Genetic Basis for Cardiac Arrhythmias
Connie R. Bezzina and Arthur A.M. Wilde

Key Points

• Several arrhythmia syndromes that for long were considered idiopathic are now known to have a genetic basis and are caused by mutations in genes primarily encoding ion channels.
• Mutations in cardiac ion channels lead to abnormal ionic current characteristics via mechanisms, such as defective channel gating or reduction in sarcolemmal channel expression. This results in the electrocardiogram (ECG) features or arrhythmogenesis in the inherited arrhythmia syndromes.
• The genetic basis for most arrhythmia syndromes is heterogeneous (a given disorder may be caused by mutations in different genes) and evidence for further genetic heterogeneity exists.
• It is becoming increasingly clear that therapy should take the type of gene affected into consideration (gene-specific therapy).
• Considerable heterogeneity may exist in disease manifestation [both in severity as well as differences in disease features] among family members carrying the same mutation.

This new edition of this book includes for the first time a chapter on the genetic basis of arrhythmias, following the remarkable advances over the past 15 years in our understanding of primary cardiac arrhythmia syndromes stemming from the discovery of mutations, primarily in ion channel genes, underlying a number of these disorders [Table 123.1].

Our increased knowledge of these relatively rare syndromes has importantly provided new opportunities for patient management, such as early (presymptomatic) identification and treatment of individuals at risk of developing fatal arrhythmias. In addition, several new syndromes have recognized long-known single entities, such as the long QT syndrome, which are now subdivided into different subtypes based on their unique molecular genetic basis. This subdivision has facilitated our understanding of the pathophysiology of these disorders and uncovered unique genotype-phenotype relationships in relation to the age of onset of disease manifestations, triggers for events, and prognosis, which necessitates gene-specific therapeutic regimens.

This chapter reviews these developments at large, with emphasis on issues relating to the pathophysiology of the various syndromes and approaches to management of affected individuals.

The Cardiac Action Potential and Ion Channels

Each heartbeat is initiated by a pulse of electrical excitation that originates in the pacemaker cells of the sinus node and subsequently spreads throughout the heart. This impulse is conducted throughout the heart, largely by means of the entry of sodium ([Na+] ions into the cardiomyocytes (Fig. 123.1A). This depolarizes the cardiomyocytes, moving them away from their negative intracellular resting membrane potential and underlies the action potential (AP) upstroke, also known as phase 0. This is followed by a transient outward potassium (K') current at phase 1 that initiates cardiomyocyte repolarization. A prolonged phase, known as phase 2 or the plateau phase, ensues. At this phase a positive membrane potential is maintained for a few hundred milliseconds by a balance between the entry of calcium ([Ca^{2+}] through membrane Ca^{2+} channels and the efflux of K' through a variety of K' channels. The entry of Ca^{2+} into the cardiomyocyte causes the release of Ca^{2+} from sarcoplasmic reticulum (SR) stores ([Ca^{2+}] -induced Ca^{2+} release), which triggers contraction. This prolonged phase ensures sufficient time for
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* Although mutations have been described in this gene in individuals with this disorder, genetic linkage to this locus has not yet been demonstrated.
¶ Subtypes numbered according to date of publication of finding.
† Although described only in sporadic patients, in vitro functional studies provide evidence for a dominant effect for the mutation.
‡ All probands described carried the same de novo mutation with the exception of two siblings who inherited the mutation from their unaffected mother who was mosaic for the mutation. SR, sarcoplasmic reticulum.
adequate contraction and pumping of blood. A subsequent increase in outward \( K^+ \) current brings about phase 3 repolarization, thereby restoring the membrane potential of the cardiomyocyte back to its negative resting potential (phase 4). Calcium ions are pumped back into intracellular stores, causing relaxation of contraction, which allows filling of the ventricles prior to the next excitation.

Each of these electrical processes is detected on the surface electrocardiogram (ECG) as a signal average of the temporal and spatial gradients generated during each phase. Electrical excitation gradients in the atria are visualized as P waves, ventricular depolarization gradients are visualized as QRS complexes, and ventricular repolarization gradients are evidenced in the T wave (Fig. 123.1A).

FIGURE 123.1. Ionic currents contributing to the ventricular action potential (A) and schematic representation of a cardiomyocyte displaying (only) those proteins involved in the pathogenesis of inherited arrhythmia syndromes (B). (A) The action potential is aligned with its approximate time of action during the ECG. (B) Ankyrin-B, an adapter protein involved in long QT syndrome type 4, is not depicted.

The rapid and selective flux of \( K^+ \), \( Na^+ \), and \( Ca^{2+} \) ions across the cardiomyocyte membrane occurs through ion channels. These consist of protein complexes, the major component of which is the \( \alpha \)-subunit [Fig. 123.2]. For voltage-gated \( K^+ \) channels, the \( \alpha \)-subunit consists of six transmembrane segments. Four of these subunits assemble as tetramers around a central ion-conducting pore that is lined by loops, the amino acid sequence of which determines ion selectivity.

FIGURE 123.2. Structure of the voltage-gated potassium (\( K^+ \)) channel \( \alpha \)-subunit. The \( K^+ \) channel \( \alpha \)-subunit consists of six transmembrane segments, S1 to S6. The S4 segment is rich in positively charged basic residues, and mediates voltage sensing. Four of these \( \alpha \)-subunits assemble as tetramers around a central ion-conducting pore, which is lined by loops, the amino acid sequence of which determines ion selectivity.
Na\(^+\) and Ca\(^{2+}\) channels display a similar architecture, with the exception that the four domains contributing to the channel structure (each roughly homologous to one K\(^+\) channel \(\alpha\)-subunit) reside in one large polypeptide. Besides ion permeation, individual ion channels are also characterized by gating properties, which is the regulated opening and closing of the channels; kinetics, which is the rate at which channels open or close; and pharmacology. The channel complex also contains auxiliary subunits, called \(\beta\)-subunits, which coassemble with \(\alpha\)-subunits to modulate the function or surface density of the channel.

The maintenance of normal cardiac rhythm is dependent on the proper movement of ions mediating the AP. Thus, abnormalities in ion channel function can have disastrous consequences that manifest themselves as arrhythmias. These disorders of cardiac ion channels, commonly referred to as cardiac channelopathies, have been brought into focus over the past 15 years as mutations in genes coding for specific channels were shown to underlie specific forms of heritable arrhythmogenic disorders occurring in the structurally normal heart (Table 123.1 and Fig. 123.1B), namely, the long QT syndrome (LQTS), Andersen syndrome (AS), Brugada syndrome (BS), catecholaminergic polymorphic ventricular tachycardia (CPVT), cardiac conduction disease (CCD), atrial standstill, and most recently, the sick sinus syndrome (SSS), short QT syndrome (SQTS), familial atrial fibrillation (FAF), and Timothy syndrome (TS).

**Long QT Syndrome**

**Background**

The LQTS is a repolarization disorder characterized by prolongation of the QT interval on the surface ECG (Fig. 123.3). It usually manifests in children and adolescents and leads to syncopal episodes. The syncope in this disorder is due to a transient, rapid, polymorphic ventricular tachycardia (VT), described as *torsades de pointes* (TdP, twisting of the points), which may degenerate into ventricular fibrillation (VF) and cardiac arrest (Fig. 123.4). Syncope and sudden death are most frequent in untreated children and adolescents.

The most frequent form is the Romano-Ward type (RWS) described independently by Romano et al.\(^1\) and Ward\(^2\) in the early 1960s. It is inherited in an autosomal dominant fashion and is roughly estimated to affect 1 per 5000 individuals.\(^3\) However, as for all primary electrical disorders, large prospective studies for determination of precise prevalence are missing. Another subtype, much rarer than the RWS, was described by Jervell and Lange-Nielsen in 1957.\(^4\) This subtype, which is inherited in an autosomal recessive fashion, is also associated with sensorineural deafness. In rare instances, QT-interval prolongation forms part of a multisystem disorder affecting other organs besides the heart. Two such disorders, Andersen syndrome\(^15\) and Timothy syndrome,\(^16\) have been recognized.

**Romano-Ward Syndrome**

For long after its initial description, the LQTS was considered “idiopathic,”\(^9\) and a breakthrough in the understanding of this disorder occurred in the first half of the 1990s when the group led by Mark T. Keating\(^10\)\(^\text{11}\) identified three genetic loci for the disorder through linkage studies in families affected with the RWS. The identification of the *KCNQ1* (also known as KvLQT1),\(^12\) *KCNH2* (HERG),\(^13\) and the *SCN5A* genes,\(^14\) all encoding ion channels, and the characterization of the QT-interval–prolonging mutations within them, ushered the field of inherited cardiac arrhythmias into a new era in which the LQTS became the paradigm for the study of these disorders (Table 123.1).

Mutations in any of these three genes constitute the most common genetic cause of LQTS. Mutations in *KCNQ1,*
underlying LQTS type 1 (LQT1), were found in 42%, mutations in KCNH2 (LQT2) in 45%, and mutations in SCN5A (LQT3) in 8% of probands tested \(n = 262\). Subsequently, mutations in KCNQ1 (minK, LQT5)\(^{15}\) and KCNE2 (MiRP1, LQT6),\(^{17}\) also encoding ion channel components, were also found to be causative of the RWS. Mutations in these two genes are found less frequently (3% and 2%, respectively).\(^{15}\) Numerous KCNQ1 and KCNH2 mutations, several SCN5A mutations, and a few KCNE1 and KCNE2 mutations leading to the RWS have been reported.\(^{18}\)

Four \(\alpha\)-subunits encoded by KCNQ1 assemble with the \(\beta\)-subunit encoded by KCNE1 to form the channel that conducts the slowly activating delayed rectifier \(K^+\) current, \(I_{Ks}\).\(^{19,20}\) Similarly, four \(\alpha\)-subunits encoded by KCNH2 are thought to assemble with the \(\beta\)-subunit encoded by KCNE2 to form the channel that conducts the rapidly activating delayed rectifier \(K^+\) current, \(I_{Kr}\).\(^{17}\) Both are key repolarizing currents, crucial in control of action potential duration (APD). SCN5A encodes the \(Na^+\) channel, which brings about the rapid influx of \(Na^+\) ions \(I_{Na}\) during cardiomyocyte depolarization.

Compound heterozygosity, where an individual carries two independent mutations within the same gene (for example, two independent mutations in KCNQ1), or double heterozygosity, where an individual carries a mutation in two different genes (for example, one in KCNQ1 and another in KCNH2), is not uncommon.\(^{21}\) It has been suggested that carriers of such defects exhibit more severe clinical manifestations, including QT prolongation, syncope, and cardiac arrest, than family members carrying a single genetic defect.\(^{21}\)

In contrast to LQT1 to 3, and 6, the gene responsible for the LQT4 subtype does not encode an ion channel. This rare subtype is caused by mutation in ANK2,\(^{22,23}\) which encodes the membrane adapter protein ankyrin-B, required for coordinated assembly of the \(Na^+/Ca^{2+}\) exchanger, the \(Na^+/K^+\) adenosine triphosphatase \((ATPase)\), and the inositol triphosphate \((InsP_3)\) receptor at transverse tubule/SR sites in cardiomyocytes.\(^{22}\) Mutation in this gene was first identified in a large French kindred in whom the clinical presentation differed from the classic presentation of LQTS.\(^{22,23}\) QT prolongation was not as severe as in other forms of LQTS, and patients also presented with pronounced sinus bradycardia, polyphasic T waves, and atrial fibrillation. An additional four mutations were subsequently reported in individuals with varied arrhythmia phenotypes.\(^{24}\)

Only about 70% of LQTS patients are successfully genotyped,\(^{15}\) implying the existence of additional, still unknown gene(s), for this disorder.

**Jervell and Lange-Nielsen Syndrome**

The Jervell and Lange-Nielsen syndrome (JLNS)\(^{4}\) arises when an individual inherits mutated KCNQ1\(^{25,26}\) or KCNE1\(^{27,28}\) alleles from both parents [Table 123.1]. The mutations inherited from each parent may be either the same because of consanguinity, or different \(\text{[compound heterozygosity]}\). KCNQ1 and KCNE1 are expressed in marginal cells of the stria vascularis,\(^{25,26}\) where they are thought to play a role in homeostasis of \(K^+\) in the endolymph, a \(K^+\)-rich fluid of the inner ear. In line with the occurrence of deafness in homozygous carriers of KCNQ1 or KCNE1 mutations, mice with targeted disruption of KCNQ1 or KCNE1 are deaf and exhibit inner ear defects.

In relatives of patients with JLNS, a prolonged or mildly prolonged QT interval may segregate as a dominant trait.\(^{26}\)

**QT Interval Prolongation in Multisystem Disorders**

Andersen syndrome \((\text{AS})\)^{5,6} also referred to as LQT7 [Table 123.1], presents with the triad of \(K^+\)-sensitive periodic paralysis, ventricular arrhythmias, and dysmorphic features. The ECG features include a prolonged QT interval and abnormal T-wave morphology often presenting with very prominent U waves. Cardiac manifestations further include frequent ventricular ectopy, bidirectional VT, recurrent polymorphic VT, syncope, and cardiac arrest. However, the risk of sudden cardiac death appears to be low as compared with other forms of LQTS. Dysmorphic features include short stature, scoliosis, cleft palate, low-set ears, hypertelorism, micrognathia, and developmental features in the limbs \((\text{clindactyly, syndactyly, brachydactyly})\). Mutations in KCN2/\((\text{kir2.1})\) have been linked to the disorder.\(^{22}\) This gene encodes the inward rectifier \(K^+\) channel that conducts outward \(K^+\) current \(I_{K1}\) during the terminal repolarization and diastolic phases of the AP, contributing to repolarization and the maintenance of the membrane potential close to the resting membrane potential in both heart and striated muscle. Although the features of AS patients suggest a role for this gene in developmental signaling, the underlying mechanism is yet unknown.

The second multisystem disorder with QT-interval prolongation is Timothy syndrome,\(^{29}\) also referred to as LQT8 [Table 123.1]. In addition to severe QT-interval prolongation, additional ECG features include bradycardia and atrioventricular block. Patients also have congenital heart defects including patent ductus arteriosus, patent foramen ovale, ventricular septal defects, and tetralogy of Fallot. Other organs affected include the skin, eyes, immune system, and brain. Among the features of the disorder are syndactyly, baldness at birth, abnormal teeth, and dysmorphic facial features. Developmental delays, consistent with language, motor, and generalized cognitive impairment, also form an important part of the clinical picture. Prognosis is severe. Ten of 17 children described with the disorder died at a mean
age of 2.5 years. Arrhythmias are the most serious aspect of the disorder, and 12 of the 17 children described had life-threatening episodes. A recurrent de novo mutation [G406R] in CACNA1C, encoding the L-type calcium (Ca²⁺) channel, has been linked to this disorder.33 Considering the widespread expression of the CACNA1C gene and the importance of Ca²⁺ as an intracellular signaling molecule, the widespread cellular and organ defects in TS are not unexpected.

Pathophysiology of QT Interval Prolongation
The plateau phase of the ventricular AP that is maintained by a delicate balance between inward and outward ionic currents determines the QT interval of the surface ECG [Fig. 123.5]. During this phase of the cardiac cycle, an increase in depolarizing (Na⁺ or Ca²⁺) current or an increase in repolarizing (K⁺) current delays repolarization, thereby prolonging the QT interval. Accordingly, LQTS-associated mutations in SCN5A increase Na⁺ current, the mutation in CACNA1C produces increased Ca²⁺ current, and mutations in KCNQ1, KCNH2, KCNE1, or KCNE2 result in decreased repolarizing K⁺ current during the AP plateau [Fig. 123.5]. Since the K⁺ current encoded by KCNJ2 is active at a more terminal phase of the AP [phase 4], mutations in this gene are expected to prolong repolarization by a decreased K⁺ current during this final repolarization phase.

Potassium Channel Defects
Insight into the pathophysiology of K⁺ channel gene mutations identified in patients with the disorder has been gained by the biophysical characterization of mutant channels introduced into heterologous systems, such as Xenopus oocytes or mammalian [kidney or ovarian] cell lines, and by patch-clamp technology.34 These experiments have consistently shown that mutated KCNQ1, KCNH2, KCNE1, KCNE2, and KCNJ2 exhibit a loss of function. Thus, the outward K⁺ current carried by the defective K⁺ channel complexes is reduced by alterations in channel gating or kinetics.35 Reduced K⁺ current is also observed when mutated subunits coexpressed with wild-type subunits, reflecting the situation where both normal [wild-type] and mutant subunits coexist as in the case of an individual who inherits a normal allele from one parent and a mutated allele from the other parent. Furthermore, in the latter situation, since K⁺ channel α-subunits assemble as tetramers, the channel is expected to be formed by a stochastic distribution of normal and mutated subunits. In some instances, the mutant subunits do not form functional channels on their own and do not assemble with normal subunits. In this case, ionic current is reduced by around 50%.

However, some defective subunits not only fail to generate functional channels themselves, but by assembling with normal subunits may function as “poison peptides,” producing a loss of function greater than 50%.36 This “dominant negative” effect is presumed to reflect dysfunction of heterotetrameric channels containing even a single mutant subunit in the tetramer. This latter mechanism underlies the autosomal dominant-type inheritance of the RWS and of AS. Reductions in current can also occur by defective intracellular processing, leading to an impaired transport of the channel to the cardiomyocyte membrane.37

In the JLNS, KCNQ1 mutations lead to α-subunits that do not form functional channels on their own and exert only a mild dominant-negative effect on wild-type subunits38 or lack such an effect altogether.39 Although missense mutations have also been described, most mutations are nonsense, deletion, or frameshift mutations,18 leading to premature truncation of the channel protein, thereby precluding assembly with wild-type subunits. This explains the recessive nature of the JLNS and the normal hearing and normal or near-normal QT-interval in some heterozygous carriers.

Sodium Channel Defects
The almost universal pathophysiological mechanism of SCN5A mutations in LQTS is enhanced persistent Na⁺ current.64 While normal Na⁺ channels undergo virtually complete fast inactivation [a process whereby the channels become nonconducting] shortly following opening, inherited mutations causing LQTS disrupt this process and actually lead to channel reopening to provide a very small depolarizing current during the AP plateau. While this persistent current is only a fraction of the total Na⁺ current responsible for cardiomyocyte depolarization, it may cause significant AP prolongation, because it occurs during a phase of the cardiac cycle when the membrane potential is governed by a delicate balance of depolarizing and repolarizing currents. Thus, small disruptions of this balance may profoundly affect membrane potential.42 A defect in one of the two inherited parental copies of the SCN5A gene is sufficient to account for the observed autosomal dominant transmission.36

Calcium Channel Defects
Only one recurrent mutation [G406R] in the CACNA1C gene has thus far been linked to TS. Expression studies demonstrated that this mutation led to an almost complete loss of voltage-dependent channel inactivation. A slowed rate of Ca²⁺ channel inactivation would prolong the inward (depolarizing) Ca²⁺ current during the plateau phase of the AP, delaying cardiomyocyte repolarization.

Ankyrin
Mutations in ankyrin-B appear to lead to loss of function, resulting in loss of expression and mislocalization of the Na⁺/Ca²⁺ exchanger, the Na⁺/K⁺ ATPase, and the InsP₃ receptor,23,24 with ensuing abnormal Ca²⁺ dynamics. In support of a role of ankyrin-B mutation in the pathogenesis of cardiac arrhythmias, mice heterozygous for a null mutation in ankyrin-B [ankyrin-B−/−] display a cardiac phenotype similar to humans.23

Recognition of the Problem
Patients with LQTS usually come to medical attention after episodes of unexplained syncope, aborted sudden death or a sudden death in their immediate family, or rarely, QT-interval prolongation on an incidental ECG. The identification of a proband with the LQTS should prompt a family
FIGURE 123.5. Pathophysiologic mechanisms of ion channel mutations in long QT syndrome (LQTS) and short QT syndrome (SQTS). (A) Schematic ECG representation. The red dotted line represents QT interval prolongation (left panel) and shortening (right panel) as can be observed in the LQTS and SQTS, respectively. (B) The ventricular action potential (AP). The red dotted line represents prolongation (left) and shortening (right) of action potential duration (APD) as can be observed in the LQTS and SQTS, respectively. (C) Effect of mutations on current characteristics in LQTS (left) and SQTS (right). By convention, upward (positive) deflections represent outward current, downward (negative) deflections represent inward current. Normal (solid gray line) and abnormal (dotted red line) current characteristics are aligned with their approximate time of action during the ECG (A) and the ventricular AP (B). Reduced I_{Ks} activity underlies APD prolongation in LQT1 and 5, while increased I_{Ks} activity underlies APD shortening in SQT2. Reduced I_{Kr} activity underlies APD prolongation in LQT2 and 6, while increased I_{Kr} activity underlies APD shortening in SQT1. Reduced I_{K1} activity during the terminal phase of repolarization underlies APD prolongation in LQT7, while increased I_{K1} activity underlies APD shortening in SQT3. An enhanced I_{Na} and an enhanced I_{Ca-L} during the AP plateau prolong APD in LQT3 and LQTS, respectively.
study for identification of other affected family members. A score system, taking into account ECG findings, clinical history, and family history, has been proposed for classification of probability that a given patient indeed suffers from LQTS.\(^\text{44}\) Probands often have more severe clinical manifestations than family members.\(^\text{44}\)

In the case of an asymptomatic individual presenting with a prolonged QT interval on an incidental ECG, a medical history is important in distinguishing drug-induced QT-interval prolongation (i.e., the acquired LQTS) from the inherited form.

The QT interval should be measured from the onset of the Q wave to the end of the T wave in an ECG lead, usually lead II, in which the amplitude of the T wave is large enough to accurately identify the termination of repolarization. The QT-interval strongly depends on heart rate. Hence, a rate correction is applied for which several formulas exist. Despite inaccuracy at both ends of the rate spectrum, the Bazett's correction is applied for which several formulas exist. Despite inaccuracy at both ends of the rate spectrum, the Bazett's formula is generally used: QTc [ms] = QT (ms)/√RR [s].\(^\text{45}\) Normal QTc (QT-interval corrected for heart rate) values for adults are ≤440 ms for males and ≤450 ms for females.

On examination, the only abnormality is the ECG. Physical examination and further (non-ECG) cardiovascular evaluation is typically without any abnormalities.

Patients with the JLNS type present with congenital neural deafness.

Diagnostic Tests

The subdivision of the LQTS into the various genetic subtypes not only has provided insight into the pathophysiological mechanisms in this disorder, but also has revealed gene-specific characteristics, particularly in relation to triggers for events and ECG waveforms. Such information (obtained not only from probands but also from affected family members) points to the gene likely affected, enabling the physician to initiate the most appropriate and safe therapy (gene-specific, see below) even before results from a genetic test become available. Furthermore, the consideration of gene-specific features can be used to direct genetic screening to the most likely culprit gene. When clinical signs have been taken into account, the yield of mutation detection in the first gene tested was as high as 90% in those patients in which the genotype could be established.\(^\text{46}\)

Such information, however, is available only for the more common subtypes (i.e., LQT1, 2, and 3). It is obvious that the methods described below do not possess 100% sensitivity and specificity.

Triggers

Events triggering syncope or cardiac arrest differ among the different LQTS subtypes. LQT1 patients experience the majority of their events during exercise.\(^\text{47,48}\) This is related to activation of the \(I_{\text{Na}}\) current by adrenergic stimulation.\(^\text{49}\) LQT2 patients experience their events with acute arousal-type emotions,\(^\text{7,48}\) while LQT3 patients are at greatest risk at rest or during sleep.\(^\text{48}\) Diving and swimming, as triggers, are almost exclusive to LQT1.\(^\text{30}\) Similarly, most of the patients experiencing events upon acoustic stimuli, such as the ringing of an alarm clock are LQT2.\(^\text{47}\)

Electrocardiograph Waveforms

The genotype also affects T-wave morphology, ST-T-wave patterns, and repolarization parameters (Fig. 123.3).\(^\text{5,51}\) In LQT1, T-wave morphology is typically broad-based with a high amplitude, in LQT2 the ST-T segment has a low amplitude in the extremity leads and is biphasic in the precordial leads, and in LQT3 the T-wave has a late onset (i.e., preceded by a long isoelectric ST-T segment).

During exercise the QT interval alters in a gene-specific way.\(^\text{52}\) Normally, QT intervals shorten with exercise, and with decreasing RR intervals QTc remains within normal limits. In concordance with the predominant occurrence of arrhythmias during exercise in LQT1, the QT-interval does not appropriately shorten (and QTc might actually lengthen),\(^\text{53}\) whereas in LQT3 the QT intervals shorten and may even become normal. In LQT2 shortening is the rule, but normalization may occur.\(^\text{53}\) In exercising LQT1 patients, the increase in heart rate is less pronounced.\(^\text{53}\) LQT3 typically displays a bradycardia related QT-lengthening.

Another gene-specific response is obtained with epinephrine i.v., a test that has been advocated to unmask silent gene-carriers.\(^\text{54-56}\) In LQT1 and LQT2, the QT-interval lengthens with epinephrine, more so in LQT1,\(^\text{54,56}\) whereas in carriers of an SCN5A mutation, the QT interval does not respond.\(^\text{35}\) At steady-state conditions (upon continuous infusion of epinephrine) QT prolongation persists in LQT1, whereas in LQT2, a shortening follows the initial lengthening.\(^\text{55}\)

Risk Stratification

Evidence-Based Medicine

The largest source of data on the natural history of LQTS patients comes from the LQTS registry.\(^\text{57}\) Initially, a number of risk factors for cardiac events were identified (congenital deafness, female sex, and a history of syncope or ventricular tachyarrhythmias).\(^\text{57}\) In a later study, a firm link between the QTc interval and the risk of cardiac events was established,\(^\text{44}\) and in 1998, the influence of genotype on the clinical course of the disease was reported.\(^\text{58}\) A higher risk of cardiac events was observed for LQT1 and LQT2 patients compared to LQT3 patients. In a more recent study, QTc was confirmed as an independent risk factor, in particular in LQT1 and LQT2 patients.\(^\text{59}\) In this study, LQT2 and LQT3 patients were found to be at higher risk compared to LQT1.\(^\text{59}\) Gender was only an independent predictor of events in (male) LQT3 patients.\(^\text{59}\)

Therapy

Since the first description of LQTS, it was noted that antiadrenergic therapy should provide protection for life-threatening arrhythmias. Surgical sympathetic denervation of the heart with left cervicothoracic sympathetic ganglionectomy was introduced before beta-blockers became available.\(^\text{60}\) With regard to beta-blockade, there are no randomized control studies but firm evidence in favor of beta-blockade has been presented by Schwartz,\(^\text{7}\) who compared the incidence of events in individuals on and off antiadrenergic therapy including beta-blockers. These drugs have minimal
effect on QT interval, but their efficacy is related to an attenuation of adrenergic-mediated trigger mechanisms. Compliance with therapy is important since discontinuation of beta-blockers unmasks rebound adrenoceptor hypersensitivity to catecholamines. It is also known that absolute protection is not provided. Additional therapy consists of sympathetic ganglionectomy,62 pacemakers,64 and implantable cardioverter defibrillators (ICDs)64,65; ICDs are currently reserved for resuscitated patients and for symptomatic patients on drugs.66 Implantable cardioverter defibrillators might be the only effective treatment in LQT3 patients, although in specific LQT3 families pacemaker therapy has been proved to be efficacious.67

In recent years, an explanation for the partial effect of beta-blockers might have become available. Indeed, its efficacy is high in LQT1 patients, high to moderate in LQT2 patients, in accordance with the adrenergic triggers in these subtypes; and low to absent in LQT3.48,61,68 Alternative pharmacologic therapy has been proposed for LQT3 patients, which, based on the molecular defect, consists of Na+ channel blockers.69,70 It is important to note, however, that failures on these drugs have been described1 and that long-term studies are not available. Additional K+ supply may be supportive in LQT2 patients,72 although on the other hand, we observed no increase in extracellular K+.73 Obviously, in any therapeutic strategy the gene-specific triggers should be avoided, lifestyle measurements should be taken accordingly, and QT-prolonging drugs should be avoided.

Prolonged QT Interval in Sudden Infant Death Syndrome

A study by Schwartz and coworkers4 presented data suggesting that a subset of sudden infant death syndrome (SIDS) cases had a prolonged QT interval. Further support for a role of QT interval prolongation in SIDS became available when a de novo mutation in SCN5A was identified in an infant who nearly died of SIDS76 and a de novo KCNQ1 mutation was identified in a child who died of SIDS.78 Pathologic SCN5A mutations in another three cases of SIDS were also subsequently described.77,78 The exact prevalence of LQTS in SIDS victims remains unknown, but in our view, it is in the order of 10%.

Acquired Long QT Syndrome

The most common cause of acquired long QT syndrome (ALQTS) is drug therapy (reviewed elsewhere9). Most recognized cases of drug-induced LQTS arise during therapy with QT-prolonging antiarrhythmics, such as quinidine, sotalol, ibutilide, and dofetilide.80 For some of these, estimates of incidence range as high as 5%. Drug-associated QT prolongation and TdP are also recognized during therapy with noncardiovascular agents, including certain antihistamines, antibiotics, and antipsychotics.80

These drugs block the Ikr channel. Features in the pore of the HERG α-subunit of this channel make it susceptible to block by these drugs.81–83 Moreover, hypokalemia, which is a very common feature among patients with drug-induced TdP, not only decreases the repolarizing Ikr current per se84,85 but also potentiates drug block of residual Ikr.86

The concept of “reduced repolarization reserve” has been put forward to explain why not all patients exposed to HERG blockers experience QT prolongation and TdP. At the center of this concept is the fact that cardiomyocyte repolarization is governed by multiple currents with a degree of redundancy. Thus, a defect in any one of these currents may remain subclinical if other pathways to normal repolarization are intact. Consequently, a subclinical defect in repolarization becomes exposed by inhibition of Ikr.

Risk factors implicated in the development of this complication of drug therapy include female sex, hypokalemia, congestive heart failure, left ventricular (LV) hypertrophy, recent conversion from atrial fibrillation, marked elevation of plasma drug concentration (especially with noncardiovascular therapies), and baseline QT prolongation.93 Genetic factors are also thought to play a role. Indeed, analysis of probands with drug-induced QT interval prolongation has identified the subclinical congenital syndrome in a minority of cases.86,90 In others, polymorphism in congenital LQTS ion channel genes are thought to constitute predisposing factors.90,91

Short QT Syndrome

Background

The short QT interval syndrome (SQTS),92 first described by Gussak et al.93 in 2000, presents with exceptionally short QT-intervals, typically shorter than 300 ms [Fig. 123.6]. The risk for an arrhythmic event that may manifest as syncope, palpitations, dizziness, or (aborted) sudden death from ventricular tachyarrhythmias is high in patients with this disorder. Often, atrial fibrillation also forms part of the clinical picture. At electrophysiologic study (EPS), effective refractory periods are very short at both the atrial and ventricular level, and a very high proportion of patients are inducible in both cardiac compartments.92

Figure 123.6. Twelve-lead ECG from a patient with short QT interval syndrome. The QTc interval is 302 ms, a value that was repeatedly measured on different ECGs. No other abnormalities were present. Calibrations are standard, i.e., 10 mm = 1 mV (vertical axis), 25 mm = 1 sec (horizontal axis).
Pathophysiology of QT Interval Shortening

Five familial and two sporadic cases have so far been reported with the disorder.93–96 In the familial cases, the disorder displayed an autosomal dominant mode of inheritance. Mutations in three of the K+ channel genes involved in the LQTS have been associated with the disorder. In two families, different mutations in the KCNH2 gene, both leading to the same amino acid change [NS88K], were identified.94 In one of the sporadic cases, the disorder was attributed to mutation in KCNQ1.95 In a father and daughter from another family, the disorder was attributable to mutation in the KCNJ2 gene.96 Other as-yet-unknown genes are also expected to cause this disorder.94

Contrary to the LQTS, in the SQTS, repolarization is hastened by an enhanced outward current during repolarization (Fig. 123.5). Accordingly, electrophysiologic studies on the KCNH2, KCNQ1, and KCNJ2 mutants found in patients with the disorder revealed an increase in \( I_K \), \( I_{\text{Kr}} \), and inward rectifier K+ current \( I_{\text{K1}} \), respectively.94–96

Recognition of the Problem

Patients thus far identified with the disorder typically have QTc ≤300 ms, although QTc could be somewhat less abbreviated in the subtype caused by mutation in KCNJ2.94 However, patients studied were few, and consequently the value of QTc diagnostic of SQTS is yet to be defined. Thus it is possible that QTc intervals that are less drastically shortened might also prove arrhythmogenic.96

Other reversible reasons for a short QT interval, such as hyperkalemia, hypercalcemia, acidosis, digitalis toxicity, hyperthermia, or alterations of the autonomic tone, have to be excluded.97,98 Acetylcholine, catecholamines, and testosterone may also shorten the QT interval.99

Apart from a constantly short QT interval, patients present with a short or even absent ST segment. T waves in the precordial leads are often tall and narrow. Although in patients with the KCNH2 or KCNQ1 defect symmetrical T waves were observed,94,95 the patients carrying the KCNJ2 defect presented with asymmetrical T waves with a rapid descending limb.96 An enhanced \( I_{\text{K1}} \) mediated repolarization at the terminal phase of the AP, has been proposed to underlie this particular T-wave presentation in these patients.

Evidence-Based Medicine

Although at present the ICD is the therapy of choice in patients with SQTS, antiarrhythmic pharmacotherapy has been proposed as an adjunct therapy or an alternative therapy in infants and children in whom ICD implantation is not feasible.92 When tested in a small number of SQTS patients with a KCNH2 genetic defect, the class III agents sotalol and ibutilide and the class IC agent flecainide failed to prolong the QT interval.94,100 For sotalol, in vitro studies demonstrated a decreased sensitivity of the channel to this drug.94 In contrast, quinidine, a class IA drug, was able to prolong the QT interval, presumably by virtue of its ability to block a number of K+ channels.100,101 Ventricular programmed stimulation showed prolongation of the ventricular effective refractory period, and VF was no longer induced.100 However, only long-term follow-up of patients with ICDs who receive quinidine will be able to clarify whether this drug may be an alternative to ICD implantation. Furthermore, as evidenced in the LQTS, it is likely that patients harboring different genetic defects respond differently to the specific agents.

Brugada Syndrome

Background

The Brugada syndrome (BS), presented as a distinct clinical entity by the Brugada brothers in 1992, is characterized by sudden cardiac death from ventricular tachyarrhythmias, in conjunction with the typical ECG feature of ST segment elevation in the right precordial leads (Fig. 123.7A).102 The clinical presentation is heterogeneous and may include palpitations, dizziness, syncope, and [aborted] sudden death, but

![FIGURE 123.7. The ECG (type I) diagnostic for Brugada syndrome, and the proposed mechanism for the disorder. (A) A 12-lead ECG from a patient with Brugada syndrome due to a mutation in the SCN5A gene. Calibrations are standard, i.e., 10 mm = 1 mV (vertical axis), 25 mm = 1 sec (horizontal axis). (B) Schematic representation of right ventricular epicardial action potential changes proposed to underlie the electrocardiographic manifestation of the Brugada syndrome. A full explanation of this figure is found in the text (see Pathophysiology under Brugada Syndrome).](image-url)
many subjects are asymptomatic. In many cases, (aborted) sudden death represents the first symptom.

The syndrome typically presents during adulthood, with arrhythmic events mostly manifesting in the fourth decade of life. However, arrhythmic events in BS may occur at all ages, from infants to the elderly.

Brugada syndrome is increasingly recognized worldwide as an important cause of sudden cardiac death. It is estimated to be responsible for at least 4% of all sudden deaths and at least 20% of sudden deaths in patients with structurally normal hearts. The ECG pattern can be dynamic and is least 20% of sudden death in patients with structurally normal hearts. It is endemic in East and Southeast Asia, where it underlies the sudden unexplained death syndrome. It is particularly prevalent in Japan and Thailand, where it is the leading cause of sudden death in young men. Although in Europe BS is extensively described, as in the United States, its prevalence there is thought to be much lower. A higher disease prevalence is observed in males, particularly in regions where the disease is endemic.

Pathophysiology

Brugada syndrome is familial in about a third of patients, in which an autosomal dominant mode of inheritance is observed. The only gene thus far linked to the disorder is SCN5A in which >70 mutations leading to BS have so far been discovered. Numerous mutations have been characterized electrophysiologically and found to be associated with a decrease in Na+ current most often due to abnormalities in channel gating, or a decrease in sarclemmal expression. The latter may also result from an impaired binding to ankyrin-G.

Mutation in SCN5A, however, is found in only around 15% of probands, indicating that other genes must be involved. Linkage to a second locus on chromosome 3p25- p22 (adjacent to SCN5A) has been described; however, the culprit gene at this locus is yet unknown. The precise mechanism for ECG manifestations and arrhythmogenesis in BS is yet unresolved. However, a longstanding hypothesis based on a pure electrophysiologic dysfunction and that is compatible with a decrease in Ikur has been proposed by Antzelevitch and coworkers. This hypothesis, which categorizes BS as a repolarization disorder, revolves around abnormal shortening of the epicardial APD. Experimental as well as clinical support for this concept has been demonstrated, but an alternative hypothesis, centered on significant conduction delay in the right ventricular outflow tract (RVOT), has also been proposed. An unequal expression of the transient outward K+ current (Ito) across the thickness of the myocardium forms the basis of the repolarization disorder hypothesis. A pronounced Ito in the epicardium, compared to the midmyocardium and endocardium, renders the epicardium more susceptible to the effects of a reduced depolarizing Ikur. Thus, in the epicardium, when Ikur is reduced, as occurs with the inherited SCN5A mutations discussed above, the epicardial AP notch is accentuated and the transmural voltage gradient, normally responsible for inscription of the J-wave, becomes exaggerated. If the epicardial repolarization precedes repolarization of the midmyocardial (M) and endocardial regions, a saddleback ST segment will arise. Additional reduction in Ikur and further accentuation of the notch may cause the epicardial APD to exceed that of the endocardium, leading to reversal of the transmural voltage gradient, which manifests as a coved-type ST segment elevation and a negative T wave, the diagnostic type 1, see below) BS ECG. With further Ikur reduction, transient outward K+ current (Ito) repolarizes the membrane beyond the voltage at which L-type Ca2+ channels are activated, resulting in loss of the epicardial AP dome. This loss, however, occurs nonuniformly: epicardial cells where the AP dome is maintained ensure that negative T-waves remain present. This dispersion of repolarization also creates a vulnerable window for local reexcitation by means of a phase-2 reentry mechanism which triggers VT/VF. This hypothesis requires that the pathologic Ikur reduction leaves the endocardial AP morphology unaltered, this is accounted for by a smaller Ikur in endocardium compared to epicardium in many species, including humans. Similarly, the presence of the ECG changes in right, but not left, precordial leads in BS is explained by larger Ikur expression in right ventricular (RV) compared to LV epicardium, while the higher disease prevalence in males is paralleled by higher epicardial Ikur density in males compared to females.

Moreover, given its predominant RV involvement, some initially considered the BS a RV cardiomyopathy, akin to arrhythmogenic right ventricular cardiomyopathy (ARVC), with subtle structural abnormalities not detectable by standard diagnostic tools. While the discovery of SCN5A gene abnormalities has since drawn attention to functional [electrophysiologic] derangements in BS, recent evidence rekindles support for an abnormal structural RV component in BS. The development of structural abnormalities as a consequence of Ikur reduction has also been put forward. Recent reports of SCN5A mutations in patients with dilated cardiomyopathy lend further credence to this hypothesis.

Recognition of the Problem

Electrocardiogram Characteristics

The diagnosis of BS rests on the pattern and extent of ST segment elevation in the right precordial leads. However, the ST segment in BS is typically highly dynamic and exhibits profound day-to-day, and even beat-to-beat variation in amplitude and morphology. In this respect, pharmacologic challenge utilizing Na+ channel blockers (see below) constitute a useful diagnostic tool.

Three different ECG repolarization patterns in the right precordial leads, not all diagnostic of Brugada syndrome, are recognized:

Type 1 is characterized by a coved ST-segment elevation ≥2 mm (0.2 mV) followed by a negative T wave (Fig. 123.7A).
Type 2 is characterized by an ST-segment with a saddleback appearance having a high takeoff ST-segment elevation of ≥2 mm, a trough displaying ≥1 mm ST elevation, and then either a positive or biphasic T wave. Type 3 is characterized by a coved or saddleback ST-segment with an elevation <1 mm.

A definite diagnosis of BS can be drawn when a type I ST-segment elevation is observed in more than one right precordial lead (V1 to V3), in the presence or absence of a Na+ channel-blocking agent, and in conjunction with one of the following: documented VF, polymorphic VT, a family history of sudden cardiac death at <45 years of age, coved-type ST-segment elevations in family members, inducibility of VT with programmed electrical stimulation, syncope, or nocturnal agonal respiration. Type 2 or 3 ECGs, which might represent normal variants in the general population, are only considered diagnostic of BS after conversion to type 1 after administration of a Na+ channel blocker (and one of the above criteria).

Placement of the right precordial leads at one or two intercostal spaces higher than usual can increase the sensitivity of the ECG for detecting the BS phenotype in some patients, either in the presence or absence of a drug challenge. Electrocardiogram findings in BS may also include right bundle branch block, considered atypical because of the absence of a wide S wave in the left lateral leads. Furthermore, signs of conduction defects, including electrical axis deviation and prolongation of PQ (reflecting AV node dysfunction) and QRS intervals are often observed, particularly in patients with a mutation in SCNSA. Occasionally the ST-segment elevation is more pronounced in the inferior leads.

**Differential Diagnosis**

ST-segment elevation or syncope can be due to various other causes, including exposure to drugs, disturbance of ionic homeostasis, acute myocardial ischemia, increase in RV pressure, and most importantly, infiltrative diseases of the RV. Clinical diagnostic evaluation should be directed at excluding each of them. Brugada syndrome might be difficult to discriminate from ARVC. As in the discrimination from the other disorders, pharmacologic challenge with Na+ channel blockers may be particularly useful. Brugada syndrome should also be distinguished from early repolarization syndrome (with an elevated J-wave amplitude in the left precordial leads) and from normal degrees of right precordial ST elevation in men and athletes, which may mimic a type 2 or 3 Brugada ECG pattern. Also here, challenge with Na+ channel blockers might facilitate a proper diagnosis.

**Precipitating and Modulating Factors**

Ventricular fibrillation and sudden death in BS usually occur at rest or at night. Besides Na+ channel blockade, other drugs that precipitate or modulate the ECG manifestations of BS include tricyclic antidepressants and cocaine. It is possible but not proven that a genetic predisposition (for example, in SCNSA) explains a hypersensitive response to drugs. Also, fever is a strong precipitating factor.

**Diagnostic Tests**

**Pharmacologic Challenge with Sodium Channel Blockers**

Intravenous administration of Na+ channel blocking agents may exaggerate the ST-segment elevation or unmask it when it is not present at baseline. Although the test is recommended in patients with types 2 and 3 ECGs for the purpose of clarifying the diagnosis, the sensitivity, specificity, reproducibility, and safety of these tests are incompletely elucidated and require further investigation. The test does not provide additional diagnostic value in patients with type 1 ECGs (and can even be dangerous). Agents of the Vaughan-Williams class IA or IC (except quinidine) including ajmaline (1 mg/kg over 5 min, IV), flecaïnide (2 mg/kg over 10 min, IV, maximum 150 mg), procainamide (10 mg/kg over 10 min, IV) or pilsicainide (1 mg/kg over 10 min, IV) are commonly used. In view of the risk of invoking serious arrhythmias, infusions of these agents should be done slowly and monitored with great caution (continuous 12-lead ECG and blood pressure) in a setting that is fully equipped for resuscitation (defibrillator and ACLS facilities close at hand). The test should be terminated when the diagnostic type 1 Brugada ECG develops, the ST segment in the type 2 ECG increases ≥2 mm, premature ventricular beats or other arrhythmias develop, or QRS widens to ≥130% of baseline. Monitoring is recommended until the ECG has normalized.

Particular caution should be exercised in patients with a preexisting atrial or ventricular conduction disturbance or in the presence of wide QRS, wide P waves, or prolonged PR intervals (i.e., infranodal conduction disease) to avoid the risk of precipitating AV block. Mechanoelectrical dissociation has been encountered in some cases. Isoproterenol and sodium lactate may be effective antidotes in this setting.

**Evidence-Based Medicine**

**Risk Stratification**

The identification of the patient at risk for sudden death is the Achilles heel in BS patient care. There is agreement that resuscitated and symptomatic patients with a baseline abnormal ECG are at high risk and should be treated accordingly. However, there is controversial evidence as to the value of EPS in asymptomatic individuals with or without an abnormal baseline ECG. Electrophysiologic study inducibility is a strong predictor for future risk in the hands of Brugada et al., but not according to others. This controversy is not well explained but may be based on differences in patient inclusion. Electrophysiologic study protocols also differ slightly as to the number of stimulation sites, the number of extrasystoles, and the coupling interval (up to refractoriness or not). Consensus reports on BS recommend stimulation from the RV apex with up to three extras with cycle lengths ≥200 ms and eventually, in the case of noninducibility, RVOT pacing. As to future risk, there are no other well-established risk markers. The HV interval, a family history, and the presence of an SCNSA mutation
have been excluded. In the short term, the presence of symptoms and late potentials predict inducibility during EPS reasonably well.\(^{109}\)

**Therapy**

With the electrophysiologic (or other) mechanisms of the signature ECG and arrhythmias of BS still awaiting resolution, the only effective prevention of sudden death so far is the ICD.\(^{142,143}\) On a theoretical basis, blockade of the transient outward current \(I_{to}\) should also be effective.\(^{126}\) Indeed, in single cases, quinidine in low doses is a potent \(I_{to}\) blocker; it was shown to resolve the ST-segment elevation,\(^{144}\) and long-term treatment proved beneficial in preventing the induction of arrhythmias on EPS and the occurrence of events on follow-up.\(^{145}\)

**Isolated Cardiac Conduction Defect**

Impulses generated in the sinoatrial node travel through the atrium before reaching the atroventricular node in the lower intraatrial septum. The impulse then conducts through the atroventricular node to the His bundle, which divides into the right and left bundle branches, distributing the impulse to the right and left ventricles, respectively, via Purkinje ramifications (Fig. 123.8B). Cardiac conduction disease may manifest from conduction slowing to complete block anywhere along this path and in every degree. Cardiac conduction disease is mostly encountered as a consequence of cardiac injury (due to ischemia or surgery), as the major cardiac manifestation of neuromuscular diseases or in association with congenital cardiac abnormalities.\(^{146,147}\) However, isolated cardiac conduction disease, with a progressive nature in some instances (also known as Lenegre\(^{148}\) and Lev\(^{149}\) disease) has also been described.

Three distinct genetic forms have been distinguished in families displaying an autosomal dominant inheritance (Table 123.1). One form involves mutation in \(SCN5A\).\(^{150}\) As for those causing BS, \(SCN5A\) mutations leading to conduction disease result in loss of Na\(^+\) channel function. This decreased \(I_{Na}\) is expected to slow the rise time of the cardiac AP (phase 0), and decrease the depolarizing current to neighboring myocytes, thereby slowing cardiac conduction (Fig. 123.8). Not surprisingly, some degree of conduction slowing is not uncommon in BS.\(^{118}\) The ultimate phenotypic manifestation of reduced \(I_{Na}\) [BS or conduction disease] is likely the result of a complex interplay between yet unknown factors. Increasing fibrosis with age has been proposed to account for the degenerative aspect of the conduction disease observed in some \(SCN5A\) mutation carriers.\(^{150}\) Fibrosis as a consequence of the Na\(^+\) channelopathy has also been proposed\(^{128}\) and is supported by findings of fibrosis in heterozygous mice with targeted disruption of \(SCN5A\).\(^{151}\)

Linkage to chromosome 19q13.2–q13.3 and chromosome 16q23–24 has respectively been identified in two kindreds presenting with the progressive form of the disorder.\(^{152,153}\) The causative gene at each of these loci is yet unidentified.

Functional 2:1 atrioventricular block has been described in neonates and infants with QT-interval prolongation due to homozygous \(KCNH2\) or \(SCN5A\) mutation. This conduction defect is functional because it results from a very prolonged ventricular effective refractory period secondary to the significant reduction in repolarization forces.

The only effective treatment for conduction disease is implantation of a pacemaker in the atrium, ventricle, or both. Timely treatment is needed, and the degree of disease progression is an important parameter in decision making. Occasionally, an internal defibrillator is needed, particularly in those patients/families where conduction disease is
associated with documented or suspected malignant ventricular arrhythmias.

**Catecholaminergic Polymorphic Ventricular Tachycardia**

**Background**

Catecholaminergic polymorphic ventricular tachycardia (CPVT) occurring in the structurally normal heart is a disorder causing syncope or sudden death from adrenergic-induced (exercise or emotion) arrhythmias in the form of bidirectional and polymorphic VT [Fig. 123.9]. The ECG at rest is normal, although a tendency to sinus bradycardia has been observed. Although the initial patient groups described with CPVT were children, the disease may also present in adulthood. Sudden cardiac death (SCD) is common in untreated individuals.

A familial presentation is observed in 30% of patients and so far, two genes encoding Ca\(^{2+}\) handling proteins have been linked to the disorder. A genome scan in a family with autosomal dominant inheritance revealed linkage to chromosome 1q42–q43 containing the RYR2 gene encoding the ryanodine receptor. The identification of causative mutations in this gene quickly followed and since then more than 30 RYR2 mutations leading to CPVT have been described.

In a minority of cases the disorder displays an autosomal recessive inheritance. This form has been linked to homozygous mutations in the CASQ2 gene encoding calsequestrin 2 located on chromosome 1p13–p21. In one family with the disorder, a heterozygous CASQ2 mutation was uncovered in affected individuals. However, since some mutation carriers did not manifest disease symptoms, it is unclear whether this represents an autosomal dominant form with reduced penetrance or whether a second mutation in another gene is also involved.

A relative bradycardia at rest is observed in both genetic subtypes. Other as-yet-unknown genes are thought to cause the disorder.

**Pathophysiology**

The pathophysiologic mechanism proposed for both gene defects is an aberrant SR Ca\(^{2+}\) release. The cardiac ryanodine receptor and calsequestrin 2 are key SR components of the excitation-contraction coupling machinery. The ryanodine receptor serves as a Ca\(^{2+}\) release channel while CASQ2 is a high-capacity Ca\(^{2+}\)-binding protein whose primary function is to store the releasable Ca\(^{2+}\) within the SR [Fig. 123.1B].

Spontaneous SR Ca\(^{2+}\) release as a consequence of Ca\(^{2+}\) overload in the SR during diastole causes a depolarizing transient inward current leading to deflections in the sarcolemmal membrane potential known as delayed afterdepolarizations (DADs). If DADs have amplitude greater than the threshold potential, depolarization will occur, and an arrhythmia can be triggered. A DAD-mediated triggered activity is believed to be the principal mechanism for CPVT-associated exercise-induced arrhythmias. Although the precise pathophysiologic mechanisms remain to be resolved, an enhanced SR Ca\(^{2+}\) release appears to underlie the pathogenesis of CPVT-causing RYR2 mutations. Experimental findings on the one CPVT-associated CASQ2 mutation studied to date are also in line with such a mechanism.

**Diagnosis**

The diagnosis is readily made with an exercise test. In a given individual ventricular (and supraventricular) arrhythmias appear at a consistent threshold heart rate. Initially a bigeminy pattern occurs which, with ongoing exercise, deteriorates into more complex arrhythmias. Eventually VF might occur. A 24-hour Holter monitoring might also be useful to establish the diagnosis. Typically, arrhythmias occur only at the more rapid heart rates. At rest, a relative bradycardia is often present. Invasive electrophysiologic testing does not add to the diagnosis with the exception of isoproterenol infusion, which might elicit an arrhythmogenic response. Incomplete penetrance and variable expressivity has been reported to be common. Individuals without arrhythmias during a diagnostic exercise test might still die suddenly. Hence, one should try to obtain a genetic diagnosis whenever possible.

The differential diagnosis of CPVT in young individuals is LQTS type 1. Inappropriate lengthening of the QTc interval during exercise is the discriminating factor. Mitral valve prolapse is another disease entity with exercise-induced ventricular arrhythmias, but an echo will reveal evidence for it. Arrhythmogenic right ventricular cardiomyopathy usually presents with monomorphic left bundle branch block (LBBB) ventricular ectopy/VT, and structural abnormalities can be
observed with echo/magnetic resonance imaging (MRI). ARVC2 has been linked to RyR2 mutations\(^\text{175}\) and presents with exercise-induced polymorphic VT. Hypertrophic cardiomyopathy is an alternative disease entity, but this is also readily diagnosed with echo. In elderly subjects ischemic heart disease should be considered. In familial cases the yield of molecular genetic testing is reasonably high.

The family history is of great importance because it is often positive for sudden cardiac death at young age and contains typical stories. In the case of the recessive form, the diagnosis is more difficult due to the absence of a positive family history. However, the clinical phenotype often presents at a younger age and seems more severe.\(^\text{159}\)

Evidence-Based Medicine

Not surprisingly, the adrenergically induced arrhythmias typically respond well to beta-blockade.\(^\text{157,159,160}\) Alternative pharmacologic treatment (i.e., cordarone, calcium antagonists) is not successful,\(^\text{157}\) although recent evidence suggests that i.v. calcium blockade might significantly reduce the arrhythmia burden.\(^\text{173}\) The beta-blocker dose should be high and the drug should not display intrinsic sympathomimetic activity. Repeated exercise tests should be used to titrate the dosage, although complete absence of ventricular ectopy is usually not achieved. Failures on beta-blockade have been described, and ICD implantation might be warranted in those cases.\(^\text{160}\)

Supraventricular Arrhythmias

Idiopathic Sick Sinus Syndrome

Idiopathic (congenital) sick sinus syndrome refers to the occurrence of sinus node dysfunction in the absence of identifiable acquired cardiac conditions, such as ischemic heart disease, cardiomyopathy, congestive heart failure, or metabolic diseases.\(^\text{174}\) It is characterized by inappropriate sinus bradycardia, sinus arrest, or chronotropic incompetence. The disorder that may clinically present with fatigue, palpitations, anxiety, dizziness, fainting, and syncope is rare.\(^\text{175}\)

Over the years, various reports describing familial occurrence with autosomal dominant\(^\text{175}\) as well as autosomal recessive\(^\text{176}\) inheritance have appeared in the literature. Recently, mutations in HCN4, one of the genes encoding the \(I_h\) channel,\(^\text{174,176}\) have been described for two sporadic cases with the disorder,\(^\text{174,176}\) while compound mutations in SCN5A have been found in families displaying an autosomal recessive inheritance.\(^\text{175}\)

Spontaneous activity in sinoatrial node cells results from a characteristic phase in their AP, the slow diastolic depolarization. During this phase, the membrane potential slowly depolarizes until the threshold for a new AP is reached. Slow diastolic depolarization results from several ionic currents, among which is the pacemaker current, \(I_h\) known as “funny” current because of several unusual features. These features include its activation at hyperpolarized potentials, and its mixed permeability to Na\(^+\) and K\(^+\). At negative potentials the inward Na\(^+\) current is dominant, generating the diastolic depolarization. The channel is cyclic adenosine monophosphate (cAMP) regulated. A high intracellular cAMP, as occurs in conditions of β-adrenergic stimulation, increases \(I_h\) amplitude, accelerating diastolic depolarization and increasing heart rate, while a decrease in intracellular cAMP (as occurs during muscarinic stimulation) decreases the current, thereby slowing heart rate. This mechanism involves a direct interaction of cAMP with the channel at its cytoplasmic side.\(^\text{179}\) One of the HCN4 mutations in sick sinus syndrome leads to a truncated channel protein lacking the domain for cAMP binding, which explains the chronotropic incompetence during exercise observed in this patient.\(^\text{178}\) The other mutation, identified in a patient who also presented with QT-interval prolongation and TdP polymorphic VT, involved an amino acid substitution that led to a reduced membrane expression of the channel.\(^\text{154}\)

Although the role of \(I_h\), arising from the Na\(^+\) channel encoded by SCN5A in sinoatrial node depolarization is unclear,\(^\text{160,161}\) compound SCN5A mutations have been identified in five patients from three families with sinus node dysfunction.\(^\text{176}\) The phenotype in these individuals comprised bradycardia that progressed to atrial inexcitability during the first decade of life, as well as prolonged QRS intervals and delayed His-ventricle conduction. The SCN5A mutations identified in affected individuals exhibited severe or mild to moderate loss of function. In all cases, a mutant allele associated with a severe defect was inherited from one parent, while an allele leading to milder channel dysfunction was inherited from the other parent. In parallel to the observance of mild QT-interval prolongation in heterozygous carriers of JLNS KCNQ1 mutations,\(^\text{26}\) carriers of one mutant SCN5A allele exhibited subclinical evidence of latent cardiac conduction disease. Interestingly, two mutations segregating as recessive alleles in two of the families have also been identified in patients with LQTS and BS with conduction disease, respectively.

Bradyarrhythmia and sinus node dysfunction is also part of the clinical picture in some families with LQT3.\(^\text{51,70,182–184}\) Since in LQT3 QT-prolongation is most pronounced at lower heart rates, bradycardia represents an important indirect factor in predisposition to lethal arrhythmias in this disorder. It is even suspected to be the direct cause of sudden death in a large family with this disorder,\(^\text{67}\) a notion supported by the observance of sinus pauses and bradycardia in mice heterozygous for the LQT3 Kþ-deletion (SCN5A\(^{-/+}\)).\(^\text{185}\) A mechanism by which Na\(^+\) channel gating defects of the LQT3–type lead to bradycardia and sinus pauses has also been presented.\(^\text{186}\)

Familial Atrial Fibrillation

Idiopathic or “lone” atrial fibrillation (not associated with acquired heart disease and in the absence of any other detectable etiology) typically occurs in young and middle-aged adults.\(^\text{187}\) Among patients with atrial fibrillation, the “lone” form accounts for 3% to 15% of cases,\(^\text{187,188}\) depending on the age of the population under consideration. A familial form of the disease has long been recognized,\(^\text{189}\) and genetic loci and genes related to the disorder are starting to be uncovered.\(^\text{191–193}\)

Linkage analyses in families displaying autosomal dominant inheritance led to the identification of two
chromosomal loci, 10q22–q24 and 6q14–q16 for the disorder. The genes involved in the disorder at these two loci are yet unknown.

In a Chinese family with autosomal dominant inheritance, Chen et al. identified linkage to the region of chromosome 11 containing the KCNQ1 gene. While LQT-associated mutations in this gene led to loss of channel function, expression studies on the KCNQ1 S140G mutation identified in this family revealed enhancement of $I_{Ks}$. This abnormality is expected to cause atrial fibrillation by shortening the atrial APD and reduction of effective refractory period, which would facilitate multiple wavelet reentry, a widely accepted conceptual model for initiation and maintenance of AF. Interestingly, carriers of this mutation did not display any shortening in their QT-intervals, as one would expect from an enhanced repolarizing $K^+$ current, which is also present in the ventricles. Some carriers even exhibited QT-interval prolongation. In another study by the same group, a mutation in the KCNE2 gene was identified in two of 28 probands with the disorder. A gain of function abnormality in the background $K^+$ current produced by interaction of the KCNQ1 and KCNE2 gene products was demonstrated. However, other family members carrying this gene defect did not have atrial fibrillation. Thus, the significance of KCNE2 mutation in causality of atrial fibrillation awaits further studies. Other genes are very likely involved in the pathogenesis of lone AF.

Atrial arrhythmias were also part of the clinical spectrum in a large family with a seemingly causal D1275N SCN5A mutation, together with conduction disturbances at all cardiac levels and, in individuals with atrial arrhythmias, evidence for reduced LV function. The role of the SCN5A mutation as to the LV reduction is as yet unexplained. However, long-standing atrial arrhythmias might cause LV dysfunction. Alternatively, it might be speculated that the channelopathy might also play a role in the fibrosis.

Atrial Standstill

Atrial standstill (AS) is an extremely rare arrhythmia, characterized by the absence of electrical and mechanical activity in the atria. Electrocardiographic features include bradycardia, the absence of P waves, and a junctional narrow complex escape rhythm. About 50% of patients have Adams-Stokes attacks. In many reports, atrial standstill usually appears secondary to other clinical disorders and only a few cases of familial clustering of primary AS have been reported. In a family with a progressive form of the disorder, co-inheritance of an SCN5A mutation and a rare genotype in the regulatory region of the gene for the atrial-specific gap junction protein connexin40 (Cx40) were proposed as the genetic basis for the development of the disorder in four affected individuals. An SCN5A-related case of BS with AS has been reported.

ACC/AHA/ESC Guidelines

The majority of the disease entities discussed in this chapter are not yet a subject in the American College of Cardiology/ American Heart Association/European Society of Cardiology [ACC/AHA/ESC] guidelines. In particular, no guidelines exist as to the role of molecular genetic testing in these syndromes. As far as therapy is concerned, for example, in the ICD guidelines, most of the syndromes are discussed. Diagnostic criteria, risk stratification schemes, and approaches to therapy in Brugada syndrome are drawn from two consensus conference reports on the disorder, endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. These recommendations are based on clinical and basic science data available to date and should be considered a work in progress that will require modification as additional data from molecular and clinical studies and prospective trials become available.

General Considerations

Genetic Testing

Genetic testing is recommended to support the clinical diagnosis, for early detection of relatives at potential risk, and to enable research into genotype-phenotype relationships.

Although genetic testing might be considered the gold standard in the diagnosis of arrhythmia syndromes, it is not without difficulties. Evidence (for further) genetic heterogeneity exists for all of the disorders covered in this chapter. Thus, the possibility exists that testing of known genes fails to identify the underlying mutation that resides in as-yet-unknown genes. Moreover, once a putative mutation in a given gene is identified, unequivocal determination of whether it represents the actual pathologic genetic defect is only possible in relatively large kindreds where one is able to demonstrate co-segregation of the genetic defect with the phenotype in a large number of affected individuals. When large kindreds are unavailable, in vitro analysis of the mutated (channel) protein to prove the pathogenicity or otherwise of a given mutation, although desirable, is often not feasible.

Genotype-Phenotype Relationship

The identification of the causative mutation in a proband allows diagnosis in other family members independently of the ECG features and the arrhythmic manifestations. As for other mendelian disorders, mutations leading to primary arrhythmias are most often associated with extensive phenotypic variability with far-reaching implications for diagnosis and therapy. For example, among family members carrying an identical mutation in a single ion channel gene, some individuals may exhibit overt ECG abnormalities or suffer fatal arrhythmias, while others might not have the ECG changes or may never develop any arrhythmias during their entire life span. Most data pointing to this fact come from patients with LQTS and BS. In these disorders, screening of family members of a genotyped proband uncovers an unexpectedly large number of carriers among relatives who were considered unaffected based on clinical evaluation. Penetrances (proportion of individuals possessing a mutation who manifest features of the disease) as low as 25% and 12.5% have been observed in the LQTS and BS, respectively. The identification of such silent mutation carri-
ers is important. These individuals have a 50% chance of transmitting the genetic defect to their offspring, who in turn might be symptomatic at an earlier age.

Diverse phenotypic manifestations (pleiotropy) is notably evident for SCN5A mutations, leading to what nowadays are commonly referred to as overlap syndromes of cardiac Na+ channelopathy. In the case of two specific mutations in SCN5A (I795insD[19] and 8K1500[11]), even paradoxical phenotypic manifestations have been observed, with some mutation carriers manifesting ECG features of both LQTS and BS, while others exhibited only features of LQTS or BS. This diversity of clinical phenotypes may be attributable to the biophysical properties of a multidysfunctional mutant Na+ channel. However, this pleiotropy also provides strong evidence that genetic modifiers play an important role in determining the ultimate phenotype in cardiac channelopathies. Thus, the ultimate clinical presentation depends not only on the mutation involved but also on the genetic background on which it occurs. This means that the clinical presentation should be considered as a complex phenotype, which is not only the product of the ion channel mutation alone, but also of genetic variation—in the form of polymorphisms occurring in a number of different genes—in genes encoding other (protein) players in that particular biologic pathway. Such possible genetic modifiers of cardiac electrical phenotypes are largely uncharacterized and only starting to emerge in the literature.

Susceptibility to Common Arrhythmias

An important parallel to be drawn here is with the genetic variation constituting susceptibility to common acquired arrhythmias, such as in ischemic heart disease, hypertrophy, or heart failure, or during the use of (QT interval-prolonging) medications (discussed above), with the difference, however, that in these disorders polymorphisms are expected to influence the susceptibility to arrhythmias in the absence of a disease causing mutation. Evidence for such an effect by a polymorphism has been provided by Splawski et al. They identified a polymorphism leading to an amino acid substitution (S1103Y) in SCN5A, found primarily in individuals of African descent [and absent in Caucasians], which was more prevalent in individuals being treated for arrhythmia than in the general population, suggesting that it increases risk.

The identification of such susceptibility genes for acquired arrhythmias, however, is still in its infancy and actually constitutes a major challenge in our understanding of the genetics of common arrhythmias. It necessitates the construction of large databases of patients phenotyped in a very standardized fashion to ensure adequate power for association studies. The number of genes expected to contribute to susceptibility is unknown but is likely to be multiple. Polymorphisms in genes encoding cardiac ion channels form very plausible candidates in which to search, but then the multitude of other players within the diverse pathways leading to arrhythmia, such as cytoskeleton proteins, structural proteins [such as those linked to sudden death in familial hypertrophic cardiomyopathy], and proteins involved in processes, such as fibrosis, inflammation, cell-to-cell communication, and electrical and structural remodeling, are also of interest. With recent advances in genotyping technology, comprehensive screening of multiple genes in different pathways is now feasible. Moreover, the availability of a high-resolution genome-wide map of polymorphisms and the evolving technology for large-scale genome-wide screens [unbiased approach], and related bioinformatics, are also expected to facilitate the study of genetics of common acquired arrhythmias. This is likely to provide novel tools for risk stratification and open new opportunities for prevention and therapy of lethal arrhythmias in the common pathologies.

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