inotropes, or extracorporeal membrane oxygenation.[5]

Regarding general rules about ICU management of patients with BrS and COVID-19 infection, we can affirm that these patients require special vigilance, and external defibrillation pads have always to be applied. A continuous ECG recording and monitoring of some parameters such as temperature, arterial blood pressure, the degree of neuromuscular block, and bispectral index (monitoring of anesthetic depth for preventing very deep anesthesia which increases vagal tone by suppression of sympathetic system) are very important (Table 1).

With regard to fever in patients with BrS and SCN5A gene mutation, a premature inactivation of the sodium channel has been shown at higher temperatures (Figure 1). For this reason, a febrile state may unmask the syndrome and determine the occurrence of arrhythmic events. Therefore, during any flu or flu-like syndrome, fever is an element to be monitored immediately at the onset with a prompt and adequate treatment of pyrexia.[3,4] Thermal variations may induce tachyarrhythmias, so the core temperature should be monitored with attention, especially in surgery or long duration sedation. Avoid unintentional parasympathetic stimulation is also important because ventricular arrhythmias in these patients usually occur during periods of bradycardia and increased vagal tone. For this reason, we provide adequate analgesia in order to prevent potential arrhythmias that may be triggered by changes of the autonomic tone.

1.2 | Cardiovascular implantable electronic device management

Permanent cardiac pacemakers and implantable cardioverter defibrillators (ICDs) can be collectively referred to as cardiac implantable electronic devices (CIEDs). The type of CIED can be identified through history-taking, patient medical records, CIED information cards, and chest radiography. In ICU management of these patients, it is useful to involve the cardiologist/electrophysiologist, as a multidisciplinary approach to perioperative CIED management ensures better outcomes because the main concern is the possible effects of electromagnetic interference on device function.

If patient has an ICD, the eventual ICU management of the device should be performed under the supervision of a cardiologist/electrophysiologist, and the ICD should be programmed with turned off of antitachycardia therapies only before surgery to prevent inappropriate shocks due to monopolar surgical diathermy. If no programmer is available, another easy way to deactivate therapies in an ICD is to place a magnet on top of the ICD pocket, this will inactivate the ICD therapies without affecting its pacing capabilities.

In patients who are entirely dependent on ventricular pacing, the device should be switched to a nonsensing mode (VOO or DOO) only

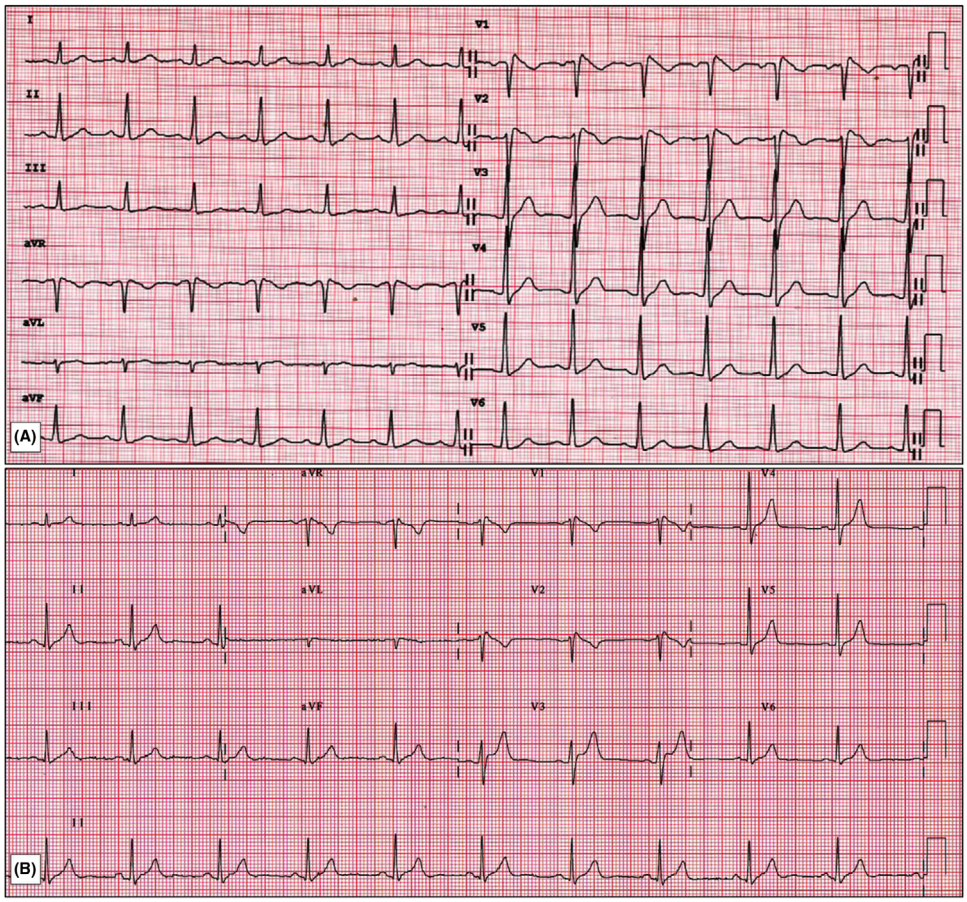

FIGURE 1 A, ECG with pronounced coved-type Brugada pattern in conjunction with fever. B, ECG after fever resolution with minor expression of coved-type Brugada pattern [Color figure can be viewed at wileyonlinelibrary.com]

during surgery so that noise and oversensing do not occur on catheters with a subsequent inhibition of the stimulation. The time spent in non-sensing mode should be limited the more possible to prevent a potential R on T phenomenon.

In case of arrhythmic storm, isoproterenol as first choice and quinidine may be used in patients with ICD and multiple shocks.[3,7,8]

1.3 | ICU drug management

In the anesthesia management of BrS patients with or without COVID-19 infection, the decision of using each drug must be made after careful consideration and in controlled conditions, avoiding drugs and other factors that are known to have the potential to induce arrhythmias (Table 2).

For these patients to date, there are some recommendations for general and regional anesthesia, and these measures are derived from clinical cases and from daily clinical practice.[3]

General anesthesia can be performed safely in these patients, both as inhalational and as balanced with opiates and induction agents as propofol, thiopental, and etomidate. Propofol bolus or infusion, commonly used as an induction agent for preoperative sedation in the ICU, was noted to have significant ST segment elevations in Brugada patients.[8] It may also induce propofol infusion syndrome (PRIS), characterized by development of metabolic acidosis and cardiac dysfunction along with at least one of rhabdomyolysis, hypertriglyceridemia, or renal failure. 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 and has also been found to inhibit cardiac L-type calcium channels, attenuate beta-adrenergic signal transduction, and augment acetylcholine receptor activity. This is a rare complication that affects patients undergoing long-term treatment with high doses of intravenous propofol, and cardiovascular manifestations of PRIS include widening of QRS complex, Brugada type 1 ECG pattern, ventricular tachyarrhythmias, cardiogenic shock, and asystole.[3,10]

To date, clinical experience does not support the recommendation of avoiding bolus dosing for induction in BrS patients, and propofol infusion for maintenance of general anesthesia is probably safe if duration and dose are limited but extreme caution is recommended when BrS patients are sedated with propofol for longer periods, and electrocardiographic changes in patients receiving propofol infusion may warn the clinician. It is recommended that for long-term sedation, propofol dose should not exceed 4 mg/kg/h, and arterial blood gases, serum

TABLE 2 Drugs to be avoided or used with caution in patients with Brugada syndrome

Drugs to be avoided or used with caution in patients with Brugada syndrome	
Should be avoided	**May be used with caution**
Bupivacaine, levobupivacaine, ropivacaine	Lidocaine and others local anesthetics (doses should be minimized)
α-Receptor agonists (norepinephrine, methoxamine, phenylephrine)	Propofol (not exceed 4 mg/kg/h)
Vasopressors with dual α and β agonist action as dopamine have unpredictable effects	Thiopental, etomidate, ketamine, sugammadex
Cholinergic agents (neostigmine, pyridostigmine, acetylcholine)	Nitrous oxide, desflurane, sevoflurane, isoflurane
Class I C antiarrhytmics (ajmaline, flecainide, pilsicainide, procainamide, propafenone, ethacizin)	Benzodiazepines, narcotics, opioids, ketorolac
Phenothiazine antipsychotics (trifluoperazine, thioridazine, perphenazine)	α-Receptor antagonists
Lithium	β-Receptor agonists (isoproterenol, dobutamine)
Antiepileptic drugs	Anticholinergics (atropine, glycopyrrolate, scopolamine)
Tricyclic antidepressants (amitriptyline, nortriptyline, clomipramine, desipramine)	Antiemetics (ondansetron, granisetron, dexamethasone)
Preferentially avoided	
β-Receptor antagonists	Amiodarone, verapamil, vernakalant, disopiramide
Carbamazepine, fluoxetine, paroxetine	Ketamine, tramadol
Indapamide	Metoclopramide
Diphenhydramine, dimenhydrinate	Phenytoin

For specific drug research, visit www.brugadadrugs.org.

lactate, and creatine kinase should be monitored frequently, especially if propofol sedation is required for more than 48 hours.[10,11] Regarding other induction agents, thiopental use has been described in multiple case reports without problems, whereas no studies reported the use of etomidate. Regarding halogenated anesthetics, they may interfere with or alter the QT interval but in BrS patients general anesthesia has been successfully maintained with nitrous oxide, desflurane, isoflurane, and sevoflurane, this last might be best since it has no effect on QT length.[3,12]

Benzodiazepines, ketorolac, narcotics, and opioids have not been associated with any adverse events but is recommended to avoid phenothiazine antipsychotics because overdoses have resulted in Brugada ECG patterns with a mechanism related to a reversible blockade of the Nav1.5 sodium current and the Kv4.3 transient outward potassium current (Ito) in rat right ventricular outflow tract (RVOT) cardiomyocytes; moreover also lithium and many antiepileptic drugs act through ion channel blockade resulting in cardiac ion channel blockade with BrS manifestation.

Alpha receptor agonists and β-receptor antagonists can worsen ECG patterns by increasing the ST segment elevation or unmasking a Brugada ECG pattern, whereas α-receptor antagonists and β-receptor agonists improve ECG patterns or decrease the ST segment elevations.

Vasopressors with dual alpha and beta agonist action as dopamine have unpredictable effects. β1 and β2 receptor agonistic activity of isoproterenol and dobutamine increases calcium current and has been used to reduce ST segment elevation and suppress arrhythmic events in patients with BrS to treat electrical storm; ephedrine was also used without complication to treat intraoperative hypotension.[3,12,13]

Given that increased vagal tone may increase arrhythmia susceptibility, the anticholinergic action of atropine, glycopyrrolate, and scopolamine drugs could exert a beneficial effect on typical ST segment changes in BrS patients.[3]

Avoid cholinergic agents, used in neuromuscular blockade antagonization, seems to be prudent even though likelihood of complications may be reduced by simultaneous administration of atropine or glycopirrolate. Neuromuscular blockade antagonization with neostigmine and pyridostigmine may increase parasympathetic drive inducing bradycardia, even if some authors have used neostigmine without complications, but in some others cases report accidents at awakening and recommend a spontaneous restoring from the neuromuscular blockade antagonization. For these reasons, to date, when using steroidal nondepolarizing agents to achieve neuromuscular blockade antagonization, sugammadex would be the reversal agent of choice.

Regional anesthesia and neuroaxial blockade may be performed with particular caution in BrS patients because local anesthetics are class Ib antiarrhythmics, and thus they block voltage-gated sodium channels. Those with rapid dissociation properties used for local anesthesia as lidocaine do seem to be safe when combined with adrenaline/epinephrine, and the amount administered is low with a local effect only, and the utmost care should be taken to avoid systemic injection. Local anesthetics with slow dissociation properties

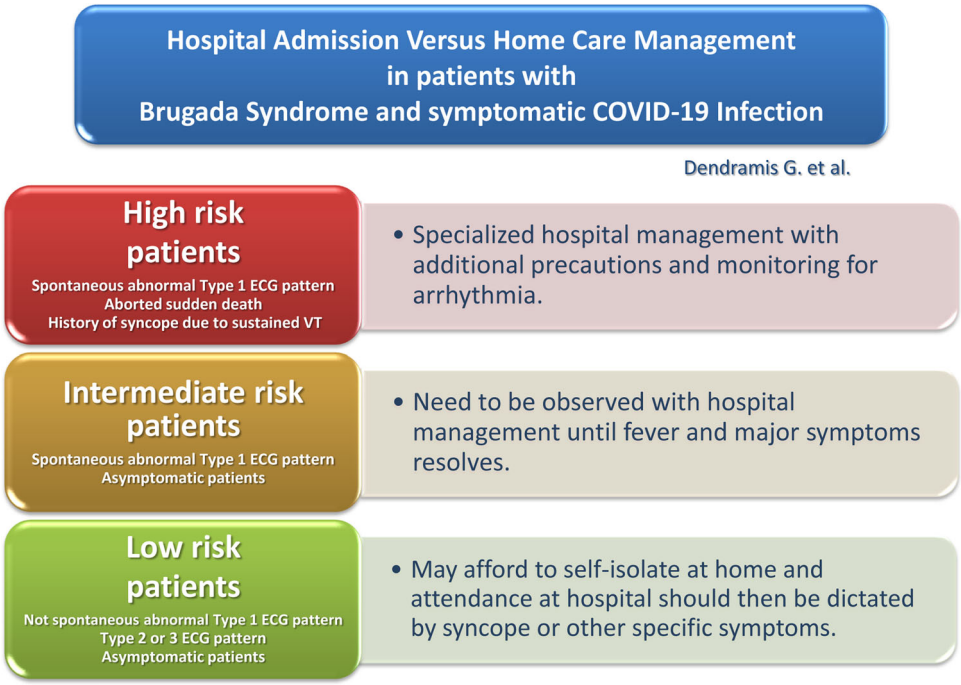

FIGURE 2 Hospital admission versus home care management in patients with BrS and symptomatic COVID-19 infection [Color figure can be viewed at wileyonlinelibrary.com]

as ropivacaine, bupivacaine, and levobupivacaine should be avoided as long as several complications have been reported, especially when performing epidural infusions and rapid absorption into the systemic circulation. The use of large amounts of these anesthetics, for these reasons, should be avoided or they should be used cautiously; doses should be minimized, and the patient should be monitored closely, even if several authors reported uneventful regional or wound infiltration with local anesthetics in these patients.

Up to half of patients receiving spinal anesthesia may develop transient hypotension and bradycardia as a consequence to the sympathetic block; in patient with BrS, this complication should be prevented and avoided. This condition usually responds to prompt fluid replacement with crystalloids but occasionally hypotension can be severe and may require vasopressors along with fluids. For all these reasons, in BrS patients ultrasound-guided peripheral nerve blocks, which implies lower doses of anesthetic and consequently lower systemic absorption, should be preferred over neuroaxial/central blockade.[13,14] Antiemetics as ondansetron, granisetron, and dexamethasone have not been associated with any reported adverse effects in BrS patients, and they may be used in patients with concomitant COVID-19 infection who need it.[3]

Chloroquine is an antimalarial drug closely related to quinidine, and it has also been investigated as a potential broad-spectrum antiviral drug. While quinidine is used as an antiarrhythmic drug in idiopathic forms of ventricular fibrillation and BrS, it is also well known for its QT-prolonging effects and malignant arrhythmias. Hydroxychloroquine sulfate, used in the chronic treatment of autoimmune diseases and recently shown to also efficiently inhibit SARS-CoV-2 infection in vitro, is metabolized by CYP3A4 and is a less toxic derivative of chloroquine but combined with additional antiviral treatments (ritonavir, lopinavir, remdesivir, azithromycin, etc.), resulting in higher plasma levels and significant QT prolongation.[15]

Especially hydroxychloroquine and azithromycin have been used to treat patients with Covid-19 disease but to date the evidence in case series, small randomized clinical trials, and observational studies on the safety and efficacy of these therapies among patients hospitalized with mild-to-moderate infection show that they did not improve clinical status at 15 days as compared with standard care.

Moreover, combination of hydroxychloroquine and azithromycin is associated with QTc prolongation with increased odds of cardiac arrest and cardiac arrhythmias, particularly in those with comorbidities. Given the long half-lives of both azithromycin and hydroxychloroquine, caution is necessary even when the two drugs are used sequentially instead of concomitantly with careful attention to drugs interactions, electrolyte monitoring, and daily electrocardiograms.[16–18]

1.4 | Hospital admission versus home care management in BrS patients

Patients with an increased risk of cardiac arrhythmias as those with inherited arrhythmia syndromes as BrS, long QT syndrome, short QT syndrome, and catecholaminergic polymorphic ventricular tachycardia may be particularly susceptible to proarrhythmic effects of COVID-19-related issues such as fever, hypoxia, electrolyte disturbances, and use of many drugs as antiviral. Preventive measures may include strict

social distancing to prevent infection, aggressive antipyretic treatment to reduce fever in patients with BrS, and ECG monitoring in patients treated with antiviral drugs.

In BrS patients with high arrhythmic risk (spontaneous type I pattern, history of previous syncope due to sustained VT, or aborted sudden death) and symptomatic COVID-19 infection that develop high fever (>38°C) despite paracetamol treatment, specialized hospital management with additional precautions and monitoring for arrhythmia is necessary.

Patients with history of asymptomatic spontaneous type 1 Brugada pattern (intermediate arrhythmic risk) will need to be observed with hospital management until fever and major symptoms resolve.

Patients who are not at higher or intermediate arrhythmic risk group and have a drug-induced type 1 Brugada pattern, as well as those with no sign of a spontaneous type 1 Brugada ECG pattern at any other time (even during a fever), are at lowest risk and may afford to self-isolate at home and attendance at hospital should then be dictated by syncope other specific symptoms (Figure 2).

2 | CONCLUSIONS

Specific data on supportive ICU care for patients with BrS and concomitant COVID-19 infection are lacking, and current recommendations are based on existing cases and from specific intensive care management of patients with BrS. Special vigilance, avoiding factors and situations that are known to have the potential to induce arrhythmias, and some general rules resulted from cases series and clinical practice, to be followed during the ICU management of patients with BrS and concomitant COVID-19 infection, are important to reduce the intrinsic arrhythmic risk of these patients during ICU and anesthesia management. Nowadays, the suggestions to be implemented are only derived from daily clinical practice and are summarized in this paper. We are aware of the need to have further investigations and strong evidence about this topic but to date we hope to have provided an adequate starting framework with useful suggestions for daily clinical practice.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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