Sudden cardiac arrest: Studies on risk and outcome
Blom, Marieke

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
CHAPTER 7

Cardiac sodium channels and inherited electrophysiological disorders: an update on the pharmacotherapy.

D.A. van Hoeijen*, M.T. Blom*, H.L. Tan
* These authors contributed equally

Since the recognition of inherited sodium (Na⁺) channel disease, the cardiac Na⁺ channel is extensively studied. Both loss-of-function and gain-of-function mutations of the cardiac Na⁺ channel are associated with cardiac arrhythmia and sudden cardiac death. Pathophysiological mechanisms that may induce arrhythmia are unravelled and include alterations in biophysical properties due to the mutation in SCN5A, drug use and circumstantial factors. Insights into the mechanisms of inherited Na⁺ channel disease may result in tailored therapy. However, due to the complexity of cardiac electrical activity and pathophysiological mechanisms, pharmacotherapy in cardiac Na⁺ channel disease remains challenging.

This review discusses various mechanisms involved in inherited Na⁺ channel disorders, focusing on Brugada Syndrome (BrS) and long QT syndrome type 3 (LQTS3). It aims to provide an overview of developments in pharmacotherapy, discussing both treatment and which drugs to avoid to prevent arrhythmia.

Altered biophysical properties of cardiac Na⁺ channels are the basis of arrhythmias in patients with inherited Na⁺ channel diseases such as BrS and LQTS3. The effects of such biophysical derangements are strongly modulated by concomitant factors. Tailored drug therapy is required to prevent arrhythmia and is best achieved by educating patients affected by Na⁺ channel disorders.
Introduction

The cardiac sodium (Na\(^+\)) channel plays a pivotal role in the propagation of electrical activity through the heart. In the past decade many mutations in SCN5A, the gene encoding the pore-forming alpha-subunit of the cardiac Na\(^+\) channel, have been identified. Knowledge on the group of cardiac disease that is associated with mutations in SCN5A is expanding, although some questions regarding underlying mechanisms and interacting factors that induce the occurrence of cardiac arrhythmias remain unanswered. This progress has aided further understanding of effects and side effects of cardiac and non-cardiac drugs that modify the function of the cardiac Na\(^+\) channel.

This review will focus on inherited electrophysiological disorders due to Na\(^+\) channel dysfunction and will give an update on pharmacotherapy.\(^1\)

Cardiac electrical activity

Cardiac electrical activity is initiated in the sinus node (SA node) in the right atrium by spontaneous excitation of pacemaker cells (Figure 1, panel A). From there the electrical signal starts activating the right and left atria and travels to the atrioventricular node (AV node). In the AV node, conduction of the excitation wave is slowed, before it propagates via the bundle of His, the bundle branches and the Purkinje fibres to the left and right ventricle. The body surface electrocardiogram (ECG) represents the net electrical activity of all action potentials (APs) in the heart.

At a cellular level, cardiac electrical activity is propagated through a complex interplay in which several ion channels and ions play a role.\(^2-4\) Ion channels form little pores in cardiac cell membranes enabling ions to cross these membranes. When ion channels are activated due to a change in membrane potential, the channels open, and allow an ion current across the membrane. The sequence of opening and closing of ion channels is time and voltage dependent (gating) and results in cardiac electrical activity and AP formation.

Cardiac action potential

The AP in ventricular cardiomyocytes consists of different phases: phase 0-4 (Figure 1, panel B). During phase 4, ventricular cardiomyocytes maintain a stable and negative membrane potential of approximately -85 mV. Phase 0 of the AP is initiated by the depolarization of the cardiomyocyte to its threshold due to an excitation wave, which results in the opening of the voltage sensitive Na\(^+\) channels. After opening of these channels, Na\(^+\) ions quickly enter the cell following the Na\(^+\) concentration gradient. As a consequence of this Na\(^+\) current (I\(_{Na}\)), the cardiomyocyte rapidly depolarizes, thereby
Figure 1: Cardiac electrical activity and cardiac ion currents.

Panel A: The electrical activity of the heart is represented on the surface electrocardiogram (ECG), and results from coordinated action potential generation in individual cardiomyocytes. The electrical activity starts by the spontaneous generation of action potentials in pacemaker cells in the sinoatrial node. Propagation of these action potentials creates an excitation wave through the atria, leading to atrial depolarization. After traveling through the atrioventricular node, the excitation wave reaches the ventricles, and leads to ventricular depolarization.

Panel B: The cardiac action potential is generated by transmembrane ion currents that are directed inwards and outwards. The inward (depolarizing) sodium and calcium currents are pointed downwards. The outward (repolarizing) potassium currents are pointed upwards.

initiating a cascade of activation and inactivation of other voltage dependent ion channels.

Early repolarization (phase 1) starts by opening and closing of potassium (K⁺) channels, leading to a small repolarizing, transient outward K⁺ current (I_TO). During phase 1, the K⁺ efflux occurs as Na⁺ channels are closing and calcium (Ca²⁺) channels are opening. Phase 2 is characterized by a plateau in the AP as a net result of depolarizing inward Ca²⁺ current (I_Ca,L) through L-type Ca²⁺ channels. Moreover, the influx of Ca²⁺ into the cardiomyocyte enables the cardiomyocyte to couple excitation to myocardial contraction, by activating filaments in the cardiomyocyte. During phase 3 of the AP, repolarizing K⁺ currents (I_K,R, I_K,s) predominate after the activation of the rapidly and slowly activating repolarizing K⁺ currents, respectively, and closing of L-type Ca²⁺ channels. This results in a rapid repolarization of the cardiomyocyte towards the resting membrane potential. During phase 3 and 4, the electrochemical gradient across the cell
membrane of the cardiomyocyte is restored by the Na\(^+-\)K\(^+\) pump that pumps Na\(^+\) ions into the cell and K\(^+\) out of the cell.

The AP is different across various areas of the heart as the result of small regional differences in gating properties or channel expression of the various ion channels. Therefore, disturbances of ion currents may modify the AP differentially in specific regions of the heart. This may introduce regional heterogeneity of the AP, provoking substantial voltage gradients that evoke cardiac arrhythmias.

Figure 2: Molecular structure of the cardiac sodium channel.

Panel A: Cartoon of the \(\alpha\)-subunit (Nav1.5) and the \(\beta\)-subunit of the cardiac sodium channel. Nav1.5 consists of four domains (DI–DIV), each containing six transmembrane segments (S1–S6); S4 segments are positively charged and act as voltage sensors. The \(\beta\)-subunit consists of one single transmembrane segment.

Panel B: The four domains of Nav1.5 fold around an ion-conducting pore, which is lined by the loops between the S5 and S6 segments. The expression and function of Nav1.5 is regulated by \(\beta\)-subunits and several directly or indirectly interacting regulatory proteins.
Cardiac Na⁺ channel

Activated cardiac Na⁺ channels rapidly depolarize the cardiomyocyte. The resulting $I_{Na}$ determines cardiac conduction velocity and cardiac excitability. Na⁺ channels consist of a pore-forming alpha subunit and several beta subunits that interact with the alpha subunit and regulate its gating properties or cellular localization. The alpha subunit has four homologous domains that each consists of six trans-membrane segments (Figure 2, panel A). The fourth segment of each domain determines voltage sensitivity. The segments are linked by intracellular and extracellular loops that regulate channel inactivation or determine channel selectivity for Na⁺. The $SCN5A$ alpha subunit acts in a large protein complex consisting of several beta subunits and many other associated proteins (Figure 2, panel B).⁵,⁶ Each protein in this complex is able to affect $I_{Na}$ and/or localization of the protein complex. Thus, modification of $I_{Na}$ can be due to several factors, including mutations in $SCN5A$, mutations in beta subunits or other $SCN5A$ associated proteins, and pharmacologic interactions between Na⁺ channels and Na⁺ channel blocking drugs.⁷ Malformation and dysfunction of Na⁺ channel protein complexes are not only the result of genetic mutations, but may also be involved in acquired cardiac disease. Consequently, cardiac Na⁺ channels are involved in acquired and inherited cardiac disease.⁸-¹⁰

Inherited Na⁺ channel disease

Mutations in $SCN5A$ are linked to different cardiac diseases. Mutations can change gating properties or cause abnormal expression of Na⁺ channels. Most mutations, either in $SCN5A$ or in beta subunits, lead to Na⁺ channel dysfunction, which cause either a gain-of-function or a loss-of-function. Some mutations cause opposing effects on Na⁺ channel properties. For instance, the 1795insD mutation in $SCN5A$ causes clinical characteristics that are consistent with both a gain and a loss of sodium channel function.¹¹ Inherited Na⁺ channel diseases, for instance Brugada Syndrome (BrS), are traditionally considered as monogenic diseases. However, mutations in $SCN5A$ in BrS do not always follow a Mendelian pattern of inheritance, indicating a more complex inheritance model. Rare variants in $SCN5A$ are not considered as disease causing mutations per se, but may act as a modifier of the disease. Therefore, common genetic variants in $SCN5A$ may also be involved in inherited Na⁺ channel disease.¹²,¹³ Due to variants in $SCN5A$, Na⁺ current may be slightly impaired, whereas additional factors may further reduce Na⁺ current and trigger cardiac events. For example, fever is recognized as such a factor. Although the mechanism is not fully understood, several explanations have been proposed by which fever can aggravate Na⁺ channel disease. First, intact cardiac Na⁺ channels have temperature dependent properties that may lead to disease symptoms during fever.¹⁴ Second, $SCN5A$ genetic variants may change these
temperature dependent properties, which lead to different activation and/or inactivation kinetics of cardiac Na\(^+\) channels.\(^{15,16}\)

Heart rate is another factor that may be relevant in inherited Na\(^+\) channel disease. On the one hand, Na\(^+\) channels have less time to recover from inactivation at fast heart rates. Accumulation of non-recovered Na\(^+\) channels results in fewer channels available for activation and initiation of the next AP. Such Na\(^+\) channel dysfunction may be further aggravated by the use of medication.\(^{17}\) On the other hand, symptoms in inherited Na\(^+\) channel diseases (e.g. arrhythmia in Brugada Syndrome and Long QT Syndrome type 3) are reported to occur often at rest or during sleep, and are thus associated with slow heart rate.\(^{18}\) These observations are ascribed to increased I\(_{\text{to}}\) current due to slow gating kinetics at slow heart rate.\(^{19}\)

Clearly, the functional consequences of inherited Na\(^+\) channel disease often result from the complex interplay of multiple factors.

**Long QT Syndrome type 3**

Some mutations in SCN5A result in gain-of-function of the cardiac Na\(^+\) channel. These mutations are associated with long QT 3 syndrome (LQTS3).\(^{4}\) Due to an increase in net I\(_{\text{Na}}\) the cardiac AP prolongs, resulting in a prolonged QT duration on the ECG (Figure 3, Panels A, B). Increased net I\(_{\text{Na}}\) can be due to several underlying mechanisms, but most mutations that cause LQTS3 disturb fast Na\(^+\) channel inactivation or inactivation stability, thereby leading to increased late Na\(^+\) current, considered the main pathologic mechanism in LQTS3 (Figure 3, panel C). As phase 2 and phase 3 of the AP are the result of the delicate balance between depolarizing and repolarizing ion currents, relatively small currents such as late I\(_{\text{Na}}\) affect this balance and prolong the AP and QT interval. Prolonged QT intervals may trigger early afterdepolarizations (EADs) during phase 2 or 3 due to reactivation of Ca\(^{2+}\) channels. EADs may trigger characteristic ventricular tachyarrhythmias (torsade de pointes, TdP). Arrhythmias in LQTS3 have been associated with bradycardia rather than with exercise or emotional stress as in LQTS type 1 or type 2. ICD implantation may be considered in those patients at highest risk for arrhythmia.\(^{18}\)

**Brugada Syndrome**

Other mutations lead to loss-of-function of the cardiac Na\(^+\) channel. The loss of cardiac Na\(^+\) channel function may lead to a reduced I\(_{\text{Na}}\) and thereby impair cardiac depolarization and excitability. These mutations are associated with Brugada Syndrome (BrS), progressive cardiac conduction disease (PCCD), and sick sinus syndrome.\(^{4}\)

BrS is characterized by typical ST-segment elevations in the right precordial ECG leads (V1-V3) (Figure 4, Panel A). It is associated with an increased risk of sudden
cardiac death due to ventricular tachyarrhythmias, typically during rest or sleep, in the absence of gross structural abnormalities. In 1998, BrS was first associated with mutations in SCN5A. Since then, >350 mutations in SCN5A have been associated with BrS, accounting for ~20% of BrS cases. In vitro studies of BrS-associated mutations in SCN5A invariably show loss of Na+ channel function.

The underlying pathophysiologic mechanisms that cause the ECG abnormalities and arrhythmias in BrS are not fully resolved. Most investigators regard BrS as the result of a disorder in cardiac depolarization or in cardiac repolarization (or combinations thereof). The repolarization disorder hypothesis states that the typical ST-segment elevation in BrS is caused by a transmural repolarization gradient in the right ventricular wall, related to regional differences in expression of ion channels (Figure 4, Panel D).

Figure 3: Long QT syndrome type 3.

Panel A: Prolonged QT intervals on the surface ECG of an individual with LQTS3.
Panel B: QT interval prolongation results from delayed repolarization of ventricular action potentials.
Panel C: Slower inactivation of the channel creates a late sodium current (light grey area).
Figure 4: Brugada syndrome.

Panel A: Coved-type ST segment elevation in the right-precordial ECG leads V1 and V2 after intravenous administration of sodium channel blocking drug ajmaline in an individual with Brugada syndrome.

Panel B: Brugada syndrome-linked SCN5A mutations often lead to peak sodium current reduction.

Panel C: Reduced peak sodium current decreases the upstroke velocity of action potential phase 0, which slows cardiac electrical conduction.

Panel D: Repolarization hypothesis: Transmural voltage gradient and the loss of the action potential dome in epicardium but not in endocardium results in the ST segment elevation and may induce arrhythmia (modified from Ref. [97] with permission).
particular, the transient outward potassium current ($I_{TO}$) is more prominent in the right ventricular outflow tract (RVOT), and $I_{TO}$ is more prominent in the epicardium than in the endocardium. Consequently, the notch in the action potential shape during phase 1 is more prominent in the epicardium, especially in the RVOT. Studies in canine wedge preparations demonstrated that a non-uniform abbreviation of the action potential in the right ventricle, related to these differences in expression of ion channels, causes the BrS ECG features.

The depolarization hypothesis states that the reduction in sodium current results in conduction delay in the RVOT (Figure 4, Panel B, C). Arrhythmias are thus facilitated by regional slowing of conduction. BrS may not be solely attributable to abnormal electrophysiological properties; several clinical studies have reported conspiring effects of conduction slowing and mild right and left ventricular structural abnormalities.

The occurrence of arrhythmias in BrS can be triggered by a combination of (acquired) factors that reduce sodium current on top of the innate reduced function or the sodium channel. For example, a recent report described that a patient with BrS only developed cardiac arrhythmias during exercise while using nortriptyline (a sodium channel blocking antidepressant).

**Overlap syndrome**

Progressive cardiac conduction disease (PCCD), also called Lev-Lenègre disease, is a type of cardiac conduction disturbance characterized by progressive impairment of impulse propagation through the His-Purkinje system. It manifests as prolongation of the P wave, PR or QRS interval, and right or left bundle branch block (without ST-segment elevation or QT-prolongation). It may degenerate into complete AV block, resulting in syncope or sudden death. It is thought to be associated with ageing-related fibrosis in the conduction system. The association of PCCD with loss-of-function mutations in SCN5A has been recognized since 1999.

Sick sinus syndrome (SSS) is a disease of the sinoatrial node and is characterized by bradycardia, sinus arrest, atrial standstill, and tachycardia-bradycardia syndrome. It has been associated with loss-of-function mutations in SCN5A, but mutations in other genes have been demonstrated as well.

Mutations in SCN5A were also associated with familial dilated cardiomyopathy (DCM), a cardiac structural disease characterized by decreased systolic function and ventricular dilatation. Interestingly, these mutations were found in families with heterogeneous phenotype that included SSS and arrhythmias.

Phenotypical variants with overlapping features have been described, e.g., BrS plus LQT3, and BrS plus PCCD. Often, these features can be explained by the net
result on INa, although the effects on various channel gating properties are sometimes subtle.

**Pharmacotherapy in sodium channel disease**

The key principle of therapy in inherited sodium channel disease is to identify the patients at highest risk for cardiac arrhythmias. While implantation of an implantable cardioverter defibrillator (ICD) may be considered in patients at high risk for potentially fatal arrhythmias, the cornerstone is prevention of arrhythmias by avoidance of medications. Also, situations that may evoke arrhythmias must be appropriately handled. For example, fever should be treated, as it may trigger arrhythmias in a substantial proportion of these patients. Although a limited number of drugs have shown antiarrhythmic effects in patients with frequent arrhythmias, the most appropriate treatment of these patients is still under debate. Case reports show conflicting results, as the same drug that prevents arrhythmia in one patient may induce arrhythmia in another patient. This supports the notion that arrhythmia in inherited Na⁺ channel disease is a multifactorial phenomenon, and that tailored therapy must be instituted.

**Pro-arrhythmic drug effects**

An up-to-date list of drugs that are generally accepted to have the properties to induce QT prolongation or TdP is available online at www.QTdrugs.org. QT prolongation by medication use can be achieved by either direct or indirect inhibition of repolarizing K⁺ currents or increase of depolarizing Na⁺ and/or Ca²⁺ current. The list contains over 160 of such drugs used for cardiac or non-cardiac disease. Patients with reduced repolarization reserve due to LQTS should avoid these drugs.

BrS patients are also advised to avoid certain cardiac and non-cardiac drugs that may have pro-arrhythmic effects (Table 1). Most of these drugs reduce cardiac IₐNa, whereas other drugs decrease inward Ca²⁺ current (I_{Ca,L}) or outward K⁺ current (I_K), directly or indirectly. An up-to-date list of these drugs is available online at www.brugadadrugs.org.

**Antiarrhythmic drugs**

Antiarrhythmic drugs that affect the cardiac sodium channel are used to unmask the type 1 BrS ECG during diagnostic drugs challenge. These drugs include ajmaline, procainamide, flecainide, and pilsicainide. Obviously, BrS patients should avoid these and other class 1A and class 1C antiarrhythmic drugs that reduce I_{Na}. The Cardiac Arrhythmia Suppression Trial (CAST) showed that the pro-arrhythmic effects of these drugs are not limited to inherited disease, but also exist in acquired heart disease.
Table 1: Clinically available drugs that affect cardiac ion channels and may induce or aggravate features of Brugada syndrome.

<table>
<thead>
<tr>
<th>Drug category</th>
<th>Drug</th>
<th>Affected ion channel (effect)</th>
<th>Evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmic drugs</td>
<td>Class 1A</td>
<td>$I_{Na}$ (↓)</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Ajmaline</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Procainamide</td>
<td></td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Cibenzoline</td>
<td></td>
<td>I Iib</td>
</tr>
<tr>
<td></td>
<td>Disopyramide</td>
<td></td>
<td>I Iib</td>
</tr>
<tr>
<td></td>
<td>Lidocaine</td>
<td></td>
<td>I Iib</td>
</tr>
<tr>
<td></td>
<td>Class 1C</td>
<td>$I_{Na}$ (↓)</td>
<td>I Iiia</td>
</tr>
<tr>
<td></td>
<td>Flecainide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pilsicainide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Propafenone</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Class 2-4</td>
<td>$\beta$-blocking, $I_K$ (↓ or ↑), $I_{Ca-L}$ (↓)</td>
<td>I Iib</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amiodarone</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vernakalant</td>
<td>$I_{Na}$ (↓), $I_{To}$ (↓, further decreasing with increasing HR)</td>
<td>I Iib</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td>$I_{Ca-L}$ (↓)</td>
<td>I Iib</td>
</tr>
<tr>
<td>Psychotropic drugs</td>
<td>Tricyclic / tetracyclic antidepressants</td>
<td>$I_{Na}$ (↓) and/or $I_{Ca-L}$ (↓)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amitriptyline</td>
<td></td>
<td>I Iiia</td>
</tr>
<tr>
<td></td>
<td>Clomipramine</td>
<td></td>
<td>I Iiia</td>
</tr>
<tr>
<td></td>
<td>Desipramine</td>
<td></td>
<td>I Iiia</td>
</tr>
<tr>
<td></td>
<td>Nortriptyline</td>
<td></td>
<td>I Iiia</td>
</tr>
<tr>
<td></td>
<td>Dosulepine</td>
<td></td>
<td>I Iib</td>
</tr>
<tr>
<td></td>
<td>Doxepine</td>
<td></td>
<td>I Iib</td>
</tr>
<tr>
<td></td>
<td>Imipramine</td>
<td></td>
<td>I Iib</td>
</tr>
<tr>
<td></td>
<td>Maprotiline</td>
<td></td>
<td>I Iib</td>
</tr>
<tr>
<td></td>
<td>Selective serotonin reuptake inhibitors</td>
<td>$I_{Na}$ (↓) and/or $I_{Ca-L}$ (↓)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td></td>
<td>I Iib</td>
</tr>
<tr>
<td></td>
<td>Fluvoxamine</td>
<td></td>
<td>I Iib</td>
</tr>
<tr>
<td></td>
<td>Paroxetine</td>
<td></td>
<td>I Iib</td>
</tr>
<tr>
<td></td>
<td>Phenothiazines</td>
<td>$I_{Na}$ (↓) and/or $I_{Ca-L}$ (↓)</td>
<td></td>
</tr>
</tbody>
</table>
Antipsychotic
Trifluoperazine IIa
Antidepressant
Cyamemazine IIb
Antidepressant
Perphenazine IIb

**Antipsychotics**

- Loxapine IIa
- Clothiapine IIb
- Thioridazine IIb
- Lithium IIb

**Table 1, continued**

<table>
<thead>
<tr>
<th>Drug category</th>
<th>Drug</th>
<th>Affected ion channel (effect)</th>
<th>Evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiepileptic drugs</strong></td>
<td><strong>Antiepileptic drugs</strong></td>
<td>$I_{Na} \downarrow$ and/or $I_{Ca,L} \downarrow$</td>
<td>IIa</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td></td>
<td></td>
<td>IIa</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
<td></td>
<td>IIb</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td></td>
<td></td>
<td>IIb</td>
</tr>
<tr>
<td><strong>Antiarrhythmic</strong></td>
<td>Phenytoin</td>
<td></td>
<td>IIb</td>
</tr>
<tr>
<td><strong>Anaesthetics/analgesics</strong></td>
<td><strong>Anaesthetics</strong></td>
<td>$I_{Na} \downarrow$ and/or $I_{Ca,L} \downarrow$</td>
<td>IIa</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td></td>
<td></td>
<td>IIa</td>
</tr>
<tr>
<td>Propofol</td>
<td></td>
<td></td>
<td>IIa</td>
</tr>
<tr>
<td>Ketamine</td>
<td></td>
<td></td>
<td>IIb</td>
</tr>
<tr>
<td><strong>Analgesics</strong></td>
<td><strong>Analgesics</strong></td>
<td>$I_{Na} \downarrow$ and/or $I_{Ca,L} \downarrow$</td>
<td>IIa</td>
</tr>
<tr>
<td>Procaine</td>
<td></td>
<td></td>
<td>IIa</td>
</tr>
<tr>
<td>Tramadol</td>
<td></td>
<td></td>
<td>IIb</td>
</tr>
<tr>
<td><strong>Other substances</strong></td>
<td>Acetylcholine</td>
<td>$I_{Ca} \downarrow$</td>
<td>IIa</td>
</tr>
<tr>
<td></td>
<td>Alcohol</td>
<td></td>
<td>IIb</td>
</tr>
<tr>
<td></td>
<td>Cocaine</td>
<td>$I_{Na} \downarrow$</td>
<td>IIa</td>
</tr>
<tr>
<td></td>
<td>Ergonovine</td>
<td>$I_{Ca} \downarrow$</td>
<td>IIb</td>
</tr>
<tr>
<td></td>
<td>Dimenhydrinate</td>
<td>$I_{Na} \downarrow$</td>
<td>IIb</td>
</tr>
<tr>
<td></td>
<td>Diphenhydramine</td>
<td>$I_{Na} \downarrow$</td>
<td>IIb</td>
</tr>
<tr>
<td></td>
<td>Edrophonium</td>
<td></td>
<td>IIb</td>
</tr>
<tr>
<td></td>
<td>Indapamide</td>
<td></td>
<td>IIb</td>
</tr>
<tr>
<td></td>
<td>Metoclopramide</td>
<td></td>
<td>IIb</td>
</tr>
<tr>
<td></td>
<td>Terfenadine / Fexofenadine</td>
<td>$I_{Na} \downarrow$</td>
<td>IIb</td>
</tr>
</tbody>
</table>


* Evidence: I: general agreement that this drug is potentially arrhythmic in BrS, IIa: conflicting evidence, but evidence points towards a potentially arrhythmic drug effect in BrS, IIb: conflicting evidence and a potentially arrhythmic drug effect is less clear in BrS.
CAST was initiated to test the hypothesis that suppression of ventricular ectopic beats after myocardial infarction with the use of class 1C antiarrhythmic drugs would prevent arrhythmias and mortality. However, the use of encainide and flecainide was discontinued as the group of patients using these drugs showed excess mortality due to arrhythmia. The CAST showed no differences between the encainide/flecainide and placebo groups in the composite endpoint of sudden cardiac death and non-fatal ischemic events, and thus reflected a switch from non-fatal to fatal ischemic events due to an interaction of ischemia and exposure to class 1C antiarrhythmic drugs. Intracellular calcium overload, as is present in heart failure, reduces Na$^+$ current. Therefore, class 1C antiarrhythmic drugs are also contra-indicated in heart failure patients.

Although class 1C antiarrhythmic drugs have potential pro-arrhythmic effect in BrS patients and patients with acquired heart disease (as found in CAST), some patients with inherited Na$^+$ channel disease might benefit from using class 1C antiarrhythmic drugs. For example, flecainide might be beneficial in some patients with a LQTS3 phenotype. However, in patients with a mixed LQTS3/BrS phenotype, flecainide may evoke potentially pro-arrhythmic gating effects.

Some class 2, 3 or 4 antiarrhythmic drugs are reported to aggravate the type 1 BrS ECG. These drugs may induce ST segment elevation directly by reduction of I$_{Ca-L}$ or I$_{Ks}$ or indirectly by blockade of the $\beta$-adrenergic signalling pathway. Recently, vernakalant was added to the list of drugs to be preferably avoided; this drug is a newly developed antiarrhythmic drug with I$_{Na}$ and I$_{TO}$ reducing properties. Quinidine was formerly suggested as a drug that can aggravate features of BrS. However, there is accumulating evidence that quinidine is able to reduce arrhythmias in severely affected BrS patients.

**Psychotropic drugs**

Psychotropic drugs are prescribed to patients with psychiatric or neurologic disease and have an effect on the nervous system. However, drugs that affect neuronal ion channels may also affect cardiac ion currents. There is accumulating evidence that several antidepressants, antipsychotics and anti-epileptics are able to induce BrS signs on the ECG by Na$^+$ or Ca$^{2+}$ channel blockade.

**Anaesthetics / analgesics**

Some drugs that are used during anaesthesia block I$_{Na}$ or I$_{Ca-L}$, and thus may induce ST segment elevation. For example, lidocaine (a class 1 antiarrhythmic drug) is commonly used for local anaesthesia. However, when administered in low dosage and in combination with epinephrine, lidocaine has only a local effect and can thus be used safely for local anaesthesia. General anaesthesia can be safely performed in BrS patients when precautions are taken.
**Other substances**

Drugs from other categories may also unmask Brugada ECG and evoke arrhythmia, including drugs that cause coronary vasospasm (e.g., acetylcholine, ergonovine), some antiemetic drugs and some antihistamines. Other substances that should be avoided by BrS patients are alcohol and cocaine. Cocaethylene (a metabolite of alcohol and cocaine) is reported to be a potent \( I_{Na} \) blocker.\(^{55, 56} \) Although the mechanism is unclear, alcohol intoxication is reported to induce ventricular fibrillation in BrS patients. Increased parasympathetic activity after the intake of alcohol is suggested as the most likely pathophysiologic mechanism.\(^{57} \)

**Drug modification**

Pro-arrhythmic drug effects may not only result from their effects to block or modify ion channel properties, but also from pharmacokinetic and pharmacogenetic effects. Inter-individual differences in metabolism and elimination of drugs are underlying these effects. Drug metabolism and elimination are dependent on the cytochrome P450 system in the liver. Genetic variation in cytochrome P450 may also decrease metabolism and elimination of pro-arrhythmic drugs. These variants do not necessarily lead to total cytochrome P450 iso-enzyme dysfunction, but may impair its function and increase the serum drug concentration. Moreover, when a drug that modifies \( Na^+ \) channel properties is co-administered with another drug that is either a substrate or a blocker of the same iso-enzyme, the serum concentration of this drug may also be higher than expected. Such combination of drugs and or genetic variants may uncover BrS ECG features and/or induce arrhythmias.\(^{58} \)

**Antiarrhythmic drug effects in Brugada Syndrome**

BrS patients may suffer from electrical storms, requiring multiple defibrillations. Intravenous injection of isoproterenol may suppress recurrent ventricular fibrillation in BrS.\(^{59-61} \) Moreover, isoproterenol may prevent the typical ST-segment elevation in the right precordial leads in BrS patients.\(^{62} \) Intravenous orciprenaline may also terminate electrical storm and reduce ST-segment elevation in BrS.\(^{63} \)

A limited number of drugs have been described to prevent long-term cardiac arrhythmias in BrS patients. Quinidine seems to be the most promising drug to prevent arrhythmia in BrS patients. Quinidine is a class 1A antiarrhythmic drug, which is thought to prevent arrhythmias by blocking \( I_{TO} \). It has been reported that the typical BrS type ECG resolves during treatment with quinidine.\(^{64} \) A beneficial effect of quinidine treatment on malignant arrhythmias has been reported in a limited number of BrS patients.\(^{59-61, 63, 65-70} \) Still, there is a need for more evidence that quinidine completely
prevent arrhythmias in all BrS patients.\textsuperscript{71} As quinidine has the potential to cause QT prolongation and arrhythmia, treatment with quinidine should be preferably only initiated in severely affected BrS patients in a safe setting in an experienced medical centre.\textsuperscript{66}

A limited number of case reports have been published on treatment of ventricular arrhythmia in BrS with the phosphodiesterase inhibitor cilostazol.\textsuperscript{70,72,73} The first published report described a patient with daily ventricular fibrillations and multiple ICD shocks. After the administration of cilostazol, this patient suffered no longer form ventricular fibrillation during 13 months follow-up. However, cilostazol was not able to prevent ventricular fibrillation in the other reported cases.

Antiarrhythmic drugs in Long QT Syndrome type 3

Blockade of the QT prolonging late Na\textsuperscript{+} current is crucial to reduce the risk for arrhythmias in LQTS3 patients. Several drugs are known to block I\textsubscript{Na}. However, most of these drugs block peak I\textsubscript{Na} more strongly than late I\textsubscript{Na}.\textsuperscript{74} Novel drugs with a high selectivity for blocking the late Na\textsuperscript{+} current have recently become available or are under development. Importantly, late Na\textsuperscript{+} current is not only increased in LQTS3, but also in common acquired cardiovascular diseases, in particular, heart failure.\textsuperscript{9,10,51} Thus, drugs developed to block late I\textsubscript{Na} in acquired cardiac disease may also prevent arrhythmia in LQTS3. For example, ranolazine, developed for the treatment of angina pectoris, may also prevent arrhythmia in LQTS3.\textsuperscript{75,76} Ranolazine blocks several ion currents, including I\textsubscript{Na}, I\textsubscript{K\*}, and I\textsubscript{Ca-L}, but shows high selectivity for blocking late I\textsubscript{Na} in ventricular myocytes (30-fold more than block of peak I\textsubscript{Na}).\textsuperscript{74,75,77} Additionally, in experimental models, block of late I\textsubscript{Na} increased with stimulating frequency, whereas its selectivity for inhibiting late I\textsubscript{Na} remained.\textsuperscript{78} Thus, ranolazine may exert its effect particularly at faster heart rates, and when administered in low dose at which it has limited or no effect on other ion currents including peak I\textsubscript{Na}.\textsuperscript{74,77} Although ranolazine is contraindicated for LQTS patients in general due to its QT prolonging effect secondary to blockade of repolarizing K\textsuperscript{+} currents, treatment with ranolazine may be beneficial for LQTS3 patients.\textsuperscript{74,75,77-80}

Other specific late I\textsubscript{Na} blockers are being developed. In experimental models, GS-458967 has shown to prevent arrhythmias by blocking late Na\textsuperscript{+} current specifically.\textsuperscript{81,82} Compared to ranolazine, GS-458967 showed a higher potency and efficacy to reduce late I\textsubscript{Na} in isolated ventricular myocytes and to prevent arrhythmias in intact hearts.\textsuperscript{81} So far, no human studies of GS-458967 have been reported. Another potent experimental blocker of the late Na\textsuperscript{+} current is F15845. However, this drug was developed to block late I\textsubscript{Na} in angina pectoris and was only experimentally tested in models of ischemia.\textsuperscript{83}
Antiarrhythmic drugs in atrial arrhythmias

As sodium channels are also involved in atrial arrhythmia, we discuss the impact of antiarrhythmic drug therapy on atrial arrhythmias. Pharmacological cardioversion with flecainide may be considered in patients with recent atrial fibrillation (AF) and without a history of structural or ischaemic heart disease.\cite{84,85} After administration of flecainide, AF may persist, may be terminated, or may develop into atrial flutter.\cite{86} If atrial flutter occurs upon flecainide, slowing of conduction in the right atria and accelerated AV conduction may facilitate 1:1 conduction through the AV node and thus a rapid ventricular response, resulting in paradoxical increase in ventricular rate. This can be avoided with the addition of a beta-blocking agent.\cite{84,85}

In patients with persistent AF, drug therapy can either be focused on rate control (e.g. by administering beta-blockers, verapamil and/or digoxin) or rhythm control (e.g., by administering class 1C antiarrhythmic drugs). However, the drugs used for rhythm control, including flecainide, should better not be administered in patients with high risk for ventricular arrhythmia, e.g., BrS patients or patients with ischemic heart disease.\cite{85} In all AF patients, therapy should also be focused on the prevention of thromboembolisms by antithrombotic therapy.\cite{84}

Conclusion

Since the recognition of inherited Na\(^+\) channel disease, the cardiac Na\(^+\) channel is extensively studied. Both loss-of-function and gain-of-function mutations of the cardiac Na\(^+\) channel are associated with cardiac arrhythmia and sudden cardiac death. Pathophysiological mechanisms that may induce arrhythmia are being unravelled and include alterations in biophysical properties due to the mutation in \(SCN5A\), drug use and circumstantial factors. Insights into the mechanisms of inherited Na\(^+\) channel disease may result in tailored therapy. However, due to the complexity of cardiac electrical activity and pathophysiological mechanisms, pharmacotherapy in cardiac sodium channel disease remains challenging.

In all BrS patients, pharmacotherapy is mainly focused on the avoidance of drugs that reduce peak sodium current and thereby induce BrS ECG features or ventricular arrhythmias. BrS patients with frequent arrhythmias and/or ICD shocks may benefit from chronic drug treatment, in particular, quinidine. However, these drugs do not completely prevent arrhythmias in all BrS patients and some of these drugs have been tested in only a small number of BrS patients.

Late Na\(^+\) current disturbs cardiac electrical activity and may lead to intracellular Na\(^+\) and Ca\(^{2+}\) overload and prolongation of the AP. These patients should avoid other drugs that can prolong the AP. Blockade of late I\(_{Na}\) is the cornerstone of pharmacotherapy in LQTS3 patients with frequent arrhythmias. Specific blockade of late Na\(^+\) current can
be achieved by low doses of ranolazine. Other drugs that specifically block late $I_{Na}$ are currently tested for safety and effect.

**Expert opinion**

Altered biophysical properties of cardiac Na+ channels are the basis of arrhythmias in patients with inherited Na+ channel diseases such as BrS and LQTS3. The effects of such biophysical derangements are strongly modulated by concomitant factors. For instance, BrS patients, who have reduced depolarization reserve due to a loss-of-function $SCN5A$ mutations, are particularly vulnerable to the pro-arrhythmic effects of additional net $I_{Na}$ reducing factors, such as drugs, concomitant disease that reduces $I_{Na}$ (e.g., cardiac ischemia, heart failure), and other factors such as fast heart rates. Tailored therapy that takes all these modulating factors into account is therefore required. Clearly, prevention of cardiac arrhythmia is the cornerstone in the clinical management of these patients. This is achieved by avoidance of certain drugs and proper management of other arrhythmia-provoking factors. Other drugs, some presently in development, may be used to treat or prevent arrhythmia in patients at high risk for arrhythmia (recurrence). Such drugs are specifically targeted at the relevant biophysical alteration. For instance, drugs for treatment of LQTS3 are specifically targeted at the late Na+ current. Future studies must resolve whether these drugs are also effective in the treatment of patients in whom late $I_{Na}$ is increased from common acquired causes, e.g., heart failure. In this way, insights gained from the treatment of these rare patients with inherited arrhythmia syndromes may advance treatment strategies for the much larger groups of patients with common acquired diseases.

At present, tailored drug therapy is best achieved by educating patients affected by Na+ channel disorders about which drugs they should avoid. Naturally, all physicians prescribing drugs should be aware of possible side effects or the prescribed medication. However, for the general practitioner or, in fact, for any physician not acquainted with inherited arrhythmia syndromes, adverse side effects of especially non-cardiac Na+ channel medication may come unexpectedly. Therefore, patients with inherited Na+ channel disorders should be provided with written information to present to their treating physician. An example of such a letter for BrS patients is available at www.brugadadrugs.org.

Many patients with inherited Na+ channel disorders may go unnoticed until an additional trigger occurs that unmask their vulnerability to cardiac arrhythmias. When prescribing Na+ channel blocking medication the physician should, while taking the medical history of the patient, specifically ask for episodes of fainting, epileptic spells, a family history of sudden death, and other events possibly related to cardiac events. In case of suspicious events, it may be useful to obtain an ECG before and during initiation of the therapy. If the patient shows signs of conduction slowing, QT prolongation
or BrS-like ECG changes while taking Na⁺ channel blocking medication a specialised cardiologist and/or geneticist should be consulted for further clinical or genetic testing, including the patient’s family. During further treatment the physician should seek to avoid the combination of factors that may together facilitate the occurrence of cardiac arrhythmias.

**Article highlights**

- Both loss-of-function (Brugada Syndrome) and gain-of-function (Long QT Syndrome 3) sodium channel mutations are associated with cardiac arrhythmias.
- Reduced peak sodium current is the main arrhythmia mechanism in Brugada Syndrome.
- Increased late sodium current is the main arrhythmia mechanism in Long QT Syndrome 3.
- Cornerstone of pharmacotherapy in inherited sodium channel disease is the avoidance of drugs that affect the cardiac sodium current.
- Tailored therapy is essential, taking into account multiple sodium channel modulating factors, e.g., drug use, concomitant disease.

**Declaration of interest**

HLT was supported by the Netherlands Organization for Scientific Research (NWO, grant ZonMW Vici 918.86.616), the Dutch Medicines Evaluation Board (MEB/CBG) the European Community’s Seventh Framework Programme (FP7, grant 241679, ARITMO), and Biobanking and Biomolecular Research Infrastructure The Netherlands (BBMRI-NL).

**Acknowledgements**

The authors would like to thank dr. A.S. Amin for his help in composing figures.
References

* of interest
** of considerable interest

* Review of the mechanisms underlying SCN5A-associated arrhythmia.
* Review of inherited mutations in non-pore-forming proteins of cardiac sodium channel complexes that cause cardiac arrhythmia.
** Study from bench to community showing the association between sudden cardiac arrest and the use of noncardiac drugs.


* Consensus statement on diagnosis and management of patients with inherited arrhythmia syndromes.


Scholarly debate on the pathophysiological mechanism underlying Brugada syndrome.

36. Szel T, Antzelevitch C. Abnormal Repolarization as the Basis for Late Potentials and Fractionated Electrograms Recorded from Epicardium in Experimental Models of Brugada Syndrome. J Am Coll Cardiol 2014.


** An up-to-date list of drugs that should be avoided by Brugada patients.


** Experimental study showing the contribution of noncardiac drugs and drug metabolism to cardiac arrhythmia.


* Review on the pathophysiologic mechanisms underlying late sodium current and the tailored therapeutic strategies to alter these mechanisms to prevent triggered arrhythmia.


** Experimental study showing the anti-arrhythmic potential of a novel late I_{Na} inhibitor.


