# Advances in treatment of pediatric arrhythmias

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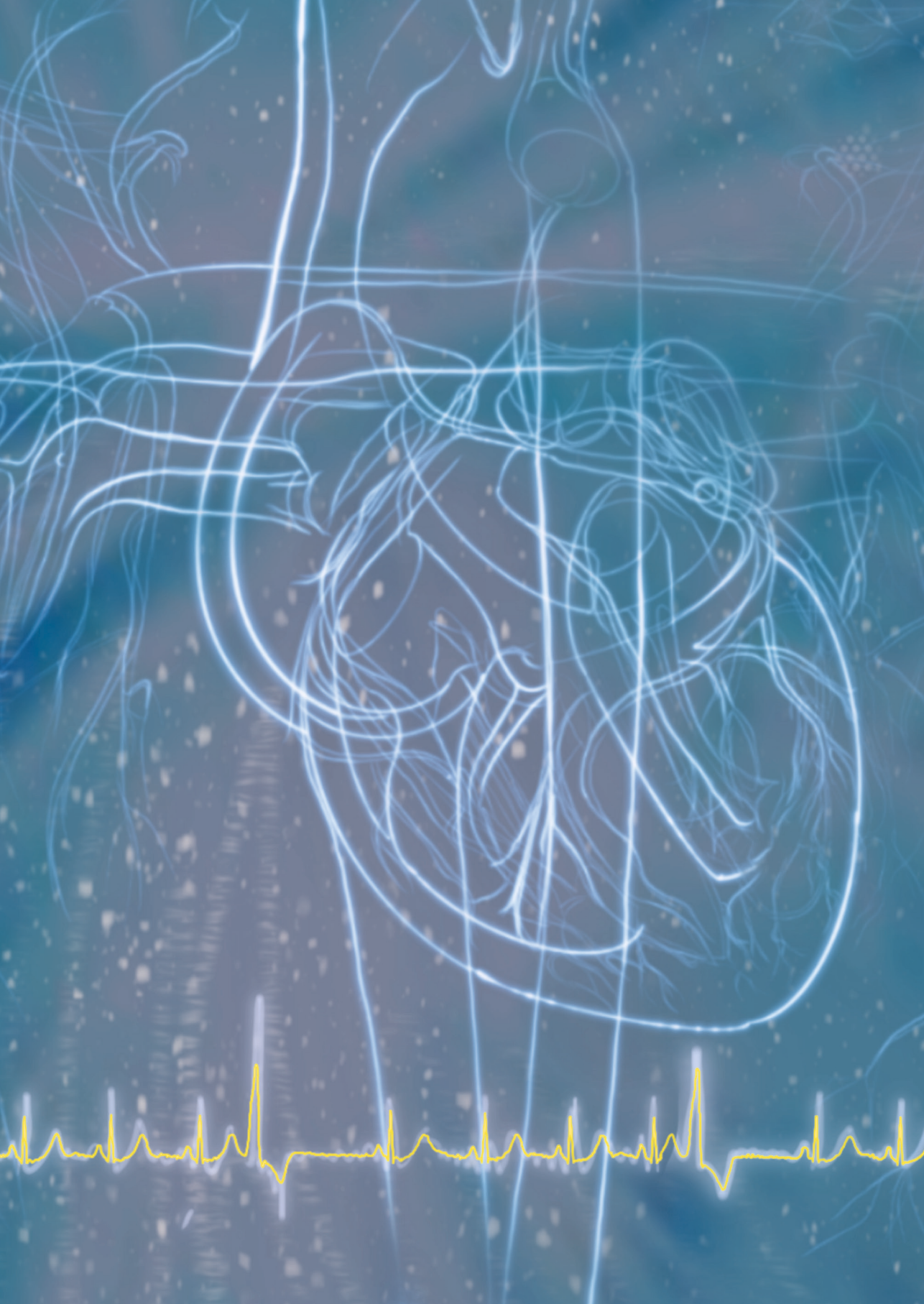

# 1 CHAPTER

# General Introduction

# BACKGROUND

The earliest case reports of arrhythmias in children date back to around 1900.(1). Children presenting with symptoms of cardiac failure and decompensation were found to have a very fast heart rate. In these cases, the tachycardia converted back to slower heart rate spontaneously or after vomiting. The tachycardia was therefore recognized as the primary cause of cardiac failure, and the first treatment with digitalis was proposed. Since these initial reports, significant advances have been made in the treatment of pediatric arrhythmias, although non-invasive treatment options like vasovagal stimuli and anti-arrhythmic medication remain the first-line treatment options. In the early 1980s, catheter ablation emerged as curative treatment for different types of arrhythmias in adults, and soon after it was also applied to children with incessant tachycardia.(2) Around the same time, the first implantable cardioverter defibrillators were implanted in humans.(3)

Arrhythmias can arise in children with a structural normal heart, in children with congenital or structural heart disease or they can be caused by an underlying genetic defect. They are typically classified as either supraventricular or ventricular arrhythmias, based on the location of the focus or circuit causing or maintaining the tachycardia. In supraventricular tachycardia (SVT), the source of the tachycardia, is localized within the atrium itself, or the atrium is at least part of the circuit. In ventricular tachycardia (VT) the source is always located within the ventricular myocardium or the ventricular conduction system.

The atrial and ventricular myocardium are separated by a fibrous ring at the level of the atrio-ventricular (AV) valves. Normally, only the bundle of His penetrates this fibrous tissue as an important part of the atrioventricular conduction system. However, in common forms of SVT in children, accessory atrio-ventricular connections breach the fibrous separation of the AV junction, to form an electrophysiological circuit causing atrio-ventricular re-entry tachycardia (AVRT). At the atrial side, the bundle of His is connected to the compact AV node, which has a border of transitional cells connecting it to the atrial myocardium. These transitional cells can form pathways with different conduction velocities, which may create a re-entry loop, resulting in tachycardia known as atrio-ventricular nodal re-entry tachycardia (AVNRT). Micro- or macro- re-entry circuits can also develop within the atrial myocardium itself, causing atrial tachycardia or atrial flutter, especially after surgery for congenital heart defects. Another source of focal atrial tachycardia is enhanced automaticity of the myocardial cells.

Monomorphic premature ventricular complexes (PVC) or ventricular tachycardia (VT) can be the result of enhanced automaticity, but the exact cause is usually unknown.(4) Other mechanisms, such as triggered activity or re-entry circuits, have been proposed as the potential underlying substrate for PVCs or VT. Another form of monomorphic VT is fascicular VT, in which a part of the left fascicle forms a re-entry circuit with the surrounding myocardium. A third form of VT in children after cardiac surgery for congenital heart defects,

is known to be caused macro re-entry circuits and monomorphic VT, as seen after repair of Tetralogy of Fallot.(5) The underlying substrates are slow conducting anatomical isthmuses bordered by surgical incisions, patch material and valve annuli.

The cause of polymorphic VT or ventricular fibrillation (VF) is more complex and usually involves patients with cardiogenetic defects. These include channelopathies, like long-QT syndrome, Brugada syndrome or catecholaminergic polymorphic VT, as well as cardiomyopathies, including hypertrophic cardiomyopathy and arrhythmogenic right ventricular tachycardia.



### Incidence

The most common arrhythmia in children is supraventricular tachycardia (SVT), with an annual incidence of 13 per 100.000,(6) although the true incidence is unknown due to absence of symptoms or spontaneous resolution of symptoms in infants. Only a small proportion of infants remain symptomatic or experience life-threatening SVT, requiring acute and/or chronic medical treatment. The second peak in incidence of SVT occurs during puberty, when many patients with an underlying substrate begin to experience symptoms such as palpitations, syncope, chest-pain or fatigue. These patients usually start with anti-arrhythmic drug treatment. However, depending on the child's age and the electrophysiological substrate, catheter ablation is generally considered to be the curative treatment option.

VT in children is rare, with sustained VT occurring at a frequency of 1.1 episodes per 100.000 children over a 10-year period.(7) Frequent PVCs are more common, though fewer than 5% of school-aged children experience more than 50 PVCs per 24 hours.(8) Idiopathic ventricular arrhythmias, such as frequent PVCs and asymptomatic VT typically have a good prognosis in children with a structural normal heart and often resolve spontaneously. However, based on adult data, it is believed that a limited number of these children may develop left ventricular (LV) dysfunction indicating the need for treatment of these ventricular arrhythmias. Catheter ablation is preferably postponed until a later age, because of concerns about the potential of lesion growth within the myocardium.(9) Ventricular arrhythmias caused by structural heart disease or genetic mutations can potentially be life-threatening and need specific anti-arrhythmic drug treatment and, in some cases, invasive procedures such as ablation and/or implantable cardioverter-defibrillator (ICD) therapy. These conditions can have a significant impact on the psycho-social well-being of young patients and their parents.(10, 11)

## AIM

This thesis aims to explore the advances in the treatment modalities for different types of pediatric arrhythmias, focusing on innovations in pharmacological interventions, catheter ablation techniques, and the use of implantable devices. By studying case series, retrospective patient cohorts, and current literature, and by performing a clinical

trial, this research seeks to provide new insights into the most effective strategies for managing pediatric arrhythmias. The ultimate goal is to provide practical insights to clinicians and researchers that can enhance both outcomes and quality of life for pediatric patients impacted by these conditions. Additionally, this work will contribute to a better understanding of pediatric arrhythmias, guiding future research directions aimed at addressing the management of arrhythmias in children**.**

# OUTLINE

### Part I: Ablation of supra-ventricular tachycardia

Catheter ablation for the treatment of supraventricular tachycardia (SVT) has been reported to be a safe and effective therapy in children with a high success rate and low complication rate.(12, 13) Concerns that remain are the relatively long radiation exposure associated with increased risk of developing malignancies later in life.(14-16) **Chapter 2** will evaluate *the effect of electro-anatomical mapping (EAM) on the success rate and fluoroscopy time in SVT ablation in children*. Catheter ablation is now generally considered to be a definite treatment option as a standard of care from around 5 years of age.(6) However, catheter ablation is sometimes warranted in even younger age groups, in cases with refractory SVTs to AAD treatment and has its specific risks and challenges. *Why, when and how to perform radiofrequency ablation of SVT in newborns and infants* is described in **chapter 3**. Although catheter ablation has a high success rate, certain cases can still be challenging and may provide new insights in the electrophysiological substrate. **Chapter 4** describes a case of *an accessory pathway with automaticity and bidirectional conductive capacity*.

### Part II: Anti-arrhythmic drug treatment of frequent PVCs

Frequent premature ventricular complexes and/or asymptomatic ventricular tachycardia Idiopathic frequent PVCs were always considered benign in all age groups.(17) However, over the past decade frequent PVCs have emerged as cause of LV dysfunction, LV dilatation and congestive heart failure in the adult population.(18, 19) Pediatric data on PVCs in relation to left ventricular dysfunction is limited. In **chapter 5** the *association of frequent premature ventricular complexes and asymptomatic ventricular tachycardia to left ventricular dysfunction in children* is examined. This chapter aims to assess which determinants of asymptomatic PVCs/VTs are related with development of LV dysfunction in children. In adults, a causal relationship is suggested by the observations that left ventricular (LV) function usually recovers after effective treatment of ventricular arrhythmia.(20, 21) Guidelines recommend beta-blockers as first-line therapy of children with symptoms and of children in whom PVCs are thought to be causative of LV dysfunction. However, literature data on efficacy and safety of AAD therapy in children are scarce and limited to small series. (20, 22, 23) Therefore, **chapter 6** examines *the efficacy of anti-arrhythmic drugs in children with idiopathic frequent symptomatic or asymptomatic premature ventricular complexes with or without asymptomatic ventricular tachycardia* in a retrospectively. In adults, recent guidelines recommend the Class IC drug flecainide as first-line therapy for idiopathic

outflow tract VTs and symptomatic patients with PVCs.(24, 25) However, to date there are no studies to support the use of flecainide as first-line therapy in children with frequent PVCs or asymptomatic VT. To further investigate the effect of beta-blockers compared to flecainide in reducing the PVC-burden in children, we performed a randomized cross-over trial in a pediatric cohort with idiopathic PVCs. **Chapter 7** describes the results of the ***ECTOPIC trial: The efficacy of flEcainide Compared To metOprolol in reducing Premature ventrIcular Contractions.***



### Part III: Optimalisation of ICD treatment

Implantable cardioverter defibrillator (ICD) therapy is effective in preventing sudden cardiac death caused by life threatening rhythm disturbances. Yet, ICD implantation is still associated with a significant complication rate, of which inappropriate ICD shocks, infections, lead related problems or ICD failure are most common.(26-30) Advancements in programming strategies of the ICD(31-35) and the introduction of remote monitoring(36-39) have led to a reduction in the number of inappropriate shocks in adults. The principles of reprogramming the ICD and the use of remote monitoring to reduce the number of inappropriate shocks, are also introduced in the pediatric population. Only few studies have assessed the effect of changing ICD programming(26, 28) and remote care in children.(40-44) **Chapter 8** investigates ***the influence of implantable cardioverter defibrillator programming and remote monitoring on the incidence of (in)appropriate shocks in children.***

### Summary

**Chapter 9** summarizes the results of these studies and gives future perspectives for clinicians and researchers.

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