# INCIDENCE AND POTENTIAL PREVENTION OF LIFE-THREATENING VENTRICULAR AND SUPRAVENTRICULAR TACHYARRHYTHMIAS IN CHILDREN

**Ph.D. thesis**


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LIST OF ABBREVIATIONS

AAD = antiarrhythmic drug

AE = adverse event

Afib = atrial fibrillation

Aflut = atrial flutter

ARVC = arrhythmogenic right ventricular cardiomyopathy

AV = atrioventricular

AVNRT = atrioventricular nodal reentrant tachycardia

AVRT = atrioventricular reciprocating tachycardia

BrS = Brugada syndrome

CHD = congenital heart disease

Class I–IV = Vaughan-Williams classification of antiarrhythmic drugs

CPR = cardiopulmonary resuscitation

CPVT = catecholaminergic polymorphic ventricular tachycardia

CT = computed tomography

DAD = delayed afterdepolarization

DCM = dilated cardiomyopathy

EAD = early afterdepolarization

ECG = electrocardiogram

EGSYS = Evaluation of Guidelines in Syncope Study

FAT = focal atrial tachycardia

GOKVI = Gottsegen National Cardiovascular Center

HCM = hypertrophic cardiomyopathy

ICD = implantable cardioverter defibrillator

JET = junctional ectopic tachycardia

LQTS = long QT syndrome

LTA = life-threatening arrhythmia

MAT =multifocal atrial tachycardia

MRI = magnetic resonance imaging

OHSCA = out-of-hospital sudden cardiac arrest

PJRT = permanent junctional reciprocating tachycardia

PSVT = paroxysmal supraventricular tachycardia

ROSC = return of spontaneous circulation

SAD = sudden arrhythmic death

SADS = sudden arrhythmic death syndrome

SCA = sudden cardiac arrest

SCD = sudden cardiac death

SHD = structural heart disease

SIDS = sudden infant death syndrome

SQTS = short QT syndrome

SVT =supraventricular tachycardia

TdP = Torsade de pointes tachycardia

VF = ventricular fibrillation

VT = ventricular tachycardia

VUS = variant of unknown significance

# 1. INTRODUCTION

Every tissue in the body relies on the heart to pump oxygenated blood for nourishment and to remove waste products. As the cardiac output depends on the heart rate and stroke volume, it is evident that any arrhythmia has the potential to result in life-threatening cardiovascular dysfunction, significant morbidity, and mortality.

Both bradycardia and tachycardia can result in low cardiac output. Hemodynamic collapse is more likely to develop when underlying left ventricular dysfunction is present or when heart rates are extremely rapid. Decreased duration of diastole and diminished cardiac output at fast heart rates may lead to reduced myocardial perfusion, deteriorating inotropic response, and progression to ventricular fibrillation (VF), causing cardiac arrest.

Arrhythmias in pediatric patients have the same basic arrhythmia mechanisms as arrhythmias in adults, but predisposing factors, clinical presentation, and prognosis are different. Understanding this clinical distinction is essential for preventing life-threatening arrhythmias (LTAs) in children.

## 1.1 Basics of arrhythmogenesis

Coordinated activation and deactivation of several ion channels, ion transporters, and ion pumps within the myocardium are required to achieve normal electrical heart activation. Abnormality in any of these may result in the development of arrhythmias. **Ion channels** are transmembrane proteins that control the movement of ions within cardiac cells. Their activity generates a cardiac **action potential**. The aggregate of ionic current activities during the cardiac cycle determines the action potential at any particular time. Currents that depolarize and repolarize contribute to action potentials in the ventricle, atrium, and nodal tissue. Differential expression of ion channels in various heart regions gives rise to differences in action potentials.

The mechanism of arrhythmogenesis is either abnormal impulse initiation or abnormal impulse propagation. **Bradycardia** occurs due to the failure of impulse initiation or block of impulse propagation. **Tachyarrhythmias** are caused by enhanced impulse

generation due to altered automaticity, triggered activity, or abnormal impulse propagation with reentry. (1)

**Abnormal automaticity** is the spontaneous development of impulses independent of preceding impulses to tissue. Its mechanism is attributed to ionic currents not ordinarily active in these cells and is usually observed following tissue injury. Its characteristic features are initial rate acceleration, deceleration before termination, and responsiveness to sympathomimetics. Clinically, it is characterized by a "warm up" of the heart rate at the onset of tachycardia and a "cool down" prior to the termination of tachycardia, as well as a fluctuating tachycardia cycle length attributable to autonomic modulation.(1)

**Triggered activity** refers to the emergence of abnormal impulses in response to the initial impulse or impulses. This mechanism involves only a tiny proportion of arrhythmias, but these are potentially life-threatening conditions. Triggered activity has two types: early- and delayed afterdepolarization (EAD and DAD).

***Early afterdepolarization*** (EAD) arises during phase 2 or 3 of the cardiac action potential prior to complete repolarization; hence, it is more common with prolonged repolarization. Long QT intervals contribute to the development of EAD. EAD in the context of increasing dispersion of refractoriness results in Torsade de pointes tachycardia (TdP), characterized by polymorphic ventricular tachycardia (VT) with a "twisting around the axis" morphology. Frequently it is preceded by long-short coupling intervals. Bradycardia can worsen the condition as it enhances the dispersion of refractoriness.

***Delayed afterdepolarization*** (DAD) occurs after the action potential has fully repolarized in the presence of intracellular Ca2+ overload, intracellular Ca2+ release channel (ryanodine receptor) malfunction, ischemia-reperfusion, and adrenergic stress. DAD arrhythmias are characterized by intracellular Ca overload, aggravation by tachycardia (which increases intracellular Ca2+), and sympathetic stimulation. In addition, burst pacing may produce DADs because it encourages intracellular calcium accumulation. (1)

**Reentry** is the most prevalent mechanism in several clinically significant cardiac arrhythmias. It arises due to altered conduction when impulses propagate in more than

one pathway, each differing in its electrophysiologic properties. With a premature beat, conduction may fail in one pathway (with a longer refractory period), creating a unidirectional block while continuing in the other one at a slower rate. By the time the impulse enters the distal point of the pathway, the tissue has recovered from refractoriness. Activation can occur in the retrograde direction along the first pathway to form a reentry circuit. The substrate for more than one pathway, each differing in its electrophysiologic properties, can be anatomically defined, such as atrioventricular (AV) accessory connections, AV nodal reentry, or around a scarred myocardium. Reentry can also occur due to functional blocks in tissues that exhibit heterogeneity in refractoriness or conduction velocities. Anisotropic reentry develops due to an increase in anisotropy (increased difference in conduction properties in different directions, e.g., in longitudinal vs. transverse direction). Phase 2 reentry develops under pathophysiological conditions; phase 2 (dome) of the action potential reenters to re-excite the myocardium. Anatomically defined reentry [atrioventricular nodal reentrant tachycardia (AVNRT), atrioventricular reciprocating tachycardia (AVRT), atrial flutter (Aflut), VT around a scar] usually has a long excitable gap. Functional reentry [atrial fibrillation (Afib), VF] does not have fixed pathways. Propagating wavefront turns on itself with the rate of turning limited only by conduction velocity or by encountering relatively refractory tissues. These circles possess no or short excitable gap and may anatomically wander, hence challenging to ablate. The conduction velocity and refractoriness of the different pathways influence the reentry wavelength. (1)

## 1.2 Differences in pathophysiology and epidemiology of arrhythmias in adults and children

The mechanism of arrhythmias in children with ***structurally normal hearts*** is usually the same as in adult patients. However, the arrhythmia substrate in children is generally congenital, whereas it is more likely to be acquired in adults.

Regarding **reentry** as an arrhythmia mechanism, accessory pathways mediated tachycardia is the most common tachycardia in children, from fetal life to adolescence. The accessory electrical AV connection results from the incomplete maturation of the annulus fibrosus and explains this peculiar age-dependent prevalence. Although the other common congenital arrhythmia substrate, which is the dual AV node physiology,

is also present at birth, the typical AV nodal tachycardia presents later in life because the fast conduction velocity and the short refractoriness of cardiac conduction tissue in the very young do not favor the development of reentry. In addition, the small dimension of the right atrium in children hinders the development of typical cavotricuspid isthmus-dependent Aflut, the third most common reentrant tachycardia.

Due to the rarity of ischemic coronary artery disease in children, an acquired substrate of reentry is far more often associated with congenital heart disease (CHD). ***In structural heart disease (SHD)***, arrhythmias may be caused by the underlying defect or surgical intervention. Chronic hemodynamic stress resulting from CHD may provide an electrophysiological and anatomical substrate favorable to reentrant arrhythmias. (2)

Although reentry is the most common arrhythmia mechanism in children, **increased or abnormal automaticity** also occurs in childhood, and this is the mechanism responsible for chronic-repetitive focal atrial tachycardia (FAT). Most ectopic atrial tachycardia arises from a single focus. Spontaneous resolution is typically seen in infants over 1 to 2 years. In older patients, the spontaneous resolution rate is low, and ectopic atrial tachycardia often requires a curative approach with catheter ablation.(2, 3)

**Triggered activity**-mediated tachycardias are rare in children. This mechanism involves benign idiopathic premature ventricular contraction, paroxysmal atrial tachycardia, and ventricular arrhythmia in primary arrhythmia syndromes. The latter are life-threatening, such as the TdP in children with long QT syndrome (LQTS). (2)

1.3 Clinical features of tachyarrhythmias in children

In general, sudden changes in heart rate or tachyarrhythmia leading to a very high ventricular rate can cause discomfort by decreasing cardiac output or losing AV synchrony. Adults and teenagers usually recognize this increased heart rate and complain of **palpitation**, breathlessness, dizziness, and chest pain. The underlying tachycardia mechanism is usually reentry, specifically in children with AVRT and AVNRT.

If the increase in heart rate is not abrupt or significantly high, patients may not recognize the arrhythmia. In the case of chronic repetitive or incessant tachycardia, patients might remain asymptomatic, and only symptoms of **heart failure** lead to the

diagnosis. FAT, or permanent junctional reciprocating tachycardia (PJRT), are typical examples.

Clinical diagnosis of tachycardia in neonates and infants can be challenging, as the lack of verbal communication may lead to late recognition and development of heart failure or complications such as **tachycardiomyopathy,** with feeding problems and failure to thrive.

A sudden, excessively high, or irregular ventricular rate can induce acute hemodynamic collapse, manifesting as **syncope or sudden cardiac arrest (SCA).** The most prevalent causes of these malignant tachycardias in kids are Afib associated with preexcitation ("fast-broad-irregular"=FBI tachycardia), or TdPs caused by hereditary or acquired channelopathies, or VF caused by cardiomyopathy. The causes of pediatric syncope are various, although in most cases, syncope is rather benign (e.g., reflex or orthostatic faints). However, in certain instances, syncope may be a symptom of more severe conditions, especially those associated with CHD, primary myocardial disease, or primary electrical disease such as channelopathies. In such situations, syncope may signify a higher risk of sudden cardiac death (SCD) (5). The most challenging subset of cardiac syncopes to diagnose is arrhythmic syncope owing to channelopathies. Unfortunately, the physical examination of a child with cardiac channelopathy following a syncopal episode is unremarkable, making it more challenging for a general physician to diagnose. In contrast, CHDs, cardiomyopathies, and pulmonary arterial hypertension have more common diagnostic signs (heart murmur, loud second 2. heart sound). Children may complain about palpitations, fatigue, and chest pain; consequently, the suspicion of cardiac syncope arises more rapidly in these cases.

In adults, due to the inaccuracies of "red flags," several different multivariate scoring systems have been established to identify syncope patients at higher risk of SCD. (4, 5)The majority of these scores have focused on the triage of emergency departments on the need for immediate hospitalization or the possibility of subsequent outpatient assessment. Adult predictors of high risk of SCD are mainly acquired cardiovascular risk factors and, in several cases, have not been validated in a specific patient validation population. Two trials have prospectively validated the accuracy of the six clinical

variables' multivariate Evaluation of Guidelines in Syncope Study (EGSYS) score. (6) Implementing diagnostic flow charts and clinical guidelines for syncope management in pediatric emergency care units has improved diagnostic efficiency. Time and resources have been saved, and hospital admissions have been reduced.(7, 8) But to date, no validated diagnostic pediatric score differentiates between different types of syncope.

In the case of nonsustained tachyarrhythmias, symptoms and complaints can be absent and only the surface electrocardiogram (ECG) of an **asymptomatic** child reveals dysrhythmia. Lack of symptoms does not mean the benignity of a given arrhythmia. Indeed, LTAs can occur without preceding symptoms. SCD can be the first presentation of potentially lethal arrhythmias.

### 1.4 Potentially life-threatening arrhythmias in children

The term "life-threatening arrhythmia" is not strictly defined. Commonly, it refers to arrhythmias that can lead to cardiac arrest in a short time if no intervention is taken. Mostly it is used to describe high-frequency or polymorphic VT and VF. Due to the high ventricular rate and the shortened diastolic time, the coronary circulation is reduced to such an extent that cardiac arrest occurs within a brief period. If help does not come in time after **SCA**, the process becomes irreversible, and **SCD** occurs.

**Sudden death** (**SD**) is defined as death without a history of heart disease, occurring within 1 hour of the onset of symptoms, and the patient was seen to be in good health within 12 hours of death. If an autopsy, including toxicological investigations, doesn't reveal any noncardiac or cardiac etiology, it is called **sudden arrhythmic death** (**SAD**).

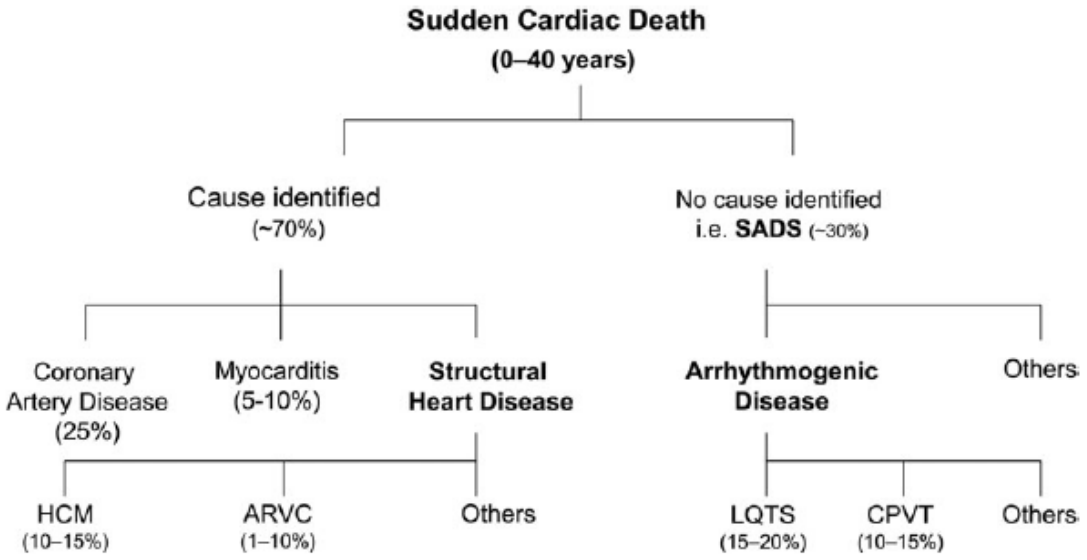


*Figure 1.Causes of sudden cardiac death in the young (0–40 years)(9)*

Coronary heart disease is rare in young people under 40 years of age, and primary myocardial diseases (cardiomyopathies) and primary electrical diseases (ion channel diseases) dominate. The autopsy may detect cardiomyopathies, but a special histopathological examination may be necessary to identify the pathologies. Autopsy of patients with ion channel diseases shows no abnormalities, so this group of SCD is also called “autopsy-negative sudden cardiac death” in addition to SAD. Because of the different clinical presentation, unexplained SCD under 1 year is commonly referred to as sudden infant death syndrome (SIDS), distinct from sudden arrhythmic death syndrome (SADS) over 1. SADS accounts for about one-third of SCDs in the young (<35 years). By targeted clinical examination of the family and molecular genetic diagnostics (molecular autopsy), an inherited primary electrical disease (channelopathy) can be identified in 25-30% of these SAD cases.(9, 10, 11, 12, 13)

**Channelopathies** are rare genetic disorders known to predispose young people to SAD. Based on the clinical picture and ECG abnormality, different clinical syndromes are distinguished: LQTS, catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome (BrS), idiopathic VF, SQTS. In these disorders, susceptibility to arrhythmia has been attributed to three distinct mechanisms: abnormal repolarization (LQTS, SQTS, BrS), delayed ventricular conduction (BrS), and aberrant intracellular Ca2+ homeostasis (CPVT). (14)

**Supraventricular tachycardia** (SVT) is often not considered a LTA; however, fatal outcomes are possible, particularly in newborns and individuals with SHD. (12-14) SVT in newborns and babies has a favorable prognosis, and fatal outcomes are uncommon. Based on published studies, mortality risk factors are believed to be associated with comorbidities, such as congenital SHD (14, 15). Given the hemodynamic instability of these individuals, the contribution of SHD is not surprising. However, very little is known regarding newborn mortality with structurally normal hearts. Although it is documented in adult studies that antiarrhythmic medication treatment may represent a danger, previous research has focused mostly on demographic characteristics and comorbidities (16). Since a control group is unavailable for ethical reasons, it is difficult to determine the significance of acute antiarrhythmic medication for death and morbidity in newborns and babies with SVT. In addition, distinguishing clinical deterioration variables during acute pharmacological arrhythmia control is difficult, particularly in postoperative patients.

### 1.5 Genetics in life-threatening pediatric arrhythmias

*Inherited arrhythmia syndrome* is the umbrella term for rare inherited heart conditions associated with a higher risk of SCD. It includes genetically determined inherited forms of ion channel disease and cardiomyopathies. The significance of this terminology and classification is that clarifying the genetic origin of SCD provides an opportunity to screen family members and prevent further tragedies.

Genetic research has shown that several gene mutations can cause inherited arrhythmias. These mutations can be simplified into four groups: variants of sarcomeric proteins causing hypertrophic cardiomyopathy (HCM); variants of cytoskeletal proteins causing dilated cardiomyopathy (DCM); variants of desmosomal proteins causing arrhythmogenic right ventricular cardiomyopathy (ARVC), and variants of ion channel proteins causing electrical diseases (or channelopathies). Several of these disorders are very lethal in childhood.

The genetic background can be a mutation affecting a single gene (monogenic etiology) or complex alterations by multiple genes (multigenic etiology). Inheritance of monogenic diseases follows Mendelian rules, and the prevalence of the disease can be

predicted in the offspring. (15, 16) On the other hand, predicting the inheritance of multifactorial, multigenic diseases strongly influenced by environmental factors is much more difficult. Similarly, the prediction of disease prevalence due to allelic heterogeneity and gene polymorphism (e.g., single nucleotide polymorphism, SNP) is also problematic. (15)

Most arrhythmia diseases are transmitted to first-degree relatives with a probability of 50%. Determining the mutation permits genetic testing on close families for prediction purposes. It is recommended that the family members of a deceased person with SCD get medical screening. If a relative carries the same genetic condition, they are likewise at elevated risk for SCA and should receive preventative treatment. Variable penetrance is characteristic of all arrhythmia syndromes, with the same variant causing a wide range of symptoms within a single family. This variability suggests that genetic modifiers and environmental factors may influence the phenotype. (21)

### 1.6 Antiarrhythmic drugs and proarrhythmia

Antiarrhythmic drugs (AADs) serve two purposes: terminate the current arrhythmia or prevent the arrhythmia from recurring. However, it should be remembered that these medications can cause the worsening of arrhythmias themselves (proarrhythmia).

The primarily used AADs act predominantly on the transmembrane transport of sodium, potassium, and calcium in cardiac myocytes. Na channel blocking agents affect the 0 phase of the ventricular action potential, whereas K channel blocking agents affect repolarization. Na channel blocking agents lead to a slowing of conduction and widening of the QRS. Blockade of outward K channels prolongs action potential duration and QT time on ECG.

The affinity of drugs to bind to receptors on the ion channel depends on the functional status of the channels (resting, open, inactivated). AADs that prefer open or inactivated channels have a more significant effect on a fast heart rate *(use dependency)*. Their effect is most potent during depolarisation and decreases exponentially during repolarisation. Drugs whose inhibitory effect on the receptors fades rapidly during diastole show no conduction velocity slowing and QRS widening at normal heart rate, but may induce significant block during tachycardia. Drugs whose receptor inhibitory

effect is reduced more slowly (e.g., Class I/C propafenone, flecainide) may already show conduction slowing and QRS widening at normal heart rate. This effect is more pronounced at higher frequencies and may even accumulate. If a significant QRS widening is seen at rest, it is feared that at higher frequencies, the conduction velocity deceleration will become so marked that it will favor the development of sustained reentry tachycardia.

Conversely, there are AADs that show a decreasing effect as the heart rate increases (*reverse use dependency*). This is particularly true of Class III agents that block the rapid component of the delayed rectifier potassium channel, thereby prolonging repolarization and refractoriness. The QT prolongation seen on ECG is more pronounced at lower frequencies than at faster frequencies. The antiarrhythmic effect of this type of drug is more limited during tachycardia, and the risk of proarrhythmic effects (TdP) is increased in the case of bradycardia.

Consequently, when evaluating the risk of proarrhythmia during antiarrhythmic medication treatment, the QRS width and QT duration at rest must be examined in this context.

## 2. OBJECTIVES

In the research projects constituting the basis for my doctoral dissertation, I examined the incidence and etiology of pediatric out-of-hospital sudden cardiac arrest (OHSCA) in Hungary and the fatality rate of neonatal SVT. Moreover, I assessed the utility of clinical "warning signs" for diagnosing cardiac channelopathies presenting with syncope, suggesting potentially LTA and risk factors for complicated clinical outcomes of neonatal SVT. The three central questions addressed were as follows:

1. What is the incidence of pediatric OHSCA in Hungary, and what are the most common etiologies? What is the possible role of genetic testing in diagnosing inherited arrhythmia syndromes to prevent LTAs?
2. How often is syncope the presenting symptom in pediatric channelopathies, and which clinical warning signs (red flags) help diagnose these children? Can the multivariable EGSYSscore identify pediatric cardiac syncope in channelopathies?
3. What is the prevalence of complicated outcomes in neonatal SVT? What are the risk factors for complicated clinical outcomes? Does pharmacological therapy play a role in fatality? What could be the potential prevention of these fatalities?

# 3. METHODS

To answer the questions of my research, I carried out three studies.

**POHSCA study:** To assess the incidence of pediatric OHSCA in Hungary (POHSCA) and the magnitude of inherited cardiac arrhythmias in the background, three databases were retrospectively analyzed.

***As a first approach,*** Utstein data sheets of children under 18 years completed by the National Ambulance Service between 01.01.2012 – 30.06.2015 were reviewed. Utstein documentation is an anonymous data form used by the National Ambulance Service, which the rescue team should fill out in case of SCA. The study's inclusion criteria were: 1. All cases indicated "cardiac" origin as etiology. 2. "Cardiac" origin was not marked, but any of the following were present: a. Defibrillation by a witness, b. The first rhythm detected was VF or VT, c. defibrillation by the ambulance team, d. Amiodarone medication. In addition, personal data related to the anonymous form with a serial number was written out manually.

***As a second approach***, records of admissions to the national tertiary pediatric heart center [Gottsegen National Cardiovascular Center (GOKVI)] between 01.01.2000-01.10.2020 because of pediatric OHSCA for further investigation and implantable cardioverter defibrillator (ICD) implantation were reviewed. Demographic data, family and personal history, primary arrhythmia, clinical investigations, and presumed etiology were analyzed.

***As a third approach***, clinical and genetic testing results were studied in patients evaluated and followed in GOKVI between 01.10.2015-01.08.2020 with suspicion of inherited arrhythmia syndromes. Presentation symptoms, presence of cardiac arrest in the history, and genetic diagnosis without clinical symptoms were in focus. Genetic testing results in patients above 18 years and asymptomatic children of families with known arrhythmia syndromes were excluded. Genetic tests were performed with next-generation sequencing (NGS) in the laboratory of Blueprint Genetics, Helsinki. For the interpretation of sequence variants, Single Nucleotide Polymorphism Database

(dbSNP), genome aggregation database (gnomAD), and in silico models (Polyphen, Sift, Muttaster) were applied.

*Study protocols were approved by the Hungarian Ethics Committee and followed Helsinki's declarations. (SE TUKEB 146/2015)*

**SYNCOPE study:** All data on children with channelopathy, followed by the single tertiary pediatric cardiac center (GOKVI) between 2000-2018 retrospectively were reviewed to study the prevalence of syncope as the presenting symptom in children with arrhythmia syndromes and if known warning signs are helpful to reveal the arrhythmic origin. Diagnosis of channelopathy was based on clinical symptoms and ECG and was supported by genetic test results when available. Children with a low probability of LQTS (Schwartz score ≤ 1) were excluded from the study. Presenting symptom was defined as the first symptom, complaint, or event which revealed the diagnosis, inducing referral for further cardiological investigations. The presence or absence of clinical symptoms and features considered typical for cardiac syncope, neurally mediated syncope, and epileptic seizures used in previous studies were examined retrospectively for presenting syncope. Additionally, multivariable EGSYS score was also calculated retrospectively for each syncope case. This score was published by Rosso et al. (4) and validated for diagnosing cardiac syncope in adults by Pasek et al. and Kariman et .al. (8, 9).

*The study was approved by the Medical Research Council (IV/4717–2/2020/EKU) and informed consent was not required.*

**PROARRHYTHMIA study:** To assess outcomes in infants and neonates with symptomatic non-post-operative SVTs and to determine risk factors for the fatal and near-fatal outcome, medical data of children treated at the single tertiary pediatric cardiac center (GOKVI) over 15 years were retrospectively reviewed with particular focus on the role of pharmacological therapy. Patients were identified by retrospective analysis of the database at the tertiary pediatric cardiac center of the GOKVI. The digital database was scanned for SVTs (BNO code: I4710, I4790, I4800, P2910), and clinical files were reviewed. Our study included all patients <1 year of age, presenting with sustained and recurrent SVT requiring therapy from January 2000 to July 2015 and

receiving follow-up at our institution. Patients who had tachycardia exclusively following cardiac surgery were excluded from the analysis.

Statistical analysis:

Continuous variables are presented as median (lower quartile upper quartile) and are compared among groups with Wilcoxon (Mann-Whitney) test; categorical variables are presented as frequencies (relative frequencies) and are compared among groups with Pearson chi-square test in the retrospective study of neonates with SVT. Unfortunately, the low number of events (complicated course n = 9, death n = 5) excluded meaningful multivariate modeling of the predictors of such outcomes. Thus, results are univariate comparisons with no control for confounding and therefore, cannot be used to establish causal conclusions.

*The Medical Research Council approved the study (IV/4718-2/2020/EKU), and informed consent was not required.*

# 4. RESULTS

## 4.1. Pediatric out-of-hospital sudden cardiac arrest (POHSCA study)

***First approach:*** The national Ambulance was alerted in 373 cases (approx. 106/year) due to cardiac arrest of patients under the age of 18 years during the 3,5 year long study period. After critical revision of Utstein data – discounting double-reported cases by different rescue teams – 84 children with pediatric cardiac arrest (approx. 24/year) were identified. "Cardiac arrest" was documented on the Utstein form in 66 cases (79%), and 18 cases (21%) were included based on other inclusion criteria detailed in the methods. The male/female ratio was 49/35 (58/42%). Return of spontaneous circulation (ROSC) was observed in 17 cases (20%), two children (2%) were transported to the hospital during continuous cardiopulmonary resuscitation (CPR), and on 3 pts (4%), CPR achieved only transient success. CPR was stopped in 3 pts (4%) and was unsuccessful in 59 cases (70%). Also calculating the case of successful resuscitation by a witness before the arrival of the National Ambulance, the rate of ROSC was 21%.

Assessment of the clinical course of children after reanimation failed because identification of the patient or his general practitioner only based on the patient's residence was impossible and the location of postmortem examination was also not documented. Therefore clarification of the etiology of pediatric out-of-hospital SCD in Hungary and the planned family screening came to grief.

***Second approach:*** During the study period of 20 years, 24 children (approx. 1/year) were admitted to the national pediatric heart center ***(GOKVI)*** after OHSCA. Male/female ratio was 14/10 (58/42%) and median age at SCA was 13+/-4,1 years. First documented rhythm was VF in 15/24, VT in 4/24, and asystole in 3/24, and it was not documented in 2/24 cases. An electrophysiological study was performed on 5/24, coronarography/coronary computed tomography (CT) on 6/24, cardiac magnetic resonance imaging (MRI) on 12/24, drug provocation test (ajmaline, epinephrine, isoproterenol) on 10/24, and genetic test on 12/24 cases. Drug abuse or SCD in the family history was not reported. Inherited arrhythmia syndromes in 11/24 (46%) and SHD in 4/24 (16%) cases could be identified, but the etiology remained unclear in the

rest of 9/24 (38%). The inherited primary arrhythmia group consisted of 5 CPVT, 5 LQTS, and 1 BrS. The SHD group consisted of 3 HCMs and one valvular aortic stenosis. 4/9 children had mitral valve prolapse in the group classified as unknown etiology, but they were mild or minimal prolapse and considered unrelated to the clinical event. (Table 1.) The genetic tests revealed a pathological variant in 6 cases (CPVT 5, LQTS 1), a variant of uncertain significance in 1 case. A variant was not identified in 5 cases. 19/24 children were treated with ICD as secondary prophylaxis.

*Table 1. Etiology of out-of-hospital sudden cardiac death in pediatric survivors based on data from Gottsegen National Cardiovascular Institute (2000-2021)*

| Group | Subgroup | Disease | Cases |
|---|---|---|---|
| **Electric cardiac disease (46%)** | channelopathy | catecholaminergic polymorphic ventricular tachycardia | 5 |
| | | Long QT syndrome | 5 |
| | | Brugada syndrome | 1 |
| **Structural cardiac disease (16%)** | cardiomyopathy | hypertrophic cardiomyopathy | 3 (mild) |
| | congenital heart disease | valvular aortic stenosis | 1 (mild) |
| **Unknown etiology (38%)** | - | - | 9 (4 mild mitral valve prolapse) |

***Third approach:*** Suspicion of inherited arrhythmia syndrome emerged in 73 children in 6 years of the study period (approx. 12/year), and it was based on pathological ECG without symptoms n=23, family screening n=21, syncope n=15, successful reanimation after SCA n=14. Genetic testing revealed pathological variation in 29/73 children (approx. 5/year) and a variant of uncertain significance in 23/73 children. In 2 children, both pathological and variant of unknown significance (VUS) variants were identified. (Table 2.) The annual case number of the three different approaches is demonstrated in Figure 1.

*Table 2. Primary abnormalities suggesting pediatric inherited arrhythmia syndrome based on data from Gottsegen National Cardiovascular Institute (2015-2021) Abbreviations: VUS=variant of unknown significance, ECG=electrocardiogram*

**Note: both pathological and VUS variants were identified in 1-1 pt.*

| Primary abnormality | Patient (n) | Mutation (n) | Genetic test result |
|---|---|---|---|
| pathological ECG (without symptoms) | 23 | 24* | pathological 11/23 |
| | | | VUS 3/23 |
| | | | negative 10/23 |
| genetic family screening (without symptoms) | 21 | 21 | pathological 7/21 |
| | | | VUS 8/21 |
| | | | negative 6/21 |
| syncope | 15 | 16* | pathological 4/15 |
| | | | VUS 9/15 |
| | | | negative 3/15 |
| sudden cardiac arrest | 14 | 14 | pathological 7/14 |
| | | | VUS 3/14 |
| | | | negative 4/14 |

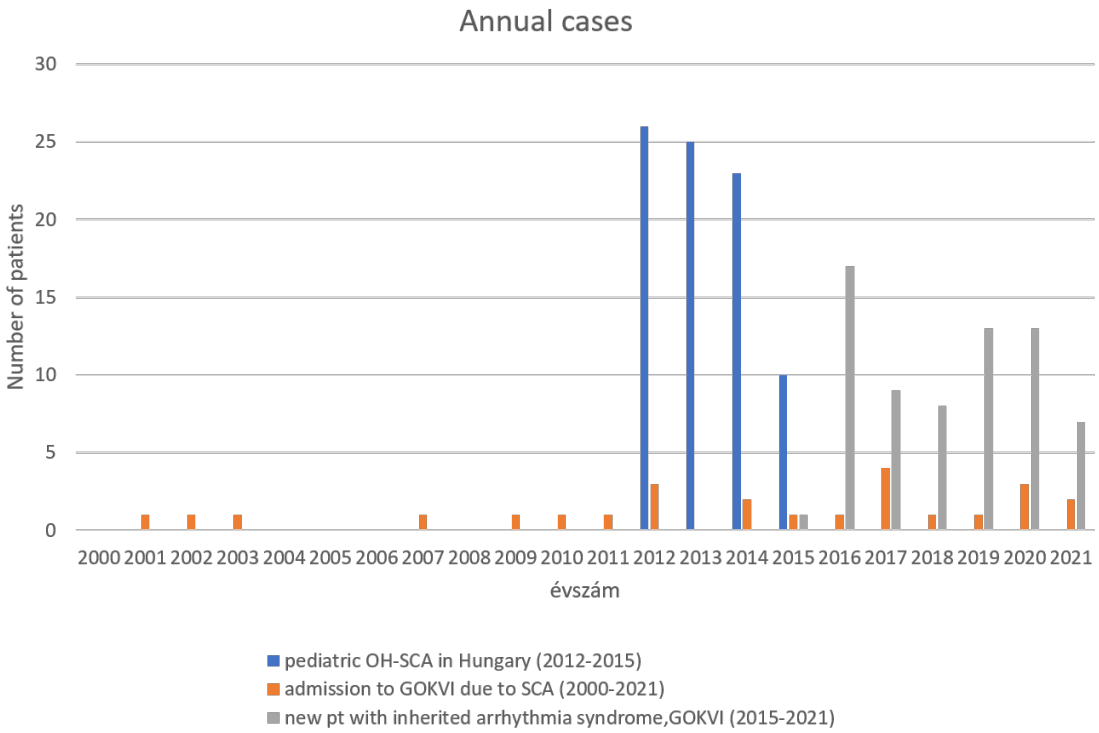


*Figure 2. The annual case number of the three different approaches (17)*

4.2 Syncope is the presenting symptom in children with arrhythmia syndromes (SYNCOPE STUDY)

Forty-eight patients were enrolled. The median age was 10,4 yrs (IQR 6,0), and 24 patients were female. Most patients were diagnosed with LQTS, but some children were followed up with CPVT and BrS, as shown in Table 3. Inherited channelopathies caused most of the LQTS cases. The distribution of subtypes was the following: LQTS1: 11/39, LQTS2: 5/39, LQTS3: 4/39, LQTS7 (Andersen-Tawil syndrome): 4/39, LQTS8 (Timothy syndrome): 2/39. There were also 3 cases of secondary LQTS, and 10 cases were unclassified 10/39. The Schwartz score of this latter group: high probability of LQTS (score ≥3,5): 4/10, intermediate probability of LQTS (score 1.5-3.0): 6/10.

*Table 3. Presenting symptoms in 48 children with primary arrhythmia syndromes. Abbreviations: LQTS=long QT syndrome, CPVT=catecholaminergic polymorphic ventricular tachycardia, Brugada=Brugada syndrome, ECG=electrocardiogram*

| | Cardiac syncope | | Sudden Cardiac Arrest | Abnormal ECG | Family screening |
|---|---|---|---|---|---|
| | correct diagnosis | misdiagnosed as epilepsy | | | |
| **LQTS n=39** | **5** | **6** | **5** | **11** | **12** |
| **CPVT n=5** | **1** | **1** | **3** | **0** | **0** |
| **Brugada n=4** | **0** | **0** | **1** | **2** | **1** |
| **Total n=48** | **6 (12,5%)** | **7 (14,5%)** | **9 (19%)** | **13 (27%)** | **13 (27%)** |

The diagnosis was supported by pharmacological provocation in 6 patients (four epinephrine tests for LQTS, two ajmaline tests for BrS) and by genetic testing in 35 children. However, genetic testing was not available for 9 LQTS children at the beginning of the study period. In addition, four children with BrS were not tested for genetics due to the lack of prognostic or therapeutic impact.

Less than half of the patients (n=22/48, 46%) were identified by their symptoms. The presenting symptom was syncope in 13/48[27%] andSCA in 9/48 [19%] children. In the remaining cases, abnormal ECG findings (13/48) [27%] and a positive family history of channelopathy (13/48) [27%] led to the diagnosis. (Table 3.)

Most children (11/13) [77%] presenting with syncope had LQTS, but two CPVT patients were also diagnosed after a syncopal event. In addition, half of the patients presenting with syncope (7/13) [50%] were misdiagnosed as epilepsy in the initial stage of their disease. As a result, they were followed up with "idiopathic," "therapy-resistant," or "atypical" epilepsy for 2-14 years.

In three of these seven patients, the cardiac examination revealed secondary LQTS, and the syncope was related to an endocrinological crisis (Addison crisis and hypocalcemia due to hypoparathyroidism and severe vitamin D deficiency). After hormonal and electrolyte substitution, the ECG normalized, and syncope recurred in no cases. Furthermore, three patients with LQTS and one with CPVT – initially mislabelled as epilepsy – remained symptom-free on AAD therapy after cessation of antiepileptic treatment.

All six patients with initially correct cardiac syncope diagnosis (LQTS 5, CPVT 1) were treated with ICD implantation. All were appropriately shocked during their subsequent clinical event while on antiarrhythmic therapy.

None of the nine patients presenting with primary SCA had a syncopal history. Seven of them were also treated with ICD implantation. Unfortunately, one child died on the waiting list for an ICD implantation, and ICD was not implanted in another child with CPVT because of an unfavorable cost/benefit ratio.

Abnormal ECG findings at a routine sports medicine screening examination revealed arrhythmia syndrome in 13 children. The most frequent pathological findings were the prolonged QT interval in four patients and the polymorphic premature ventricular beats in four children. The latter is characteristic of the Andersen-Tawil syndrome (LQTS7). Functional AV blocks revealed LQTS3 in two patients and Timothy syndrome (LQTS8) in one. In addition, two children had a spontaneous diagnostic Type I Brugada ECG.

Positive family history was the reason for cardiological work-up in 12 LQTS patients and one child with BrS.

Description of syncope by the child or an adult witness was available in 8/13 cases. The most typical cardiac warning sign/"red flag" was effort syncope. However, somewhat

confusingly, warning signs considered typical for epileptic seizure or neurally mediated syncope (colonization > 15 s and prodrome, respectively) were similarly frequent in this patient group of arrhythmic syncope. (Table 4.)

*Table 4. Incidence of different warning signs („red flags") in cardiac syncope (n=8). Abbreviations: SCA=sudden cardiac arrest, SCD=sudden cardiac death*

| | | |
|---|---|---|
| **"red flags" for cardiac syncope** | **palpitation before/after syncope** | **2/8** |
| | **effort syncope** | **6/8** |
| | **syncope while supine** | **0/8** |
| | **syncope without a prodrome** | **4/8** |
| | **presence of structural heart disease** | **0/8** |
| | **heart disease in family history** | **1/8** |
| | **SCA/SCD in family history** | **2/8** |
| **"red flags" for neurally mediated syncope** | **typical predisposition** | **1/8** |
| | **autonomic prodromes** | **6/8** |
| | **avoided by sitting down** | **3/8** |
| | **vegetative symptoms during recovery** | **3/8** |
| **"red flags" for epileptic seizure** | **epilepsy in patient history** | **2/8** |
| | **epilepsy in family history** | **0/8** |
| | **tongue biting** | **0/8** |
| | **enuresis** | **2/8** |
| | **clonic phase duration > 15 seconds** | **3/8** |
| | **postictal confusion** | **0/8** |
| | **postictal neurological symptom** | **0/8** |
| | **anterograde / retrograde amnesia** | **1/8** |

Multivariable EGSYS score was calculated retrospectively for the presenting syncope, and it suggested a cardiac origin (≥3 points) in seven children (88%). One patient not identified by the score had a medium probability of having LQTS. (Table 5.)

*Table 5. Multivariable EGSYS score in eight patients with syncope as presenting symptom. Abbreviations: SHD=structural heart disease, EGSYS=Evaluation of Guidelines in Syncope Study, Schwartz score=diagnostic score for long QT syndrome, LQTS=long QT syndrome, CPVT=catecholaminergic polymorphic ventricular tachycardia, ECG=electrocardiogram*

| **Parameters** | **Patients** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Patient nr.** | **#1** | **#2** | **#3** | **#4** | **#5** | **#6** | **#7** | **#8** |
| **Diagnosis** | **LQTS** | **LQTS** | **LQTS** | **LQTS** | **LQTS** | **LQTS** | **CPVT** | **CPVT** |
| **SHD and/or abnormal ECG** | **3** | **3** | **3** | **3** | **3** | **3** | **0** | **3** |
| **Palpitations preceding syncope** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** |
| **Syncope during effort** | **3** | **3** | **0** | **3** | **3** | **0** | **3** | **3** |
| **Syncope while supine** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** |
| **Precipitating and/or predisposing factors** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **-1** |
| **Autonomic prodromes** | **-1** | **0** | **0** | **0** | **0** | **-1** | **0** | **0** |
| **EGSYS score** | **5** | **6** | **3** | **6** | **6** | **2** | **3** | **5** |
| **Schwartz score** | **5.5** | **5** | **4.5** | **8** | **6** | **2** | **-** | **-** |

4.3 Supraventricular tachycardia in neonates with fatal or near-fatal outcome (PROARRHYTHMIA study)

A total of 159 patients met the inclusion criteria. 115 (72%) patients were younger than 31 days at their first index admission for tachycardia. Body weight was 3805 +/- 1435 g.

A history of intrauterine tachycardia was present in 63 patients (40%), of whom nine patients (6%) required transplacental AAD therapy, and 6 of them (4%) developed hydrops. 52 (33%) children were born after urgent Caesarian section, and 47 (30%) children were born prematurely. CHD, cardiomyopathy, or cardiac tumor was present in 34 patients (21%), and 25 children (16%) suspected systemic infection during initial therapy. On echocardiography, 90/146 (62%) had preserved left ventricular (LV) function, and 67 patients (42%) had clinical signs of heart failure.

Tachycardia mechanisms were paroxysmal supraventricular tachycardia (PSVT) n=107 (67%), focal atrial tachycardia (FAT) n=27 (17%), multifocal atrial tachycardia (MAT) n=5 (3%), junctional ectopic tachycardia (JET) n=5 (3%), PJRT n=3 (2%), Aflut n=10 (6%) and Afib n=2 (1%).

CHDs were present in 33 patients (20%), and SHD (1 hypertrophic obstructive cardiomyopathy) in 1 patient (1%). CHD was complex in 12 patients (Ebstein anomaly 3, double outlet right ventricle 2, coarctation of aorta 2, Fallot tetralogy 1, AV septal defect 1, tricuspid atresia 1, truncus arteriosus communis 1, double inlet right ventricle 1) and simple in 21 patients (atrial septal defect 9, ventricular septal defect 5, supravalvular pulmonary stenosis 2, bicuspid aortic valve 2, significant persistent ductus arteriosus requiring ligation 1).

AAD treatment was performed with one antiarrhythmic agent (n=81) or with a combination of two (n=78) or three agents (n=6). (See Table 6) In 6 patients, more than one combination was used until treatment success. The mode of initial AAD administration was intravenous in 109 cases (69 %). One neonate underwent catheter ablation because multiple AADs or combinations of drugs could not control tachycardia.

*Table 6. Antiarrhythmic drugs and combinations used for acute treatment (ineffective and final effective therapies are also included). Abbreviations: AAD=antiarrhythmic drug*

| **Single AAD therapy** (n=81) | |
|---|---|
| propafenon: | 43 |
| digoxin: | 24 |
| amiodarone: | 11 |
| metoprolol: | 8 |
| sotalol: | 4 |

| **Triple AAD therapy** (n=6) | |
|---|---|
| propafenon+amiodarone+ metoprolol: | 2 |
| propafenon+metoprolol+ digoxin: | 2 |
| propafenon+amiodarone + digoxin: | 1 |
| amiodarone + flecainid + digoxin: | 1 |

| **Double AAD therapy** (n=78) | |
|---|---|
| propafenone+digoxin | 22 |
| sotalol+digoxin | 15 |
| propafenon+metoprolol | 12 |
| propafenon + amiodarone | 9 |
| amiodarone + metoprolol | 7 |
| metoprolol + digoxin | 5 |
| amiodarone + digoxin | 5 |
| amiodarone + flecainid: | 2 |
| propafenon + sotalol: | 1 |
| verapamil + metoprolol: | 1 |
| amiodarone + lidocain: | 2 |

There were five patient deaths (3%) and four complicated clinical courses with multiorgan failure or irreversible hypoxic-ischemic encephalopathy (3%). Seven of these nine patients (78%) were neonates.

Clinical and demographic characteristics of the 159 patients classified after complicated (death or multiorgan failure) or uncomplicated courses are shown in Table 7.

*Table 7. Comparison of complicated and non-complicated group. Abbreviations: AA=antiarrhythmic, AAD=antiarrhythmic drug, PSVT=paroxysmal supraventricular tachycardia, FAT=focal atrial tachycardia,VT=ventricular tachycardia, iv=intravenous*

| **Clinical parameters** | **Fatal or near-fatal** | **Non-fatal** | **p-value** |
|---|---|---|---|
| | **n=9** | **n=150** | |
| Body weight (g) | 3385 ± 1923 | 3830 ± 1405 | 0.056 |
| **Age at treatment (days)** | **37.0 ± 88.8** | **39.9 ±69.2** | **0.020** |
| **Prenatal tachycardia** | **7 (78%)** | **56 (37%)** | **0.016** |
| **Prenatal AA therapy** | **2 (22%)** | **7 (5%)** | **0.027** |
| Structural and congenital heart disease | 2 (22%) | 32 (21%) | 0.95 |
| Fetal hydrops | 1 (11%) | 5 (3%) | 0.234 |
| **Urgent caesarian section** | **8 (89%)** | **44 (29%)** | **<0.001** |
| Prematurity | 4 (44%) | 43 (29%) | 0.314 |
| Suspicion of infection | 2 (22%) | 23 (15%) | 0.581 |
| Circulatory failure at presentation | 6 (67%) | 67 (42%) | 0.125 |
| Preserved left ventricular function | 3/9 (33%) | 87/146 (62%) | 0.549 |
| Type of arrhythmia: PSVT | 5 (56%) | 102 (68%) | 0,739 |
| FAT | 2 (22%) | 25 (17%) | |
| all else | 2 (22%) | 23 (14%) | |
| Catheter ablation | 0 (0%) | 1 (1%) | 0.806 |
| **Proarrhythmia** | **4 (44%)** | **2 (1%)** | **<0.001** |
| ECG sign of impending proarrhythmia | 1 (11%) | 5 (3%) | 0.234 |
| **Major adverse events of AAD** | **2 (22%)** | **0 (0%)** | **<0.001** |

There were significant differences between the groups regarding age, history of prenatal tachycardia and treatment, urgent cesarean section, proarrhythmia, and major adverse events (AEs).

Proarrhythmia – new onset arrhythmia – was identified in 6 cases. Three of five patients (60%) died, one of four (25%) survivors with severe complications, and two of 150 (1%) survivors without complications had proarrhythmia ($p<0.001$). In three cases (50%), proarrhythmia was related to intravenous Class IC (propafenone n= 3) use, in 2 cases (33%) to digoxin use, and in 1 case (17%) to amiodarone administration.

One (17%) patient in the group with fatal outcome, one patient (20%) in the group of survivors with severe complication, and 0 (0%) in the group of survivors without complication had a major AE with severe hypotension ($p<0.001$). Both AEs occurred during intravenous propafenone therapy.

ECG signs of impending proarrhythmia were detected in 6 cases related to i.v. propafenone treatment (4%). In all cases, QRS duration increased by>25% from baseline. Details of AAD therapy are shown in Table 8-9.

The only patient who died without proarrhythmia or major AEs had severe HCM and Afib. The combination of amiodarone and metoprolol controlled his tachycardia following electrical cardioversion, but he subsequently died due to intractable heart failure. The only patient in the complicated, non-fatal group without signs of pharmacological AEs was born with an urgent cesarean section with severe LV dysfunction and heart failure. Adenosine revealed Aflut with a high ventricular rate. He developed hypoxaemic ischemic encephalopathy despite effective arrhythmia control with amiodarone following electrical cardioversion, mechanical ventilation, and inotropic support. One patient in the complicated, non-fatal group had ECG signs of impending proarrhythmia (QRS duration increase), so propafenone infusion was stopped. The patient developed clinical deterioration and multiorgan failure in the further clinical course.

*Table 8. Details of cases with fatal outcomes. Abbreviations: AAD=antiarrhythmic drug, AE=adverse event, Afib=atrial fibrillation, BW=body weight, FAT=focal atrial tachycardia, HOCM=hypertrophic obstructive cardiomyopathy, PSVT=paroxysmal supraventricular tachycardia*

| Pt. | BW (kg) | Age (days) | Arrhythmia | AAD | Loading dose | Maintenance dose | Cumulative dose | Response | Classification |
|---|---|---|---|---|---|---|---|---|---|
| NGYb | 4,0 | 50 | PSVT | propafenone | 1 mg/kg over 2 h | - | 0,25mg/kg over 15 min | pulseless VT | proarrhythmia |
| SJb | 3,3 | 1 | PSVT | propafenone | 1 mg/kg over 1 h<br><br>6x0,2mg/kg over 0,5 h | - | 2,2 mg/kg over 1,5 h | Severe hypotension, desaturation, bradycardia, QRS duration increase | major AE |
| NL | 1,9 | 1 | PSVT | propafenone | no loading | 6µg/kg/ min | 8,2 mg/kg over 19 h | QRS duration increase, pulseless VT | proarrhythmia |
| KK | 2,6 | 4 | FAT | digoxin | 11 µg/kg iv bolus | - | 11 µg/kg | sinus bradycardia | proarrhythmia |
| FZ | 3,8 | 60 | Afib | amiodarone | 5 mg/kg over 4 h | 12,5mg/kg over 24 h | 12,5 mg x 21 days | effective rate control | unremarkable AAD therapy (severe HOCM) |

*Table 9. Details of cases with near-fatal outcomes. Abbreviations: AAD=antiarrhythmic drug, ECG=electrocardiogram, JET=junctional ectopic tachycardia, AE=adverse event, MOF=multiorgan failure, PSVT=paroxysmal supraventricular tachycardia, VF=ventricular fibrillation*

| Pt. | BW (kg) | Age (days) | Arrhythmia | AAD | Loading dose | Maintenance dose | Cumulative dose | Response | Classification |
|---|---|---|---|---|---|---|---|---|---|
| AN | 8,2 | 268 | JET | propafenone | 2 mg/kg over 2 h | 8 µg/kg/min | 24 mg/kg over 2 days | severe hypotension cardiac failure, QRS width increase, MOF | major AE |
| DO | 2,9 | 1 | PSVT | digoxin | 10 µg/kg iv bolus | - | 10 µg/kg | QRS duration increase, VF, cardioversion, MOF | proarrhythmia |
| RM | 2,8 | 1 | atrial flutter | amiodarone | 5 mg/kg over 4 h | 12,5 mg/kg over 24 h | stopped after 24 h | sinus rhythm | unremarkable AAD therapy |
| LS | 1,9 | 1 | PSVT | amiodarone | 5 mg/kg over 2 h | 13,6 mg/kg over 24 h | 28,6 mg/kg over 48 h | sinus rhythm, but QRS duration increase | ECG sign of impending proarrhythmia |

# 5. DISCUSSION

The main result of the research work is that real clinical data on two groups of unexpected arrhythmic cardiac arrest in children in Hungary have been collected which gives the opportunity of prevention of these arrhythmic events.

## 5.1 Out-of-hospital sudden cardiac arrest in children

Data from National Ambulance and a single tertiary pediatric cardiac center suggest that the incidence of pediatric OHSCA in Hungary is about 20-25 children/year. The survival rate without serious complications is about 5%. The finding that more than half of the survivors had genetic heart disease and one-fifth of the patients with inherited primary arrhythmia syndrome diagnosed and followed during childhood were recognized after SCA gives details about the etiology of OHSCA in Hungary and provides the possibility of prevention. The study also showed that identifying children with unsuccessful rescues from anonymous rescue data sheets is impossible; therefore, the cardiogenetic family screening is unresolved and needs a solution.

Pediatric OHSCA is a rare event with a poor prognosis. Publications report an incidence between 0,5-2,5/100.000 patients-year (18, 19, 20, 21, 22) and 2-6% of cases with hospital discharge (19, 23, 24, 25), although the development of pediatric emergency medicine ensures better results, 17.6-40,2% in some countries. (22, 26). Based on our results, the estimated incidence of pediatric OHSCA in Hungary (1,20/100.000 patient-year) fits the published data, although it has limitations, e.g., due to the retrospective study design.

The incidence of pediatric OHSCA cases with hospital discharge seems low if we only calculate the number of children admitted to GOKVI and treated with ICD. (This is the only center in Hungary dedicated to ICD implantation in children.) However, if we consider that the survival rate without serious neurological complications is 1-4% (19, 23, 24, 25, 27) and presume that cases with severe neurological complications were not referred to the national center for further evaluation and ICD implantation, then the case number with hospital discharge can be underestimated.

Half of the survivors without serious neurological complications had underlying genetic heart disease, which is not surprising as the distribution of etiologies of SCA differs in children and adults. SHDs, inherited primary arrhythmia syndromes and cardiomyopathies dominate in children, and secondary heart diseases (e.g., inflammatory heart disease, coronary sclerosis) are rare (28, 29, 30). It is important to note that the etiology of cardiac arrest can affect the success rate of reanimation; therefore, our data about etiology can be biased.

In terms of prevention, the early diagnosis and treatment of predisposing diseases are crucial; therefore, the other finding that one-fifth of the patients with inherited primary arrhythmia syndrome diagnosed and followed during childhood was recognized after SCA is of primary importance. Both results indicate that a more effective early diagnosis of genetic arrhythmia syndromes prior to clinical symptoms could decrease the number of pediatric OHSCAs.

In monogenic heart diseases, genetic family screening is an advantageous prevention mode. Clear pathological gene variants made it possible in one-third of our cases, but the extended clarification of VUS in the future can improve this ratio.

The possibility and need for family screening beyond genetics are pointed out by the fact that one-fourth of children with inherited primary arrhythmia syndromes were diagnosed because of affected family members. That is why creating and organizing a standardized cardiological-cardio genetic screening for families involved in pediatric SCA or SCD due to unsuccessful rescue seems indispensable.

Since closing this study, The National eHealth Infrastructure (EESZT) was introduced in the Hungarian health care system, which enables at least the theoretical possibility of retrospective identification of pediatric OHSCA nonsurvivors, linking of clinical information with autopsy findings and allows initiation of family screening. However, further elaboration is required to work up this complex screening method.

### 5.2 Early diagnosis of inherited arrhythmia syndromes

The results of this study show that syncope is not a typical first presenting symptom in children with cardiac channelopathies. Moreover, syncopal episodes are not common prodromal events beforeSCA, and common “red flags” alone did not raise the

clinical suspicion of cardiac syncope. However, the multivariable EGSYS score using also ECG parameters could identify all but one case of syncope in children with cardiac channelopathy, including patients initially misdiagnosed with epilepsy. The study was not extended to other forms of pediatric syncope, considering that channelopathies are the diagnostically most challenging subgroup of cardiac syncope in the absence of any cardiological physical signs or complaints.

Our patient selection likely influenced the observed rarity of syncopal presentation in potentially fatal arrhythmia syndromes due to the different probabilities of syncope in different subtypes of arrhythmias. (6, 31) The study focused intentionally on children with very subtle clinical symptoms and signs despite their high risk for SAD. The most common etiology was LQTS, followed by CPVT and BrS, which is in accordance with the reported prevalence of these diseases. (6, 32)

A high level of suspicion is needed to identify the presenting symptoms and signs of these life-threatening syndromes. Screening focused only on positive family history might miss new cases, and the effectiveness and clinical rationality of general pediatric ECG screening are low and are subject to the ongoing debate. In contrast, the EGSYS score seems able to arouse the suspicion of arrhythmic syncope and enables the diagnosis before more severe symptoms develop.(33)Clinical astuteness and knowledge of pathology are required for the diagnosis, as ECG alterations may be subtle or intermittent. Definitive diagnosis of channelopathy is usually required considering these cases, even after resting ECG evaluation as ECG changes can be rather subtle or one may miss recording intermittent signs. Moreover, sometimes even genetic testing may not lead to a definite diagnosis. (30, 34) Sometimes, the syncope is the final crucial factor for the diagnosis, and subsequent tests may confirm the suspected diagnosis.

Even if there are recurrent clinical signs like syncope, this does not always provide a diagnosis. A salient result of our study was that half of the patients diagnosed with syncope were originally diagnosed with epilepsy. Only the "drug-resistant, atypical" nature of the disease prompted an expanded diagnostic approach, including cardiological consultation, which only years later led to a correct diagnosis. The relationship between epilepsy and syncope has been extensively reviewed in recent years. (33, 35, 36, 37). Using implantable loop recorders, it has been demonstrated that

a substantial proportion of patients with refractory epilepsy experience arrhythmic syncope. (38)

Our finding that appropriate shock for VT or VF was given during follow-up in nearly all patients with a proper diagnosis of initial cardiac syncope treated with antiarrhythmic medication and ICD highlights the importance of promptly finding the correct etiology of arrhythmic syncope.

SCA, as a presentation, can be seen in almost all hereditary primary arrhythmic syndromes.(39, 40). Thus, the finding that one in five children with childhood channelopathy is diagnosed with SCA is puzzling, but not completely unexpected. It also re-emphasizes the need to diagnose potentially fatal arrhythmia syndromes before the onset of more advanced symptoms.

The new finding of our study is that it demonstrated the utility of the multivariate EGSYS score for identifying cardiac syncope in children with LTA syndrome. We have shown that the combination of clinical parameters, in particular, syncope during effort with ECG, can identify arrhythmia syncope in children with channelopathies. This is reasonable since, in these arrhythmic syndromes (LQTS, CPVT), the typical provocation of arrhythmia is a high level of adrenergic stress. The multivariate EGSYS score for pediatric syncope aids in detecting cardiac syncope by focusing on specific conditions and making ECG essential.

### 5.3 Therapy-resistant neonatal supraventricular tachycardia

The study's main finding was that the fatal or near-fatal outcome of SVT in neonates and infants without cardiac surgery is small but not insignificant. Adverse clinical outcomes may be related to prenatal history and medical management of tachycardia, and intravenous antiarrhythmic therapy may be a risk factor for fatal and near-fatal consequences. Results also indicate that detecting proarrhythmias associated with class I/C drugs in neonates can be difficult and requires vigilance.

Our cohort's 3% mortality rate is consistent with some previous studies. However, they included patients with tachycardia after cardiac surgery. (41, 42, 43, 44) Salerno et al. (42) investigated SVT, including all subjects younger than 25 years. They

conclude that the overall mortality of SVT in children is low (4%), but it appears to be more common in neonates and those with associated SHD. The contribution of SHD is not surprising, given that these patients are more at risk for hemodynamic instability and a predisposition to cardiovascular collapse during the tachycardia episode. Salerno et al. argued that the observational nature of their study precludes the inference of a causal relationship between mortality and SVT diagnosis, especially in patients with SHD who may have had cardiac surgery. Our study excluded patients who only developed tachycardia after heart surgery. This may explain why poor outcomes in our study were not related to structural heart defects. However, their other result that the highest mortality was observed in newborns is consistent with our results. The authors did not analyze prenatal anamnesis and pharmacological treatment. But six of the nine deaths occurred in children under one year of age with an apparently normal heart.

The relationship between intrauterine tachycardia, transplacental therapy, and emergency cesarean section with the complicated outcome is also not unexpected, but the mechanism is not entirely clear. It is uncertain whether this finding reflects the poor clinical condition of the newborn or the untreatability of the tachycardia. Gilliam (41) has reported a 6% fatality rate in a single-center study of 109 patients with SVT less than 30 days old. Of the five neonates who died, four were born with severe heart failure (3 hydrops), and one was born prematurely. The contribution of pharmacological treatment in these lethal cases has not been described. In his fetal SVT study, O'Leary (45) concluded that gestational age impacts the onset of hydrops, so that later gestational age at fetal diagnosis and depressed fetal ventricular function, but not hydrops, is a predictive factor for arrhythmia burden after birth. This reporting strengthens the hypothesis that our observation reflects the difficult-to-treat character of tachycardia. This may explain why there were no significant differences in congestive heart failure and left ventricular function between the complicated and uncomplicated groups in our study. One might expect the type of tachycardia differs between the complicated and uncomplicated groups. However, if one considers that the cellular pathomechanism of tachycardia (reentry, increased automaticity, triggered activity) and the AADs used for treatment are the same, this may not be so striking.

Our study suggests that pharmacological therapy for acute tachycardia is inherently risky (through proarrhythmias and adverse effects). Some papers have recently dealt with this issue. However, these data mostly report on the use of oral AADs for secondary prevention, rather than acute treatment for intractable tachycardia. (46, 47, 48, 49) Chu et al. (44)evaluated an extensive multicentre database on the management of SVT in infants. The overall death rate was 2% (CHD group, 6%), and theAE rate was 18%. However, these only consist of AEs during the infant's secondary prevention therapy. Seslar et al.(43)reported no deaths in a multicentre study of hospital care for SVT in neonates and infants. Our patient group was younger than theirs, and we also included intravenous administration of IC-class drugs (propafenone, flecainide). While the safety of flecainide has been published recently by Cunningham and colleagues, no data on the intravenous use of flecainide for intractable neonatal tachycardia have been reported (50). About the inherent risk of AADs, Saul and colleagues published a double-blind, randomized, multicenter, dose-response study on the safety and efficacy of intravenous amiodarone (Class III) (51). They also observed that side effects were frequent (87%) and dose-dependent and concluded that the dose-dependent risk of intravenous amiodarone should be considered in managing children with incessant arrhythmias. Garson also described dose-related AEs associated with intravenous propafenone.(52)Digoxin has a long history of use in managing pediatric SVT, but its safety is still under debate.(49, 53)

Our result on propafenone-induced proarrhythmia is of great significance, as proarrhythmia in children triggered by sodium channel blockers is not often recognized and reported. Although these events may be infrequent, they can remain largely unnoticed. In contrast to TdP induced by QT-prolonging drugs, ventricular arrhythmias induced by sodium channel-blocking drugs do not have a characteristic ECG feature that would facilitate their detection and differentiation from other forms of VT or VF. VT may also be encountered in patients with hyperkalemia, severe diffuse ischemia, advanced left ventricular dysfunction, and heart failure. It may be infeasible to differentiate drug-induced proarrhythmias in these settings solely based on the ECG. (1, 54)

The increased frequency of proarrhythmia associated with the intravenous use of propafenone in our patient population may represent the use dependence feature of Class IC drugs. A characteristic feature of sodium channel blockers is that they have a more pronounced effect at faster heart rates. Consequently, conduction slowing and QRS prolongation at normal heart rates can be subtle, especially in neonates. If a significant (20%) prolongation of the QRS interval is observed at rest with IC class sodium channel blockers, the dose should be reduced because even more significant conduction slowing may occur over time. This conduction slowing may increase the risk of reentrant arrhythmias and lead to sustained tachycardia. (1, 54)

The prevalence of ECG signs of impending proarrhythmia did not show significant differences between groups. Therefore, we cannot rule out the possibility that we do not recognize them in complicated cases and cannot prove that we have prevented proarrhythmia by responding to ECG signals by stopping AAD. It is assumed that the conduction slowing of propafenone has been missed in some of our patients, and therefore a new onset arrhythmia - proarrhythmia - has emerged. Therefore, vigilance and active search for signs of proarrhythmia are recommended, especially during intravenous drug treatment of intractable SVT in neonates.

Limitations:

The results of the research can only be evaluated concerning the limitations. In the POHSCA study, findings regarding etiology can be biased as we could only study the survivors. Even though we included every consecutive channelopathy patient in our SYNCOPE study, there were few cases. The multivariate EGSYS score has not been studied in non arrhythmic pediatric syncopes; however, channelopathies are the most challenging subset of cardiac syncope to diagnose in the absence of physical symptoms or complaints. Since our group of patients is heterogeneous and represents the spectrum of cardiac channel disorders, we have recognized that the relative prevalence of symptoms may also vary according to the electrophysiological and genetic background. In the PROARRHYTHMIA study, the low prevalence of mortality and proarrhythmia impeded multivariate statistical analysis from protecting confounders. Thus, it constrained the ability to establish causal inferences. Given the limited sample size,

nonsignificant results should not be interpreted as strong evidence of no effect. The retrospective nature of the study impeded the evaluation of dose-related effects.

The main result of the research work is that real clinical data on two groups of unexpected arrhythmic cardiac arrest in children in Hungary have been collected which is essential for prevention of these arrhythmic events.

The survey of the prevalence of out-of-hospital cardiac death in Hungary showed that the proportion of children who survive without serious neurological injury is low and the prevalence of inherited arrhythmia syndromes among these patients is significant. Because of the hereditary nature of the disease, family screening would be essential. Still, in cases with unsuccessful resuscitation, it was not possible to obtain the results of the children's autopsy and organize family screening during the study. The part of the study that looked at data from patients cared for in a national pediatric heart center for hereditary arrhythmia syndrome also showed that SCD is often the first symptom leading to diagnosis. General ECG screening for hereditary arrhythmia syndromes has a low chance of success, so targeted screening of the at-risk population is emerging. Recurrent syncope may be suggestive of an inherited arrhythmia syndrome, and research could demonstrate that the EGSYS score combining clinical data and ECG criteria has a high chance of identifying these patients, thus preventing more serious complications in the patient and the family.

The survey of complications and mortality in neonates treated for SVT has demonstrated that, although little attention is paid to it, it exists and not exclusively in neonates born with a congenital structural abnormality. A study of risk factors for complicated outcomes showed that, in addition to prenatal history, intravenous antiarrhythmic therapy may be a risk factor and that the proarrhythmic effect of I/C-induced AADs may be challenging to detect in neonates. Moderate QRS widening indicative of proarrhythmic accumulation of the effects of these drugs in the neonatal setting of a very narrow QRS may be very difficult to assess and may be a late sign. This finding of the research has the potential to raise awareness of this risk factor to prevent LTAs.

## 6. CONCLUSIONS

Based on the results detailed above, we have drawn the following main conclusions:

1. According to the National Ambulance Service, 20-25 children in Hungary yearly suffer out-of-hospital cardiac arrest. One-fifth of cases are successfully resuscitated. One-fifth of the surviving children had no serious complications or neurological deficits and were subsequently referred for additional diagnosis and ICD management (5% of childhood cardiac arrests).
2. An inherited arrhythmia syndrome was detected later in half of the surviving patients. One-fifth of children screened and followed up for inherited arrhythmia syndrome at the national center were identified after cardiac arrest. Syncope is not a frequent symptom of channelopathy, and it does not always precede sudden cardiac arrest.
3. Physical examination and commonly used "red flags" of cardiac syncope alone are insufficient to identify primary arrhythmia syndromes in children. But the combination of clinical and ECG-based features, such as the multivariate EGSYS score, can reveal the arrhythmic syncope with high precision.
4. Based on these findings, performing ECG and multivariable EGSYSscore should be considered for each child with pediatric syncope and refractory epilepsy.
5. The mortality rate in neonates and infants with non-postoperative supraventricular tachycardias is low (3%).
6. A complicated course and outcome are associated with age, prenatal history and therapy of tachycardia, proarrhythmia of antiarrhythmic medication, and major adverse events.
7. The increased incidence of proarrhythmia, major adverse events, and ECG signs of impending proarrhythmia in patients with fatal or near-fatal outcomes suggests that acute intravenous pharmacologic therapy of supraventricular tachycardias in neonates might pose a risk and should be used with caution. Nevertheless, detecting proarrhythmia related to Class I/C drugs in neonates might be difficult and warrants alertness.

## 7. SUMMARY

In my doctoral dissertation, I discussed the mechanism of life-threatening arrhythmias specific to the pediatric age group. I examined the incidence and etiology of fatal or near-fatal neonatal supraventricular tachycardia and pediatric out-of-hospital sudden cardiac arrest in Hungary to determine possible prevention methods.

My research studies showed that the incidence of pediatric out-of-hospital sudden cardiac arrest in Hungary corresponds to published data in the literature; however, the exact determination of etiology remains challenging because of the low survival rate.

The Documentation system of medical rescue in Hungary does not allow the identification of families with pediatric sudden cardiac death and hinders the initiation of family screening.

The high prevalence of inherited arrhythmia syndromes in surviving children gives the chance of genetic testing in affected families for prevention and the challenging early clinical diagnosis of channelopathies before clinical symptoms and cardiac arrest also supports the significance of family screening.

My retrospective observational study demonstrated that in the neonatal age group, even supraventricular tachycardia has a non-negligible risk of fatal or near-fatal outcomes, and antiarrhythmic medication may contribute to it.

New findings of my research are the verification of the utility of the EGSYS score to diagnose cardiac syncope in children with channelopathies and to point out that challenging diagnosis of Class I/C proarrhythmia (QRS duration increase and ventricular tachycardia) in neonates may contribute to underestimation of its role in poor clinical outcome.

My answer to the principal question of my dissertation regarding prevention of potentially life-threatening arrhythmias in children is the following: Several children’s lives could be saved by the identification of families with pediatric sudden cardiac arrest and inherited arrhythmia syndrome to initiate genetic family screening, by a more effective diagnosis of pediatric cardiac syncope with EGSYS score and by increased alertness for proarrhythmia during intravenous therapy of neonatal supraventricular tachycardia with Class I/C antiarrhythmic drugs.

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