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A Common Angiotensin-Converting Enzyme (ACE) Polymorphism and Preoperative ACE Inhibition Modify Risk of Tachyarrhythmias After Congenital Heart Surgery

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Abstract

Background—The angiotensin-converting enzyme insertion/deletion (ACE I/D) polymorphism is described in association with numerous phenotypes including arrhythmias, and may provide predictive value among pediatric patients undergoing congenital heart surgery.

Objective—To examine the role of a common polymorphism on postoperative tachyarrhythmias in a large cohort of pediatric patients undergoing congenital heart surgery with cardiopulmonary bypass (CPB).

Methods—Subjects undergoing congenital heart surgery with CPB at our institution were consecutively enrolled from September 2007 through December 2012. In addition to DNA, perioperative clinical data were obtained from subjects.

Results—Postoperative tachyarrhythmias were documented in 45% of 886 enrollees, and were associated with prolonged mechanical ventilation ($p < 0.001$) and ICU length of stay ($p < 0.001$). ACE I/D was in Hardy-Weinberg equilibrium (19% I/I, 49% I/D, 32% D/D). I/D or D/D genotypes were independently associated with a 60% increase in odds of new tachyarrhythmia (OR 1.6, 95%CI 1.1–2.3, $p = 0.02$). Preoperative ACE inhibitor administration was independently associated with a 47% reduction in odds of postoperative tachyarrhythmia in the entire cohort (OR

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0.53, 95% CI 0.32–0.88, $p=0.01$), driven by a five-fold reduction in tachyarrhythmias among I/I genotype patients (OR 0.19, 95% CI 0.04–0.88, $p=0.02$).

Conclusions—The risk of tachyarrhythmias after congenital heart surgery is independently affected by the ACE I/D polymorphism. Preoperative ACE inhibition is associated with a lower risk of postoperative tachyarrhythmias, an antiarrhythmic effect that appears genotype dependent. An understanding of genotype variation may play an important role in the perioperative management of congenital heart surgery.

Keywords

Cardiac surgery; Congenital heart disease; Pharmacogenetics; Genomics; Arrhythmias

Introduction

Despite substantial reductions in mortality following congenital heart surgery, associated morbidity remains a challenging element of postoperative management.^{1,2} Arrhythmias following congenital heart surgery are common, with variable reported incidence (typically 30–50%), owing in part to variation in both patient population and types of arrhythmias considered.^{3–6} Early postoperative arrhythmias are also clinically significant, accounting for increases in duration of mechanical ventilation, as well as intensive care unit and hospital stays.^{7,8} Furthermore, early postoperative arrhythmias are associated with increased operative mortality, as well as increasing risk for interstage mortality following a Stage 1 (Norwood) palliation for hypoplastic left heart syndrome (HLHS).^{8–10}

Multiple perioperative factors such as type of operative repair, aortic cross clamp duration, and inotrope utilization have been associated with an increased incidence of postoperative arrhythmias, but little is known concerning potential variations in patient susceptibility.^{5,11,12} While potential genetic contributions to risk of postoperative arrhythmias and response to antiarrhythmic pharmacotherapy are described in adult patient populations, little is known concerning such relationships in children following congenital heart surgery.^{13–15} We have previously identified the common angiotensin converting enzyme insertion/deletion (ACE I/D) polymorphism as a significant predictor of postoperative junctional ectopic tachycardia (JET) following specific congenital heart surgeries.¹⁶ However, the potential proarrhythmic effects of renin-angiotensin-aldosterone system (RAAS) derangements are not limited to one arrhythmia substrate, and the ACE I/D polymorphism specifically has also been associated with atrial arrhythmias and postoperative ventricular arrhythmias in adults.^{17–19} We therefore tested the hypothesis that this genetic variant (ACE I/D) alters the risk of any tachyarrhythmia following congenital heart surgery, and investigated the effect of preoperative modulation of the RAAS on postoperative tachyarrhythmias. Here we show that independent of other significant risk factors, patients with at least 1 copy of the ACE I/D deletion allele (I/D or D/D genotypes) have a 60% increased odds of postoperative tachyarrhythmias relative to patients with an I/I genotype. Furthermore, we identify a novel pharmacogenetic interaction, demonstrating that preoperative ACE inhibitor therapy in patients with two copies of the ACE I/D insertion allele is associated with a significant reduction in the incidence of postoperative tachyarrhythmias.

Methods

Patient population

The subjects included in the present analysis were enrolled in an ongoing prospective, observational Postoperative Arrhythmias in Congenital Heart Surgery (PACS) study. All patients undergoing congenital heart surgery at Monroe Carell Jr. Children's Hospital at Vanderbilt and subsequently admitted to the pediatric cardiac intensive care unit (CICU) from September 2007 through December 2012 were approached for enrollment in the study, which specifically includes consent to genetic analysis. Each patient's parents or legal guardians provided written informed consent, and patient assent was obtained as age appropriate. The Vanderbilt University Institutional Review Board for Research on Human Subjects approved the present study.

Data collection

Perioperative data collection included patient demographic characteristics, anatomic diagnoses, noncardiac medical history, preoperative medications, history of prior arrhythmias, and family history of arrhythmias. Past history of preoperative arrhythmias were ascertained both through chart review and history taken at the time of enrollment. The operative details noted included the primary procedure and associated secondary procedures, in addition to the aortic cross-clamp and cardiopulmonary bypass times. Operative procedures were also categorized according to the Risk Adjusted Classification for Congenital Heart Surgery, version 1 (RACHS-1) category where applicable.²⁰

Early postoperative data recorded included admission pH, serum lactate, hematocrit, serum electrolytes, and continuous infusions administered on admission to the CICU. Patients underwent continuous monitoring with a full-disclosure telemetry system (Philips Medical Systems, Bothell, Washington) for the duration of their hospitalization. Study personnel reviewed the telemetry recordings daily, and all arrhythmias were confirmed by pediatric electrophysiologists. Each postoperative arrhythmia was coded with respect to time of onset, mechanism, and any associated therapy. Serum electrolytes were assessed and replaced either parenterally or enterally at the discretion of the provider, traditionally with goals of maintaining potassium 3.5 to 5.0 mEq/L, ionized calcium 4.5 to 5.5 mg/dL, and serum magnesium 1.8 to 2.2 mEq/L. Sedation, analgesia, and neuromuscular blockade were all managed at the discretion of the anesthesia and CICU teams.

The present study was designed to capture all arrhythmias, including those clearly resulting from discrete events such as myocardial ischemia or hypoxia. Postoperative recurrences of arrhythmias documented preoperatively were not considered for analysis. Numerous subjects experienced more than one class of arrhythmia after a single operative procedure. Monomorphic ventricular tachycardia was defined as a uniform, wide-complex tachycardia consistent with a ventricular origin, >2 beats in duration (nonsustained) or 30 seconds in duration (sustained). Ventricular tachycardia and junctional ectopic tachycardia were each differentiated from accelerated ventricular and junctional rhythm, respectively, by an increase in rate of >10% above the baseline rate, noted before the onset of tachycardia. When feasible, atrial electrograms using temporary epicardial pacing wires (routinely placed

during surgery at our center) were utilized to aid in discerning tachycardia mechanisms. The data collection period for each subject was from the time of the surgical procedure to discharge home, or to the next surgical procedure if performed prior to discharge from the hospital. Only subjects undergoing an operative intervention requiring intraoperative support with cardiopulmonary bypass were considered in our analysis.

Genotyping

Blood or saliva was collected from each patient, and genomic DNA was extracted by the Vanderbilt Center for Human Genetics Research DNA Resources Core using the Autopure instrument manufactured and supported by Qiagen (Valencia, CA). Genotyping of the common ACE I/D polymorphism was performed with the TaqMan PCR Core Reagent Kit (Applied Biosystems, Foster City, CA) with slight modifications to the protocol as outlined in Koh et al.²¹ 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 test or analysis of variance test for continuous variables and the chi-square test or Fisher’s exact test, where appropriate, for categorical variables. Descriptive statistics are presented as medians with interquartile ranges (IQR) for continuous non-normally distributed data and frequencies with percentages for categorical variables. Hardy–Weinberg equilibrium was assessed using the χ^2 test, while a linear-by-linear association test was used to assess for a gene–dose effect.²² Assuming a postoperative tachyarrhythmia incidence of 50% among patients with an I/D or D/D ACE I/D genotype, one would require 106 patients with an I/I genotype and 424 patients with an I/D or D/D genotype to demonstrate a 15% absolute reduction in postoperative tachyarrhythmia incidence at 80% power among patients homozygous for the ACE I/D insertion allele.²³ The odds of tachyarrhythmia were assessed through both univariate and multivariate logistic regression analyses. Variables with a univariate significance threshold (determined *a priori*) of $p < 0.1$ were considered for inclusion within the multivariate logistic regression model after assessing for multicollinearity. Patient age and cardiopulmonary bypass times, although significant in univariate analysis, were each excluded from additional multivariate analysis due to multicollinearity with patient weight ($R^2 = 0.87$, $p < 0.001$) and aortic cross clamp time ($R^2 = 0.39$, $p < 0.001$), respectively. The number of covariates included within the model was limited to one covariate for every 10 events. All multivariate models underwent assessment of fit with the Hosmer and Lemeshow goodness-of-fit test. Data from logistic regression analyses are reported as estimated odds ratios (ORs) and 95% confidence intervals (CIs). The present analysis includes subjects reported in our previous investigation of JET, so a secondary multivariate analysis was performed excluding all patients with JET, to confirm the association between the ACE I/D polymorphism and other postoperative tachyarrhythmias.¹⁶ Statistical analysis was performed using SPSS statistical package, version 20.0 (SPSS, Inc., Chicago, IL). 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

Baseline characteristics

Over the 63-month study period, a total of 933 consented subjects underwent 1,161 operative procedures with cardiopulmonary bypass. In this study cohort, 886 subjects (95%) were successfully genotyped for the ACE I/D polymorphism, underwent at least one operative intervention with cardiopulmonary bypass, and are presented in the current analysis. Operative cases beyond each subject's index case were excluded from further consideration for this study. Preoperative and operative data of this cohort are summarized in Table 1. Most common diagnoses included atrioventricular canal defects (13%), Tetralogy of Fallot (12%), ventricular septal defects (11%), and HLHS (10%). Most common operative interventions included ventricular septal defect closure (12%), Stage 1 (Norwood) palliation for HLHS (10%), Tetralogy of Fallot repair (10%), and atrioventricular canal repair (9%); over half had operative complexity RACHS-1 scores of 3 or higher. Nearly one-third of subjects reported a history of arrhythmia preoperatively, with 9% receiving treatment for arrhythmia preoperatively. Genotyping of the ACE I/D polymorphism was consistent with Hardy-Weinberg equilibrium (19% I/I, 49% I/D, 32% D/D, $p=0.79$).

At least one tachyarrhythmia was reported in 45% ($n=397$) of index cases. Most common tachyarrhythmias included ventricular tachycardia ($n=137$, 16%), junctional ectopic tachycardia ($n=97$, 11%), atrial tachycardia ($n=92$, 10%), accelerated junctional rhythm ($n=91$, 10%), and accelerated ventricular rhythm ($n=73$, 8%). Tachyarrhythmia onset most commonly occurred on postoperative day 0 ($n=185$, 47%) or postoperative day 1 ($n=94$, 24%). Univariate analysis with respect to the incidence of postoperative tachyarrhythmias in 886 index cases is summarized in Table 2. A significant increase in the incidence of postoperative tachyarrhythmia was associated with younger age ($p<0.001$) and lower weight ($p<0.001$). Patients with postoperative tachyarrhythmias were more likely to have received beta-blockers preoperatively (7% vs. 4%, $p=0.04$). Among patients receiving ACE inhibitors (specifically enalapril in 94% of those receiving an ACE inhibitor), there was a trend toward significantly fewer tachyarrhythmias (8% vs. 13%, $p=0.05$). Operative factors including cardiopulmonary bypass time ($p<0.001$) and aortic cross clamp time ($p<0.001$), in addition to several infusions and laboratory indices on admission to the intensive care unit were associated with postoperative tachyarrhythmia incidence. Postoperative tachyarrhythmias in this cohort were clinically significant and associated with prolonged mechanical ventilation ($p<0.001$), CICU stay ($p<0.001$), and hospital stay ($p<0.001$). Tachyarrhythmias were noted in 47% of index cases with I/D or D/D genotypes, compared to 36% of cases with an I/I genotype (OR 1.6, 95% CI 1.1–2.2, $p=0.01$). Furthermore, linear-by-linear association suggested a gene-dose effect, with an increasing tachyarrhythmia incidence with additional D copies of the I/D polymorphism ($p=0.02$). A subgroup analysis was performed among a more homogenous population of patients undergoing either ventricular septal defect closure or complete repair of a balanced atrioventricular canal defect. Among this subgroup, tachyarrhythmias were noted in 50% of cases with I/D or D/D genotypes, compared to 27% of cases with an I/I genotype (OR 2.7, 95% CI 1.3–5.7, $p=0.007$). Furthermore, linear-by-

linear association again suggested a gene-dose effect, with an increasing tachyarrhythmia incidence with additional D copies of the I/D polymorphism ($p=0.007$).

A multivariate analysis was performed among the entire cohort to assess for independent predictors of postoperative tachyarrhythmia, including ACE I/D genotype. As reported in Table 3, multivariate logistic regression analysis demonstrated that presence of the ACE I/D deletion genotype (I/D or D/D) was independently associated with a 60% increase in the odds of postoperative tachyarrhythmia (OR 1.6, 95%CI 1.1–2.3, $p=0.02$), despite accounting for clinically significant covariates identified through univariate analysis. Given our previous report of an association between JET and the ACE I/D deletion genotype, a secondary multivariate analysis was performed excluding patients experiencing junctional ectopic tachycardia in the early postoperative period. This again confirms an independent relationship between presence of the ACE I/D deletion genotype (I/D or D/D) and an increased incidence of other early postoperative tachyarrhythmias (OR 1.6 95% CI 1.02–2.37, $p=0.04$).

Preoperative ACE inhibition was also independently associated with a reduction of postoperative tachyarrhythmias (OR 0.53, 95%CI 0.32–0.88, $p=0.01$), prompting a secondary analysis to assess for any relationship between ACE I/D genotype and preoperative administration of ACE inhibitor. There was no significant difference among genotypes with respect to preoperative administration of ACE inhibitor (I/I 10.8%, I/D 11.7%, D/D 9.0%, $p=0.52$). As demonstrated in Figure 1, while preoperative ACE inhibition was indeed associated with a significant five-fold reduction in the odds of a postoperative arrhythmia in patients with an I/I genotype (OR 0.19, 95%CI 0.04–0.88, $p=0.02$), preoperative ACE inhibition among those patients with I/D or D/D genotypes was not associated with significant changes in the incidence of a postoperative tachyarrhythmia.

Discussion

In this single-center prospective investigation, we demonstrate that independent of other commonly reported risk factors, patients with at least one copy of the ACE I/D deletion demonstrate an increase in the incidence of postoperative tachyarrhythmias following congenital heart surgery with cardiopulmonary bypass. Furthermore, we demonstrate a significant reduction in postoperative tachyarrhythmias associated with preoperative therapy with angiotensin converting enzyme inhibitors. Interestingly, this protective effect was seen almost exclusively in patients homozygous for the ACE I/D insertion (I/I) allele.

Postoperative tachyarrhythmias are commonly encountered following congenital heart surgery, and are associated with substantial morbidity including increases in CICU resource utilization, durations of mechanical ventilation and hospital stay. Consistent with previous studies, we report a similar overall incidence of postoperative tachyarrhythmias, as well as significant increases in duration of mechanical ventilation (by two days) and ICU length of stay (by four days), supporting the clinical relevance of these tachyarrhythmias. While efforts in the immediate postoperative period to mitigate the risk of postoperative tachyarrhythmias have been described, the identification of preoperative risk factors may prove useful in guiding preemptive therapy to reduce potential risk in the early postoperative

period.^{24–26} Interestingly, in contrast to ACE-inhibition, preoperative beta-blocker therapy was not associated with a decrease in postoperative arrhythmias, but rather an increased incidence. This could be attributable to up-regulation of β -adrenergic receptors with subsequent postoperative exposure to catecholamine infusions. Aside from electrolyte supplementation or antiarrhythmic administration however, an attractive pharmacotherapeutic target is the renin-angiotensin-aldosterone system. The RAAS has long been reported to serve as a crucial cardiovascular homeostatic mechanism, with derangements associated with common cardiovascular diseases, including arrhythmias.^{18, 27–29} Studies in adult populations following coronary artery bypass grafting have yielded conflicting results with respect to the utility of preoperative angiotensin converting enzyme inhibition and reduction in the incidence of postoperative atrial fibrillation.^{30–33} To our knowledge, no series to date has evaluated for a potential association between preoperative ACE inhibition and postoperative tachyarrhythmias in children.

The angiotensin converting enzyme is a zinc metallopeptidase that serves a vital function in the RAAS-mediated production of angiotensin II, resulting in alterations in membrane ion channel permeability, intracellular calcium cycling, as well as increased oxidative stress.^{17,34} The gene encoding angiotensin converting enzyme (ACE), located on the long arm of chromosome 17 (17q23), includes 26 exons across 21 kilobases.³⁴ Plasma ACE levels, while relatively constant in a given individual, are highly variable between individuals, independent of other hormonal or environmental factors.³⁵ The ACE insertion/deletion polymorphism (ACE I/D), a 287-bp intronic sequence (NCBI ref. SNP ID: rs 1799752) accounts for nearly half of the total variance in serum ACE concentrations between individuals.³⁶ Furthermore, the deletion allele of the ACE I/D polymorphism is associated with gene-dose related increases in levels of both angiotensin converting enzyme and angiotensin II.^{36–38} Thus, the mechanism underlying the genetic risk for tachyarrhythmias is higher angiotensin II activity associated with the deletion allele. Our finding of a higher proportion of postoperative tachyarrhythmias observed in patients with one or more copies of the ACE deletion (I/D or D/D) is consistent with the proposed mechanism. The finding that preoperative ACE inhibition is associated with lower risk of postoperative tachyarrhythmias is also consistent with the proposed “antiarrhythmic” mechanisms of RAAS modulation.

Interestingly, our secondary analysis revealed an important pharmacogenetic interaction. The protective effect of preoperative ACE inhibition was derived almost exclusively from the subset of I/I individuals, with a 5-fold reduction in odds of postoperative tachyarrhythmias associated with pre-operative ACE inhibitors. A non-significant trend was observed in heterozygotes, and almost no effect was evident in D/D patients (Figure 1). This indicates that patients homozygous for the insertion allele may receive antiarrhythmic benefits from preoperative ACE inhibitors, while no benefit was observed among patients homozygous for the deletion allele. Evidence for “resistance” to ACE inhibitors among patients with a D/D genotype is supported by elevated levels of aldosterone among these patients, relative to I/D and I/I genotype patients receiving similar doses of ACE inhibition.³⁹ Together, these findings suggest that modulation of the RAAS as a strategy to reduce postoperative arrhythmias in patients with one or more deletion allele may not be

feasible, or may require higher doses of ACE inhibitors than those used in standard clinical practice.

Interpretation of these study results is subject to several limitations. First, despite adjusting for potential confounders, there remains the possibility of unaccounted-for covariates within our univariate analysis that may contribute to the differences in tachyarrhythmia incidence among ACE I/D genotypes observed in this series. The sample size limitations in this study precluded our ability to assess for genotype-specific effects of ACE inhibition upon more homogenous subgroups. Second, as this analysis was performed in all patients enrolled without a validation cohort, further studies are necessary to replicate these findings. Third, preoperative administration of ACE inhibitors was neither standardized nor randomized, and ACE inhibitors were routinely initiated for clinical indications other than antiarrhythmic prophylaxis. The duration of preoperative ACE inhibition was also not accounted for in this study. Finally, the association we have described between preoperative ACE inhibitor exposure and the incidence of postoperative tachyarrhythmia is not necessarily a causal relationship. Further prospective and randomized investigation is necessary to delineate a possible pharmacologic means of reducing tachyarrhythmia risk in a population of patients with a specific genotype.

In conclusion, independent of reported risk factors, the presence of at least one copy of the ACE I/D deletion (I/D or D/D) is associated with a significant increase in the incidence of postoperative tachyarrhythmias following congenital heart surgery with cardiopulmonary bypass. Preoperative modulation of the RAAS with angiotensin converting enzyme inhibition is independently associated with a significant reduction in the incidence of tachyarrhythmias, an effect apparent only in patients homozygous for the ACE I/D insertion (I/I) allele. Future prospective investigation of genotype-specific medical therapies may prove useful in subpopulations of patients at risk for clinically relevant morbidities following congenital heart surgery.

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Figure 1.

Relationship between preoperative angiotensin converting enzyme inhibition and ACE I/D genotype with respect to postoperative tachyarrhythmia. Preoperative inhibition was associated with a significant reduction in postoperative tachyarrhythmia incidence only in patients with the I/I genotype (OR 0.19, 95% CI 0.04–0.88, $p=0.02$).

Table 1

Baseline demographic and operative characteristics of the study cohort (n=886).

Variable	
Age (months)	5.6 (1.1, 33)
Weight (kg)	6.2 (3.8, 12.5)
Male gender (%)	487 (55%)
Chromosomal anomaly	219 (25%)
Primary diagnosis	
AV canal defect	117 (13%)
Tetralogy of Fallot	102 (12%)
Ventricular septal defect	100 (11%)
Hypoplastic left heart syndrome	88 (10%)
Atrial septal defect	78 (9%)
Primary surgical procedure	
Ventricular septal defect closure	104 (12%)
Stage 1 (Norwood) palliation	86 (10%)
Repair Tetralogy of Fallot	87 (10%)
Repair AV canal defect	81 (9%)
Secundum ASD closure	60 (7%)
History of arrhythmia preoperatively	277 (31%)
Arrhythmia treatment preoperatively	81 (9%)
Preoperative medications	
ACE inhibitor	93 (11%)
β -blocker	45 (5%)
Digoxin	150 (17%)
ACE I/D Genotype	
I/I	171 (19%)
I/D	432 (49%)
D/D	283 (32%)
Cardiopulmonary bypass time (min)	116 (82, 159)
Aortic cross clamp time (min)	45 (28, 71)
RACHS-1 classification	
RACHS 1	86 (10%)
RACHS 2	295 (33%)
RACHS 3	252 (28%)
RACHS 4	107 (12%)
RACHS 5 or 6	101 (11%)
Unable to classify	45 (5%)

Continuous variables are reported as median (25th, 75th %ile). Categorical variables are reported as frequency (%). AV: atrioventricular; ASD: atrial septal defect; ACE: Angiotensin converting enzyme; I/D: Insertion/Deletion; RACHS-1: Risk Adjustment in Congenital Heart Surgery, Version 1.

Table 2

Perioperative characteristics with respect to incidence of postoperative tachyarrhythmia.

Variable	No tachyarrhythmia (n=489)	Tachyarrhythmia (n=397)	Sig.
Age (months)	8.9 (3.7, 48)	4.0 (0.3, 9.6)	<0.001
Weight (kg)	7.4 (4.7, 14.9)	5.1 (3.5, 8.5)	<0.001
Male gender (%)	257 (53%)	230 (58%)	0.11
Chromosomal anomaly	119 (24%)	100 (25%)	0.77
History of arrhythmia preoperatively	141 (29%)	136 (34%)	0.08
Preoperative medication			
ACE inhibitor	60 (13%)	33 (8%)	0.05
β -blocker	18 (4%)	27 (7%)	0.04
Digoxin	80 (17%)	70 (18%)	0.66
ACE I/D Genotype			0.02*
I/I	109 (22%)	62 (16%)	
I/D	234 (48%)	198 (50%)	
D/D	146 (30%)	137 (35%)	
Cardiopulmonary bypass time (min)	102 (73, 145)	133 (100, 174)	<0.001
Aortic cross clamp time (min)	40 (20, 58)	53 (36, 81)	<0.001
RACHS-1 classification			
RACHS 1	66 (14%)	20 (5%)	<0.001
RACHS 2	172 (35%)	122 (31%)	0.14
RACHS 3	133 (27%)	119 (30%)	0.36
RACHS 4	45 (9%)	62 (16%)	0.004
RACHS 5 or 6	49 (10%)	52 (13%)	0.15
Admission infusions			
Calcium chloride	39 (8%)	71 (18%)	<0.001
Dopamine	97 (20%)	115 (29%)	0.002
Epinephrine	68 (14%)	100 (25%)	<0.001
Milrinone	348 (71%)	335 (84%)	<0.001
Dexmedetomidine	151 (31%)	76 (19%)	<0.001
Admission laboratories			
pH	7.36 (7.31, 7.41)	7.35 (7.29, 7.41)	0.15
pCO ₂ (mmHg)	44 (39, 50)	45 (40, 51)	0.08
pO ₂ (mmHg)	101 (59, 168)	83 (52, 146)	0.02
Lactate (mmol/L)	1.8 (1.2, 3.1)	2.8 (1.6, 5.0)	<0.001
Hematocrit (mg/dL)	39 (34, 43)	40 (36, 44)	0.005
K (mmol/L)	3.6 (3.3, 4.0)	3.6 (3.2, 4.1)	0.80
iCa (mg/dL)	5.5 (5.1, 6.1)	5.6 (5.1, 6.3)	0.07
Duration mechanical ventilation	1 (0, 2)	3 (1, 8)	<0.001
CICU length of stay	2 (1, 6)	6 (3, 14)	<0.001
Hospital length of stay	7 (4, 13)	12 (7, 29)	<0.001

Continuous variables are reported as median (25th, 75th percentile). Categorical variables are reported as frequency (%).

* Linear-by-linear association.

Table 3

Multivariate analysis of tachyarrhythmia predictors.

Covariate	Adjusted Odds Ratio	Sig.
Aortic cross clamp time	1.01 (1.01–1.02)	<0.001
ACE I/D deletion present	1.6 (1.1–2.3)	0.02
Preoperative ACE inhibition	0.53 (0.32–0.88)	0.01
On admission		
Calcium chloride infusion	1.9 (1.1–3.2)	0.02
Serum lactate	1.1 (1.0–1.2)	0.01
Hematocrit	1.03 (1.01–1.06)	0.02

* Other covariates included in the model: Preoperative β -blockade ($p=0.11$), RACHS-1 score, history of preoperative arrhythmia ($p=0.15$), dopamine ($p=0.18$), epinephrine ($p=0.74$), milrinone ($p=0.21$) and dexmedetomidine ($p=0.23$) infusions on admission, arterial pCO_2 ($p=0.60$), arterial pO_2 ($p=0.72$), and serum ionized calcium ($p=0.66$).

** Hosmer and Lemeshow Test $p=0.57$.