Outcome after cardiopulmonary resuscitation in patients with congenital heart disease

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Abstract

Background: Outcome after cardiopulmonary resuscitation (CPR) in patients with underlying congenital heart disease is uncertain. This study aimed at evaluating outcome after CPR in patients with underlying congenital heart disease, factors related to worse outcome after CPR and whether survivors of sudden cardiac death (SCD) have a worse outcome when compared to an age, gender and disease-matched control population.

Methods: Between 1984 and 2015, all patients with congenital heart disease who received in or out-of-hospital CPR were identified from the database of congenital heart disease from the University Hospitals Leuven. Postoperative and neonatal (<6 months of age) CPR was excluded. For each survivor of SCD, two control patients matched for gender, age and underlying heart defect were included in the study.

Results: Thirty-eight patients (66% men; median age 25 years (interquartile range 9–40); 68% out-of-hospital) were identified, of which 27 (66%) survived the event. The main cause of SCD was ventricular tachycardia or fibrillation (n=21). Heart defect complexity (odds ratio (OR) 5.1; 95% confidence interval (CI) 1.2–21.9; P=0.027), pulmonary hypertension (OR 13.8; 95% CI 2.1–89.5; P=0.006) and time to return of spontaneous circulation (OR 1.1; 95% CI 1.0–1.1; P=0.046) were related to worse outcome. Survivors of SCD had a worse prognosis when compared to an age, gender and disease-matched control group (5-year survival 76% vs. 98%; P=0.002).

Conclusions: The complexity of underlying heart defect, pulmonary hypertension and time to return of spontaneous circulation are related to worse outcome in the case of CPR. Survivors of SCD have a worse outcome when compared to matched controls, indicating the need for adequate implantable cardioverter defibrillator indication assessment and for stringent follow-up of patients with worsening haemodynamics.

Keywords

Congenital heart disease, cardiopulmonary resuscitation, sudden cardiac death, outcome

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Introduction

The overall survival of patients with congenital heart disease has improved dramatically due to advances in cardiac surgery, intensive care and diagnostic capabilities, with 88% of children surviving into adulthood.¹ However, sudden cardiac death (SCD) remains an important concern in patients with congenital heart disease. Although the annual incidence of SCD in the congenital heart disease population is low (0.09% per year), it is higher when compared to age-matched controls,² and constitutes an important cause of
Previous studies have identified risk factors for SCD for the adult congenital heart disease population, or subpopulations such as patients with tetralogy of Fallot (ToF) or transposition of the great arteries (TGA), but there is little information on the outcome of cardiopulmonary resuscitation (CPR) in this group of patients.

Even if CPR is initiated in the case of a cardiac arrest, outcome remains poor, with 17.6% of patients surviving in the case of in-hospital cardiac arrest, but only 7.6% in the case of out-of-hospital cardiac arrest (OHCA). In non-congenital heart disease patients, it has been shown that long-term survival after OHCA is similar to age, gender and disease-matched patients.

Therefore, this study aimed at evaluating outcome after CPR in patients with underlying congenital heart disease, factors related to worse outcome after CPR, and outcome of survivors of SCD when compared to an age, gender and disease-matched control population.

Methods

Patient population

This was a single-centre, retrospective study. All congenital heart disease patients who received in or out-of-hospital CPR between 1984 and 2015 were identified from the database of Congenital and Structural Cardiology at the University Hospitals Leuven. SCD was defined as sudden loss of consciousness with either documented underlying arrhythmic cause or loss of pulse without arrhythmia. Congenital heart disease was defined as a structural abnormality of the heart or intrathoracic great vessels with actual or potential functional significance. Patients who were diagnosed with cardiomyopathy or arrhythmia without structural abnormality were excluded from the analysis. Patients who received CPR in the neonatal period (before 6 months of age) or in the perioperative period of cardiac surgery were also excluded. The study complies with the Declaration of Helsinki and was approved by both the medical ethics committee of the University Hospitals Leuven and by the medical ethics committee of the University of Leuven.

Data collection

Demographic data, medical history (type of congenital heart defect, presence of pulmonary hypertension), first-recorded cardiac rhythm at event, pre-hospital management and intensive care unit (ICU) admission were reviewed from the patients’ medical records. Date of death, reason of death and data of the last out or inpatient visit censored at 31 December 2015 were extracted from the database.

Patients were classified according to the complexity of their underlying congenital heart defect as outlined by Task Force 1 of the 32nd Bethesda Conference. Early mortality was defined as any death occurring within the first 30 days after presentation or an in-hospital death occurring more than 30 days after presentation but during the first admission. Late mortality was defined as any death occurring later than 30 days after presentation and occurring after the first hospital admission. For each included patient who survived until discharge, two controls without prior SCD were matched for age (plus or minus 5 years as compared to corresponding case), gender and underlying congenital heart defect. Controls were randomly selected from the database of Congenital and Structural Cardiology at the University Hospitals Leuven.

Statistical analysis

Data analyses were performed using SPSS software for Mac (22.0 for Mac; SPSS Inc., Chicago, IL, USA). For all analyses, a two-tailed P value less than 0.05 was considered statistically significant. Continuous variables are presented by means and standard deviations or, in the case of serious deviations from the normal assumption, by medians and ranges. Categorical variables are presented using observed frequencies and percentages relative to the total number of non-missing data points. When frequencies and means were compared across subgroups, one-way analysis of variance with Tukey’s post-hoc test and Fisher’s exact test were performed. To identify variables related to inhospital mortality, univariate binary logistic regression analysis was performed. No multivariate analysis was performed because of the small number of patients. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). For each survivor of SCD, two control patients were identified and matched to: age (+– 5 years of age) at the time of the event; gender; and underlying heart defect. Controls were randomly selected in the database of Congenital and Structural Cardiology. Kaplan–Meier analysis and log-rank testing was performed to compare the outcome of survivors of SCD with a matched control population.

Results

Patient selection

The initial search of the database of Congenital and Structural Cardiology yielded a total of 113 patients. At initial review, 54 patients were excluded. Reasons for exclusion were a morphologically normal heart (n=35), cardiomyopathy without structural abnormality (n=12), presentation at less than 6 months of age (n=6) or a cardiac tumour without associated congenital heart disease (n=1). The patient files of the remaining 59 patients were reviewed and an additional 21 patients were excluded from further analysis because the event occurred in the perioperative period of cardiac surgery (n=18) or because the circumstances of the CPR were unclear (n=3). A total of 38 patients remained for final analysis. The study selection process is depicted in Figure 1.
Patient characteristics

Overall, the median age at resuscitation was 25 years (interquartile range (IQR) 9–40). Twenty-five patients (66%) were men. Four patients (3%) had mild, 18 (48%) moderate and 16 (42%) severe complexity of the underlying congenital heart defect. The median age at resuscitation for each category of severity was 19 (IQR 5–37), 28 (IQR 8–44) and 25 (IQR 10–39) years, respectively. Eight patients (21%) had pulmonary hypertension. Echocardiographic data in the year before the event were available in 16 patients (42%). Five had moderately reduced systolic ventricular function and two had severely reduced systolic ventricular function. For two patients (5.3%), SCD was the first manifestation of their underlying congenital heart defect. Eleven patients (30%) presented with SCD between years 1984 and 2000 and 27 patients (70%) after year 2000. Patients with more severe congenital heart disease were more likely to have pulmonary hypertension ($P=0.021$). Additional demographic data stratified for the severity of underlying congenital heart disease are presented in Table 1.

Event characteristics

In 35 patients (92%) the cardiac arrest was considered to be of primary cardiac nature. In three patients requiring CPR, the immediate cause of arrest was non-cardiac. One occurred in the setting of a severe gastrointestinal bleed, one was related to hypoxia after aspiration and one occurred during an anaphylactic reaction.

Rhythm documentation was available in 29 patients (76%) and showed ventricular fibrillation in 18 (62%), pulseless electrical activity in five (17%), ventricular tachycardia in three (10%), supraventricular tachycardia in two (7%) and asystole in one (3%) (Table 2).

Twenty-one (68%) patients experienced an OHCA. Of those presenting with OHCA, 15 (71%) received bystander CPR and 18 (86%) received advanced life support. One patient did not receive any life support prehospital. The median time to return of spontaneous circulation (ROSC) was 23 minutes (IQR 15–34). This is longer, but not statistically different, from patients with inhospital cardiac arrest (median 10 minutes (IQR 4–41); $P=0.330$).

Overall, 23 (79%) patients presented with a shockable rhythm, of which 13 (57%) received one or more direct current (DC) shocks. When applied, the median number of DC shocks was three (IQR 1–5). Fourteen patients (64%) were administered at least one shot of epinephrine and five patients (23%) received atropine. Twenty patients (69%) were admitted to the (cardiac) ICU. Twenty-two patients (79%) required intubation and mechanical ventilation. Two patients (7%) received extracorporeal membrane oxygenation. Twelve patients (44%) were transferred to our hospital from a secondary care centre for further management. There was no patient with significant coronary artery disease. Additional event characteristics stratified for the severity of congenital heart disease can be seen in Table 3.

Outcome: early mortality

Of 38 patients included, 25 patients (66%) survived until hospital discharge. Of those 25 patients, five patients died over a median follow-up time of 3 years (IQR 1–8). Outcome data were missing in two patients. Twelve patients

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**Figure 1.** Flow diaphragm depicting patient selection process. *Four patients with long QT-syndrome, one with Wolff–Parkinson–White syndrome and one with automated atrial ectopic tachycardia. CPR: cardiopulmonary resuscitation.*
received an implantable cardioverter defibrillator (ICD) after the event. The median age at ICD implantation was 38 years (IQR 18–44). Of 13 survivors who did not receive an ICD, seven had a reversible risk factor for cardiac arrest, two collapsed due to atrial arrhythmia, two patients had cardiac arrest in the early ICD era and for two patients the reason to withhold ICD were unclear from the charts.

Univariate binary logistic regression analysis showed that the complexity of the underlying heart defect (OR 5.1; 95% CI 1.2–21.9; \(P=0.027\)), pulmonary hypertension (OR 13.8; 95% CI 2.1–89.5; \(P=0.006\)) and time to ROSC (OR 1.1; 95% CI 1.0–1.1; \(P=0.046\)) were related to worse survival (Table 4 and Figure 2(a)).

There was no difference in early mortality between children and adults (21% vs. 36%; \(P=0.467\)) or according to the event happening before or after the year 2000 (30% vs. 31%, \(P=1.000\)).

Outcome: late mortality

For 25 survivors of SCD, 48 suitable age, disease and gender-matched controls were identified. For one patient, we were unable to identify a suitable matched control and this patient was therefore excluded from further analysis. This patient was an 8-year-old girl with mitral valve dysplasia and severe mitral valve regurgitation who survived after cardiac arrest due to ventricular fibrillation. She died 2 years later from sudden death. Survivors of SCD had a worse survival when compared to controls (5-year survival 76% vs. 98%; \(P=0.002\)) (Figure 2(b)).

Discussion

This study described patient and event characteristics of congenital heart disease patients requiring CPR. Overall,
early mortality was 34% and was mainly related to the severity of the underlying congenital heart disease, the presence of pulmonary hypertension and time to ROSC. Moreover, the long-term outcome of survivors of SCD is worse when compared to an age, gender and disease-matched control population.

### Patient and event characteristics

The underlying congenital heart defects of patients who received CPR in this study were similar to previous reports on SCD in congenital heart disease, with the majority of patients having moderate or severe congenital heart disease. Previous studies have identified risk factors for SCD in subpopulations such as ToF (age, number and type of surgeries, QRS duration, pulmonary regurgitation, left ventricular dysfunction) or patients with a systemic right ventricle (history of atrial arrhythmia, systemic ventricular dysfunction/history of heart failure). In patients with univentricular physiology, SCD accounts for 9% of late deaths but no predictors have been identified. Surprisingly, four patients who required CPR had underlying septal defect lesions in which ventricular arrhythmias would be considered uncommon.

The majority of patients were men (66%). A male majority is often seen in SCD studies and has been explained by...
by an increased risk of ischaemia in men.\textsuperscript{21} However, the male predominance in our study is explained by the high male-to-female ratio in patients with complex congenital heart disease (hypoplastic left heart syndrome, TGA and ToF) as compared to patients with mild congenital heart disease.\textsuperscript{23} Our patients were also on average 30–40 years younger than patients included in resuscitation trials,\textsuperscript{15,16,19–22} stressing the need to be aware of and look for risk factors associated with SCD, even at a young age.

In those patients with rhythm documentation, 79% presented with a shockable rhythm, which is different from the general population.\textsuperscript{16–22} It should be noted that supraventricular tachycardia in patients with TGA who underwent atrial rerouting (Mustard or Senning repair) or patients with univentricular physiology is not well tolerated as the absence of atria as a capacitance chamber,\textsuperscript{24} or the absence of a subpulmonary ventricle\textsuperscript{25} will limit ventricular filling, decrease cardiac output and may eventually cause cardiac arrest. Primary ventricular arrhythmia is a possible, but rare, cause of SCD in patients with univentricular physiology.\textsuperscript{14}

**Early mortality**

Whereas previous reports primarily focused on the identification of predictors of SCD in patients with congenital heart disease,\textsuperscript{2,4,5} to the best of our knowledge, this is the first study to evaluate the outcome of CPR in patients with structural heart defects.

The main aim of CPR is to provide adequate stroke volume with chest compressions in order to maintain coronary perfusion, pulmonary blood flow and cerebral perfusion. In patients with underlying heart defects, the maintenance of stroke volume during CPR may be far more difficult and determinants of prognosis after CPR may be related to the complexity of the underlying heart defect.\textsuperscript{26,27} Our data do indicate a relationship with the complexity of the underlying heart defect, which appears to be driven by the presence of pulmonary hypertension. A high pulmonary vascular resistance limiting adequate pulmonary blood flow and poor right ventricular coronary perfusion may explain the poor results of CPR in patients with pulmonary hypertension. This confirms a previous report evaluating CPR in patients with pulmonary arterial hypertension in which only six of 132 patients with pulmonary arterial hypertension in whom CPR was instituted survived more than 90 days.\textsuperscript{28} Similarly, one may suggest that effective CPR is complicated in univentricular physiology because there is no equivalent for the atrioventricular valves to prevent retrograde flow to the caval system when the subpulmonary system is being compressed. However, there was no relationship between univentricular heart and outcome in our series. Nevertheless, it is surprising that, overall, early mortality was still lower when compared to data in the general population.\textsuperscript{15–22} Presumably this is explained by a younger age, fewer comorbidities, and a higher proportion of shockable rhythms at the time of presentation in our population, all of which have been associated with better outcomes.\textsuperscript{15,16,19} Other factors that may have contributed are awareness of the presence of an underlying heart defect, leading to early initiation of CPR either in hospital (with the patient being followed more closely) or out-of-hospital (with more awareness among family members).

Although none of our patients had evidence of coronary artery disease, it is important that with an aging population, coronary artery disease should be considered. As worsening underlying haemodynamics may play a role, all patients should undergo careful haemodynamic evaluation.

**Late mortality**

In patients without structural heart defects, long-term survival after SCD is similar when compared to an age, gender

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**Figure 2.** (a) Kaplan–Meier indicating survival in patients with congenital heart disease and cardiopulmonary resuscitation for sudden cardiac death (SCD) stratified according to the severity of the underlying congenital heart defect. Patients with severe complexity of underlying congenital heart disease had worse survival, which is mainly related to early mortality. When censoring the initial hospitalisation, there is no significant difference between the two groups ($P=0.824$ by log-rank test). (blue: mild/moderate complexity – green: severe complexity). (b) Kaplan–Meier indicating worse long-term event-free survival in survivors of SCD when compared to age, gender and disease-matched controls. (blue: survivors of SCD; green: age, gender and disease-matched controls).
Table 5. Characteristics of patients who died after survival of initial cardiac arrest.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Original anatomy</th>
<th>Cardiac arrest</th>
<th>Cause of death</th>
<th>Survival time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Male, 10 months</td>
<td>Coarctation of the aorta, aortic stenosis</td>
<td>Initial rhythm: ventricular fibrillation</td>
<td>Unknown</td>
<td>662 days</td>
</tr>
<tr>
<td>2. Male, 17 years</td>
<td>Double inlet left ventricle, transposition of the great arteries, ventricular septal defect, aortic stenosis</td>
<td>Initial rhythm: atrial fibrillation</td>
<td>Postoperative orthotopic heart transplantation</td>
<td>2211 days</td>
</tr>
<tr>
<td>3. Female, 8 years</td>
<td>Mitral insufficiency due to dysplastic mitral valve, pulmonary hypertension</td>
<td>Initial rhythm: ventricular fibrillation</td>
<td>Sudden death, initial rhythm unknown</td>
<td>659 days</td>
</tr>
<tr>
<td>4. Male, 23 years</td>
<td>Univentricular heart, tricuspid atresia, pulmonary stenosis, transposition of the great arteries, ventricular septal defect</td>
<td>Initial rhythm: ventricular fibrillation</td>
<td>Sudden death, initial rhythm unknown</td>
<td>1106 days</td>
</tr>
<tr>
<td>5. Male, 40 years</td>
<td>Perimembranous ventricular septal defect, right-sided aortic arch</td>
<td>Initial rhythm: ventricular fibrillation</td>
<td>Sudden death, ICD failure (guidant vitality 2 VR (T175))</td>
<td>3324 days</td>
</tr>
</tbody>
</table>

ICD: implantable cardioverter defibrillator.

and disease-matched control population. In contrast, our study indicates that congenital heart disease patients have a worse prognosis after SCD when compared to an age, gender and disease-matched control population with a 5-year survival of 76% (versus 98% for matched controls). So, although the success rate of CPR may be higher, there is ongoing mortality after the index event. It could be that there is less reserve cardiac capacity to shoulder the damage attained after a cardiac arrest in congenital heart disease due to the degree of cardiac dysfunction already present. Moreover, sustained damage after cardiac arrest could stimulate arrhythmogenesis and therefore predispose for the recurrence of SCD. Unfortunately, we had little information on the cause of death after discharge after cardiac arrest for the patients in our study (Table 5). Because of the abrupt nature of most deaths in our patients we can suspect that the recurrence of arrhythmia was a major contributor to late mortality. This information supports the consensus recommendation that ICD placement is indicated in secondary prevention for patients with congenital heart disease. In our centre, every patient with congenital heart disease who had aborted SCD is evaluated to determine the exact cause of the event. An ICD in secondary prevention is implanted when no reversible cause for the event can be identified. In some patients, the event is a reflection of worsening haemodynamics and the occurrence of heart failure. Although implantation of an ICD will protect the patient from ventricular arrhythmias, it will not protect the patient from worsening heart failure. Therefore, close follow-up and timely consideration of advanced heart failure options is indicated.

**Limitations**

Our study has the following limitations. First, the study was based on retrospective registry data with the risk of missing data. Second, the study was a single-centre tertiary care study. This introduces the risk of referral bias with overrepresentation of complex congenital heart disease due to mild cases being handled in secondary care centres without them being referred to us. Although patient data in the database is regularly updated, there is a risk of selection bias as some patients with OHCA admitted to other hospitals are missed. Third, only data on survival after SCD were assessed and not on more advanced outcome measures so we cannot comment on the general state of patients after SCD. Fourth, we did not include patients without structural heart disease in the analysis. The database of Congenital and Structural Cardiology of the University Hospitals Leuven is maintained by the paediatric cardiology and adult congenital cardiology department. Adult patients without structural heart disease are not included in the data-base and therefore including patients without structural heart disease would have introduced a significant bias. Fifth, due to the relative rarity of SCD in congenital heart disease patients, our study population was small, which means a lack of power to demonstrate variables with a lower relative risk of early mortality. This also illustrates the need to create a larger, multicentre database on SCD in congenital heart disease in order to answer some of the emerging questions in this growing patient population.

**Conclusion**

The complexity of underlying heart defect, especially pulmonary hypertension and time to ROSC are related to worse outcomes in the case of CPR. Survivors of SCD have a worse outcome when compared to matched controls, indicating the need for adequate ICD indication assessment and for stringent follow-up of patients with worsening haemodynamics.

**Conflict of interest**

The authors declare that there are no conflicts of interest.

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