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Circumstances of death in adult congenital heart disease

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ABSTRACT

Background: Circumstances of death have been described for various cardiovascular diseases, but this study is the first for adults with congenital heart disease (CHD).
Methods: Review of medical records and additional information from treating cardiologists and general practitioners, for circumstances of all deaths in a national registry of over 8000 adults with CHD.
Results: Of 8595 patients, 231 (2.7%) patients died over 26,500 patient years. Main causes of death were progressive heart failure (26%) and sudden cardiac death (22%). Mortality was highest in the northern, most rural region of the country ($p \leq 0.05$). Overall, death occurred out-of-hospital in approximately 35%, but more frequently in rural than in urban areas (55% versus 32%, $p \leq 0.05$). Mortality was almost equally distributed throughout the seasons, although fall showed a slightly higher mortality rate. Cardiovascular death occurred suddenly in nearly 40%. Sudden cardiovascular death occurred in 8% during exercise, and most often out-of-hospital (62%). Of non-sudden cardiovascular deaths 18% had occurred out-of-hospital.
Conclusion: In adult patients with congenital heart disease, mortality shows substantial regional and subtle seasonal variation. Death usually occurs at rest; approximately 1 of 10 sudden cardiovascular deaths occur during exercise.

1. Introduction

An increasing number of patients with congenital heart disease (CHD) reach adulthood due to improved developments in paediatric cardiology, cardiac surgery and thorough monitoring [1]. However, high morbidity and premature death in adulthood have often been described [2–6]. Yet, little is known about the circumstances and modes of death in these patients.

Several studies have described regional, weekly and/or seasonal variations in cardiovascular mortality, especially in heart failure death, sudden cardiac death (SCD), death due to acute myocardial infarction and death from stroke [7–16]. Whether such variation is also seen in adult patients with CHD has not been investigated. As CHD patients are at increased risk for premature death, there is a need for more detailed research on modes and circumstances of death, as better insight may help identify and avoid high-risk situations, and improve survival.

Although we know that some deaths occur in high-risk situations (e.g. perioperative [17]), others are unexpected events [18] occurring in various settings. Heavy physical exercise as trigger for sudden death (SD) in adults with CHD has been suggested, but is not as well reported as for coronary artery disease, (isolated) coronary artery anomalies, and hypertrophic cardiomyopathy [19–23].

We systematically reviewed all deaths recorded in the CONCOR registry, a national database for adults with CHD, to assess the circumstances of death.

2. Methods

2.1. CONCOR registry

The CONCOR (CONgenital CORvitia) Dutch national registry and DNA bank of adult patients with congenital heart disease database has been described in detail previously

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[24]. In brief, CONCOR aims to facilitate research into the aetiology of CHD and on its outcome. Between November 2001 and January 2010, nearly 12,000 patients with CHD aged 18 years or older have been included through their treating cardiologist or via response to advertisements in local and national media. Clinical data such as diagnosis, clinical events and procedures – classified using the European Paediatric Cardiac Code Short List coding scheme [25] – as well as patient and family history were obtained. In case of multiple diagnoses in one patient, a pre-specified hierarchical scheme founded on consensus-based classification of severity of diagnoses [26] was used, by means of which the diagnosis with the worst prognosis was established as main diagnosis. After entry, data on major cardiac events prior to entry and during follow-up (including death) were systematically recorded from medical letters on patients' condition written by their cardiologist. Currently, 102 hospitals are participating, including all eight tertiary referral centres from which approximately 77% of registered patients originate. From CONCOR, date of birth, inclusion date, gender, causes and circumstances of death were derived of the patients who died in the period of January 1st, 2002, to January 1st, 2008.

2.2. Circumstances of death

The circumstances of death were classified as follows. *Regional mortality*: the Netherlands were divided into 4 regions: North, East, South and West. Patients were classified into these regions according to their postal codes. Thereafter, mortality rate per region was determined. *Urban mortality*: urbanization has been classified according to definitions of the Dutch Central Bureau of Statistics, using patient's postal codes. The level of urbanization was classified as urban (>1500 addresses per kilometre), semi urban (500–1500 addresses per kilometre), and rural (<500 addresses per kilometre) [27]. *Place of death*: (a) at home; including nursing home, (b) in hospital; including hospice or psychiatric facility, and (c) outdoors; including at work, in public areas/buildings, in the ambulance, or exercising. *Seasonal mortality*: based on the patients' date of death, seasonal mortality was determined.

Additional circumstances of death were explored for cardiovascular death only, and were defined as follows. *Death during exercise*: exercise intensity was measured by metabolic equivalents (METs). Exercise was defined as METs >3 (moderate and vigorous activity) [28]. *Witnessed death*: death was either classified as being witnessed or unwitnessed. *Cardio Pulmonary Resuscitation (CPR)*: (attempted) CPR prior to death. *Infection prior to death*: signs of infection (fever/leucocytosis/CRP ↑/positive blood cultures) and/or use of antibiotic therapy in the last 2 weeks prior to death.

Circumstances of death were determined based on chart review including available autopsy reports (n = 24). Where needed, treating cardiologists and general practitioners were contacted for additional information.

2.3. Modes of death

The circumstances of death were determined for all cause mortality and cardiovascular mortality. *All cause mortality* was defined as death from all causes. *Cardiovascular mortality*: death from cardiac and vascular causes.

To gain further insights in the circumstances of death, we explored cardiovascular mortality in more dept, and therefore we defined 2 modes of death. *Sudden cardiovascular death (SCVD)*: unexpected cardiovascular death soon after new acute symptoms emerge (<24 h) or unwitnessed death during sleep. When patients were successfully resuscitated but never regained consciousness, death was classified as sudden. We used the 24-hour definition to include also those patients who were found dead but seen alive within 24 h of the event. *Non-sudden cardiovascular death (N-SCVD)*: all other cardiovascular deaths not classified as being sudden; for patients with symptoms >24 h. When patients died suddenly (presumably due to arrhythmias) while being hospitalized with (progressive) heart failure, or were known with terminal heart failure, death was classified as non-sudden cardiovascular death.

Seven patients could not be classified into sudden or non-sudden cardiovascular death due to insufficient data, and were therefore not analyzed according to these modes of death.

2.4. Data analysis

Age at death was presented as median (range). Differences within the regional and urban distribution of mortality were analyzed using the χ^2 or Fisher's exact test. For the purpose of this study seasons were defined as follows: *winter* = December 21 to March 20; *spring* = March 21 to June 20; *summer* = June 21 to September 20; *fall* = September 21 to December 20. In order to analyze seasonal variation in mortality, the number of events in each season was adjusted to a 90-day season, by dividing the number of cases by the number of days in the related season and multiplying by 90. This method was also used to adjust the number of events in each month to a 30-day month. Assuming that mortality does not vary by season or month, we examined the null hypothesis that mortality was equally distributed across the seasons and months, using χ^2 (goodness-of-fit) tests to compare observed numbers with those expected on the basis of even distribution. Differences between sudden and non-sudden cardiovascular death were analyzed using the χ^2 or Fisher's exact test. The level of significance was set at $p \leq 0.05$ (2-sided). Statistical analysis was performed with the SPSS version 16.0.1 (SPSS Inc., Chicago, IL, USA).

3. Results

Of 8595 patients, 231 (2.7%) died during a total follow up period of 26,500 patient years (mean follow up period was 37.1 ± 0.2 months). Median age at death was 48.4 years (range, 20.2 to 91.2 years); 57% were males. Table 1 shows the distribution of defects in CONCOR and among the deceased patients. The most common defects in CONCOR were atrial septal defect (17%), ventricular septal defect (16%), aortic stenosis/bicuspid aortic valve (14%), tetralogy of Fallot (10%), and aortic coarctation (10%). Highest mortality was found in the patients with tricuspid atresia (14.7%) and patients with univentricular hearts or double inlet left ventricle (11.4%).

Fig. 1 displays the causes of death by underlying defect. Progressive heart failure (26%) and sudden cardiac death (22%) were the predominant causes of death, together accounting for nearly 50% of deaths. Non-cardiovascular deaths occurred in nearly a quarter of patients, with malignancy (8.6%) and pneumonia (4.1%) as the main causes of death.

Circumstances of deaths from all cause and cardiovascular deaths are presented in Table 2. Mortality in the total CONCOR population was higher in the northern region than in other parts of the country ($p \leq 0.05$). There were no regional differences in the distribution of causes of death or severity of underlying defect. Mortality was slightly higher in rural regions. More patients in rural areas had died out-of-hospital than in urban regions (55% versus 32%, $p \leq 0.05$). Death from cardiovascular causes had occurred out-of-hospital in approximately 35%. Little variation in seasonal mortality was observed, although highest mortality was seen in fall. Per season, causes of death were equally distributed.

3.1. Modes of death

Table 3 shows circumstances of sudden cardiovascular death and non-sudden cardiovascular death. Regional variation was again present. No more than 40% of SCVD had occurred in hospital (versus 80% of N-SCVD, $p \leq 0.05$), and merely 8% of SCVD occurred during exercise. In 27% of N-SCVD death was preceded by an infection, which occurred most frequently in winter and fall (61%).

Table 1
Proportional distribution of main diagnosis among study subjects and among deceased patients.

Defect	Distribution in CONCOR (%) n = 8595	Distribution among deceased (%) n = 231	Proportion deceased per defect (%)
ASD	17.1	19.0	3.0
VSD	15.8	7.4	1.3
AoS and BAV	13.7	8.2	1.0
TOF	10.1	12.1	3.2
AoC	10.1	5.6	1.5
PS	7.3	3.9	1.4
TGA	4.8	6.1	3.4
Marfan	4.8	4.3	2.4
PA	1.8	5.2	7.7
Ebstein	1.6	3.5	5.7
AVSD	1.5	3.5	6.1
UVH and DILV	1.2	5.2	11.7
TA	0.8	4.3	14.7
ccTGA	1.3	3.5	7.3
DORV	0.7	2.6	9.4
Other	7.4	6.1	2.2

ASD = atrial septal defect; VSD = ventricular septal defect; AoS/BAV = aortic stenosis and/or bicuspid aortic valve; TOF = tetralogy of Fallot; AoC = aortic coarctation; PS = pulmonary stenosis; TGA = transposition of the great arteries; Marfan = Marfan syndrome; PA = pulmonary atresia; Ebstein = Ebstein's anomaly; AVSD = atrioventricular septal defect; UVH/DILV = univentricular heart/double inlet left ventricle; TA = tricuspid atresia; cc-TGA = congenitally corrected transposition of the great arteries; DORV = double outlet right ventricle; Other defects comprise defects with n<60.