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A Genetic Contribution to Risk for Postoperative Junctional Ectopic Tachycardia in Children Undergoing Surgery for Congenital Heart Disease

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Abstract

Background—Junctional ectopic tachycardia (JET) is a common arrhythmia complicating pediatric cardiac surgery, with many identifiable clinical risk factors, but no genetic risk factors to date.

Objective—To test the hypothesis that the angiotensin converting enzyme insertion/deletion (ACE I/D) polymorphism associates with postoperative JET.

Methods—DNA samples were collected from children undergoing the Norwood procedure, arterial switch operation, and repairs of Tetralogy of Fallot (TOF), balanced atrioventricular septal defect (AVSD), and ventricular septal defect (VSD) at a single center. The incidence of postoperative JET was associated with previously identified clinical risk factors and ACE I/D genotype.

Results—Of 174 children who underwent the above surgeries, 21% developed JET. Post-operative JET developed in 31% of children with the D/D genotype and only 16% of those with I/I or I/D genotype (p=0.02). Clinical predictors of JET were selected *a priori* and included age, inotrope score, cardiopulmonary bypass and cross clamp times. Multivariable logistic regression identified a significant correlation between the D/D genotype and postoperative JET independent of these predictors (OR=2.4; 95% CI, 1.04-5.34; p=0.04). A gene-dose effect was apparent in the homogenous subset of AVSD subjects (58% JET in D/D subjects, 12% JET in I/D, and 0% JET in I/I; p<0.01).

Conclusion—The common ACE deletion polymorphism is associated with a greater than two-fold increase in the odds of developing JET in children undergoing surgical repair of AVSD, TOF, VSD, or Norwood or arterial switch procedures. These findings may support the potential role of the renin-angiotensin-aldosterone system in the etiology of JET.

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Keywords

Arrhythmia; Pediatrics; Heart defects; congenital; Genetics; ACE polymorphism

Introduction

Postoperative arrhythmias are a significant concern in the care of children undergoing surgical repair of congenital heart disease. The development of arrhythmias in the postoperative period with accompanying hemodynamic compromise has been repeatedly linked to increased morbidity and mortality [1-3]. Junctional ectopic tachycardia (JET) is the most commonly observed arrhythmia in children after cardiac surgery [3, 4] with reported incidences ranging from 6 to 12% [5, 6]. Specific surgical procedures, such as complete repair of Tetralogy of Fallot and atrioventricular septal defect carry particularly high risk, with incidence rates as high as 22% [2]. While JET is a self-limited arrhythmia that typically resolves within several days, associated increases in heart rate along with loss of atrioventricular synchrony, in the setting of potential systolic or diastolic dysfunction, can be detrimental. Patients who develop JET have increased morbidity, including prolonged ventilation times and intensive care unit stays, and mortality compared to their counterparts without JET [2, 3, 5-8]. Pharmacologic therapy may have adverse hemodynamic effects and is sometimes ineffective, and additional treatments ranging from therapeutic hypothermia to catheter ablation to extracorporeal cardiac support may be required, each with variable efficacy and their own related complications [9].

With such morbidity there has been a search for predictive factors to aid in the anticipation, diagnosis, and treatment of this postoperative complication. Several studies have reported clinical risk factors associated with the development of postoperative JET including younger age, smaller size, longer cardiopulmonary bypass and aortic cross clamp times, higher complexity of surgery, and the degree of inotropic support [5-7, 10], yet the genetic contribution to this arrhythmia has not been examined. Given the high frequency of postoperative JET among children requiring certain surgical procedures, we hypothesize that genetic variants which are common in the general population may predispose children to JET, which is only manifested after the insult of certain cardiac surgeries. Evidence is growing that the renin-angiotensin-aldosterone system has proarrhythmic effects, [11] and the common insertion/deletion polymorphism in the angiotensin converting enzyme gene (ACE I/D, rs4646994) has been previously associated with various arrhythmias [12, 13]. The purpose of this study was to test the hypothesis that the ACE I/D polymorphism affects the risk of postoperative JET in children undergoing surgical repair of congenital heart defects.

Methods

Patient Population

Pediatric patients undergoing cardiac surgery at the Monroe Carell Jr. Children's Hospital at Vanderbilt and subsequently admitted to the pediatric cardiac intensive care unit from September 2007 to May 2010 were prospectively enrolled. As the risk of JET varies with the type of surgical procedure [2], for this study we only included patients who underwent one of the following operations: the Norwood procedure for hypoplastic left heart syndrome variants, arterial switch operation for transposition of the great arteries, repair of Tetralogy of Fallot (TOF), repair of balanced atrioventricular septal defect (AVSD), or repair of ventricular septal defect (VSD). Although the specific insult that results in the increased risk of JET for certain surgical procedures is not precisely understood, these procedures were chosen due to the observed high proportion of JET associated with each. Patients undergoing other cardiac surgeries were not included in the analysis as it was felt that even

patients with a genetic predisposition to JET would not develop the arrhythmia following surgeries with very low observed incidences of postoperative JET.

Data collection

Perioperative data collection included patient demographics, prior medical history, preoperative arrhythmias, and operative details including aortic cross clamp and cardiopulmonary bypass times, medications administered, and laboratory values. Patients underwent continuous monitoring with a full-disclosure telemetry system (Phillips Medical Systems, Bothell WA) for the duration of their hospitalization. Study personnel reviewed recordings daily and a pediatric electrophysiologist blinded to the genotype results confirmed all arrhythmias. JET was defined as tachycardia (usually > 170 beats per minute) with rate > 110% of the preceding sinus rate with the following features: 1) a QRS complex similar to conducted sinus beats; 2) a ventricular rate greater or equal to the atrial rate, usually exhibiting a pattern of "warm-up" at initiation, consistent with an automatic mechanism; 3) ventriculoatrial dissociation, or variable or 1:1 retrograde association [14]. Further diagnostic maneuvers including recording of the atrial electrogram, adenosine, and temporary atrial or ventricular pacing were performed when the diagnosis was unclear with inspection of telemetry alone. This study was approved by the Vanderbilt University Institutional Review Board for Research on Human Subjects. Written informed consent was obtained from each subject's parent or legal guardian.

Genotyping

Blood or saliva was collected from each patient and genomic DNA was extracted through the Vanderbilt Center for Human Genetics Research DNA Resources Core using the Autopure instrument manufactured and supported by Qiagen. Genotyping of the common angiotensin converting enzyme insertion/deletion (ACE I/D) polymorphism was performed using a TaqMan PCR Core Reagent kit (Applied Biosystems, Foster City, CA) with slight modifications to the protocol as outlined in Koh, et al [15]. Laboratory personnel performing genotyping were unaware of the clinical status of enrolled subjects.

Data Analysis

Demographic and clinical data were compared using the Mann-Whitney U or analysis of variance tests for continuous variables and the Chi-Square or Fisher's exact test where appropriate for categorical variables. Descriptive statistics are shown as medians with ranges for continuous non-normally distributed data, and frequencies with percentages for categorical variables. Hardy-Weinberg equilibrium was assessed using the chi square test [16]. Clinical and genetic predictors of JET were selected *a priori* based on previously published data and include cardiopulmonary bypass time, aortic cross clamp time, age at surgery, and inotrope score. The inotrope score, which has been previously associated with JET[10], is a calculated score based on the dose of inotropic medications at the initiation of JET or, in those who do not develop JET, the highest dose the patient receives in the first three post-operative days. It was calculated according to the following formula created by Batra et al: $(\text{dopamine}+\text{dobutamine})+(\text{milrinone}\times 20)+[(\text{epinephrine}+\text{norepinephrine})\times 100]^2$ [10].

Multivariable logistic regression was then used to assess the effect of genotype on the development of JET independent of the clinical predictors. In addition to the *a priori* selected variables, those with $p<0.1$ in univariate analysis were used in multivariable analysis. The exception to this is body surface area which was highly correlated with patient age ($r_s=0.86$). In order to avoid multicollinearity, body surface area was excluded from the multivariate regression.

Due to the number of previously identified variables associated with JET, we conducted a sensitivity analysis using a propensity score adjustment to assess for a bias through overfitting. A propensity score was calculated using the beta coefficients of age, aortic cross clamp time, cardiopulmonary bypass time, and inotrope score from a binary logistic regression with the D/D genotype as the outcome. In this way, all of the *a priori* selected clinical variables were condensed into one variable. A logistic regression was then performed with the development of JET as the outcome and the propensity score and D/D genotype as variables. 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. Following analyses of all surgical procedures, the association between the ACE I/D allele and JET was examined in the clinically homogenous subgroup of patients undergoing repair of AVSD. In addition to having a high incidence of JET, this was the only subgroup without neonatal repairs. In this group univariate analysis was performed with the *a priori* selected variables noted above as well as a linear-by-linear association test to assess for a gene-dose effect. Multivariable logistic regression was then performed including all variables with p-value <0.1 in the univariate analysis. Statistical significance was defined as a two-tailed P-value < 0.05. Statistical analysis was performed using SPSS statistical package, release 17.0 (SPSS, Inc., Chicago, IL, USA). The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

During the 32 month enrollment period, 174 consented patients underwent the above mentioned surgeries which were selected due to their high risk of JET, and were included in the analysis. Thirty-six of these patients (21%) developed postoperative JET. The average heart rate during JET was 185 beats per minute, the average duration was 64 hours, and onset was most commonly observed within the first 24 hours after surgery. Retrograde conduction was common with dissociation and intermittent sinus capture beats also observed. Therapeutic measures included cooling, atrial pacing, and intravenous amiodarone. Clinical characteristics of the patients are listed in Table 1. Genotype frequencies were similar among the different surgical procedures. The cohort contained 143 Caucasians, 19 African Americans, 10 biracial patients, and 2 Asians. There were no significant differences in allelic frequency or proportion with JET among these subgroups.

The ACE I/D genotype distribution was in Hardy-Weinberg equilibrium (17% I/I, 49% I/D, 34% D/D). There were no significant differences in aortic cross clamp times or cardiopulmonary bypass times among the ACE genotypes for the entire cohort or for each surgical subgroup. Post-operative JET developed in 31% of children with the D/D genotype and only 16% of those with I/I or I/D genotype (p=0.02). A significant association was present between JET and bypass time (p= 0.01), aortic cross clamp time (p<0.01), age at surgery (p=0.01), and body surface area (p<0.01). In this population, inotrope score did not associate with JET (p=0.73). The results of the multivariable analysis are in Table 2. Patients with the D/D genotype had a greater than two-fold increase in the odds of developing JET as compared to those with I/I or I/D genotype after adjusting for aortic cross clamp and cardiopulmonary bypass times, age, and inotrope score (OR= 2.4; 95%CI, 1.04-5.34; p=0.04). The propensity score and Caucasian subgroup analysis, conducted as sensitivity analyses, yielded similar results (propensity score adjusted OR= 2.2; 95% CI, 1.01-4.60; p=0.05; Caucasian subgroup adjusted OR= 2.8; 95%CI, 1.08-7.00; p=0.03) indicating neither over-fitting nor race negates the impact of the D/D genotype on the development of JET.

The association of the D/D genotype with JET was assessed in the homogenous group of 34 patients undergoing AVSD repair, 9 of whom (27%) developed JET. Hardy-Weinberg equilibrium was maintained in this subset (15% I/I, 50% I/D, 35% D/D), and the D/D genotype remained a significant predictor of JET (12% JET in I/I or I/D; 56% JET in D/D, $p<0.01$) in univariate analysis. The only significant predictors of JET in univariate analysis were the ACE polymorphism, aortic cross clamp ($p<0.01$) and bypass times ($p=0.05$). Age ($p=0.70$) and inotrope score ($p=0.70$) were not associated with JET in this clinically homogenous group. With multivariable analysis, the ACE genotype remained a significant predictor of JET after adjusting for bypass and aortic cross clamp times (OR= 25.9; 95%CI, 1.77-378.05; $p=0.02$). Additionally, a gene-dose effect was seen such that none of the patients with I/I genotype, 12% of those with I/D genotype, and 58% of those with D/D genotyped developed JET ($p<0.01$). Of note, 68% of this group had Trisomy 21 but there was not a significant difference in genotype frequencies or development of JET between those with and without Trisomy 21.

Discussion

This study is the first to demonstrate a genetic predisposition to postoperative junctional ectopic tachycardia, the most prevalent arrhythmia in the post-operative period among children undergoing congenital cardiac surgery. Specifically, the ACE D/D genotype displayed a significant association with the development of postoperative JET in this cohort of children undergoing an array of common congenital cardiac operations: arterial switch operation, Norwood procedure, and surgical repair of Tetralogy of Fallot, ventricular septal defect, and balanced atrioventricular septal defects. The magnitude of the association is clinically significant, as the D/D genotype more than doubles the odds of developing JET while previously identified clinical predictive factors only slightly increase the odds of this arrhythmia. Furthermore, a gene dose effect is illustrated in the relatively homogenous group of patients who had an atrioventricular septal defect repair, supporting a causative association. Determination of a genetic predisposition for postoperative JET could provide an increased ability to predict this arrhythmia and suggest novel treatment modalities which could impact patient management and outcomes. Therefore, further investigation of this association is warranted.

To our knowledge, genetic contributions to risk for postoperative arrhythmias in children have not been investigated. A genetic predisposition to postoperative JET is suggested by the highly familial nature of non-postoperative JET [17]. While no specific genes have yet been identified in this rare syndrome, it is presumably caused by variants that are rare in the general population, but with strong effects resulting in the clinical phenotype of JET without requiring the insult of cardiac surgery. Given the relatively common nature of the postoperative form of JET after certain cardiac surgeries, we hypothesized that variants which are common in the general population could result in no arrhythmia phenotype at baseline, but would increase the risk for JET when combined with the insult of cardiac surgery. We chose to test the ACE I/D polymorphism due to its frequency and known proarrhythmic effects, making it a reasonable candidate to increase risk for postoperative JET.

Whether the association between the D/D ACE genotype and postoperative JET is due to a causative effect is unclear and warrants further investigation. While the precise cellular mechanism of JET is unknown, multiple lines of evidence support a biologically plausible link between the ACE polymorphism and postoperative JET. ACE cleaves angiotensin I into angiotensin II, which triggers multiple signaling pathways, directly modulating membrane ion channels, intracellular calcium handling, and gap junctions, as well as increasing oxidative stress [11]. It has been well established that the ACE I/D polymorphism affects

plasma ACE levels [18], cellular levels of angiotensin I and II [19], and cardiac ACE activity, with higher ACE activity and angiotensin II levels in D/D subjects compared to I/I subjects, and intermediate levels in heterozygotes [20]. Thus, our finding of higher risk for postoperative JET in D/D subjects, and an apparent gene-dose effect in subjects with AVSD, is consistent with a proarrhythmic state from higher ACE and angiotensin II levels. The polymorphism has been previously associated with atrial fibrillation [12] and reperfusion-induced ventricular arrhythmias[19], as well as prolonged AV nodal conduction in patients with structural heart disease [21]. Our association of the polymorphism with post-operative JET in children may reflect either a direct effect, or possibly indirect mechanisms that lead to proarrhythmia.

In addition to identifying patients at higher risk for the development of JET, these results raise the possibility of new preventative treatments for postoperative JET. Postoperative JET is common after procedures with mechanical stretch in the area of the AV node, and in lesions with chronic volume (VSD/AVSD) or pressure (TOF) overload resulting in myocardial hypertrophy and/or congestive heart failure. Pulsatile stretch simulating such conditions results in electrical remodeling of ion channels and gap junction proteins in cardiac myocytes [22], and these changes are prevented by pharmacologic angiotensin II blockers [23, 24]. It has previously been shown that response to antiarrhythmic therapy for atrial fibrillation is affected by ACE genotype [25]. Modulating ACE activity with ACE inhibitors or angiotensin receptor blockers specifically in patients with the D/D genotype may decrease the incidence of postoperative JET in this highly susceptible population. Additionally, a pharmacogenomic interaction between the ACE I/D polymorphism and beta-blockers has been demonstrated in patients with congestive heart failure [26]. Transplant-free survival was poorer for patients with the D allele, but only in those not treated with a beta-blocker. Given the high adrenergic states associated with postoperative JET, beta-blockers may similarly protect susceptible D/D individuals from postoperative JET. Further study of this association and potential pharmacogenomic implications will need to be completed.

Limitations

While this study's findings are clinically relevant and have implications for management and prevention of postoperative JET, there are limitations. One drawback is the relatively small sample size. Clinical predictors with weaker effects may not be identified, and additional analysis adjusting for patients receiving ACE inhibitors or other medications affecting the renin-angiotensin-aldosterone system could not be performed. Genetic results were not known at the time of surgery, thus preventive measures could not be tested in those with D/D genotype. Like all genetic association studies, these results must be replicated.

Conclusion

The incidence of postoperative JET remains high in children after arterial switch operation, Norwood procedure, and repair of TOF, VSD, and AVSD. A common deletion polymorphism in the ACE gene is independently associated with a greater than two-fold increased risk of postoperative JET in these children, with a stronger effect compared to previously established clinical predictors. A gene-dose effect is apparent in the relatively homogenous subgroup of patients undergoing repair of AVSD. Together, these results support a role for the renin-angiotensin-aldosterone system in the etiology of JET.

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Abbreviations

JET	Junctional Ectopic Tachycardia
TOF	Tetralogy of Fallot
AVSD	Atrioventricular Septal Defect
VSD	Ventricular Septal Defect
ACE	Angiotensin Converting Enzyme

Table 1

Demographic and baseline clinical characteristics

	Without JET* n=138	With JET* n=36	P Value
Age - days	157 (1-4262)	96.5 (3-229)	0.01
Body Surface Area - m^2	0.31 (0.17-1.91)	0.26 (0.13-0.47)	<0.01
Cross-clamp time - min	51 (21- 217)	79 (8-110)	<0.01
CPB time -min	111 (53-404)	141 (57-263)	0.01
Inotrope score	10 (0-36)	10 (0-25)	0.73
Race			0.77
Caucasian	114 (80%)	29 (20%)	
Not Caucasian	24 (77%)	7 (23%)	
Gender			0.79
Male	80 (80%)	20 (20%)	
Female	58 (78%)	16 (22%)	
ACE I/D Genotype			0.02
I/I or I/D	97 (84%)	18 (16%)	
(I/I)	25 (83%)	5 (17%)	
(I/D)	72 (86%)	13 (14%)	
D/D	41 (69%)	18 (31%)	
Surgical Procedures			0.47
Arterial Switch	14 (78%)	4 (22%)	
AVSD Repair	25 (74%)	9 (27%)	
Norwood	14 (82%)	3 (18%)	
TOF repair	26 (72%)	10 (28%)	
VSD repair	59 (85%)	10 (15%)	

* Data are given as medians with ranges for continuous data and frequencies with percentages for categorical variables.

ACE I/D= Angiotensin Converting Enzyme insertion/deletion; AVSD= Atrioventricular Septal Defect; CPB= Cardiopulmonary Bypass; JET= Junctional Ectopic Tachycardia; TOF= Tetralogy of Fallot; VSD= Ventricular Septal Defect

Table 2

Multivariable analysis of covariates associated with development of JET

Variable	Adjusted Odds Ratio (95% CI)	Adjusted P Values
D/D Genotype	2.4 (1.04-5.34)	0.04
Aortic cross clamp time	1.02 (1.00-1.04)	0.04
Cardiopulmonary bypass time	1.00 (0.99-1.01)	0.99
Age	0.99 (0.98-0.99)	0.01
Inotrope Score	0.92 (0.85-0.99)	0.03

JET= Junctional Ectopic Tachycardia