Advances in treatment of pediatric arrhythmias

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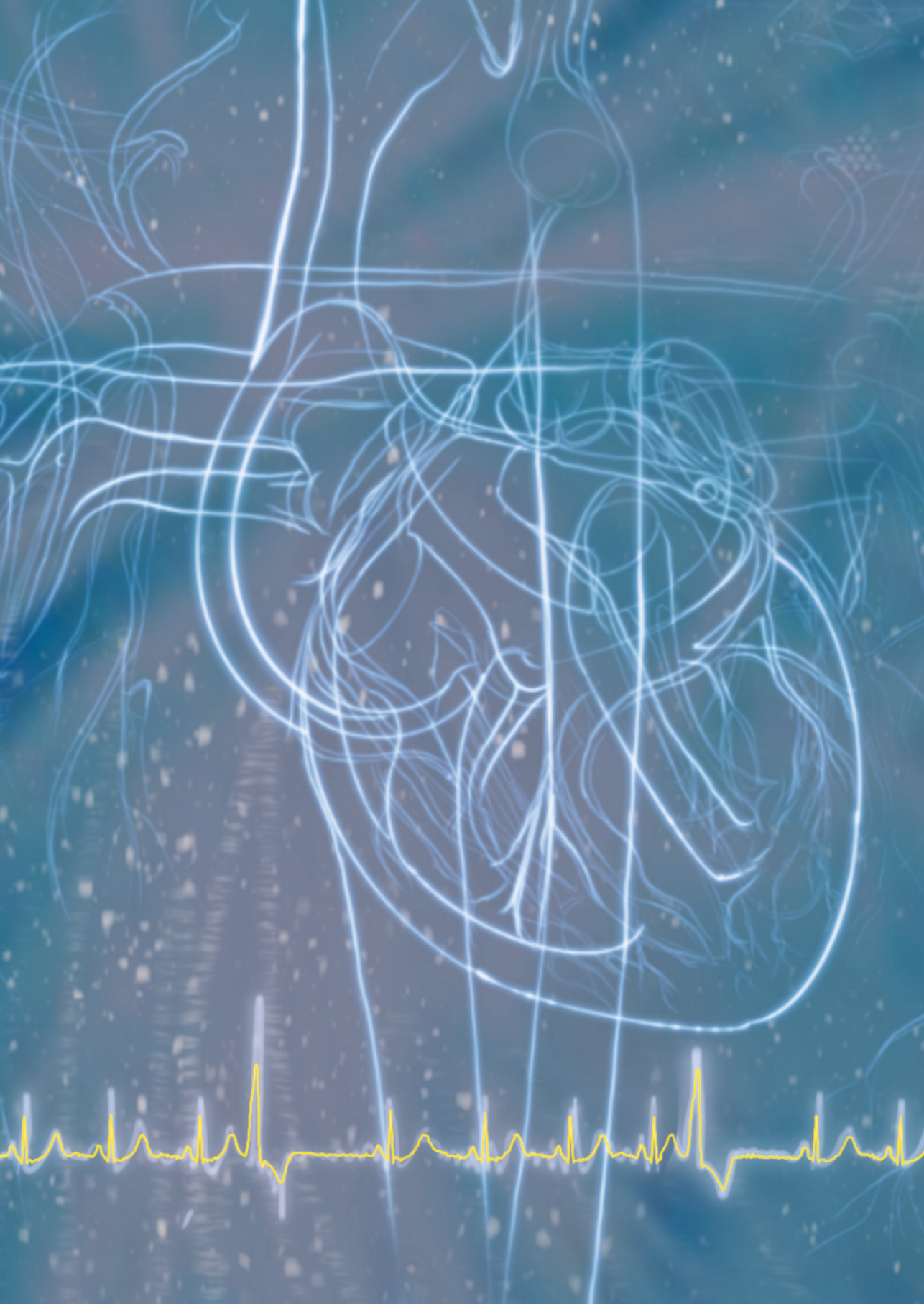
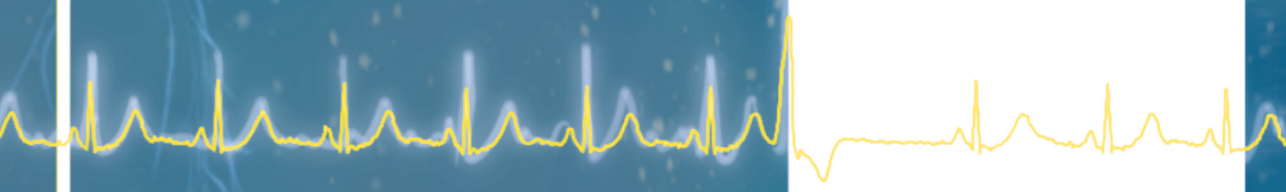


9 CHAPTER

Summary and future perspectives



SUMMARY

Aim

Cardiac arrhythmias have been well known in children for over 100 years, and during this time, treatment has evolved to the point where most children can be treated successfully, and life-threatening arrhythmias have become rare. Despite these advancements, the physical and psycho-social impact of symptoms and treatment in children can be high. This thesis aimed to explore the advances in the treatment modalities for different types of pediatric arrhythmias, including innovations in pharmacological interventions, catheter ablation techniques, and the use of implantable devices. By studying case series, retrospective patient cohorts, and current literature, along with performing a clinical trial, this research sought to identify the most effective strategies for managing pediatric arrhythmia. The ultimate goal was to provide clinicians and researchers with practical insights that can enhance both outcomes and quality of life for pediatric patients affected by these conditions.

Part I: Ablation of supraventricular tachycardia

Catheter ablation for the treatment of supraventricular tachycardia (SVT) has been shown to be a safe and effective therapy in children, with a high success rate and low complication rate.(1, 2). Maximal reduction of radiation exposure is important to minimize the risk of developing malignancies later in life.(3-5) **Chapter 2** reports on the results of ablation of a cohort of patients who underwent their first SVT ablation in the Leiden University Medical Center between 2014-2020. To evaluate the effect of electro-anatomical mapping (EAM) on the success rate and fluoroscopy time, procedures were categorized into those that used only fluoroscopy and those that used EAM.

The outcomes of ablation of 373 electro-anatomical substrates in 351 patients were analysed. The acute success rate in the fluoro-group (n=170) was 95.9%, compared to 94.5% in the EAM-group (n=181) which is consistent with international registries of ablation in children.(6) Most of these registries reported results using only one type of imaging, either fluoroscopy or EAM, making it difficult to compare the historical cohort using fluoroscopy with more recent cohorts using EAM. Several confounders such as differences in ablation technique (RF-energy vs cryo-energy) may influence the results.

The strength of the current study lies in the fact that the only difference between the two groups was the introduction of EAM. Both groups had the similar patient and tachycardia characteristics and were treated by the same two electrophysiologist with the standard use of cryo-energy for AVNRT and septal pathways. In addition to maintaining high acute success rate, the recurrence rate remained low, 6.1% in the fluoro-group and 6.4% in the EAM-group after a 12-months follow up. Redo-ablations were performed in 12 cases in the fluoro-group and 10 cases in the EAM-group, with success rates of 83.3% and 80.0%

respectively, resulting in overall success rates of 95.9% in the fluoro-group and 92.8% in the EAM-group after 12-months.

The most notable improvement was the reduction of the fluoroscopy time and dose area product. Both decreased significantly, from a median of 16.00 minutes to 2.00 minutes, and from a median of 210.5 μGym^2 to 32.9 μGym^2 respectively. These results, from one of the largest single-centre pediatric studies demonstrate that ablation of SVT substrates in children remain a highly effective and safe treatment after the introduction of EAM as a standard of care, significantly reducing fluoroscopy time and dose area product.

Supraventricular tachycardias in infants are typically well-managed with antiarrhythmic drug therapy and often resolve spontaneously within the first year of life. However, if SVTs become drug-refractory and lead to severe hemodynamic instability or tachycardia-induced cardiomyopathy, radiofrequency catheter ablation (RFCA) may be necessary. **Chapter 3** describes a case series of six infants with incessant SVT who were treated with RFCA, along with a review of the current literature on the indications, techniques, and outcomes of RFCA in young infants.

A review of the literature revealed a lack of large-scale studies involving newborns and young infants, leading to ongoing concerns about the risks of major complications associated with ablation energy in small hearts. Potential risks include coronary artery lesions, ablation lesion growth, valve damage, vessel injury, and complications related to the transseptal puncture. The six infants in this series were successfully ablated, without any complications. Anti-arrhythmic drug treatment was discontinued after the procedure. Two patients had a recurrence within a week and received a successful redo procedure. No other tachycardia recurrences were observed during a mean follow-up of 11 ± 6 months. This case series demonstrates that through advancements in materials, refinements in ablation techniques, and increased expertise RFCA can be safely performed in young children.

The success rate of catheter ablation depends on a comprehensive understanding of the electrophysiological properties of the substrate causing the tachycardia. This is illustrated in **chapter 4**, which presents a case of a 12-year-old boy referred for catheter ablation, with recurrent palpitations and documented paroxysmal supraventricular tachycardia. During the electrophysiological (EP) study intermittent pre-excitation was observed, with the earliest ventricular activation located halfway the coronary sinus (CS). Two spontaneous ventricular rhythms with a right bundle branch block morphology were observed: the first showed simultaneous atrial and ventricular activation, with the atrial and ventricular earliest activation at the mid CS; the second showed the earliest ventricular activation at mid CS, with retrograde atrial activation via the His bundle. Additionally, an atrial rhythm arising from mid CS was present, both with and without pre-excitation. After one RFCA application the ectopic rhythms disappeared, leaving only sinus rhythm without pre-excitation.

The EP study revealed the presence of an accessory pathway with inherent automaticity and bidirectional conductive capacity, a phenomenon not previously described. This underscores the need for continued improvement in our understanding of the underlying substrates to perform effective ablations of accessory pathways. The electrophysiological model of the conduction system and arrhythmia substrates with all its biological variation, needs further refinement to improve the success rates of challenging ablations.

Part II: Anti-arrhythmic drug treatment of frequent PVCs

Frequent premature ventricular contractions (PVCs) or asymptomatic ventricular tachycardia (VT) in children with structurally normal hearts are usually considered benign.(7) However, this thesis showed that in certain cases, frequent PVCs may lead to left ventricular dysfunction, necessitating treatment. As only a small portion of children develops LV dysfunction, it is important to identify risk factors related to its development.

Chapter 5 reports on a retrospective study of 72 children with frequent PVCs with or without asymptomatic VT. Six patients showed LV dysfunction at diagnosis, with a mean age of 10 years. Only 2 of these patients had symptoms such as syncope, palpitations, fatigue, and dizziness. The remaining 66 children, with a mean age of 8 years, showed normal LV function of which 22 had symptoms. Patients with LV dysfunction had a significant higher percentage of PVCs, a higher prevalence of VT, and a higher number of couplets on Holter recordings. In adult literature, a high PVC burden, and non-sustained VT are recognized as risk factors for the development of LV dysfunction. This study is among the first to show this correlation in children, demonstrating that LV dysfunction is reversible after treatment. Of the 6 patients with LV dysfunction, 2 responded to medication and 5 underwent ablation, one of which was unsuccessful. During follow up, LV function normalized after successful treatment of ventricular arrhythmia in 5 of the 6 patients. In patients with a normal function, none developed LV dysfunction during follow up.

In conclusion, in children with idiopathic PVCs and asymptomatic VTs, development of LV dysfunction is associated with a higher burden of PVCs, the presence of sustained VTs, and couplets. Since LV dysfunction appears to be reversible when the burden of PVCs is decreased by medication or ablation, preventive treatment is not warranted in patients with these risk factors.

The optimal anti-arrhythmic drugs (AAD) regimen to treat frequent PVCs in children with LV dysfunction or symptoms is not well known. Guidelines recommend beta-blockers as first-line therapy, (8) but data on efficacy and safety of AAD therapy in children are scarce and limited to small series. (9-11) **Chapter 6** describes a literature review and retrospective study comparing the efficacy of flecainide, beta-blockers, sotalol, and verapamil in children with frequent PVCs, with or without asymptomatic VT. The literature review showed that most series are small and primarily focus on patients with VT.(11, 12) All AAD classes were used with conflicting and non-significant results.

In the present retrospective multi-center study, both symptomatic and asymptomatic children with a PVC burden of 5% or more, with or without asymptomatic runs of VT, were included. Patients who received AAD therapy were compared to an untreated control group by analyzing consecutive 24-hour Holter recordings. A medication episode was defined as a timeframe during which the highest fixed dosage of a single drug was used. A total of 35 children and 46 medication episodes were included. The overall change in PVC burden on Holter as a result of AAD treatment was -4.4 percentage points, and was almost similar to the -4.2 percentage points in the untreated control group of 14 patients. This indicates that the effect of AAD in reducing PVCs is very limited. Only the mean reduction in PVC burden of -13.8 percentage points in patients receiving flecainide was significant.

This finding contradicts current guidelines, which advocate beta-blockers as the first line treatment for frequent PVCs in children. Studies in adults have already demonstrated the significant effect of class IC AAD on frequent PVCs.(13) Even more, there is evidence that beta-blockers may increase the PVC burden in some patients, as PVCs are typically reduced at higher heartrates.(14) To conclude, this study showed that the efficacy of anti-arrhythmic drug therapy on frequent PVCs or asymptomatic VTs in children is very limited. Only flecainide appeared to be effective in decreasing the PVC burden.

To further evaluate the effectiveness of AAD in reducing the PVC burden in children, a prospective randomized cross-over trial was performed in children with a PVC-burden of >15% on Holter. **Chapter 7** of this thesis presents the outcomes of this trial. Of the 60 patients that were screened, only 19 patients could be included. The inclusion in this investigator-initiated study was delayed because of the COVID pandemic and had to be stopped because of limited personal and financial resources. Children were successively treated with metoprolol and flecainide or vice versa, with a drug free interval of at least two weeks. Holter measurements were repeated before and after the start of the AAD.

The median age at the start was 13.9 years. The patients had a mean baseline PVC-burden of 21.7% before the start of flecainide and 21.2% before the start of metoprolol. A linear mixed model was used to analyze effect sizes in this cross-over trial. Flecainide reduced the PVC-burden by an estimated mean of 10.6 percentage points, compared to 2.4 percentage points for metoprolol. This led to a significant difference of 8.2 percentage-points.

This is the first prospective randomized study in children to provide compelling evidence that flecainide is superior to metoprolol in the treatment of frequent PVCs. However, it also demonstrated that flecainide is only effective in a subgroup of patients. Exploratory analysis revealed that 9 of 18 patients treated with flecainide had a reduction to a PVC-burden below 5%. No discriminating factors based on ECG or Holter parameters between flecainide-responders and non-responders were found. In addition, the flecainide dosage did not appear to influence the effect, since the mean plasma level was not significantly different between the responders and non-responders.

To conclude, this is the first prospective randomized cross-over study in children to show that treatment of frequent PVCs with flecainide leads to a significant greater reduction of PVC-burden compared to metoprolol. Although flecainide was effective in only a subgroup of patients, it may be considered the first line of treatment for symptomatic children with frequent PVCs and a structurally normal heart.

Part III: Optimalisation of implantable cardioverter defibrillator treatment

Implantable cardioverter defibrillator (ICD) therapy is effective in preventing sudden cardiac death caused by life-threatening arrhythmias in children. However, unnecessary shocks should be avoided, and current preventive strategies are primarily based on adult guidelines and research.(15-26) Further research is needed to adapt and confirm these strategies for the pediatric population. **Chapter 8** summarizes the results of a literature review and a retrospective multi-center study including all pediatric patients, who underwent a transvenous or epicardial ICD implantation ***before*** or ***after*** 2010. The cut-off year 2010 was chosen, because it marks the period when data on the Dutch pediatric ICD patient cohort(27) were published and when adult ICD studies concerning specific programming strategies led to changes in ICD management for children. Retrospective data on all ICD shock episodes were collected, including ICD programming variables and the application of remote monitoring.

A total of 116 patients were included, with 53 having an ICD implanted ***before*** 2010 and 63 ***after*** 2010. The median age at implantation was 13.4 years. The proportion of patients with shocks (57% to 40%) and appropriate shocks (42% to 29%) decreased significantly, ***before*** versus ***after*** 2010 respectively. There was no increase in cardiac related death. With a median follow-up of 5.2 years, this corresponds to an annual appropriate shock rate of 7.8% ***before*** 2010 and 5.8% ***after*** 2010, which is in line with other pediatric series from the past decade, where appropriate shock rates ranged from 2.9 to 13.9%. The proportion of patients with inappropriate shocks did not decrease significantly ***before*** versus ***after*** 2010 (23% and 13% respectively).

Among the ICD programming variables examined, the programmed VF zone was programmed significantly higher (≥210 BPM) in a larger proportion of appropriate shocks versus inappropriate shocks. In addition, there was a trend towards a higher VF zone (≥210 BPM) in patients without shocks compared to the group with shocks; and in the patients with an ICD implanted ***after*** 2010 compared to ***before*** 2010. These findings align with ICD studies in adults.(28)

Furthermore, this study provides evidence that application of remote monitoring is related to a decrease of the number of shocks in children. It showed that the application of remote monitoring significantly increased from 34% to 83% ***before*** 2010 versus ***after*** 2010, and was

associated with a significant decrease in mean cumulative number of total and appropriate shocks.

To conclude, this study is one of the largest cohorts of pediatric patients to show that the incidence of ICD shocks has significantly decreased over the last decade. Compared to the literature, it is one of the first to confirm that a higher programmed VF-zone and the application of remote monitoring are correlated with this decrease, thus justifying their use in strategies to prevent unnecessary shocks in children.

FUTURE PERSPECTIVES

Supraventricular tachycardia is usually well treated by catheter ablation, with good results, as shown in **chapter 2**. We have also demonstrated that the negative impact of the treatment caused by radiation exposure can be significantly reduced by the use of electro-anatomical mapping (EAM). Since the introduction of EAM, it has also become possible to map and locate the substrate of the SVT very precisely, which might have led to expectations of a better acute success rate for procedures using EAM compared to those performed with fluoroscopy alone. However, as in our series, other studies have also shown that the acute success rate does not increase with EAM. Most likely, the already high success rate of fluoroscopy-only procedures, makes it difficult to improve upon with EAM. Furthermore, unsuccessful procedures likely involve substrates that are difficult to access from the endocardium. Future research should focus on these difficult-to-reach substrates.

Younger children with SVT can now also be safely treated with catheter ablation, including infants with drug-refractory SVT, as we presented in **chapter 3**. Since many of these SVT's are congenital, the ultimate goal would be to provide curative treatment as soon as symptoms emerge to avoid years of AAD treatment with the associated side effects and impact on psycho-social wellbeing. Ablation techniques and materials should therefore be further developed and refined to allow safe ablation in the youngest children. For example, smaller ablation catheters with good steerability, and multiple electrodes to be able to show the curve of the catheter on EAM are needed. However, this development is limited by the relatively small number of patients and strict medical devices regulations, which makes it difficult for companies to justify the large investments required.

Premature ventricular contractions and ventricular tachycardia can lead to LV dysfunction in some children, as we have shown in **chapter 5**. The challenge remains to predict which patients will develop LV dysfunction. As this research has demonstrated, a high burden of PVCs and the presence of VT or couplets might be used to stratify patients at risk, who require careful follow-up. Conversely, in most patients, PVCs will not cause LV dysfunction or symptoms and may disappear spontaneously. Being able to identify these low risk patients would reduce the need for follow-up and hospital visits, diminishing the impact on the patient, and reducing costs for society. Larger prospective multi-center studies will

be needed to investigate other risk factors such as echocardiographic parameters. In the follow-up of the ECTOPIC trial, clinical and echocardiographic data has been collected and these data will be analysed for predictors of LV dysfunction, based on the concept that the severity of dyssynchrony caused by the PVCs leads to reduced cardiac output and LV dilatation.

For patients with frequent PVCs or asymptomatic VT who do need treatment, because of LV dysfunction or symptoms, it is of importance to establish which AAD treatment is effective, as catheter ablation is preferably postponed in younger children, due to possibility of spontaneous resolution and, importantly, the risk of growth and arrhythmogenicity of ablation lesions in the ventricular myocardium. **Chapter 6 and 7** have shown that flecainide is very effective in reducing PVCs and should be advocated as first-line treatment option, contrary to current guidelines for children. However, since flecainide is only effective in a subset of patients, research should focus on the underlying pathophysiological mechanisms of idiopathic PVCs in relation to the effects of flecainide. The exact causes of idiopathic PVCs remain unclear, but they are thought to arise from different electrophysiological mechanisms, such as triggered activity, automaticity or re-entry. Flecainide is known to reduce triggered activity, which may be the underlying mechanism of PVCs in the subgroup of patients with an excellent response to flecainide. This concept could be explored in future studies, evaluating the effectiveness of other AADs in patients who do not respond to flecainide. Ivabradine could be a potential candidate due to its known ability to reduce automaticity.(29)

Implantable cardioverter device therapy remains the last-resort in treatment of patients with life-threatening VT or VF to prevent sudden cardiac death. The ultimate goal of arrhythmia control in these patients would be to prevent ICD implantation through AAD treatment that is 100% effective in the prevention of life threatening VT or VF. In patients with underlying cardiogenetic diseases, research also focusses on gene-therapy to provide a definite cure of underlying disease. Currently, however, these patients remain dependent on an ICD to abort fast VT or VF. Minimizing the number of shocks and ICD-related complications is of utmost importance. **Chapter 8** of this thesis examines the effect of device programming and the use of remote monitoring on the number of appropriate and inappropriate shocks, showing a significant reduction in the number of shocks over the past decade.

The current study supports the concept of programming pediatric ICDs with high VF zones (above 220-250/min) and long detection times, alongside the application of remote monitoring. The effect of fast VT (FVT) and VT zone programming on the incidence of appropriate and inappropriate ICD shocks needs to be further investigated. In general, therapy in lower (F)VT zones can be implemented for patients with decreased LV function or those at risk for slow VTs that are not hemodynamically tolerated. In addition, future studies should also focus on the use of detection algorithms and enhancing lead longevity, especially in young children, to further prevent inappropriate shocks. For example, the

optimal position of the shock coil and ICD in relation to age and growth in patients with non-transvenous ICD systems remains unclear. In pediatric patients, both transvenous and subcutaneous ICD systems, along with alternative ICD systems that utilize epicardial pacing and sensing leads combined with subcutaneous, pleural, or pericardial shock coils, each have their own advantages and limitations.(30) The newly developed extravascular and substernal position, might offer another option.(31) Larger international studies are needed to further evaluate the best position of ICD leads in children.

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