Syncope in patients with inherited arrhythmogenic syndromes. Is it enough to justify ICD implantation?

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Primary Inherited Arrhythmia Syndromes

- In the context of inherited arrhythmogenic disorders, the occurrence of syncope is an important indicator of arrhythmic risk.
- Although there is no definition to differentiate a syncopal episode caused by ventricular arrhythmias from an otherwise unexplained syncope, the term “syncope” implies the exclusion of events that are likely due to vasovagal events.
- The presence of symptoms including syncope is, in the majority of channelopathies, an independent predictor of cardiac arrest at follow-up.

Long QT Syndrome

- LQTS exposes patients to an increased risk of fatal (SCD) and nonfatal arrhythmic events that persist from an early age and progress almost unabated until adulthood.


- The overall annual rate of SCD in patients with untreated LQTS is approximately 0.9%.


- Syncope is a frequent event in patients with LQTS, with an annual rate of approximately 5% in untreated patients, and some variability based on the underlying genetic defect.

Long QT Syndrome: the role of syncope

- A clinical history of a syncopal event is a strong predictor of adverse outcome\(^1\)
- A single syncopal event in the absence of β-blocker treatment has been associated with a six-fold increase in the risk of subsequent SCD\(^2\)
- Patients who experience multiple syncopes in the absence of β-blocker treatment have twice the risk of experiencing a cardiac event compared with patients who have a single syncopal event\(^3\)

Data from the International Long QT Syndrome Registry

- LQTS patients with syncope more than 10 years ago are not at significantly increased risk.
- One syncopal event 2-10 years ago: HR of 2.7
- Two or more syncopal events 2-10 years ago: HR of 5.8
- **One syncopal episode in the last 2 years**: HR of 11.7
- **Two or more syncopal episodes in the last 2 years**: HR of 18.1
- QTc of 530 ms or longer has been associated with increased risk (HR of 2.3).
- Males between the ages of 10 and 12 years had higher risk than females (HR of 4.0).
- No significant independent association between genotype and life-threatening events.

Hobbs et al. JAMA. 2006;296:1249-1254
The cumulative probability of aborted cardiac arrest or SCD by the presence of prior syncopal events

Long QT Syndrome: the role of syncope

- The occurrence of syncope during β-blocker treatment is the most powerful predictor of subsequent life-threatening events\(^1\)

Long QT Syndrome: 2010 Heart Rhythm UK position statement

- Near zero mortality in LQT1 patients treated with β-blockers long-term.
- LQT2 patients are also best treated with β-blockers as the first line of management.
- LQT3 patients are less likely to present with warning symptoms, with the first event potentially being SCD. However, β-blockers remain the initial treatment for many LQT3 patients and there is evidence that LCSD can be very effective in their management.
- LQTS patients experiencing **continuing syncope despite β-blockade or LCSD** (when VT/ VF has not been excluded as the cause of syncope) should undergo ICD implantation.
- The identification of an LQT2 or LQT3 genotype should not by itself constitute an indication for ICD implantation.

Heart Rhythm UK position statement on clinical indications for implantable cardioverter defibrillators in adult patients with familial sudden cardiac death syndromes. Europace 2010; 12:1156–1175
Long QT Syndrome: 2013 HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes

- **Class IIa**
  - ICD implantation can be useful in patients with a diagnosis of LQTS who experience *recurrent syncopal events* while on β-blocker therapy.

- **Class III**
  - Except under special circumstances, ICD implantation is not indicated in asymptomatic LQTS patients who have not been tried on β-blocker therapy.

**Take home message:** a single syncope in LQTS should not be treated with an ICD; multiple episodes despite β-blockade are needed to justify ICD implantation

Management of LQTS
Do we follow the guidelines?

- The vast majority (91%) of the patients were symptomatic at baseline, with almost equal proportions of those who had experienced syncope only (47%) and those with cardiac arrest (44%).
- Unexpectedly, **9% of patients were asymptomatic before ICD.**
- **More than half of the patients (60%) with syncope displayed at least one syncopal episode despite therapy.**
- In 38 of the 102 patients (37%) who experienced a cardiac arrest, this was the presenting sign.
- Appropriate ICD therapies were predicted by age 20 years at implantation, a QTc 500 milliseconds, prior cardiac arrest, and cardiac events despite therapy; within 7 years, appropriate shocks occurred in no patients with none of these factors and in 70% of those with all factors.
- **Adverse events occurred in 25%.**

Clinical dilemmas: Who is a highest risk and should receive an ICD?

- Highly malignant subtypes
  - Jervell and Lange-Nielsen syndrome
  - Timothy syndrome (LQT8)

- Specific locations/types of mutations (we need more data)
Short QT Syndrome: diagnosis

- The SQTS is highly arrhythmogenic (VF and AF) and highly lethal

- The SQTS is diagnosed in the presence of a QTc ≤330 ms

- The SQTS can be diagnosed in the presence of a QTc <360 ms and one or more of the following:
  - A pathogenic mutation;
  - Family history of SQTS;
  - Family history of sudden death at age ≤40;
  - Survival of a VT/VF episode in the absence of heart disease.

Short QT Syndrome: how to make the correct diagnosis?

- **Gollob’s score (≥ 4 points is considered high probability)**
- **Electrocardiographic criteria:**
  - QT interval corrected by Bazett’s formula < 370 ms (1 point),
  - < 350 ms (2 points)
  - < 330 ms (3 points)
  - J point-T peak interval duration in ms: Jp-Tp < 120 ms (1 point);
- **Personal clinical history dates:**
  - history of sudden cardiac arrest (2 points),
  - documented polymorphic VT or VF (2 points),
  - unexplained syncope (1 point)
  - AF (1 point);
- **Family history parameters:**
  - first-or second-degree relative with high probability of SQTS (2 points),
  - first-or second-degree relative with autopsy negative SCD (1 point),
  - sudden infant death syndrome (1 point);
- **Genetic findings:**
  - genotype-positive (2 points)
  - mutation of undetermined significance in a culprit gene (1 point).

Identification of risk factors in SQTS: a ticking bomb

- 73 probands with SQTS.
- **Cardiac arrest is the most frequent presenting symptom** (40% of probands; range: <1 month to 41 years).
- Neither the presence of a very short QT interval nor the history of syncope alone identifies patients at higher risk of cardiac arrest.
- Inducibility of VT/VF at PES is not an independent predictor of risk in SQTS.
- **Survivors of cardiac arrest have a high cardiac arrest recurrence rate**; therefore, ICD implantation is strongly recommended in this group of patients.
- The prognostic score proposed by Gollob et al. is not able to identify patients who experienced cardiac arrest in this SQTS population.

Mazzanti et al. J Am Coll Cardiol 2014;63:1300-8
Long-Term follow-up of a pediatric cohort with short QT syndrome

- 25 patients <21 years of age were followed up for 5.9 years
- Median corrected QT interval for heart rate was 312 ms (range: 194 to 355 ms)
- Symptoms occurred in 14 (56%) of 25 patients and included aborted sudden cardiac death in 6 patients (24%) and syncope in 4 patients (16%)
- A gene mutation associated with SQTS was identified in 5 (24%) of 21 probands
- Symptomatic patients had a higher median modified Gollob score (excluding points for clinical events) compared with asymptomatic patients (5 vs. 4)
- Young SQTS patients have a high rate of inappropriate ICD shocks

Short QT Syndrome
What current guidelines advise us?

- **Class I**
  - ICD implantation is recommended in symptomatic patients with a diagnosis of SQTS who are survivors of a cardiac arrest and/or have documented spontaneous sustained VT with or without syncope.

- **Class IIb.**
  - ICD implantation may be considered in asymptomatic patients with a diagnosis of SQTS and a family history of SCD.

**Something is missing.... SYNCOPE!!!!!**
SQTS: 17 years-old boy with history of syncope

- Short QTc interval: 283ms
- ERS
- Brugada like pattern
- Paroxysmal AV block
- Very short ERPs at EPS
- ICD implantation
- Syncope associated with car accident 3 years later
- ICD interrogation: appropriate shock

Take home message: SQTS is highly lethal and an ICD should be implanted in patients with a history of syncope

Brugada Syndrome

- BrS is a primary electrical disease characterized by complete or incomplete RBBB and ST-segment elevation in leads V1 through V3 on surface electrocardiogram (ECG).
- Proposed risk factors: aborted sudden death, syncope, spontaneous type 1 pattern, inducible arrhythmias at PVS, QRS fragmentation, family history of SCD.
- Risk stratification still remains problematic.
Brugada Syndrome: Syncope is an independent predictor of future arrhythmic events

FINGER study\textsuperscript{1}

PRELUDE study\textsuperscript{2}

Brugada Syndrome: is syncope a single clinical risk factor able to identify subjects at highest risk?

- A multiparametric approach (including syncope, family history of SCD, and positive EPS) helps to identify populations at highest risk; subjects at highest risk are those with a spontaneous type 1 ECG and at least two risk factors; the remainder are at low risk.

Identification of high-risk syncope related to ventricular fibrillation in patients with Brugada Syndrome

- High incidence of neurally-mediated syncope in BrS patients\(^1\)
- 20% of the patients with VF events experience prodromes before the onset of VF\(^2\)
- Prodromal symptoms before VF were blurred vision (rare), palpitations, and chest discomfort\(^2\)
- VF often occurred at rest in the supine position and was accompanied by convulsion and abnormal respiration during the episode\(^2\)
- Non-VF episodes usually occurred with prodrome (especially blurred vision and diaphoresis) while patients were standing or urinating\(^2\)
- Absence of prodrome (especially blurred vision) and existence of abnormal respiration and f-QRS were important risk factors for the occurrence of VF in patients with BrS and syncope\(^2\)

Class I

ICD implantation is recommended in patients with a diagnosis of BrS who:
- Are survivors of a cardiac arrest and/or
- Have documented spontaneous sustained VT with or without syncope.

Class IIa

ICD implantation can be useful in patients with a spontaneous diagnostic type 1 ECG who have a history of syncope judged to be likely caused by ventricular arrhythmias.
Brugada Syndrome: 2010 Heart Rhythm UK position statement

- BrS patients presenting with ventricular fibrillation/cardiac arrest without reversible precipitant should undergo ICD implantation.

- Brs patients with syncope (when VT/VF has not been excluded as the cause of syncope) should undergo ICD implantation.

Take home message: arrhythmic syncope in BrS justifies ICD implantation


Catecholaminergic Polymorphic Ventricular Tachycardia

- CPVT is a rare arrhythmogenic disorder characterized by adrenergic-induced bidirectional and polymorphic VT\(^1\)
- Patients are usually children, adolescents, or young adults presenting with syncope occurring during physical exercise or emotion\(^1\)
- Symptoms can occur in early childhood and the mean age of onset of the first syncope is 12 years\(^1\)
- Limited data from small studies show that about 75% of affected individuals become symptomatic before the age of 20 years\(^1\)
- RyR2 and CASQ2 gene mutations\(^1\)

Catecholaminergic Polymorphic Ventricular Tachycardia: predictors of a worse outcome

- In the absence of treatment, the disease is highly lethal, with an estimated incidence of sudden death before 40 years of age of 30% \(^1\)
- The occurrence of cardiac arrest before diagnosis is associated with higher risk of arrhythmic episodes at follow-up \(^2\)
- However, **this is not true for syncopal episodes** \(^2\)
- Diagnosis in childhood is a predictor of adverse outcome \(^2\)
- The persistence of complex ectopy in exercise tests is a marker for worse outcome \(^2\)

**Syncope before diagnosis (without treatment) is not associated with higher risk of arrhythmic episodes at follow-up**

Catecholaminergic Polymorphic Ventricular Tachycardia: management

- The mainstay of treatment is conscientious administration of β-blockers in the highest tolerable doses

- Some patients, however, despite compliance with β-blockers, continue to experience ventricular arrhythmia

- Flecainide appears to be effective in a subgroup of patients, but long-term efficacy has yet to be established

- Left cardiac sympathetic denervation (LCSD)

Catecholaminergic Polymorphic Ventricular Tachycardia: fatal or near fatal events while on β-blockers

- The largest series by Hayashi et al. reported 4 year and 8 year fatal or near fatal event rates on β-blocker treatment of 1% and 11%, respectively.

- In systematic analysis on the efficacy of β-blockers in all CPVT patient series reported to date, **4 year and 8 year fatal or near-fatal event rates were 7.2% and 14.3%, respectively.**

- **A significant proportion of events may be due to poor drug compliance**, so CPVT patients should be well informed about the potentially fatal consequences of non-compliance.

Patients with syncopal episode should receive the highest tolerable β-blocker dose: treatment should be intensified

Catecholaminergic Polymorphic Ventricular Tachycardia
How to manage these patients??

- In patients who have experienced an aborted cardiac arrest before initiation of therapy, β-blockers, or β-blockers and flecainide, should be started and an ICD should be implanted.

- An ICD should be considered in symptomatic CPVT patients who do not respond to an optimal medical management and when LCSD is not possible.

Catecholaminergic Polymorphic Ventricular Tachycardia
How to manage these patients??

- CPVT patients presenting with VF/cardiac arrest should undergo ICD implantation in addition to oral β-blockade or LCSD\(^1\)
- **CPVT patients experiencing sustained VT or syncope despite β-blockade or LCSD should be considered for ICD implantation\(^1\)**
- ICD programming can be complex / ICD therapies have been associated with electrical storms\(^2\)
- In a series, among appropriate shocks, 20 (32%) were effective in terminating sustained arrhythmia and 43 (68%) were ineffective. Shocks delivered to triggered arrhythmias nearly always failed, while shocks delivered to VF were usually successful effective\(^2\)

**Take home message:** syncope in CPVT needs intensified β-blocker treatment; a single syncopal episode does not justify an ICD

What are we doing in routine clinical practice? Results of the EHRA Survey

- **The first-line therapy in LQTS is drugs (76%),** drugs and implantable cardioverter-defibrillator (ICD) (19%), ablation and ICD (3%), whereas no specific treatment was reported by 3% of the centres.

- **For SQTS, it is ICD (50%),** drugs (21%), ICD and drugs (18%), or nothing (12%).

- **In BrS, the first-line treatment is ICD (48.65%),** drugs (11%), ICD and drugs (8%), ablation and ICD (3%), or nothing (30%).

- **In CPVT, first-line therapy is drugs (47%),** ICD (11.11%), or ICD and drugs (42%), whereas in IVF, it is ICD (67%), drugs (9%), ICD and drugs (18%), ablation and ICD (3%), or none (3%).

Hocini et al. Europace 2014;16: 600–603
Risks and challenges of ICDs in the young

- Programming may be challenging

- High rate of complications
  - Implantation risk
  - Infections
  - Lead issues
  - Inappropriate shocks

Thank you very much for your attention