The New Kids on the Block of Arrhythmogenic Disorders: Short QT Syndrome and Early Repolarization

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Abstract

Short QT Syndrome (SQTS) is a one of the rarest inheritable cardiac channelopathy, characterized by an accelerated cardiac repolarization, which is also the substrate for the development of life-threatening ventricular arrhythmias. Up to this date, fewer than 200 SQTS cases have been reported in the literature worldwide. Patients with SQTS may experience a cardiac arrest as early as in the neonatal period or as late as 80 years old. The cumulative probability of experiencing a cardiac arrest by the fifth decade of life approaches 40%, highlighting the importance of early recognition and management. SQTS is an autosomal dominant disease with five identified causative genes, including three that encode for potassium channels (*KCNH2*, *KCNQ1*, *KCNJ2*) and two that encode for subunits of the L-type calcium channels (*CACNA1C* and *CACNB2*).

The term "early repolarization" (ER) has long been used to refer to a heterogeneous group of specific QRS-T junction patterns that are commonly found on the ECGs of young healthy subjects. In the last decade it has been suggested that in some individuals the presence of ER may be associated with an increased risk of sudden cardiac death, and thus the term "Early Repolarization Syndrome" (ERS) has progressively entered into use. Up to this point, however, whether ER constitutes a true primary arrhythmic disorder or whether it is simply a predisposing substrate that facilitates arrhythmias in the presence of other triggers remains an unresolved issue.

In this review paper, we aim to integrate the current literature on SQTS and ERS. For each we will describe the key steps that first led to the identification of the syndrome before moving into a discussion of our current understanding of each entity, including the epidemiology, genetics, diagnosis, clinical manifestations, and management.

Keywords: Short QT Syndrome, Early Repolarization, Sudden Cardiac Death.

Introduction

Advancements in genetic technologies and an expanding research focus on cardiac channelopathies have promoted an increased understanding of a variety of arrhythmogenic disorders. Recent investigations have led to the emergence of two new entities originally characterized by specific patterns on electrocardiogram (ECG): Short QT Syndrome (SQTS) and Early Repolarization Syndrome (ERS).

Currently, there exists a clear clinical definition for SQTS, although much remains unclear regarding the genetic background, risk stratification, and therapeutic options behind the condition. In contrast, as a scientific community we are still working to understand and define ERS as a clinical entity. Studying both of these syndromes has proven to be challenging, particularly given the lack of consensus terminology and the small population of identified affected patients, but significant developments have been made.

In this review paper, we aim to integrate the current literature on SQTS and ERS, the two newest arrhythmogenic disorders. For each we will describe the key steps that first led to the identification of the syndrome before moving into a discussion of our current understanding of each entity, including the epidemiology, genetics, diagnosis, clinical manifestations, and management.

Short QT Syndrome

Introduction

SQTS is a rare inheritable cardiac channelopathy, characterized by an accelerated cardiac repolarization, which is also responsible for the development of life-threatening ventricular arrhythmias.

Historical Background

Prior to the 1990s, the discussion regarding QT interval was predominantly focused on its pathologic prolongation; a shortened QT interval, if noted at all, was viewed as a benign finding. Early suggestions of a possible correlation between short QT interval and an increased risk of ventricular arrhythmias were reported in 1986 by O'Rourke et al.[1] in a study of arterial hemodynamics in kangaroos, who are known to have markedly short QT intervals and high rates of sudden cardiac death (SCD). The group observed that during left ventricular catheterization, 10 of the 14 kangaroos studied developed ventricular fibrillation (VF) upon contact of the catheter tip with endocardial tissue. The authors postulated that the short QT interval might be implicated in the high frequency of sudden death noted in these animals. Several years later, the mechanical inducibility of VF would again be observed during the evaluation of patients with SQTS.[2]

The pathogenicity of shortened QT intervals in humans was initially postulated in 1993 when Algra et al.[3] investigated the correlation between the duration of QT interval assessed by 24-hour ECG and the 2-year risk of sudden death in 6,693 consecutive patients. This seminal study concluded that a mean corrected QT interval (QTc) under 400 ms was associated with a 2.4-fold (95% CI 1.4 to 4.3) increased risk of sudden death, a risk equivalent to that of having a QTc greater than 440 ms (i.e., a prolonged QT interval) in the same population.

Less than a decade later, the first case of SCD in the setting of a short QTc was documented, when Gussak et al.[4] reported a 37-year-old woman who passed away suddenly 2 days after presenting with syncope and a QTc of 300 ms. In the same paper the Authors provided also support for the heritable nature of a shortened QT interval, reporting a three-generations family with four members showing shortened QTc intervals, one of which had atrial fibrillation requiring electrical cardioversion.[4]

Finally, in 2003 Gaita et al[2] conclusively defined SQTS, reporting on two unrelated families with extensive histories of SCD and uniformly shortened QT intervals (QTc under 300 ms).

Since then, a significant amount of literature[5, 6] has contributed to our collective understanding of the epidemiology, pathophysiology, genetics, diagnosis, and management of patients with SQTS.

Epidemiology

SQTS is regarded as an extremely rare disease and, to date, fewer than 200 confirmed cases have been addressed in the literature worldwide.

Even though it can be expected that with growing awareness an increasing number of cases will be disclosed, epidemiological data confirm that an "abnormally" short QT interval is not a frequent finding.[7]

The reports[8-10] addressing the prevalence of short QT intervals have varied in the definition used to identify the lower limits of normality, with thresholds varying between 300 and 360 ms. Studies on healthy populations calculate the prevalence of QTc intervals under 360 ms and under 340 ms to be far less than 2% and 0.5%, respectively.[11] Unsurprisingly, studies assessing QTc values under 300 ms observe an almost undetectable prevalence. Reinig et al.[12] in 2007 were unable to validate any QTc under 300 ms in 106,432 American patients, and a more recent evaluation of 1.7 million American patients only identified 45 cases under this value (prevalence of 0.003%).[13]

One of the possible explanations for the rarity of individuals with short QT intervals in the general population is that the majority of studies focused on an adult population. Since SQTS patients may experience fatal arrhythmias in the early phases of life, screening of adults would fail to identify them, thereby leading to an underestimation of both the frequency and lethality of SQTS.

Genetic Background

SQTS is an autosomal dominant disease with five identified causative genes, including three that encode for potassium channels (*KCNH2*[14], *KCNQ1*[15], *KCNJ2*[16]) and two that encode for subunits of the L-type calcium channels (*CACNA1C* and *CACNB2*[17]) (Figure 1). A sixth gene, coding for the delta subunit of the L-type calcium channel[18] was reported as causative for SQTS in one family, but without a clear segregation pattern, the association with SQTS of this gene needs to be evaluated further.

Of note, the overall yield of genetic screening in SQTS patients is still extremely low (about 15% in our experience[6]), with none of the identified genes affecting more than 5% of the known SQTS population.[6, 19] This suggests that the genetic heterogeneity of SQTS is wide and it should be expected that further causative genes will be identified.

Interestingly, the same genes involved in the pathogenesis of SQTS are also associated with Long QT Syndrome (LQTS) and Brugada Syndrome (BrS). The three implicated potassium channel genes are respectively affected in LQT2, LQT1, and LQT7. However, while in LQTS the causative defects cause *loss-of-function* mutations, in SQTS they induce much rarer *gain-of-function* mutations, increasing potassium current conduction and thereby shortening the duration of the ventricular action potential.

Specifically, the mutations harbored in genes coding for the potassium channels (SQT1-3) share a common biophysical consequence, leading to increased repolarizing currents during the early portion of the plateau phase. In this phase of the action potential, the net repolarizing current is physiologically absent. The alterations of the gating properties of the potassium channels caused by SQTS-related variants result in an increased efflux of potassium ions during the plateau phase. This globally accelerates the cardiac repolarization and results in a remarkable and inhomogeneous shortening of the ventricular action potential duration, which represents the mechanism underlying arrhythmic susceptibility and sudden death risk.

In contrast, mutations harbored in genes coding for the subunits of the voltage-dependent calcium channels (SQT4-5) lead to decreased channel function. These variants are often associated with an overlapping appearance of SQTS and BrS.[17]

Due to the rarity of this disease, few studies exist that focus on the interplay between genotype and phenotype in SQTS. However, with the recent collection and availability of larger datasets of SQTS patients with a common genetic background, initial correlations are beginning to emerge, particularly for patients with *KCNH2* mutations (SQT1).

SQT1 patients have been found to present with the shortest QTc values among all SQTS patients[5], a later age of manifestation of the disease as compared to non-SQT1 patients[20] and a striking response to the antiarrhythmic drug hydroquinidine, which is able to restore "normal" QTc values in them.[5, 21]

Furthermore, both SQT1 and SQT2 patients have a high incidence of atrial arrhythmias, including atrial fibrillation and atrial flutter, which usually occur in the absence of structural heart disease and are possibly related to the very short atrial refractory periods that favor the generation and the sustenance of arrhythmias.[22]

Diagnosis

Population-based studies demonstrate that QTc values under 340 ms are exceedingly rare in the general population and the majority of identified probands with SQTS-related mutations exhibit QTc intervals up to 340 ms.[6] Thus, according to current guidelines, patients with QTc ≤ 340 ms are diagnosed with SQTS even in the absence of symptoms.[23]

Similarly, population studies show that relatively few patients have QTc intervals shorter than 360 ms and these values should probably be regarded as "short." Consequently, SQTS *should be considered* in the presence of a QTc < 360 ms with one or more of the following:

(a) history of documented ventricular tachycardia (VT) or VF in the absence of heart disease or reversible causes;

(b) family history of SQTS;

(c) family history of unexplained sudden death at age ≤40; or

(d) a confirmed pathogenic mutation.[23]

As with QT prolongation, the first step in clarifying the diagnosis among patients with a suspected short QT is performing repeat ECGs to further study the QT duration and T-wave morphology at different heart rates, since the Bazett formula may overcorrect the QTc when heart rate is under 60 bpm: Kobza et al.[9] found that less than 5% of all young males had QTc <360 ms, but when accounting only for ECGs recorded during sinus bradycardia, the percentage rose to approximately 20%.

Patients with SQTS show a characteristically reduced adaptation of the QT interval to changes in heart rate, which may aid in the diagnosis of uncertain cases. In other words, these patients have QTc intervals in the low–to-normal range at heart rates around 60 bpm that fail to shorten adequately at faster heart rates. Recording ECGs with different QT intervals at different heart rates may help distinguish the common patient with innocent QTc shortening during bradycardia from the rare SQTS patient with a "flat" QTc/R-R relationship. To address this point, Giustetto et al.[24] compared the QT interval behavior during exercise in a cohort of 20 SQTS patients and in an age- and sex-matched control group. In addition to shorter QT intervals both at rest and at peak exercise, the SQTS group exhibited an impaired adaptation of the QT interval to the increasing heart rate. In fact, the mean QT variation from baseline to peak exercise was only 48±14 ms in SQTS patients as compared to 120±20 ms in control group ($p<0.0001$), although the change in heart rate was not significantly different in both groups.

Clinical Manifestations

Patients with SQTS may present as early as in the neonatal period or as late as 80 years old.[6, 25]

Cardiac arrest was the initial presenting symptom in 28% of patients in a case series of 29 patients and 32% of patients in a case series of 53 patients[5, 25]. The cumulative risk of cardiac arrest by age 40 is greater than 40%[6], highlighting the importance of early recognition and management.

In contrast to LQTS but in analogy to BrS, SQTS patients show an increased arrhythmic risk at rest.[6] Interestingly, the circumstances of cardiac arrest appear to be reproducible in patients with multiple events.[6]

Both male and female SQTS patients exhibit arrhythmias, but while women appear to be at risk during their entire lifespan, males show a higher risk between mid-adolescence to 40 years of age, suggesting a possible hormonal (e.g., androgen related) influence on arrhythmias. The correlation of testosterone with QTc shortening has been shown in several studies.[26, 27] Interestingly, a study[27] of women with polycystic ovarian syndrome (a state of elevated androgen levels) found a correlation between high testosterone levels and shortened QTc but failed to demonstrate an increased arrhythmic risk.

Lastly, atrial arrhythmias, including atrial fibrillation or flutter, are characteristically seen in SQTS patients (particularly SQT1), often occurring at a young age and without an association with myocardial abnormalities.

Risk Stratification

Determining which patients with short QT intervals are at highest risk of cardiac events is paramount given the high arrhythmic burden that may characterize SQTS. Unfortunately, the clinical manifestations of SQTS are variable, even within the same family, and a risk stratification scheme for asymptomatic patients with SQTS is not yet available. Importantly, and in contrast with LQTS, a relationship between the degree of QT interval shortening and an increased susceptibility to arrhythmias has not been demonstrated, nor has there been any support for the use of genotype to assess cardiac risk.[6]

Importantly, no clinical predictors of risk have been identified in asymptomatic individuals. In fact, several studies have reported adults with QTc up to 320 ms who remained asymptomatic during their entire life.[8, 9, 28]

Gollob et al.[29] proposed diagnostic criteria consisting of QT interval length, length of J-point to T-peak interval, clinical history, family history, and genotype. This scoring system was modified with the removal of event history to be used for risk stratification. Initial analyses have proved successful in predicting rates of SCD in the pediatric population.[30] However, a subsequent analysis[6] of a new cohort of 62 patients diagnosed with SQTS showed that neither the score nor the length of the QT interval correlated with event rate. The only predictor of arrhythmias in this study population was history of a previous cardiac arrest.

Management

SQTS patients who survived an episode of cardiac arrest or have documented spontaneous episodes of sustained VT/VF are candidates for an implantable cardioverter defibrillator (ICD), as the lifetime risk of recurrence has been shown to be as high as 60%.[6]

In patients with syncope of unknown origin, when there are not specific indications for the implant of an ICD, an implantable loop recorder may aid in correlating symptoms with alterations in cardiac rhythms as well as detecting asymptomatic arrhythmias.

Similarly, there are no data to support ICD implantation in asymptomatic SQTS patients and therefore management should be tailored to each individual.

Several pharmacological approaches have been also attempted in patients with SQTS, all aiming to prolong the duration of ventricular repolarization toward normal values.

Gaita et al. first evaluated several antiarrhythmic drugs (flecainide, sotalol, ibutilide, and hydroquinidine) in the first two SQTS families described who carried the Asn588Lys mutation in the *KCNH2* gene[31] and found that hydroquinidine (HQ) was the only agent able to provoke a significant prolongation of the QT interval (from 290 ± 12 ms to 405 ± 26ms), lengthen the ventricular effective refractory period above 200ms and abolish the inducibility of ventricular arrhythmias during programmed electrical stimulation. The greater efficacy of HQ would later be explained by Wolpert et al., who found that the Asn588Lys mutation induced a 5.8-fold decrease in sensitivity of the mutant IKr potassium channel to HQ, in contrast to the 20-fold decrease in the effect of sotalol.[21] In 2011 Giustetto et al. reported on the long-term antiarrhythmic efficacy of HQ on all SQTS subtypes, despite the fact that patients without the *KNCNH2* mutation exhibited a reduced and less homogenous lengthening of the QTc.[5]

Current guidelines recommend the consideration of HQ in patients who decline or have contraindications to ICD implantation and in asymptomatic patients with a diagnosis of SQTS and a family history of SCD.[32] The former setting is especially useful in infants and pediatric patients, who have not yet reached an adequate age to implant an ICD. Furthermore, HQ can also be considered as an adjunctive therapy to prevent appropriate discharges in patients with ICDs and recurrent shocks.

The use of other antiarrhythmic drugs (including sotalol, propafenone, flecainide, disopyramide, amiodarone, vernakalant, and ranolazine) has also been suggested, but the experience in humans is limited at this time and therefore their use in clinical practice needs to be evaluated on a patient specific basis.[33-38]

Early Repolarization

Initial Understanding of Early Repolarization and Sudden Cardiac Death

Introduction

The term "early repolarization" (ER) has long been used to refer to a heterogeneous group of specific QRS-T junction patterns that are commonly found on the ECGs of young healthy subjects. In the last decade it has been suggested that in some individuals the presence of ER may be associated with an increased risk of VF, and thus the term "Early Repolarization Syndrome" (ERS) has progressively entered into use. Up to this point, however, whether ER constitutes a true primary arrhythmic disorder or whether it is simply a predisposing substrate that facilitates arrhythmias in the presence of other triggers remains an unresolved issue.

Historical Background

"Early repolarization" was first coined almost 70 years ago in reference to the ascending elevation of the QRS-T junction (also known as the "J-point") that was frequently observed in young healthy individuals. For over 60 years after the first description by Shipley and Hallaran in 1936[39], this ECG finding was considered a benign phenomenon; in fact, it was also referred to as "juvenile ST-pattern" or "normal RS-T-segment elevation variant" to specifically distinguish it from the pathological ST-segment elevation that is typical of acute coronary syndromes.[39, 40]

Independent of this first phenomenon, the term "J-wave" (or Osborn wave) has been introduced to describe a low-frequency deflection that is morphologically similar to a P-wave but appears at the end of the QRS complex in the ECGs of severely hypothermic patients. In 1953, Osborn first associated this "current of injury" (from which the "J" in J-wave originates) with the onset of spontaneous VF during hypothermia.[41]

Since then, the term "ER" has been ambiguously used to describe either of these ECG signs,[42, 43] perhaps due to the confusing inclusion of a "J" in both terms. Although these findings can theoretically coexist in some individuals, they should be considered separately.[44] The isolated J-point elevation is a frequent and very likely benign finding, whereas the presence of even a several millimeter long J-wave is an extremely rare and potentially ominous sign (Figure 2).[44]

Epidemiology

In the last 30 years, a heterogeneously defined ER pattern has been reported as a frequent finding in **survivors of idiopathic VF** (IVF). Therefore, the conviction has arisen that, similar to other arrhythmogenic conditions, ERS may be a cause of SCD in young individuals.

In 1984, Otto et al.[45] first reported the presence of ER in three young male Southeast Asian refugees with IVF. Over the following decades, several other case-reports reinforced the association of ER with spontaneous VF.[46-51]

In 2008, a landmark study by Haissaguerre et al.[52] showed an increased presence of ER in the ECGs of malignant ventricular arrhythmia survivors, as compared to matched controls (31% v. 5%,

p<0.005). Nam et al. reinforced this finding in their correspondence[53], citing that 60% of their IVF cohort (n=15) exhibited ER on ECGs, versus 3.3% of control subjects (n=1395).

More recently, Siebermair et al.[54] investigated the correlation between ER and the propensity to develop life-threatening ventricular arrhythmias, identifying ER as the only predictor of arrhythmia recurrence in a cohort of 35 IVF survivors followed for 9 years (hazard ratio 3.9, 95% CI 1.4-11.0; P=0.01).

In all of the aforementioned works, the definition of ER included the "elevation of the J-point, (presenting either as) QRS notching or slurring (J-wave)", supporting the original idea by Osborn that is the presence of a J-wave that increases the risk of VF. Nam et al.[53] reinforced this concept, stating that a "transient accentuation of J-waves across the precordial and limb leads (was observed) before the development of electrical storms".

Along the same line, in 2013 Aizawa et al.[55] performed a case study on 91 survivors of IVF without structural heart disease or known electrical disease and found that the presence of J-waves was observed in 93% of patients with history of arrhythmic storms as compared to 36% of those without storms (p<0.0001).

Since data from IVF cohorts could not be immediately translated to healthy subjects, **large community-based trials** have been conducted to test the association of ER with SCD on a population basis.

Tikkanen et al.[56] in 2008 first reported an increased incidence of arrhythmic death associated with the presence of ER (relative risk 2.92 adjusted relative risk, 2.92; 95% CI, 1.45 - 5.89; P=0.01) in a cohort of 10,864 Finnish, middle-aged individuals with a prolonged follow-up of 30±11 years. Also in this case the definition used included the presence of a J-wave.

Despite large studies demonstrating an association, there remains controversy. For instance, as part of the Atherosclerosis Risk in Communities (ARIC) study, Olson et al. evaluated the ECGs of 15,141 middle-aged subjects for presence of ER in any lead. After adjustment for possible confounders including demographic, clinical, lifestyle, and laboratory variables, ER was not significantly related to SCD (adjusted hazard ratio 1.23, 95% CI 0.87-1.75). Interestingly, the definition of ER used by Olson et al. included only J-point elevation.[42]

In an attempt to summarize the large amount of data published since the first reports, Cheng et al.[43] recently conducted a meta-analysis of 16 studies and 334,524 subjects to examine the link between ER and the risk of SCD. The work is methodologically interesting, as it included not only case-control studies, but also four cohorts that selected SCD as the endpoint of interest, for a total of 39,587 patients. Based on these data, the overall average prevalence of ER in the general population was estimated at 6.7% (95% confidence interval, CI, 2.5-17.7). Furthermore, it was calculated that ER is associated with an absolute risk increase of 140 additional SCD per 100,000 person-years (95% CI

130-149) and is therefore responsible for 7.3% of SCD in the general population (95% CI 1.9-15.2). As expected, the meta-analysis confirmed that case-control studies showed higher risk estimates than prospective and retrospective cohort studies (pooled odds ratio from case-control studies 4.25, 95% CI 1.84–9.81 *vs*. relative risk from cohort studies 1.33, 95% CI 1.13-1.57, P=0.005). Nonetheless, the clinical significance of ER was also confirmed in cohort studies and, globally, subjects with ER were found to have twice the risk of SCD as compared to those without ER (relative risk 2.18; 95% CI 1.29– 3.68).

Is there enough evidence to consider ER an "arrhythmogenic syndrome"?

Although the link between ER and SCD appears convincing, a causal relation of the first on the second has not yet been demonstrated. Several points have to first be clarified to determine whether ER qualifies as an independent arrhythmogenic syndrome.

- First, there is considerable **discrepancy in the prevalence of ER** reported **across** several **studies**, ranging from 2% to 31% in population studies and reaching up to 90% in athletes.[57, 58] This variation highlights that misdiagnosis of ER is a true limiting factor in our ability to understand this condition and which forms are most dangerous. It has been stated that the prevalence of ER varies among ethnicities, genders and ages, but these discrepancies more likely reflect methodological issues than true variance among studied populations. As an example, in 2003 Klatsky et al.[59] published the results of a longitudinal ECG study involving more than 73,000 individuals. The prevalence of ER was reported to be 0.9% when the ECG analysis was "not specific;" however, a secondary analysis performed on a subgroup of 2,234 ECGs from the same population that was specifically aimed to detect the presence of ER found a prevalence of 29%.

- Second, there are **ethnic-related differences in the risk of SCD associated with ER**. In Asians and Caucasians, the presence of ER translated to an increased risk of SCD (relative risk 2.01, 95% CI 1.3-3.1 and 1.5, 95% CI 1.08-2.07, respectively), but not among African Americans (relative risk 0.82, 95% CI 0.52-1.3) despite a higher prevalence.[43, 60] These data raise the possibility that other factors, beyond the presence of ER, may influence the susceptibility to SCD at the population level.

- Lastly, there is the **potential existence of confounding variables.** Observational studies are not substantial enough to establish a causal link between the presence of ER on ECG and the risk of SCD. Although ER has been associated with an increased risk of SCD independent of conventional cardiovascular risk factors (such as body mass index, cholesterol, diabetes, hypertension, smoking, heart rate, history of coronary artery disease), correction for other

possible markers of an increased arrhythmic risk (such as QT interval duration or the presence of left ventricular hypertrophy) have been rarely tested[56], if ever. Furthermore, in large population-based trials,[56] survival curves of patients with and without ER diverge in middle age subjects, whereas the majority of SCD related to inherited arrhythmogenic disorders occur at younger ages.[6, 61-63]

To demonstrate the difficulty in establishing a causal link between ER and SCD in 2011, Derval et al[64] utilized preliminary CASPER data to shed light on the prevalence of ER in a cohort of 100 patients with unexplained cardiac arrest and normal coronary arteries. Significant ER was present in 19% of all cardiac arrest survivors, but there was no difference in ER prevalence between patients eventually found to have a primary diagnosis (for instance, BrS) as compared to those with confirmed IVF (P=0.24). It seems therefore that ER represents more a risk factor for life-threatening arrhythmias than an arrhythmogenic syndrome on its own.

ER as a risk modifier in patients with acquired and congenital cardiovascular diseases

The late burden of mortality associated with ER, together with the large amount of heterogeneity observed in the results of studies, strengthens the view of ER acting as a proarrhythmic substrate with additional external factors precipitating the final onset of life-threatening arrhythmias at the population level.

In **chronic coronary heart disease** patients, the prevalence of ER in inferior leads was about three-fold higher among patients receiving appropriate ICD therapy for VT/VF than in those without ventricular arrhythmias, independent of ejection fraction (23% *vs.* 8% P=0.03).[65] The same observation has been made in the context of **acute myocardial infarction**: Zhang et al.[66] conducted a meta-analysis of 7 studies with a total of 1,565 patients (299 with ER and 1,266 without ER) demonstrating that patients with ER showed an increased risk of VF, as compared with age- and sex-matched control subjects (odds ratio 3.75, 95% CI: 2.62-5.37, P< 0.00001).

Additionally, in **inherited arrhythmogenic syndromes** the presence of ER has been found to portend an increased risk of life-threatening arrhythmias.

In patients with **BrS**, Kamakura et al.[67] found that VF mostly recurs in patients with ER associated with the presence of a spontaneous type 1 Brugada pattern in any right precordial lead, including the upper intercostal leads. Georgopoulos et al.[68] conducted a meta-analysis of five studies comprising a total of 1,375 patients with BrS and found an ER pattern in 12.8% of cases. During follow-up (45-93 months), 143 patients (10.4%) suffered an arrhythmic event. Overall, BrS patients with ER pattern displayed an increased risk of arrhythmic events compared to patients without ER (odds ratio 3.29, 95% CI: 2.06-5.26, P<0.00001).

A special link between ER and **SQTS** has been postulated to exist since the observation by Haissaguerre et al.[52] who reported that, among patients with IVF, the QT interval was shorter in patients with ER than in those without. Subsequently, Watanabe et al.[69] showed that ER had a prevalence of 88% in a cohort of SQTS patients and as well as that ER was associated with arrhythmic events in his cohort compared to both a control cohort of asymptomatic short QT patients (odds ratio 5.64, 95% CI 1.97-16.15, P=0.001) and to a cohort of subjects with normal QT (odds ratio 16.58, 95% CI 7.2-38.21, P<0.001).

These observations motivated us to assess the prevalence of ER as defined by MacFarlane et al.[70] in our cohort of 73 SQTS patients,[6] and we found that ER was present in 29% of our cases. This prevalence was comparable with that observed in 146 age- and sex-matched controls, who demonstrated a prevalence of 27% (P=0.83). Furthermore, this ECG pattern was not associated with an increased risk of experiencing life-threatening arrhythmias in our SQTS cohort, thus confirming that risk stratification in SQTS remains challenging (unpublished data).

Modern Approach to Early Repolarization: Focus on the J-Wave

Toward a Shared Definition for Early Repolarization

The lack of a shared definition is currently the main limitation to understanding ER. The controversy of the benign or malignant nature of ER can be attributed to the erroneously interchangeable definitions, which include either the presence of a J-wave, a J-point elevation, or both.

Since the work by Haissaguerre et al.[52] was published in 2008, the definition of ER has gradually shifted away from the traditional focus on ST-segment elevation towards the J-wave, which can manifest as QRS notching or slurring.

In 2015 a unified definition of the ER pattern was proposed for the first time, which took into account the concept of ER as a potential arrhythmogenic marker.[70]

According to the expert consensus, [70] the "modern" definition of ER includes both:

(1) a J-wave: a notch and/or slur of the end-QRS segment (i.e., occurring on the final 50% of the downslope of an R-wave), lying entirely above the baseline; and

(2) a J-point elevation of ≥0.1 mV in two consecutive inferior and/or lateral leads (leads V1-V3 are excluded from the evaluation). The J-point corresponds to the peak of the notch or to the onset of the slur.

Importantly, all ST-segment elevations without notching and/or slurring of the QRS were removed from the definition, as well as those ECGs with QRS duration > 120 ms.

Furthermore, at present the term "Early Repolarization Syndrome" (ERS) should be reserved to patients who display ER in the inferior and/or lateral leads presenting with aborted cardiac arrest, documented VF, or polymorphic VT.[71]

A multiparametric diagnostic score system for ERS, referred to as the *Proposed Shanghai ERS Score*, has been recently proposed,[71] but it will need to undergo validation in future studies before entering in the clinical practice.

Understanding the pathophysiology of Early Repolarization

Not only has the definition of ER varied in the literature, but the pathophysiology of ER has also engendered controversy. Two hypotheses exist for the origin of the J-wave on the ECG.

The first hypothesis proposes that the notch at the end of QRS is a depolarization abnormality dependent on a delay in intraventricular conduction. In a study of 22 IVF cases, patients with ER also showed a significantly greater incidence of late potentials, which is a marker of depolarization, than those without ER (86% vs. 27%, P=0.02).[72] Since repolarization markers did not differ between the groups, the investigators concluded that ER may be more closely associated with a depolarization abnormality. However, a larger study of 206 subjects with idiopathic VF showed a similar prevalence of late potentials in patients with ER on their ECG as compared to a control group with no ER pattern (11% *vs.* 13%, P=0.84)[52], suggesting that ER is not a depolarization phenomenon. Furthermore, it is important to remember that delayed conduction is usually exaggerated at faster heart rates, whereas the J-wave of ER is typically increased during bradycardia and mitigated at faster rates.[71]

According to an alternate hypothesis, ER would be a marker of increased transmural heterogeneity of ventricular repolarization, which might increase the vulnerability to VF.[73] Accordingly, the inscription of the J-wave on the ECG would be secondary to the presence of repolarizing gradients across different layers of the left ventricular wall. These might be the result of increased outward potassium currents (mediated by Ito, IK-ATP and IK-Ach channels) or decreased inward depolarizing currents (mediated by INa or ICaL channels).[71]

Today, the latter theory is the most accredited and also provides support for the mechanisms involved in the association between ER and mortality. The transmural heterogeneous distribution of repolarizing forces, in fact, would create a prominent Ito-mediated action potential notch in the epicardium, but not the endocardium. Further accentuation of Ito current, for example during an episode of myocardial ischemia, would lead to a disproportionate shortening of the epicardial action potential thus facilitating the generation of phase 2 reentries and VF.[71] According to this view, the ER pattern might serve as a substrate that can increase sudden death risk in the presence of triggers, such as Purkinje extrasystoles with a short coupling interval, which account for the majority of VF onset in younger individuals, or myocardial ischemia, which commonly precipitates episodes of VF in adult patients with coronary artery disease.

Delineating the identikit of malignant ER

As the scientific community has been working towards a consensus on a unifying diagnosis, there have also been efforts to identify ECG characteristics that may help us distinguish benign ER from its

malignant counterpart. Various features of the J-wave, ST-segment, and T-wave have all been highlighted as ECG findings that portend an increased arrhythmogenic risk.

A large research focus has been placed on identifying key attributes of the J-wave that may signal a more malignant form of ER. As one example, the **notching morphology** is associated with up to a four-fold increased risk of SCD when compared to the slurring morphology (odds ratio 3.85, P=0.002).[66]

Separately, the risk of experiencing SCD among subjects with a **J-point elevation of more than 0.2 mV** in the inferior leads was 3 times as high as the risk of SCD among those who did not demonstrate ER (relative risk 2.92, 95% CI 1.45– 5.89, P=0.003).[43]

With respect to the **duration of the J-wave**, a literature review by Cristoforetti et al. suggested that a duration **> 60 ms** is a marker of increased risk of VF (P<0.001).[74] Additional studies have sought to investigate if the **localization** of the J-wave is of any importance and have concluded that **global J-waves in both inferior and lateral leads** are associated with the highest risk of arrhythmic events (odds ratio 4.87, 95% CI: 2.64 to 9.01, P< 0.00001),[68] followed by J waves in inferior leads (hazard ratio 3, 95% CI 1.45-5.89 P<0.01).[56]

Other ECG findings that have been investigated include the ST-segment and the T-wave. An ST-segment that is horizontal or down-sloping portends a higher risk in both the general population and in IVF patients (relative risk 2.03; 95% CI 1.10- 3.74; P=0.02)[43]. To contrast this, the ST-segment in the J-point elevation that is often seen in healthy young adults is typically ascending.

Finally, a recent paper found that there is higher prevalence of **low-voltage T waves** among patients with ER and VF when compared to asymptomatic patients with ER (29% *vs.* 3%, P 0.001).[75]

All of the above ECG parameters have been demonstrated to be associated with arrhythmia risk in separate studies; however, the absolute risk conferred by each variant is small and, in isolation, these ECG markers are of limited value as risk stratification tools in clinical practice.

A Genetic Background for ER

Several studies suggest that the finding of an ER pattern on ECGs is "familial".[76-78]

Due to the heterogeneity of its manifestations, it is conceivable that various genetic forms of ER may exist, ranging from complex polygenic variants to highly penetrant Mendelian forms. A study[78] of 505 British families suggested a 2.5 times increased risk in offspring of subjects with ER (95% CI 1.33-4.84, P=0.005). Likewise, an analysis of the Framingham population showed a two-fold increase in risk.[76] Recently Gourraud et al.[79] identified four large families with apparently autosomal dominant transmission of ER and with several cases of early sudden death, but the genetic background of these families is not reported. To further complicate the subject, a large scale meta-analysis of genome-wide association studies involving over 14,500 individuals provides some opposing evidence and did not identify any common variants significantly associated with ER. [73]

Thus far, genetic variants in seven genes associated with ER have been identified.[71]

Two variants reported in ERS patients are *KCNJ8* and *ABCC9*, responsible for the pore-forming and ATP-sensing subunits of the IK-ATP channel, which have been shown to generate ER in canine ventricular wedge preparations.[80, 81] Additionally, loss-of-function variations in the α1, β2, and α2δ subunits of the cardiac L-type calcium channel (*CACNA1C, CACNB2, CACNA2D1*) and the α1 subunit of $Na_V1.5$ and $Na_V1.8$ (*SCN5A*, *SCN10A*) have been reported in patients with ER.[82-84]

Importantly, only a small number of these variants have been examined using functional expression studies and thus causality cannot be established unless clear segregation data exist. The lack of functional or biologic validation of mutation effects remains the most severe limitation of genetic test interpretation.[71] Therefore, given the very limited understanding of the genetic basis of ER, genetic testing for the condition may have low sensitivity and specificity as well as a risk of discovering a genetic variant of unknown clinical significance. Genetic testing of ER cases is therefore restricted to the research field since it does not have clear clinical utility yet.

Management of patients with ER

The crux of the modern approach towards managing ER is to stratification by SCD risk.

According to current guidelines, survivors of an episode of VF with documentation of ER have a class I indication for the implant of an ICD.[23]

No guidelines exist for the treatment of patients with ER who have syncope or are asymptomatic. In particular, there are no indications for the implant of an ICD in these patients groups and treatment needs to be personalized for each individual.

For patients presenting with syncope, the circumstances of the syncopal event need to be carefully investigated. In the presence of syncope occurring without an alternative cause, an implantable loop recorder may be considered, particularly in patients with "high risk" ER and/or family history of SCD.

The majority of patients with ER on ECG, however, are asymptomatic and likely do not require any intervention. In fact, until a more precise definition of "malignant" ER is reached, ER needs to be considered a normal variant from a population perspective, given its high overall frequency.

Furthermore, large epidemiological studies suggest that the risk of SCD associated with ER in the general population is low: data from Rosso et al. show that the finding of ER in a young adult would increase the probability of idiopathic VF from 1 in 30,000 to 1 in 10,000 individuals per year[85]. This risk is obviously too low to suggest any specific intervention.

Further prospective studies concentrating on the estimated prevalence of "high risk" ER and its correlation to outcome are necessary.

Conclusion

In the last 20 years SQTS has emerged as a new inheritable arrhythmogenic syndrome. Several aspects of its pathophysiology and of the natural history of affected individuals have been clarified; furthermore, initial insights in genotype-phenotype correlations are emerging. Much more, however, needs to done, to better understand its heterogeneous genetic background, to learn how to risk stratify asymptomatic individuals for the risk of SCD and to find therapeutic strategies able to prevent arrhythmias. Progressing towards these goals will require identified patients to be referred to a shared registry and genetic testing of each case will be vital.

Early Repolarization has also emerged as a possible arrhythmogenic condition, after having been considered a physiological variant of a normal ECG for decades. This modern view of ER is related to the presence of a J-wave and, in order to gain a better understanding of its pathological role, the scientific community will need to progressively abandon the use of "ER" to refer to the ECG appearance of young and healthy individuals.

If we will not be able to reach a consensus on a shared definition for ER, the noise surrounding this term will remain so loud that the concept of ER as a potentially independent arrhythmogenic syndrome will gradually fade.

Figure legends.

Figure 1. Electrocardiographic Characteristics of Genotype-Positive SQTS families. Each row refers to a kindred. Columns from left to right show gene and mutation identified; ECG of probands; the family tree; QTc interval duration, as numbered in the family tree. In the pedigree column, affected subjects are indicated by the solid symbols, unaffected subjects by open symbols, and sudden death victims by the grey symbols. + = mutation carrier; − = mutation non-carrier; → = probands; □= male patients; O = female patients. ECG = electrocardiogram; QTc = corrected QT interval. Modified with permission from Mazzanti A. et al. *Journal of the American College of Cardiology.* 2014;63(13):1300-1308.

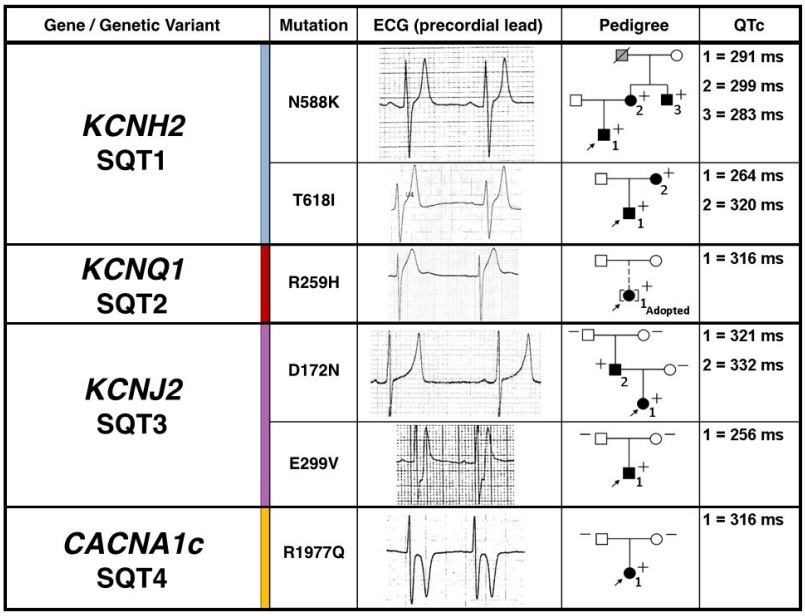
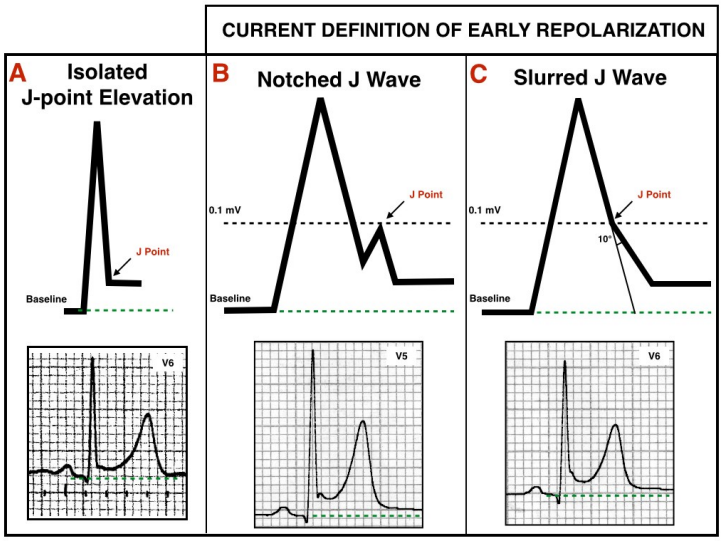


Figure 2. Differentiating isolated J-point elevation from Early Repolarization (ER). Panel A shows an example of isolated J-point elevation in a 25 year-old asymptomatic male athlete. Panels B and C show the two aspects of Early Repolarization pattern as proposed by MacFarlane et al. Panel B illustrates the end-QRS notching variant accompanied by, while panel C illustrates the slurring variant. When the angle between the initial downslope of the R-wave and the end-QRS inscription exceeds 10°, a slur is defined as present. The definitions are taken from MacFarlane et al. ((*Journal of the American College of Cardiology.* 2015;66(4):470-477).



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