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Analysis of Clinical and Candidate Genetic Risk Factors for Postoperative Atrial Tachycardia after Congenital Heart Surgery in Infants

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Abstract

Background—Atrial tachycardia (AT) after infant congenital heart disease (CHD) surgery is associated with increased mortality. Polymorphisms in *PITX2* (rs2200733) and *IL6* (rs1800795) are associated with postoperative atrial fibrillation in adults, but have not been studied in CHD.

Objective—To test the hypothesis that clinical factors and variants in *PITX2* and *IL6* are associated with postoperative AT in infants with CHD.

Methods—Infants (less than one year of age) undergoing CHD surgery between September 2007 and May 2016 were included. Subjects had daily assessment of telemetry and were genotyped for the two variants. Univariate and multivariate analysis were performed to test for factors independently associated with AT.

Results—Of 1067 enrolled infants, 164 had postoperative AT (15.4%); 95 required treatment (8.9%). AT was associated with risk for ECMO, operative mortality, and longer duration of ventilation, as well as ICU and hospital stays. *PITX2* and *IL6* genotypes were not associated with AT or AT requiring treatment. In multivariate analysis, use of two or more inotropes, age 28 days, RACHS-1 score 3, and bypass time were all independently associated with AT. Factors independently associated with treated AT include use of two or more inotropes, age 28 days, and RACHS-1 score 3.

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Conclusion—AT occurs in 15% of infants after CHD surgery and is associated with increased morbidity and mortality. Risk factors include use of two or more inotropes, neonatal age, and higher surgical complexity score. We observed no association between common genetic variants in *PITX2* and *IL6* and atrial tachycardia in infants after CHD surgery.

Keywords

congenital heart surgery; atrial tachycardia; genetics

INTRODUCTION

Postoperative arrhythmias in children after congenital heart disease (CHD) surgery are common with reported incidences ranging from 30–50%, partly due to the diversity in patient anatomy and surgical procedures.^{1,2} Similarly, the range of arrhythmia mechanisms observed are diverse and include bradyarrhythmias, such as complete heart block, as well as supraventricular, junctional, and ventricular tachycardias. Early postoperative arrhythmias are associated with increased morbidity including longer duration of ventilation, intensive care unit (ICU) stays, hospital stays, and need for extracorporeal membrane oxygenation (ECMO) support.^{3,4} Atrial tachycardia specifically has been associated with increased mortality in infants (less than one year of age) undergoing CHD surgery.⁵

The concept that common genetic polymorphisms can increase risk for postoperative arrhythmias after CHD surgery is beginning to be appreciated. We have previously identified a genetic contribution to risk for postoperative tachyarrhythmias in general,³ the most common specific postoperative tachycardia - junctional ectopic tachycardia,⁶ and postoperative complete heart block.⁷ Studies investigating the role of common genetic variants specifically in postoperative atrial tachycardia have not been performed in children. Variants that have been associated with postoperative atrial fibrillation (AF) in adults after cardiac surgery are logical candidates for postoperative atrial tachycardias in children. Common polymorphisms in *PITX2* (rs2200733) and *IL-6* (–174 G/C, rs1800795) have been independently associated with risk for postoperative AF after coronary artery bypass surgery.^{8–10} *PITX2* has been shown to be integral in the development of pulmonary myocardium sleeves in the left atrium, and directs left/right atrial identity.^{11,12} *IL-6* is produced by endothelial cells, vascular smooth muscle cells and ischemic myocytes, and has been associated with AF in the setting of coronary disease, and after cardiac surgery, cardioversion, and catheter ablation.¹³ The primary objective of this study is to evaluate clinical and genetic factors associated with postoperative atrial tachycardia (AT) in infants after CHD surgery. We tested the hypothesis that the common polymorphisms in *IL6* and *PITX2* are associated with postoperative atrial tachycardia in the infant CHD population.

METHODS

This study utilized an ongoing observational cohort study of children enrolled at the time of cardiac surgery for CHD. Children less than 1 year of age, undergoing their first surgery for CHD at Monroe Carell Jr. Children's Hospital at Vanderbilt between September 2007 and May 2016 who consented to the study were included. The Institutional Review Board at

Vanderbilt University Medical Center approved this study. Written consent was obtained from parents or legal guardians. Patients whose parents or guardians did not consent and procedures for pacemaker insertion only were excluded. Anticoagulated blood, saliva, or buccal swabs were collected from each subject and genomic DNA was extracted through the Vanderbilt Technologies for Advanced Genomics (VANTAGE) Core laboratory using the Autopure instrument (Qiagen, Valencia, CA). Genotyping of rs1800795 and rs2200733 was performed with the TaqMan PCR Core Reagent Kit (Applied Biosystems, Foster City, CA). Subjects' preoperative, operative, and postoperative data were obtained from the patients' electronic medical record in a systematic fashion in order to minimize observer bias. This information was maintained in a REDCap database.

Every subject had repeated daily assessment of telemetry, and any possible arrhythmias were documented and stored in the study record. Relevant clinical information at the onset of the arrhythmia, including current lab values and medications were collected. Therapies directed at treating the arrhythmia, including electrolyte correction, medications, hypothermia, temporary pacing, and cardioversion were noted. The decision to treat any arrhythmias was left to the discretion of the treating ICU physician and/or cardiologist. Arrhythmia mechanisms were determined with the assistance of atrial electrograms (obtained from temporary atrial wires placed at the time of surgery; routine at our institution) and additional diagnostic maneuvers by pediatric electrophysiologists.

The primary outcome for this study was AT, defined as 3 or more consecutive beats of tachycardia originating from an atrial site that was clearly non-sinus, whether sustained or non-sustained. This definition is intentionally broad, and includes both nonsustained (< 30 seconds) and sustained atrial tachycardias. We performed a secondary analysis comparing patients with treated AT, a marker of clinical severity, to the rest of the cohort (those with no AT and those with AT who did not receive therapy). Other arrhythmia subtypes that were observed did not affect assignment of the primary outcome. Only postoperative arrhythmias occurring prior to hospital discharge, or prior to the next surgical procedure, if occurring before discharge, were recorded. Risk factors for atrial tachycardia were selected based on previous literature and tested for association with univariate and multivariate analysis, as outlined below.^{3,5} Neonates were defined as infants < 28 days at the time of surgery. Racial and ethnic categories were classified according to US National Institutes of Health definitions. Operative procedures were categorized according to the Risk Adjusted classification for Congenital Heart Surgery, Version 1 (RACHS-1) method.¹⁴ In addition, two specific diagnoses, total anomalous pulmonary venous return (TAPVR) and transposition of the great arteries (TGA) were tested for association based on previous independent associations with AT.⁵ Exposure to specific inotropes at ICU admission, as well as the number of inotropes used were tested for association, as use of three or more inotropes has been independently associated with AT.⁵ The durations of ICU and hospital stays were defined as the number of days from the date of surgery to the date of transfer from the ICU and discharge date, respectively. Duration of intubation was defined as the number of days from the date of surgery to the date of permanent extubation.

Statistical Analysis

Continuous data are reported as mean $\pm$ standard deviation, or median (interquartile range) for non-normally distributed variables. Categorical variables are reported as frequencies with percentages. The outcome of AT is dichotomous, and univariate analyses between AT and nominal variables were conducted using a chi-square or Fisher's exact test where appropriate. For continuous variables, a Mann-Whitney U test was employed to compare patients with and without AT. We repeated the analyses comparing patients with AT requiring therapy with those who did not. For genetic associations we considered both co-dominant and dominant modes of inheritance. Due to the predominance of Caucasians in the cohort, stratification by race was not possible; hence a subgroup analysis including only Caucasian subjects was performed. Factors that reached statistical significance in univariate analysis were evaluated using stepwise multivariate logistic regression analysis. Age was evaluated as a continuous variable, as well as 2 separate dichotomous variables (using cutoffs of 28 days, the definition of neonates, and 6 months based on previous literature).⁵ All three age variables were placed into a stepwise multivariate logistic regression model, which retained only the strongest age predictor. Similarly RACHS-1 score was entered as an ordinal variable, as well as two dichotomized variables (3 or higher, and 4 or higher) with all three placed in the stepwise regression model, which retained only the strongest RACHS-1 predictor. Exposure to two or more and three or more inotropes were treated similarly. All multivariate models underwent assessment of fit with the Hosmer and Lemeshow goodness-of-fit test. Significance tests were two-tailed, with a p-value of < 0.05 considered significant. Data was analyzed using SPSS for Windows version 24 (SPSS Inc., Chicago, IL).

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RESULTS

A total of 1067 infants with a median age of 2 months (IQR 0.3 – 5.1) were included in our study. Characteristics of the entire study cohort are listed in Table 1. Overall operative mortality was 6.3%, and median duration of ventilation, ICU stay and hospital stay were 2, 6, and 11 days respectively. A total of 167 patients (15.4%) developed AT at a median of 5 days post-operatively (inter-quartile range 2–8 days). Patients who developed AT were younger, had higher surgical complexity scores, longer bypass and cross-clamp times and more use of inotropic agents. AT was associated with higher risk for ECMO, operative mortality, and longer duration of ventilation, ICU and hospital stays. Univariate analysis comparing infants with and without AT is presented in Supplemental Table 1. Of note, TAPVR and Hispanic ethnicity, 2 factors previously identified as risk factors for AT,⁵ were not associated with AT in our cohort. As a surrogate marker of clinical severity, we also

analyzed the subgroup of patients with AT that received therapy. Of the 167 patients with AT, 95 received therapy for AT. Univariate analysis comparing infants with and without AT requiring therapy is presented in Supplemental Table 2. Factors that associated with AT also significantly associated with AT requiring therapy.

The univariate analyses of genotypes with AT and AT requiring therapy are presented in Table 2. A total of 915 patients were successfully genotyped for *PITX2* (rs2200733). Genotype frequencies were in Hardy-Weinberg equilibrium and were as follows: 75.8% CC, 22.1% TC, and 2.1% TT. The genotype frequencies did not differ significantly with respect to AT or AT requiring therapy. We also considered a dominant mode of inheritance for the minor allele, with similar results [OR and 95% CI 1.13 (0.75–1.69) for AT, 0.9 (0.52–1.56) for AT requiring therapy]. The Caucasian only subgroup analyses also yielded non-significant results (P-value 0.98 for AT; 0.62 for AT requiring therapy). A total of 917 patients were successfully genotyped for *IL6* (rs1800795). Genotype frequencies were in Hardy-Weinberg equilibrium and were as follows: 42% GG, 44.6% CG, and 13.4% CC. Genotype frequencies did not differ significantly with respect to AT or AT requiring therapy. Similar results were observed when considering a dominant mode of inheritance [OR and 95% CI 1.26 (0.87–1.81) for AT, 1.56 (0.96–2.54) for AT requiring therapy]. The Caucasian only subgroup analyses also yielded non-significant results (P-value 0.32 for AT; 0.09 for AT requiring therapy).

Multivariate analysis was then performed for AT and treated AT investigating all factors with significance in univariate analysis. On multivariate analysis, use of 2 or more inotropes, age 28 days, RACHS-1 score 3, and bypass time were all independently associated with AT. Factors independently associated with treated AT include use of 2 or more inotropes, age 28 days, and RACHS-1 score 3. Results of multivariate analysis are presented in Table 3.

DISCUSSION

In this cohort of over 1000 infants undergoing CHD surgery, we observed AT in 15.4% and identified a number of clinical risk factors independently associated with AT, including use of two or more inotropes, higher surgical complexity score, neonatal age at surgery, and cardiopulmonary bypass time. We also investigated two common genetic variants in *PITX2* and *IL6* which have been associated with postoperative AF in adults, but found no association with postoperative AT in infants. Patients with AT had higher morbidity, as evidenced by increased use of ECMO support, and longer durations of ventilation, ICU stay, and hospital stay, as well as higher mortality. This association with mortality does not imply causation; rather AT may be a marker of generalized cardiovascular morbidity.

The lack of any association between our candidate genetic variants and AT deserves comment. Both of these variants have been previously associated with post-operative AF in adults after coronary artery bypass surgery, *PITX2* (rs2200733) with an OR of 2.14 and *IL6* (rs1800795) with an OR of 3.25.^{8,9} With our sample size of genotyped patients and observed genotype frequencies, we were adequately powered to detect an OR of 1.77 or greater.¹⁵ The lack of an association may be secondary to differences in underlying substrates between postoperative AF in adults and postoperative AT in children after CHD surgery. There are

multiple pathways by which *PITX2* could regulate arrhythmogenesis, including effects on atrial function, ion channel regulation, and non-protein targets including microRNAs.¹⁶ *PITX2* has been shown to be integral in the development of pulmonary myocardium sleeves in the left atrium.¹¹ The pulmonary myocardial sleeves are common origins for triggered beats initiating AF and are targeted in AF catheter ablation procedures. In contrast, the origins of postoperative AT in children with CHD are more likely in areas of suture lines, inflammation, or scar which are varied depending on the child's anatomy and surgical procedures. We also investigated the *IL6* polymorphism, because of its role in mediating inflammation, which is thought to potentiate postoperative arrhythmias in infants, but did not find an association. These are not the only variants to be previously associated with post-operative AF, but were selected for study as the magnitude of their effect size in previous studies exceeded our detectable effect size and the differing functions of *PITX2* and *IL6* allowed us to investigate complementary potential arrhythmic pathways, while limiting the number of simultaneous multiple comparisons.

The incidence of AT in our study is higher than previous estimates, likely due to prospective active surveillance, inclusion of nonsustained and untreated AT, and the restriction of our study cohort to infants (< 1 year of age). Two previous smaller studies (with 17 AT subjects each) were not restricted to infants, but identified AT primarily in younger subjects.^{17,18} One previous study with an 8.2% incidence of AT in infants required alteration of therapy for inclusion,⁵ which is similar to our definition of treated AT, for which we observed a similar incidence (8.9%). In that large study, age 6 months or less, TAPVR, use of three or more inotropes, heterotaxy syndrome, and TGA were significantly associated with AT in multivariate analysis. In our population, TAPVR was not associated with AT, nor treated AT, and TGA was significant in univariate analysis, but not in multivariate analysis. We did not have heterotaxy status reliably captured in our database, thus did not evaluate this risk factor. We did replicate the finding that age and use of inotropes were independently associated with AT (and treated AT), but found cutoffs of 28 days and two or more inotropes were stronger predictors in our cohort. Another recent study which reported an 8% incidence of AT captured only sustained (>30 seconds) AT, most of which (88%) were treated.¹⁸ That study identified age < 30 days at surgery and milrinone use as the only 2 variables independently associated with post-operative AT.

Limitations of this study include the following: this was a single center study without an external replication cohort; additional factors which were unaccounted for (including heterotaxy, delayed sternal closure, or the presence of intracardiac lines) may associate with atrial tachycardia; we investigated only early postoperative arrhythmias and in hospital mortality so these results cannot be generalized to late atrial arrhythmias or long-term mortality. Furthermore, this study was restricted to infants therefore it is possible that the polymorphisms investigated here would be relevant in older subjects after congenital heart surgery.

Conclusions

In conclusion, AT occurs in 15% of infants after congenital heart surgery and is associated with increased morbidity and mortality. Risk factors for AT include use of two or more

inotropes, neonatal age at surgery, and higher surgical complexity score. We found no association between common genetic variants in *PITX2* and *IL6* and atrial tachycardia in infants after congenital heart surgery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ABBREVIATIONS

AF	Atrial fibrillation
AT	Atrial Tachycardia
CHD	Congenital Heart Disease
ECMO	Extracorporeal Membrane Oxygenation
ICU	Intensive Care Unit
HLHS	Hypoplastic Left Heart Syndrome
OR	Odds Ratio
RACHS	Risk Adjusted classification for Congenital Heart Surgery
TAPVR	Total Anomalous Pulmonary Venous Return
TGA	Transposition of the Great Arteries

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TABLE 1

DEMOGRAPHIC AND CLINICAL VARIABLES OF 1067 INFANTS IN THE STUDY COHORT

Median Age (mo)	2.0 (0.3 – 5.1)
Neonate (≤ 28 days)	468 (43.9%)
Age < 6 months	895 (83.9%)
Male sex	575 (53.9%)
Hispanic Ethnicity	51 (4.8%)
Race	
White	902 (84.5%)
Black or African American	109 (10.2%)
Other	56 (5.3%)
TAPVR	22 (2.1%)
TGA	77 (7.2%)
Single ventricle	247 (23.1%)
RACHS-1 score ^I	
1	45 (4.3%)
2	347 (33.3%)
3	380 (36.5%)
4	130 (12.5%)
5	2 (0.2%)
6	137 (13.2%)
Bypass time (min)	111 (67 – 151)
Cross-clamp time (min)	46 (22–74)
On ICU admission	
pH	7.35 (7.29 – 7.40)
Lactate	1.9 (1.2 – 3.7)
Dopamine	212 (19.9%)
Epinephrine	285 (26.7%)
Milrinone	719 (67.4%)
Use of ≥ 2 inotropes	419 (39.3%)
Use of ≥ 3 inotropes	166 (15.6%)
In-hospital mortality	67 (6.3%)
ECMO requirement	74 (6.9%)
Hospital stay (days)	11 (7 – 27)
ICU stay (days)	6 (3 – 13)
Mechanical ventilation (days)	2 (1 – 7)

Data represented as N (%) or median (interquartile range)

ECMO = Extracorporeal Membrane Oxygenation

ICU = Intensive Care Unit

RACHS = Risk Adjustment for Congenital Heart Surgery

TAPVR = Total Anomalous Pulmonary Venous Return

TGA = Transposition of the Great Arteries

I_{26} operations not classifiable and excluded from analysis

Number of inotropes includes calcium, dopamine, dobutamine, epinephrine, norepinephrine, milrinone, and isoproterenol.

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TABLE 2

ANALYSIS OF GENOTYPE ASSOCIATIONS FOR *PITX2* AND *IL6* POLYMORPHISMS

	AT (n = 164)	No AT (n = 903)	P-value
<i>PITX2</i> (rs2200733) genotype			0.62
CC	105 (73.9%)	589 (76.2%)	
TC	35 (24.6%)	167 (21.6%)	
TT	2 (1.4%)	17 (2.2%)	
<i>IL-6</i> (rs1800795) genotype			0.37
GG	53 (37.3%)	332 (42.8%)	
CG	66 (46.5%)	343 (44.3%)	
CC	23 (16.2%)	100 (12.9%)	
	Treated AT (n = 95)	No treated AT (n = 972)	P-value
<i>PITX2</i> (rs2200733) genotype			0.39
CC	62 (77.5%)	632 (75.7%)	
TC	18 (22.5%)	184 (22%)	
TT	0 (0%)	19 (2.3%)	
<i>IL-6</i> (rs1800795) genotype			0.19
GG	26 (32.5%)	359 (42.9%)	
CG	42 (52.5%)	367 (43.8%)	
CC	12 (15%)	111 (13.3%)	

TABLE 3**MULTIVARIATE ANALYSIS**

	OR for AT	95% CI	OR for Treated AT	95% CI
Use of 2 inotropes	2.27	1.45 – 3.55	3.32	1.93 – 5.69
Neonate	1.89	1.23 – 2.88	2.06	1.18 – 3.61
RACHS-1 score 3	1.8	1.07 – 3.03	2.31	1.1 – 4.82
Bypass time	1.002	1 – 1.005	NS	NS

Other covariates included for consideration in the stepwise binary logistic regression model: Age (continuous), Age < 6 months, single ventricle, transposition of the great arteries, RACHS-1 score (ordinal), RACHS-1 score 4, use of 3 inotropes, cross-clamp time, lactate, epinephrine, and milrinone. Dopamine was considered as a covariate for AT only. Hosmer and Lemeshow test $p=0.066$ and 0.588.