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Brugada syndrome and anesthesia

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SUMMARY

Brugada syndrome is a ion channelopathy (Na+) characterized by right bundle branch block (RBBB) and ST segment elevation in the right precordial leads of the electrocardiogram (ECG) without any apparent structural abnormality in the heart, which is associated with syncope and sudden death. A 54 years old male with bilateral radicular pain presented for spine surgery. He had no history of syncope or arrhythmia, however, his preoperative ECG showed ST elevation (2 mm) in V2 y V3 and RBBB. After tracheal intubation developed bradycardia and ventricular beats, and further ST elevation 4 mm (0.4 mV); 1 mg of atropine was administered to normalize his heart rate and the ST segment elevation to baseline values, and the sinus rhythm was maintained. The patient was admitted to the cardiac intensive care unit for a postoperative period of 48 h.

Key words: Brugada syndrome, anesthesia.

RESUMEN

El síndrome de Brugada es una enfermedad de canal iónico (Na^+), caracterizada por bloqueo de rama derecha (BRD) y elevación del segmento ST en precordiales derechas, sin anormalidades estructurales del corazón y asociada a síncope y muerte súbita. Presentamos el caso de un varón de 54 años con dolor radicular bilateral programado para cirugía de columna lumbar. Sin historia de síncope o arritmias, sin embargo su ECG preoperatorio con elevación del segmento ST (2 mm) en V2 y V3 y BRD. Luego de la intubación traqueal presentó bradicardia y latidos ventriculares, con elevación del segmento ST de 2 a 4 mm. Se administró atropina con normalización de frecuencia cardíaca y de la elevación del segmento ST a valores basales, conservando el ritmo sinusal. El paciente fue admitido a la unidad de cuidados coronarios durante 48 h en el período postoperatorio.

Palabras clave: *Síndrome de Brugada, anestesia.*

INTRODUCTION

During anesthetic care, even in a healthy heart, a number of situations can cause arrhythmias that usually are benign. In presence of structural alterations such as ischemic cardiopathy, myocardial dilation or hypertrophy, myocarditis or primary electrical disorders, the risk increases and the severity of arrhythmias becomes a serious perioperative problem. In the above mentioned conditions, small hemodynamic alterations, changes in autonomic modulation, increase in adrenergic stimulation, anesthetic drugs and raise of the body temperature, are the stimulus for the potentially lethal alterations of the cardiac rhythm of the Brugada syndrome (BS).

CLINICAL CASE

A 54-year-old man with radicular compression syndrome had intense radicular pain in both legs was programmed for release and instrumentation of L4-L5-S1.

The patient had history of heavy smoking of 1 packet of cigarettes per day for 20 years that stopped five years ago. There was no history of cardiopathy, diabetes mellitus or hypertension, neither family history of heart diseases.

Physical examination: weight 76 kg, height 170 cm, L4-L5 bilateral radiculopathy. No further abnormalities were found in the physical exam.

Laboratory results: Hemoglobin 14.3 g/dL, hematocrit 45%, platelets 240,000 prothrombin time 98%, partial thromboplastin time 27", control 29", glucose 97 mg/dL, creatinine 0.9 mg/dL, blood urea nitrogen 19 mg/dL. Serum electrolytes results were, Na 145 mmol/L, K 4.1 mmol/L, Chlorine 110 mmol/L. The chest X-ray was normal. The electrocardiogram results were: heart frequency of 50x', QTc: 0.44, right bundle branch block with ST elevation in V2, V3 (Figure 1); the echocardiogram was normal; the cardiac stress test was negative, without evidence of ischemia or changes in the ST segment. The imaging studies revealed at L4-L5 and L3-L4 listhesis and L4-L5 disk herniation.

The patient was monitored with two-lead surface electrocardiograms (DII and V2), and continuous analysis of the ST segment, invasive blood pressure in the right radial artery, pulse oximetry, gas analysis, capnography, non-invasive blood pressure, bladder catheter to asses urinary output and esophageal thermometer.

Vital signs at entering: blood pressure 120/68 mmHg, heart rate 52 beats per min, oximetry 95%.

Induction: 300µ fentanyl, 6 mg cisatracurium, 20 mg ethomidate. Mechanical ventilation to keep CO_2Et between 32 and 36 mm Hg was initiated by performing orotracheal intubation with an 8 mm tube.

After being induced, the patient had bradycardia that was treated with 1 mg of atropine. He recovered his baseline heart frequency figures within 5 minutes. During this interval, he had isolated ventricular beats with a frequency of 4-5 per minute and ST segment elevation from 2 mm (baseline) to 4 mm. These changes reverted after the cardiac frequency was back to normal.

The patient was kept with 0.8 and 1.4 CAM sevofluorane and 1700 µ fentanyl and 60% O_2.

The anesthetic and surgical procedures were uneventful and the patient was shifted to the coronary unit where he stayed 48 hours. He was with stable hemodynamics and without evidence of rhythm alterations.

ION CHANNEL DISEASES

This group of diseases, also called primary electrical diseases, has been described as a problem that is exclusively electrical, without any structural alteration of the heart. The cell depolarization and repolarization and the action potential are the result of the balance of the ionic flow that is mediated through the process called gating, which is a coordinating opening and closing of the ion channels (Table I). The progress of the molecular genetics analysis and of the no-invasive methods of the heart, have allowed to find out that mutations in SNC5A are associated with several diseases such as the Lenègre Lev disease, atrioventricular blockade, Sick sinus syndrome, Infant sudden death syndrome, long-QT syndrome and Brugada syndrome[1].

The molecular structure of the Na^+ ionic channel has been described as the connection of subunits that integrate the trans-membrane pore and one regulatory sub-unit of the channel activity during the heart electric cycle.

The main channel of cardiac sodium voltage activated is $Na_v1.5$, which generates the rapid phase of depolarization and plays a key role in cardiac conduction (Figure 2). Its importance in the normal cardiac function has been exemplified in the description of numerous genetic variations that occur commonly in the gen SCN5A that codifies for $Na_v1.5$ and it is associated with above mentioned diseases. Among them, the long-QT type 3 syndrome and the Bruga-

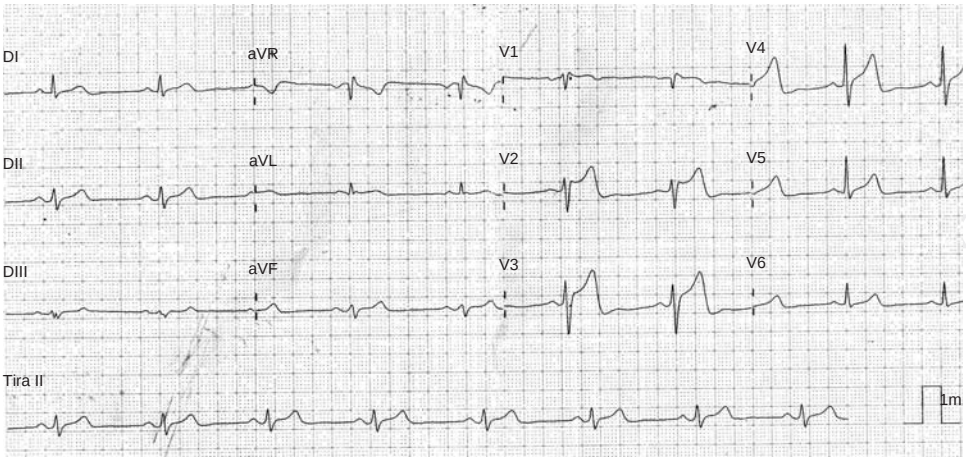

Figure 1. Surface electrocardiogram with image of right bundle branch block and ST segment elevation in right precordial leads (V1 to V3). *Brugada pattern*.

Table I. Nomenclature and some functions of sodium channels.

Protein	Gen	Ancillary subunits	Expression	Associated to human channelopathies
$Na_v\alpha1.1$	SCN1A	β1, β2, β3, β4	Central neurons and cardiac myocytes	Febrile epilepsy, GEFS epilepsy general, myoclonic epilepsy
$Na_v\alpha1.2$	SCN2A	β1, β2, β3, β4	Central neurons	Febrile convulsions and epilepsy
$Na_v\alpha1.3$	SCN3A	β1, β3	Central neurons and cardiac myocytes	Unknown
$Na_v\alpha1.4$	SCN4A	β1	Muscle and skeleton	Periodic paralysis, hypercalcemia, congenital paramyotonia and potassium-aggravated myotonia
$Na_v\alpha1.5$	SCN5A	β1, β2, β3, β4	Central neurons, cardiac myocytes	Long QT syndrome, Brugada syndrome , idiopathic ventricular fibrillation
$Na_v\alpha1.6$	SCN8A	β1, β2	Central neurons, dorsal root ganglia, peripheral neurons	Unknown
$Na_va1.7$	SCN9A	b1, b2	Dorsal root ganglia, sympathetic neurons, Schwann cells and neuroendocrine cells	Erythromelalgia, and channelopathy associated with pain insensitivity
$Na_v\alpha1.8$	SCN10A	Unknown	Dorsal root ganglia	Unknown
$Na_v\alpha1.9$	SCN11A	Unknown	Dorsal root ganglia	Unknown

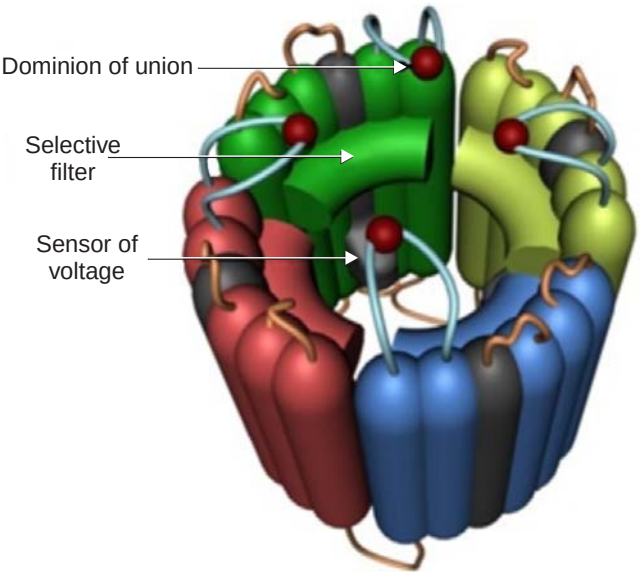

Figure 2. Cardiac sodium channel activated per voltage.

da syndrome are caused by the increase and decrease of the $Na_v1.5$ function, respectively. $Na_v1.5$ is a protein subunit (α) that forms the cardiac Na^+ channel pore. Its molecular weight is 220 kDa and is associated with at least four types of small (β) ancillary subunits (30 to 35 kDa)[2].

The genetic basis of this syndrome had been found out: a mutation in SNC5A of chromosome 3, which codifies the alpha chain of the voltage-gated Na+ channels. The family presentation has been described with a dominant pattern of autonomic transmission; although there is certain degree of heterogeneity of transmission and variability of expression, because there are patients with evidence of mutation without the typical changes in the electrocardiogram[3].

Initially, three different mutations and one polymorphism in the Na+ channel were described in two families and in one sporadic patient. One affects exon 28 (reading error), other the intron 7 (introduction of two M bases) and the last, represents a subtraction of the A nucleotide at the SCN5 gen. To date, more than 30 mutations of SCN5A have been identified[4].

Brugada syndrome

Usually the patient is a man in his fifties, healthy, without previous clinical history and in his more productive years. The illness occurs without previous notice and regularly, it kills the patient when is asleep. It is a life of permanent fear and cardiac implants. This condition was just recently discovered. Clinical cases have been described since 1917; however, no medical doctor had discovered the etiology of this unexplained condition. In 1992, the Brugada brothers discovered an unusual pattern in the electrocardiogram of patients who died from the same enigmatic cause. Actually, most investigations were carried out in Asia, because the disease is endemic of this continent. Natives of Thai-

land and Guam knew the disease as *bangungot* which is the Tagalog word for nightmares. According to them, healthy men died under the influence of terrible nightmares. In many tribes, this disease gained legendary popularity. As almost all the victims were men, the natives invented that a widow's ghost was responsible for the deaths of all these young men. Many natives had fear to suffer this disease, and they dressed like women before going to bed to cheat the widow's ghost, but the cause is not such a ghost, but a gen. Actually, this condition is heterogeneous, which means that more than one gen participates in its development. Furthermore, it keeps a dominant pattern of transmission.

In 1992, Brugada and Brugada described eight patients that survived cardiac arrest without myocardial structural abnormalities; these patients had right bundle branch block and ST elevation in leads V1, V2 and V3. These cases supported the recognition of a syndrome with specific electrocardiographic changes and high chance of sudden death, without evidence of cardiac structural abnormalities. It is more common in men than in women with a ratio of 8:1. The age of presentation is between 30 and 50 years, although it can occur in the extreme ages of life, mainly in different ethnic groups from Southeast Asia[5].

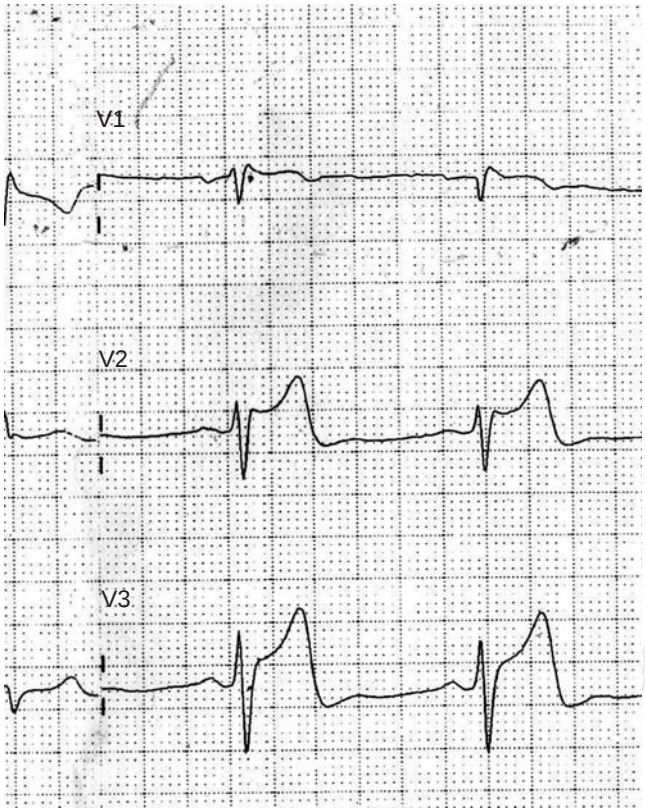

Figure 3. Image of right precordial leads with concave pattern «saddleback».

Three types of patterns have been described in BS. Type 1 pattern is characterized by a prominent convex elevation of ST segment that forms the J wave or an elevation greater or equal to 2 mm or 0.2 mV, followed by a negative T wave. In Type 2 pattern, the ST segment elevation has a saddleback pattern, where the descendent movement of ST is between two elevations followed by a positive T wave or biphasic (Figure 3). The type 3 pattern is similar to type 2, excepting that the ST elevation in right precordial ECG leads is less than 1 mm, and in both patterns: convex type and saddleback type, the ST middle part reaches the baseline[6].

The ECG characteristic pattern of ST elevation in right precordial leads that is observed in BS can occur with or without right bundle branch block. In most patients, the ECG tracing becomes transitorily normal, and it might be unnoticed in a routine ECG. It turns out to be evident in situations such as fever, electrolytes alterations, and increase in vagal tone, compression of the right ventricular outflow tract and after taking several drugs such as tricyclic antidepressants, beta blockers, Na+ channel blockers – Class Ic antiarrhythmic agents such as procainamide, flecainide 2 mg/kg, maximum 150 mg, and ajmaline – 1 mg/kg-- which had been used as diagnostic tests to unmask and exaggerate ST changes[7].

Patients with BS can have symptoms such as syncope or reanimated cardiac arrest. This condition occurs in 40% to 60% of all idiopathic ventricular fibrillation cases, 4%-12% of all sudden deaths and in approximately 20% of all deaths of patients with a structurally healthy heart. Ventricular arrhythmias are polymorphous rapid arrhythmias. An idiopathic ventricular fibrillation in the context of right ventricle ECG abnormalities and absence of heart structural disease is what defines BS[8]. Prior to the arrhythmia episode most patients have normal sinus rhythm without changes in the repolarization phase neither in the QT interval. It has been suggested that the beginning of arrhythmias is dependent of bradycardia. This could explain the higher incidence of sudden death at night of the BS patients. Nonetheless, not all patients die at night, neither the pacemaker's stimulation averts sudden death[9].

Brugada et al, proposed that in asymptomatic patients that are in risk of sudden death (approximately 60% of patients in the first year after being diagnosed) is justified an aggressive preventive treatment that consists in the implantation of an automatic internal cardiac defibrillator (AICD). A prospective study showed that the risk of cardiac arrest is infrequent enough to propose the implantation of an AICD. Many determining

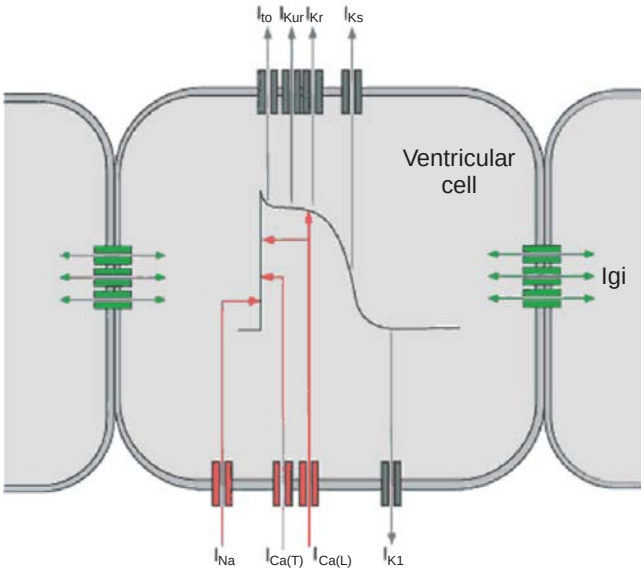

Figure 4. Currents that generate the cardiac action potential.

factors, such as hyperthermia, bradycardia and anesthetic drugs during general anesthesia procedures, can precipitate the occurrence of malignant arrhythmia in these patients[10].

Electric activity of the heart

The synchronized contraction of the cardiac cells makes possible the pumping function of the heart. This coordination is reached by an electrical network that includes the sinoatrial node, atrioventricular node, Purkinje fibers and finally the ionic channels of the cell membranes of each cardiac myocyte. The normal action potential (AP) that is described in the atrial and ventricular rapid response cells and the Purkinje system, is due to the rapid Na+ inward flow through the voltage activated Na+ channels, which corresponds to phase 0; then, repolarization contains phase 1, due to the transitory outward flow of potassium (Ito)=, the phase 2 due to the balance between calcium inward flow through the voltage dependent type L calcium channels and slow K+ channels. Phase 3 is generated by potassium inward flow through the Ikr and Ik1 channels, which are also responsible for the resting potential of phase 4 (Figure 4). The slow response cells, such as the sinus node, and the atrioventricular node, show a slow spontaneous depolarization during phase 4 due to the opening of the L-type calcium channels and probably of type-T calcium channels, which correspond to the pacemaker activity.

Physiopathology of Brugada syndrome

A net reduction of the depolarization forces is what forms the basis of the two hypotheses that have been proposed to explain the physiopathology mechanisms of BS.

The final common pathway in both hypotheses is the following: voltage gradients between the epicardium and endocardium that conduct the electrotonic forces, cause ST segment elevation and phase 2 transmural reentry type arrhythmias.

In the first hypothesis (delayed conduction) theoretical and *in vivo* experimental considerations support the idea that heterogeneity of repolarization through the outflow tract wall of the right ventricle contributes to the electrocardiographic patterns and to the genesis of BS arrhythmias.

In contrast to endocardial cells, action potentials of epicardial cells show a prolonged phase 1, known as a «spike and dome» morphology. The transient current outward potassium –Ito- current that happens in epicardial cells and is almost absent in endocardial cells explains the different configuration between the action potentials[11].

The morphology of spike and dome is the result of at least three different currents: I_{Na}, I_{to} and the L-type calcium current, I_{Ca}. The magnitude and duration of the Na+ current, I_{Na}, during phase 0, determine the level of voltage to which phase 1 begins. This will have a direct impact on the activation/deactivation characteristics of I_{to}, and indirectly on the L-type I_{Ca}. The alterations in these and maybe in other currents, (for instance, I_{Cl}) can take to an important reduction of the epicardial potential action, with the resulting potential for the re-excitement based on the heterogeneity of the epicardial-endocardial repolarization.

The spike and dome configuration of the action potentials correspond with the J waves in the surface ECG. The lost of the dome in epicardial cells, but not in the endocardial cells can cause transmural heterogeneity and ST segment elevation as a consequence of transmural current flow from the endocardium to the epicardium. Due to the thin wall of the right ventricle and to the bigger contribution of the epicardial action potential to the surface ECG, the changes are more visible in the right precordial leads that are focused in the outward tract of the right ventricle (V_1-V_2) than in the left precordial leads (Figure 5).

In the second hypothesis (premature repolarization) a reduction in I_{Na} and L-type I_{Ca} or an increase in I_{to} can cause the above described changes. Experiments carried out in dog's hearts support the notion that the epicardial-endocardial heterogeneity causes arrhythmias. The Na^+ channel sodium blockers reduce the amplitude of phase 0. The presence of I_{to} subsequently decreases the nadir of phase I and the availability of L-type I_{Ca} will be decreased, thus causing immediate repolarization.

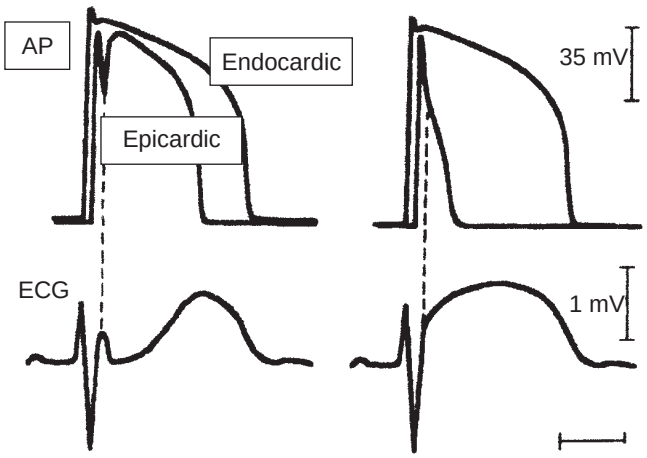

Figure 5. Difference between epicardic and endocardic action potentials (transmural heterogeneity) that generate the ST segment elevation. AP = action potential, ECG = electrocardiogram.

This reduction of Na^+ current launches a voltage gradient through the right ventricle wall, (elevation of J point and ST segment changes), due to the excessive shortening of the epicardial action potential. This disequilibrium of current, allows the reactivation of the right ventricle epicardium through neighboring regions of myocardium with longest action potentials, generating a functional reentry, commonly termed phase 2 reentry.

The role of type L Ca^{2+} channels in the pathogenesis of BS was underestimated until recently: a mutation with loss of function in genes that codify the type L Ca^{2+} channel (CACNA1C, -subunit α1- and CACNAB2, -subunit β2b) has been associated with a clinical entity that accompanies the Brugada phenotype, with short QT interval. To date, it is unknown the percentage of SB patients that have mutations of these genes[13].

DISCUSSION

The autonomic stimulation or suppression causes profound effects on patients with BS. It is expected that beta-adrenergic stimulation would reduce electric heterogeneity when type L I_{Ca} increases, which in turn increases the epicardial action potential. In this way, β-adrenergic stimulation, both, physiological and pharmacological, reduces the ST segment elevation, and β-blockers increase the ST segment elevation in right precordial leads. Also, increase of ST segment elevation due to á-adrenergic agonists and to muscarinic stimulation had been described.

Anesthetic treatment

The anesthetic treatment for patients with BS is always worrying due to the electrical adverse events that accompany this syndrome[14].

First, the diagnosis of the syndrome must be confirmed. It has been suggested to using Gussak criteria to diagnose the Brugada syndrome. This author proposes that the presence of one major and one minor criterion makes possible to make the diagnosis of Brugada syndrome with higher sensitivity than the presence of one isolated criterion.

Major criteria

1. An ECG Brugada pattern in patients with an otherwise structurally normal heart.
2. Appearance of the ECG Brugada pattern after injecting Na^+ channels blockers.

Minor criteria

1. Family history of sudden cardiac death
2. Syncope of unknown origin
3. Documented episodes of ventricular tachycardia/ventricular fibrillation
4. Positive programmed electrocardiostimulation test on ventricular tachycardia/ventricular fibrillation
5. Genetic mutations of ion channels[15].

Documenting a positive family history of syncope and/or sudden death, determines in some way, the magnitude of the risk for the occurrence of lethal arrhythmia during surgery[16]. It must be excluded causes of the ECG tracing that resemble BS, including anteroseptal myocardial infarction, early repolarization syndrome, pulmonary embolism and hiperkalemia.

The anesthetic considerations include: minimization of the factors that triggers ventricular arrhythmias, such as adrenergic stimulation (response to surgical stress), changes in autonomic modulation -increased vagal tone-, hemodynamic alterations due to anesthetic drugs and body temperature changes.

The register of the central body temperature (esophageal) must be done, because the changes in the Na^+ channels related to the temperature are well documented. Temperature increase will trigger ventricular arrhythmia. In the clinical case we´re addressing, the patient's temperature was maintained constant. At the end of the surgical procedure, a discrete decrease of 0.5ºC in relation to the baseline temperature was registered.

It is needed to have a defibrillator in the operating theatre and if the patient has a AICD, this must be deactivated before the surgical procedure.

It is advisable to avoid monopolar cauterization, ideally is better to use bipolar cauterization due to the chance of causing arrhythmias during surgery.

The first dilemma is the choice of monitorization –invasive or not- in relation to the surgical risk, and not only considering the potential BS complications. Therefore, monitoring with a central venous catheter or with a catheter in the pulmonary artery it takes the risk of causing arrhythmias, even in healthy patients, this can be required for patients undergoing surgery that implies hemodynamic instability and/or great blood loses requiring high volume of fluids. Monitoring ECG with two channels: DII and focusing in right precordial leads (V_1 or V_2 instead of V_5) including the analysis of the ST segment, it allows ascertaining the worsening of the BS characteristic gap, and its relationship with triggering factors, such as body temperature, use of anesthetic drugs and patient's hemodynamic status.

Radial artery cannulation to obtain invasive systemic blood pressure must be performed to get strict hemodynamic control, not only during surgery, but in the post-anesthetic care unit. Also, it is useful to obtain serial blood samples to figure out electrolytes and the blood levels of potential drugs that trigger the event. The monitoring activities also include pulse oximetry, breath gas analysis and CO_2ET.

The induction of SB patients by using propofol has been reported successful[18]. Although, until recently, this drug has been proposed as contraindicated given to its potential interaction with Na^+ and Ca^+ channels[19]. In our clinical case, induction with ethomidate, fentanyl and cisatracurium caused 21% decrease of the heart rate; At the beginning it was 52 beats per min, then decreased to 41 beats per min. This decrease required muscarinic blockade (1 mg atropine), with slow recovery of the heart rate (5 minutes) to the baseline figures (54x'). During this interval, the ECG monitoring showed an increase of the ST segment from 2 to 4 mm, along with up to 5 isolated ventricle beats per minute. Situation that was reversed when the heart rate increased to the baseline figures after administering atropine.

Maintenance with fentanyl is safe, considering avoiding use of remifentanil and sufentanil, given that these can induce bradycardia.

Volatile anesthetics interfere with QT interval in patients without BS. Isoflurane causes a significant increase of the QT interval, without changes with sevoflurane and shortened by halothane. We used sevoflurane without noticeable changes of the QT interval, and without elevations during surgery.

Although in our clinical case, no local anesthetics were used, local anesthesia and regional anesthesia represent a risk for ionic channel diseases, due to the fact that local anesthetics can alter the temporary dispersion of the effective refractory period and induce severe bradycardia and sudden cardiac arrest.

Na^+ channels blockers have been used to show BS in patients with transiently normal ECG. Class Ib drugs (particularly lidocaine) do not induce the characteristic ECG changes. However, bupivacaine causes a much greater depression in the quick phase of the Purkinje fibers depolarization and in the ventricle muscle than lidocaine and stays linked to the sodium channels for longer period. There are reports that peridural administration of bupivacaine can induce the characteristic pattern of BS[20].

Appearance of arrhythmias, even in the general population, is most probable that occur during the post operative period. Therefore, continuous monitoring is needed in this phase. In SB patients, this possibility increases, due to the presence of residual anesthetic effects, autonomic changes related to pain, control of the body temperature and changes in the circulating volume, among other factors. Thus the anesthetic recovery should be at the coronary unit or intensive care unit, where any conduction change can be detected and managed timely. There is no agreement regarding the surveillance time at the intensive care unit. The type of surgical problem, the risk level of the patient and the trans-surgical progress will determine the surveillance time.

CONCLUSSIONS

The electrocardiographic image of BS must alert about the possibility of lethal ventricle arrhythmias. Anesthetic care in these patients should be aimed at avoiding posterior dysfunction of the sodium channel. Among the triggering factors are: hyperthermia, increased vagal tone and local anesthetics, among others. Classifying the level of risk, as well as the kind of surgery will determine how invasive monitorization should be, thermometry, invasive blood pressure, surface ECG and ST segment analysis will provide early warnings of an imminent arrhythmia. The choice of the anesthetic drugs is given by its effect on the autonomous nervous system, keeping the heart frequency within normal parameters, and at the same time, stopping the sympathetic response due to surgical stress.

Availability of a defibrillator in the operating theater is required because this is the only effective treatment for BS ventricle arrhythmias. Surveillance of the patient at an intensive care unit during the post operative period, with continuous ECG monitoring, which includes ST segment analysis, is required.

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