Heterotaxy syndrome and associated arrhythmias in pediatric patients

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BACKGROUND Heterotaxy syndrome (HS) is a rare disorder with complex anatomy involving misarrangements of the cardiac conduction system. Arrhythmias may be related to anatomic variations and contribute to morbidity.

OBJECTIVE The purpose of this study was to investigate the associations between arrhythmias, anatomy, and outcomes in a large HS cohort.

METHODS A single-center retrospective review of patients ≤21 years of age diagnosed with HS was performed.

RESULTS A total of 337 patients were included in the study. During median follow-up of 7 years (interquartile range 2–16 years), 129 patients (38%) had ≥1 clinically significant rhythm disturbance: tachyarrhythmias in 75 (22%), bradyarrhythmias in 29 (9%), and both in 25 (7%). Factors associated with tachyarrhythmia by multivariate analysis were at least moderate atrioventricular valve regurgitation (hazard ratio [HR] 1.66; 95% confidence interval [CI] 1.11–2.50), single ventricle anatomy (HR 2.30; 95% CI 1.09–4.85), and pulmonary venous obstruction (HR 2.33; 95% CI 1.45–3.76). Isomerism subtype was not associated with tachyarrhythmias. In adjusted and unadjusted analyses, bradyarrhythmias (symptomatic sinus/atrial bradycardia and high-grade or complete heart block) were associated with left atrial isomerism (LAI) compared to right atrial isomerism (HR 7.12; 95% CI 3.01–16.9). The overall transplant-free survival of the cohort was 66%. Tachyarrhythmias, but not bradyarrhythmias, were associated with mortality or need for transplant (HR 2.24; 95% CI 1.45–3.46).

CONCLUSION Clinically significant arrhythmias are common in HS. Although bradyarrhythmias are associated with LAI, tachyarrhythmia occurrence may depend more on hemodynamic and anatomic factors than isomerism subtype. Tachyarrhythmias, but not bradyarrhythmias, are associated with death or need for transplant.

KEYWORDS Arrhythmia; Congenital heart defects; Heart block; Heterotaxy; Outcome

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Introduction

Heterotaxy syndrome (HS) occurs in 1–1.44 per 10,000 live births[1–3] and is characterized by abnormal lateralization of the abdominal viscera, thoracic organs, and cardiac segments.[4] Although the constellation of anomalies found in HS patients are varied in association and complexity, the presence of complex cardiovascular lesions remains one of the hallmarks of HS.[1,4,5] These morphologic defects and disarrangements are frequently accompanied by rhythm disturbances, which contribute importantly to morbidity and mortality.[3,6,7] Data regarding the arrhythmias associated with HS have been largely limited to case reports, small series, and subsets of patients with HS.[3,6,7] Clinically, right atrial isomerism (RAI) is thought to be associated with twin AV nodes and supraventricular tachycardia (SVT), whereas bradyarrhythmias and heart block are often associated with left atrial isomerism (LAI).[8] Whether isomerism subtype influences arrhythmia development and outcome is not known. The purpose of this study was to describe the incidence of arrhythmias, their relationship to anatomic substrates, and associated outcomes in a large cohort of pediatric patients with HS.

Methods

We performed a single-center retrospective review of patients diagnosed with HS before age 21 years at Texas Children's Hospital between January 1980 and December 2012. Heterotaxy patients without congenital heart disease (CHD) were excluded. Approval for medical chart review was obtained from the Institutional Review Board at Baylor College of Medicine. Details regarding data collection are available in the Supplemental Materials.

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Heterotaxy classification

Heterotaxy cases were classified as RAI subtype (also known as asplenia syndrome), LAI subtype (also known as polysplenia syndrome),[9] or indeterminate/mixed type atrial isomerism when indeterminate atrial morphology or overlapping RAI and LAI features were present. Further details are available in the Supplemental Materials.

Arrhythmia classification

Clinically significant tachyarrhythmias were defined as (1) hemodynamically significant or requiring treatment; (2) nonsustained (≥3 beats, <30-second duration) or sustained (≥30-second duration) ventricular tachycardia (VT); and (3) sustained (≥30-second duration) SVT. SVT was further categorized into ectopic atrial tachycardia (EAT), atrial flutter and/or atrial fibrillation (AFF), junctional tachycardia, reentrant SVT, and SVT not otherwise specified (SVT NOS) when the distinction between EAT and reentrant SVT could not be made. Additional information on arrhythmia classification is available in the Supplemental Materials.

Bradyarrhythmias were defined as (1) symptomatic sinus or primary atrial bradycardia warranting pacing (based on physician clinical judgment); or (2) any advanced or complete atrioventricular block (AVB).

All arrhythmia substrates were initially diagnosed by an electrophysiologist and confirmed during this study by a single electrophysiologist (CM). Perioperative arrhythmias were defined as arrhythmias occurring within 30 days post surgery or hospital stay (whichever was longer). Transient rhythm problems in the operating room that did not recur postoperatively were not included.

Statistical analysis

Descriptive data are expressed as counts with percentages for categorical variables, and as either mean ± SD or median with interquartile range (IQR) for continuous variables. Baseline categorical patient and cardiac characteristics were compared using the χ^2 and Fisher exact tests as appropriate. Continuous variables were compared using the Student *t* test or Mann–Whitney *U* test as appropriate.

Analyses were performed to determine whether (1) anatomic factors were associated with tachyarrhythmia or bradyarrhythmia incidence; and (2) tachyarrhythmia and bradyarrhythmia were associated with death or cardiac transplant. Cox regression was used to calculate hazard ratios and *P* values. Kaplan–Meier survival graphs were used to visualize data. In the transplant-free survival analysis, tachyarrhythmia and bradyarrhythmia were evaluated as time-dependent covariates. Because the greatest attrition in HS with fetal bradyarrhythmia occurs between the prenatal and neonatal periods,[7,10,11] fetal bradyarrhythmia cases expiring ≤30 days were excluded from the survival analysis in order to create a model that assesses survival in live births. An exploratory secondary survival analysis was performed in which bradyarrhythmia cases were divided into two groups: (1) fetal or congenital bradycardia (fixed covariate) or (2) postnatal bradycardia (time-dependent covariate).

Variables achieving a significance of $P < .10$ for the outcome were included in the multivariate Cox regression analysis. A subsequent $P < .05$ was defined as significant. Bonferroni correction was applied to the level of significance for associations with categorical variables with >2 groups of interest. Variables for tachyarrhythmia and bradyarrhythmia were retained *a priori* in the multivariate model for transplant-free survival. Additional analyses were performed to evaluate interaction effects between tachyarrhythmias and bradyarrhythmias to determine the differential impact of having an arrhythmia of 1 type followed by an arrhythmia of the other type. All analyses were performed with SPSS version 20 (SPSS Inc., Chicago, IL) or R version 3.3.2 (ref: R Core Team: R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2012).[12]

Results

Study patients and baseline characteristics

Between January 1980 and December 2012, 337 patients with HS were followed at Texas Children's Hospital. Over median follow-up of 7 years (IQR 2–16 years), 129 patients (38%) had ≥1 clinically significant rhythm disturbance (Supplemental Table S1). Arrhythmias were common: tachyarrhythmias occurred in 75 (22%), bradyarrhythmias in 29 (9%), and both in 25 (7%) (Figure 1). Freedom from overall arrhythmia was 78% ± 2.3% at 1 year, 68% ± 2.8% at 5 years, and 60% ± 3.2% at 10 years (Figure 2). Patient characteristics and arrhythmia occurrence are given in Supplemental Table S1 and Supplemental Discussion. Although Hispanic patients comprise 35% of inpatient admissions with CHD at our center,[13] they represented 51% of heterotaxy cases in this study. Most patients (83%) were diagnosed with HS by 1 month of age, and nearly all patients (90%) required surgical intervention; the majority of these procedures (56%) occurred within the first month of life. There was a significant association between arrhythmia occurrence and age at HS diagnosis, pulmonary venous obstruction, and outflow tract obstruction type ($P < .001$, .007, and .01, respectively) (Supplemental Table S1).

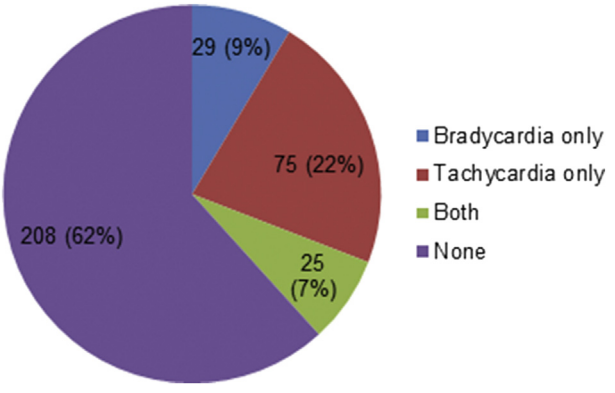

Figure 1 Occurrence of arrhythmias in patients with heterotaxy syndrome.