Chapter

Inherited Ventricular Arrhythmias, the Channelopathies and SCD: Current Knowledge and Future Speculations - Risk Stratification, Management Plans and Future Speculations

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Abstract

Channelopathy constitutes significant proportion of SCD worldwide (around 10% or 370,000 deaths annually). It was creating a mysterious group of diseases until the second half of the last century when Anton Jervell and Fred Lange-Nielsen described Jervell Lange-Nielsen syndrome in 1957. It was late until 1995 where genetic characterization commenced. Later on, the massive genetic information with the discovery of genetic heterogeneity and allelic het¬erogeneity was a major victory in the field. The basic sciences in cellular electrophysiology and genetics complemented by meticulous clinical detection and the different clinical trials in the field opened a new era of wide therapeutic choices for clinicians. The knowledge obtained from the different experimental platforms especially the induced pluripotent stem cells is promising. The revolutionary move in SCD and channelopathies is described where correlation between the arrhythmogenesis and fluctuation in SGMA is established and must be investigated. The observation of the arrhythmogenicity of SGMA fluctuation and its effect on HRV together with the differential effect of certain sympathovagal tones (more sympathetic innervation is favoring VT/VF in LQTS1, LQTS2 and SQTS but not BrS or ERS) are all future directions to optimize our preventive, diagnostic as well as therapeutic options of SCD and channelopathy in humans.

Keywords: arrhythmia, BrS: Brugada syndrome, CC: cardiac coherence, catecholaminergic polymorphic ventricular tachycardia, ERS: Early repolarization syndrome, heart rate variability, LQTS: Long QT syndrome, 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 persons, families and societies is the sudden death experience of a close relative

or a beloved one. 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. In the United States, around 300,000 deaths occur every year because of SCD. 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 a young member of the family. Sadly, life-threatening arrhythmias and sudden cardiac death can be the first presenting symptom. Scientists and clinicians were 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 discuss the available risk stratification for channelopathies and detailed management steps with focus on the different trials for pharmaceutical approach of the different channelopathies. The electrical therapy in the form of ICD is a critical management step but will be prioritized according to channelopathy type and clinical settings. Future speculations of fatal ventricular rhythms are going to be discussed with special reference to solar and geomagnetic activity fluctuation and heart rate variability (HRV) correlations to SCD and the up to the moment knowledge in its impact on channelopathies.

2. Management of ventricular arrhythmias in suspected channelopathies

2.1 The long QT syndromes' risk stratification and management plan

The yield of genetic mutations in LQTS is better than in other channelopathies but still did not exceed 50%. The cutoff numbers for QTc interval before labeling it long is 480 and 470 ms in post pubertal women and men, respectively. In the 12 leads ECG, manual measurement from limb lead 2 or chest lead V5 using Bazzet's formula ($\mathbf{QTc = QT/\sqrt{RR}}$) is a must. Moss and Schwartz developed a reliable scoring system for better risk stratification of LQTS individuals (**Table 1**) [1, 2]. Goldenburg criteria for risk stratification in long QT are also useful to add in clinical practice (**Table 2**) [3]. There must be no medications affecting ECG.

Schwartz score is more commonly used. The Schwartz score was proposed in 1993 and revised in 2011 by Schwartz and Crotti [4]. Schwartz Moss scoring system comprises clinical, electrocardiographic as well as familial historical data. It is designed for use for the index case but not others. It was found to have high correlation to positive genetic testing with 75% likelihood if the score is more than 4 points. It is not of use for a family member with long QT interval but with no symptoms [5]. T-wave abnormalities are important indicators for electrical instability. The score will count 1 point for positive T-wave alternans in the TWA test and another 1 point for notched T waves that are considered as poor prognostic sign. Poor prognostic factors with more likelihood for SCD are QTc more than 500 ms, LQTS symptoms, genotype of LQT2 or LQT3 and female gender. Male gender with LQT1 refers to lower risk group. The strongest indicator for SCD is the QTc interval [6]. Survival from cardiac arrest before age 7 or development of syncope before puberty carries worse overall prognosis [7]. Risk of recurrence is very high if syncope or cardiac arrest happens in the first year of life [8]. Genetic testing carries important prognostic value as asymptomatic positive mutation individuals below 40 years of age carry 10% higher risk of life-threatening arrhythmia if not treated [9]. Placebo controlled

Risk factor	Points
EKG findings	
A: QTc	
≥480 ms	3
460–479 ms	2
450–459 (men)	1
B: QTc fourth minute of recovery from exercise	1
Stress test ≥480 ms	
C: TdP	2
D: T-wave alternans	1
E: Notched T-wave in 3 leads	1
F: Low heart rate for age (resting heart rate below the second percentile for age)	0.5
Clinical History	
A: Syncope	
With stress	2
Without stress	1
B: Congenital deafness	0.5
Family History	
A: Family members with definite LQTS	1
B: Unexplained SCD at age < 30 years among immediate family members	0.5
Score ≤ 1 point: low probability of LQTS. 1.5–3 points: intermediate probability of LQTS. ≥3.5 points: high probability of LQTS.	

Table 1.
Updated Schwartz score: The same family member cannot be counted in A and B.

randomized trials in LQTS management are lacking (except 2019 AHA editorial Published online 2019 May 29. doi: 10.1161/JAHA.119.012833, entitled "Energy Drinks: Another Cause of QT Prolongation?") The assignment of placebo group in LQTS creates difficult ethical choices. Almost all present strategic plans in LQTS management were deduced from registries with beta blockers and cardioverter defibrillator (ICD) therapy [10]. Electrolytes disturbances correction like hypokalemia and hypomagnesaemia is a critical primary step in LQTS management. Magnesium sulfate intravenously proved to be safe and effective for acquired or congenital TdP management [11]. Beta blockers are the first line and the easiest therapeutic choice for both LQT1 and LQT2. In the current medical literature, there is controversy regarding the use of beta blockers in LQT3. For LQT1 and LQT2, propranolol and nadolol seem to be more effective than metoprolol [12]. Nadolol with its longer half life (twice a day) and sustained release propranolol seem to be attractive options. There are data suggesting that propranolol is more effective than atenolol [13]. Disease-specific favorable responses are suggested with nadolol providing the sole significant risk reducer in LQT2, while metoprolol, atenolol, propranolol and

Very high risk (secondary prevention)
Postcardiopulmonary resuscitation
Spontaneous TdP
High risk (primary prevention)
QTc >500 ms
Prior syncope
Low risk
Qtc <500 ms and no prior syncope

Table 2.
Goldenburg criteria for LQTS risk stratification.

nadolol have similar risk reduction in LQT1 [14]. No significant scientific evidence is favoring selective beta blockers over the non-selective group [15]. It is always advised to keep beta blockers as adjunct treatment after ICD implants. The sympathetic surge after delivery of a shock is always a risk for recurrence [16]. There are experimental data supporting the use of beta blockers in LQT3 [17] and others contradicting its use [18]. Analysis of 493 LQT3 patients derived from 9 registries supports the use of beta blockers [19]. There is in the horizon an early evidence suggesting significant therapeutic role of sodium channel blockers like ranolazine, mexiletine and flecainide in LQT3 treatment [20–22]. Mexiletine was proved also of being an effective therapeutic option in LQT3 as well as LQT1 and LQT2 [23].

Rarely, cautious use of mexiletine in LQT3 is needed as it may cause QT interval prolongation [24]. Successful shortening of the QTc interval (565 ± 60 ms to 461 ± 23 ms; $P < 0.04$) was achieved with flecainide. With its potent sodium blockage properties, flecainide was able to normalize QTc in five patients with LQT3 with DKPQ mutation [25]. Ranolazine, a late INa blocker, was seen to be effective to shorten the QT interval as well as suppress TdP as proved by experimental models of LQT3 [26]. Dose-dependent shortening of QT interval was achieved in human patients with DKPQ mutation of LQT3 using ranolazine [27]. What seems to be a therapeutic paradox is the benefit of adrenergic stimulation in cases with acquired LQTS and low heart rate with pauses. In the absence of concomitant gene mutations, epinephrine and isoproterenol were found to be effective in acquired LQTS [28]. In addition, selective effect of β-adrenergic stimulation was reported in the different LQTSs. The effect was seen in canine models as induction of TdP in LQT1 and LQT2 but suppression in LQT3 [29]. This concludes that therapeutic paradox is evident in LQTSs, as beta blockers are therapy of LQT1 and LQT2 but beta adrenergic stimulation is therapy for LQT3. Pause-dependent TdP in case of acquired or congenital LQT can be minimized using temporary pacing [30].

The implantation of an ICD is pivotal secondary prevention in LQTS and a reasonable primary prevention approach in selected cases [31]. Thoughtful ICD programming to prevent inappropriate shocks is important. In our practice, for LQTS secondary prevention, we do not incorporate tiered therapy for this type of patients but program the ICD to VF-only zone (detect rate, >220 beats per minute). ICD is indicated in the following conditions:

1. As secondary prevention after aborted cardiac arrest
2. Failure of optimal medical therapy to control events of cardiac arrest
3. Intolerance to primary pharmacotherapy (β-blockers)
4. Symptomatic patients with QTc of 500 ms or greater, especially women with LQT2
5. LQT3 genotype

Well-accepted treatment option in LQTS patients is left cardiac sympathetic denervation (LCSD). It is an exceptional therapeutic option that can be leaned on in selected cases like LQT1 and LQT2 patients with no proper response to beta blockers, intolerance to beta blockers, or after ICD implant with recurrent arrhythmias [32]. LCSD can be chosen as a primary treatment option or secondary, with what is described as excellent results in selected patients [33]. It seems that there are specific selection criteria to obtain optimal outcome of LCSD. More

than half of high-risk patients did not benefit from the procedure. Addition of right cardiac sympathetic denervation to LCSD might be of benefit in selected patients [34]. At all times, LCSD is not a replacement of the beta blockers and/or ICD therapy.

2.2 Brugada syndrome risk stratification and management plan

Any patient that survived a VF arrest or with syncope and an ECG consistent with spontaneous type I pattern should undergo permanent cardiac defibrillator. Other high-risk factors include male gender, atrial fibrillation or a fragmented QRS. There is no consensus on the use of electrophysiologic study to risk stratify patients. Importantly, the programmed electrical stimulation predictive value (PRELUDE) registry showed that the inability to induce arrhythmias does not correlate with a negative predictive value [35]. A family history of SCD and the presence of an SCN5A mutation have proven to be high risk predictors as well. Criteria to diagnose Brugada syndrome [36] in symptomatic patients are as follows: Type I ST segment elevation via drug challenge or spontaneously in at least 1 right precordial lead (V1 or V2). In asymptomatic patients, the situation is little bit guarded. Constellation of strong and concealed electrocardiographic manifestation should be looked for. Attenuation of the ST segment during maximum exercise with subsequent coved ST segment elevation when rested is an important finding, in the setting of absent structural heart disease. StT wave alternans (TWA), development of spontaneous left bundle branch or PVCs are all relevant to alert to BrS diagnosis in the absence of symptoms. Other subtle electrical alerts are first-degree AV block and left axis deviation as well as fragmented QRS. In TWA test, late potentials are additional alerting alarm. During electrophysiological study, a ventricular effective refractory period less than 200 ms is alarming also. Other alerts are the fragmentation of QRS as well as the presence of atrial fibrillation.

BrS is well known to be triggered by febrile illness. This is why meticulous fever management should be carried out in Brugada patients and their families. Pharmaceutical agents inducing Brugada arrhythmias should be avoided. Physicians and public may refer to (www.brugadadrugs.org) for reliable information in this regard. Sympathovagal imbalance with dominant parasympathetic tone predisposes to ventricular arrhythmias in BrS patients. Isoproterenol intravenously is used with success to control VF storms in BrS patients [37]. In a limited study, quinidine was found to be of a role in asymptomatic individuals [38]. In case of frequent ICD shocks, quinidine can be used as adjunct treatment. Quinidine effectiveness was found to be 85% in a follow-up of up to 4 years with a dose of $\leq$600 mg per day [39]. An empirical quinidine registry for asymptomatic Brugada individuals recommended doses of 600–900 mg per day if tolerated [40]. The decision of ICD implant in asymptomatic Brugada individuals needs true contemplation in view of the rarity of the events. Annual rate of cardiac events in this group is 0.5% versus 7.7%–10.2% in VF patients and 0.6%–1.2% in syncope patients [41]. Many authorities in the field do not recommend ICD implant in asymptomatic Brugada individuals [42]. With a history of VT/VF or arrhythmia-related syncope, in Brugada individuals, ICD must be the first-line management. In contrast to what we have mentioned earlier in LQTS management, tiered therapy is recommended in BrS ICD programming. Fractionated late potentials in the anterior aspect of right ventricular out flow tract (RVOT) were detected in nine patients with VF storm due to Brugada syndrome [43]. Ablation at this site normalized the Brugada ECG findings in majority of patients (with one patient only left with amiodarone) [44]. These electrocardiographic findings and site ablation results were repeated in recent works [45, 46].

2.3 Catecholaminergic PMVT risk stratification and management plan

Catecholaminergic polymorphic VT (CPVT) is a syndrome of exercise- or stress-induced PMVT in the absence of overt structural heart disease or abnormalities on the baseline ECG. CPVT should be suspected in patients with exertional presyncope/syncope and a normal resting QTc interval. The most useful diagnostic test is the stress ECG. The hallmark finding is exertional bidirectional VT, although more commonly exertional ventricular ectopy or short runs of PMVT may occur [47, 48]. The prevalence of CPVT is estimated to be 1 in 10,000, and it is often diagnosed among healthy children or young adults [49]. High doses (nadolol, 3–5 mg/kg) may be necessary to suppress exertional ectopy; doses can be titrated to effect based on inducibility of ventricular arrhythmias with stress testing [50]. Because of the high risk of recurrent events and SCD on β-blockers, adjunctive ICD implantation is recommended in all symptomatic patients.

Pharmaceutical emergency management involves intravenous beta blockers. Anesthetic measures to reduce adrenergic sympathetic surge like conscious sedation or even general anesthesia might be used in emergency situation especially with ICD shock storm. This approach still lacks scientific evidence. In spite of the pivotal role of beta blockers in CPVT management, recurrence of arrhythmic events is still high. Eleven studies have been reviewed comprising 493 patients, and 88% were on beta blockers, with follow-up periods of 20–96 months. The eight-year arrhythmic event rate was 37.2%, with a near-fatal event rate of 15.3% and a fatal event rate of 6.4% [51]. This review alerts the arrhythmia community to very important management alert, where suppression of arrhythmia induced by exercise with beta blockers does not imply long-term effectiveness.

If gene mutation is positive for CPVT, without using beta blockers, SCD may occur even if exercise test is negative [52]. Flecainide is also a promising first-line drug. It might be used as second-line treatment combined with beta blockers regardless of the presence or absence of genetic mutation [53, 54]. It was proved to target the calcium waves inducing arrhythmia as it targets RYR2 channels [55]. Flecainide was shown to be highly effective if combined with beta blockers compared to beta blockers alone ($P < 0.003$) [56]. The recommended daily dose of flecainide is 150–200 mg with maximum dose not exceeding 300 mg/day. In genotype-negative CPVT patients, flecainide was shown to reduce VT during exercise test [57].

Surgical option represented by left cardiac sympathetic denervation (LCSD) is an effective choice as a hybrid therapy to pharmaceutical agents. It was found to be safe and effective and requires minimal endoscopic surgery, although its availability is a problem. LCSD was found to raise the VT threshold and ventricular refractoriness [58]. In high-risk patients, it might be advisable to be done early in the treatment plan. Larger cohort studies are needed for better understanding the role of LCSD in PCVT [59].

ICD, with primary termination, was able to clear VT in 24 young patients with PCVT. In spite of its critical role in management, ICD may act as proarrhythmic due to its induction of adrenergic state [60]. In certain patients with cautious personalities, ICD may act paradoxically to increase arrhythmic events through emotionally higher adrenergic state of fear. This is why reducing negative emotions should be thought of as primary essential non-pharmaceutical measure to inhibit arrhythmic events in any adrenergic-mediated arrhythmia [61]. This should be emphasized more in younger age group and patients with higher shock frequency. It was found that patients younger than 50 years of age might be at higher risk due to life style disruption and distressing social comparisons [62]. Programming ICD in PCVT patients should be tiered therapy with three zones of management (SVT, VT and VF). This is important to avoid inappropriate shocks with its vicious cycle

arrhythmic effects. Symptomatic CPVT patients should avoid exercise. Guarded exercise might be allowed to asymptomatic CPVT individuals.

As we emphasized above, suppression of exercise-induced ventricular arrhythmias with β-blocker therapy does not necessarily translate into long-term effectiveness of therapy [63].

2.4 Early repolarization syndrome (ERS) risk stratification and management plan

This is a steep repolarization of transmural AP gradients that was thought to be benign and was proven to be truly arrhythmogenic in 2008 after Haïssaguerre et al.'s landmark study [64]. Because of their similar pathophysiological mechanisms, it is not surprising that the approach to therapy of ERS is similar to that of BrS. β-adrenergic activation with isoproterenol is effective in suppressing ER arrhythmias by enhancing inward calcium current [65]. As cardiac transient outward potassium current (I_{to}) inhibitor, quinidine is also effective [66]. An observational cohort study of 122 patients (age 25–49, 90 male patients) with ERS who implanted ICD was done [67]. Follow-up was done through ICD interrogation. Successful suppression of VF in this cohort was demonstrated using isoproterenol (100% success) in acute cases, while quinidine was shown superior in chronic cases. Quinidine was able to abolish all VF attacks over 2 years. Quinidine success was extraordinarily confirmed as it was able to restore normal ECG. To the surprise, medications like β-blockers, amiodarone, class 1C agents, mexiletine and verapamil were found not to be effective. In another publication of five BrS and two ERS patients, a combination of cilostazol and bepridil was found to suppress VF effectively [68]. Cilostazol inhibits the activity of phosphodiesterase III in the heart. It thereby increases the inward calcium current (ICa) via elevation of the intracellular concentrations of cyclic adenosine monophosphate (cyclic AMP), which shares some pharmacological features with isoproterenol. Cilostazol can cause symptomatic palpitations and its long-term effects have not been reported. Bepridil (calcium antagonist with fast kinetic block of sodium currents) inhibits most types of potassium currents, including (I_{to}) and could decrease the number of sudden VF episodes in patients with idiopathic VF (including those with BrS). The addition of bepridil could attenuate cilostazol-induced palpitations without preventing the suppressive effects of cilostazol on VF [69].

If VT or VF is documented, then ICD is indicated. No available clinical strategy is present for asymptomatic individuals with ERS electrocardiographic manifestation. Syncope correlation to the arrhythmia in ESR is unusual. The presence of syncope in ERS-diagnosed individuals should warrant more investigations.

2.5 Idiopathic VF management plan

Although the exit list of primary arrhythmias from idiopathic VF circle is increasing, it still stands alone as a primary diagnosis. Acute suppression of the VF can be achieved successfully with Isoproterenol or quinidine [70, 71]. The mechanism of quinidine effect in idiopathic VF is unknown [72]. The famous Ca++ channel blocker, verapamil, also proves to be successful acutely [73]. Ventricular ectopy mostly originating from the distal Purkinje system is observed in up to 30% of cases of idiopathic ventricular fibrillation VF [74].

Promising publications report the successful ablation of the triggering PVC with cure rate of 89% [75]. After ablation rate of recurrence is low (18%), there is a possibility that the recurrence is due to another site of triggering PVC [76]. For patients who were lucky to be retrieved after VF, ICD implant is a MUST.

2.6 Progressive cardiac conduction disease (PCCD) and inherited sinus node dysfunction (SND) management plan

Both PCCD and SND contain channelopathy elements and overlap with channelopathy syndromes in some cases. Until the research in genetic engineering and tissue engineering reaches to revolutionary solutions for those two conductions, device therapy with pacemakers and ICDs will be the standard management. ICD (which carries pacer capabilities) will be the choice in rare cases of the overlap nature with other tachyarrhythmias. In this condition, hybrid pharmaceutical agent might be used.

3. Future speculations on the approach to channelopathy

The explosive medical informatics that we have obtained as human species about SCD in the last three decades are landmarks in human history. In addition to continuation of the gracious efforts in the arena of cardiovascular genetics, epigenetics and molecular genetics, it is always advisable to dive more into the microperspective, as well as macroperspective. It is a way of interpreting facts with the true spectrum of the creature and biology from genes to galaxies. This is a visionary way of thinking that we and our team adopted since 2006 in the King of Organs series for advanced cardiac sciences conferences (2006, 2008, 2010, 2012 and 2019). Channelopathy and its related experimental research especially exploring the secrets of SCD are creating an ideal example of scientific incorporation of this new visionary understanding. Induced pluripotent stem cell–derived cardiomyocytes provide a new platform for studying arrhythmic disorders leading to sudden cardiac death. Cellular transfection models, which are the most commonly used cellular models, are able to mimic the expression of a single-ion channel. Both are amenable for the weak electromagnetic currents that are in common between genes and cosmos.

3.1 Future speculations in the genetic arena

Tremendous progress has been made in the discovery of putative mutations and genes responsible for different channelopathies. In the way of advances to scrutinize the pathogenic mutations comes the growing number of variants of unknown significance (VUS). It is an allele, or variant form of a gene, that has been identified through genetic testing but whose significance to the function or health of an organism is not identified. Researchers continue to work on better understanding how to stratify the risk of life-threatening arrhythmia based on the genotype and phenotype of the individual. Giustetto, C and hsi colleagues reported finding on a study of 53 patients from the European Short QT Registry. They found that A familial or personal history of cardiac arrest was present in 89%. Sudden death was the clinical presentation in 32%. The average QTc was 314 ± 23 ms. A mutation in genes related to SQTS was found in 23% of the probands; most of them had a gain of function mutation in HERG (SQTS1). Almost 43(45 %) of patients received an implantable cardioverter defibrillator, and 12(23%) patients received long-term prophylaxis with hydroquinidine. Patients with a HERG mutation had shorter QTc at baseline and a greater QTc prolongation after treatment with HQ. During follow-up, 2(4%) already symptomatic patients received appropriate implantable cardioverter defibrillator shocks and 1(2%) had syncope. The event rate was 4.9% per year in the patients without antiarrhythmic therapy. No arrhythmic events

occurred in patients receiving HQ [77]. The delta T50 is a measure of the variability of ventricular repolarization (at 50% of the T-wave downslope). It has been used to identify patients with LQTS in combination with QT interval cutoffs, as well as to identify patients at higher risk for cardiac events [78]. Rest and exercise QT interval measurements have been used to create a validated algorithm for diagnosing LQTS [79]. End-recovery QT interval measurements have also been used and, in combination with clinical history and mutation-specific information, can aid in understanding the pathogenicity of VUS [80]. Copy number variations (CNV) are a form of genetic abnormality that may explain the genetic basis of channelopathies in cases where there is no identifiable point mutation [81]. It is conceivable that in the future CNV may be added to genetic screens. Despite our increasingly sophisticated knowledge of the underlying pathophysiology, novel medical therapies tailored specifically for these syndromes have yet emerged in the clinical setting. Novel forms of treatment that specifically address the aberrant molecular pathophysiology defining these conditions will be our immediate priority step in order to effectively suppress arrhythmic events and to ultimately obviate the need for ICD implants.

3.2 Decoding the channelopathies' mysteries using induced pluripotent stem cell-derived cardiomyocyte research

The available platforms, shaping the future, to develop and investigate pharmaceutical therapeutic mechanisms for successful channelopathies treatment can be classified into different levels. First is at the organism level including clinical as well as animal models. Second is at the tissue and organ level (Purkinje fibers). Third is at cellular and molecular level (cardiac ions, induced pluripotent stem cells) [82]. Since the first report in 2006, bench researchers have made use of "induced pluripotent stem cell" (iPS) systems to study the electrophysiological and pharmacological characteristics of cardiomyocyte cells that are specific to an individual patient and his/her mutation and channelopathy. This technology has huge potential to promote our understanding of individual channelopathies and further steer the management of channelopathies in an individualistic, genotype-specific manner in the future [83, 84]. It provides a robust platform to advance the science and clinical care of sudden cardiac death. Major ion channels of the human heart are expressed in the human induced pluripotent stem cell-derived cardiomyocyte (iPSC-CM). The iPSC-CMs are created by somatic cells reprogramming into pluripotent stem cells using viral transduction or non-viral transfection or soluble proteins to introduce transcriptional factors to the somatic cell [85]. The resulting induced pluripotent stem cell can be differentiated specifically to induced pluripotent stem cell-derived cardiomyocyte (iPSC-CM) [86]. The iPSC-CMs can express encoded genes of the heart that might be absent in the original donor somatic cell. An ion channel disease can be expressed and recapitulated electrophysiologically so clinical diagnosis can be identified as well as genetic screening in the family. Variant of uncertain significance (VUS) can be developed where electrophysiological testing can be examined in the produced iPSC-CMs. Then comparison to the index case can be done. As the case in genetic testing, iPSC-CM may miss identifying the arrhythmia. In this situation, we will rely on clinical evaluation and family screening. Induced pluripotent stem of human cardiomyocyte (iPSC-CM) is superior to animal models or heterologous transfection models for channelopathies research (**Figure 1**) [87]. Its capabilities to create specific therapeutic options and its abilities to define disease-specific drug toxicity are unique.

This level of research is expected to illuminate our understanding of the true pathophysiology of channelopathies and their targeted therapies.

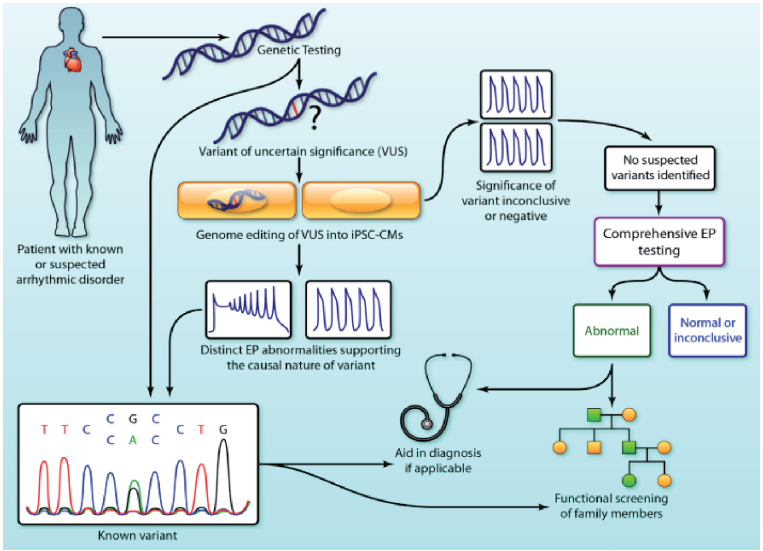

Figure 1.
Potential role for iPSC-CMs in the evaluation of patients with known or at risk for arrhythmic disorders. Clinical genetic testing attempts to identify a rare variant in genes commonly associated with arrhythmic disorders. (illustration credit: Ben smith) [87].

3.3 Fine-tuning the sympathovagal balance

Since the early 1990s, ICD have become a standard therapeutic option for VT/VF in channelopathy subjects and in most of the times the first therapeutic choice to defibrillate the fatal rhythms. As time passed, we gained the knowledge of how to fine-tune our ICD subjects to minimize or abolish shocks without using medications as much as possible. Despite the effectiveness of the ICD in preventing sudden death, anxiety, depression and post-traumatic stress disorder (PTSD) plays a contributing role in the high 1-year mortality rate observed after ICD implantation. ICD patients are at higher risk of having arrhythmias and therefore of receiving shocks, because of their fear of receiving shocks. Negative emotions lead to an increased incidence of disorders in heart rhythms and in the autonomic nervous system functioning. On the other hand, the positive psychophysiological state, called heart coherence, is associated with high performance, stress reduction and greater emotional stability, and less arrhythmic events. Heart rate variability (HRV) is considered a measure of neurocardiac function that reflects heart-brain interactions and autonomic nervous system (ANS) dynamics. HRV pattern with cardiac coherence (CC) is seen as sine wave highly regular pattern compared to the chaotic pattern seen with anger, frustration and other negative emotions. The HeartMath Institute (California, Boulder Creek) developed a heart rhythm monitoring and feedback system that enables physiological coherence to be objectively monitored and quantified.

Training ICD patients' to self-regulate emotions can produce broad improvements in increasing or strengthening self-regulatory capacity, making them less vulnerable to depletions and fear of and consequently less rhythmic events. Resilience is defined by the HeartMath researchers as the capacity to prepare for, recover from and adapt in the face of stress, adversity, trauma or challenge. It reflects the state of sympathovagal balance where the ion travel across the cellular membrane channels is in true physiological homeostasis. Teaching how to improve self-resilience is especially important for highly potential subjects for PTSD like ICD patients. In view of the role of the effects of negative emotions on induction

of T-wave alternans (TWA) and repolarization instability and its relation to future ventricular arrhythmias in patients with ICDs, we postulate that teaching the importance of positive emotional states and building a heart coherent pattern are excellent life choices that can interrupt the negative emotion, fatal rhythm and shock continuum for ICD patients [88, 89].

3.4 Earth geomagnetic activity orchestrating autonomic nervous system, arrhythmogenesis and SCD

New perspective is evident disclosing the scientific background of historical and philosophical dilemmas. The human heart rate variability as a measure of the autonomic nervous system (ANS) functions is in delicate resonance with planetary magnetic field. Statistically significant correlations have been established linking earth's magnetic activity to psychophysiological well-being including arrhythmias and sudden cardiac death. Different pathomechanisms are operating through which ANS induces the fatal heart rhythms. Andrew Armor, the pioneer of neurocardiology, elaborates in this direction as well as heart brain communications [90]. The state of cardiac coherence (CC) where HRV-dominant frequency peak is in the 0.04–0.26 Hz range and more peculiarly around 0.1 Hz carries the secrets of psychophysiological well-being and planetary resonance [91–93]. Daily autonomic nervous system activity not only responds to changes in solar and geomagnetic activity (SGMA), but it is also synchronized with the time-varying magnetic fields associated with geomagnetic field-line resonances and Schumann resonances [94, 95]. The great planetary frequency around 0.1 Hz acts also indirectly toward normal heart rhythm by reducing systemic blood pressure in hypertensive subjects [96, 97]. SCD and cerebral strokes and increase in emergency calls were linked to periods of geomagnetic disturbances (low level) and higher level of cosmic rays. This is suggesting biophysical cause effect relationship between cosmic rays and medical events of elderly humans [98, 99]. Daily autonomic nervous system activity not only responds to changes in solar and geomagnetic activity, but it is also synchronized with the time-varying magnetic fields associated with geomagnetic field-line resonances and Schumann resonances [100].

In this direction, the longest record of human heart activity synchronized to solar wind indices as well as Schumann resonances and the cosmic rays has been done by our group. A total of 97,000 hours of records were managed statistically. We have satisfying scientific evidence illustrating daily changes of the ANS in response to solar as well as geomagnetic activity. Those ANS responses are initiated after different times of the changes of the solar and planetary activities and when it occurs and it persists for varying times. Increasing heart rate was correlated to increase in solar wind intensity. This is explained as biological stress response of solar winds on human heart through sophisticated mechanisms. The rise of Schumann resonance power, solar radio flux and cosmic rays are all reflected in the increase of parasympathetic tone and HRV. The degree of effect of those energetic environmental stressors on human cardiovascular system affects different people differently depending on their health, sensitivity and self-regulation capabilities [101]. The scientific community in the field is active to establish the effect of SGMA on heart rhythm at cellular level. Laboratory findings demonstrate the effect of ion cyclotron mechanism on extracted myocardial cell regulation [102]. It seems that Schumann resonance is a major interlayer in the SGMA effect on ion channels and the ion transport in cardiac cells and accordingly in the susceptibility of channelopathic subjects to the fatal rhythms. The influence of extremely weak magnetic field in the Schumann resonances (ScR) on the creatine kinase (CK) release, calcium transients as well as spontaneous contractions of rat cardiac cell

cultures was examined. The application of 7.8 Hz, magnetic field of 90 nT was associated with gradual reduction in the spontaneous Ca++ transient amplitude. After 40 minutes of magnetic field application, 28% of the initial amplitude was reached. This reduction was associated with the calcium transient time gradually reduced. The effect is frequency dependent. The described changes occurred only in the 7.6–8 Hz. The frequency of 7.8 Hz is frequency of both central nervous system and cardiovascular system. It is the basic frequency responsible for the resonance between us humans as well as the biology on one hand and the cosmic environment on the other hand. The application of 7.8 Hz, magnetic field of 90 nT for 90 minutes results in the reduction of creatine kinase (CK) release to the buffer. This result was obtained during normal conditions, hypoxic environment and use of 80 μM H_2O_2 to induce oxidative stress. It sees that the first range of ScR has an effect on cardiac cell characterized by CK release reduction as a stress response and this effect is of a protective effect [103]. Magnetic field dynamics could add to our future understanding of the SGMA interaction with human heart in health and disease. The known transmembrane pacemaker protein CHN4, present in both sinoatrial and AV nodal cells, could interact with field information to provide specificity in an electronic key-to-lock mechanism interaction [104]. It is conspicuous that the near future is carrying more details to disclose the true pathomechanism of how modulation of HRV with fluctuation of SGMA can trigger the fatal rhythms and sudden death. More intelligent preventive as well as therapeutic strategies will be then available.

4. Summary

Risk stratification for LQTSs is available with high correlation to positive genetic testing with 75% likelihood if the score is more than 4 points. Half of LQTS cases prove positive mutation. This is not the case with other channelopathies where paucity of positive mutations is the role. Beta blockers (propranolol and nadolol than metoprolol) are the first-line and easiest therapeutic choice for both LQT1 and LQT2. There is no scientific evidence favoring selective over non-selective beta blockers. It is always advised to keep beta blockers as adjunct treatment after ICD implants. In the current medical literature, there is controversy regarding the use of beta blockers in LQT3. Scientific evidence is suggesting significant therapeutic role of sodium channel blockers like ranolazine, mexiletine and flecainide in LQT3 treatment. Mexiletine was proved also of being an effective therapeutic option in LQT3 as well as LQT1 and LQT2. In the absence of concomitant gene mutations, epinephrine and isoproterenol were found to be effective in acquired LQTS. The implantation of an ICD is pivotal secondary prevention in LQTS and a reasonable primary prevention approach in selected cases. Surgical therapy in the form of left cardiac sympathetic denervation (LCSD) is a well-accepted treatment option in LQTS patients. It is an option in selected cases like LQT1 and LQT2 patients with no proper response to beta blockers, intolerance to beta blockers, or after ICD implant with recurrent arrhythmias. Aggressive management of febrile illnesses as well as avoidance of drugs inducing VT/VF is critical in BrS arrhythmia patients. Isoproterenol intravenously is used with success to control VF storms in BrS. ICD implant is a must for secondary prevention but is guarded in primary prevention especially in asymptomatic individuals. In case of frequent ICD shocks, quinidine can be used as adjunct treatment (up to 600 mg a day). Ablation of the anterior aspect of RVOT seems a promising and successful option in BrS patients. In PCVT, high doses of nadolol (3–5 mg/kg) may be necessary to suppress exertional ectopy. Because of the high risk of recurrent events and SCD on β-blockers, adjunctive ICD implantation is recommended in all PCVT symptomatic patients. Physicians must

never rely on exercise test result for PCVT management. Flecainide (150–200 mg a day) is a promising first-line drug or as adjunct with beta blockers. Surgical option for PCVT represented by LCSD is an effective choice as a hybrid therapy to pharmaceutical agents. ICD, with primary termination, is the golden choice. Due to the role of emotional upset to induce attacks of VT/VF in PCVT, emotional management is of paramount importance. ER pattern was proven to be truly arrhythmogenic in 2008. Pathophysiological mechanism, as well as therapeutic approaches of ERS, is similar to that of BrS. Enhancing inward calcium current with β-adrenergic activation using isoproterenol is effective in suppressing ER arrhythmias in acute cases. Inhibiting cardiac transient outward potassium current (I_{to}) using quinidine is also effective to suppress ER arrhythmias and was of proven superiority in chronic cases. A combination of cilostazol and bepridil was found to suppress VF in ERS and BrS effectively. In idiopathic VF (IVF) secondary prevention; immediate ICD implantation is a must. Acute suppression of the VF can be achieved successfully with isoproterenol or quinidine. Verapamil was found to be also successful acutely. Ablation of the triggering PVC seems to be a very promising choice. For PCCD and SND with channelopathy elements, ICD with pacemaker capabilities is the standard choice. Toward the discovery of putative mutations and genes comes *variants of unknown significance (VUS)* (looking for functional significance of allele or gene variant). The delta T50 (a measure of the variability of ventricular repolarization at 50% of the T-wave downslope) is a new tool to improve our diagnostic accuracy of channelopathies. In the absence of identifiable point mutation, *copy number variation (CNV)* is a form of genetic abnormality, which may explain the genetic basis of channelopathies. The psychophysiological well-being associated with positive emotional state orchestrates the sympathovagal tone favorably. Cardiac coherence (CC) (where heart frequencies dominate in the range of 0.04–0.26 Hz) is a state of recruiting positive emotion by special training resulting in homogeneity between all body functions and systems. It is seen as sine wave appearance of HRV. Training ICD patients to self-regulate emotions with cardiac coherence can increase self-regulatory capacity, making them less vulnerable to depletions and fear of and consequently less rhythmic events. In view of the complexity of the different channelopathies and its variable responses to different treatment modalities, it is believed that comprehensive global perspective is highly needed. We adopted new universal perspective for diseases management extending from genes to galaxies. Experimental research on channelopathies is a model in this direction. Induced pluripotent stem cell–derived cardiomyocytes provide a new platform for studying arrhythmic disorders leading to sudden cardiac death. Cellular transfection models are able to mimic the expression of a single-ion channel. Both are amenable for the weak electromagnetic currents that are common between genes and cosmos. The rise of Schumann resonance power, solar radio flux and cosmic rays are all reflected in the increase of parasympathetic tone and HRV. The degree of effect of those energetic environmental stressors on human cardiovascular system affects different people differently depending on their health, sensitivity and self-regulation capabilities. The protective effect of simulated weak magnetic field in the range of the first Schumann resonance (7.8 Hz) is proven at cellular level. The future in this direction is promising to revolutionize our interventional capabilities to treat and prevent channelopathies in the human kind.

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Conflict of interest

The author declares no conflict of interest.

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Appendices and nomenclature

BrS	Brugada syndrome
CC	cardiac coherence
CPVT	catecholaminergic polymorphic ventricular tachycardia
ERS	early repolarization syndrome
HRV	heart rate variability
LQTS	long QT syndrome
PCCD	progressive cardiac conduction disease
SCD	sudden cardiac death
ScR	Schumann resonance
SGMA	solar geomagnetic activity
SNP	single-nucleotide polymorphism
SQTS	short-QT syndrome
VF	ventricular fibrillation
VT	ventricular tachycardia

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