Chapter

Inherited Ventricular Arrhythmias, the Channelopathies and SCD; Current Knowledge and Future Speculation – Epidemiology and Basic Electrophysiology

Abdullah Abdulrhman Al Abdulgader

Abstract

This chapter represents advanced scientific exploration in the different disciplines of SCD and channelopathy. Epidemiology of SCD and channelopathy is given special attention. The essence of detailed electrophysiological bases of the different diseases of channelopathies and the diverse cellular pathways mandated detailed discussion that can open the closed doors that we faced to the next generation(s). Special sections have been devoted to spatial as well as temporal heterogeneity of the cardiac action potential. Genetic heterogeneity and allelic heterogeneity are two prominent findings of channelopathies that confirm the fact of the major overlap in the field. The way we present the clinical findings is a true call for the next generation(s) of clinicians and researchers to revolutionize the field in the near future. Detailed management plans based on the up to date basic sciences findings for the different channelopathies give better therapeutic options for the clinicians in the field. Unique to this chapter is the new directions to look for channelopathies beyond the human body. The new understanding of the psychophysiological well-being of HRV and the sympathovagal balance extending to cosmic resonances and its possible effect on cardiac ion channels carries new era of promising preventive, diagnostic and therapeutic options.

Keywords: arrhythmia, Brugada syndrome (BrS), cardiac coherence (CC), catecholaminergic polymorphic ventricular tachycardia, ERS early repolarization syndrome, heart rate variability, long QT syndrome (LQTS), progressive cardiac conduction disease, sudden cardiac death, Schumann resonance, solar geomagnetic activity, SNP, SQTS

1. Introduction

One of the most devastating life moments that may impact the whole life of a person, family and society is sudden death experience of close relative or beloved. The whole medical provision is dedicated to prevent or delay death while

maintaining good quality of life (QOL). For this reason, sudden loss of human life is creating the most serious challenge for medical professionals and decision-makers.

Sudden cardiac death (SCD) is defined as death occurring unexpectedly in the first hour after symptoms commence [1]. In the United States, around 300,000 deaths are occurring every year because of SCD [2]. It is conspicuous that this huge loss in the world communities is creating a major social impact. This impact is undoubtedly more destructive with the loss of young member of the family [3]. Ion channels in the myocardial cellular membrane are responsible for creating the basic unit of the electromagnetic foundation in humans known as cardiac action potential (AP). This is the result of an elegant interplay of ions at the cellular level. Genetic mutations in these channels can predispose to wide spectrum of clinical presentations and syndromes referred collectively to channelopathies (ionopathies). The basic pathology is genetic mutations creating disturbance in the process of critical ions traffic (Na^+, Ca^{2+}, K^+) across the cell membrane. The delicate miraculous balance in this ion traffic is the basic unit of the normal action potential. Disturbance of this balance in terms of loss or gain of function is the source of the fatal heart rhythm. Sadly, life-threatening arrhythmias and sudden cardiac death can be the first presenting symptom. Scientists and clinicians are racing in the last two decades in a unique complementary scientific effort to reconcile the rapidly growing body of knowledge of the molecular mechanisms and clinical correlates of SCD. In this chapter, we will review the epidemiology of the sudden cardiac death (SCD), then we will discuss the basic science of cellular action potential and its anomalies. We will navigate in detail in the genetic characterization of arrhythmic phenotypes, which started in 1995 with discovery of LQTS mutations, and the subsequent characterization of the diversity of genetic and molecular derangements, which can lead to channelopathies and the fatal rhythms.

2. Epidemiology of sudden cardiac death

Incidence and prevalence calculation in any disease in medicine is inevitably underestimation of the actual figures. This is due to the fact that underdiagnosis is the role. The most common cause of sudden death (SD) is SCD. Sudden cardiac death (SCD) is defined as sudden death within 1 h of the appearance of witnessed symptom or within 24 h of unwitnessed symptom in an individual without potentially lethal diagnosis [1].

Many cases of SCD have identifiable abnormalities such as hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, coronary artery anomalies or myocarditis [4]. However, a significant proportion of SD (3–53%) has no identifiable cause on autopsy examination, and these are labelled sudden unexpected death (SUD). Cardiac channelopathies (used interchangeably with ionopathy) account for approximately one-third of SUD cases. Worldwide records demonstrated that around 3,700,000 death per annum are due to SCD. In the western world (the United States and Europe), 1–2 death per 2000 of the general population are lost due to SCD. SCD in male gender is 3 times higher than female [2]. Channelopathies such as long QT syndrome (LQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), short QT syndrome (SQTS), early repolarization syndrome (ERS) and idiopathic VF are estimated to be responsible for 10% of SCDs [5]. It is believed that about one-third of SUD cases are due to channelopathies.

2.1 Epidemiology of channelopathies

2.1.1 Long QT syndrome

Long QT syndrome (LQTS) is an inherited genetically heterogeneous group of arrhythmias characterized by a prolonged QTc interval in the 12-lead ECGs

(with QTc values >470 ms for males and >480 ms for females, representing approximate 99th percentile values). The prevalence of LQTS in what seems to be healthy live births in Italy is 1:2500 [6]. In New Zealand, the reported prevalence is 1:4500 [7]. In Korean males, they reported QT prolongation (equal or more than 460 ms) as 1:5000 [8]. In Japanese males with high likelihood of LQTS score >3.5, the prevalence was similar to Italy (approximately 1:2500) [9].

In conclusion, the Asian reported prevalence is comparable to the west (1:5000–1:2500). At least 17 genes were identified contributing to LQTS. Mutations have been found in more than half of them (40–70%) [10]. In spite of the complexity of the subject, clinicians need to know for their practice more than 75% of mutations in congenital LQTS are located in the KCNQ1 (LQT1), KCNH2 (LQT2) or SCN5A (LQT3) genes [10]. The prevalence of the different gene mutations for LQT1, LQT2, LQT3 and others is 52%, 33%, 7% and 1.2%, respectively. A Japanese survey of 41 individuals reported genotypes in 71% constituting LQT1 38%, LQT2 38%, LQT3 21% and LQT8 3% [11]. The International LQTS Registry documented cardiac events (syncope, cardiac arrest and SCD) in LQTS individuals to be 63% for LQT1, 46% for LQT2 and 18% for LQT3 [12]. Cardiac events in LQT3, although being the less frequent, were shown to be more lethal than the other two types [12]. The triggers of the different LQTS are of special diagnostic indication. LQT1 is known to be triggered by exercise (typically swimming), while LQT2 has been linked to emotional events, like startle (typically alarm clocks) and delivery [13]. LQT3 is the 'inevitable' as it occurs during periods of rest or sleep. During childhood, boys with LQTS tends to develop more fatal attacks, compared to girls. After childhood, the incidence is comparable [14].

2.1.2 Short QT syndrome (SQTS)

SQTS was described in 2000, and it is a clinical entity characterized by short QT intervals on ECG (generally, QTc < 350 ms), high incidence of VT/VF, absence of structural heart disease, familial history of SCD and resuscitated cardiac arrest [15]. It is the severest form of the major channelopathies, with cardiac arrest/SCD being the most common presentation. Events occur during rest, sleep or exertion [4]. For this reason, high index of suspicion should be practiced in order to be able to diagnose this type of malignant channelopathies. Among 10,984 Japanese with approximately equal sex distribution, 1:3400 individuals showed QTc less than 300 ms [16]. Parts of idiopathic VF cases are likely to be borderline or latent SQTS individuals. SQTS was diagnosed in 12% of idiopathic VF survivors [17]. The course of SQTS individuals is more malignant with higher risk of recurrence of life-threatening arrhythmias and SCDs [18].

2.1.3 Brugada syndrome (BrS)

There is general impression that BrS incidence is underestimated. In one publication, BrS accounts for 4–12% of SCD [4]. It appears to be related to mutations affecting Na^+ channels. There are currently more than 300 mutations described, mostly autosomal dominant, affecting the SCN5A gene, leading to loss of Na^+ channel function in a variety of ways (interestingly, mutations in other parts of this gene lead to LQTS3). Other genes affecting the Na^+ channel are also implicated in BrS. BrS is characterized electrocardiographically by classical finding of coved ST-segment elevation in anterior precordial leads. Cardiac events secondary to ventricular tachycardia typically occur in young adults but have been described in children and infants [4]. Individuals with BrS develop a monomorphic ventricular tachycardia; often precipitated during sleep or rest, and during febrile illnesses [19].

It is thought that some SCN5A mutations alter the Na^+ channel in a temperature-dependent manner. Males have arrhythmic events more frequently, and there is thought to be a gender effect on ion channel expression [20]. The estimated prevalence of BrS ranges from 0.02 to 0.1% in Europe and from 0.1 to 0.25% in Asia [5]. Lai Tai means the southern pattern (referring to the mode of death during sleep) is a famous horror term in Thailand and 'Pokkuri'. The death secret has been diagnosed as Brugada syndrome, which is thought to be endemic heart electrical disease in this part of the world [21]. Later on, Europeans were shown to have similar prevalence [5]. About one-third of cases have been attributed to SCN5A mutations [22]. Mutations attributed to CACNA1C and CACNB2 are seen in around 12% of cases. Minor percentages are due to other gene mutations like GPD1L, SCN1B, KCNE3 and SCN3B [23–27]. In 50–80% of patients with BrS, VF or VT can be induced by ventricular extra stimuli in an EPS. There is dispersion of opinions in the ionopathy literature regarding the prognostic value of VT/VF inducibility in EPS. Nobuyuki Murakoshi and colleague consider inducibility as a poor prognostic factor, while many other authors do not believe of any significant correlation [5].

2.1.4 Early repolarization syndrome (ERS)

ERS is characterized by elevation of the QRS-ST junction (J point) and QRS notching or slurring (J wave) in multiple leads, especially the inferior and/or left precordial leads [28]. The slurred J point elevation which was interpreted by cardiology communities as normal electrocardiographic variant distracted Haissaguerre et al. who reported very important observation in this regard. Among 207 victims of idiopathic VF, 30% were found to have the slurred J point pattern (ER pattern) compared to 5% of controls [29].

In the Framingham Heart Study, the ER pattern was found in 6.1% of American and European persons and 5.8% in Finnish population [30, 31]. In Asia, the story seems to be more impressive. J wave elevation of at least 0.05 mV was detected in 7.26% of Chinese subjects [32]. In Japan, the incidence rate was 715 per 100,000 person-years [33].

In general, reviewing todays medical literature will reveal ERS prevalence figures which range from approximately 6 to 13% in the general population [34]. Male sex, younger age, lower systolic blood pressure, higher Sokolow-Lyon index for LVH calculation (S in V_1 + R in V_5 or V_6 (whichever is larger) ≥ 35 mm (≥7 large squares) or R in aVL ≥ 11 mm) and lower Cornell voltage (S in V_3 + R in aVL > 28 mm (men) or S in V_3 + R in aVL > 20 mm (women)) are independently associated with the presence of the ER pattern [30]. An important observation in that regard points to the proportionality of ER amplitude to the risk of arrhythmic death.

ER of 0.2 mV or more in ECG inferior leads was shown to have much increased risk than those without. This was concluded after long mean follow-up of 29–41 years [35]. Notching of the J point was found to be associated with worse prognosis [5]. The rapid rise of ST segment and dominance of ST pattern in athletes was found to be benign variant of ERS. Looking with eye of scrutiny will show the similarities of clinical, electrocardiographic and genetic aspects between BrS and ERS. Future research could prove both syndromes to be a spectrum of one pathology.

2.1.5 Catecholaminergic polymorphic ventricular tachycardia (CPVT)

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmogenic disorder characterized by polymorphic VT induced by physical or emotional stress without any detectable morphological abnormalities in the

heart [36]. Two important gene mutations has been described: mutations in genes encoding cardiac ryanodine type 2 receptor (RYR2) [autosomal dominant] and calsequestrin 2 (CASQ2) [autosomal recessive] [37, 38]. A subunit for inward-rectifier potassium channels called Kir2.1. Mutation in this subunit (KCNJ2) is responsible of a third variant of CPVT [39]. A Japanese report of 50 cases ranks the CPVT mutations frequency as follows: RYR2 (56%), CASQ (22%) and KCNJ2 (22%) [40]. CPVT is gaining more attention although being a rare disease compared to other channelopathies (1:10,000) because of its tendency to affect children and young adults [41]. In fact, CPVT is considered as highly malignant heart rhythm if neglected. In those situations, by the age of 20–30 years, the mortality is 30–50% [42].

2.1.6 Heart channelopathies and systemic involvement

Action potential is the basic unit of human body electricity. It is conceivable that ionopathic involvement of other systems is a fact. This will result in symptoms and syndromes that deserve attention for proper risk stratification of ionopathic subjects. Behere and Weindling elaborated on this in their unique review [43].

Jervell and Lange-Nielsen syndrome (JLNS) has been associated with about 4% of patients with the bilateral sensorineural loss [44]. However, Chang et al. challenged this concept. They thought that this association may have been overestimated in the era before genetic testing, and newer studies seem to reflect the similar rate of LQTS causing mutations in deaf children, as in the general population [45]. There is overlap between seizure disorders and cardiac channelopathies. Sudden unexpected death in epilepsy (SUDEP) has an incidence of 6–9/1000 person-years in epilepsy surgery programs. Channelopathy-associated mutations have been identified in 13% of patients with SUDEP [46]. Seizures triggered by exercise, emotion, sudden stimuli, seizures unresponsive to anti-seizure medications and seizures in the setting of family history of SD, syncope or obvious electrocardiographic abnormalities should all be viewed with high index of suspicion for underlying channelopathy [47]. In patients with BrS, fever is a well-known arrhythmogenic trigger because SCN5A mutations alter the temperature sensitivity of fast inactivation of the Na^+ channel. This may cause 'apparent life-threatening events (ALTEs)' and even SUD or sudden infant death syndrome (SIDS) in susceptible infants in the setting of febrile illnesses [48]. As many as 30% of victims of drowning-related deaths have been found to have cardiac channelopathies [49, 50]. Patients with SCN5A mutations have been found to have irritable bowel syndrome (IBS). In a recent study, 2% of patients with IBS were found to have SCN5A mutations, and in one case, mexiletine administration even caused normalization of bowel habits. It is hypothesized that channelopathies are involved in the pathogenesis of some forms of IBS [51]. There is also a co-existence of iron-deficiency anaemia, hypergastrinemia and gastric hyperplasia associated with LQT1. This suggests not only a role for the gene KCNQ1 in gastric secretion but also a role for gastrin as a marker of arrhythmia severity [52, 53]. Interestingly, in a study from the United States, 36% of patients with drug-induced LQTS possessed known arrhythmia-associated mutations [54].

2.1.7 Cardiac channelopathies and sudden infant death syndrome (SIDS)

SIDS is defined as SD of seemingly healthy children of age <1 year. The incidence of SIDS varies across the world [54]. About 10–20% of SIDS cases are attributed to genetic mutations associated with channelopathies [19, 54, 55]. Mutations associated with LQTS1 and LQTS3 have been related to SIDS [54]. Mutations in the

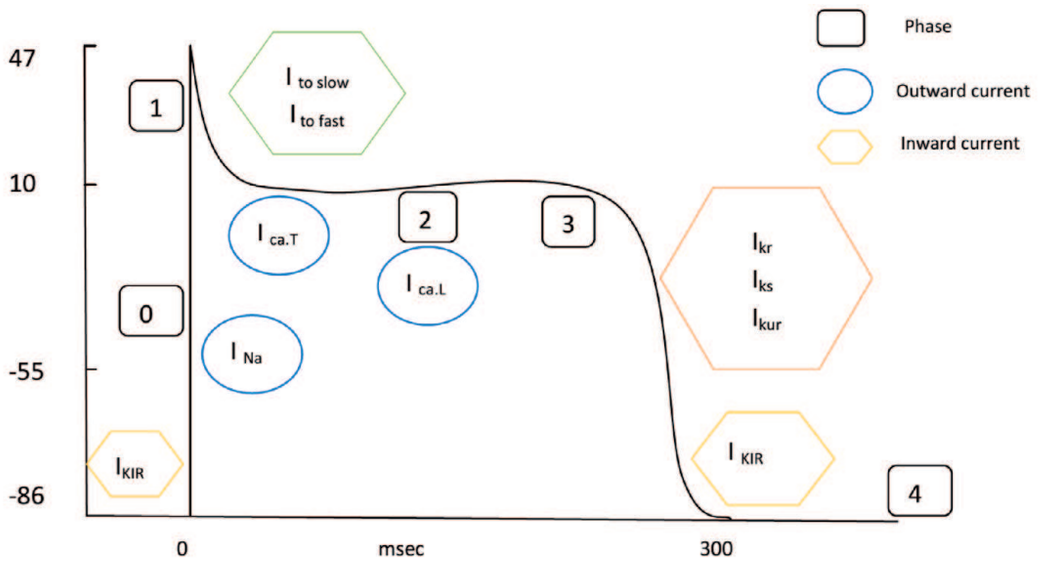
genes encoding the beta sub-units of Na channels have also been implicated [56]. Interestingly, a loss of function mutation in the K^+ channel encoding gene KCNJ8 has also been associated with SIDS. It is hypothesized that this mutation causes maladaptation to stress such as endotoxemia [55]. A Japanese study looking more broadly at the characteristics of all infantile LQTS found that 84% of all cases were diagnosed in the foetal or neonatal period. LQTS1 was associated with most risk of a first cardiac event, but LQTS2 and LQTS3 more exclusively caused VT or TdP [11]. QT intervals were found to be longest around 2 months of age [57]. Foetal magnetocardiography and echocardiography have been used to assess foetal LQTS. Sinus bradycardia is a common finding. Trans-placental magnesium and lidocaine, and prenatal beta-blocker therapies have been used for management [58]. While less commonly studied or identified, mutations associated with CPVT, SQTS, and BS have been linked to SIDS [54].

3. The basic electrophysiology of the myocyte and myocardium in ion channel disease

Basic understanding of the electrophysiology of cardiac cells action potential (AP) and its anomalies constitutes the corner stone to dive and disclose the secrets of ionopathies and the resultant fatal cardiac rhythm. Basic research uses molecular techniques, as well as animal models. Phases of the ventricular action potential with description of major events (**Figure 1**) proved extremely useful in improving the arrhythmia communities' knowledge of inherited arrhythmogenic syndromes. The discussion of the myocyte action potential is invariably the discussion of the ion channels of the cellular membrane since the delicate trans-membrane traffic of ions is the source of cardiac action potential during normal electrophysiological function of the heart. It is critical to perceive that abnormal heart rhythms including the fatal ventricular arrhythmias are primarily due to abnormal formation or mutations of those trans-membrane pores or its regulatory subunits. 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 AP formation or abnormal AP propagation. Martin CA et al. authored unique review in this regard [59].

3.1 Abnormal AP formation and propagation

Aberrancy of AP formation can be interpreted through three main mechanisms: reentry, triggered activity or automaticity. Acceleration of depolarization of pacemaker tissue will end up with autonomous formation of AP called enhanced automaticity. This can be precipitated by underlying sympathovagal imbalance in favour of excessive sympathetic tone, hypokalaemia or drugs such as digitalis. Triggered activity referred to extra systole generated outside the primary pacemaker tissue [59]. The underlying mechanism is called afterdepolarization, which is oscillations of cardiac cell membrane potential generated before the previous AP, ending up with premature new AP. If this premature AP magnitude is reaching threshold, it will produce triggered beat. According to the timing of this triggered activity, it can be early or late. Triggered activity during repolarization of the original AP is called early afterdepolarization (EAD). It occurs when AP duration is prolonged until a degree where L-type Ca^{2+} channels are recovered from inactivation during the time of membrane depolarization. Inward ICa-L current will initiate the new premature depolarization of the membrane and will initiate the afterdepolarization [60]. Triggered activity after completion of repolarization or near completion is called delayed afterdepolarization (DAD). It occurs due to enhanced Ca^{2+} release from the cellular calcium store organelle called sarcoplasmic



Phase 0 Rapid depolarization	Phase 1 Early repolarization	Phase 2 Action potential plateau	Phase 3 Final rapid repolarization	Phase 4 Resting membrane depolarization and diastolic depolarization
Excitatory stimulus or pacemaker potential depolarizes cell membrane beyond −70 mV At −70 mV, Na^+ channels are activated and allow inward current I_{Na} (channel NaV1.5). This current is brief but enormous, peaking the membrane potential at +47 mV.	The increase in potential from phase 0 results in opening of outward K^+channels and inward Ca^{2+} channels. There is repolarization from +47 mV to +10 mV due to rapid closure of $I_{Nav1.5}$ and activation of transient outward K^+current $I_{Kto,\ slow}$ (channel KV1.4) and $I_{Kto,\ fast}$ (channel KV4.2/4.3)	The membrane potential remains depolarized near 0 mV. Plateau phase is maintained by two inward Ca^{2+} currents – $I_{Ca.T}$ (channel CaVT.2) and $I_{Ca.L}$ (channel CaV1.2) and four outward K^+ currents	As the time dependent inward currents above inactivate, the outward K^+ currents dominate and cause rapid repolarization. These are rapid I_{Kr} (channel KHERG), ultrarapid I_{Kur} (channel KV1.5) and slow I_{KS} (channel KLVQT1)	The outward K^+ channels in phase 3 deactivate, the membrane is repolarized to -40 mV. The inward rectifier current I_{Kir} (channel Kir2.1) continues to drive the membrane potential to -70 mV, and the voltage dependent Na^+ channel which causes phase 0 remains inactivated till this happens

Figure 1.
Phases of the ventricular action potential with description of major events [59].

reticulum (SR) due to either activation of the Na^+/Ca^{2+} exchanger or Ca^{2+}-activated Cl-current. Classical examples of this Ca^{2+} overload environment is during digitalis toxicity or Catecholaminergic Polymorphic VT [61] (**Figure 2A**). The reentrant mechanism is unique. It requires an electrical obstacle around which AP is able to go around, disproportionately conducting exit pathways, one conducting fast and the other conducting slow and finally unidirectional conduction block. It is the most important mechanism as it is widely spread in much pathologies and most importantly the only type that is amenable for study and ablation in electrophysiology laboratory. The most common arrhythmias in clinical electrophysiology like atrioventricular nodal reentry tachycardia (AVNRT) and atrioventricular reentrant tachycardia (AVRT) are both reentrant and amenable for ablation. It is the underlying mechanism in patients with ventricular scarring, usually from old myocardial infarction, cardiomyopathy and infiltrative disease (**Figure 2B**).

3.2 Spatial electrophysiological heterogeneity

The human heart has been created in miraculous way where the structure supports and complements the function. After initiation of the normal impulse in the

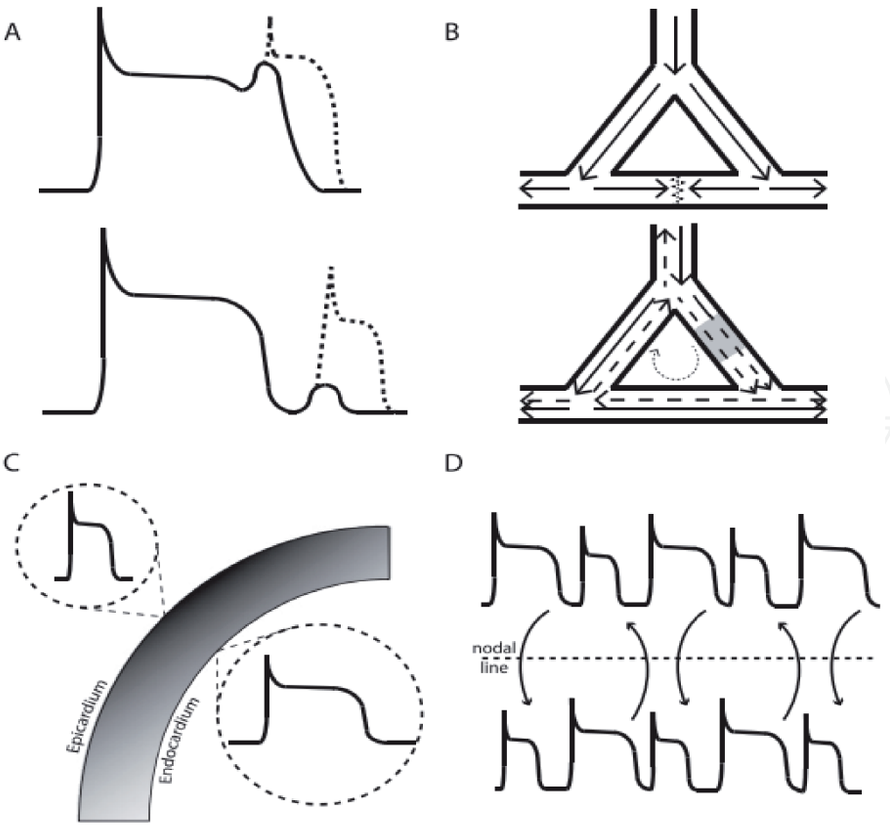


Figure 2.
Different mechanisms of arrhythmias [59]: (A) triggered activity: early after depolarization (EAD) (upper trace) and delayed after depolarization (DAD) (lower trace). Dotted lines represent formation of new AP. (B) Reentrant circuit: normal impulse propagation in two equal conduction velocities with collision in the middle and termination of the impulse (upper diagram). Presence of slow limb in the circuit (solid line) will end up with the normal impulse pass through and circulates around the other limb which is the fast limb at a time where its refractoriness is over (dotted). This will end up with excitation of the myocardium and initiation of tachycardia (lower diagram). (C) Transmural gradients due to heterogeneity of AP in different locations: shorter AP in epicardium compared to endocardium will end up with reexcitation. (D) Heterogenity of AP timing: creating duration alternans with the result of nodal line when the alternans time out creating block predisposing to reentry in the presence of triggered impulse.

sinus node, the wave of action potentials is characterized by highly sophisticated levels of gradients of depolarization and repolarizations, to maintain the normal electro-mechanical activation sequence for the pumping heart functions. The dominant determiner of these spatial gradients is the regional differences in repolarizing K^+ channels. These include channel density variations, kinetics and cycling traffic between membrane and cytoplasm. The substrate for reentry is created by disturbances in these gradients, which may permit depolarized regions to reexcite polarized areas [59]. Transmural gradients alterations correlated with arrhythmogenic tendencies in a number of both pharmacological canine and genetic murine models for LQTS and BrS. The reexcitation may occur when the epicardial action potential duration is much shorter than the endocardial, potentially leading to new AP (**Figure 2C**).

This new environment of electrical dispersion within the cardiac tissue was proved to be arrhythmogenic in cardiomyopathies. This spatial heterogeneity was linked to T wave alternans (TWA) and ventricular tachycardia [62]. Reentry created by epicardial dispersion of repolarization was seen to be the trigger for ventricular tachycardia in preparation of canine right ventricular wedge [63] and the $Scn5a^{+/-}$ mouse model [64]. Source of arrhythmia in Brugada syndrome is thought to be secondary to AP duration differences between left ventricle and right ventricle. This is reflected in Brugada patients as ST elevation in right precordial leads and right epicardial AP changes [65].

3.3 Temporal electrophysiological heterogeneity

Electrical dispersion may also affect activation sequence. Temporal beat-to-beat variation in the AP amplitude or duration, a phenomenon known as alternant (**Figure 2D**), has been associated with arrhythmogenesis in both clinical and experimental studies [66, 67]. This can have significant consequences on the spatial organization of repolarization across the ventricle, amplifying the heterogeneities of repolarization present at baseline into pathophysiological heterogeneities of sufficient magnitude to produce conduction block and reentrant excitation. Regions which alternate out of phase generate a line of block called the nodal line between them. This has the potential to act as a focus for reentrant circuits following the addition of a triggered beat.

3.4 The channelopathies

3.4.1 Long QT syndromes

LQTS constitute a group of genetic disorders distinguished by long QT interval in the electrocardiogram, representing prolongation of repolarization period associated with the risk of ventricular arrhythmias (in specific torsade de point) and sudden death. In comparison to Brugada syndrome, the genetic mutations in LQTS result in tendency for electrical disturbance, affecting depolarization rather than repolarization. An arrhythmic substrate with prolonged AP duration was implicated in several mouse models [68] (**Figure 3**). Functional block pockets are created by prolonged depolarization phase during which the impulse pathway will be refractory. This functional block will create reentry focus and myocardial excitation. In addition, repolarization potentials dispersion across the myocardium will provide a functional reentry pathway facilitating initiation of torsade de point. Prolonged depolarization may result in EAD with consequent polymorphic VT. Data from transgenic rabbits [69], have recently been instrumental to support a novel view on the arrhythmogenesis in LQTS by Chang et al. [70]. These authors developed an in silico model (i.e. computational modelling, simulation and visualization of the cardiomyocyte electrophysiological behaviour and arrhythmogenesis in a virtual computerized environment) of prolonged repolarization. They were able to demonstrate that arrhythmogenesis is initiated by two types of spiral waves: short cycle and long cycle. The short cycle is mediated through *I*Na (**Figure 4A**) and the long cycle is mediated through slow L-type calcium current (ICa) (**Figure 4B**) [70]. The alteration of those two types of waves gives what resemble torsade de point in the ECG. Arrhythmogenesis in LQT1 was investigated by Kim et al. using transgenic rabbit models. Multiple EAD foci were demonstrated as well as AP bimodal distribution compatible with the concept of two excitation types [70].

3.4.2 Brugada syndrome (BrS)

BrS is clearly distinguished between other channelopathies with its electrocardiographic manifestation in the form of delayed right ventricular activation with posterior T wave manifested mainly in V1 and V2. Clinically it is characterized by episodic history of poly morphic VT and ventricular fibrillation (VF) [59]. Genetic heterogeneity is a hall mark feature of BrS where multiple genetic mutations result in the same phenotype. All mutations end up with imbalance of the currents favouring repolarization over depolarization (in contrast to LQTS). The most famous BrS mutation is the SCN5A gene where there is loss of function encoding the alpha subunit of the Na^+ voltage-gated channel. INa reduction seems to be the underlying mechanism.

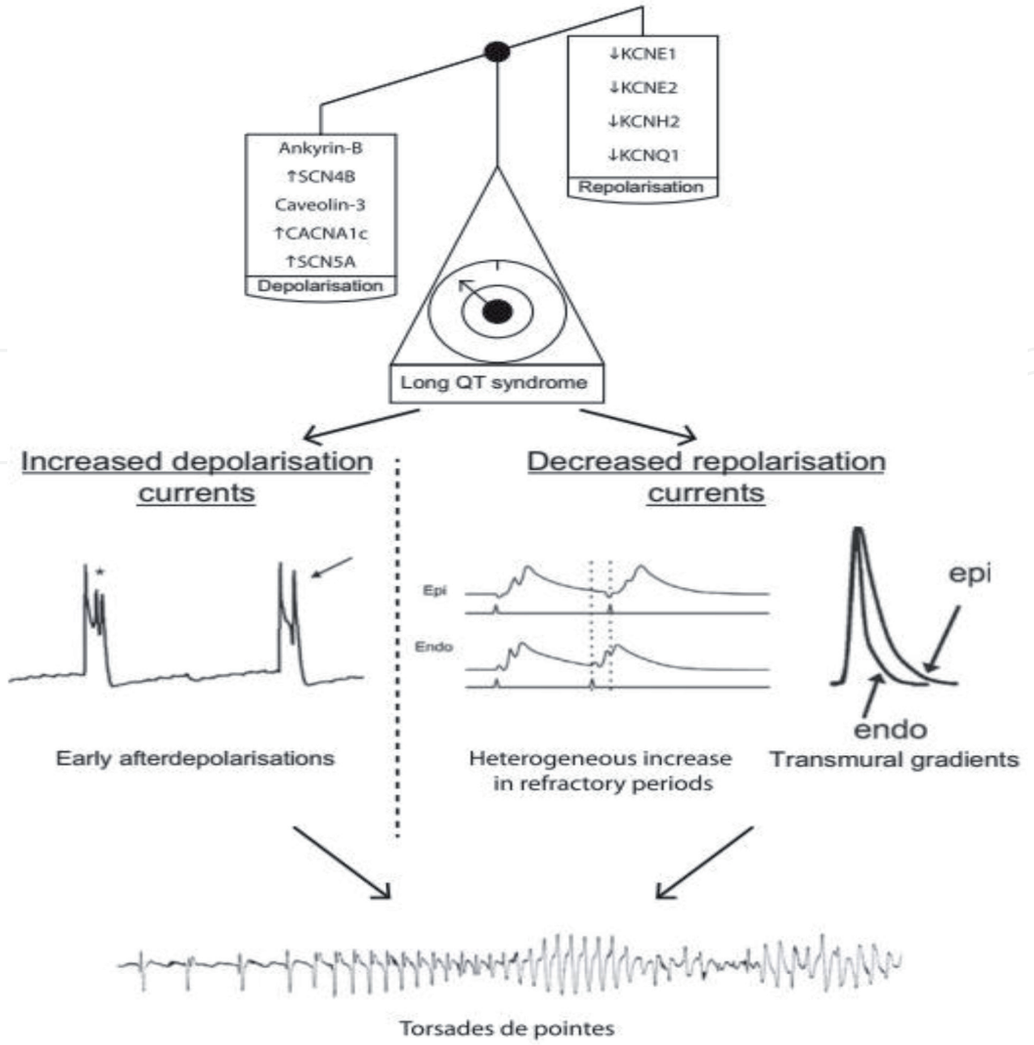


Figure 3.
LQTS mechanistic representation of arrhythmogenesis as understood from animal model. Scales showed genetic mutations can give rise to either gain of depolarization currents or loss of repolarization currents. EAD (triggered activity) will result as well as transmural gradients and refractory pockets formation. The clinical outcome as seen in ECG is represented by the trace at the bottom of the graph (torsade de pointes) [59].

Experimental studies using canine hearts as well as clinical studies support this pathophysiological mechanism underlying BrS [71, 72]. Reduction of Na^+ current can impose its effect represented by the deep notch of phase 1 of the epicedial AP, which is most impressive in RV. This reduction in Na^+ current creates voltage gradient across RV. This state of electrical imbalance in RV epicardium facilitates participation of the proximal myocardium to reactivate RV, ending up with reentry. This type of reentry is called phase 2 reentry (**Figure 5**). Another perspective to interpret the ECG manifestations of BrS is based on right ventricular out flow (RVOT) conduction delay perspective [73]. This perspective was derived from echocardiographic measurements, signal-averaged ECG (SAECG) potentials and mapping of body surface [74, 75]. An ex vivo experiment demonstrating RVOT conduction delay was published [76]. Fractionated late potentials that was amenable for catheter ablation was documented in the anterior aspect of RVOT epicardium. This specific site ablation normalized ECG and prevented VT and VF associated with BrS [77].

3.4.3 Catecholaminergic polymorphic ventricular tachycardia (CPVT)

Surge of catecholamines due to stress or exercise is the substrate fuel of bidirectional VT leading to syncope or SCD. This is creating an important category

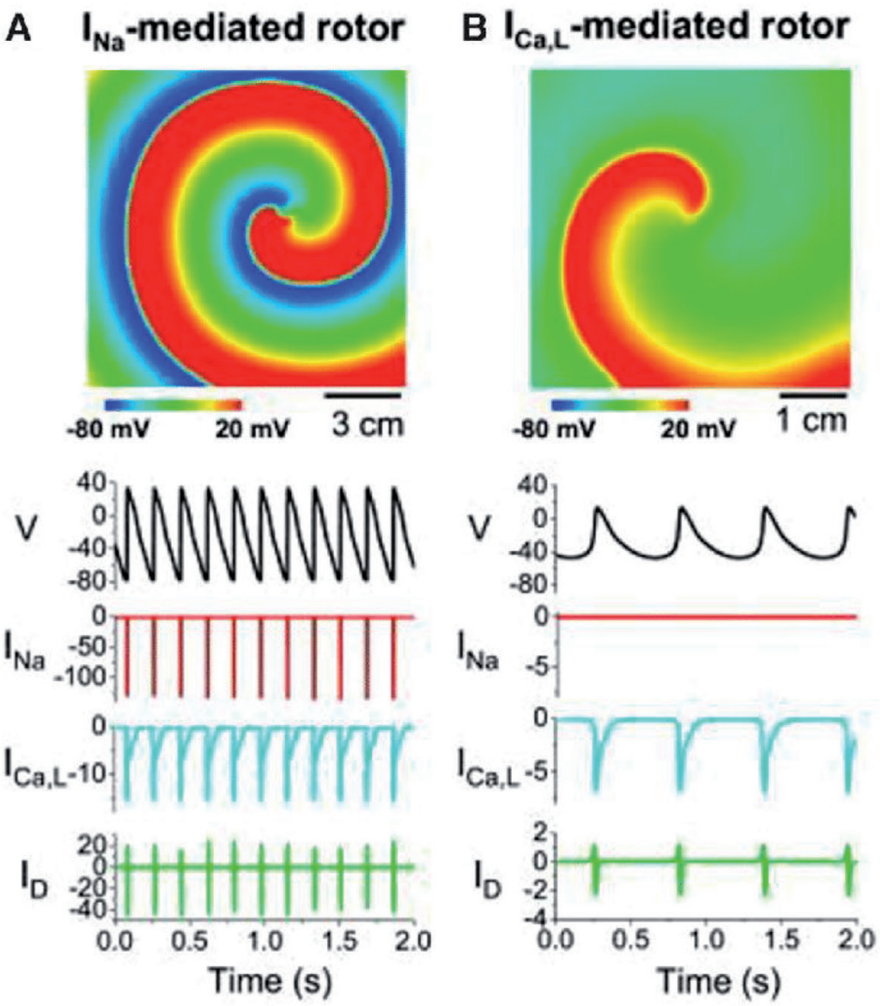


Figure 4.
In silico cardiac tissue model of prolonged repolarization. Arrhythmogenesis is initiated by two types of spiral waves: short cycle and long cycle. The short cycle is mediated through INa (A) and the long cycle is mediated through slow L-type calcium current (ICa) (B) [70].

of channelopathies called CPVT. At cellular level, enhanced Ca^{2+} release from the cellular calcium store organelle called sarcoplasmic reticulum (SR) is the operating mechanism. This enhanced Ca^{2+} release is due to gain of function gene mutation encoding ryanodine receptor 2 (RyR2), which is an important regulator of Ca^{2+} release for myocardial cells excitation contraction coupling [78]. The other important gene mutation results in loss of function affecting calsequestrin (CASQ2) protein, which is in normal situations functioning as SR calcium buffering protein [79]. This Ca^{+} release affects AP in a way favouring DAD as in digitalis toxicity concluded in arrhythmic trigger [36] (**Figure 6**). A net inward current is generated secondary to cytosolic Ca^{+} overload in vitro studies with RyR2 and CASQ2 mutations [61, 80]. RyR2 [81] or in CASQ2 [82] genes deliberately inserted into transgenic animals (mouse in this situation) revealed abnormal Ca^{+} transients and bidirectional VT. This level of evidence is supporting the idea that inward current might be the underlying mechanism of DAD triggering the abnormal beat. RYR2 mutations have also been suggested to be associated with dilated cardiomyopathy [83], hypertrophic cardiomyopathy [84] and arrhythmogenic right ventricular cardiomyopathy [85].

3.4.4 Other syndromes

While a majority of cases of SCD in the absence of structural heart abnormalities are caused by LQTS, BrS and CVVT, other less common syndromes are of

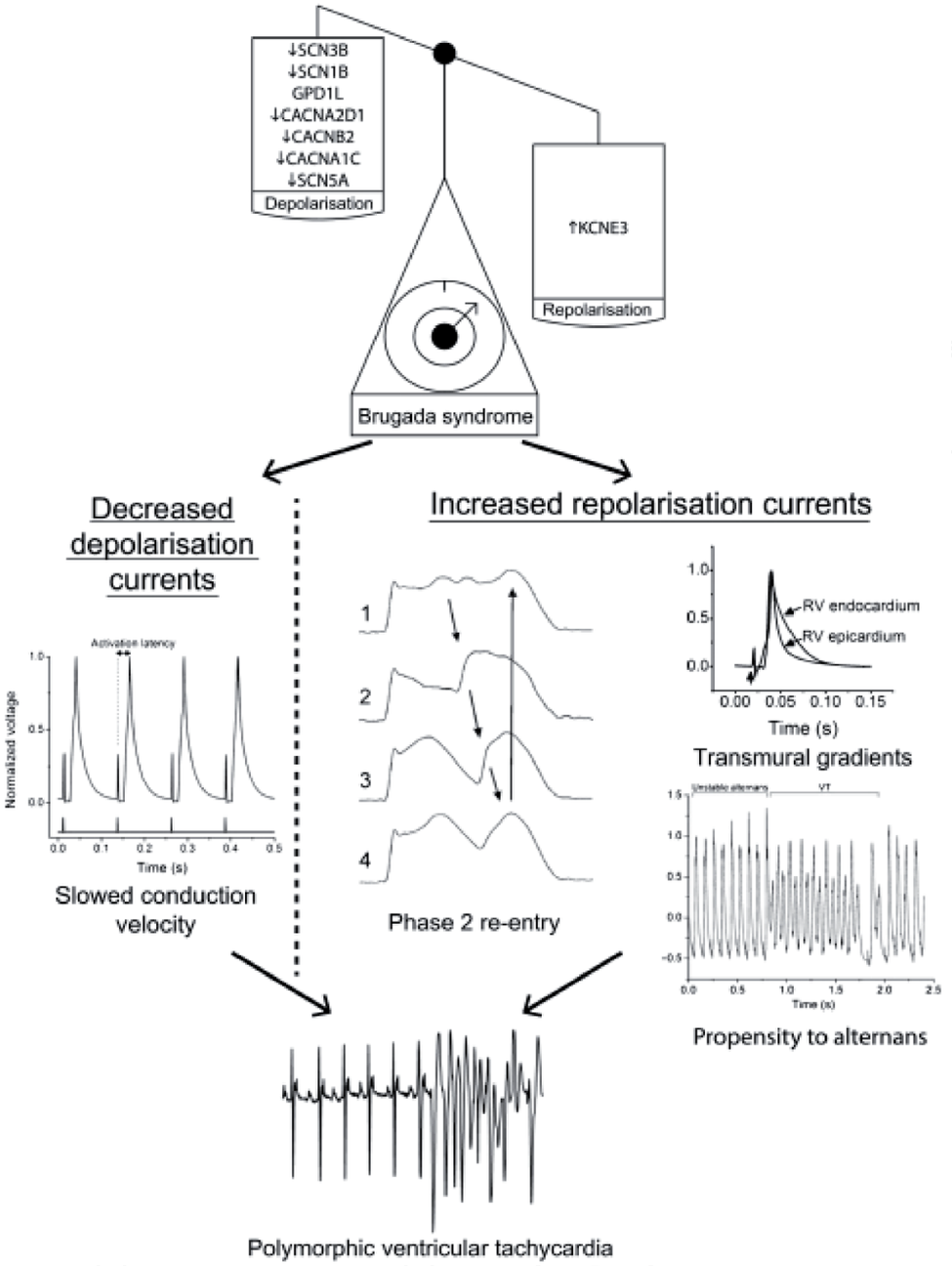


Figure 5.
Brugada syndrome's mechanistic representation of arrhythmogenesis as understood from animal model. Scales showed genetic mutations can give rise to either loss of depolarization currents or gain of repolarization currents. The ultimate outcome of those AP changes is more likelihood for alternans and phase 2 reentry. The clinical outcome as seen in ECG is represented by the trace at the bottom of the graph (polymorphic VT) [59].

importance. Short AP and accordingly QT intervals in short QT syndrome (SQTS) is due to mutations causing gain of function handling K^+ channels [86] or mutations causing loss of function handling Ca^+ channels [87]. An increase in repolarization gradients was seen to be the underlying mechanism [88]. In early repolarization syndrome (ERS), J point elevation with prominent T wave is seen (early repolarization pattern). This electrocardiographic pattern is associated clinically with VT and sudden death [89]. The exact mechanism is still obscure although AP early phase increment in transmural gradients has been suggested in canines hearts [90]. Rarely, reduction in inward Ca^+ current [91] or increment in outward K^+ current mutations [92] has been described, although a majority of cases lack genetic mutations. The weight of evidence nowadays is supporting that the ER pattern is polygenic with an important contribution of epigenetic and environmental factors.

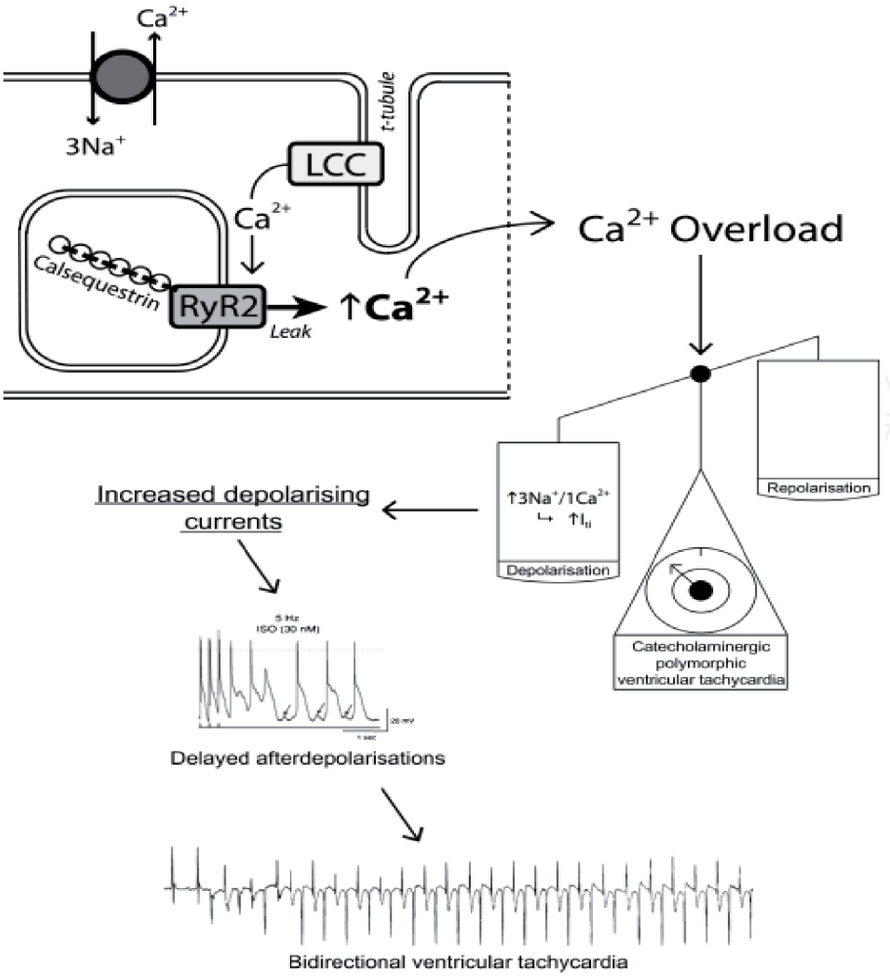


Figure 6.
CPVT mechanistic representation of arrhythmogenesis as understood from animal model. DAD-triggered activity is due to genetic mutation causing rise in cytosolic Ca^{+} which in turn will result in depolarization current obeying the electrogenic nature of the Na^{+}/Ca^{2+} exchanger. The clinical outcome as seen in ECG is represented by the trace at the bottom of the graph (bidirectional VT) [59].

Progressive cardiac conduction disease (PCCD) also known as Lenegre's disease is a rare progressive degenerative disease of the cardiac conduction system with autosomal dominant pattern of inheritance that may end up with widening of QRS complexes, long pauses and bradycardia. It is a cause of SCD. The first gene mutation of PCCD described was SCN5A. This mutation can be associated with complex phenotype of PCCD, Brs and LQT3, sometimes referred as (overlap syndrome) [93]. Recently, PCCD was seen as an association with altered expressions of other gene proteins encoding impulse propagation like Ca^{+}-activated ion channel and cytoskeletal components. The conclusive phenotype as seen in mouse experiments is thought to be an additive effect of genetic components with environmental modifiers and aging [94].

4. Summary

SCD is extreme, devastating and traumatic life event. Inherited ventricular arrhythmias, which is due to disturbed ionic traffic across cardiac cell membrane (channelopathy), comprised 1/3 of all cases of SUD and 10% of SCD as a whole. Channelopathies occupies strategic location in the basic science as well as clinical and research arenas due to its recalcitrant behaviour and complexity. The discoveries of the genetic mutations of channelopathies heralded in 1995 have

expanded drastically, resulting in revolutionary understanding of the disease. The most important described channelopathies up to date are long QT syndromes (LQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), short QT syndrome (SQTS), early repolarization syndrome (ERS) and idiopathic VF. New disease entities are expected to be discovered in the near future. LQTS is an inherited genetically heterogeneous group of arrhythmias characterized by a prolonged QTc interval in the 12-lead ECGs (with QTc values >470 ms for males and >480 ms for females, representing approximate 99th percentile values). LQTSs as a whole occurs in 1:2500 of the general population. At least 17 genes were identified contributing to LQTSs with mutations positive in about half of the affected individuals. The incidence of LQTSs in decreasing frequency illustrates LQT1 as the commonest (35%) followed by LQT2 (30%) and then LQT3 (10%). The least frequent but most lethal and more difficult to manage is LQT3. Other rare types of LQTSs account for less than 1%. It seems that the normal range of QTc interval is critical for normal AP and normal heart rhythm. Prolongation or shortening of QTc interval is arrhythmogenic. Short QT syndrome with QTc < 350 ms (reported in 1:3400) is etiologically proven cause of malignant VT and VF. Brugada syndrome diagnosed as coved ST-segment elevation in anterior precordial leads occurs in approximately 0.02% up to 0.20% in general population. It overlaps with some of the genetic and clinical features of LQT3. Catecholaminergic polymorphic ventricular tachycardia (CPVT) is relatively a rarely inherited arrhythmogenic disorder (1;10,000) characterized by polymorphic VT induced by physical or emotional stress without any detectable morphological abnormalities in the heart. The most important mutations causing CPVT are in genes encoding cardiac ryanodine type 2 receptor (RYR2) [autosomal dominant] and calsequestrin 2 (CASQ2) [autosomal recessive]. It is considered as highly malignant heart rhythm if neglected. ERS is characterized by elevation of the QRS-ST junction (J point) and QRS notching or slurring (J wave) in multiple leads, especially the inferior and/or left precordial leads. It seems to be more frequent than ever thought with ranges from approximately 6–13% in the general population. Approaching channelopathies in its broad spectrum is an excellent example of the demand of system biology approach in medicine. Channelopathies involving the heart may overlap with manifestations in the nervous system, gastrointestinal system, hearing, infant death syndrome and others. Fatal ventricular arrhythmias are due primarily to abnormal formation or mutations of trans-membrane pores or its regulatory subunits. Aberrancy of cardiac action potential (AP) formation can be interpreted through three main mechanisms: reentry, triggered activity or automaticity. All the different mechanisms described will end up with anomalous action potential. Spatial as well as temporal electrophysiological heterogeneity are important basic electrophysiological derangements that underline cardiac action potential anomalies. Heterogeneity of AP in time and location between myocardium and epicardium are critical predisposing factors to the fatal cardiac rhythm. In comparison to Brugada syndrome, the genetic mutations in LQTS result in tendency for electrical disturbance affecting depolarization rather than repolarization. Surge of catecholamines due to stress or exercise is the substrate fuel of bidirectional VT leading to syncope or SCD in CPVT. RYR2 mutations have also been suggested to be associated with dilated cardiomyopathy, hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy. ER pattern is thought to be polygenic with an important contribution of epigenetic and environmental factors. Advances in our knowledge and understanding of disease epidemiology and the basic electrophysiological derangements of channelopathies are intelligent directions that should guide all diagnostic and therapeutic approaches.

Acknowledgements

To the spirit of the later crown prince of Saudi Arabia HRH Sultan Bin Abdulaziz Al Saud, who made my dreams in establishing the prestigious Prince Sultan Cardiac Center reality and from which this science and others are introduced to the world.

Conflict of interest

I declare no conflict of interest.

Notes/thanks/other declarations

Showers of mercy to the spirit of my Great Beloved Father who shocked me with his sudden agonizing absences during writing this chapter. Prayers for long peaceful life for my great mother. Both of them fed me the love to all humanity and all biology. Thanks to all my teachers who taught me that sky is not the limit.

Appendices and nomenclature

BrS	Brugada syndrome
CC	cardiac coherence
CPVT	catecholaminergic polymorphic ventricular tachycardia
ERS	early repolarization syndrome
LQTS	long QT syndrome
PCCD	progressive cardiac conduction disease
SCD	sudden cardiac death
SQTS	short-QT syndrome
VF	ventricular fibrillation
VT	ventricular tachycardia

Author details

Abdullah Abdulrhman Al Abdulgader
Senior Congenital Cardiologist and Invasive Electrophysiologist, Prince Sultan Cardiac Center, Alhasa, Hofuf, Saudi Arabia

*Address all correspondence to: kidsecho@yahoo.com

References

[1] Zipes DP, Wellens HJJ. Sudden cardiac death. Circulation. 1998;**98**(21):2334-2351

[2] Fishman GI, Chugh SS, Dimarco JP, Albert CM, Anderson ME, Bonow RO, et al. Sudden cardiac death prediction and prevention. Circulation. 2010;**122**(22):2335-2348

[3] Werf CVD, Langen IMV, Wilde AA. Sudden death in the young. Circulation. Arrhythmia and Electrophysiology. 2010;**3**(1):96-104

[4] Sarquella-Brugada G, Campuzano O, Iglesias A, Sánchez-Malagón J, Guerra-Balic M, Brugada J, et al. Genetics of sudden cardiac death in children and young athletes. Cardiology in the Young. 2013;**23**(2):159-173

[5] Murakoshi N, Aonuma K. Epidemiology of arrhythmias and sudden cardiac death in Asia. Circulation Journal. 2013;**77**(10):2419-2431

[6] Schwartz PJ, Stramba-Badiale M, Crotti L, Pedrazzini M, Besana A, Bosi G, et al. Prevalence of the congenital long-QT syndrome. Circulation. 2009;**120**(18):1761-1767

[7] Earle N, Crawford J, Smith W, Hayes I, Shelling A, Hood M, et al. Community detection of long QT syndrome with a clinical registry: An alternative to ECG screening programs? Heart Rhythm. 2013;**10**(2):233-238

[8] Uhm J-S, Hwang I-U, Oh Y-S, Choi M-S, Jang S-W, Shin W-S, et al. Prevalence of electrocardiographic findings suggestive of sudden cardiac death risk in 10,867 apparently healthy young Korean men. Pacing and Clinical Electrophysiology. 2011;**34**(6):717-723

[9] Hayashi K, Fujino N, Uchiyama K, Ino H, Sakata K, Konno T, et al. Long QT syndrome and associated gene mutation carriers in Japanese children: Results from ECG screening examinations. Clinical Science. 2009;**117**(12):415-424

[10] Mahida S, Hogarth AJ, Cowan C, Tayebjee MH, Graham LN, Pepper CB. Genetics of congenital and drug-induced long QT syndromes: Current evidence and future research perspectives. Journal of Interventional Cardiac Electrophysiology. 2013;**37**(1):9-19

[11] Horigome H, Nagashima M, Sumitomo N, Yoshinaga M, Ushinohama H, Iwamoto M, et al. Clinical characteristics and genetic background of congenital long-QT syndrome diagnosed in fetal, neonatal, and infantile life. Circulation. Arrhythmia and Electrophysiology. 2010;**3**(1):10-17

[12] Zareba W, Moss AJ, Schwartz PJ, Vincent GM, Robinson JL, Priori SG, et al. Influence of the genotype on the clinical course of the long-QT syndrome. The New England Journal of Medicine. 1998;**339**(14):960-965

[13] Skinner JR. Guidelines for the diagnosis and management of familial long QT syndrome. Heart, Lung & Circulation. 2007;**16**(1):22-24

[14] Goldenberg I, Moss AJ, Peterson DR, Mcnitt S, Zareba W, Andrews ML, et al. Risk factors for aborted cardiac arrest and sudden cardiac death in children with the congenital long-QT syndrome. Circulation. 2008;**117**(17):2184-2191

[15] Gaita F, Giustetto C, Bianchi F, Wolpert C, Schimpf R, Riccardi R, et al. Short QT syndrome. Circulation. 2003;**108**(8):965-970

[16] Funada A, Hayashi K, Ino H, Fujino N, Uchiyama K, Sakata K, et al. Assessment of QT intervals and

prevalence of short QT syndrome in Japan. Clinical Cardiology. 2008;**31**(6):270-274

[17] Maury P, Extramiana F, Sbragia P, Giustetto C, Schimpf R, Duparc A, et al. Short QT syndrome. Update on a recent entity. Archives of Cardiovascular Diseases. 2008;**101**(11-12):779-786

[18] Giustetto C, Schimpf R, Mazzanti A, Scrocco C, Maury P, Anttonen O, et al. Long-term follow-up of patients with short QT syndrome. Journal of the American College of Cardiology. 2011;**58**(6):587-595

[19] Chockalingam P, Wilde A. The multifaceted cardiac sodium channel and its clinical implications. Heart. 2012;**98**(17):1318-1324

[20] Amin AS, Asghari-Roodsari A, Tan HL. Cardiac sodium channelopathies. Pflügers Archiv - European Journal of Physiology. 2010;**460**(2):223-237

[21] Gaw AC, Lee B, Gervacio-Domingo G, Antzelevitch C, Divinagracia R, Jocano F Jr. Unraveling the enigma of bangungut. Is sudden unexplained nocturnal death syndrome (SUNDs) in the Philippines a disease allelic to the Brugada syndrome? Philippine Journal of Internal Medicine. 2011;**49**:165-176

[22] Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P, et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. Nature. 1998;**392**(6673):293-296

[23] Hedley PL, Jørgensen P, Schlamowitz S, Moolman-Smook J, Kanters JK, Corfield VA, et al. The genetic basis of Brugada syndrome: A mutation update. Human Mutation. 2009;**30**(9):1256-1266

[24] Priori SG, Napolitano C, Gasparini M, Pappone C, Bella PD, Brignole M, et al. Clinical and genetic heterogeneity of right bundle branch block and ST-segment elevation syndrome. Circulation. 2000;**102**(20):2509-2515

[25] Brugada J, Brugada R, Antzelevitch C, Towbin J, Nademanee K, Brugada P. Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V 1 to V 3. Circulation. 2002;**105**(1):73-78

[26] Probst V, Veltmann C, Eckardt L, Meregalli P, Gaita F, Tan H, et al. Long-term prognosis of patients diagnosed with Brugada syndrome. Circulation. 2010;**121**(5):635-643

[27] Kamakura S, Ohe T, Nakazawa K, Aizawa Y, Shimizu A, Horie M, et al. Long-term prognosis of Probands with Brugada-pattern ST-elevation in leads V 1–V 3. Circulation. Arrhythmia and Electrophysiology. 2009;**2**(5):495-503

[28] Antzelevitch C. Genetic, molecular and cellular mechanisms underlying the J wave syndromes. Circulation Journal. 2012;**76**(5):1054-1065

[29] Haïssaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, Roy LD, et al. Sudden cardiac arrest associated with early repolarization. New England Journal of Medicine. 2008;**358**(19):2016-2023

[30] Noseworthy P, Porthan K, Tikkanen J, Peloso G, Merchant F, Pietila A, et al. The early repolarization pattern: Clinical correlates and heritability. Journal of the American College of Cardiology. 2011;**57**(14)

[31] Tikkanen JT, Anttonen O, Junttila MJ, Aro AL, Kerola T, Rissanen HA, et al. Long-term outcome associated with early repolarization on electrocardiography. The New England Journal of Medicine. 2009;**361**(26):2529-2537

[32] Kui C, Congxin H, Xi W, Yan-Hong T, Okello E, Salim M, et al. Characteristic of the prevalence of J wave in apparently healthy Chinese adults. Archives of Medical Research. 2008;**39**(2):232-235

[33] Haruta D, Matsuo K, Tsuneto A, Ichimaru S, Hida A, Sera N, et al. Incidence and prognostic value of early repolarization pattern in the 12-Lead electrocardiogram. Circulation. 2011;**123**(25):2931-2937

[34] Obeyesekere MN, Klein GJ, Nattel S, Leong-Sit P, Gula LJ, Skanes AC, et al. A clinical approach to early repolarization. Circulation. 2013;**127**(15):1620-1629

[35] Tikkanen JT, Junttila MJ, Anttonen O, Aro AL, Luttinen S, Kerola T, et al. Early repolarization. Circulation. 2011;**123**(23):2666-2673

[36] Leenhardt A, Lucet V, Denjoy I, Grau F, Ngoc DD, Coumel P. catecholaminergic polymorphic ventricular tachycardia in children. Circulation 1995;91(5):1512-1519.

[37] Priori SG, Napolitano C, Tiso N, Memmi M, Vignati G, Bloise R, et al. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. Circulation. 2001;**103**(2):196-200

[38] Lahat H, Pras E, Olender T, Avidan N, Ben-Asher E, Man O, et al. A missense mutation in a highly conserved region of CASQ2 is associated with autosomal recessive catecholamine-induced polymorphic ventricular tachycardia in Bedouin families from Israel. American Journal of Human Genetics. 2001;**69**(6):1378-1384

[39] Vega AL, Tester DJ, Ackerman MJ, Makielski JC. Protein kinase A-dependent biophysical phenotype for V227F-KCNJ2 mutation in catecholaminergic polymorphic ventricular tachycardia. Circulation. Arrhythmia and Electrophysiology. 2009;**2**(5):540-547

[40] Kawamura M, Ohno S, Naiki N, Nagaoka I, Dochi K, Wang Q, et al. Genetic background of catecholaminergic polymorphic ventricular tachycardia in Japan. Circulation Journal. 2013;**77**(7):1705-1713

[41] Hayashi M, Denjoy I, Extramiana F, Maltret A, Buisson NR, Lupoglazoff J-M, et al. Incidence and risk factors of arrhythmic events in catecholaminergic polymorphic ventricular tachycardia. Circulation. 2009;**119**(18):2426-2434

[42] Swan H, Piippo K, Viitasalo M, Heikkilä P, Paavonen T, Kainulainen K, et al. Arrhythmic disorder mapped to chromosome 1q42–q43 causes malignant polymorphic ventricular tachycardia in structurally normal hearts. Journal of the American College of Cardiology. 1999;**34**(7):2035-2042

[43] Behere S, Weindling S. Inherited arrhythmias: The cardiac channelopathies. Annals of Pediatric Cardiology. 2015;**8**(3):210

[44] Niaz A, Rizvi SF, Khurram D. Prevalence of long QT syndrome and other cardiac defects in deaf-mute children. Journal of Ayub Medical College, Abbottabad. 2011;**23**(1):5-8

[45] Chang RK, Lan YT, Silka MJ, Morrow H, Kwong A, Smith-Lang J, et al. Genetic variants for long QT syndrome among infants and children from a statewide newborn hearing screening program cohort. The Journal of Pediatrics. Mar 2014;**164**(3):590-5.e1-3

[46] Partemi S, Cestèle S, Pezzella M, Campuzano O, Paravidino R, Pascali VL, et al. Loss-of-function KCNH2 mutation in a family with long QT syndrome, epilepsy, and sudden death. Epilepsia. Aug 2013;**54**(8):e112-e116

[47] Hazle MA, Shellhaas RA, Bradley DJ, Dick M, Lapage MJ. Arrhythmogenic channelopathy syndromes presenting as refractory epilepsy. Pediatric Neurology. 2013;**49**(2):134-137

[48] Chockalingam P, Rammeloo LA, Postema PG, Hruda J, Clur S-AB, Blom NA, et al. Fever-induced life-threatening arrhythmias in children harboring an SCN5A mutation. Pediatrics. 2010;**127**(1)

[49] Kenny D, Martin R. Drowning and sudden cardiac death. Archives of Disease in Childhood. 2010;**96**(1):5-8

[50] Tester DJ, Medeiros-Domingo A, Will ML, Ackerman MJ. Unexplained drownings and the cardiac channelopathies: A molecular autopsy series. Mayo Clinic Proceedings. 2011;**86**(10):941-947

[51] Beyder A, Mazzone A, Strege PR, Tester DJ, Saito YA, Bernard CE, et al. Loss-of-function of the voltage-gated sodium channel NaV1.5 (channelopathies) in patients with irritable bowel syndrome. Gastroenterology. 2014;**146**(7):1659-1668

[52] Diamant U-B, Jensen SM, Winbo A, Stattin E-L, Rydberg A. Vectorcardiographic recordings of the Q-T interval in a pediatric long Q-T syndrome population. Pediatric Cardiology. 2012;**34**(2):245-249

[53] Rice KS, Dickson G, Lane M, Crawford J, Chung S-K, Rees MI, et al. Elevated serum gastrin levels in Jervell and Lange-Nielsen syndrome: A marker of severe KCNQ1 dysfunction? Heart Rhythm. 2011;**8**(4):551-554

[54] Ramirez AH, Shaffer CM, Delaney JT, Sexton DP, Levy SE, Rieder MJ, et al. Novel rare variants in congenital cardiac arrhythmia genes are frequent in drug-induced torsades de pointes. The Pharmacogenomics Journal. 2012;**13**(4):325-329

[55] Tester DJ, Tan B-H, Medeiros-Domingo A, Song C, Makielski JC, Ackerman MJ. Loss-of-function mutations in the KCNJ8-encoded Kir6.1 K ATP channel and sudden infant death syndrome. Circulation. Cardiovascular Genetics. 2011;**4**(5):510-515

[56] Tan B-H, Pundi KN, Norstrand DWV, Valdivia CR, Tester DJ, Medeiros-Domingo A, et al. Sudden infant death syndrome–associated mutations in the sodium channel beta subunits. Heart Rhythm. 2010;**7**(6):771-778

[57] Yoshinaga M, Ushinohama H, Sato S, Tauchi N, Horigome H, Takahashi H, et al. Electrocardiographic screening of 1-month-old infants for identifying prolonged QT intervals. Circulation. Arrhythmia and Electrophysiology. 2013;**6**(5):932-938

[58] Anuwutnavin S, Wanitpongpan P, Chungsomprasong P, Soongswang J, Srisantiroj N, Wataganara T. Fetal long QT syndrome manifested as atrioventricular block and ventricular tachycardia: A case report and a review of the literature. Pediatric Cardiology. 2012;**34**(8):1955-1962

[59] Martin CA, Matthews GDK, Huang CL-H. Sudden cardiac death and inherited channelopathy: The basic electrophysiology of the myocyte and myocardium in ion channel disease. Heart. 2012;**98**(7):536-543

[60] January CT, Riddle JM, Salata JJ. A model for early afterdepolarizations: Induction with the Ca2 channel agonist bay K 8644. Circulation Research. 1988;**62**(3):563-571

[61] Jiang D, Wang R, Xiao B, Kong H, Hunt DJ, Choi P, et al. Enhanced store overload–induced Ca 2 release and channel sensitivity to luminal Ca 2 activation are common defects of RyR2 mutations linked to

ventricular tachycardia and sudden death. Circulation Research. 2005;**97**(11):1173-1181

[62] Chauhan VS, Downar E, Nanthakumar K, Parker JD, Ross HJ, Chan W, et al. Increased ventricular repolarization heterogeneity in patients with ventricular arrhythmia vulnerability and cardiomyopathy: A human in vivo study. American Journal of Physiology—Heart and Circulatory Physiology. Jan 2006;**290**(1):H79-H86

[63] Morita H, Zipes DP, Fukushima-Kusano K, Nagase S, Nakamura K, Morita ST, et al. Repolarization heterogeneity in the right ventricular outflow tract: Correlation with ventricular arrhythmias in Brugada patients and in an in vitro canine Brugada model. Heart Rhythm. 2008;**5**(5):725-733

[64] Martin CA, Grace AA, Huang CL. Spatial and temporal heterogeneities are localized to the right ventricular outflow tract in a heterozygotic Scn5a mouse model. American Journal of Physiology—Heart and Circulatory Physiology. 2011;**300**(2):H605-16

[65] Kurita T, Shimizu W, Inagaki M, Suyama K, Taguchi A, Satomi K, et al. The electrophysiologic mechanism of ST-segment elevation in Brugada syndrome. Journal of the American College of Cardiology. 2002;**40**(2):330-334

[66] Rosenbaum DS, Jackson LE, Smith JM, Garan H, Ruskin JN, Cohen RJ. Electrical alternans and vulnerability to ventricular arrhythmias. The New England Journal of Medicine. 1994;**330**(4):235-241

[67] Pastore JM, Girouard SD, Laurita KR, Akar FG, Rosenbaum DS. Mechanism linking T-wave alternans to the genesis of cardiac fibrillation. Circulation. 1999;**99**(10):1385-1394

[68] Salama G, London B. Mouse models of long QT syndrome. The Journal of Physiology. 2006;**578**(1):43-53

[69] Kim TY, Kunitomo Y, Pfeiffer Z, Patel D, Hwang J, Harrison K, et al. Complex excitation dynamics underlie polymorphic ventricular tachycardia in a transgenic rabbit model of long QT syndrome type 1. Heart Rhythm. 2015;**12**(1):220-228

[70] Chang MG, Sato D, Lange ED, Lee J-H, Karagueuzian HS, Garfinkel A, et al. Bi-stable wave propagation and early afterdepolarization–mediated cardiac arrhythmias. Heart Rhythm. 2012;**9**(1):115-122

[71] Yan G-X, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. Circulation. 1999;**100**(15):1660-1666

[72] Shimizu W, Aiba T, Kurita T, Kamakura S. Paradoxic abbreviation of repolarization in epicardium of the right ventricular outflow tract during augmentation of Brugada-type ST segment elevation. Journal of Cardiovascular Electrophysiology. 2001;**12**(12):1418-1421

[73] Meregalli P, Wilde A, Tan H. Pathophysiological mechanisms of Brugada syndrome: Depolarization disorder, repolarization disorder, or more? Cardiovascular Research. 2005;**67**(3):367-378

[74] Tukkie R, Sogaard P, Vleugels J, Groot IKD, Wilde AA, Tan HL. Delay in right ventricular activation contributes to Brugada syndrome. Circulation. 2004;**109**(10):1272-1277

[75] Eckardt L, Bruns H-J, Paul M, Kirchhof P, Schulze-Bahr E, Wichter T, et al. Body surface area of ST elevation and the presence of late potentials correlate to the inducibility of ventricular tachyarrhythmias in Brugada

syndrome. Journal of Cardiovascular Electrophysiology. 2002;**13**(8):742-749

[76] Coronel R, Casini S, Koopmann TT, Wilms-Schopman FJ, Verkerk AO, Groot JRD, et al. Right ventricular fibrosis and conduction delay in a patient with clinical signs of Brugada syndrome. Circulation. 2005;**112**(18):2769-2777

[77] Nademanee K, Veerakul G, Chandanamattha P, Chaothawee L, Ariyachaipanich A, Jirasirirojanakorn K, et al. Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. Circulation. 2011;**123**(12):1270-1279

[78] Marks AR, Priori S, Memmi M, Kontula K, Laitinen PIJ. Involvement of the cardiac ryanodine receptor/calcium release channel in catecholaminergic polymorphic ventricular tachycardia. Journal of Cellular Physiology. 2002;**190**(1):1-6

[79] Lahat H, Eldar M, Levy-Nissenbaum E, Bahan T, Friedman E, Khoury A, et al. Autosomal recessive catecholamine- or exercise-induced polymorphic ventricular tachycardia. Circulation. 2001;**103**(23):2822-2827

[80] Lehnart SE, Wehrens XH, Laitinen PJ, Reiken SR, Deng S-X, Cheng Z, et al. Sudden death in familial polymorphic ventricular tachycardia associated with calcium release channel (ryanodine receptor) leak. Circulation. 2004;**109**(25):3208-3214

[81] Liu N, Colombi B, Memmi M, Zissimopoulos S, Rizzi N, Negri S, et al. Arrhythmogenesis in catecholaminergic polymorphic ventricular tachycardia. Circulation Research. 2006;**99**(3):292-298

[82] Knollmann BC, Chopra N, Hlaing T, Akin B, Yang T, Ettensohn K, et al. Casq2 deletion causes sarcoplasmic reticulum volume increase, premature Ca^{2+} release, and catecholaminergic polymorphic ventricular tachycardia. Journal of Clinical Investigation. Sep 2006;**116**(9):2510-2520

[83] Bhuiyan ZA, Berg MPVD, Tintelen JPV, Bink-Boelkens MT, Wiesfeld AC, Alders M, et al. Expanding Spectrum of human RYR2-related disease. Circulation. 2007;**116**(14):1569-1576

[84] Tang Y, Tian X, Wang R, Fill M, Chen SW. Abnormal termination of Ca^{2+} release is a common defect of RyR2 mutations associated with cardiomyopathies. Circulation Research. 2012;**110**(7):968-977

[85] Tiso N. Identification of mutations in the cardiac ryanodine receptor gene in families affected with arrhythmogenic right ventricular cardiomyopathy type 2 (ARVD2). Human Molecular Genetics. 2001

[86] Brugada R, Hong K, Dumaine R, Cordeiro J, Gaita F, Borggrefe M, et al. Sudden death associated with short-QT syndrome linked to mutations in HERG. Circulation. 2004;**109**(1):30-35

[87] Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, Aizawa Y, et al. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. Circulation. 2007;**115**(4):442-449

[88] Extramiana F, Antzelevitch C. Amplified transmural dispersion of repolarization as the basis for arrhythmogenesis in a canine ventricular-wedge model of short-QT syndrome. Circulation. 2004;**110**(24):3661-3666

[89] Mehta M, Jain AC, Mehta A. Early repolarization. Clinical Cardiology. 1999;**22**(2):59-65

[90] Yan G-X, Antzelevitch C. Cellular basis for the electrocardiographic J wave. Circulation. 1996;**93**(2):372-379

[91] Burashnikov E, Pfeiffer R, Barajas-Martinez H, Delpón E, Hu D, Desai M, et al. Mutations in the cardiac L-type calcium channel associated with inherited J-wave syndromes and sudden cardiac death. Heart Rhythm. 2010;**7**(12):1872-1882

[92] Haïssaguerre M, Chatel S, Sacher F, Weerasooriya R, Probst V, Loussouarn G, et al. Ventricular fibrillation with prominent early repolarization associated with a rare variant of KCNJ8/KATP channel. Journal of Cardiovascular Electrophysiology. 2009;**20**(1):93-98

[93] Grant AO, Carboni MP, Neplioueva V, Starmer CF, Memmi M, Napolitano C, et al. Long QT syndrome, Brugada syndrome, and conduction system disease are linked to a single sodium channel mutation. Journal of Clinical Investigation. 2002;**110**(8):1201-1209

[94] Veen TAV, Stein M, Royer A, Le Quang K, Charpentier F, Colledge WH, et al. Impaired impulse propagation in Scn5a-knockout mice. Circulation. 2005;**112**(13):1927-1935