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Atrial tachyarrhythmias late after Fontan operation are related to increase in mortality and hospitalization

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ABSTRACT

Background: Atrial tachyarrhythmias are a known complication late after Fontan operation. Limited information is available on their prognostic value.
Methods: All patients with previous Fontan operation followed at our institution since 1999 were identified from the electronic database and included in this study. Demographic and clinical characteristics including history of atrial tachyarrhythmias were recorded at the earliest full clinical assessment and patients were followed thereafter for all-cause mortality and hospitalization.
Results: A total of 98 patients, mean age 31.5 ± 8.9 years, 43.8% male, 31.6% with a total cavopulmonary connection (TCPC) were identified. A history of atrial tachyarrhythmia was present at baseline in 60.2% of patients who were older (33.0 ± 8.3 vs 29.1 ± 9.4 years, $p = 0.002$), less likely to have a TCPC (13.5% vs 58.9%, $p < 0.001$), and more symptomatic in terms of NYHA class (51.9% vs 26.7%, $p = 0.007$) compared to arrhythmia-free patients. During a median follow-up of 6.7 years 18 patients died and 64 patients were hospitalized. Even after adjustment for baseline clinical characteristics, atrial tachyarrhythmia was an independent predictor of death (propensity score adjusted HR 9.35, 95% CI: 1.10–79.18, $p = 0.04$, c-statistic 0.88) and composite of death or hospitalization (propensity score adjusted HR 5.00, 95% CI: 2.47–10.09, $p < 0.0001$).
Conclusions: In adult patients with a Fontan-type operation, the presence of atrial tachyarrhythmias is associated with higher morbidity and mortality at mid-term follow-up. Whether early arrhythmia targeting intervention may improve clinical outcome needs to be studied in a prospective manner.

1. Introduction

Patients with univentricular heart and prior Fontan surgery nowadays survive well into adulthood. As this population ages, the risk of complications increases compromising longer term outcome. It is well known that atrial tachyarrhythmias are common amongst patients with a Fontan circulation and their prevalence increases with time. Moreover, atrial arrhythmias are related to the structural changes and functional deterioration of the Fontan circuit, such as increased right atrial pressures, right atrial dilatation, ventricular impairment, systemic atrioventricular valve regurgitation as well as functional capacity [1,2]. However, the impact of atrial tachyarrhythmias on longer term outcome, including survival, remains unclear. We hypothesized that the presence of atrial tachyarrhythmias is associated with higher morbidity and mortality in adult patients with a Fontan-type circulation.

2. Methods

2.1. Patients

All patients with previous Fontan operation followed at our institution from January 1999 to October 2008 were identified from the electronic database and included in this study. Demographic and clinical characteristics were recorded at the oldest complete clinical assessment and patients were followed thereafter for hospitalizations, interventional procedures and mortality.

2.2. Clinical characteristics at baseline

Cardiac anatomy was categorized in accordance with previously defined nomenclature on the basis of the findings of preoperative studies and surgical observations [3]. Type of Fontan surgery was classified into the following 2 categories: atrioventricular/atriopulmonary connection or total cavopulmonary connection (TCPC). Protein-losing enteropathy was defined based on the presence of hypoalbuminemia (<3.0 mg/dL) for >3 months in the absence of significant liver or renal disease, associated with ascites, pleural effusion, edema, diarrhea, or abdominal pain for

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>3 months [4]. Cyanosis was defined as resting saturations ≤90% in room air after 2 min of complete rest. Functional impairment was assessed using the New York Heart Association (NYHA) classification. Systolic systemic ventricular function and atrioventricular valve competence were recorded from echocardiography or cardiac magnetic resonance using the following semiquantitative classification: 1 = normal, 2 = mildly impaired, 3 = moderately impaired and 4 = severely impaired systolic function. Atrial tachyarrhythmia was defined as atrial fibrillation or regular atrial tachyarrhythmia lasting more than 30 s, documented by Holter recordings or 12-lead electrocardiography at least 30 days after the index Fontan operation. Atrial fibrillation was defined as an irregular tachycardia without organized atrial activity. Regular atrial tachycardia was defined as tachycardia with regular organized atrial activity.

2.3. Endpoints

The endpoints of the study were time to all-cause mortality, the composite of death or hospitalization and invasive interventions such as hemodynamic catheter interventions, electrophysiologic studies, device implantation and TCPC conversion or other cardiac surgery. Elective day-case admissions for diagnostic investigations were excluded from the analysis. Follow-up data were obtained from hospital records and through the National Health Service computer system, linked to a national database of patient survival held by Office for National Statistics. Deaths were defined as sudden when occurring within 1 h of acute symptoms. Deaths were classified as secondary to heart failure when occurring after progressive worsening heart failure with evidence of at least one of the following: orthopnea, nocturnal dyspnea, pulmonary edema, increasing peripheral edema, renal hypoperfusion (worsening renal function), or radiological signs of congestive heart failure. Deaths were classified as perioperative when occurring within 30 days of surgery or prior to hospital discharge. Remaining deaths were classified as "others" and qualified as "unknown" if the cause of death could not be accurately detected [5].

2.4. Data analysis

Numerical values are presented as mean ± standard deviation, with the exception of age at Fontan, age at TCPC and time of follow-up, which are reported as median (interquartile range, IQR). Categorical variables are reported as percentage of total. Comparisons between groups were performed using the Wilcoxon's rank sums for continuous variables and Fisher's exact test for categorical variables. Cox regression analysis was used to assess the relation between atrial tachyarrhythmia and time to clinical outcomes (all-cause death, first hospitalization, and first intervention). In order to account for clinically relevant baseline demographic and clinical characteristics a propensity score analysis was also performed. Propensity scores were used to create a covariate that summarizes confounders within baseline demographic and clinical characteristics. A logistic regression model was constructed predicting the probability that a patient with certain characteristics would have a history of atrial tachyarrhythmia. Variables in the logistic regression model included the following parameters: age, sex, prior palliative surgery, cardiac anatomy (tricuspid atresia/other), prior TCPC, systemic ventricular dysfunction, atrioventricular valve regurgitation, symptomatic status and medication (including anticoagulants, antiplatelets, beta-blockers, angiotensin converting enzyme inhibitors/angiotensin receptor blockers and diuretics). The C-statistic of the model was 0.88, suggesting optimal accuracy in predicting atrial tachyarrhythmia. All patients received an estimated propensity score and this was inserted as a covariate (quartiles of propensity score, together with atrial tachyarrhythmia) in the Cox regression models predicting clinical outcomes, thus adjusting for the above covariates. Unadjusted Kaplan–Meier and adjusted cumulative mortality curves for a patient in the second propensity score quartile (propensity score 0.32–0.67) were plotted. All p-values were two-sided and a p-value of less than 0.05 was considered to indicate statistical significance. Analyses were performed using R version 2.7.0. (R Development Core Team (2008). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, www.R-project.org).

3. Results

3.1. Patient characteristics

Data on 98 patients with Fontan operation (mean age 31.5 ± 8.9, 43.8% male) were analyzed. Median age at Fontan was 8.4 years (IQR 4.9–14.5 years). Thirty-one patients (31.6%) had prior TCPC at baseline assessment, in 3 (9.7%) of whom this was conversion from a previous Fontan operation. In the remainder, TCPC had been performed de novo at a median age of 10.5 years (IQR 5.9–20.7 years). The vast majority of patients had a morphological left systemic ventricle and 21.8% were cyanotic at rest. Most patients were asymptomatic in terms of NYHA class at baseline assessment and had normal systemic ventricular function and a competent atrioventricular valve (Table 1).

Fifty nine patients (60.2%) had a history of atrial tachyarrhythmia at baseline assessment, regular atrial tachyarrhythmia in 62%, atrial fibrillation in 20%, and both tachycardias in 18%. Patients with a history of atrial tachyarrhythmia were older, less likely to have had TCPC, more likely to be functionally impaired, and receive antiarrhythmic treatment, beta-blockers, angiotensin enzyme inhibitors or angiotensin receptor blockers, diuretics, and warfarin (Table 1).

3.2. Clinical outcome

During a median follow-up of 6.7 years (IQR 4.8–8.0 years) 18 patients died (mortality rate of 3.0% per year, 95% CI 1.8–4.8%). Mean age at death was 29 ± 9 years (range 18 to 48) and occurred at a median of 16.5 years (IQR 14.3–21.6 years) after the index Fontan operation. Overall, 4 deaths were sudden, 4 due to heart failure, 3 perioperative, 1 due to sepsis, 1 due to arrhythmia intervention (general anaesthesia for cardioversion), and 5 were classified as others (1 malignancy and 4 unknown causes).

Sixty-six patients reached the combined endpoint of death or hospitalization during follow-up (hospitalization n = 64). Reasons for hospitalization included arrhythmia (n = 22), heart failure (n = 7), invasive intervention (n = 16), worsening cyanosis (n = 2), infection (n = 5), pulmonary embolism (n = 4) and other (n = 8). During the follow-up period, 39 patients underwent at least one intervention (electrophysiologic study n = 18, TCPC conversion n = 9, catheter intervention n = 8, pacemaker implantation n = 2, surgery other than TCPC n = 2).

Patients with atrial tachyarrhythmias were at higher risk of death (HR 11.8, 95% CI: 1.57–88.7, p = 0.002, Fig. 1A), death or hospitalization (HR 5.81, 95% CI 3.13–10.80, p < 0.0001, Fig. 2A), and interventions (HR 3.09, 95% CI 1.26–7.56, p = 0.01, Fig. 3A) on unadjusted univariate analysis. After adjusting for baseline characteristics by means of propensity scores, patients with atrial tachyarrhythmias were at higher risk of death (HR 9.35, 95% CI: 1.10–79.18, p = 0.04, Fig. 1B), and death or hospitalization (HR 5.00, 95% CI: 2.48–10.09, p < 0.0001, Fig. 2B). A trend towards higher risk of interventions (HR 1.12, 95% CI: 0.76–1.65, p = 0.068) was also seen in the propensity score adjusted model (Fig. 3B).

4. Discussion

Our study shows that atrial tachyarrhythmias occur frequently late after Fontan operation. We also showed that atrial arrhythmias are associated with increased all-cause mortality and morbidity at mid-term follow-up even after adjusting for the demographic and clinical characteristics. The occurrence of atrial arrhythmias in these patients may warrant careful assessment and vigilant follow-up as they could be a precursor of adverse outcome.

Sixty percent of patients in this Fontan cohort had a history of atrial tachyarrhythmia. This was higher than previous studies in Fontan patients [6–11]. Durongpisitkul et al. reported a 17% prevalence of atrial tachyarrhythmia 5 years after the Fontan-type operation, whereas Gelatt et al. reported a prevalence of 29% of patients who received an atriopulmonary connection, and 14% in those who received a TCPC at a mean interval of 4.4 years [8,10]. It is known that the prevalence of atrial arrhythmias increases with age and time after Fontan operation, especially in patients with atriopulmonary Fontan [7,10–12]. The high prevalence of atrial arrhythmias in our cohort may be explained by the fact that patients were older (mean age 31 years), with a higher prevalence of atriopulmonary-type operation (68% of non-TCPC operations) and longer follow-up (median follow-up 6.7 years) compared to previous studies [8,10].

The propensity of atrial tachyarrhythmias in Fontan patients can be explained by the underlying atrial conduction characteristics of the Fontan circulation. Anisotropic atrial conduction, as a result of non-