ARRHYTHMIAS

The multifaceted cardiac sodium channel and its clinical implications

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Sudden cardiac death (SCD), defined as death from a cardiac cause occurring shortly after the onset of symptoms, is most often due to an organic cardiac abnormality such as coronary artery disease or structural heart disease.[1] However, death in young, active and previously healthy individuals with no identifiable cause on postmortem examination, termed sudden unexplained death (SUD), constitutes about 5% of SCD. When sudden death of unknown aetiology occurs in a child below 1 year of age, it is termed sudden infant death syndrome (SIDS). Unravelling the mystery surrounding SUD and SIDS has been the focus of research efforts recently.[2 3] As a result of this increased interest as well as the concurrent advances in molecular, genetic, experimental and clinical sciences, there has been an exponential increase in knowledge about the genetic background of SUD and SIDS in the past two decades. Ion channels of the heart have been found to play an integral role in this ever expanding realm of young unexpected death. Currently, primary arrhythmogenic diseases due to mutant dysfunctional ion channels, referred to as cardiac channelopathies, account for ~35% of SUD and ~20% of SIDS cases.[4 5]

The sodium (Na^+) channel, a ubiquitous member of the cardiac, neural and muscular conduction systems, has been implicated in the pathogenesis of an array of human disorders. Mutations associated with the cardiac Na^+ channel are responsible for a wide spectrum of diseases of which Brugada syndrome (BrS) and congenital long QT syndrome type 3 (LQT3) are the best described.[6] The clinical manifestations of cardiac Na^+ channel diseases are closely linked to the morphological and functional characteristics of the channel itself.

Spectrum of cardiac Na^+ channelopathic diseases

- Brugada syndrome
- Congenital LQT3
- Cardiac conduction disease
- Dilated cardiomyopathy
- Sick sinus syndrome
- Familial atrial fibrillation

CARDIAC NA^+ CHANNEL: STRUCTURE AND FUNCTION

The cardiac Na^+ channels, which are members of the voltage dependent family of ion channels, are transmembrane proteins involved in the generation and transmission of action potentials. They are large molecular complexes containing an α-subunit, four ancillary β-subunits, and several regulatory proteins. The α-subunit of the channel (designated $Na_v1.5$) forms the ion conducting pore and is encoded by the SCN5A gene located on the short arm of chromosome 3 (3p21).[7] $Na_v1.5$ consists of four homologous domains, DI to DIV, joined by interdomain linkers (figure 1). These three linkers, as well as the N terminus and the C terminus of the protein, are cytoplasmic. Each domain contains six transmembrane helices (S1 to S6) linked by intracellular or extracellular loops; S5 and S6 in each domain form the pore lining helices while S4 serves as the voltage sensor. Although $Na_v1.5$ α-subunits can act as voltage gated Na^+ channels in their own right, in vivo the Na^+ channel is part of a large multiprotein complex, existing in close association with specific cytoskeletal, regulatory, trafficking, cell adhesion, and gap junction proteins.[8] The β-subunits β1 to β4, auxiliary proteins of the cardiac Na^+ channel, are encoded by SCN1B to SCN4B genes, respectively, and have significant interactions with $Na_v1.5$.

The cardiac Na^+ channel conducts a large depolarising Na^+ current (I_{Na}) into the cell during phase 0 of the action potential. The S4 segments in each domain of $Na_v1.5$ are held responsible for voltage dependent activation. At the end of the action potential upstroke, most Na^+ channels are inactivated and do not allow further passage of ions. Inactivation is thought to be mediated mainly by the inactivation gate (DIII to DIV linker), which blocks the inside of the channel shortly after it has been activated. Furthermore, the C-terminal cytoplasmic domain plays an important role in inactivation. Channels can only be reactivated after recovery from inactivation during phase 4. However, a small percentage of channels remain available to conduct and may reopen during the plateau phase of the action potential (phases 2 and 3). This fraction of channels, <1% of total available Na^+ channels, contributes a small but potentially significant late Na^+ current (I_{NaL}).[w1]

CLINICAL MANIFESTATIONS OF SODIUM CHANNELOPATHIES

As a delicate balance exists between the flow of ions into and out of the cardiac cells, and Na^+ current plays a particularly integral role in the

physiology of the cardiac action potential, disturbances in the channel function leading to either a loss or a gain in the functional properties may result in clinically significant consequences. The most common symptoms and signs of these channelopathies are depicted in figure 2.

LOSS-OF-FUNCTION Na^+ CHANNELOPATHIES

Loss-of-function Na^+ channelopathies are a group of diseases with a loss or reduction of Na^+ channel function and are caused by mutations in SCN5A and its associated genes. The prototype of this group of diseases, BrS, was initially described as a clinical entity in 1992,[9] with the earliest report of an underlying genetic mutation in 1998.[10] There are currently more than 300 known SCN5A BrS related mutations, accounting for up to 21% of BrS probands.[11] These mutations lead to a loss of Na^+ channel function through several mechanisms, including trafficking defects, generation of truncated proteins, faster channel inactivation, shift of voltage dependence of steady state activation towards more depolarised membrane potentials or slower recovery from inactivation. Apart from SCN5A, mutations in Na^+ channel β-subunits (SCN1B and SCN3B), L-type calcium channels (CACNA1C, CACNB2b, and CACNA2D1), glycerol-3-phosphate dehydrogenase 1-like enzyme gene, KCNE3, KCNJ8, KCND3, ankyrin-G, and MOG1 have also been implicated in BrS related phenotypes.[8]

The hallmark of BrS is the presence of a coved-type ST segment elevation in the anterior precordial leads (V1 to V3) on the ECG, termed type 1 ECG. Frequently, and particular so when aberrant sodium channels are involved, conduction abnormalities in all cardiac departments are present as well.[12] Drug challenge with sodium channel blockers such as flecainide or ajmaline is quite often used to unmask the type 1 ECG in affected patients (figure 3). While BrS typically manifests as ventricular fibrillation and SCD in middle aged men, individuals of all ages and both sexes may be affected. Infants and young children (<2 years of age) typically present with rapid wide complex (monomorphic) ventricular tachycardia or with evidence of prolonged conduction intervals.[13] Fever, which is an established arrhythmia trigger in BrS patients, often plays a significant role in exposing infants and young children harbouring loss-of-function Na^+ channelopathies.[w2 w3]

Cardiac conduction disease, originally described by Lenègre and Lev in elderly patients, is characterised by progressive alteration of cardiac conduction through the His-Purkinje system with right or left bundle branch block and widening of QRS complexes, eventually leading to complete atrioventricular block, syncope, and sudden death. An SCN5A mutation that segregates with cardiac conduction disease in an autosomal dominant manner was first reported in 1999.[14] Apart from the Na^+ channel genes SCN5A and SCN1B, the LMNA (lamin A/C) gene has been implicated in a complex phenotype of conduction disease associated with dilated cardiomyopathy. Dilated cardiomyopathy, in combination with atrial and ventricular arrhythmias and conduction disease, was then identified as a manifestation of SCN5A mutations.[15] Sick sinus syndrome refers to diseases of the sinus node (brady-tachy syndrome, sinus bradycardia, sinus arrest). It may be associated with loss-of-function Na^+ channelopathies and is especially severe in patients with compound heterozygous mutations (figure 4).[16] SCN5A mutations or rare variants have recently been implicated in familial atrial fibrillation, the most common arrhythmia in clinical practice.[17]

The Na^+ channel genes implicated in loss-of-function channelopathies are SCN5A, SCN1B, SCN2B, and SCN3B.[6] While each disease phenotype poses a unique clinical entity, there is also convincing evidence to suggest that all these disorders may represent a spectrum or continuum of conduction abnormalities in a given patient. Moreover, genetic studies in affected families have shown these mutations, in particular in SCN5A, to have variable penetrance and disease expression, manifesting with varying severity and phenotypes across members of the same or different generations, referred to as 'overlap syndromes'.[w4 w5] The nature of the SCN5A mutation, namely truncation and severe missense mutations with total loss of function, was found to underlie a more severe phenotype when compared with other missense mutations where some of the channel function was preserved.[18]

Brugada syndrome (BrS)

- Loss-of-function sodium channelopathy
- Prevalence: 1 in 5000
- Inheritance: autosomal dominant
- Implicated in 20% of cases of sudden unexplained death and over 10% of sudden infant death syndrome
- 15–30% of BrS patients have SCN5A mutations
- Hallmark: coved-type ST segment elevation in V1 to V3 (type 1 ECG)
- Flecainide/ajmaline challenge test used to unmask type 1 ECG
- Presents as syncope, sudden cardiac arrest, ventricular fibrillation, ventricular tachycardia, sudden cardiac death
- Cardiac events common during sleep, rest, fever

LQT3

Na^+ channel mutations that cause an increase in persistent inward sodium current during myocardial repolarisation (I_{NaL}) are referred to as gain-of-function mutations. LQT3 is a gain-of-function sodium channelopathy, accounting for 7–10% of genotyped long QT syndrome (LQTS) patients, and is characterised by cardiac events occurring predominantly at rest or sleep, prolonged QT interval on the ECG, and high lethality (figure 5).[19] The ΔKPQ—an SCN5A deletion mutation—seems to result particularly in a more virulent type of LQTS.[w6] Apart from SCN5A, other genes including

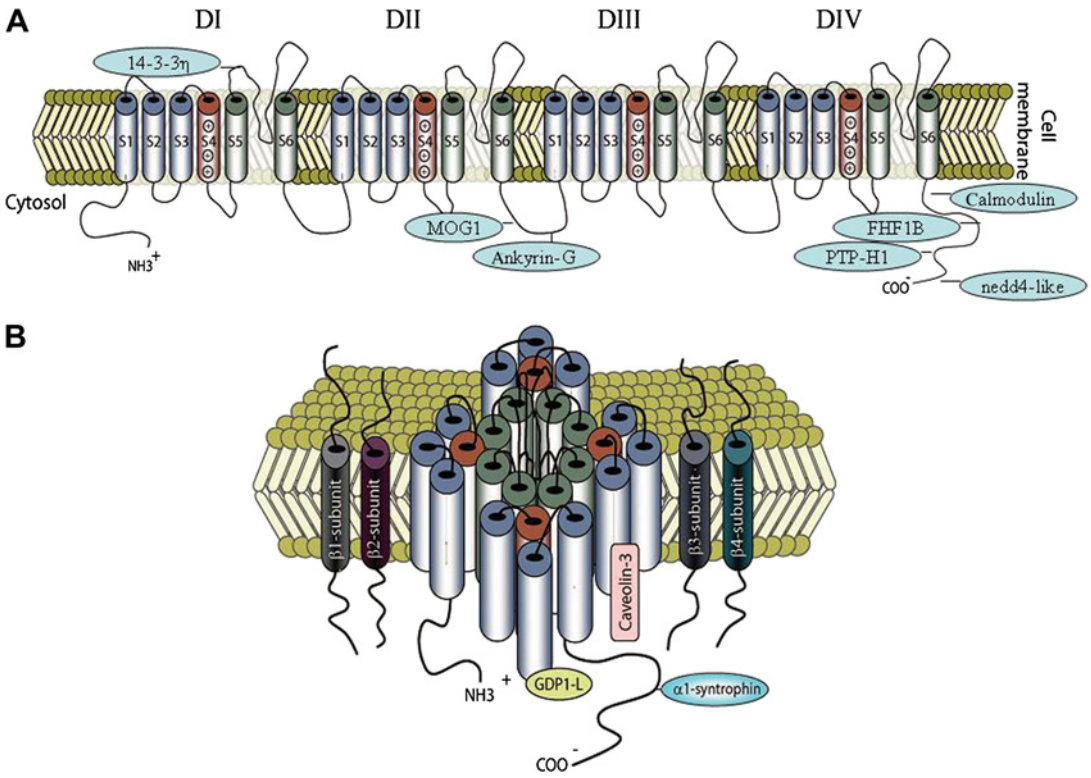

Figure 1 Schematic representation of the cardiac sodium channel. The predicted membrane topology of the α-subunit ($Na_v1.5$) is illustrated in A and the interacting β-subunits are shown in B. Other regulatory proteins, reported to interact with $Na_v1.5$, are represented schematically in A and B.

SCN4B have been implicated in LQTS by way of increased late sodium current.[6 w7]

NA^+ CHANNELOPATHIES AND SIDS

Cardiac ion channelopathies are responsible for ~20% of SIDS cases, with over half of them being attributable to SCN5A related genes, which pose as the most malignant ones.[5] Fever, a frequent accompaniment of infection and vaccination in infants and young children, could potentially play a pivotal role in the causation of ventricular arrhythmias and SIDS, especially in patients with loss-of-function Na^+ channelopathies.[w8] Population based studies on SIDS cases, seeking particularly for a temporal association with fever and/or vaccination, are warranted to confirm this potentially significant aetiopathogenesis of SIDS in vulnerable infants.

LQT3

- Gain-of-function sodium channelopathy
- Accounts for 7–10% of long QT syndrome patients
- Inheritance: autosomal dominant
- Hallmark: prolonged heart rate corrected QT (QTc) interval on ECG
- Present as syncope, sudden cardiac arrest, polymorphic ventricular tachycardia, ventricular fibrillation, sudden cardiac death
- Cardiac events common during sleep and rest

DIAGNOSTIC WORK-UP

The diagnosis of cardiac Na^+ channelopathies is established in the majority of cases by a high level of clinical suspicion on the part of the treating physician. While SCA/SCD in a previously healthy individual with a structurally normal heart is a definite and typical red flag sign, it has to be highlighted that more and more atypical presentations are being recognised. Although ventricular fibrillation and polymorphic ventricular tachycardia are the hallmarks of these diseases, other dysrhythmias such as monomorphic ventricular tachycardia, prolonged conduction intervals, atrial fibrillation, sinus bradycardia and sinus arrest, or a combination of these should prompt a 'channelopathic approach' to diagnosis. A thorough understanding of the genotype–phenotype correlations is essential to be able to spot an obvious association. For example, cardiac events occurring during rest/sleep are common in SCN5A related diseases such as BrS and LQT3, as opposed to exercise and emotional stress triggered arrhythmias in other inheritable arrhythmias. Fever associated arrhythmias in seemingly healthy young individuals are suggestive of loss-of-function Na^+ channelopathies.[w8] The relevance of elucidating a complete and comprehensive family history in index patients cannot be overemphasised.

An ECG (resting ECG, 24 h ECG or drug challenge ECG) is quite often the most useful diagnostic tool in many cases. A systematic scrutiny of all aspects of the ECG should be carried out as atrial

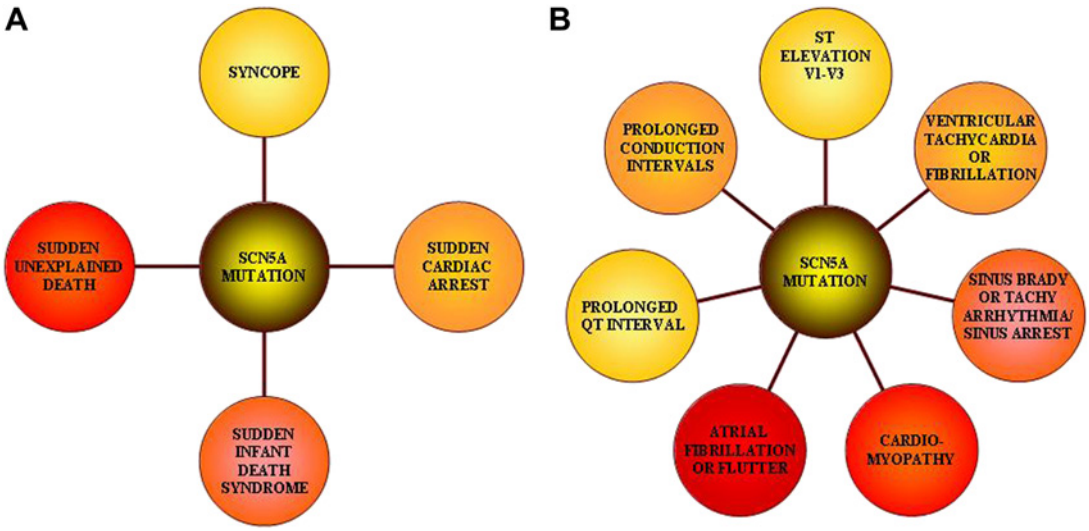

Figure 2 The most common symptoms (A) and signs (B) of cardiac sodium channelopathies.

and/or ventricular depolarisation and repolarisation abnormalities may exist. In patients with symptoms suggestive of channelopathies and an apparently normal resting ECG, 24 h ECG or an implantable loop recorder may provide additional clues to diagnosis. A prolonged QTc in an individual with SCA during rest is suggestive of LQT3. Drug challenge with Na^+ channel blockers such as flecainide and ajmaline is used to characterise better the not-so-typical ECG signs of BrS in patients with a convincing clinical picture. The role of electrophysiological testing in the diagnosis and prognosis of BrS patients has been an issue of debate and warrants further studies, particularly focusing on the various protocols used and their relation to inducibility of arrhythmias.[w9]

Echocardiography and cardiac imaging are conducted to either exclude or better delineate

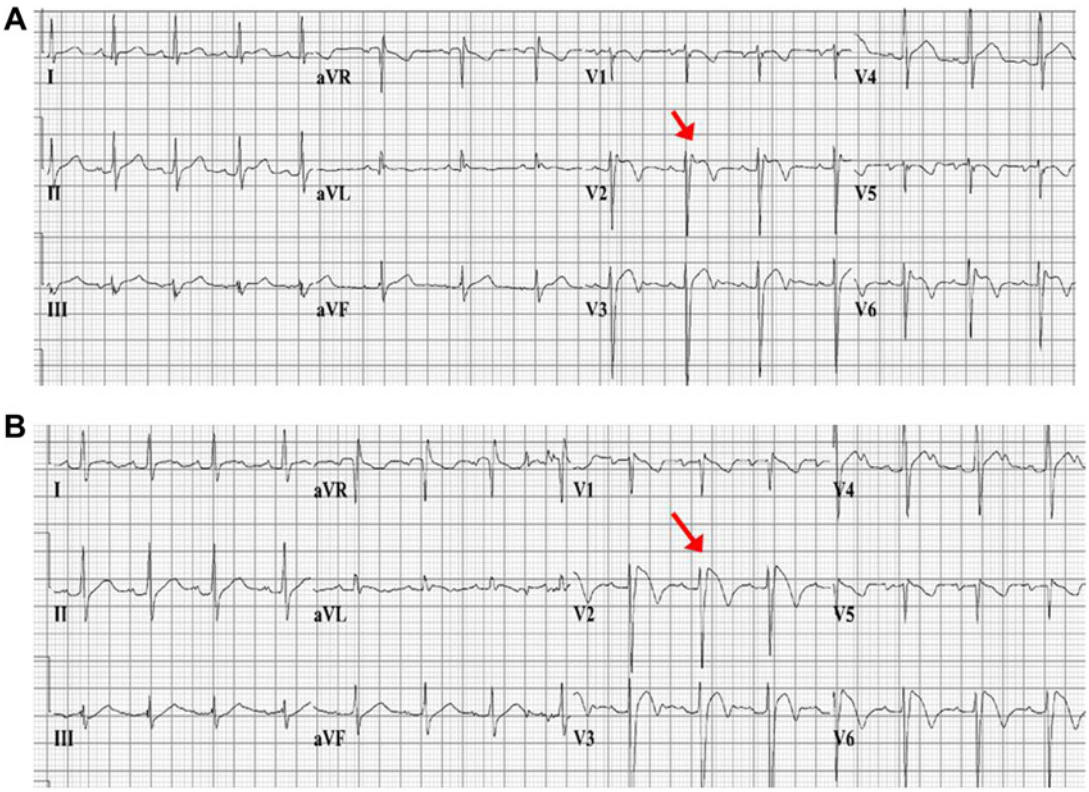

Figure 3 Twelve lead ECG tracings in a 5-year-old male patient with Brugada syndrome. Resting ECG (A) shows saddleback-type ST segment elevation in V2 (red arrow); ECG (B) after intravenous administration of flecainide unmasks the diagnostic type 1 ECG with coved-type ST segment elevation (red arrow).

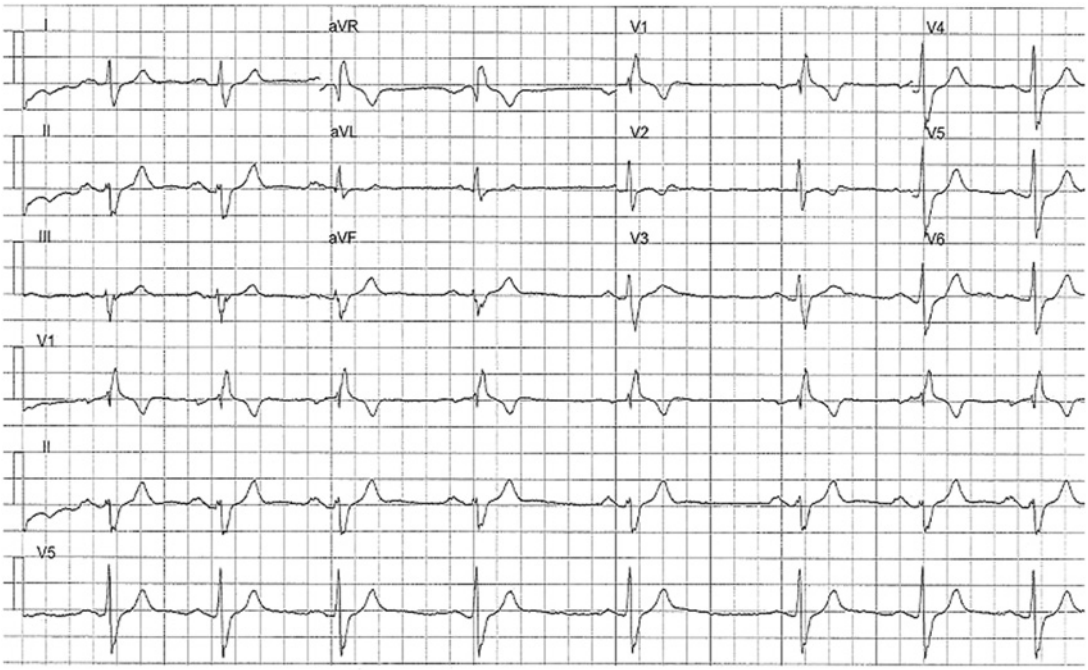

Figure 4 Twelve lead ECG tracing in a 14-year-old female patient with loss-of-function cardiac sodium channelopathy (compound heterozygous). Sinus bradycardia (53 beats/min), prolonged PR interval (225 ms), prolonged QRS duration (154 ms), and right bundle branch block morphology are seen.

associated structural abnormalities of the heart. However, the presence of congenital cardiac defects in a patient could potentially mask or delay the identification of additional channelopathic disease. Genetic testing has a significant role in diagnosing and risk-stratifying this group of disorders. It is, however, an evolving tool that complements clinical evaluation. For example, only around 20–30% of patients with BrS have identifiable SCN5A mutations. While incomplete disease penetrance and genetic heterogeneity pose challenges to efficient diagnosis and treatment of the index patients and their family members, it is clear that knowing the genetic status of a family with inherited diseases is without doubt relevant in the appropriate management of each individual.[w10] Active cascade screening[20] has proven effective in presymptomatic treatment of mutation carriers and should be an integral part of patient management in these potentially lethal disorders.

Diagnosing cardiac sodium channelopathies

- Symptoms: syncope, palpitations, sudden cardiac arrest, sudden cardiac death, sudden infant death syndrome
- Symptom trigger: sleep, rest, fever
- Family history: sudden unexplained death (SUD), sudden infant death syndrome (SIDS), arrhythmia, any of the above symptoms
- Resting ECG, 24 h ECG, drug challenge ECG
- Genetic analysis (molecular autopsy in SUD/SIDS victims)
- Family screening

RISK STRATIFICATION AND TARGETED THERAPY

The 'risk stratification triad' includes a prudent assessment of the following: severity of symptoms, extent of electrocardiographic abnormalities, and nature of underlying mutations. The aim of treating high risk patients is to provide continuous long term arrhythmia protection, thereby reducing the mortality and morbidity due to severe ventricular arrhythmias; the implantable cardioverter defibrillator (ICD) is currently the therapy of choice in this group of patients. However, concerns have been raised about the overuse of ICDs and the associated complications.[21] The role of pharmacological therapy in these patients is under evaluation at present. In BrS related phenotypes, quinidine (due to its I_{to}-blocking effect)[22] and β-blockers (due to their ability to control tachycardia related arrhythmias such as fever induced ventricular tachycardia in infants) have been proven to be efficient.[w3 w8] In LQT3, β-blockers were considered to be of questionable value (compared with LQT1 and LQT2 where they are the mainstay of treatment), but are now emerging to be potentially beneficial. Pharmacologic studies have shown that mexiletine, flecainide, and ranolazine are effective in QTc shortening in LQT3 patients with specific mutations; however, long term clinical experience with these drugs is lacking.[w12 w13] Surgical left cardiac sympathetic denervation has been used successfully in some LQT3 patients.[w14 w15] Avoidance of drugs that can potentially trigger arrhythmias in BrS patients and prolong the QT interval in LQT3 patients is an important aspect of management and often involves raising patient awareness and alerting other medical personnel.[w16]

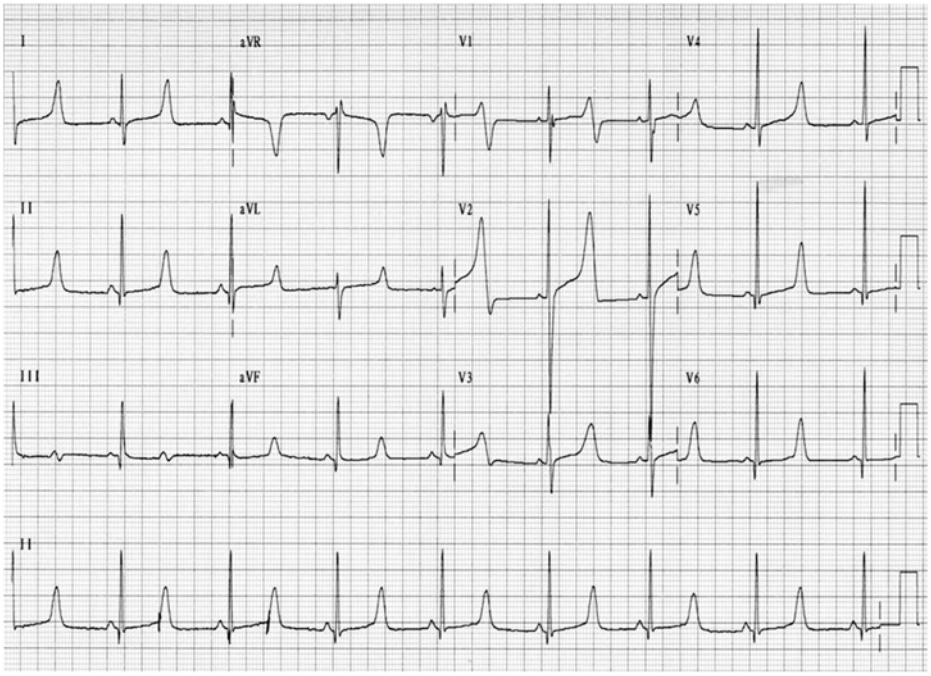

Figure 5 Standard 12 lead ECG tracing in a 12-year-old male patient with LQT3. Note the sinus bradycardia (50 beats/min), extremely prolonged QTc (550 ms), and abnormal morphology of the T waves.

Managing cardiac sodium channelopathies

- Risk stratification triad: severity of symptoms, ECG findings, and underlying mutations
- Implantable cardioverter defibrillator (ICD) therapy in high risk patients (weigh arrhythmia risk against potential ICD complications, especially in infants and young children)
- Pharmacological therapy: β-blockers, quinidine, ranolazine
- Surgical left cardiac sympathetic denervation

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MANAGING THE FAMILY MEMBERS OF SCD/SIDS VICTIMS

Postmortem genetic analysis of SCD/SIDS victims is the most imperative step in unravelling the disease-causing mutation. This knowledge not only allows for genetic counselling and expert care to be provided for the family of the deceased, but also becomes useful in screening at-risk family members, paving the way for early and accurate diagnosis and targeted therapy.

SUMMARY

The cardiac sodium channel plays an integral role in the evolution of our understanding of the aetiopathogenesis of sudden and unexpected young deaths. New and significant genetic mutations associated with a wide array of potentially lethal clinical conditions are being discovered at a rapid pace, thanks to unsurpassed advances in molecular techniques and medical acumen. A precise understanding of the structure and functions of the ion channels, combined with knowledge of the associated pathological manifestations, will enable appropriate diagnostic and therapeutic decisions to be made for this challenging group of disorders.

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