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Genotypic and phenotypic predictors of complete heart block and recovery of conduction after surgical repair of congenital heart disease

Laura E. Murray, MD[*], **Andrew H. Smith, MD, MSCI, MMHC**[†,‡], **English C. Flack, MD, MS**[†], **Kim Crum, RN**[†], **Jill Owen, RN**[†], and **Prince J. Kannankeril, MD, MSCI, FHRS**[†]

[*]Vanderbilt University Medical Center, Nashville, Tennessee

[†]Department of Pediatrics, Thomas P. Graham Jr. Division of Cardiology, Nashville, Tennessee

[‡]Division of Critical Care Medicine, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, Tennessee

Abstract

BACKGROUND—Complete heart block (CHB) is a major complication that occurs after congenital heart surgery. We hypothesized that genetic and clinical factors are associated with the development of postoperative CHB and recovery of atrioventricular (AV) conduction.

OBJECTIVE—The purpose of this study was to identify predictors of CHB and recovery after congenital heart surgery.

METHODS—Patients undergoing congenital heart surgery at our institution from September 2007 through June 2015 were prospectively enrolled in a parent study of postoperative arrhythmias. Patients with onset of CHB within 48 hours postoperatively were included in the study. Daily rhythm assessment was performed until demonstration of 1:1 conduction or pacemaker implantation.

RESULTS—Of 1199 subjects enrolled, 56 (4.7%) developed post-operative CHB. In multivariate analysis, preoperative digoxin exposure (odds ratio [OR] 2.4, 95% confidence interval [CI] 1.3–4.4), aortic cross-clamp time (OR 1.08, 95% CI 1.04–1.11), ventricular septal defect closure (OR 2.2, 95% CI 1.2–4.1), and a common polymorphism in the gene encoding connexin-40 (GJA5 rs10465885 TT genotype; OR 2.1, 95% CI 1.2–3.8) were independently associated with postoperative CHB. Junctional acceleration (JA) (OR 4.0, 95% CI 1.1–15.1) and intermittent conduction noted during complete AV block (OR 9.1, 95% CI 1.0–80) were independently associated with 1:1 AV conduction recovery. Use of a multivariate model including both JA and intermittent conduction demonstrated good discrimination with a positive predictive value of 86% (95% CI 67%–96%) in predicting 1:1 conduction recovery.

Address reprint requests and correspondence: Dr. LauraE. Murray, Monroe Carell Jr. Children's Hospital at Vanderbilt, Doctors' Office Tower 8247, 2200 Children's Way, Nashville, TN37232. laura.e.murray@vanderbilt.edu.

Appendix

Supplementary data

Supplementary data are available in the online version of this article at http://dx.doi.org/10.1016/j.hrthm.2016.11.010

CONCLUSION—Preoperative factors, including a missense polymorphism in GJA5, are independently associated with increased risk for CHB. JA and intermittent conduction may prove useful in predicting recovery of AV conduction among patients with CHB after congenital heart surgery.

Keywords

Arrhythmia; Congenital heart defect; Heart block; Pacemaker; Pediatrics; Genotype; Junctional acceleration

Introduction

Complete heart block (CHB) is a well-described complication occurring after cardiac surgery for congenital heart disease.[1,2] Whereas CHB that persists beyond the immediate postoperative period may require implantation of a permanent pacemaker (PM), in many cases postoperative CHB is transient, with recovery of 1:1 atrioventricular (AV) conduction in the early postoperative period. Weindling et al[3] reported recovery of conduction in > 60% of patients with postoperative CHB, mostly by postoperative day (POD) 7. Accordingly, expert guidelines advocate for "postoperative advanced second or third degree AV block that is not expected to resolve or that persists at least 7 days after cardiac surgery" as a class I indication for PM implantation.[4] Regrettably, clinicians have little indication as to whether AV conduction is "expected to recover" and face the conundrum of waiting several days (with associated costs and morbidity of prolonged hospitalization) before implanting a PM, or risking unnecessary PM placement in a patient who will recover conduction.[5] An association between junctional tachycardia and recovery of 1:1 conduction in pediatric patients with postoperative heart block has been described recently.[6–8]

After cardiac surgery, CHB may result from inflammation or edema causing transient block, or from direct mechanical insult to the AV node and/or conduction system causing permanent injury. Advances in surgical techniques have resulted in a decline in the incidence of CHB from > 10% to <3%; however, this rate has remained constant for more than a decade.[1] This suggests there may also be intrinsic factors that predispose children to developing postoperative complete AV block, regardless of cardiac anatomy and surgical procedure. A rare missense mutation (Q58L) in *GJA5*, which encodes connexin-40, results in impaired gap junction formation and is associated with a familial form of progressive CHB.[9] A common polymorphism (rs10465885) in the promoter region of *GJA5* alters connexin-40 expression and has been associated with arrhythmias.[10] In view of these reports, we tested the hypothesis that the common *GJA5* polymorphism, as well as clinical factors, may predict both CHB incidence and recovery.

Methods

Between September 2007 and June 2015, all patients undergoing congenital heart disease surgery at our institution were approached to consent for a prospective study of postoperative arrhythmias as previously described.[11] Eligible subjects were of all ages undergoing either corrective or palliative cardiac surgical intervention with cardiopulmonary bypass, with congenital heart disease as the primary indication for the procedure. Each

patient's parents or legal guardians provided written informed consent, and patient assent was obtained when appropriate. The Vanderbilt University Institutional Review Board for Research on Human Subjects approved the study. Patients were admitted to the cardiac intensive care unit (CICU) for routine management and underwent continuous monitoring with full-disclosure telemetry. All patients who gave consent provided a DNA sample and underwent a daily rhythm assessment and complete telemetry review by study personnel with confirmation by an electrophysiologist. We performed a retrospective review of all patients in the cohort with new-onset CHB in the operating room or within 48 hours postoperatively that persisted upon admission to the CICU.

Patients who undergo cardiac surgery routinely receive temporary pacing wires. Patients who demonstrated CHB were supported with temporary pacing and had at least daily assessment of the underlying rhythm until recovery of 1:1 conduction or PM implantation. We categorized the underlying rhythms as persistence of complete AV block; 1:1 AV conduction (including conduction with prolonged PR interval); or intermittent conduction including recognizable forms of second-degree AV block (Mobitz I or II, or 2:1 AV block) as well as high-grade AV block with intermittent conduction. Junctional acceleration (JA) was defined as a tachycardia with the following features: (1) a QRS complex similar to conducted sinus beats; (2) a ventricular rate greater than the atrial rate, usually exhibiting a pattern of "warmup" at initiation, consistent with an automatic mechanism; or (3) ventriculoatrial dissociation, or variable or 1:1 retrograde association. Further diagnostic maneuvers including recording of the atrial electrogram, adenosine administration, and temporary atrial or ventricular pacing were performed when the diagnosis was unclear with inspection of telemetry alone. JA included both junctional ectopic tachycardia (JET), defined as a ventricular rate > 110% of the preceding sinus rate, and accelerated junctional rhythm (AJR), defined as a ventricular rate < 110% of the preceding sinus rate. We compared patients who recovered 1:1 AV conduction at any time with those who did not. PM implantation was performed at the discretion of the clinical team and was not affected by enrollment in this study. We also compared patients who required a permanent PM with those who did not.

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 (Qiagen, Valencia, CA). Genotyping of the common *GJA5* missense polymorphism (rs10465885) 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.[12] 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 for continuous variables and the χ^2 test or Fisher exact test, where appropriate, for categorical variables. Descriptive statistics are presented as median with interquartile range (IQR) for continuous data and frequency with percentage for categorical variables. Hardy–Weinberg

equilibrium was assessed using the χ^2 test, whereas a linear-by-linear association test was used to assess for a gene–dose effect.[13] Predictors of postoperative CHB and CHB recovery were assessed by both univariate and multivariate logistic regression analyses. Covariates with a univariate significance threshold (determined *a priori*) of $P < .1$ were considered for inclusion within a stepwise multivariate logistic regression model after assessing for multicollinearity. 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 ratio (OR) and 95% confidence interval (CI). Statistical analysis was performed using SPSS statistical package, release 23.0 (SPSS Inc, Chicago, IL).

Results

During the study period, 1199 patients consented to the study and were successfully genotyped at the *GJA5* polymorphism of interest (rs10465885). The 1199 patients underwent a total of 1526 operative procedures, but only 1 surgical case per patient was used in analysis. Demographic and baseline clinical characteristics of the cohort are given in Table 1. The most common primary surgical procedures included ventricular septal defect (VSD) repair, AV canal repair, tetralogy of Fallot repair, and stage 1 (Norwood) palliation. Fifty-six patients (4.7%) experienced CHB in the operating room or within 48 hours after surgery that persisted on admission to the CICU. Table 2A summarizes perioperative characteristics with respect to development of postoperative CHB. Preoperative factors associated with postoperative CHB in univariate analysis included age at surgery, patient weight, preoperative digoxin use, surgical era, and the *GJA5 rs10465885* TT genotype. *GJA5* genotypes were in Hardy–Weinberg equilibrium ($P = .53$). The genotype frequencies for the 5 main subcohorts are given in Online Supplemental Table 1. Notably, there was an apparent gene–dose effect with increasing numbers of T alleles conferring an increased likelihood of early postoperative complete AV block ($P = .009$). Overall risk for CHB by genotype was C/C 2.8%, C/T 3.9%, and T/T 7.2%. As noted in Table 2A, 36% of the patients with CHB had a chromosomal anomaly. The majority of these were trisomy 21 (14 patients). The remaining 6 were DiGeorge syndrome (2), Jacobsen syndrome (1), and other (3). Intraoperative factors associated with postoperative CHB in univariate analysis included cardiopulmonary bypass time, aortic cross-clamp time, and procedures that included VSD closure (genotype frequencies stratified by procedures, which include VSD closure for the entire cohort and for those with CHB are given in Online Supplemental Tables 2 and 3). Table 2B summarizes postoperative characteristics with respect to the incidence of postoperative third-degree AV block. Postoperatively, patients with CHB were more likely to receive dopamine and milrinone infusions, presented with higher serum lactate and ionized calcium on admission to the CICU, and were more likely to require extracorporeal membrane oxygenation support. Patients with CHB had longer duration of ventilation, CICU and hospital stay, and higher hospital mortality.

Multivariate analysis was then performed among the entire cohort to assess for independent predictors of early postoperative CHB, including *GJA5* rs10465885 TT genotype. The TT genotype conferred a 2-fold increased odds of new-onset CHB (OR 2.1, 95% CI 1.2–3.8, $P = .009$), independent of other significant predictors including weight, preoperative digoxin administration, chromosomal anomaly, operative procedure including VSD closure, and

aortic cross-clamp time (Table 3). This model demonstrated good discrimination as noted in Figure 1, with an associated *c*-statistic of 0.75 (95% CI 0.69–0.81, $P < .001$).

Of the 56 patients with CHB, 35 (63%) demonstrated recovery of 1:1 AV conduction, and PM-free recovery was noted in 27 patients (48%), with median recovery time of 3 days (IQR 2–8 days). Diagnoses and surgical procedures in these 35 patients are given in Online Supplemental Table 4. Of the 21 patients who did not recover conduction, 18 received a permanent PM; the remaining 3 did not survive to PM implantation. Eight additional patients received a PM despite recovery of 1:1 conduction: 3 with recovery of 1:1 AV conduction had subsequent episodes of abrupt and transient high-grade AV block that required therapy received a PM on POD 7, 8, and 10; 3 with recovery of 1:1 AV conduction with a prolonged PR interval and periods of second-degree AV block who received a PM on POD 18, 18 and 21; 1 with complex single ventricle anatomy with L-transposition of the great arteries who had recovery of conduction on POD 5 received a PM on POD 7 due to a history of recurrent intermittent AV block with anesthesia; and 1 who received a PM on POD 13 due to continued CHB who had recovery of 1:1 AV conduction noted in clinic on POD 101.

Among patients with early postoperative AV block, preoperative angiotensin-converting enzyme inhibitor use was the only preoperative predictor of AV conduction recovery (Table 4). We also observed that patients who developed AJR or JET in the immediate postoperative period were more likely to recover 1:1 conduction. Furthermore, patients with intermittent conduction (second-degree AV block, 2:1 block) were more likely to recover 1:1 conduction, with 13 of 35 patients (37%) with recovery noted to have intermittent conduction by median POD 2 (0.5, 5.5). The TT genotype for *GJA5* rs10465885 was not a predictor of recovery. In a multivariate model, both junctional rhythm (OR 4.0, 95% CI 1.1–15.1, $P = .04$) and intermittent conduction (OR 9.1, 95% CI 1.0–80, $P = .05$) were independent predictors of AV conduction recovery (Table 5). This model demonstrated good discrimination (Figure 2), with an associated *c*-statistic of 0.76 (95% CI 0.64–0.89, $P = .001$) and a positive predictive value of 86% (95% CI 67%–96%) in identifying those likely to recover conduction.

Discussion

In this study, we demonstrated that a common missense polymorphism in *GJA5* is an independent predictor of CHB after congenital heart surgery. We also identified preoperative digoxin use, intraoperative factors including VSD closure, and aortic cross-clamp time as predictors of CHB. Furthermore, we demonstrated that JA and intermittent AV conduction together serve as reliable predictors of AV conduction recovery after postsurgical CHB.

The incidence of postoperative CHB (4.7 % overall, 1.4% permanent) observed in this study is similar to rates observed in contemporary studies (3%–7% overall, 1%–3% permanent).[1,7,8] We report an independent association between a specific common polymorphism in *GJA5* and the risk of CHB, an association not previously reported to our knowledge. Makita et al[9] demonstrated a link between a *GJA5* mutation and a progressive form of familial heart block. The connexin-40 protein encoded by this gene is found in the

atria and the His–Purkinje system, with high levels of expression (both at mRNA and protein levels) in the compact AV node and penetrating bundle in humans,[14] and is essential for gap junction formation. Mice deficient in connexin-40 consistently show abnormalities characteristic of AV block,[15] with prolongation of AH and HV intervals,[16] confirming a role for this gene in AV nodal conduction. We demonstrated that patients homozygous for a common missense polymorphism (rs10464884) are more likely to develop CHB after congenital heart surgery than those with the T/C or C/C allele. This polymorphism is known to alter connexin-40 mRNA expression in humans.[10] We speculate that patients with genetically determined altered connexin-40 expression in the AV node are more prone to develop CHB when subjected to the environmental insult of congenital heart surgery. Among patients with CHB, however, the *GJA5* polymorphism did not associate with recovery of 1:1 conduction. These results suggest that there may be intrinsic patient factors that predispose patients to early postoperative CHB. The question remains as to whether an improved understanding of these factors would impact clinical decision-making.

We also identified procedures including VSD closure, preoperative digoxin use, and aortic cross-clamp time as risk factors for CHB. It has long been recognized that procedures that include VSD closure as part of the operation (including repair of VSD, atrioventricular canal, and tetralogy of Fallot) are associated with increased risk for CHB.[3,17] Preoperative use of digoxin may simply be a surrogate marker of a large VSD requiring medical therapy for congestive heart failure. However, we cannot exclude a true association between preoperative digoxin and postoperative CHB by a separate mechanism. Aortic cross-clamp time was also an independent predictor of CHB in the multivariate model. Although this reached statistical significance, the effect size (OR 1.08, 95% CI 1.04–1.11) may limit its clinical relevance.

Another important observation is that patients with JA in the first 48 hours after surgery were more likely to recover 1:1 AV conduction. Paech et al[8] described 32 patients with CHB, in whom JET perfectly correlated with recovery of 1:1 AV conduction (JET observed in 18/18 who recovered and 0/14 who did not), Ayyildiz et al[7] reported JET in 41% of patients with CHB who recovered 1:1 AV conduction compared to only 13% of those who did not. Our findings are similar to the latter study in that JET/AJR was observed in 54% of patients with CHB who recovered and in 19% of those without recovery. We also report a relationship between intermittent conduction (Mobitz I or II, or 2:1 AV block) and AV conduction recovery. When taken together with JA in a multivariate analysis, we report a model that is a strong discriminator of those achieving 1:1 conduction recovery in the early postoperative period.

Study limitations

This study has several important limitations. It was a nonrandomized observational study from a single center. Although we examined multiple clinical factors, additional variables that were not accounted for may contribute to risk of CHB and recovery. Although there is a biologically plausible relationship, we cannot rule out the possibility that the GJA5 polymorphism does not directly influence risk of CHB but is associated with other unaccounted for factors that increase the risk for CHB. For example, the anatomic subset

most skewed toward TT homozygotes (although not significantly, as this subset is in Hardy–Weinberg equilibrium) is the subset undergoing repair of tetralogy of Fallot (37% TT, overall 28% TT, see Online Supplemental Table 1). If this group was most prone to CHB, then this might also explain an apparent but spurious genetic association. However, the CHB rate in tetralogy of Fallot (5%) was lower than that observed for AV canal (7%) or VSD (9%). The association between JA and recovery of conduction has been observed in 3 separate studies, but the genetic association with development of CHB needs to be replicated in an independent cohort. We investigated the common GJA5 variant because of its known role in human connexin-40 expression in humans and the gene's established role in familial heart block. Our study is inadequately powered to examine additional genetic risk factors, many of which could also contribute to risk of CHB. Although we did not perform an *a priori* power calculation, with our observed CHB incidence and minor allele frequency, we had 76% power with alpha = 0.05 for a single genetic association; we would be underpowered to investigate other genetic variants.

Conclusion

The risk of CHB after congenital heart surgery is associated with a common polymorphism in *GJA5* as well as clinical factors. Intermittent conduction and JA are both strong predictors of recovery of conduction. These findings may impact decisions regarding timing of PM placement for CHB after surgery for congenital heart disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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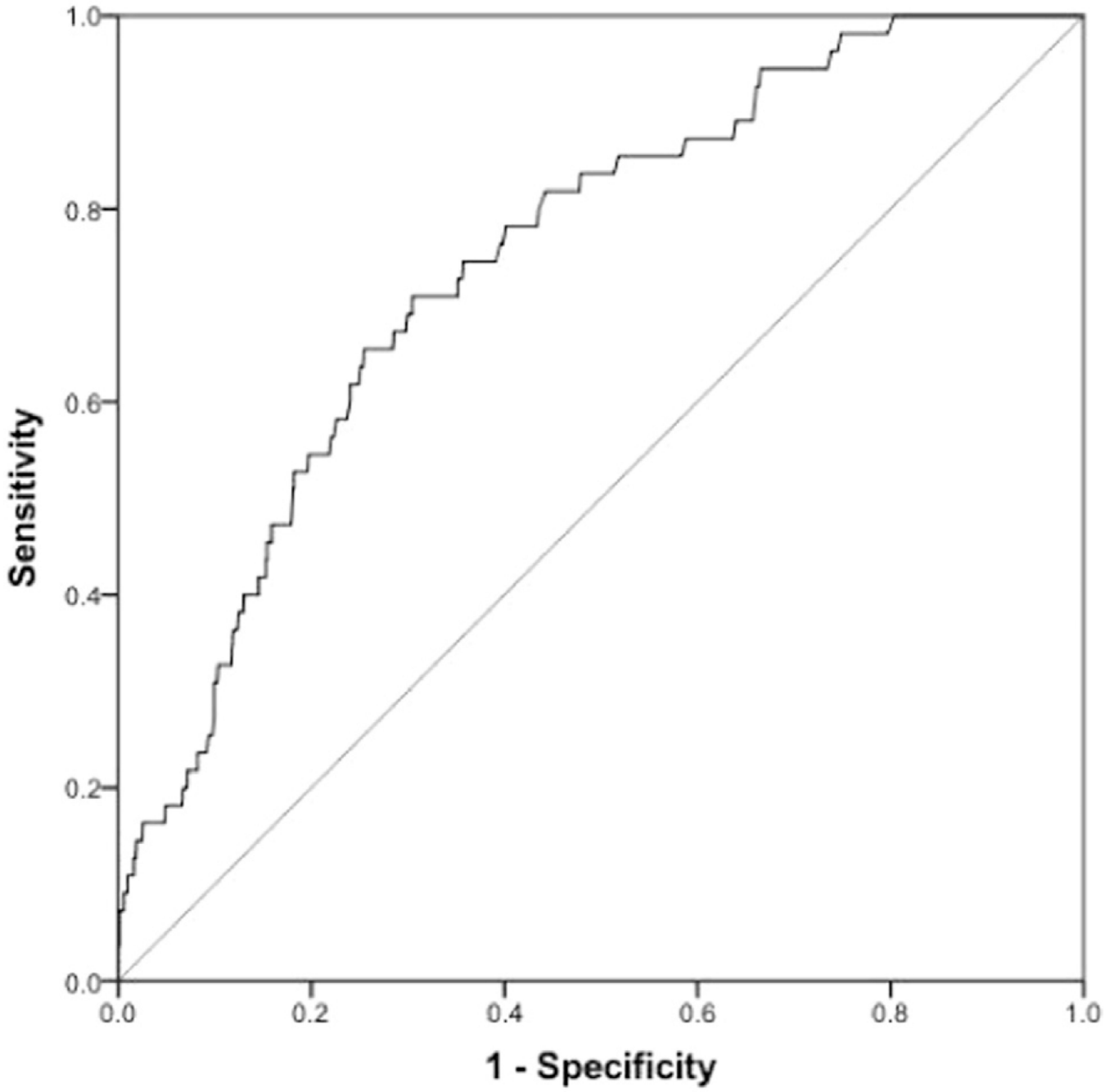

Figure 1.
Receiver operating characteristic curve generated from predictive modeling in Table 3. AUC = area under the curve; CI = confidence interval.

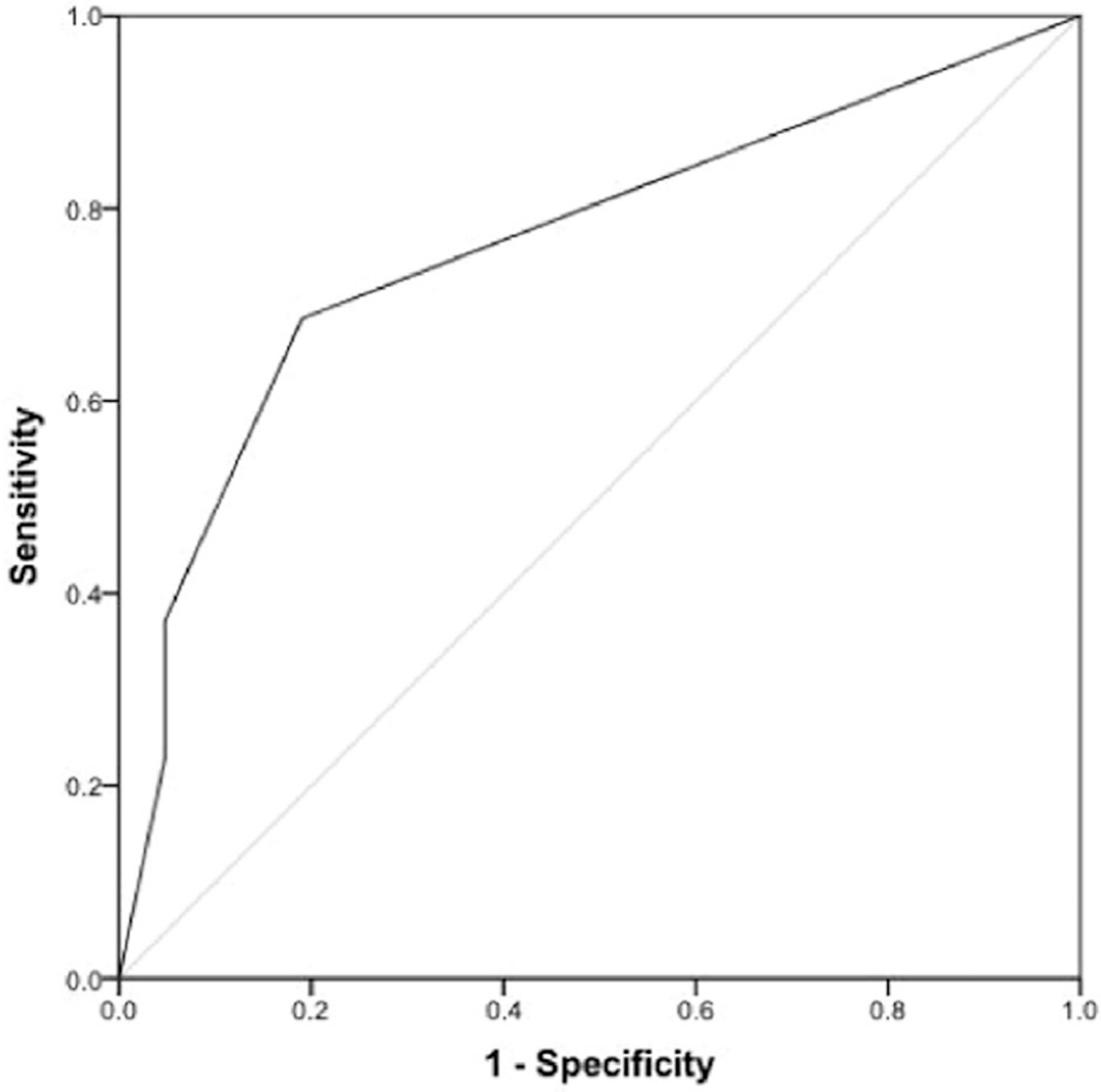

Figure 2.

Receiver operating characteristic curve generated from predictive modeling in Table 5. AUC = area under the curve; CI = confidence interval.

Table 1

Baseline demographic and operative characteristics of the study cohort (n = 1199).

Age (months)	6.0 (1.0, 43)
Weight (kg)	6.4 (3.8, 14.3)
Male gender (%)	628 (52%)
Chromosomal anomaly	307 (26%)
Primary diagnosis	
Tetralogy of Fallot	136 (11.3%)
VSD	125 (10.4%)
Hypoplastic left heart syndrome	110 (9.2%)
Atrial septal defect	100 (8.3%)
Complete atrioventricular canal defect	88 (7.3%)
Primary surgical procedure	
VSD closure	129 (10.8%)
Repair transitional or complete AV canal defect	129 (10.8%)
Repair tetralogy of Fallot	119 (9.9%)
Stage 1 (Norwood) palliation	118 (9.8%)
Secundum ASD closure	90 (7.5%)
Procedure includes VSD closure	486 (41%)
Third-degree AV block	56 (4.7%)
Preoperative medications	
Beta-blocker	55 (4.6%)
Digoxin	180 (15%)
Other antiarrhythmic drug	8 (0.7%)
ACE inhibitor	125 (10.4%)
GJA5 rs10465885 genotype	
C/C	245 (20%)
T/C	607 (51%)
T/T	347 (29%)
Cardiopulmonary bypass time (min)	115 (80, 157)
Aortic cross-clamp time (min) (n = 1099)	50 (33, 76)
Postoperative extracorporeal membrane oxygenation support	63 (5.3%)
Hospital mortality	54 (4.7%)

Continuous variables are given as median (25th, 75th percentile) and categorical variables as frequency (%).

ACE = angiotensin-converting enzyme; ASD = atrial septal defect; AV = atrioventricular; VSD = ventricular septal defect.

Table 2

A Perioperative characteristics with respect to incidence of postoperative third-degree AV block.

Variable	No third-degree block (n = 1143)	Third-degree block (n = 56)	*P* value
Age (months)	6.1 (1.0, 46)	4 (1, 8.3)	.007
Weight (kg)	6.5 (3.8, 15)	4.6 (3.8, 6.8)	.003
Male gender (%)	604 (53%)	25 (45%)	.24
Chromosomal anomaly	287 (25%)	20 (36%)	.08
Preoperative medication			
Digoxin	161 (14%)	19 (34%)	<.001
Beta-blocker	51 (4.5%)	4 (7%)	.35
Other antiarrhythmic drug	8 (0.7%)	0 (0%)	.53
ACE inhibitor	115 (10%)	10 (18%)	.06
Era (reported as percent of row)			
2007–2010	478 (94%)	31 (6.1%)	.045
2011–2015	665 (96%)	25 (3.6%)	
Surgeon (reported as percent of row)			.61
Surgeon A	460 (95%)	26 (5.3%)	
Surgeon B	435 (95%)	21 (4.6%)	
Surgeon C	236 (97%)	8 (3.3%)	
Surgeon D	12 (92%)	1 (8%)	
GJA5 rs10465885 genotype			.028*
C/C	238 (21%)	7 (12%)	
T/C	583 (51%)	24 (43%)	
T/T	322 (28%)	25 (45%)	
Cardiopulmonary bypass time (min)	114 (79, 156)	135 (107, 192)	.001
Aortic cross-clamp time (n = 1099) (min)	49 (33, 75)	74 (52, 93)	<.001
Procedure includes VSD closure	447 (39%)	39 (70%)	<.001
Most common lesions			.002
Tetralogy of Fallot	131 (12%)	5 (8.9%)	
VSD	115 (10%)	10 (18%)	
Hypoplastic left heart syndrome	106 (9.3%)	4 (7.1%)	
Atrial septal defect	99 (8.7%)	1 (1.8%)	
Complete AV canal defect	79 (6.9%)	9 (16%)	
Most common surgical procedures			<.001
VSD closure	117 (10%)	12 (21%)	
Repair transitional or complete AV canal	120 (11%)	9 (16%)	
Repair tetralogy of Fallot	113 (10%)	6 (11%)	
Stage 1 (Norwood) palliation	116 (10%)	2 (3.6%)	
Secundum ASD closure	89 (8%)	1 (1.8%)	

B Postoperative characteristics with respect to incidence of postoperative third-degree AV block.

Variable	No third-degree block (n = 1143)	Third-degree block (n = 56)	*P* value
Admission infusions			
Calcium chloride	168 (15%)	5 (9%)	.23
Dopamine	210 (18%)	22 (39%)	<.001
Epinephrine	248 (22%)	14 (25%)	.56
Milrinone	815 (71%)	49 (88%)	.008
Dexmedetomidine	408 (36%)	14 (26%)	.10
Admission laboratory test results			
pH	7.37 (7.31, 7.41)	7.35 (7.29, 7.40)	.63
p_{CO_2} (mm Hg)	43 (38, 49)	44 (41, 52)	.10
p_{O_2} (mm Hg)	99 (61, 167)	85 (54, 113)	.04
Base excess	−0.8 (−3.3, 1.6)	−1.6 (−4.0, 1.8)	.38
Lactate (mmol/L)	1.9 (1.2, 3.6)	2.8 (1.6, 4.2)	.014
Hematocrit (mg/dL)	38 (34, 43)	39 (35, 43)	.52
K (mmol/L)	3.6 (3.2, 4.0)	3.8 (3.2, 4.4)	.06
i_{Ca} (mg/dL)	5.6 (5.1, 6.1)	5.9(5.3, 6.4)	.01
Postoperative extracorporeal membrane oxygenation	55 (4.8%)	8 (14%)	.002
Days to intermittent conduction (n = 14)		2.5 (0.75, 5.3)	
Days to junctional rhythm (n = 23)		1 (0, 2)	
Days to recovery (n = 35)		3 (2, 7)	
Days to pacemaker implant (n = 26)		9 (7, 12.2)	
Duration mechanical ventilation (days)	1 (0, 4)	3 (1, 8)	.001
CICU length of stay (days)	4 (2, 8)	10 (6, 17)	<.001
Hospital length of stay (days)	8 (5, 19)	16 (10, 31)	<.001
Hospital mortality	45 (3.9%)	9 (16%)	<.001

Continuous variables are given as median (25th, 75th percentile) and categorical variables as frequency (%).

ACE = angiotensin-converting enzyme; ASD = atrial septal defect; AV = atrioventricular; VSD = ventricular septal defect.

* Linear-by-linear association.

AV = atrioventricular; CICU = cardiac intensive care unit.

Table 3

Multivariate analysis of preoperative and intraoperative predictors for postoperative third-degree AV block.

Covariate	Adjusted odds ratio (95% confidence interval)	*P* value
Taking digoxin preoperatively	2.4 (1.3–4.4)	.007
Procedure included VSD closure	2.2 (1.2–4.1)	.013
GJA5 rs10465885 TT genotype	2.1 (1.2–3.8)	.009
Aortic cross-clamp time (per 5 minutes)	1.08 (1.04–1.11)	<.001

Other covariates considered for inclusion in the stepwise binary logistic regression model were chromosomal anomaly, weight, surgical era, and angiotensin-converting inhibitor administration. Age and cardiopulmonary bypass time were excluded due to collinearity with weight and aortic cross-clamp time, respectively. Hosmer and Lemeshow test $P = .49$.

AV = atrioventricular; VSD = ventricular septal defect.

Table 4

Characteristics with respect to conduction recovery after incidence of postoperative third-degree AV block.

Variable	No recovery (n = 21)	Conduction recovery (n = 35)	*P* value
Age (days)	127 (26, 305)	100 (29, 229)	.36
Weight (kg)	5.3 (3.8, 7.4)	4.5 (3.8, 5.9)	.45
Male gender (%)	8 (38%)	17 (49%)	.45
Chromosomal anomaly	7 (33%)	13 (37%)	.77
Preoperative medication			
Digoxin	8 (38%)	11 (31%)	.61
Beta-blocker	1 (3%)	3 (14%)	.11
Other antiarrhythmic drug	0 (0%)	0 (0%)	
ACE inhibitor	3 (9%)	7 (33%)	.02
GJA5 rs10465885 genotype			.48
C/C	4 (19%)	3(8%)	
T/C	8 (38%)	16 (46%)	
T/T	9 (43%)	16 (44%)	
Cardiopulmonary bypass time (min)	140 (111, 206)	134 (106, 184)	.59
Aortic cross-clamp time (min)	77 (54, 106)	70 (46, 85)	.16
Procedure includes VSD closure	14 (67%)	25 (71%)	.71
Surgical era			.15
2007–2010	9 (43%)	22 (63%)	
2011–2015	12 (57%)	13 (37%)	
Surgeon			.25
Surgeon A	10 (48%)	16 (46%)	
Surgeon B	9 (43%)	12 (34%)	
Surgeon C	1 (4.8%)	7 (20%)	
Surgeon D	1 (4.8%)	0 (0%)	
Admission laboratory test results			
pH	7.34 (7.30, 7.39)	7.35 (7.28, 7.40)	.80
pCO_2 (mm Hg)	43 (41, 51)	46 (40, 55)	.55
pO_2 (mm Hg)	85 (63, 109)	75 (47, 132)	.61
Base excess	−2.2 (−4.6, 1.4)	−1.5 (−3.5, 2.0)	.62
Lactate (mmol/L)	2.3 (1.1, 3.5)	3.1 (1.9, 5.1)	.11
Hematocrit (mg/dL)	38 (35, 43)	40 (35, 45)	.25
K (mmol/L)	3.9 (3.1, 4.7)	3.8 (3.5, 4.5)	.71
i_{Ca} (mg/dL)	6.0 (5.5, 6.6)	5.6 (5.2, 6.1)	.24
Postoperative extracorporeal membrane oxygenation	4 (19%)	4 (11%)	.43
Junctional acceleration (AJR, JET)	4 (19%)	19 (54%)	.012
Time to junctional acceleration (days)	0 (0, 1.5)	1 (0, 2)	
Intermittent conduction	1 (5%)	13 (37%)	.009

Variable	No recovery (n = 21)	Conduction recovery (n = 35)	*P* value
Time to intermittent conduction (days)		2 (0.5, 5.5)	
PM implantation	18 (86%)	8 (23%)	<.001
Time to PM implantation (days)	7.5 (6, 11.3)	11.5 (7.3, 18)	
Duration mechanical ventilation (days)	2 (1, 5)	3 (1, 22)	.25
CICU length of stay (days)	11 (7, 14)	10 (5, 24)	.93
Hospital length of stay (days)	15 (10, 23)	16 (10, 39)	.38
Hospital mortality	3 (14%)	6 (17%)	.78

Continuous variables are given as median (25th, 75th percentile) and categorical variables as frequency (%).

ACE = angiotensin-converting enzyme; AJR = accelerated junctional rhythm; AV = atrioventricular; CICU = cardiac intensive care unit; JET = junctional ectopic tachycardia; PM = pacemaker; VSD = ventricular septal defect.

Table 5

Multivariate analysis of predictors for 1:1 recovery from postoperative third-degree AV block.

Covariate	Adjusted odds ratio (95% confidence interval)	*P* value
Intermittent conduction	9.1 (1.0–80)	.045
Junctional acceleration	4.0 (1.1–15.1)	.044

Other covariate considered for inclusion in the stepwise binary logistic regression model was preoperative angiotensin-converting enzyme inhibitor. Hosmer and Lemeshow test $P = .31$.