THE PRESENCE OF CHANNELOPATHIES IN DROWNING AND NEAR-DROWNING-EVENTS IN PAEDIATRIC POPULATION

FINAL DEGREE PROJECT

Paediatric Arrhythmias, Electrophysiology and Sudden Death Unit

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Making things simple is the ultimate form of sophistication.

Josep Brugada

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1. LIST OF ABREVIATIONS

SCD: sudden cardiac death
LQTS: long QT syndrome
CPVT: catecholaminergic polymorphic ventricular tachycardia
SQTS: short QT syndrome
BrS: Brugada syndrome
QTc: corrected QT
ECG: electrocardiogram
AV block: auriculoventricular block
SEM: servicios de emergencias médicas
SJD: Sant Joan de Déu
SJDH: Sant Joan de Déu Hospital
HR: heart rate
BPM: beats per minute
ICU: intensive care unit
VF: ventricular fibrillation
VT: ventricular tachycardia

2. ABSTRACT

INTRODUCTION:

Drowning incidents are the cause of the 52'7 % of all the death in people under 15 years (372.000 deaths per year). For each child dead by a drowning episode, it is estimated than another four children experience a serious non-fatal drowning event.

In comparison with other activities, swimming is now a well-stablished trigger of arrhythmia in people who have LQTS or CPVT.

HYPOTHESIS AND OBJECTIVES:

The aim of this retrospective descriptive study is to discover if there are underlying cardiac channelopathies in drowning and near-drowning incidents that happened between 1997 and 2017 in patients registered in Emergencies and Intensive Care Units of SJD Hospital.

METHODS:

A registry of 155 patients listed for having suffered a drowning or near-drowning event was described and analysed, attending to epidemiological data, clinical aspects, familiar background, all diagnostic tools used and their results.

RESULTS:

ECG was performed in 26,5% patients of those 155 patients registered, five of them were positive for LQTS, what supposes a 12,2% of these 41 performed ECG. Five patients did have a genetic test performed, all of them resulted positive.

CONCLUSIONS:

Because ECGs and genetic tests are not performed as part of the drowning and near-drowning events protocol, there is a potential underestimation in the diagnosis of these channelopathies in cases of drowning and near-drowning events. ECGs and genetic tests are both fundamental in the diagnosis of both LQTS and CPVT diseases. Due to this fact, it is essential to proceed to do both of them when a patient has suffered from a drowning or near-drowning event, apart from a stress test to unmask a possible underlying CPVT once patients have recovered from the incident.

KEYWORDS: Children, LQTS, CPVT, Drowning, Near-Drowning, arrhythmia, sudden cardiac death.

3. INTRODUCTION

1. DROWNING AS A GLOBAL PUBLIC HEALTH THREAT

Drowning is defined as dying through submersion in and inhalation of water. Furthermore, near-drowning definition is the same as the previous but it does not have a fatal ending

Drowning is a leading killer of young people, with more than a half (52'7%) of all the deaths occurring in people under 15 years old, which are estimated to be 372.000 deaths per year (1), besides one third of those victims are known to be accomplished swimmers.

Moreover, for each children death caused by a drowning episode, it is estimated than another 4 children experience a serious non-fatal drowning event. Many of these children will be left with chronic disabilities, such as long-term neurological deficits (2). This is a serious problem that causes a huge impact in societies and which could be avoided if we avoid triggers that may cause drowning.

A significant number of these drownings are thought to be result of poor swimming ability, lack of adult supervision, alcohol or drug abuse, or even risky behaviour. However, the reality is that a high quantity of these events remains unexplained.

In 1999, the Mayo Clinica published the first *postmortem* molecular diagnosis of an arrythmic disorder: they diagnosed a LQTS in a girl who was 19 years old and died after a near-drowning event (3). After this first publication, other articles which discovered similar cases were posted. For instance, in 2003, Lunetta et al (4) identified a single LQT2 mutation in 1 of 165 consecutive bodies that had been found in water (in Finland). Moreover, in 2005, the Mayo Clinica also discovered that it was not just LQTS what may cause this drowning event, but CPVT may be in relation with these drowning and near drowning events too (5).

In comparison with other activities, swimming is now a well-stablished trigger of arrhythmia in people who have LQTS or CPVT. Besides, as far as LQTS is concerned, it is also known that the LQT1 subtype is the one more associated to these occurrence happenings (6).

2. CHANNELOPATHIES

Channelopathies are those alterations that affect genes which codify the formation of ionic channels or associated proteins. Ionic channels are proteins in the cellular membrane that are in charge of regulating the ionic pass through them (7), as represented in fig. 1.

They may affect different organs such as muscles, cardiac tissue… Cardiac channelopathies are liable of the most part of hereditary arrhythmias and a high percentage of sudden cardiac deaths (6).

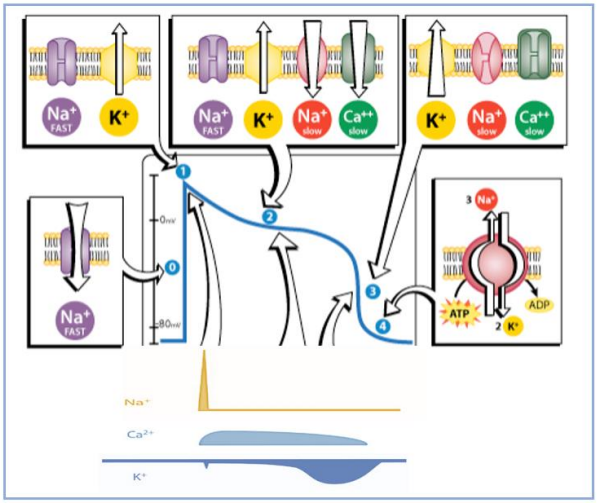

Figure 1. Representation of action potential and ionic channels implicated. This image is being used courtesy of Dr. Georgia Sarquella-Brugada

These cardiac channelopathies are not identified by a special clinical sign but by characteristic ECG abnormalities due to the fact that they are not usually associated to morphological heart defects. (8)

However, these ECG patterns which characterize and distinguish these disorders may be masked due to the incomplete penetrance and variable expressivity in inherited disorders. Moreover, these diseases often have a low penetrance, and low ECG expressivity, although it may vary because of environmental factors, as It is shown in fig. 2. Because of that, genetic diagnosis may be a good technique to identify the pathological alterations and their genetic carrier (8).

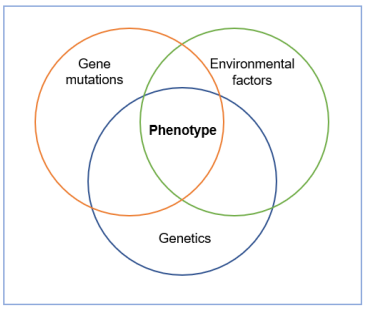

Figure 2. Proposed scheme of how the interaction of gene mutation, genetics and environmental factors can module a disease's phenotype.

2.1. Long QT syndrome

I. Definition and History

Long QT syndrome consists of an arrhythmogenic ion channel disorder which is characterized by several abnormal ventricular repolarization, which results in an electrocardiographic prolongation of the QT interval despite an apparently normal heart structure (9). This disease increases the risk of syncope, seizures, and sudden cardiac death, normally after a precipitation event, which may be extreme emotions, auditory trigger… due to ventricular arrhythmias in form of *torsade de pointes*. (6).

It was first described both clinical and electrocardiographically by Anton Jervell and Fred Lange Nielsen in 1957 as a result of the study of a family in which 4 out of 6 children had congenital deafness and suffered from syncope and 3 out of them had a sudden cardiac death event.
In 1964 Romano and Ward (10) published independently a study of a family with syncope episodes and antecedent of sudden cardiac death, and prolongation of QT interval seen in the electrocardiogram, but without deafness.
Some years later, genetic studies demonstrated that, on one hand, the syndrome that Nielsen had described, defined a more aggressive phenotype and that it was due to homozygotic mutations, while, on the other hand, the one described by Romano and Ward, known as Romano-Ward syndrome is caused by mutations which are normally heterozygotes and without clinical connexion with deafness (11,12).

II. Epidemiology, Aethiology and Molecular bases

The incidence of those mutations that cause these channelopathies is estimated to be 1 out of 3.000-5.000 cases (13). However, nearly a third part of asymptomatic carriers may have a normal QT (corrected by frequency) they may transmit that mutation to the progeny, which is more vulnerable to malignant arrythmias, if we compare them to the rest of the long QT syndrome population(14).

This long QT syndrome is very heterogenic and many mutations have been found in relation with it. Besides, these mutations are distributed in 10 genes: KCNQ1, HERG, SCN5A, KCNE1… However, despite of the improvement of technology, nowadays still the fourth part of patients have no genetic diagnosis. (12,15)

In 1995 the principal genes were first described and this disease was classified as a channelopathy. Some of those genes are represented in fig. 8 (page 21).

Molecular bases of congenital LQTS are represented in table 1(12,16)**.**

Table 1. Analysis of the transmission of LQTS subtypes.

Transmission	subgroup	Chromosome	Gen	Affected flow	Frequency (%)
Romano-Ward Syndrome					
Dominant Autosomal	LQT1	11p15.5	KCNQ1/KVLQT1	I_{ks}	30-35
	LQT2	7q35-36	KCNH2/HERG	I_{kr}	30-35
	LQT3	3p21-p24	SCN5A	I_{NA}	5-10
	LQT4	4q25-p27	ANKB	Na/Ca	<1
	LQT5	21q22.1	KCNE1/MinK	I_{ks}	<1
	LQT6	21q22.1	KCNE2/MiRP1	I_{kr}	<1
Jervell-Lange Nielsen Syndrome					
Recessive autosomal	JLN1	11p15.5	KCNQ1/KVLQT1	I_{ks}	80
	JLN2	21q22.1	KCNE1/MinK	I_{ks}	20
Andersen-Tawill					
Dominant Autosomal	ATS1	17q23	KCNJ2	I_{k1}	50
Timothy Syndrome					
Sporadic	TS1	1q42-q43	CACNA1C	I_{Ca}	-

III. Clinical presentation

Two of the three most important genes in relation with this syndrome affect the potassium and one does to sodium channel. These three mutations explain abut a 65% of cases. These three mutations are compared in table 2 (17–19). The 7 gene mutation that rest, of the ten that were described before, only explain a 5% (12,15,20,21).

Table 2. Comparison of SQTL1, SQTL2, SQTL3.

LQTS type	Gen alteration	Channel Flow	Functional effect	Frequency	Resting ECG	ECG at arrhythmia start	SCD Trigger	Penetrance
SQTL1	KCNQ1	Potassium (Ik5)	Decrease	30-35%	Wide based slowly generated T wave 	No pause	**Exercise**, emotions, rest…	62%
SQTL2	KCNH2 or HERG	Potassium (Ikr)	Decrease	25-30%	Low amplitude T wave, double humped T wave 	Pause common	Exercise, **emotions,** rest	75%
SQTL3	SCN5A	Sodium (Nav)	increase	5-10%	Long isoelectric ST segment, bradycardia 	Unknown	Exercise, emotions, **rest**	90%

IV. Diagnosis and clinical management

Long QT syndrome is diagnosed trough an index of several diagnosis criteria (which are mentioned in table 3 (22)) which are divided in three main groups,

based on where they are found: if they are electrocardiogram findings, clinical signs or family background.

Table 3 .LQTS diagnosis criteria.

ECG findings	**Points**
QTc (Bazzet's formula)	
>/= 480 ms	3
460-470 ms	2
450 ms (in men)	1
Torsade es pointes	2
T wave alternant	1
Notched t-waves	1
Low CF in relation with age	0'5
Clinical history	
Syncope	
- With stress	2
- Without stress	1
Congenital deafness	0'5
Family history	
Some relative diagnosed of congenital LQTS	1
SCD in a direct relative under of 30 years old	0'5

Counting these items and adding their value, probability of having a LQTS diagnosis is measured:

- Low probability of diagnosis: ≤1 point
- Intermediate probability: 2-3 points
- High probability: ≥4

In the study of a patient with long QT syndrome, many items must be taken into account.

- Clinical history: it is essential to know if there has been familiar and/or personal sudden cardiac death event or a syncope, with or without stress as a trigger. It is crucial for both diagnosing and knowing the risk of the syndrome. Moreover, it is helpful to know the conditions where the sudden cardiac episode or the syncope has taken place. It is also relevant to know if there may have been drugs or alcohol taking part.

  Furthermore, as it is described in some forms of long QT syndrome, it is also relevant if there are personal or familiar antecedents of deafness. (12,16).

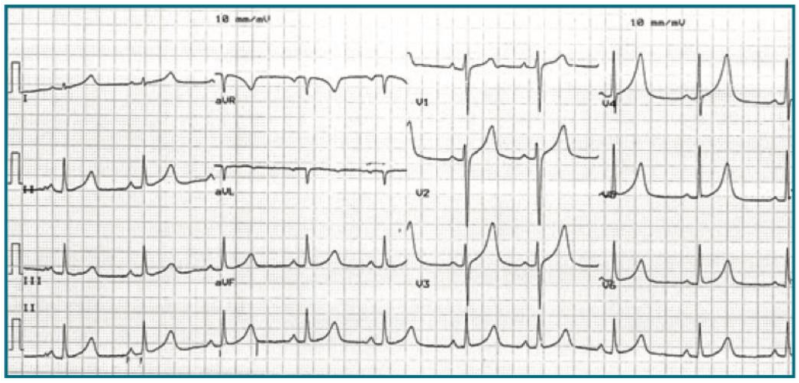

Figure 3. Long QT syndrome ECG. (QTc 480 ms. T waves wide and peaky).

- Electrocardiogram: One of the most important findings is the elongation of the QT interval, as it can be appreciated in fig. 3 (16). This elongation is better measured in two concrete ECG leads. Those leads are II and V5. It must be corrected by the cardiac frequency (using Bazzet's formula) since interval QT may vary according to the cardiac frequency (21,23,24). For this, interval RR and interval QT must be located as shown in fig.4.

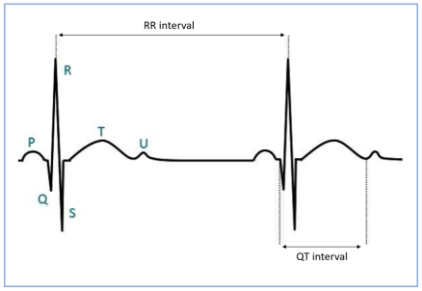

Figure 4. Representation of a normal ECG with RR interval and QT interval named and pointed.

Another electrocardiographic alteration, such as ventricular tachycardia as *torsade des pointes*, T wave alternant, notched T-waves in at least three derivations, or low cardiac frequency in comparison with the age of the patient (15,16).

- Holter: with it the sanitary or technical personal is able to record if there are spontaneous asymptomatic arrythmias or another kind of alterations such as sinusal node disfunction or AV block (12).

- Stress test/Visking test/Exercise test: it is very useful for risk stratification. These SQTL patients are not able to reach their maximum heart rate calculated by the age. Therefore, in stress situations, QT interval may get longer instead of getting shorter (25,26). Moreover, as mentioned in ECG register, ECG during exercise test may have different expression depending on SQTL subtype: SQTL1 have marked elongation of interval QT and do not reach maximum heart rate, on the

contrary SQTL2 use to reach maximum HR but do not present a marked interval QT elongation (27,28). Finally, QSTL3 patients have, in general lines, a normal physiological answer to exercise and stress, which means having a shortening in interval QT (29).

- Genetic tests: It is particularly useful for high risky patients, and its main application is for the genetic counselling. However, it is also used to orientate treatment depending on which SQTL subtype does each patient have (27,30,31). Particular mutations in relation with SQTL subtypes are commented in fig. 8.

- *Postmortem* studies: Some post mortem genetic studies, that have autopsy, have revealed that almost a 10% of children did have a genetic alteration which may be related to long QT syndrome (32,33), and nearly a 35% in adult population (34).

- Adrenaline test: it may be used in some cases where QTc is not long enough to be defined as a long QT syndrome, but it is not also that short to be considered as normal. With a low dose of adrenaline, long QT syndrome may be unmasked. It is particularly useful to detect asymptomatic forms of SQTL1 subtype (35,36).

V. Prognostic, Prevention and Therapeutic options

Symptomatic patient must be treated compulsory, if not the mortality is known to be among 20% in one year, and around 50% in 10 years. In asymptomatic cases is estimated that sudden cardiac death may be the first symptom in a 9% of cases.

The progression of this syndrome is very variable, but it is in relation with the measure of QTc interval, environmental factors, pregnancy (especially during the *postpartum* period), age, genotype and its response to treatment (37,38)**.**

LQTS is considered to be high risk if it is in association with the following characteristics, which are also grouped as a proposed scheme of risk stratification in fig. 5.

1. Congenital deafness (known as Jervell-Lange-Nielsen).
2. Frequent syncope episodes.
3. Familiar cases of sudden cardiac death.
4. QTc>500ms.
5. AV block 2:1.
6. Electrical alternance in T wave.
7. SQTL3 subtype.

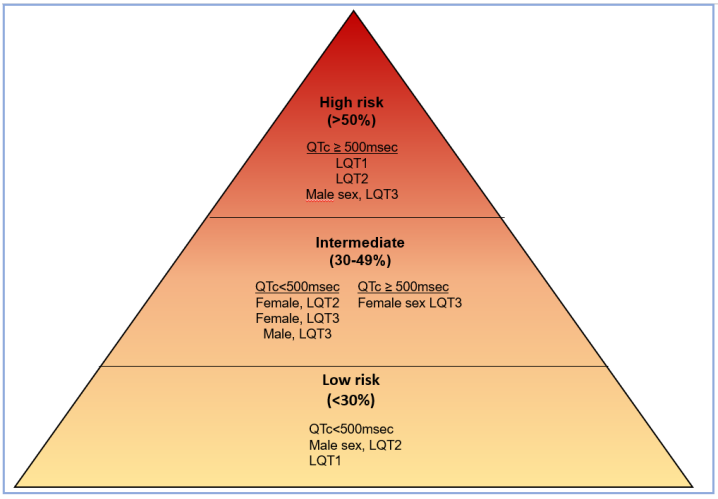

Figure 5. Proposed scheme for risk stratification in LQTS according to genotype and sex. *Risk groups have been defined based on the probability of a first cardiac event before the age of 40 and before therapy. Syncope, cardiac arrest or sudden death are meant to be cardiac events. This figure is thanks to Dr. Sarquella-Brugada.*

In order to make a good prevention of symptoms, risk stratification must be taken into account, and it will also be very useful to make some important decision according to the treatment, considering clinical and electrocardiographic markers.

It is compulsory to inform and warn patients that some drugs elongate the QT interval -and trigger ventricular arrhythmias- and the importance of avoiding them.

Beta blockers

This kind of drugs constitute the first line in LQTS treatment. They must be administrated in every single person diagnosed with LQTS.

They reduces to a 64% the risk of suffering a cardiovascular event, but they are particularly efficient in SQTL1(39,40) (which is caused by alterations in Ik_5 channel, but not so efficient for SQTL3 (a 32% will continue symptomatic, due to the fact that in these patients ventricular arrhythmias are more frequent while having low cardiac rates). Nevertheless it is usually initiated in this last kind of patients (41).

Their mechanism does not consist in the modification of QT interval, but in its dispersion.

However, a low percent of patients will continue symptomatic despite of the treatment (42).

The exercise test is helpful to stablish the correct dose. Moreover, the maximum heart rate must not be over 130 beats per minute.

Sodium channel blockers

They are useful in SQTL3 due to the fact that these patients have mutations in sodium channel causing a bad inactivation of it. Studies have revealed that with flecainide both heart rate and ECG alterations improve (43).

Potassium supplements and sparing-potassium drugs

These two types of drugs may decrease QT interval in approximately a 24% of cases, mostly in patients with SQTL1 and 2 (44).

Pacemaker and defibrillator

Pacemakers have been used in patients with pause-dependant arrhythmias. As patients with SQTL3 have a major prevalence of bradycardia, they are the group which take more benefit of pacemakers. DDD stimulation is indicated in those cases with arrhythmia that depend on pause or an AV 2x1 block (high grade). Heart programmed rates under 70 bpm are not useful to prevent ventricular arrythmias.

Automatic implantable defibrillator, plus beta-blockers therapy, decrease in such an important way the SCD incidence. It is clearly indicated in high-risk patients. However, this device has some complications, like arrhythmic Storm, for instance. Incidence of arrhythmic storm is estimated to be a 15% and it is caused mainly by an increase in sympathetic nervous system tone after the DAI discharge. This problem can be solved with an increase on beta-blockers dose (45,46).

Left sympathectomy

It was first introduced in 1971, but it was in 1991 when Schwartz et al. demonstrated a 94% of survival in 5 years.

Nowadays it is recommended for those high-risk patients who despite of beta-blockers treatment and/or pacemaker, still suffer from syncope. It is also useful if after the pacemaker implantation they have many discharges.

Left sympathectomy consists of a resection in the Stellate ganglion inferior portion and left thoracic sympathic ganglion chains (T2 to T4) (47).

2.2. Catecholaminergic Polymorphic Ventricular Tachycardia

I. Definition and History

It is an inherited arrhythmia, first described in 1975, characterized by a bidirectional ventricular tachycardia mainly caused by an autosomal dominant mutation of the gene encoding the cardiac ryanodine receptor (RYR2) (16).

It was described for the first time in 1978 (11). He discovered in some boys aged of 4 years and without structural cardiopathies, that they suffered from syncope episodes with and ECG which showed a ventricular polymorphic tachycardia.

II. Epidemiology, Inheritance and Aethiopathology (Genetic Factors).

The prevalence of this disease is estimated that about 1 out of 10,000 (48). The high prevalence of simplex cases and lethality at a young age suggest that the overall prevalence of CPVT is significantly lower than that of other inherited arrhythmogenic disorders(49), as LQTS, for instance. CPVT is a genetic disease what means that it is caused by a mutation that can be passed on through families(16).

This disease is due to an alteration in how the myocyte use the intracellular calcium, what suggests that there exist mutations on the cardiac ryanodine receptor. This cardiac ryanodine receptor (RYR2) is an intracellular calcium liberator and it is necessary for the coordination of excitation and contraction. It is located in the *endoplasmatic reticulum* (50).

Its main arrhythmogenic trigger is an adrenergic stimulus such as high impact exercise, emotions or stress (16).

Two variants have been identified. One is transmitted as an autosomal dominant form, and is the one caused by RyR2 mutations(51). The other is inherited in an autosomal recessive way and it is due to mutations in the cardiac isoform gen of calsequestrin (CASQ2)

III. Clinical presentation and Diagnosis.

CPVT affects mainly children and young adults. First symptoms usually to take place during the infancy or teenage years, being the media age 7'8 ± 4. However, there are some cases of SCD described in babies, in relation with RyR2 alterations.(49)

A 30% of the cases have familiar background of syncope, convulsions or sudden cardiac death in relation with stress.

The most common symptoms are palpitations or fainting and collapse, particularly during exercise. Nevertheless, basal ECG is absolutely normal: QTc interval, AV and intraventricular conduction are normal too. In some patients some prominent U waves or a sinusal bradycardia may be seen. Despite having a normal ECG pattern at rest, diagnostic can be done performing an exercise test, as physical exercise is known to be a trigger. This fact is schemed in fig. 6. In this test isolated ventricular extrasystoles, ventricular bigeminism, and bidirectional ventricular tachycardia (in some cases can degenerate to ventricular fibrillation) (16,49).(16,49)

1. ECG

This is the most basic test. It is normal in rest, so additional or repeated ECG-test are sometimes necessary (48).

2. Exercise test (stress test)
   It is a normal ECG with its electrodes putted onto the chest in its normal position, but it is recorded before, during and exercising on a treadmill or an exercise bike. This help us to record any changes in the electrical heart activity during exercise (50).

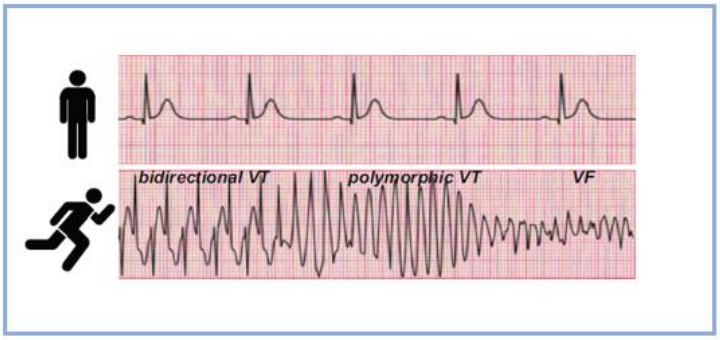

Figure 6. First cartoon shows that CPVT patients have a normal ECG pattern at rest. Second cartoon, on the contrary, shows how CPVT patients at exercise have severe, potentially life-threatening arrhythmias. Traces are idealized sketches.

3. Holter monitoring

4. Echocardiogram
   It is not for diagnosing CPVT but to confirm there is no other structural heart disease

5. Genetic testing
   Over a half of CPVT families are carriers of RYR2-gene mutation, this particular mutation has a dominant autosomal inheritance. On the other hand, in patients with autosomal recessive CPVT two mutations can be found in the CASQ2 gene, which are represented in fig. 7.

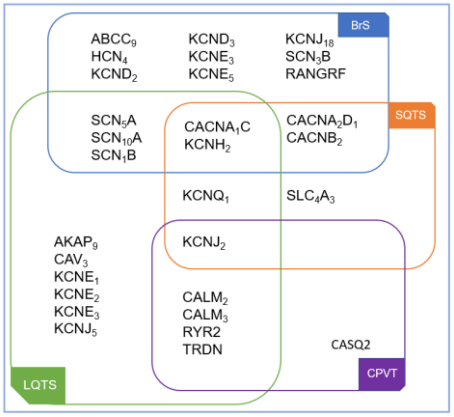

Figure 7. Genes associated to channelopathies. Reproduced with permission of Dr. Sarquella-Brugada.

IV. Prognostic, Prevention and Therapeutical options.

It is an arrhythmogenic cardiac disease with high mortality. In non-treated patients the mortality about 40 years old is between 30 and 50%, being sudden cardiac deaths one possible initial clinical sign (48).

The most important precipitants are stress and exercise, so these two triggers may be avoided as long as possible. Ventricular extrasystoles are observed in these patients when cardiac frequency is above 110-130 bpm.

Cardiologists give these patients some advices/recommendations for them and their families to prevent these arrhythmias:

- In general, to avoid competitive and extreme sport.
- Use of beta blockers (only if prescribed)
- Encourage relatives to be screened

Besides, the possibility of passing on the condition to their descendants can lead patients to anxiety. Medical social workers or psychologists may be helpful for the patients and their family members.

There are two reliable options which are well tolerated and have great results in the major part of the affected. These two options are:

- Treatment with beta blockers
- Treatment with an implantable cardioverter defibrillator (ICD)

V. Familiar screening

If a mutation in a gene is found in a patient with CPVT, family members of this patient should be able to have a genetic testing. If they turn out to be carriers of the mutation they must be followed up by a cardiologist and take the same preventive measures (48).

As it was mentioned in section above, CPVT patients may experience their first symptoms during childhood, therefore it is very important to proceed to genetic and hearing testing.

4. JUSTIFICATION

The chronogram of this study is represented in *figure 13*. There is also a brief scheme in *figure 8*.

This study begins in 2016 with the need of giving an explanation to those cases of drowning and near-drowning events that each year arrived to Sant Joan de Déu Hospital, especially during the summer holiday period. For this reason, in 2016, a retrospective descriptive study from 2015 onwards was proposed. It was about 19 patients who suffered from drowning and near drowning events. 11 out of those 19 patients had an underlying cardiac channelopathy which explained these events (*fig. 8.*). This fact permitted the diagnosis of these pathologies and, moreover, it started a monitoring of these patients and their disease with its accurate treatment and preventive measures.

This fact impulse this actual work in which the retrospective study was amplified until 1997. We made a revision of all those patients that entered with a drowning or near-drowning incident into the Sant Joan de Déu hospital Emergencies Service or into the Intensive Care Unit of the same entity, from all over Catalonia.

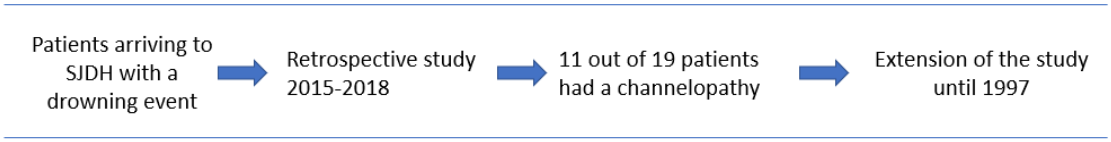

Figure 8. Representation of how this work arose..

The idea of this project is to make a pilot study, due to the lack of registered cases, in order to provide evidence for building subsequently a tool which may be diagnostic and preventive for the whole population so they sanitary system would be able to prevent those accidents that can cause a social and familiar impact.

5. HYPOTHESIS AND OBJETIVES

HYPOTHESIS

1. Cardiac channelopathies are responsible of a significant number of non-fatal and fatal drowning events in paediatric population.
2. Doing an ECG in patients that suffer a drowning or near drowning event is helpful to diagnose the underlying cardiac disease

OBJECTIVES

Primary objectives

- To make a retrospective revision, looking for drowning or near-drowning events since 1997 to 2017.
- To analyse epidemiological data of these drowning and near-drowning events.
- To quantify/calculate the incidence of drowning and near-drowning patients who had an underlying channelopathy.
- To analyse the importance of doing and ECG in drowning and near-drowning patients at the arrival to Emergencies Unit, and during the stage at the UCI service.
- To determinate in how many patients ECG has been done and to calculate QTc interval in those patients who have an ECG
- To analyse the importance of doing a genetic test in drowning and near-drowning patients.

Secondary objectives

- To impulse the recruitment and elaboration of a bigger project in this hospital with new cases with these characteristics from 2019 to the future.
- To make a base for a multicentric study.
- To know if there are classification bias cases, for example, in patients diagnosed of epilepsy.

6. PATIENTS AND METHODS

Population characteristics

The study population was based on paediatric patients who entered into the Urgency or Intensive Unit Care Services of Sant Joan de Déu Hospital, in Barcelona, because of a drowning or near-drowning event

One hundred and fifty-seven patients aged between one and seventeen years old entered into these services between 1997 and 2017.

Inclusion criteria

The only criteria for being accepted in this study was to have suffered from a drowning or near drowning event in children under 21 years old at the time of inclusion.

Sample

A non-probabilistic consecutive sampling method was performed from our study population. Finally, a total of 156 anonymous patients entered at the Emergencies and ICU Units of Sant Joan de Déu Hospital from 1997 to 2017 who accomplished the inclusion criteria were included in the study in a completely anonymous way.

With this sample size, in a bilateral contrast and with an alpha risk of 5%, the statistical power is 70%

Computations were carried out with the Prof. Dr. Marc Saez's software based on the library pwr of the free statistical environment R (version 3.6.2).

Study Variables

Dependent variable

Having a channelopathy was the dependent variable in this study. It was analysed as a categorical dichotomous variable depending on if a pathological ECG or a positive genetic test for any genetic mutation in relation with this kind of diseases was performed or not.

Independent Variable

The independent variable in this study is the fact of having suffered from a drowning or near drowning event.

Co-Variables

- Age at the incident time in years old, measured as a quantitative continuous variable
- Sex: female or male. It was analysed as a categorical dichotomous variable.
- *Exitus:* *d*ead or alive. it was also analysed as a categorical dichotomous variable.
- Family history: of sudden cardiac death in relatives at a young age or relatives diagnosed of any channelopathy.
- Presence of cardiac and/or neurologic personal antecedents. It has been registered as a categorical dichotomous variable whereas patients had it at the clinical history or not. However, in case of having a positive result in this dichotomous variable, the name of the disease has been registered as a categorical nominal variable.
- Genetic Test: It was measured as a dichotomic variable in order to know how many genetic tests were performed, but it was also considered the concrete mutation the patients presented to know if they were related to channelopathies, and also to know how many patients of each genetic mutation appeared in our sample.
- Swimming abilities: it has been measured as a dichotomic variable taking into account if the adult who accompanied the child at the arrival to SJDH said in an explicit way that the child was not able to swim well enough to avoid drowning or did not know how to swim at all.

Procedures

i. Data acquisition

From June 19th to July 12th, clinical histories of all these drowning and near-drowning patients were carefully revised with HCIS program, which is the program that SJD doctors use in their daily hospital life, and also those Clinical Histories that were not available in this informatic program have been revised in its paper form.

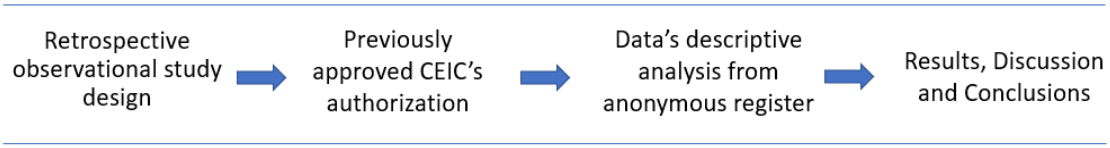

Figure 9. Data acquisition's representation

In order to access to the data registry, permission to the Ethical Committee of Sant Joan de Déu Research Foundation was requested. Once authorization was approved, these anonymized data were analysed and exposed in this study in a completely anonymous way and numerically codified. The process was made by the Department of Medical Informatics of the centre, registering all data needed in an anonymous database platform hosted on the servers of the hospital. An excel with all these cases was made. In which figure all drowning and near drowning events that have happened between 1997 and 2017.

During this process, they were revised looking for concrete information that could help us to clarify the cause of those drowning and near drowning events:

- First of all, epidemiological data were looked for. As it was one of this project's objective: age and sex were noted in order to know how much of these patients were girls and how many were boys. On the other hand, their age at the event time was registered, however afterward they were grouped in 4 different group ages: new-born babies to five years old, from five to ten, ten to fifteen and more than fifteen. Moreover, we found interesting the incidence of this kind of events depending on the month of the year, because it was noted when they occurred.

  On the other hand, familiar background was checked: it was interesting to know if there had been familiar background of sudden cardiac death in relatives of these children at a young age, however not much information about this was found.

- Besides, personal background was also checked, looking for information about other cardiac symptoms or symptoms related with LQTS, for instance deafness, or in relation with CPVT (these related symptoms are commented in section 3.2.). Moreover, epilepsy diagnose was also looked for as there are registered cases of children who had been wrongly diagnosed of epilepsy when they really suffered from LQTS (52,53,54). Of course, it was also registered if these patients already had a channelopathy diagnosis.

- For the information gathering it was also noted how the drowning or near-drowning accident was. It was sought to clarify if there was an evident trigger that could explain these episodes, for instance, a previous head trauma.

  Moreover, it was noted that during the clinical interview to the parents or tutors of the patients, some of them told the correspondent doctor that their children was not able to swim. This was a relevant information; however, it does not exclude the possibility of having suffered from a drowning or near-drowning event, because of that these patients were not excluded from the sample of this study; however, this information was noted to be aware of it.

- Clinical data was also registered. One of the aims of this project was to know if during a normal actuation in front of a drowning or near drowning event, personal of SJD Hospital proceeded to do an ECG as part of the protocol. In order to know this, in every clinical record an ECG during the patient admission because of this kind of accident was looked for. However, as there were many cases in which ECG was not performed at this time, and it was important to know if these children had a channelopathy to give an answer to other of the objectives of this project, it was also sought for ECG records in another time apart from the drowning accident date.

Besides, as another part of the diagnosis of channelopathies is the genetic test, we also looked for genetic tests in which the possibility of diagnosing a channelopathy was excluded.

ii. Systematic interpretation of an ECG

It is really important to follow a systematic revision (55) (annex II) when an analysis of an ECG has to be done in order to avoid passing by any alteration that may be significant. It must bed proved that the ECG that is being analysed has a sinusal, rhythm, does not present left or right bundle branch block, has a normal heart rate, has normal PR interval, QRS complex… But what was most interesting for this project was if there were any alterations in the QT longitude or if an arrhythmia is found at the incident time.

Interval QT is better measured in two concrete ECG leads. Those leads are II and V5.

It must be corrected by the cardiac frequency since interval QT may vary according it (23,24). For its correct measurement, Bazett formula must be used:

$$QTc = \frac{QT}{\sqrt{RR}}$$

In this formula, each value must be measured in seconds. And it is pathological if it measures more than 470ms.

In order to measure QTc correctly, we should be aware of three important points:

a. If there is a sinusal arrythmia, several QTc intervals must be calculated in a rhythm strip and an average must be done. If this is procedure is not done, an overestimation or underestimation may appear.

b. U wave is frequent in teenagers. It is a small positive wave that may appear after T wave. It must be excluded in the measurement of QT interval.

c. If the end of the T wave is not well seen, tangent's method may be used following fig. 10. exemple. This method regards that T wave ends in the intersection of the most inclined part of the descendent T wave portion and the base line.

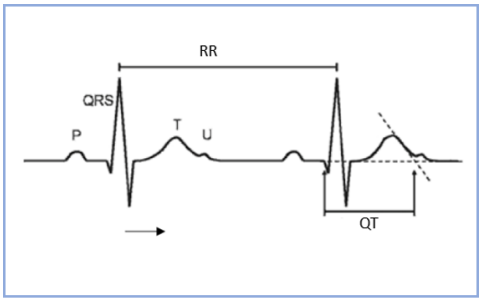

Figure 10. Measurement of T wave Tangent.

iii. Data analysis

Statistical analyses were carried out using the IBM SPSS software package (version 10.0, SPSS Inc., Chicago, IL, USA). A *p-value* under 0.05 was considered statistically significant.

For the univariate analysis, the age of drowning and near-drowning patients (which is a quantitative continuous variable) was presented as a mean with its standard deviation and its interquartile range of 25-75. The rest of variables, which were qualitative ones, were presented as proportions, being treated as dichotomous variable.

For the bivariate analysis, bar plot and contingency tables were used.

Moreover, the independency hypothesis was contrasted using Chi-square of Pearson test, however, when frequencies were expected to be under 5, the exact-test of Fisher was used.

7. ETHICAL CONSIDERATIONS

The *Declaration of Helsinki* establishes the ethical principles about researching involving human subjects and which were established long ago by the World Medical Association. Due to the participation of humans, the design and the treatment of patients personal data will be carried out respecting the Basic Ethical Principles, and, moreover the study will respect the criteria established by the

Nuremberg Code, the Belmont Report, the Declaration of Helsinki (1964, last update in 2016) and the Oviedo Convention.

Before the start of this study and its predecessor, the projects were evaluated by the Clinical Research Ethical Committee of Fundació Sant Joan de Déu Hospital, in Barcelona.

All gathered data were registered and analysed anonymously and under non-identifying numeric codes, according to the legal framework of human rights and data confidentiality specified in *Organic Law 3/2018,* of the December 5th about the Personal Data Protection and Digital Rights Guarantee. The information about patients was only used for the research purpose.

The *41/2002 Law*, of December 14th was also followed, which regulates the autonomy of the patients and their right to be informed and to access to clinical documentation. Moreover, the *1720/2007 Royal Decree/Ordinance* of December 21st regulates the security of files which contain patient data was also taken into account.

In case a genetic test had to be performed during any part of the study process, the *14/2007 Law* and the *1716/2011 Royal Decree/Ordinance* were followed/fulfilled, both law and decree regulate aspects in relation with biologic samples. If a paediatric patient resulted to have a positive result of the genetic test, a first-degree relatives screening process should have been advised. In this situation, the language used to communicate the relatives the finding of a genetic rare disease was extremely careful and legal and ethical premises were always followed.

This study does not have any commercial bias or interests.

8. RESULTS

A total sample of 155 patients younger than 21 years old and who had suffered from a drowning or near drowning event were registered from 1997 to 2017. Over this population ECG exam had been performed in only 41 patients (26’5%), of which 5 patients presented a positive ECG for these pathologies. These values are summarised in table 5.

Table 4. Population in which ECG was performed. Values are n(%).

ECG	
ECG realized	41
Pathological ECG	5 (12’2%)

In the sample of these study only in 41 of these patients, an ECG was performed at their arrival to US or during their stage and the ICU, this number represents a 26’5% of the total drowning and near-drowning population. Furthermore, it was calculated that 5 of these 41 patients had a positive ECG, this represents a 3’2% of the whole population but a 12’2% in the sample in which ECG has performed (p value <0’001 and X^2=14,366; confidence interval = (1,016- 1,277)).

- Previous Genetics

Table 5. .Population in which genetic test were carried out and their results. Values are n(%).

Genetics	N patients
TRIP12 (AD)	1(0,64%)
SCN1A	1(0,64%)
RYR2	1(0,64%)
KCNQ1	1(0,64%)
Pending	1(0,64%)
No Genetics	150 (96,77%)

In this sample, 2 of these 5 patients (20%) did have a previous pathological ECG (p value <0, ,001). Genetic tests performed to these 5 patients (although the result of one of them was not available at the moment of data acquisitiong) represents a 2’58%. They are represented separately mentioning each particular mutation in table 6.

Of this population sample 101 (65,2%) of them were males and 53 (34,2%) were females, as it is represented in table 7 and fig. 15.

Table 6. Population demographic data. Values are n(%) and mean ± DS.

Demographic data		N patients
Sex		
	Male	101 (65,2%)
	Female	53 (34,2%)
Age		
	Mean age	5,77 ± 4,703
	0-5 years old	85 (54,8%)
	5-10 years old	31 (20%)
	10-15 years old	28 (18,2%)
	15-20 years old	12 (6,4%)

The mean age of our sample is 5,77 ± 4,703 (being 4,703 the standard deviation). Patients were divided in 5 groups of age (0 to 5 years old, 5 to 10, 10 to 15 and

15 to 20). With these division, the most affected range of age was the one that include patients between new-born babies and 5-years old (54,8%).

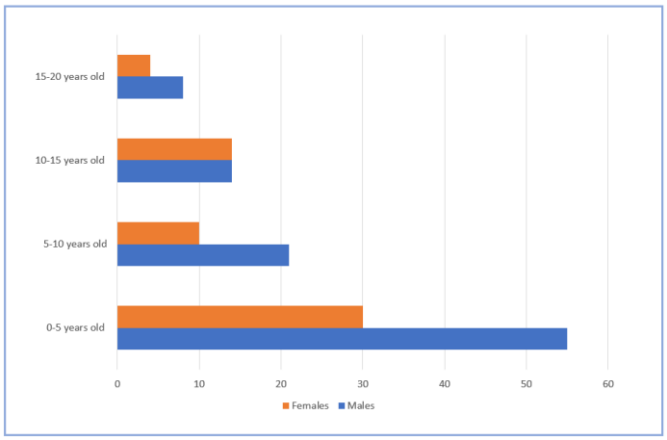

Figure 11. Comparison between sex and age.

As our sample by age does not have a symmetrical distribution (fig. 11), the median should be calculated, its value is 4 (2-10) *(Median (Q1-Q3)).*

-*Exitus:* the total number of exitus in this sample, and their classification by groups of age are represented in table 8.

Table 7. Number of exitus in this sample. Values are n(%).

Exitus	Patients
Total	9 (5,8%)
0-5 years old	4
5-10 years old	3
10-15 years old	0
15-20 years old	2

An ECG was performed in only three of the total number of patients who died (X^2= 0,233). Of these three patients, 2 (66,6%) had a pathological ECG for LQTS.

Exitus and pathological ECG: of the total of *exitus*, two of them (22'2% of the *exitus*) had a pathological ECG (p value <0.001 and chi-square value is 11,045)

Exitus and genetics: only the one that appears as pending died, the five restant patients survive to the incident.

- Drowning by month:

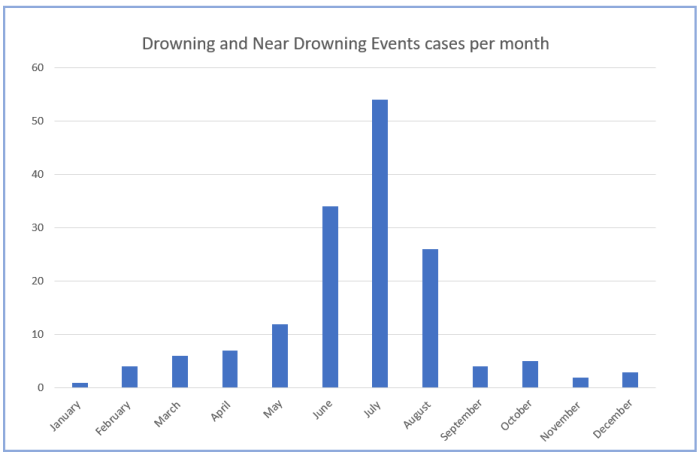

Figure 12. Representation of drowning and near-drowning incidents per month.

The main part of these events was registered during summer, as it can be appreciated in this bar plot (fig 16.) Between June and August, 144 drowning cases have been recorded. This represents a 73,55% of all the drowning and near-drowning events of our sample.

- Epilepsy:

Seven out of 155 patients of our sample were diagnosed of epilepsy before their drowning or near-drowning event. This represents a 4,5%. In only one (14,3%) of these seven patients an ECG had been performed at their stage at Emergencies or Intensive Care Services. This proportion give us a X^2 value of 0,558 and a p-value of 0,455. This only ECG had a negative result.

- Was not able to swim/ did not know to swim:

In this sample 7 patients (4’5%) were listed as patients who were not able to swim so well so they could avoid drowning or who did not know how to swim at all by their parents, relatives or people who were taking care of them when the incident occurred.

ECG was not performed in any of these patients who were listed as “was not able to swim”. This was the main limitation of our study.

9. DISCUSION

As far as cardiac channelopathies are concerned, it has been demonstrated that they are responsible for a significant number of drowning or near-drowning events all over the world (2,57). Nevertheless, in this sample channelopathies diagnostic

tools were performed in a little number of cases. Despite this fact, if the part of the sample in which ECGs were performed is analysed, a non-negligible number of patients had a pathological ECG pattern for LQTS. This concrete disease can be diagnosed with a simple 12-leads ECG, but, however, there were registered few cases in which ECG pattern was normal, but which had a genetic test had with a positive result for genetic mutations in relation with this syndrome. It must be said that genetic tests were performed in a fewer number of patients than ECG was. Nevertheless, this was only as far as LQTS is concerned, but what about CPVT? This channelopathy can have a normal ECG pattern (50), so this tool cannot discard having a CPVT if electrical alterations are not found in a normal ECG realized at their arrival to Emergencies or intensive care units. Moreover Stress-tests, which is an important instrument in CPVT diagnosis, were not performed to any of these drowning cases.

All these facts support the need of performing a genetic test in these situations, a part from a normal 12-leads ECG during their stage at the hospital and a Stress-test once patients have recovered from the event. Taking into account this little sample in which diagnosis tools were performed, we cannot say with a great grade of evidence that the rest of the population had no channelopathy.

For what this hypothesis refers to, channelopathies are the underlying reason of a non-despicable number of cases if we only use ECG as a diagnostic instrument, however, Hospitals should stablish a diagnosis protocol for this kind of events in order to know the true reason that causes these incidents.

As mentioned before, in this sample, a considerable number of patients who suffered a drowning or near drowning event, and had a registered ECG, did have a pathological ECG pattern for LQTS. This fact permitted the diagnose of these patients who are actually being followed in Arrythmia Unit in SJDH. In addition, there were few patients in which a genetic test had been performed for other reasons, a 25% of these patients did have a previous pathological ECG, however, the rest of these patients did not have a channelopathy with ECG expression, so making this test helped to their accurate diagnosis.
With all these reasons and facts and in consideration of the evidence that ECG is not the only diagnosis tool in these diseases, we can conclude that ECG is helpful to diagnose the underlying cardiac disease in drowning and near-drowning patients but it should not be the only tool used to reach to their final diagnosis. The drowning protocol should also consider making a stress test and a genetic test (*in vivo* or *posmortem necropsy*) to achieve the maximum number of final diagnosis with a high grade of accuracy.

Of all the patients registered in this study, with a total sample of 155 patients younger than 21 years old, 53 of them were females and 101 were males. These diseases have an autosomal dominant and recessive heritance, and their prevalence is similar in both sexes (16). Because of this, it would be good to do an investigation of the reason why this sex difference appears (Figure 11), in order to know if there could be some variables that may be skewing our results. However, as there is a little sample in this study in which channelopathies

diagnostic tools were performed, we cannot ensure that there are no external variables distorting these results.

The mean age of our sample is 5,77 and the most affected range of age was the one that included patients between new-born babies and 5-years old, being this group more than a half of the sample. Besides, the median of the population was four. In this range of age is where the heaviest symptoms of these channelopathies are manifested, however, it is also the age where children are more vulnerable and are not able to swim so well that they can avoid suffering a drowning event. Due to this reason, it is very important to make an ECG (in rest at their arrival to the hospital or during their stage, and a stress test once they recovered, apart from a genetic test) in this kind of patients to discern which of these patients are suffering a disease expression and which ones are suffering a non-parental control incident.

Therefore, the main part of these events was registered during summer season, when children spend their free time activities in aquatic environment, either swimming pools or beaches and rivers. Because of this, parents, relatives and free-time activities monitors should be aware of this problem and should be conscious about the measures they should take to keep these children save. This point is in relation with the following point because, with the obtained and analysed results we have observed that having a previous diagnose of channelopathies can prevent having a fatal drowning event.

In our sample, five out of 155 patients had a previous genetic test that confirmed a genetic mutation in relation with a channelopathy disease. On the other hand, five patients had a positive ECG for LQTS. These two aspects sum together a fifth part of the patients in our sample who had a diagnostic tool performed. Moreover, being aware of Dr. Cuellar previous work in which ECG were performed more frequently and which obtained 11 out of 19 patients who had a positive ECG for channelopathies; we can conclude that channelopathies are the cause of a non-despicable number of drowning and near-drowning events. The reason of this percentage difference between the previous Dr. Cuellar work and this one is that going back in time we realized that ECGs were not frequently performed. From 2015 onwards, sanitary personal started taking conscience and ECGs started to be more usually done. For that reason, neither a third of this project sample had an ECG registered.

Apart from this, of those patients who had a previous genetic test that confirmed their disease, none died because of the near-drowning incident. We can conclude that having a previous diagnosis tool realized and being aware of the existence of a channelopathy is a protector factor in front of drowning fatal events.

In this sample, only a fourth of all drowning and near-drowning patients have a ECG performed after their incident, although just a 12’2% had a positive ECG for LQTS of the sample part in which an ECG had been realized; as mentioned in the introduction of this project, this is not the final diagnosis tool so there may be some misdiagnosed cases in our sample (as it will be explained in section 10), either for LQTS or CPVT. Due to this fact, we can conclude that ECG helps us to diagnose LQTS. However, it is not the most appropriate instrument for CPVT

diagnosis. As stated above, it would be better to use more tools apart from ECG in order to achieve a more accurate diagnosis.

On the other hand, there are published articles which demonstrated that there were LQTS patients misdiagnosed because they were classified and diagnosed as epileptic patients (52,58–60). In this sample patients who were previously diagnosed of epilepsy, no ECG was performed. Just in one case it was realized, being the result a negative one. Apart from this, they did not have either stress test or genetic test, although stress test would not be so important in these patients because CPVT is not related with epilepsy.

Nevertheless, although there is no relation described, we can ensure our affirmation by performing a genetic test despite the fact that there is a lack of publications in this field.

However, with this only negative case we cannot say that the rest of these patients do not have a channelopathy with a high accuracy grade.

10. LIMITATIONS

Due to the retrospective and descriptive nature of this study, many limitations should be mentioned:

- The principal limitation of our study was having a few number of patients in which an ECG had been performed (only a 26’5% of the total drowning and near-drowning population had had an ECG performed). This hindered the correct diagnosis and classification of the rest of the drowning population we had. We lack information on the reasons why ECGs were not performed in all these cases.
- many Clinical Histories were uncompleted or with few information about the drowning event.
- This kind of studies are not very useful in research of rare diseases (such as the CPVT in children).
- ECG in patients with CPVT is usually normal.
- This study is retrospective and observational, so there is a high risk of confounding variables intervening on it.
- As ECG and genetic tests are not part of the previous protocol in case of drowning or near-drowning events, there are not many patients in which an ECG was performed at their arrival to the Emergencies Service of SJD Hospital. Moreover, due to the fact that it is a retrospective and observational study, there is no manner to have any register of the cardiac function of these patients in the moment they suffered the accident. Data obtained from these patients cannot be modified and other parameters cannot be asked to them. Cause-effect relationships between risk factors and the disease cannot be exactly determined because no temporal sequence was followed, each patient was only registered once in a concrete moment.
- There are some patients whose progenitors or supervisors admitted that their children did not know how to swim or did not know how to swim so good to survive in some special conditions. This might be a counfusonal variable.
- There are some children with psychomotor delay who have not been excluded due to the fact that having this kind of affection does not mean not having a channelopathy.
- There was 1 case of a near-drowning event in the bath, which mechanism may be different than those episodes which take place in swimming pools or beaches, due to the fact that the syncope caused by channelopathies are described in situations where the trigger is the contact with cold water.
- There was no information about the familiar background in relation with sudden cardiac death
- Some ECG were blurry inked due to the pass of time. This fact hindered their accurate interpretation.
- It has been demonstrated that there are several LQTS patients who are diagnosed as epileptic. In our sample, there are 7 patients with a previous epilepsy diagnose, and we guess that due to this fact, an ECG at their arrival to the hospital, an ECG was not performed. This point brings us a problem because we do not know if they are epileptic patients or, on the contrary, they are inside this misdiagnosed group.

11. CONCLUSIONS

- In our sample, cardiac channelopathies were responsible of the fifth part of those cases in which a diagnostic tool was performed. However, there is a potential underestimation in the diagnosis of these channelopathies in cases of drowning and near-drowning events since no ECG neither

genetic tests are nor performed in order to look for some mutations in relation with these diseases.

- ECG and genetic test are both fundamental in the diagnosis of both LQTS and CPVT diseases. Due to this fact, it is essential to proceed to do both of them when a patient has suffered from a drowning or near drowning event, a stress test should also be performed to unmask a possible underlying CPVT once patients are recovered from the incident. Because of these, it is necessary to do a protocol in Sant Joan de Déu Hospital for those patients that arrive to the hospital because they suffered a drowning event. In this protocol, apart from the obvious intensive cares, ECG (at rest and during exercise, known as Stress-test) and genetic test must be included in order to know the real incidence of channelopathies in relation with drowning.
- The most vulnerable age group of our sample were the one that include from new-borns to children under five years old.
- Less than a third part of the patients in this sample had a diagnostic tool performed, leaving the major part of patients with unexplained events.
- In this analysed sample, fatal and non-fatal drowning events have higher incidence during the summer season, especially during July and August (73,55%). Our country gets really hot and sunny during those months, so it is when the major part of summer camps take place and when parents and sons and daughters usually go on holidays to the beach to some littoral places, as the Catalan coast, or to some camps or private houses with swimming pools. This fact emphasizes the need of defibrillator implantation and population awareness in these places in order to prevent new events and treat them as quick as possible if new incidents happen.
- Although LQTS and CPVT are not very prevalent, they are underdiagnosed in the total population due to the fact that ECG and genetic tests are not performed as part of paediatric population screening. This measure should be introduced in our sanitary system in order to avoid fatal cases in relation with SCD.
- In those cases where ECG cannot be performed due to the *exitus* of the individual, a necropsy should be done in order to look for associated to channelopathies mutations.
- Although some patients already have other diagnosis of diseases which are related to syncope, or it is said by people taking care of them that they were not able to swim at the incident time, it would be interesting to proceed to an ECG test. Otherwise, they could have a hidden channelopathy.

12. WORKING PLAN

Phase 1: Initiation process

On 2016 sanitary personal of the Arrhythmia Unit of SJDH started realizing that there were misdiagnosed cases of channelopathies in drowning and near-drowning events.

After this, they asked for CEICs permission to acquire and analyse those clinical histories in which drowning or near drowning incidents did happen.

Phase 2: Data extraction and processing database

During my practical clinical stage during June and July, we started looking for cases between 2015 and 2018. This fact was the keystone for my Final Degree Project, which I would start the following summer.
From June to September 2018 all data was collected for this first project
Therefore, from May to August 2019 we also collected drowning and near-drowning incidents data from 2017 until 1997, which form the population of my Final Degree Project.

Phase 3: Statistical analysis and result analysis

Initial data was used by Dr. Hector Cuellar for his Final Master Work. Once all data was collected, Dr. Héctor Cuellar and myself analysed first project data. I helped him during the summer season of 2019, at the same time that I collected and analysed those data for my project.
I analysed those results during September 2019 and during October 2019 statistical analysis was performed with the support of Dr. Marc Saez.

Phase 4: Final Article elaboration and results publication

On November 2019 this Final Degree Project is delivered and exhibited/shown in front of a tribunal. After it is shown, it will be published.

Phase 5: Scientific diffusion and further research

As it is mentioned in the last section of this Final Degree Project (section 14), the aim of these two projects is to impulse the creation of a drowning and near-drowning protocol in SJDH and to make a prospective study from 2019 onwards. Therefore, form de Arrhythmia Unit of SJDH, sanitary personal and other workers in relation with this unit, are trying to make a multicentric study in order to have a bigger sample so they would be able to give those unclarified drowning cases, an accurate reason and diagnosis.

Of note, this study has already been submitted to the AEPC (Association for European Paediatric Cardiology) Congress that will be held in Gothenburg in 2020.

STAGES	2016	2018		2019			2020
		J-S	O-D	J-A	M-A	S-O	
PHASE 1: INITIATION PROCESS							
study elaboration							
ceic permission							
PHASE 2: DATA EXTRACTION AND PROCESSING DATABASE							
First project data collection							
Second project data collection							
PHASE 3: STATISTICAL ANALYSIS AND RESULT ANALYSIS							
First project statistical analysis and results							
Second project statistical analysis							
Second project result analysis							
PHASE 4: FINAL ARTICLE ELABORATION AND RESULT PUBLICATION							
PHASE 5: SCIENTIFIC DIFFUSION AND FURTHER RESEARCH							
Conferences, meetings…							

Figure 13. Representation of this project's chronogram.

13. REFERENCES

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14. PLANS FOR THE FUTURE

As mentioned in section 4, this project stems from the necessity of giving an explanation to those unexplained sudden drowning and near drowning events. Moreover, as it may be seen, drowning and near drowning events are such an important problem in paediatric population and being aware of it is a medical challenge.
With the results and conclusions of this project, the following aim is to propose a monocentric prospective study to continue inquiring in these accidents in those paediatric patients arriving to SJD Hospital. In order to achieve this objective of giving an explanation to these incidents, it is compulsory to propose and draft a Drowning and Near-Drowning protocol. This protocol must include an ECG at the moment that the patients arrive to the Emergencies or Intensive Care Units, a posterior effort test (once the patients is recovered) and a genetic test to discard or to confirm mutations related to channelopathies.
As this sample is, luckily, a little one and may not be enough to give a strong answer. Due to this fact, the posterior idea, once the first prospective study has begun, is to promote a bigger study which may embrace other centres. The aim of the Arrhythmia Unit in SJD Hospital is to promote a multicentric study to have a bigger sample in which results may be more reliable and answer more questions about this kind of incidents.

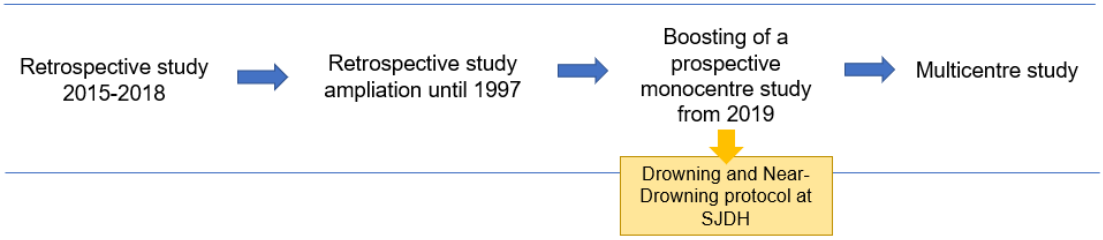

Figure 14. Lineal chronogram representation of the following future plans in relation with this project.

On the other hand, it is not just about boosting a protocol for these incidents, but to make population conscious about this problem. The Arrhythmia Unit in SJD Hospital is currently trying to disclose the importance of diagnosing channelopathies and structural heart diseases in relation with arrythmias, such as hypertrophic or dilated myocardiopathy, in early period in order to prevent symptoms and possible fatal outcomes. Therefore, it is not just about disclosing, but sanitary professionals should promote the fact of doing massive ECG as part of a population cribbage.

Moreover, as this problem occurs mainly during the summery season, summer-camp instructors and beaches and swimming pool lifeguards should be aware of the importance of the correct management in these situations.

Finally, what is really important is to make ICU and Urgency services aware of all of these facts, because they are the ones in closer contact with these patients

and they have a big responsibility. In order to avoid more drowning or near drowning events, it would be very interesting that both services participate in the disclose of the protocol and the population awareness.

TAKE HOME MESSAGES:

- Because of the already mentioned section 11, prevention and treatment measures should be implanted in those places where drowning and near drowning events may occur, such as public swimming-pools and beaches. Moreover, lifeguards and SEM workers should be aware of the importance of monitoring drowning patients with an ECG register
- Besides, as it is known that channelopathies are underdiagnosed and its first clinical manifestation may be a cardiac event (including syncope, cardiac arrest and sudden death) it would be a good option to include ECG as part of the paediatric screening due to the clinical impact that first clinical manifestation of these diseases may have. Moreover, it is a cheap and quick procedure.

The forward protocol should include:

- Clinical History of the patients in relation with cardiac symptoms (palpitations, syncope, SCD), apart form familiar background in relation with cardiac symptoms in relatives under the age of 50 years old.
- Basal ECG, standing ECG, Brugada position ECG, Stress test.
- Parents ECG.
- Genetic test.

ANNEX I: CEIC's permission

Fundació Sant Joan de Déu

CEIC Fundació Sant Joan de Déu

Informe Dictamen Favorable
Proyecto Investigación Biomédica
C.I. PIC-09-15
11 de febrero de 2016

Dr. Pau Ferrer Salvans
Secretario del CEIC Fundació Sant Joan de Déu

CERTIFICA

1º. Que el CEIC Fundació Sant Joan de Déu en su reunión del día 28/01/2016, ha evaluado la respuesta a las aclaraciones de la propuesta del promotor referida al estudio:
Título: "**Improving Diagnosis and Treatment in CPVT**"
Código interno: PIC-09-15
Investigador Principal: Dra. Georgia Sarquella Brugada (HSJD. Cardiología)

Considera que:

- El proyecto se plantea siguiendo los requisitos de la Ley 14/2007, de 3 de julio, de Investigación Biomédica y su realización es pertinente.
- Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.
- Son adecuados tanto el procedimiento para obtener el consentimiento informado como la compensación prevista para los sujetos por daños que pudieran derivarse de su participación en el estudio.
- El alcance de las compensaciones económicas previstas no interfiere con el respeto a los postulados éticos.
- La capacidad de los investigadores y los medios disponibles son apropiados para llevar a cabo el estudio.

2º. Por lo que este CEIC emite un **DICTAMEN FAVORABLE**.

3º. Este CEIC acepta que dicho estudio sea realizado en los siguientes CEIC/Centros por los Investigadores:
- **HOSPITAL SANT JOAN DE DEU. Dra. Georgia Sarquella Brugada.**

Lo que firmo en Esplugues de Llobregat, a 11 de febrero de 2016

Fdo:

Fundació Sant Joan de Déu

Dr. Pau Ferrer Salvans
Secretario del CEIC Fundació Sant Joan de Déu

ANNEX II: ECG SISTEMATIC INTERPRETATION

There are many possible ways/manners to analyse an ECG. Down below, one of them is explained:

1. First of all, we must check if the patient has a sinusal rhythm. This exists if there is a p wave before each QRS complex, these p waves must be positives in the inferior leads (II,III, aVF) and in I. if sinusal rhythm is not present, our patient may have an arrhythmia, as it can be appreciated in fig 15.

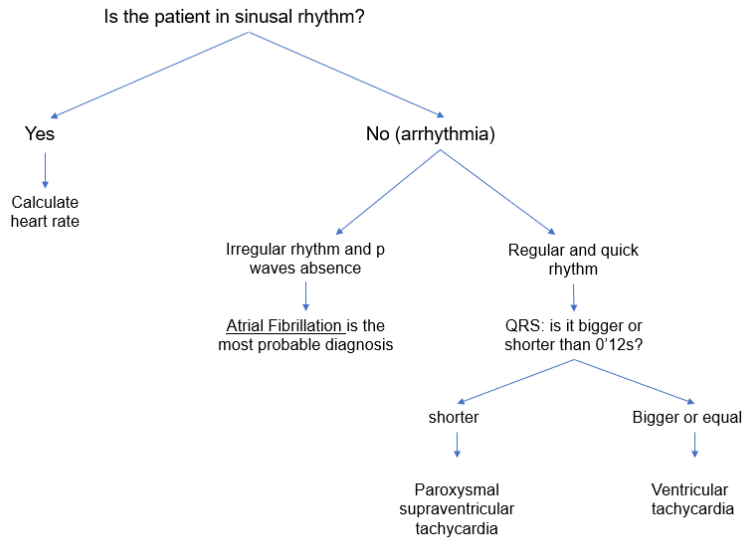

Figure 15. Arrhythmia algorithm.

2. If p-waves are sinusals, it must be checked if all of these p-waves are followed by a QRS complex. If this does not happen, we may be in front a second or third grade AV block.

3. Do p-waves have any alteration in its morphology?

   It is important to notice if there are electrical signs of right auricula growth (high and peaky p-wave: *p pulmonale*) or left auricula growth (wide p-wave: *p mitrale*). In normal conditions, p-wave elevation and amplitude should not be over 100 milliseconds.

4. Which is the heart rate of the patient? There are two possible ways to calculate it.
   A. It can be calculated dividing 1500 by the number of milliseconds that separate two following QRS complexes.
   B. On the other hand, there is a quick trick to calculate the heart rate. It consists on finding an R wave that peaks on a heavy black line, which will be the start line. After this first step, count off the next following

lines after “300, 150, 100, 75, 60, 50”, as represented in the figure 16 (56)

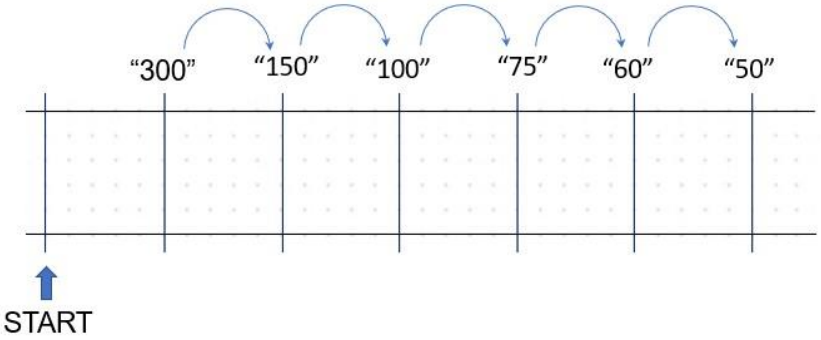

Figure 16. Representation of how heart rate is calculated.

Once HR has been calculated, we talk about sinusal bradycardia if HR is under 60 bpm, and about sinusal tachycardia if it overpasses 100 bpm.

5. How long interval PR is? It must measure between 120 and 200 milliseconds. If it is longer and there is a QRS complex after each p wave, there is a first grade AV block. However, if it is less than 120 milliseconds, it may have an accessory via.

6. Is there any alteration in the morphology and/or in the amplitude of the QRS complex? First of all, Q wave must be looked for, because if it exists, the patient may have suffered in the past from an infarct. In this case, the infarct localization may be known looking in what leads does this Q wave appears. This correlation between leads and location of infarction is summarised in table 4.

Table 8. Relation between leads and acute myocardial infarction location.

II, III, aVF	Inferior
V1 and V2	Septal
V3 and V4	Anterior
V5, V6, I and aVL	Lateral

Moreover, morphology of branch block must be looked for in V1 lead, where this complex normally has an rS morphology. If there is an rSr’ morphology, it means there exists a right branch block. However, if instead of rSr’, there is a QS morphology, we will talk about a left branch block.
This branch block will be considered as complete, if the QRS complex amplitude is over 120 milliseconds, if not, it will be considered as an incomplete branch block.
It is also important to exclude the existence of a delta wave, which is related to Wolf-Parkinson-White Syndrome.

7. Which is the QRS axis? QRS axis is considered to be normal if it exists between 0º and 90º, so QRS has to be positive in I, II and aVF leads. Some

alterations in this QRS axis can give information of some structural diseases:

- If it is negative at lead I, it means that the axis is shifted to the right, and this can be due to a right ventricle growth or a posterior hemiblock.
- It QRS is negative at aVF, the axis is distracted to the left, for instance, because of a left ventricle hypertrophy. Moreover, if it was also negative at lead II, it would mean an axis heavily distracted to the left (less than -30º) and it would probably be due to an anterior hemiblock.

8. Are there any alterations in ST segment?
   On one hand, a decreased ST segment may be sign of a subendocardial myocardial damage, left ventricle hypertrophy or digitalis toxicity development.
   On the other hand, an elevated ST segment can be due to subepicardial or transmural myocardial damage (acute myocardial infarction) or due to an acute pericarditis.
   It can also appear in a healthy patient, because in some young healthy patients this ST segment elevation appears.

- Is interval QT elongated? This is one of the most important aspects in this project. Interval QT is better measured in two concrete ECG derivations. Those derivations are II and V5.

  It must be corrected by the cardiac frequency since interval QT may vary according to the cardiac frequency (23,24). For its correct measurement, Bazett formula must be used:

$$QTc = \frac{QT}{\sqrt{RR}}$$

  In this formula, each value must be measured in seconds.

  In order to measure QTc correctly, we should be aware of three important points:

d. If there is a sinusal arrythmia, several QTc intervals must be calculated in a rhythm strip and an average must be done. If this procedure is not done, an overestimation or underestimation may appear.

e. U wave is frequent in teenagers. It is a small positive wave that may appear after T wave. It must be excluded in the measurement of QT interval.

f. If the end of the T wave is not well seen, tangent's method may be used following fig. 17. exemple. This method regards that T wave ends in the intersection/junction of the most inclined part of the descendent/decreasing T wave portion and the base line.

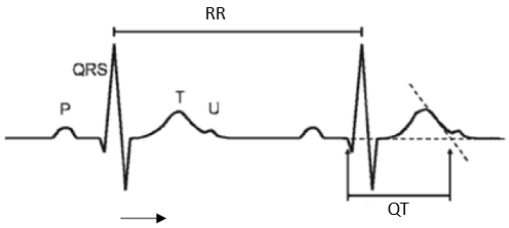

Figure 17. Measurement of T wave Tangent.

9. Does any alteration on T wave exist? There are two possible alterations:
   - If the T wave is negative, it may indicate subepicardial myocardial ischemia or left ventricular hypertrophy.
   - *High and peaky T wave* may be due to a subendocardial ischemia o secondary to a hyperpotassaemia.