Addressing the diagnostic and therapeutic challenges in inheritable arrhythmia syndromes: with emphasis on the pediatric population

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Chapter 1

General Introduction
Adapted from: The Multifaceted Cardiac Sodium Channel and its Clinical Implications

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Heart (in press)
Inheritable arrhythmia syndromes are primary electrical abnormalities of the heart caused by derangements in the structure and function of the cardiac ion-channels. Ion-channels are pore-forming proteins that provide pathways for the controlled transmembrane movement of ions. When mutations in the genes encoding the ion-channels of the heart, namely Na+, K+ and Ca++ channels, and their associated proteins, underlie the dysfunction, they are referred to as “cardiac channelopathies”.

These are typically monogenic disorders, that is, disorders that follow a clear Mendelian pattern of inheritance, being most often inherited in an autosomal dominant pattern, and rarely in an autosomal recessive manner or as de novo mutations.

The clinical manifestations of these diseases span a wide spectrum ranging from lack of symptoms to arrhythmias and sudden death.

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. However, death in young, active and previously healthy individuals with no identifiable cause on post-mortem examination, termed sudden unexplained death (SUD), constitutes about 5% of SCD. When sudden death of unknown etiology occurs in a child below one year of age, it is termed sudden infant death syndrome (SIDS). Unraveling the mystery surrounding SUD and SIDS has been the focus of numerous research efforts recently.

As a result of this increased interest as well as the concurrent advances in molecular, genetic, experimental and clinical medicine, we have witnessed an exponential increase in knowledge on the genetic background of SUD and SIDS in the recent past. Inheritable arrhythmia syndromes play an integral role in this ever-expanding realm of young unexpected deaths and are currently implicated in ~35% of SUD and ~20% of SIDS cases.

Normal cardiac excitability results from a balance of depolarizing and repolarizing ionic currents. Each ionic current can be distinguished by its ionic selectivity and time course, which are properties that are conferred by specific ion-channels. Mutations in any of the genes involved in regulation of cardiac ion-channels may potentially result in arrhythmias and may be classified as arising from either abnormal action potential formation or abnormal action potential propagation.

With the discovery of the genetic bases of congenital long QT syndrome about two decades ago, a growing number of channelopathies have been described including Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia and short QT syndrome. Based on the underlying genetic mutations, the effect on the dysfunctional ion-channels could be either a loss or a gain of their ionic conductance, which allows for further classification of these disorders into loss-of-function and gain-of-function channelopathies, respectively (Table 1).

This thesis addresses two groups of inheritable arrhythmia syndromes, namely congenital long QT syndrome, and loss-of-function sodium channelopathies, specifically focussing on the current diagnostic and therapeutic challenges. The common clinical manifestations of these diseases are shown in Figure 1.
**Table 1. Cardiac channelopathies and their phenotypes**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein / Current affected</th>
<th>Effect of mutation</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KCNQ1</strong></td>
<td>KvLQT1 Potassium outflow ($I_{Ks}$)</td>
<td>Loss-of-function</td>
<td>Long QT syndrome type 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gain-of-function</td>
<td>Short QT syndrome type 2</td>
</tr>
<tr>
<td><strong>KCNH2</strong></td>
<td>HERG Potassium outflow ($I_{Kr}$)</td>
<td>Loss-of-function</td>
<td>Long QT syndrome type 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gain-of-function</td>
<td>Short QT syndrome type 1</td>
</tr>
<tr>
<td><strong>SCN5A</strong></td>
<td>Nav1.5 Sodium inflow ($I_{Na}$)</td>
<td>Loss-of-function</td>
<td>Brugada syndrome type 1, Cardiac conduction disease, Sick sinus syndrome, Atrial fibrillation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gain-of-function</td>
<td>Long QT syndrome type 3</td>
</tr>
<tr>
<td><strong>ANK2</strong></td>
<td>Ankyrin B, anchoring protein</td>
<td>Loss-of-function</td>
<td>Long QT syndrome type 4</td>
</tr>
<tr>
<td><strong>KCNE1</strong></td>
<td>MinK Potassium outflow ($I_{Ks}$)</td>
<td>Loss-of-function</td>
<td>Long QT syndrome type 5</td>
</tr>
<tr>
<td><strong>KCNE2</strong></td>
<td>MiRP Potassium outflow ($I_{Kr}$)</td>
<td>Loss-of-function</td>
<td>Long QT syndrome type 6</td>
</tr>
<tr>
<td><strong>KCNJ2</strong></td>
<td>Kir2.1 Potassium outflow ($I_{Ks}$)</td>
<td>Loss-of-function</td>
<td>Long QT syndrome type 7 (Anderson syndrome)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gain-of-function</td>
<td>Short QT syndrome type 3</td>
</tr>
<tr>
<td><strong>CACNA1c</strong></td>
<td>Cav1.2 Calcium outflow</td>
<td>Loss-of-function</td>
<td>Long QT syndrome type 8 (Timothy syndrome)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gain-of-function</td>
<td>Brugada syndrome type 3</td>
</tr>
<tr>
<td><strong>CAV3</strong></td>
<td>Caveolin Sodium inflow</td>
<td>Gain-of-function</td>
<td>Long QT Syndrome type 9</td>
</tr>
<tr>
<td><strong>SCN4B</strong></td>
<td>Sodium channel β-4 subunit ($I_{Na}$)</td>
<td>Gain-of-function</td>
<td>Long QT syndrome type 10</td>
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<tr>
<td><strong>AKAP9</strong> (Yotiao)</td>
<td>A-kinase anchoring protein ($I_{Ks}$)</td>
<td>Reduced current due to loss of cAMP sensitivity</td>
<td>Long QT syndrome type 11</td>
</tr>
<tr>
<td><strong>SNTA1</strong></td>
<td>α-1 syntrophin ($I_{Na}$)</td>
<td>Increased current due to S-nitrosylation of SCN5A</td>
<td>Long QT Syndrome type 12</td>
</tr>
<tr>
<td><strong>KCNJ5</strong></td>
<td>Kir3.4 ($I_{K,scn}$)</td>
<td>Loss-of-function</td>
<td>Long QT Syndrome type 13</td>
</tr>
<tr>
<td><strong>GPD1L</strong></td>
<td>Glycerol-3-phosphate dehydrogenase 1-like</td>
<td>Reduced sodium current</td>
<td>Brugada syndrome type 2</td>
</tr>
<tr>
<td><strong>CACNB2b</strong></td>
<td>Calcium channel α-subunit</td>
<td>Loss-of-function</td>
<td>Brugada syndrome type 4</td>
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<tr>
<td><strong>SCN1B</strong></td>
<td>Sodium channel β-1 subunit</td>
<td>Loss-of-function</td>
<td>Brugada syndrome type 5</td>
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<tr>
<td><strong>KCNE3</strong></td>
<td>$I_{Ks}$ and $I_{Kr}$ channels β-subunit</td>
<td>Gain-of-function</td>
<td>Brugada syndrome type 6</td>
</tr>
</tbody>
</table>

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Congenital long QT syndrome (LQTS) encompasses a heterogeneous family of disorders characterized by delayed cardiac repolarization and a propensity to syncope and fatal ventricular arrhythmias including torsades de pointes (TdP). The estimated prevalence is ~1:2000 in the western world. On the surface electrocardiogram (ECG), heart rate corrected QT (QTc) interval prolongation is the hallmark feature; however, due to incomplete disease penetrance and variable expressivity, genetically affected individuals may have a normal ECG. At present, over 600 mutations in 13 genes are implicated in the causation of the different variants; nevertheless, LQTS types 1, 2 and 3 account for up to 85% to 90% of the genotyped cases. LQT1 and LQT2 are caused by loss-of-function mutations in the genes \(\text{KCNQ1}\) and \(\text{KCNH2}\) encoding the \(I_{\text{Ks}}\) and \(I_{\text{Kr}}\) respectively, and each accounts for approximately 40% of genotype-positive LQTS patients.
LQT3, on the other hand, is caused by gain-of-function mutations of the gene (SCN5A) encoding the α subunit of the cardiac Na⁺ channel, causing an increase in persistent inward sodium current (I_{NaL}) during myocardial repolarization. Although predominantly of autosomal dominant inheritance, a severe recessive form of LQTS, termed Jervell and Lange-Nielsen syndrome, occurs rarely, and is associated with congenital deafness and severe QTc prolongation. Since the identification of genes for LQT1 (KCNQ1), LQT2 (KCNH2) and LQT3 (SCN5A) in the mid-90’s, not only has our understanding of the genotype-phenotype correlations of LQTS broadened significantly but also mutations in other associated genes and their regulatory proteins have become known, paving the way for genotype-specific management.

**Diagnostic Work-Up**

Clinical evaluation, provocation testing and molecular screening, all play integral roles in the diagnosis of LQTS, but a gold-standard diagnostic tool is still lacking. Clinical criteria incorporating family history, nature of symptoms and ECG characteristics are used extensively in the initial evaluation of patients presenting with evidence of LQTS. Based on the revised Schwartz criteria (2011), ≤1 point indicates low probability of LQTS, 1.5 to 3 points indicates intermediate probability of LQTS, and ≥3.5 points indicates high probability of LQTS. History-taking, carried out with care for detail, goes a long way in establishing or excluding a diagnosis of LQTS in an index patient. Pertinent symptoms include palpitations, syncope, seizures, sudden cardiac arrest (SCA), SCD and SIDS. The relationship of cardiac events to a particular set of triggers quite often gives a clue to the underlying genetic disorder, namely adrenergic stimuli related symptoms in LQT1 and LQT2, and sleep or rest related symptoms in LQT3. Physical exercise, particularly swimming, is a known arrhythmogenic factor.

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**Figure 2.** Schematic representation of the α-subunits of potassium channels responsible for I_{Kur}, I_{Ks}, I_{Kr}, I_{K1}, and I_{f}, showing one single domain with six (A) or two (B) transmembrane segments. Four subunits (domains) co-assemble to form one functional channel (from Amin et al. with permission).
in LQT1 and hence a personal or family history of swimming related symptoms and near-drowning should be elicited; on the other hand, emotional stress and sudden loud auditory stimuli such as wake-up alarms or telephone bells are recognized triggers for arrhythmic events in LQT2 patients. While history of unexplained SCD or aborted SCA of young family members gives a clue to the possibility of inherited arrhythmia syndromes, specific history of exercise/emotion related syncope or TdP is more typical of LQT1 and LQT2. History of drug intake and electrolyte status at the time of event occurrence is extremely relevant in order to rule-out acquired long QT syndrome. TdP, prevalent in both the congenital and acquired forms of long QT syndrome, is a dangerous arrhythmia, requiring prompt abortive measures as well as long-term preventive treatment.

Systematic ECG analysis with accurate measurement of the QT interval is an absolute prerequisite in the evaluation of patients for LQTS. The QT interval is measured manually from the beginning of the QRS complex to the end of the T wave in lead II or V5. The end of the T wave is the intersection point between the isoelectric baseline and the tangent representing the maximal downward slope of the positive T wave or maximal upward slope of the negative T wave, as shown in Figure 3. The mean of three consecutive QT intervals is calculated and QTc is obtained using the Bazett’s formula (QT / √RR). Different repolarization patterns on the ECG are associated with different genotypes: broad based prolonged T wave in LQT1, low amplitude moderately delayed T wave in LQT2, and the late appearing non-distinct T wave in LQT3. Figure 4 gives examples of each of these ECG types. Since affected patients may first be encountered by family doctors, internists or pediatricians, it is important that all physicians are aware of and can identify the clues to underlying pathology. Although prompt recognition of disease and application of established

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**Figure 3.** Illustration of QTc measurement technique. A tangent is drawn to the steepest slope of the last limb of the T wave in lead II or V5. The end of the T wave is the intersection of the tangent with the baseline. QT is heart rate corrected with Bazett’s formula with use of the preceding RR interval (from Postema et al with permission).
Interventions lead to a significant reduction in mortality, delayed diagnosis of LQTS is not uncommon. The most common alternative diagnosis is seizure disorder, especially in LQT2 patients. While diagnosing patients with a clearly prolonged QTc (>500 ms) is usually straightforward, challenges arise when QTc values lie in the normal or borderline zone. It is for this reason that the lying-standing test, exercise stress test and epinephrine challenge test are used in unmasking subclinical LQT1 and LQT2 cases. Continuous recording of the electrical activity of the heart, with Holter monitor or insertable loop recorder, is sometimes employed when cardiac events are reported to occur in relation to a particular activity or time of day, which the resting ECG does not capture.

Genetic Testing and Risk Stratification
The evolution of genetic testing into a clinical diagnostic tool has undoubtedly revolutionized the management of patients with LQTS and other inheritable arrhythmia syndromes. It has significantly altered the dynamics of diagnosing LQTS, especially in patients with a nondiagnostic QTc where clinical scoring loses efficacy. In addition to the genotype-phenotype correlations that have emerged from genetic testing of

Figure 4. Standard twelve-lead ECG tracings, in a 13-year old male patient with LQT1 (A, QTc 580 ms), in a 12-year old female patient with LQT2 (B, QTc 600 ms), and in a 12-year old male patient with LQT3 (C, QTc 550 ms).
large cohorts of LQTS patients, an abundance of information has become available on the location, type, and biophysical function of mutations, as independent risk factors influencing the clinical course of the disorder. Age, gender, QTc, nature of genetic mutation, and response to beta-blocker therapy, could be called the “Big Five” determinants of risk of SCD in an individual with LQTS. While LQT1 males are at increased risk for cardiac events in childhood in particular, LQT2 females, probably due to sensitivity to changes in sex hormones, experience events mainly after the onset of adolescence or menopause and in the postpartum period. Occurrence of SCA in the first year of life has been found to put patients at a very high risk of subsequent SCA/SCD during the next 10 years of life. QTc >500 ms is a powerful indicator of risk; however, a quarter of LQTS mutation carriers have a normal range QTc but still exhibit a greater than 10-fold increase in life-threatening events compared to unaffected family members. Combined assessment of clinical and mutation specific data, such as their site of occurrence in the ion-channels, has recently been identified as relevant in the risk stratification of LQTS. Patients, particularly women, with intracellular cytoplasmic loop (C-loop) missense mutations in the KCNQ1 gene exhibit a high risk for life-threatening events, whereas among LQT2 patients, men with pore-loop KCNH2 mutations are more prone to SCA/SCD. A study on LQT3 patients has shown that the clinical course of patients with AKPQ mutations is more virulent than those with D1790G mutations, this effect being independent of QTc duration.

A patient with a robust clinical diagnosis of LQTS has a 75% chance that a mutation will be found in one of the disease-causing genes. However, genetic testing is still a time and cost consuming tool and is not readily and uniformly available in all centres. For these reasons, it is imperative that easily available tests like exercise stress test and Holter monitoring are effectively applied in identifying or ruling-out LQTS, particularly in silent mutation carriers and in asymptomatic relatives of affected probands. As with any clinical test, understanding the spectrum of background noise within a given genetic test is critical to interpreting the test results. Specifically, systematic evaluation of a genetic test’s “signal-to-noise” ratio is crucial to determine whether a previously unidentified variant might be the biomarker responsible for disease or whether it is a rare genetic variant with no relevance to the disease in question.

Treatment Modalities and the Challenges Therein

β-Blockers are the mainstay in managing LQTS due to their efficacy in reducing mortality among affected patients. They represent the first choice therapy in symptomatic LQTS patients, unless specific contraindications exist. The impairment in the Iks current makes LQT1 patients particularly sensitive to catecholamines and quite responsive to β-blockade; so they seldom need more than antiadrenergic therapy. Although β-blockers are the first-line treatment in LQT2 and LQT3 patients as well, their risk of cardiac events while receiving therapy (ie. breakthrough cardiac events, BCE), is higher than in LQT1 patients. The occurrence of BCE has largely been attributed to a high risk status prior to start of therapy, non-compliance and use of other QT-prolonging drugs. However, suspicion that not all β-blockers
offer equivalent protection in LQTS has prevailed,\textsuperscript{73} and has now been confirmed by our study (Chockalingam et al, provisional accept J Am Coll Cardiol). Due to an unexpectedly high risk of BCE with metoprolol compared to propranolol and nadolol, among LQT1 and LQT2 patients, we recommend that symptomatic LQT1 and LQT2 patients should be treated with either propranolol or nadolol, and to avoid the use of metoprolol in these cases. Pharmacological management of LQT3 has remained a challenge particularly due to its high risk profile and the relative paucity of literature (which is closely associated with the low disease prevalence). While sodium channel blockers like mexiletine and flecainide have proven to be efficacious in managing specific \textit{SCN5A} mutations,\textsuperscript{74-76} a large multicentre study on nearly 400 LQT3 patients (Wilde et al, submitted for publication) supports the belief that β-blockers are generally extremely effective in treating those LQT3 patients who do not have cardiac events in the first year of life.\textsuperscript{77}

The adjunctive treatment of LQTS includes left cardiac sympathetic denervation (LCSD) and implantable cardioverter defibrillator (ICD) therapy, both of which are reserved for patients with symptoms despite β-blockers, and the survivors of SCA. However, β-blocker therapy is continued with the adjunctive therapy, unless contraindicated. Whenever syncopal episodes recur despite full dose β-blockers, LCSD should be considered and implemented if possible.\textsuperscript{78,79} Surgical LCSD has also been used successfully in some LQT3 patients.\textsuperscript{68,80} ICD therapy, though life-saving in many instances, has the inherent drawbacks of inappropriate shocks, mechanical failures, and poor psychological impact, leading to major setbacks in patients of all ages, more so in the pediatric population.\textsuperscript{81,82} To overcome these disadvantages, newer, advanced, and more user-friendly devices and techniques are being successfully deployed in adults and children who qualify for ICD therapy.\textsuperscript{83,84} Other general measures undertaken to prevent arrhythmias are lifestyle modifications such as avoidance of competitive sports particularly in LQT1, potassium supplementation in LQT2, and avoidance of QT-prolonging drugs in all LQTS types (www.qtdrugs.org).

Part 2. Loss-of-Function Sodium Channelopathies

Loss-of-function sodium (Na⁺) channelopathies are a group of diseases with a loss or reduction of Na⁺ channel function and are caused by mutations in the \textit{SCN5A} gene and its associated proteins (Figure 5). The prototype of this group of diseases, Brugada Syndrome (BrS), was initially described as a clinical entity in 1992,\textsuperscript{85} with the earliest report of an underlying genetic mutation in 1998.\textsuperscript{86} There are currently more than 300 known \textit{SCN5A} BrS-related mutations, accounting for up to 21% of BrS probands.\textsuperscript{87} 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 toward more depolarized membrane potentials or slower recovery from inactivation. Apart from \textit{SCN5A}, mutations in Na⁺ channel β-subunits (\textit{SCN1B} and \textit{SCN3B}), L-type calcium channels (\textit{CACNA1C}, \textit{CACNB2b} and \textit{CACNA2D1}), glycerol-3-phosphate dehydrogenase 1-like enzyme gene
(GPD1L), KCNE3, KCNJ8, KCND3, Ankyrin-G and MOG1 have also been implicated in BrS-related phenotypes.

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.88 Frequently, and in particular so, when aberrant sodium channels are involved, conduction abnormalities in all cardiac departments are present as well.89 Drug challenge with sodium channel blockers such as flecainide or ajmaline is quite often used to unmask the Type 1 ECG in affected patients with a near normal resting ECG (Figure 6). 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.90 Fever, an established arrhythmia trigger in BrS patients, often plays a significant role in exposing infants and young children harbouring loss-of-function Na+ channelopathies.91,92

Cardiac conduction disease (CCD), originally described by Lenègre and Lev in elderly patients, is characterized by progressive alteration of cardiac conduction through the His-Purkinje system, with right or left bundle branch block, and widening of QRS complexes,
leading to complete atrioventricular block, syncope and sudden death. An SCN5A mutation that segregates with CCD in an autosomal dominant manner was first reported in 1999.93 Apart from the Na+ channel genes SCN5A and SCN1B, LMNA (lamin A/C) gene has been implicated in a complex phenotype of CCD associated with dilated cardiomyopathy (DCM). DCM in combination with atrial and ventricular arrhythmias and conduction disease was subsequently identified as a manifestation of SCN5A mutations.94 Sick sinus syndrome (SSS) 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.95 SCN5A mutations and other rare variants have recently been implicated in familial atrial fibrillation (AF), the most common arrhythmia in clinical practice.96

The Na+ channel genes implicated in loss-of-function channelopathies are SCN5A, SCN1B, SCN2B and SCN3B.9 While each disease phenotype poses a unique clinical entity, there is also convincing evidence to believe that all these disorders may represent a spectrum or continuum of conduction abnormalities in a given patient.
Moreover, genetic studies in large families have shown these mutations to have variable penetrance and disease expression, manifesting with varying severity and phenotypes across members of the same or different generations, and even in the same individual, referred to as "overlap syndromes."\textsuperscript{97,98} The nature of the SCN5A mutation has been identified to play a role in severity of presentation: namely truncation and severe missense mutations with (near) total loss of function underlie a more severe phenotype, when compared to other missense mutations where some of the channel function is preserved.\textsuperscript{99}

**Diagnostic Work-Up**

The diagnosis of loss-of-function Na\textsuperscript{+} 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 recognized. Although ventricular fibrillation and polymorphic ventricular tachycardia are the hallmarks of these diseases, other dysrhythmias such as monomorphic ventricular tachycardia, atrial fibrillation, sinusal bradycardia and sinusal arrest or a combination of these should prompt a "channelopathic approach" to diagnosis. As described earlier, a thorough understanding of the genotype-phenotype correlations is essential to be able to spot an obvious association. For instance, 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 LQTS types. Fever associated arrhythmias in otherwise healthy children are suggestive of loss-of-function Na\textsuperscript{+} channelopathies. The relevance of elucidating a complete and comprehensive family history in index cases cannot be overemphasized. An ECG (resting ECG, 24-hour ECG or drug challenge ECG) is quite often the most useful diagnostic tool in many of these patients. A systematic scrutiny of all aspects of the ECG should be carried out as atrial and/or ventricular depolarization and repolarization abnormalities may coexist. In patients with symptoms suggestive of channelopathies and an apparently normal resting ECG, a 24-hour ECG or an implantable loop recorder may provide additional clues to diagnosis. Drug challenge with Na\textsuperscript{+} channel blockers such as flecainide and ajmaline is used in better characterization of 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 scrutiny, particularly focussing on the various protocols used and their relationship to inducibility of arrhythmias.\textsuperscript{100} Echocardiography and cardiac imaging are sought to either exclude or better delineate associated structural abnormalities of the heart, while evaluating cases. 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 only complements clinical evaluation. For instance, only around 20\% to 30\% of patients with BrS have identifiable SCN5A mutations. While incomplete
disease penetrance and genetic heterogeneity pose challenges to efficient diagnosis and treatment of 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 appropriate management of each individual.101 Active cascade-screening has proven effective in presymptomatic treatment of mutation carriers and should be an integral part of patient management in all the channelopathies.

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.103 Presentation with syncope, SCA, near-SIDS, spontaneous Type 1 ECG, truncation mutations and compound heterozygosity have been recognized as signs of poor prognosis in these channelopathies (Chockalingam et al, provisional accept Heart Rhythm). The attempt to accurately risk stratify patients is currently being challenged by the high frequency of SCD among asymptomatic individuals with a dynamic ECG picture.104 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; ICD is currently the therapy of choice in this segment of patients. However, concerns have been raised about the overuse of ICD and the associated complications.82 The role of pharmacological therapy in loss-of-function Na+ channelopathies is under evaluation at present. In BrS-related phenotypes, quinidine (due to its Ito-blocking effect) and β-blockers (due to their ability to control tachycardia-related arrhythmias such as fever-induced ventricular tachycardia in infants) are proven to be efficient (Chockalingam et al, provisional accept Heart Rhythm). Avoidance of drugs that can potentially trigger arrhythmias in patients with loss-of-function Na+ channelopathies is an important aspect of management and often involves raising patient/parent awareness and alerting other medical personnel that are involved in the care of patients.106

Overlap Syndromes
The past decade has witnessed the evolution of various SCN5A-related arrhythmia syndromes which are now known to display mixed phenotypes with both loss-of-function and gain-of-function properties within families and even in the same individual under different conditions; these are known as cardiac sodium channel overlap syndromes.97,107,108 In The Netherlands, the founder mutation 1795insD in SCN5A gene has been studied extensively and is causative of a unique overlap of LQT3, BrS and progressive CCD.109 The biophysical factors and genetic modifiers that play a role in these overlap syndromes are currently being studied.

Idiopathic Ventricular Fibrillation
Idiopathic ventricular fibrillation (IVF), as the term suggests, refers to spontaneous ventricular fibrillation in patients with structurally normal hearts, the cause of which remains unknown after detailed cardiac and extracardiac evaluation.1,110 The last decade
has witnessed significant revelations concerning IVF and its association with early repolarization,\textsuperscript{111} SCN5A mutations,\textsuperscript{112} and with DPP6, a founder mutation causative of a highly lethal form of familial IVF in The Netherlands.\textsuperscript{113} With more and more information becoming available on the plausible pathogenetic mechanisms of what was considered "idiopathic" earlier, our understanding of the pathophysiology of SCD is also rapidly widening.

**Sudden Death: Managing the Victim and the Family Members**

Unexpected and premature death of a person is not only a mental shock to the family but also a great loss to society and all efforts have to be taken to unearth the cause. While a complete post-mortem examination is the norm in these cases, post-mortem genetic analysis or “molecular autopsy” of SCD/SIDS victims is extremely imperative in unraveling the underlying disease-causing mutation.\textsuperscript{114,115} This knowledge not only allows for providing genetic counselling and expert care to 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 of affected individuals.\textsuperscript{116,117} Family-screening of surviving relatives of unexplained SCD victims has been shown to be a useful tool in unravelling the underlying genetic disorders, particularly leading to a high yield of 70% diagnosis for victims in the age-group 0-10 years.\textsuperscript{116-119}

**Summary**

In this era of exponential advances in molecular cardiology, the conundrum of sudden unexplained death in the young and apparently healthy individuals is being solved at a rapid pace. Practitioners are required to be up to date with these scientific advances, not only to be able to diagnose and treat their patients appropriately, but also to be well equipped to cater to the demands and queries of the highly empowered and knowledgeable generation of the present day. Imparting evidence based information to patients/parents, thereby enabling them to make well informed choices and decisions, forms the cornerstone in managing these potentially lethal diseases.

**References**


18. Giudicessi JR, Ackerman MJ. Potassium-channel mutations and cardiac arrhythmias-diagnosis and therapy. *Nat Rev Cardiol.* 2012;9:319-332


INTRODUCTION


Outline of the Thesis

Inheritable arrhythmia syndromes constitute a new and exciting field of medicine, the understanding of which has called for the collaboration and combined efforts of cardiologists, molecular biologists, clinical geneticists, pediatricians, family practitioners, pathologists, psychologists and social workers. As detailed in Chapter 1, vast strides have been made in the last 2-3 decades in the quest for unraveling the causes of sudden unexplained death in children and young adults with structurally normal hearts; however, this being a group of phenotypically and genetically heterogeneous diseases, our diagnostic accuracy and therapeutic certainty are currently limited when confronted with patients with not-so-typical features. The purpose of this thesis is to address these challenges, both by analyzing the advantages and disadvantages of existing strategies, and by providing clinically relevant and efficient solutions for the management of these disorders, particularly congenital long QT syndrome (LQTS) and loss-of-function sodium channelopathies.

Provocation testing, using either physical exercise or pharmacological agents, has been extensively used in diagnosing patients with channelopathies. In Chapter 2, the role of the epinephrine challenge test in the evaluation of children with clinical suspicion of LQTS has been investigated by performing a prospective single centre cohort study.

In the diagnosis of LQTS, the issue of incomplete disease penetrance is compounded by lack of uniform availability of genetic testing facilities, together posing a huge dilemma to physicians. In Chapter 3, we have derived a simple exercise-based algorithm for the prediction of mutation carriehership of relatives of LQTS patients; and in Chapter 4 we have analyzed the role of Holter QTc in the diagnosis of LQTS in probands with normal range QTc.

In Chapter 5, the hypothesis that not all β-blockers are equivalent in protecting LQTS patients against arrhythmias has been investigated. By studying the electrocardiographic and clinical characteristics of a large cohort of LQT1 and LQT2 patients, we have made extremely significant findings regarding the dissimilar efficacies of the commonly used β-blockers.

Loss-of-function sodium channelopathies are increasingly being recognized as causes of (aborted) sudden cardiac death in infants and young children. As the spectrum of clinical manifestations in these disorders is very wide, cases are often being missed or misdiagnosed.

In Chapter 6, we describe the dramatic presentation and subsequent management strategies employed in an infant and her sibling detected with a loss-of-function sodium channel mutation. The unusual clinical course of the children described in chapter 6 instigated us to delve into the characteristics of this so-called “disease of middle aged men” in the pediatric population. Chapter 7 reports the findings of a multicentre study on children with loss-of-function sodium channelopathies, throwing light on the varied presenting symptoms, the often-missed diagnostic clues, and the current best practices in the treatment of affected children.
Chapter 8 reports the unique diagnosis of idiopathic ventricular fibrillation in two infants, one of whom subsequently and unexpectedly developed evidence of underlying cardiac pathology.

Chapter 9 summarizes the most important findings of the thesis and ponders on the potential future developments that this exciting and rapidly evolving branch of medicine is likely to encounter. The summary in English is followed by a Dutch summary (Samenvatting) in Chapter 10. A brief note about the author and her word of thanks follow the summary.