Prevention of sudden cardiac death in adults with congenital heart disease

Vehmeijer, J.T.

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1. Introduction and outline

**GENERAL INTRODUCTION**

**Congenital heart disease**

The heart is an organ with one seemingly simple function: pumping blood to the lungs and to the rest of the body. However, in order for this mechanism to work, all of the components need to be built with absolute precision, without any leaks or failures. For example, it is highly important to separate the oxygen-poor blood entering the heart on the right side from the oxygen-rich blood being pumped out by the left ventricle. Failure to do so would lead to an inefficient mix of oxygen-rich and oxygen-poor blood to be transported to the rest of the body. Additionally, the relatively weak right side of the heart and circulatory system would be exposed to pressures that only the muscular left side of the heart can withstand. Many critical steps need to occur in exactly the right order at exactly the right time in the embryonic stage for the heart to develop normally. Therefore, it is not very surprising that normal development is not always the case, and congenital heart defects may occur (Figure). 0.8% to 1.6% of all new-born babies are affected by congenital heart defects. These range from simple defects, such as a small atrial septum defect, to complex defects, for example, a single ventricle connected to both the pulmonary artery and the aorta. Decades ago, about 80% of children born with a congenital heart defect passed away during infancy or childhood. Since then, there has been formidable improvement in the detection of congenital heart defects, as well as surgical and medical management of these patients. This has led to survival of the vast majority (~90%) of patients with a congenital heart disease to adulthood. Therefore, a rapid increase in the population of adult congenital heart disease (ACHD) patients is in progress, particularly among patients with severe defects, who would have not survived several decades ago.

**Cardiac arrhythmias and sudden cardiac death**

ACHD patients are at risk of long-term complications. Although the initial congenital defect may be repaired successfully, many patients will need repeated surgical or interventional treatment, for example due to remaining defects or slowly worsening valve stenosis or regurgitation. Additionally, ACHD patients are growing older and are becoming more at risk of ventricular dysfunction and coronary events. A possible consequence of a congenital heart defect, its repair or these complications may be cardiac arrhythmia, which is common in ACHD patients. An important reason for this is that surgical atrial and ventricular scars are a substrate for re-entry, which in turn is a mechanism by which cardiac arrhythmias can occur. Additionally, increased filling pressures, heart failure, ischemic stress, fibrosis and cyanosis also play an important role in the occurrence of cardiac arrhythmias.
Cardiac arrhythmias can be classified according to their location: when located in the atria, arrhythmias are considered mostly benign. However, arrhythmias located in the ventricles, i.e. ventricular tachycardia (VT) or ventricular fibrillation (VF), can cause the mechanical action of the heart to cease entirely: cardiac arrest. This often occurs at home or at other locations outside of the hospital (out-of-hospital cardiac arrest, OHCA). Patients with OHCA need immediate cardiopulmonary resuscitation and often need defibrillation for VT or VF. Many studies have provided data on causes of OHCA and survival in the general population.\(^{26,27}\) However, not much is known of these parameters for ACHD patients with an ICD.

Sudden cardiac death (SCD), usually caused by VT or VF, is defined as an unexpected natural death from a cardiac cause within one hour after onset of symptoms. SCD is one of the most common causes of death in ACHD patients. It accounts for about 20-40% of all deaths in these patients.\(^{14,19,28-33}\) Likewise, up to 20% of all SCDs in young persons, i.e. those below the age of 35 years, is due to congenital heart disease.\(^{34-36}\)

**Implantable cardioverter-defibrillator**

The implantable cardioverter-defibrillator (ICD) was designed to prevent SCD by delivering a life-saving electrical shock to terminate VT or VF. In patients with ischemic or non-ischemic cardiomyopathy, the ICD has been widely used for primary prevention of SCD, i.e. before any sustained VT or VF has been documented.\(^{37,38}\) Similarly, ICDs are used for primary prevention of SCD in hypertrophic cardiomyopathy and Brugada syndrome.\(^{39,40}\)

In ACHD patients, beneficial effects of the ICD have been described in the form of appropriate shocks, likely saving many lives. However, ICD implantation in ACHD patients is also plagued by a high risk of complications, such as pneumothorax, lead failure and infections. In addition, the rate of inappropriate shocks, e.g. for non-life-threatening arrhythmia, appears to be high in ACHD patients. Many studies have described these potential beneficial and adverse effects, but a clear overall picture has thus far not been published.\(^{13,21,41-45}\)

**Risk stratification for sudden cardiac death in adults with congenital heart disease**

Because the risk of SCD is very high in patients who have survived sustained VT or VF without a treatable or reversible cause, the choice for ICD implantation for secondary prevention may be self-evident.\(^{13,21,42,45}\) Thus, ICD implantation for secondary prevention is widely recommended in for AHCD patients in consensus documents and international guidelines.\(^{18,46-48}\)
However, prediction of SCD before any ventricular arrhythmia has occurred remains very difficult, and as a result, ICD implantation in ACHD patients for primary prevention of SCD is infrequently performed. The AHCD population is highly heterogeneous and the risk of sudden cardiac death varies greatly per congenital defect. As mentioned before, many different mechanisms are responsible for SCD. Therefore, risk stratification for SCD is often based upon multiple risk factors. Systemic systolic ventricular function, heart failure symptoms and QRS prolongation have been described as risk factors for SCD most often. \(^{13,15,19-21,28}\)

In a 2012 study, Koyak et al. described a large cohort of ACHD patients who died of SCD and compared their risk factors to living control patients matched by age, gender, congenital defect and surgical procedure.\(^{28}\) In that study, subpulmonary systolic ventricular dysfunction, atrial arrhythmias, coronary artery disease, QRS-prolongation and QT-dispersion were also found significantly more often in SCD cases than in living control patients. A part of this thesis builds on the findings of the study by Koyak et al. and the risk factors described therein. However, it remains essential to discover new risk factors associated with SCD in order to refine risk stratification. This is a challenge, as data from many of the current state-of-the-art medical examinations are lacking in patients who died from SCD. For example, MRI data could provide more precise measurement of ventricular ejection fractions and scar burden.\(^{49}\) Since such data is often not available, derivatives from examinations that are widely available, for example ECG and echocardiogram, must be used to provide measurements for risk stratification.
**THESIS OUTLINE**

*Part 1: the impending issue: what are the outcomes of ACHD patients without an ICD (those with out-of-hospital cardiac arrest), and on the other hand, those with an ICD implanted, and thirdly, how well can we currently predict SCD?*

The aim of **chapter 2** is to examine the causes and outcomes of ACHD patients who are resuscitated because of OHCA. In **chapter 3**, a systematic review and meta-analysis is described encompassing all known data on ICD implantation in ACHD patients. In **chapter 4**, the current criteria for ICD implantation for primary prevention of SCD are discussed. Then, these criteria are tested in **chapter 5** by establishing whether patients who died of SCD would have been identified as ICD candidates based on their risk factors prior to death, compared to living control patients.

*Part 2: improving risk stratification for sudden cardiac death: chapter 6 describes a new risk score model to predict SCD in ACHD patients as well as the design for the study to validate this risk score model (PREVENTION-ACHD), and in **chapter 7**, the results of PREVENTION-ACHD are shown.***

*Part 3: exploring new risk factors: the aim of **chapter 8** and **chapter 9** are to explore the association of two new risk factors with SCD in ACHD patients, namely fragmented QRS complexes and the Tpeak-Tend interval, respectively.*
REFERENCES


18. Khairy P, Van Hare GF, Balaji S, et al. PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology (ACC), the American Heart Association (AHA), the European Heart Rhythm Association (EHRA), the Canadian Heart Rhythm Society (CHRAS), and the International Society for Adult Congenital Heart Disease (ISACHD). *Heart Rhythm.* 2014;11(10):e102-165.


