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Cause of death in adults with congenital heart disease — An analysis of the German National Register for Congenital Heart Defects

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ABSTRACT

Background: Due to the great advances in the care of patients with congenital heart disease (CHD), mortality has decreased significantly over the last decades. Nonetheless, mortality for adults with congenital heart disease (ACHD) is still higher than for the general population. An analysis regarding causes of death in a nationwide contemporary cohort of ACHD is lacking.
Methods: A well-characterized cohort of the German National Register for Congenital Heart Defects was screened for patients over the age of 18 years who died between January 2001 and January 2015. Data relating to the cardiac diagnosis, symptoms, operations, interventions, comorbidities, and causes of death were analyzed.
Results: During a median follow-up of 3.67 years (IQR 1.32–9.41), 239 (9.2%) out of 2596 patients died during the study period (110 female (46%), mean age at death 39.8 ± 17.8 years). The majority of these deaths was CHD-related (171 patients (71.5%)). Leading causes of death were heart failure (n = 66, 27.6%), and sudden cardiac death (n = 55, 23.0%). Deceased patients had a more complex CHD and more extracardiac comorbidities compared with living patients.
Conclusions: Causes of death of ACHD patients in a large contemporary cohort from a national register are in the majority still CHD-related, with heart failure being the leading cause of death. Additionally, extracardiac comorbidities gain increasing importance.

1. Introduction

Due to the great advances in pediatric cardiology, cardiac surgery and intensive care medicine the mortality of patients with congenital heart disease (CHD) has decreased significantly over the last decades. Thus, more patients with CHD enter adulthood [1–3]. But a cure can rarely be achieved, while residua and sequela are common. Despite continuous improvements and success in the treatment of CHD, the mortality in adults with congenital heart disease (ACHD) is still higher than in the general population [4,5]. To further improve the long-term outcome of this patient cohort, a contemporary analysis of the causes of death is needed. Previous studies have investigated the causes of death in ACHD, but were either single center studies or focused on historic patient cohorts that do not resemble the contemporary cohort of ACHD [4,6].

The aim of the current study is to investigate the causes of death in a nationwide contemporary cohort of ACHD.

2. Methods

The German National Register for Congenital Heart Defects provides a nationwide data base with a uniquely large population of patients with congenital heart disease not primarily gathered by tertiary referral centers but rather representing the community based population. This study is based on a well-characterized sample cohort from this register consisting of 2596 patients over the age of 18 years. All patients who died between January 2001 and January 2015 were identified. The diagnosis of congenital heart disease was based on echocardiography, cardiovascular magnetic resonance, or cardiac catheterization data in all

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patients. Patients with a patent foramen ovale as the only finding (not representing CHD) were excluded, as well as patients with cardiomyopathies and congenital arrhythmias without any structural changes. Data on age, gender, cardiac and extracardiac diagnosis, New York Heart Association (NYHA) functional class, and cause of death were retrieved from medical reports. Complexity of cardiac lesions was classified according to the Bethesda classification [7].

For the purpose of this study, cyanosis was defined as a resting oxygen saturation of <90%. History of arrhythmia encompasses any type of supraventricular or ventricular arrhythmia requiring therapy. Lung disease includes any form of lung disease (asthma, chronic obstructive lung disease, emphysema, etc.) and patients with diabetes include both insulin-dependent and non-insulin-dependent cases.

The surgical history was categorized in five groups: 1. no cardiac surgery; 2. surgical repair, defined as a major modification of the CHD such as closure of a shunt (atrial/ventricular), valve replacement, operation for aortic coarctation and anatomic correction, e.g. in Tetralogy of Fallot or arterial switch for transposition of the great arteries (TGA); 3. palliative surgery, defined as operations that improve symptoms without any anatomic correction, e.g. Blalock–Taussig shunts; 4. Fontan operation leading to univentricular physiology; and 5. heart/lung transplantations.

Percutaneous interventions were categorized into four groups: 1. intervention for the left ventricular outflow tract (LVOT) including interventions for coarctation of the aorta; 2. intervention for the right ventricular outflow tract (RVOT) including transcatheter pulmonary valve replacement; 3. intervention for the closure of shunts; and 4. miscellaneous (e.g. balloon atrial septostomy).

Information on the cause of death was retrieved from the medical records. If the cause of death was not available from the medical records, we contacted family care practitioners to obtain further information on the cause of death. The different causes of death were categorized in CHD-related and non CHD-related. CHD-related death included perioperative death that is defined as intraoperative death or death within 30 days from index cardiac surgery or during same admission of any duration. Further causes for CHD-related death included progressive heart failure, which was defined as death due to progressive myocardial failure of either the systemic or pulmonary ventricle [6,8]. Sudden cardiac death was defined as previously described as death within 1 h of the patient's usual state of health or unwitnessed death during sleep [6,8]. Further CHD-related causes of death were complications arising after heart/lung transplantation, e.g. infections or acute rejection.

Non CHD-related causes of death were due to malignancies, infections (non-CHD related), thromboembolic events, lung diseases as COPD, and neurological events.

Furthermore, taking into account the progress made during the study period in the treatment of CHD patients (e.g. implantable defibrillator therapy) two time periods were analyzed in more detail: January 2001–December 2008, and January 2009–January 2015.

Approval by the appropriate Ethics Committee was obtained.

2.1. Statistics

Statistical analyses were performed using SPSS version 22 (IBM, USA). Continuous variables are presented as mean ± standard deviation or median (interquartile range), whereas categorical variables are presented as number (percentage). Comparison between groups was performed using the Mann–Whitney U test or Student's *t*-test for continuous and Chi-square test for categorical variables. All tests were performed two-sided and for all analyses, a p-value <0.05 was considered statistically significant.

3. Results

During a median follow-up of 3.67 years (IQR 1.32–9.41; corresponding to a total of 14,114 patient-years), 239 out of 2596 patients died during the study period (129 male (54%) and 110 female (46%), mean age at death 39.8 ± 17.8 years). This yields a mortality rate of 1.7 per hundred patient-years.

There was a significant difference regarding the complexity of the CHD and comorbidities between patients who died and those who were alive (Table 1).

Alive patients had in the majority a CHD of moderate complexity (52.9%), while deceased patients had in the majority of cases a severe CHD (59.8%). Furthermore, deceased patients had significantly more extracardiac comorbidities (Table 1).

A congenital syndrome was present in 150 (6.4%) of alive patients (Down syndrome in 113, micro-deletion syndrome 22q11 in 19, Williams–Beuren syndrome in 7, Noonan syndrome in 6, and Turner syndrome in 5), and in 33 (13.8%) of deceased patients (Down syndrome in 24, micro-deletion syndrome 22q11 in 4, miscellaneous in 5). The difference was statistically significant ($p < 0.001$).

Regarding causes of death, 171 patients (71.5%) died CHD-related, 43 patients (18.0%) died non-CHD related, and in 25 patients (10.5%) no information regarding the cause of death was available (Fig. 1, Table 2).

The most common cause of CHD-related death was progressive heart failure (n = 66, 27.6%), followed by sudden cardiac death (n = 55, 23.0%). Perioperative death occurred in 16.3% (n = 39) of patients. Out of these 79.5% occurred during a reoperation. Causes of perioperative deaths were sepsis (n = 10, 4.2%), heart failure (n = 16, 6.7%), hemorrhage (n = 8, 3.3%), brain damage (n = 3, 1.3%) and acute rejection after transplantation (n = 2, 0.8%). Further causes for CHD-related death included infection (n = 7, 2.9%), and hemorrhage and rejection after transplantation (n = 4, 1.7%).

Non CHD-related causes of death were due to malignancies (n = 12, 5.0%), infections (n = 6, 2.5%), perioperative (non-cardiac surgery) (n = 3, 1.3%) and other causes (n = 22, 9.2%) like complications of lung diseases, and neurological events.

There was a significant difference between the mean age at death between patients who died CHD-related (34.5 ± 13.1 years) and those who died non CHD-related (57.6 ± 20.5 years, $p < 0.001$).

The majority of the deceased patients had severe CHD (n = 143 (59.8%)). There were 63 patients with moderate CHD (26.4%) and 28 with simple CHD (11.7%). Other defects (not categorized in the Bethesda classification) [7] were present in 5 patients (3 with a Marfan syndrome, 1 anomalous left coronary artery origin from pulmonary artery, 1 cor triatriatrum sinistrum). Patients with CHD-related death had a more complex defect compared to patients with non CHD-related death ($p < 0.001$, Table 2).

Overall, 63 patients were in NYHA class I or II (26.4%), and 156 in NYHA class III or IV (65.3%). In 20 patients (8.4%) information regarding NYHA class was not available. Severe heart failure (NYHA class III/IV)

Table 1
Demographics and baseline characteristics.

	Alive n (%)	Deceased n (%)	p
All	2357	239	
Age (years)	33.4 ± 13.1	39.8 ± 17.8	<0.001
Male	1143 (48.5%)	129 (54.0%)	n.s.
Female	1214 (51.5%)	110 (46.0%)	
Complexity of CHD			
Simple	461 (19.6%)	28 (11.7%)	
Moderate	1248 (52.9%)	63 (26.4%)	<0.001
Severe	574 (24.4%)	143 (59.8%)	
Others	74 (3.1%)	5 (2.1%)	
Lung disease	115 (4.9%)	44 (18.4%)	<0.001
Liver disease	34 (1.4%)	15 (6.3%)	<0.001
Diabetes	58 (2.5%)	10 (4.2%)	n.s.
Renal disease	74 (3.1%)	50 (20.9%)	<0.001
Syndrome	150 (6.4%)	33 (13.8%)	<0.001

Others: Marfan syndrome, anomalous left coronary artery origin from pulmonary artery, cor triatriatum sinistrum.