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Impact of age and sex on survival and causes of death in adults with congenital heart disease

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ABSTRACT

Background: The impact of gender and aging on relative survival and causes of death in adults with congenital heart disease (ACHD) are not well known.
Methods: Single center observational longitudinal study of 3311 consecutive ACHD (50.5% males) followed up to 25 years. Patients were divided by the age at last follow-up into three groups: <40, 40–65 and >65 years old. Their vital status was verified by crosschecking the Spanish National Death Index. Regression model for relative survival from reference population was performed. Cause of death was classified according to the International Classification of Diseases (ICD-10). Patients who died from cardiovascular (CV) causes were further investigated on a case-by-case basis.
Results: During a cumulative follow-up time of 37,608 person-years 336 patients died (10%). Age-adjusted relative survival in females was significantly worse than in males (hazard ratio [HR] 1.25; 95% confidence interval [CI] 1.0–1.6; $p = 0.046$), and sex-adjusted relative survival improved across the three group of ages (HR 0.98; 95% CI 0.97–0.99; $p < 0.001$). There was a temporal decline of CV deaths with aging in both genders ($p < 0.001$). The leading cause of CV death was heart failure but sudden death prevailed in subjects <40 years ($p = 0.004$). While sudden death progressively declined with aging heart failure significantly increased ($p < 0.001$).
Conclusions: Women with CHD fare worse than men. There are a decline in CV deaths and a major temporal shift in the causes of CV deaths with aging. Heart failure surpasses sudden death as the primary cause of death in survivors over 40 years.

1. Introduction

Due to advances in interventions and changes in socio-economic circumstances, up to 90% of live births with congenital heart diseases (CHD) in industrialized countries nowadays survive until adulthood [1,2]. Despite this improvement in outcomes, adults with CHD (ACHD) have globally reduced survival compared with the reference population whatever the anatomical complexity of the underlying heart disease or the repair status [3–5]. Recent studies have identified predictors of excess mortality that include anatomical residua, hemodynamic and electrophysiological sequela or acquired complications [5,6], and sex differences in cardiac outcomes for ACHD have already been recognized [7–11]. However, there is comparatively little data about the role of gender and aging in individual survival risk assessment.

Several studies that have addressed global mortality and causes of death in ACHD have noted mixed results [12–19]. Most of these studies were either population-based or multicenter registries and the characteristics of the study sample varied widely between them with different ages at death, time of follow-up, underlying CHD and repair strategies. Moreover, accuracy of causes of death data extracted from national mortality statistics coding according to International Classification of Diseases has been largely criticized and reliable circumstances of death diagnosis might require a more precise knowledge of the patients' history [20]. We hypothesized that there would be significant temporal changes in survival and causes of death with sex, follow up time and CHD complexity. The aim of this study was to investigate the impact of sex and aging on relative survival and causes of death in a large contemporary cohort of ACHD followed up to 25 years at a single tertiary referral center.

2. Methods

2.1. Study population

The clinical database at the ACHD unit at La Paz University Hospital in Madrid, Spain between December 1989 and June 2014 was searched to identify all patients ≥18 years

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old diagnosed with CHD. For the present study, CHD was defined according to the criteria of Mitchell et al. [21]. Specifically, patients diagnosed with isolated patent foramen ovale, mitral valve prolapse, congenital electrophysiological abnormalities without structural cardiac disease, non-ischemic congenital coronary artery anomalies, functionless abnormalities of the great vessels, congenital cardiomyopathies, and inherited aortopathies were excluded. Patients whose demographic information (date of birth, hospital medical record number or National Identification Number) was incomplete were also excluded. Patients entered the study cohort on the date of first visit at the ACHD unit or on 1 January 1990, whether their first visit occurred before database construction. Data were prospectively entered and updated by the senior investigator (JMO). The study was approved by the local research ethics committee.

2.2. Mortality data and causes of death

The vital status of each patient at the end of the study (June 30th, 2014) was verified by cross checking the available identifying information to the Spanish National Death Index. Death from any cause during the follow-up period constituted the primary endpoint. The causes of death were obtained from the national mortality registry, coded according to the 10th revision of the International Statistical Classification (ICD-10) or the 9th revision (ICD-9) for patients who died before 1999, and classified into cardiovascular (CV) or non-CV deaths. Non-CV causes of death were further sub-classified according to the main ICD-10 groups. Since insufficient agreement has been reported between causes of death obtained from administrative and clinical registries, the circumstances of CV death were further investigated on a case by case basis with interviews of family members by doctors with full knowledge of patients' history. The immediate cause of CV death was then classified as heart failure (HF), sudden cardiac death (SCD), perioperative, and other CV deaths. Heart failure related-death was defined as death due to progressive (>1 h) worsening of HF symptoms. Sudden cardiac death was defined as death within 1 h of symptom onset or unwitnessed death during sleep. Perioperative death was defined as intraoperative death or death within 30 days after cardiac surgery or heart transplantation. Other CV deaths included myocardial infarction, aortic dissection or rupture, stroke, pulmonary or systemic thromboembolism, infective endocarditis or severe hemoptysis.

2.3. Classifications

To classify patients by the complexity of their heart defects, we used a modified version of the categories outlined by Task Force 1 of the 32nd Bethesda Conference [22]: simple; moderate; and severe (Table 1). Patients diagnosed with sinus venosus type of atrial septal defect or with anomalous pulmonary venous connection were considered together in moderate complexity, and patients with Eisenmenger syndrome and other conditions with pulmonary vascular disease in severe complexity. The individual diagnostic categories that were documented in <20 patients were grouped as others. To evaluate whether outcomes over time differed among natural or unnatural survival patterns described by Perloff [23], we stratified the cohort into childhood repair (when CHD repair was performed before the age of 18 years) and unrepaired survivors to adult life (which also included those patients with only palliative interventions). For the purpose of the study, patients were divided according to age at death or censored into three groups: <40 years old (young adults), 40–65 years old (middle-age), and >65 years old (old age).

2.4. Data collection

Patient follow-up was arranged at our institution according to the general recommendations [24,25] but customized as needed. Details regarding to demographic characteristics, clinical history, vital status, Doppler two-dimensional echocardiography (2DE), cardiac magnetic resonance imaging (MRI) and computed tomography angiography (CTA) were extracted from the database. The following outcomes were considered events of interest: all-cause death, CV cause of death, severe pulmonary hypertension, aortic syndrome (aneurysm, dissection, and aortic surgery) and clinical arrhythmia. Severe pulmonary hypertension was assumed to exist when a systolic pressure gradient between right ventricle and right atria >50 mm Hg was measured by Doppler echocardiography (maximum tricuspid regurgitation jet velocity > 3.5 m/s.) in the absence of significant pulmonary stenosis. Aortic aneurysm was defined as a dilatation of the aortic root and ascending aorta > 5.0 cm or dilatation of the descending aorta > 4.0 cm by MRI or CTA. Clinical arrhythmias included symptomatic supraventricular or ventricular tachyarrhythmias, except for premature complexes and accessory pathways, and bradyarrhythmias including symptomatic sinus sick syndrome and advanced AV block requiring pacemaker. Infective endocarditis was defined as the presence of a prolonged febrile syndrome with positive blood cultures with proper diagnosis and adequate therapy. The most recently recorded cardiac outcome preceding endpoints was requested.

2.5. Statistical analysis

All analyses were performed with statistical package of R Version 3.1.2 (available at https://www.r-project.org). Continuous variables were expressed as mean ± SD for normally distributed or median and interquartile range (IQR) for skewed data. Categorical variables were summarized as numbers and percentages and compared using chi-squared test. Annual death rate was measured by relating the number of death to the person-years at risk during the measurement period. Survival analysis was performed using standard right-censored Kaplan–Meier with follow-up time as time scale and compared by two-sample log-rank test. The adjusted effect of age, sex, CHD complexity, childhood repair and cardiac outcomes on survival were calculated by using a Cox regression model for relative survival. It was performed by the transforming model using *relsurv* library in R [26]. To calculate the expected survival from the Spanish reference population by the Hakulinen method, data available in www.mortality.org (Human Mortality Database) organized as an object of class *ratetable* by the function *transrate.hmd* was used. Standardized mortality ratio (SMR) from age-and-sex–adjusted reference population was calculated as the ratio between observed and expected survival using one-sample log-rank test [27]. In both genders, CV and non-CV causes of death by age at death groups were compared with the most recent available age- and cause-specific mortality data, (update November 25th, 2015) and age-specific population data, for Spain [28]. Two-tailed p values < 0.05 were considered statistically significant.

Table 1
Demographic data of 3311 adults with congenital heart disease (CHD).

Complexity	Diagnostic category	N (%)	Males N (%)	Age at entry Median (IQR)	Follow-up Median (IQR)	Death N (%)
I. Simple	Overall	1625 (49)	798 (49)	26.3 (19–46)	11.3 (6–18)	153 (9.4)
	Ostium secundum ASD	369 (11)	109 (30)	39.4 (23–55)	10.4 (4–18)	51 (14)
	Ventricular septal defect	356 (11)	167 (47)	19.1 (17–23)	10.1 (5–19)	5 (1.4)
	Patent ductus arteriosus	90 (2.7)	19 (21)	28.1 (19–44)	13.3 (7–18)	10 (11)
	Aortic valve disease	547 (17)	387 (71)	38.1 (21–55)	12.2 (8–18)	77 (14)
	Pulmonary valve disease	227 (6.9)	99 (44)	20.2 (18–32)	11.1 (5–19)	9 (4.0)
	Mitral valve disease	36 (1.1)	17 (47)	19.7 (17–30)	11.0 (6–20)	1 (2.8)
II. Moderate	Overall	1278 (39)	654 (51)	21.2 (18–34)	9.9 (4–18)	96 (7.5)
	Sinus venosus ASD-PVAC	103 (3.1)	52 (51)	31.6 (20–50)	8.6 (4–14)	6 (5.8)
	AV septal defect	148 (4.5)	57 (39)	20.0 (17–29)	10.5 (5–18)	8 (5.4)
	Subvalvar aortic stenosis	115 (3.5)	57 (50)	30.6 (18–51)	13.5 (6–19)	26 (23)
	Supravalvar aortic stenosis	30 (0.9)	18 (60)	19.2 (18–23)	15.8 (6–21)	0
	Coarctation of the aorta	353 (11)	206 (58)	20.2 (18–29)	9.4 (4–19)	21 (5.9)
	Subvalvar pulmonic stenosis	50 (1.5)	30 (60)	21.7 (18–32)	9.7 (5–18)	1 (2.0)
	Supravalvar pulmonic stenosis	24 (0.7)	10 (42)	22.1 (20–28)	6.2 (1.5–11)	0
	Ebstein anomaly	76 (2.3)	21 (28)	32.4 (20–47)	7.9 (2–16)	9 (12)
	Tetralogy of Fallot	327 (9.9)	177 (54)	20.3 (18–27)	10.3 (4–20)	18 (5.5)
	Other moderate CHD	52 (1.6)	26 (50)	26.4 (18–48)	5.7 (1 − 13)	7 (13)
III. Severe	Overall	408 (12.3)	221 (54)	21.2 (18–28)	8.4 (3–18)	87 (21)
	Transposition of the great arteries	122 (3.7)	79 (65)	19.1 (17–22)	10.6 (5–18)	11 (9.0)
	AV discordance	42 (1.3)	25 (60)	29.4 (20–48)	5.0 (1–14)	12 (29)
	Double outlet right ventricle	19 (0.6)	10 (53)	21.1 (18–29)	7.9 (3–17)	2 (11)
	Pulmonary atresia (all forms)	53 (1.6)	30 (57)	21.0 (18–30)	7.6 (3–17)	8 (15)
	Pulmonary vascular disease	67 (2.0)	30 (34)	27.7 (21–35)	9.3 (4–18)	28 (42)
	Single ventricle physiology	101 (3.1)	50 (50)	22.5 (21 − 32)	8.5 (3–18)	22 (22)
	Other severe complexity CHD	4 (0.1)	4 (100)	52 (43–60)	4.6 (2 − 11)	4 (100)
Total		3311	1673 (50.5)	22.5 (18–39)	10.5 (4–18)	336 (10)