



Universiteit
Leiden
The Netherlands

Advances in treatment of pediatric arrhythmias

Bertels, R.A.

Citation

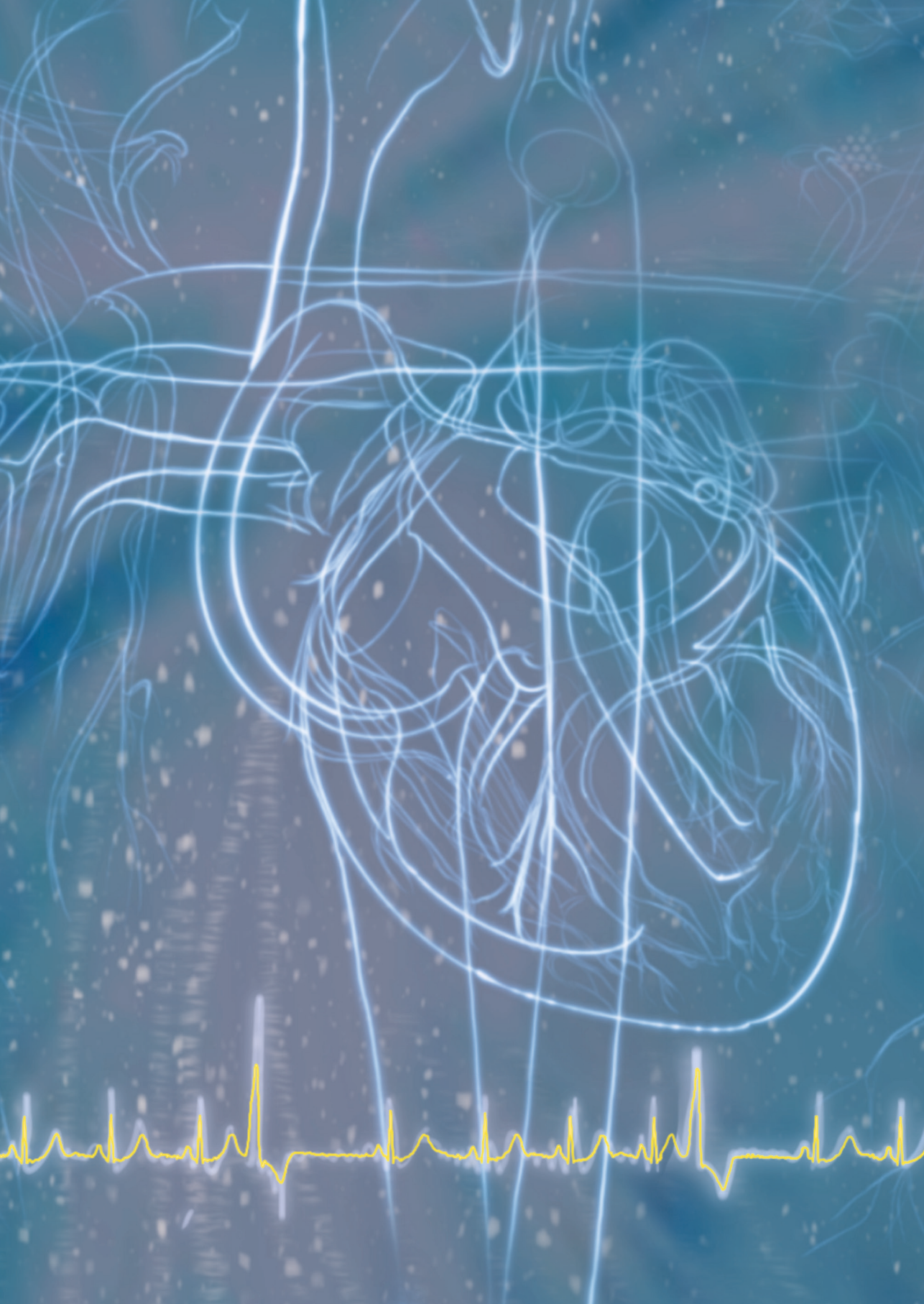
Bertels, R. A. (2025, July 3). *Advances in treatment of pediatric arrhythmias*. Retrieved from <https://hdl.handle.net/1887/4252717>

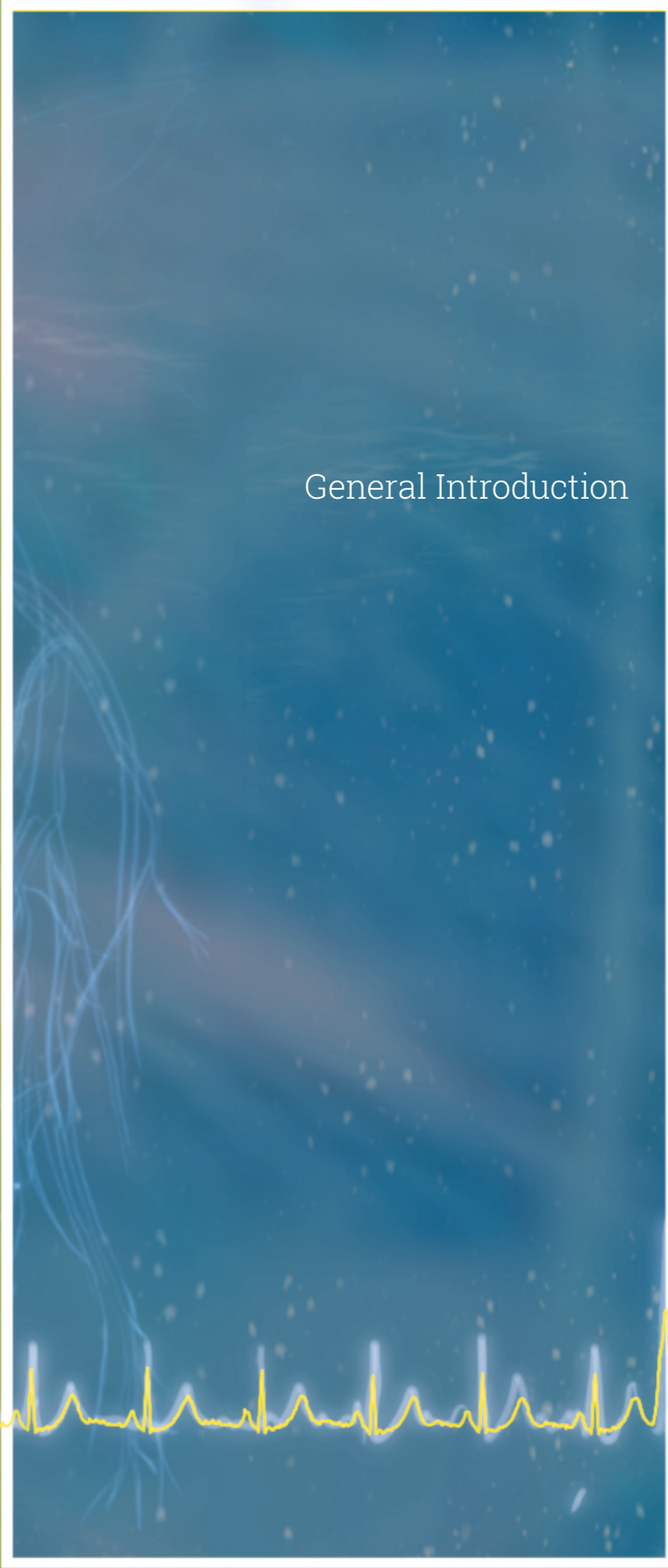
Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/4252717>

Note: To cite this publication please use the final published version (if applicable).





General Introduction

1

CHAPTER

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: Optimisation 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.

REFERENCES

- Hutchison R, Parkinson J. Paroxysmal Tachycardia in a Child, aged 2(3/4). *Proc R Soc Med.* 1914;7(Med Sect):117-24.
- Silka MJ, Gillette PC, Garson A, Jr., Zinner A. Transvenous catheter ablation of a right atrial automatic ectopic tachycardia. *J Am Coll Cardiol.* 1985;5(4):999-1001.
- Mirowski M, Mower MM, Reid PR. The automatic implantable defibrillator. *Am Heart J.* 1980;100(6 Pt 2):1089-92.
- Hoogendijk MG, Geczy T, Yap SC, Szili-Torok T. Pathophysiological Mechanisms of Premature Ventricular Complexes. *Front Physiol.* 2020;11:406.
- Zeppenfeld K, Wijnmaalen AP. Clinical Aspects and Ablation of Ventricular Arrhythmias in Tetralogy of Fallot. *Card Electrophysiol Clin.* 2017;9(2):285-94.
- Brugada J, Blom N, Sarquella-Brugada G, Blomstrom-Lundqvist C, Deanfield J, Janousek J, et al. Pharmacological and non-pharmacological therapy for arrhythmias in the pediatric population: EHRA and AEPC-Arrhythmia Working Group joint consensus statement. *Europace.* 2013;15(9):1337-82.
- Roggen A, Pavlovic M, Pfammatter JP. Frequency of spontaneous ventricular tachycardia in a pediatric population. *Am J Cardiol.* 2008;101(6):852-4.
- Nagashima M, Matsushima M, Ogawa A, Ohsuga A, Kaneko T, Yazaki T, et al. Cardiac arrhythmias in healthy children revealed by 24-hour ambulatory ECG monitoring. *Pediatric cardiology.* 1987;8(2):103-8.
- Khairy P, Guerra PG, Rivard L, Tanguay JF, Landry E, Guertin MC, et al. Enlargement of catheter ablation lesions in infant hearts with cryothermal versus radiofrequency energy: an animal study. *Circ Arrhythm Electrophysiol.* 2011;4(2):211-7.
- Pyngottu A, Werner H, Lehmann P, Balmer C. Health-Related Quality of Life and Psychological Adjustment of Children and Adolescents with Pacemakers and Implantable Cardioverter Defibrillators: A Systematic Review. *Pediatric cardiology.* 2019;40(1):1-16.
- Schneider LM, Wong JJ, Adams R, Bates B, Chen S, Ceresnak SR, et al. Posttraumatic stress disorder in pediatric patients with implantable cardioverter-defibrillators and their parents. *Heart Rhythm.* 2022;19(9):1524-9.
- Dubin AM, Jorgensen NW, Radbill AE, Bradley DJ, Silva JN, Tsao S, et al. What have we learned in the last 20 years? A comparison of a modern era pediatric and congenital catheter ablation registry to previous pediatric ablation registries. *Heart Rhythm.* 2019;16(1):57-63.
- Van Hare GF, Javitz H, Carmelli D, Saul JP, Tanel RE, Fischbach PS, et al. Prospective assessment after pediatric cardiac ablation: Demographics, medical profiles, and initial outcomes. *J Cardiovasc Electr.* 2004;15(7):759-70.
- Bacher K, Bogaert E, Lapere R, De Wolf D, Thierens H. Patient-specific dose and radiation risk estimation in pediatric cardiac catheterization. *Circulation.* 2005;111(1):83-9.
- Lindsay BD, Eichling JO, Ambos HD, Cain ME. Radiation exposure to patients and medical personnel during radiofrequency catheter ablation for supraventricular tachycardia. *Am J Cardiol.* 1992;70(2):218-23.
- McFadden SL, Mooney RB, Shepherd PH. X-ray dose and associated risks from radiofrequency catheter ablation procedures. *Br J Radiol.* 2002;75(891):253-65.
- Pfammatter JP, Bauersfeld U. Idiopathic ventricular tachycardias in infants and children. *Card Electrophysiol Rev.* 2002;6(1-2):88-92.
- Agarwal SK, Simpson RJ, Jr., Rautaharju P, Alonso A, Shahar E, Massing M, et al. Relation of ventricular premature complexes to heart failure (from the Atherosclerosis Risk In Communities [ARIC] Study). *Am J Cardiol.* 2012;109(1):105-9.
- Hasdemir C, Kartal Y, Simsek E, Yavuzgil O, Aydin M, Can LH. Time course of recovery of left ventricular systolic dysfunction in patients with premature ventricular contraction-induced cardiomyopathy. *Pacing Clin Electrophysiol.* 2013;36(5):612-7.
- Kakavand B, Ballard HO, Disessa TG. Frequent ventricular premature beats in children with a structurally normal heart: a cause for reversible left ventricular dysfunction? *Pediatr Cardiol.* 2010;31(7):986-90.
- Bertels RA, Hartevelde LM, Filippini LH, Clur SA, Blom NA. Left ventricular dysfunction is associated with frequent premature ventricular complexes and asymptomatic ventricular tachycardia in children. *Europace.* 2017;19(4):617-21.
- Wang S, Zhu W, Hamilton RM, Kirsh JA, Stephenson EA, Gross GJ. Diagnosis-specific characteristics of ventricular tachycardia in children with structurally normal hearts. *Heart Rhythm.* 2010;7(12):1725-31.

23. Iwamoto M, Niimura I, Shibata T, Yasui K, Takigiku K, Nishizawa T, et al. Long-term course and clinical characteristics of ventricular tachycardia detected in children by school-based heart disease screening. *Circulation journal : official journal of the Japanese Circulation Society*. 2005;69(3):273-6.
24. Dan GA, Martinez-Rubio A, Agewall S, Boriani G, Borggrefe M, Gaita F, et al. Antiarrhythmic drugs-clinical use and clinical decision making: a consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology (ESC) Working Group on Cardiovascular Pharmacology, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and International Society of Cardiovascular Pharmacotherapy (ISCP). *Europace*. 2018;20(5):731-2an.
25. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J*. 2015;36(41):2793-867.
26. Norrish G, Chubb H, Field E, McLeod K, Ilina M, Spentzou G, et al. Clinical outcomes and programming strategies of implantable cardioverter-defibrillator devices in paediatric hypertrophic cardiomyopathy: a UK National Cohort Study. *Europace*. 2021;23(3):400-8.
27. Song MK, Uhm JS, Baek JS, Yoon JK, Na JY, Yu HT, et al. Clinical Outcomes of Implantable Cardioverter-Defibrillator in Pediatric Patients - A Korean Multicenter Study. *Circulation journal : official journal of the Japanese Circulation Society*. 2021;85(8):1356-64.
28. Einbinder T, Machtei A, Birk E, Schamroth Pravda N, Frenkel G, Amir G, et al. Low Risk of Inappropriate Shock Among Pediatric Patients With an Implantable Cardioverter Defibrillator: A Single Center Experience. *Pediatric cardiology*. 2023.
29. Robinson JA, LaPage MJ, Atallah J, Webster G, Miyake CY, Ratnasamy C, et al. Outcomes of Pediatric Patients With Defibrillators Following Initial Presentation With Sudden Cardiac Arrest. *Circ Arrhythm Electrophysiol*. 2021;14(2):e008517.
30. Lewandowski M, Syska P, Kowalik I, Maciag A, Sterlinski M, Atenska-Pawlowska J, et al. Fifteen years' experience of implantable cardioverter defibrillator in children and young adults: Mortality and complications study. *Pediatr Int*. 2018;60(10):923-30.
31. Gasparini M, Proclemer A, Klersy C, Kloppe A, Lunati M, Ferrer JB, et al. Effect of long-detection interval vs standard-detection interval for implantable cardioverter-defibrillators on antitachycardia pacing and shock delivery: the ADVANCE III randomized clinical trial. *JAMA*. 2013;309(18):1903-11.
32. Kloppe A, Proclemer A, Arenal A, Lunati M, Martinez Ferrer JB, Hersi A, et al. Efficacy of long-detection interval implantable cardioverter-defibrillator settings in secondary prevention population: data from the Avoid Delivering Therapies for Nonsustained Arrhythmias in ICD Patients III (ADVANCE III) trial. *Circulation*. 2014;130(4):308-14.
33. Mastenbroek MH, Pedersen SS, van der Tweel I, Doevendans PA, Meine M. Results of ENHANCED Implantable Cardioverter Defibrillator Programming to Reduce Therapies and Improve Quality of Life (from the ENHANCED-ICD Study). *Am J Cardiol*. 2016;117(4):596-604.
34. Moss AJ, Schuger C, Beck CA, Brown MW, Cannon DS, Daubert JP, et al. Reduction in inappropriate therapy and mortality through ICD programming. *N Engl J Med*. 2012;367(24):2275-83.
35. Tan VH, Wilton SB, Kuriachan V, Sumner GL, Exner DV. Impact of programming strategies aimed at reducing nonessential implantable cardioverter defibrillator therapies on mortality: a systematic review and meta-analysis. *Circ Arrhythm Electrophysiol*. 2014;7(1):164-70.
36. Ploux S, Swerdlow CD, Strik M, Welte N, Klotz N, Ritter P, et al. Towards eradication of inappropriate therapies for ICD lead failure by combining comprehensive remote monitoring and lead noise alerts. *J Cardiovasc Electrophysiol*. 2018;29(8):1125-34.
37. Soth-Hansen M, Witt CT, Rasmussen M, Kristensen J, Gerdes C, Nielsen JC. Time until diagnosis of clinical events with different remote monitoring systems in implantable cardioverter-defibrillator patients. *Heart Rhythm*. 2018;15(11):1648-54.
38. Callum K, Graune C, Bowman E, Molden E, Leslie SJ. Remote monitoring of implantable defibrillators is associated with fewer inappropriate shocks and reduced time to medical assessment in a remote and rural area. *World J Cardiol*. 2021;13(3):46-54.
39. Perrin T, Boveda S, Defaye P, Rosier A, Sadoul N, Bordachar P, et al. Role of medical reaction in management of inappropriate ventricular arrhythmia diagnosis: the inappropriate Therapy and Home monitoriNG (THORN) registry. *Europace*. 2019;21(4):607-15.

40. Boyer SL, Silka MJ, Bar-Cohen Y. Current practices in the monitoring of cardiac rhythm devices in pediatrics and congenital heart disease. *Pediatric cardiology*. 2015;36(4):821-6.
41. de Asmundis C, Ricciardi D, Namdar M, Chierchia GB, Sarkozy A, Brugada P. Role of home monitoring in children with implantable cardioverter defibrillators for Brugada syndrome. *Europace*. 2013;15 Suppl 1:i17-i25.
42. Malloy LE, Gingerich J, Olson MD, Atkins DL. Remote monitoring of cardiovascular implantable devices in the pediatric population improves detection of adverse events. *Pediatric cardiology*. 2014;35(2):301-6.
43. Dechert BE, Bradley DJ, Serwer GA, Dick M, 2nd, LaPage MJ. Frequency of CIED remote monitoring: A quality improvement follow-up study. *Pacing Clin Electrophysiol*. 2019;42(7):959-62.
44. Tsao S. What is the optimal remote monitoring schedule in pediatric patients with cardiovascular implantable electronic devices? *Pacing Clin Electrophysiol*. 2019;42(7):963-4.

