Received: 6 July 2021 | Revised: 13 September 2021 | Accepted: 13 October 2021

DOI: 10.1111/cts.13178

ARTICLE

β1-receptor polymorphisms and junctional ectopic tachycardia in children after cardiac surgery

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Funding information
Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under University of Florida Clinical and Translational Science Awards TL1TR001428 and UL1TR001427, and National Heart, Lung, and Blood Institute of the National Institutes of Health award number F31HL154563 awarded to L.D

Abstract

Junctional ectopic tachycardia (JET) is a potentially life-threatening postoperative arrhythmia in children with specific congenital heart defects and can contribute significantly to postoperative morbidity for at-risk populations. In adults, β1-adrenergic receptor (*ADRB1*) and β2-adrenergic receptor (*ADRB2*) genotypes have been associated with increased risk for arrhythmias. However, their association with arrhythmia risk in children is unknown. We aimed to test associations between *ADRB1* and *ADRB2* genotypes and postoperative JET in patients with congenital heart defects. Children who underwent cardiac surgery were genotyped for the *ADRB1* p.Ser49Gly (rs1801252; c.145A>G), p.Arg389Gly (rs1801253; c.1165C>G), *ADRB2* p.Arg16Gly (rs1042713; c.46A>G), and p.Glu27Gln (rs1042714; c.79G>C) polymorphisms. The occurrence of postoperative JET was assessed via cardiologist-interpreted electrocardiograms. Genotype associations with JET were analyzed via logistic regression, adjusted for clinical variables associated with JET, with separate analysis in patients not on a β-blocker. Of the 343 children included (median age 8 months, 53% boys, 69% European ancestry), 45 (13%) developed JET. The Arg389Arg genotype was not significantly associated with JET in the overall population (odds ratio [OR] = 1.96, 95% confidence interval [CI] = 0.96–4.03, $p = 0.064$), but was nominally associated in patients not taking a β-blocker ($n = 324$, OR = 2.25, 95% CI = 1.05–4.80. $p = 0.034$). None of the other variants were associated with JET. These data suggest that the *ADRB1* Arg389Arg genotype may predict risk for JET following cardiac surgery

in pediatric patients in the absence of β-blockade. Whether treatment with a β-blocker ameliorates this association requires further research.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
ADRB variants have been associated with arrhythmias in an adult population; however, the contribution of these variants to postoperative arrhythmia risk in children with congenital heart disease is unknown.

WHAT QUESTION DID THIS STUDY ADDRESS?
Is there an association among *ADRB1* Ser49Gly, *ADRB1* Arg389Gly, *ADRB2* Arg16Gly, or *ADRB2* Gln27Glu genotypes and postoperative junctional ectopic tachycardia (JET) occurrence in children undergoing cardiac surgery?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
ADRB1 Arg389Arg genotype may help predict risk for JET following cardiac surgery in pediatric patients in the absence of β-blockade.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
These findings serve as a foundation for further study of postoperative JET risk and *ADRB1* Arg389Arg genotype and suggest a potential role of β-blockade in reducing genotype-mediated risk for JET in *ADRB1* Arg389Arg genotype patients.

INTRODUCTION

Postoperative arrhythmia is a major cause for morbidity and mortality in children undergoing cardiac surgery for repair of congenital heart defects (CHD).[1] Junctional ectopic tachycardia (JET) is a potentially life-threatening postoperative arrhythmia occurring in 10% to 15% of patients in this setting[2,3] and is especially common following repair of atrioventricular septal defect, ventricular septal defect, or Tetralogy of Fallot.[4,5] The morbidity associated with JET leads to prolonged ventilation time, increased intensive care unit (ICU) length of stay, and higher ICU mortality.[3,6] Ideally, if risk of JET could be predicted preoperatively, measures could be undertaken to prevent or minimize its occurrence postoperatively.

β-adrenergic receptors play a significant role in the regulation of heart rate, cardiac contractility, and cardiac electrical activity.[7,8] The β1- and β2-adrenergic receptors are encoded by the *ADRB1* and *ADRB2* genes, respectively. The *ADRB1* p. Ser49Gly (rs1801252; c.145A>G) and p. Arg389Gly (rs1801253; c.1165C>G) polymorphisms as well as the *ADRB2* p. Arg16Gly (rs1042713; c.46A>G) and p. Gln27Glu (rs1042714; c.79G>C) polymorphisms have been associated with altered adrenergic receptor signaling in vitro.[9,10] Specifically, the *ADRB1* Ser49 and Arg389 alleles confer greater agonist-mediated response, and the *ADRB2* Gly16 and Gln27 alleles lead to enhanced agonist-mediated receptor downregulation and increased agonist-mediated responsiveness, respectively.[10,11] Among adults undergoing cardiac surgery, the *ADRB1* Arg389Gly polymorphism was associated with an increased risk for postoperative atrial fibrillation.[12] In a case-control study of patients with idiopathic ventricular arrhythmias, the *ADRB2* Gly16 and Glu27 variants were linked to increased risk of ventricular arrhythmias.[13] However, the contribution of these variants to arrhythmia risk in children with CHD is unknown. The purpose of this study was to investigate the association among *ADRB1* Ser49Gly, *ADRB1* Arg389Gly, *ADRB2* Arg16Gly, and *ADRB2* Gln27Glu and postoperative JET occurrence in children undergoing cardiac surgery.

METHODS

Study population

The Molecular Genetics of Pediatric Patients with Congenital Heart Disease Sample and Data Bank (hereafter referred to as the CHD Bank) included data and samples for genetic analysis from pediatric patients (age ≤21 years) who underwent cardiac surgery at the University of Florida between 2012 and 2017. This study was approved by the University of Florida Institutional Review Board for Research on Human Subjects. Written informed consent was obtained from each patient included in this analysis, or from his/her parent or legal guardian.

Data and sample collection

A blood or buccal cell sample for genetic analysis was collected prior to or during cardiac surgery. Demographic and clinical data from the time of the hospitalization associated with surgery were manually abstracted from the electronic health record and entered into the CHD Bank. Electrocardiograms (ECGs) done between the operation and hospital discharge were reviewed by a pediatric cardiologist to determine the occurrence of postoperative JET. Using self-reported race from the electronic health record (i.e., White, Black, or Asian), patient ancestries were categorized as European, African, or other.

Genotyping

DNA was extracted from blood or buccal cells using the FlexiGene DNA Kit (Qiagen, Valencia, CA). DNA concentration and quality were assessed via a NanoDrop 2000c Spectrophotometer (Thermo Fisher Scientific, Waltham, MA). Genotyping of the *ADRB1* Ser49Gly (rs1801252), *ADRB1* Arg389Gly (rs1801253), *ADRB2* Arg16Gly (rs1042713), and *ADRB2* Glu27Gln (rs1042714) polymorphisms was performed via TaqMan Assay on a QuantStudio 12k Flex (Thermo Fisher Scientific) genotyping platform.[14] Given the linkage disequilibrium between the *ADRB1* Ser49Gly and Arg389Gly genotypes, we also investigated the association between the *ADRB1* haplotype and risk for JET.[14,15] The number of haplotype copies for *ADRB1* Ser49Arg389 was generated using the genotype data with PHASE version 2.1.1.[16,17]

Statistical analysis

Clinical and operative characteristics were compared between patients with and without JET occurrence using a *t*-test for continuous data and chi-square analysis for categorical data. Because of lower frequencies of the homozygous variants, the *ADRB1* Ser49Gly, Arg389Gly, and *ADRB2* Glu27Gln genotypes were tested using the dominant model. For the *ADRB2* Arg16Gly genotype, the Gly16 variant is the major allele and so the recessive model was used for consistency. Associations between genotype or haplotype and JET were analyzed using a multivariable logistic regression model. Regression models were adjusted for variables previously shown to be associated with pediatric postoperative JET, such as age, sex, procedures at high-risk for postoperative JET, aortic cross-clamp (ACC) time, cardiopulmonary bypass time (CPB), inotrope use, and β-blocker use.[2,4,18–21] Body surface area was not included in this adjustment because of its significant correlation (r = 0.94) with age. Procedures considered high-risk for postoperative JET were arterial switch procedure, atrioventricular septal defect repairs, Fontan procedure, Norwood procedure, tetralogy of Fallot (TOF) repair, total anomalous pulmonary venous return repair, and ventricular septal defect repair.[2,3,21–23] Based on the number of participants enrolled in this prospective cohort, we had 80% power to detect an odds ratio (OR) of two for the *ADRB1* Arg389Gly genotype.

Because β-blockers may attenuate any effect of genotype on arrhythmia risk, a prespecified subgroup analysis was performed in patients without recorded use of perioperative β-blockers prior to JET occurrence.[20] All analyses were performed using R version 4.0.2.

RESULTS

A total of 343 patients from the CHD Bank were included in the analysis. The median age of the overall population was 7.9 months (interquartile range [IQR]: 1.6–59.9 months); 183 (53%) patients were boys, and 235 (69%) were of European ancestry (Table 1). The most common surgical procedures were atrial septal defect repair and ventricular septal defect repair, with 124 (36%) patients undergoing a combination of procedures. One hundred sixty-two (47%) patients underwent at least one procedure deemed high-risk for postoperative JET. A total of 161 (47%) patients received inotropic support prior to the occurrence of JET (161; 47%), most commonly with milrinone (154; 45%) and epinephrine (119; 35%). Nineteen patients (6%) were started on β-blocker therapy prior to JET occurrence.

Genotype frequencies were consistent with previously reported frequencies (Table 2), and all single nucleotide polymorphisms (SNPs) were in Hardy Weinberg equilibrium.[24]

Overall, 45 (13%) patients developed JET. Consistent with previous reports, patients with JET were significantly younger, of smaller body size, underwent more procedures deemed high-risk for postoperative JET, and had longer ACC and CPB times (Table 1). In the population overall, there was no significant association between the *ADRB1* Arg389Arg genotype and risk for JET (adjusted $p = 0.064$). However, in the subset of patients who were not taking a β-blocker prior to JET occurrence, the Arg389Arg genotype was nominally associated with an increased risk for JET (adjusted OR = 2.25, 95% confidence interval [CI] = 1.05–4.80, adjusted $p = 0.034$). There were no associations between JET and *ADRB1* Ser49Gly, *ADRB2* Arg16Gly, or *ADRB2* Glu27Gln genotypes in the population overall or in patients not treated with a β-blocker prior to JET occurrence (Table 3). There

TABLE 1 Clinical and operative characteristics

	Total $n = 343$	With JET $n = 45$	Without JET $n = 298$	p value (with JET vs. without JET)
Age, months	7.9 (1.6–59.9)	2.3 (0.4–8.2)	10.3 (2.7–65.5)	2.76×10^{-6}
Male sex	183 (53%)	22 (54%)	161 (48%)	0.519
Ancestry				
European	235 (69%)	205 (66%)	30 (68%)	0.875
African	70 (20%)	61 (20%)	9 (20%)	
Other	38 (11%)	32 (13%)	6 (10%)	
Body surface area, m^2	0.58 ± 0.48	0.36 ± 0.28	0.62 ± 0.50	2.40×10^{-6}
Aortic cross-clamp time, min	55.1 ± 32.2	65.2 ± 31.5	53.4 ± 32.1	0.029
Cardiopulmonary bypass time, min	89.4 ± 48.0	103.4 ± 44.0	87.1 ± 48.3	0.026
Surgical procedure[a]				
Procedure for high-risk for postoperative JET	162 (47%)	36 (80%)	126 (42%)	2.31×10^{-6}
ASD repair	102 (30%)	20 (44%)	82 (28%)	
VSD repair	77 (22%)	21 (47%)	56 (29%)	
TOF repair	30 (8%)	11 (24%)	19 (6%)	
AVSD repair	28 (8%)	5 (11%)	23 (8%)	
Norwood	20 (6%)	3 (7%)	17 (6%)	
Perioperative medications				
β-blocker use	19 (6%)	3 (7%)	16 (5%)	0.723
Inotrope use[b]	161 (47%)	135 (58%)	26 (45%)	0.118

Note: Mean ±SD, median (interquartile range [IQR]), or *N* (%).

Abbreviations: AA, aortic arch; ASD, atrial septal defect; AVSD, atrioventricular septal defect; JET, junctional ectopic tachycardia; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

[a]Some patients underwent multiple concurrent procedures.

[b]Consisted of milrinone ($n = 154$, 45%) and epinephrine ($n = 119$, 35%).

was also no significant association between Ser49Arg389 haplotype and JET in the population overall ($p = 0.068$) or among patients not on β-blockers ($p = 0.064$).

DISCUSSION

In this study, the *ADRB1* Arg389Arg genotype was associated with JET occurrence following cardiac surgery in pediatric patients not on a β-blocker, but not when considering all patients. The etiology of postoperative arrhythmias after pediatric and congenital cardiac surgery is multifactorial; however, adrenergic activation has been implicated in the pathogenesis of arrhythmias.[25,26] Postoperative arrhythmias are specifically hypothesized to occur due to stress-induced catecholamine release (i.e., adrenergic stimulation) during surgery.[27] Variation in adrenergic signaling has been reported secondary to the *ADRB1* Arg389Arg genotype, with increased agonist-stimulated adenylyl cyclase activity with the Arg389 versus Gly389 allele.[9,28,29] Conversely, Gly389 is associated with decreased G-protein coupling of the β1-adrenergic receptor, and consequently, a reduction of cyclic AMP levels.[9] Therefore, it is plausible that an increased risk of

TABLE 2 Frequencies of *ADRB1* and *ADRB2* genotypes

Gene	Codon	Genotype	*N* (%)
ADRB1	49	Ser49Ser	234 (68%)
		Ser49Gly	99 (29%)
		Gly49Gly	10 (3%)
	389	Arg389Arg	179 (52%)
		Gly389Arg	133 (39%)
		Gly389Gly	31 (9%)
ADRB2	16	Arg16Arg	59 (17%)
		Gly16Arg	156 (45%)
		Gly16Gly	128 (37%)
	27	Gln27Gln	161 (47%)
		Gln27Glu	138 (40%)
		Glu27Glu	44 (13%)

TABLE 3 *ADRB1* and *ADRB2* genotype associations with JET

	All patients			No β-blocker use		
	OR	95% CI	Adj. *p* value[a]	OR	95% CI	Adj. *p* value[a]
ADRB1 Gly49 (Ref. Ser49Ser)	1.09	0.51–2.31	0.821	1.01	0.47–2.16	0.988
ADRB1 Arg389Arg (Ref. Gly389)	1.96	0.96–4.03	0.064	2.25	1.05–4.80	**0.034**
ADRB2 Gly16Gly (Ref. Arg16)	1.71	0.85–3.43	0.132	1.50	0.72–3.09	0.273
ADRB2 Glu27 (Ref. Gln27Gln)	1.41	0.70–2.84	0.333	1.44	0.70–2.96	0.325
ADRB1 Ser49Arg389 (Number of haplotypes)	1.61	0.96–2.71	0.068	1.65	0.97–2.81	0.064

Abbreviations: CI, confidence interval; JET, junctional ectopic tachycardia; OR, odds ratio.

[a]Models adjusted for age, sex, procedure high-risk for postoperative JET, and aortic cross-clamp time, cardiopulmonary bypass time, inotropes use, and β-blocker use (except in the substudy with patients without β-blocker use).

cardiovascular-related events, and specifically susceptibility for arrhythmia, may occur secondary to the greater catecholamine-mediated response with the Arg389 allele.[10] In contrast to our findings, a study of adults undergoing cardiac surgery reported that the Gly389Gly genotype was associated with an increased risk for postoperative atrial fibrillation.[12] However, our findings are consistent with other studies in adult populations with cardiac disease showing a higher prevalence of ventricular arrhythmias with the Arg389Arg genotype.[30,31] Our findings (and those of others) may be explained by decreased β1-adrenergic receptor signaling associated with the Gly allele, potentially providing protection against tachycardia-inducing sympathetic surges, which can occur during surgery.

The association we observed in patients untreated versus treated with β-blockers indicates that preemptive β-blocker administration could potentially attenuate the risk of postoperative JET associated with the Arg389Arg genotype. Evidence suggests that adrenergic antagonists—via reductions in adrenergic stimulation—decrease the risk of JET and could be a potential preventive therapy.[32] Specifically, dexmedetomidine, an α2-adrenergic receptor agonist with sympatholytic effects, decreases the incidence of postoperative JET.[33,34] Similarly, pre-operative use of propranolol, a nonselective β-blocker, reduced the incidence of postoperative JET after TOF repair.[20] Our data suggest that β-blockers may specifically attenuate the risk associated with the *ADRB1* genotype for postoperative JET occurrence in children undergoing cardiac surgery. Similarly, Pacanowski et al. found that, compared to verapamil treatment, atenolol reduced the risk for death among patients with hypertension with the *ADRB1* Ser49Arg389 haplotype.[14] Although not reaching statistical significance, we observed a trend in association between this haplotype and risk for JET. β-blockers have also been shown to modify the effect of the Arg389Arg genotype on nonsurgical arrhythmia risk, as reported in a genetic substudy of the β-Blocker Evaluation of Survival Trial in patients with heart failure.[35] The increased risk for ventricular tachycardia and fibrillation observed with the Arg389Arg genotype in the placebo arm was attenuated with bucindolol treatment. Conversely, bucindolol treatment had no impact on arrhythmia risk in Gly389 allele carriers.[35] Whereas these data help to support the use of β-blockers to potentially attenuate an arrhythmogenic genotype effect, considering the small number of patients taking β-blockers in our study, our results should be considered hypothesis-generating, and additional studies are needed to determine whether prophylactic use of β-blockers may reduce the risk for JET in pediatric patients undergoing procedures deemed high-risk for postoperative JET based on genotype.

We acknowledge a few limitations in our study. In addition to the small number of patients treated with β-blockers, our overall total cohort was relatively small, and we were underpowered to detect smaller effect sizes and to detect haplotype associations. Data on use of dexmedetomidine was not available in the CHD Bank and, thus, we were unable to account for any potential effects of the drug on the occurrence of JET. We also did not consider the role of other SNPs that may be associated with the incidence of postoperative JET.[36] In particular, the *GRK5* gene encodes GRK5, a kinase that phosphorylates cardiac β-adrenergic receptors and regulates G protein coupling and signaling.[37,38] The *GRK5* rs2230345 variant (Gln41Leu), which occurs at a much higher frequency in African ancestral populations, has been shown to increase the desensitization of the β1-adrenergic receptor, which in turn leads to lower receptor stimulation and cAMP production, essentially acting as endogenous β-blockade.[24,38] Further studies assessing the combination of variants that influence risk for postoperative arrhythmia are warranted.

In conclusion, our data suggest that the *ADRB1* Arg389Arg genotype may be useful in predicting risk for postoperative JET in pediatric patients undergoing cardiac surgery. Whether β-blockers may have a role in risk

reduction in patients with the Arg389Arg genotype remains to be determined.

ACKNOWLEDGMENTS

The authors would like to thank the research participants for their participation. We would also like to thank Lisa Schnabel, Lynda Stauffer, and Cheryl Galloway for their logistical support throughout the project.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

L.D., J.D.D., and L.H.C. wrote the manuscript. L.D., M.C., T.L., D.H.Z., D.L., J.A.J., G.J.P., J.P.J., M.S.B., and L.H.C. designed the research. L.D., M.C., B.Q.D., D.H.Z., F.H., J.F.H., J.D., T.L., and C.M. performed the research. L.D. and F.H. analyzed the data.

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How to cite this article: Dumeny L, Chantra M, Langaee T, et al. β1-receptor polymorphisms and junctional ectopic tachycardia in children after cardiac surgery. *Clin Transl Sci*. 2022;15:619–625. doi:10.1111/cts.13178