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The Association between Peri-Operative Dexmedetomidine and Arrhythmias after Surgery for Congenital Heart Disease

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Abstract

Background—Dexmedetomidine is commonly used after congenital heart surgery and may be associated with a decreased incidence of post-operative tachyarrhythmias. Using a large cohort of patients undergoing congenital heart surgery, we examined for an association between dexmedetomidine use in the immediate post-operative period and subsequent arrhythmia development.

Methods and Results—A total of 1,593 surgical procedures for congenital heart disease were performed. Dexmedetomidine was administered in the immediate post-operative period after 468 (29%) surgical procedures. Compared to 1,125 controls, the group receiving dexmedetomidine demonstrated significantly fewer tachyarrhythmias (29% vs. 38%, p<0.001), tachyarrhythmias receiving intervention (14% vs. 23%, p<0.001), bradyarrhythmias (18% vs. 22%, p=0.03) and bradyarrhythmias receiving intervention (12% vs. 16%, p=0.04). After propensity score matching with 468 controls, the arrhythmia incidence between groups became similar: tachyarrhythmias (29% vs. 31%, p=0.66), tachyarrhythmias receiving intervention (14% vs. 17%, p=0.16), bradyarrhythmias (18% vs. 15%, p=0.44) and bradyarrhythmias receiving intervention (12% vs. 9%, p=0.17). After excluding controls exposed to dexmedetomidine at a later time in the hospitalization, dexmedetomidine was associated with increased odds of bradyarrhythmias receiving intervention (odds ratio [OR] 2.18, 95% confidence interval (CI) 1.02 – 4.65). Furthermore, there was a dose-dependent increase in the odds of bradyarrhythmias (OR 1.04, 95% CI 1.01 – 1.07) and bradyarrhythmias receiving intervention (OR 1.05, 95% CI 1.01 – 1.08).

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Conclusions—While dexmedetomidine exposure in the immediate post-operative period is not associated with a clinically meaningful difference in the incidence of tachyarrhythmias after congenital heart surgery, it may be associated with increased odds of bradyarrhythmias.

Keywords

pediatric; heart defects; congenital; arrhythmia; surgery

Post-operative arrhythmias are a common complication after cardiac surgery for congenital heart disease, with a reported incidence of up to 50%.[1–4] Post-operative tachyarrhythmias are often poorly tolerated in this patient population, causing significant hemodynamic instability and are associated with increased early post-operative morbidity and mortality.[4–7] The management of these arrhythmias can present a challenge, as antiarrhythmic therapies may be ineffective and/or associated with significant adverse effects.

Dexmedetomidine is a selective alpha$_2$-adrenergic agonist that provides sedation, anxiolysis and analgesia with minimal to no respiratory depression. As a result it has become widely used in a variety of settings, including the peri-operative period for congenital heart surgery.[8–11] Dexmedetomidine acts as a peripheral parasympathomimetic and a central sympatholytic, decreasing both heart rate and blood pressure.[8–11] Furthermore, dexmedetomidine has been shown to depress sinus and atrioventricular node function in children undergoing intracardiac electrophysiology studies.[8, 10] Previous studies have suggested that post-operative dexmedetomidine use may decrease the incidence of tachyarrhythmias after congenital heart surgery, but have also raised concerns over the development of bradyarrhythmias as an adverse effect.[5, 8–13]

Our primary objective was to evaluate the association between dexmedetomidine administration in the immediate post-operative period and the development of subsequent post-operative tachyarrhythmias in a large cohort of patients undergoing congenital heart surgery. A secondary objective was to evaluate whether dexmedetomidine administration was associated with an increased incidence of bradyarrhythmias. Therefore, we tested the following hypotheses: 1) dexmedetomidine use at the time of admission to the pediatric cardiac intensive care unit (PCICU) is associated with decreased post-operative tachyarrhythmias; and 2) dexmedetomidine use is associated with increased post-operative bradyarrhythmias.

Methods

Study Population

Subjects in our study were enrolled in an ongoing prospective observational study of post-operative arrhythmias after congenital heart surgery. All patients undergoing cardiac surgery for congenital heart disease at Monroe Carell, Jr. Children’s Hospital at Vanderbilt University and subsequently admitted to the PCICU from September 2007 to September 2013 were eligible for enrollment. The study subject, or their parents/legal guardians, provided written informed consent to inclusion within the study and to a review of the medical record; including collection and storage of their demographic and peri-operative

data into a common database. The sole exclusion criterion was refusal to provide consent for participation within the study, as per the patient or their parents/legal guardians. For the purposes of our study, data for each subject were then analyzed retrospectively from the common database. This study was approved by the Vanderbilt University Institutional Review Board for Research on Human Subjects.

Dexmedetomidine Use and Data Collection

Subjects were included in the dexmedetomidine group if they were receiving dexmedetomidine at the time of admission to the PCICU and were included in the control group if they were not. Our primary objective was to evaluate the association of dexmedetomidine use in the immediate post-operative period at PCICU admission with subsequent arrhythmia development, therefore subjects who were exposed to dexmedetomidine at a later point were considered controls for the initial statistical analysis. A subsequent sensitivity analysis was then performed, excluding control subjects that were exposed to dexmedetomidine at some point after PCICU admission. The decision to initiate dexmedetomidine was at the discretion of the cardiac anesthesiologists and intensivists. Pre-operative data collected included age, gender, race, weight, height, body surface area (BSA) and type of congenital heart defect. Intra-operative data included surgical procedure performed, cardiopulmonary bypass (CPB) use and length of time, aortic cross-clamp length of time, and use of deep hypothermic circulatory arrest. Operative procedures were classified according to the Risk Adjustment for Congenital Heart Surgery, version 1 (RACHS-1) method.[14] Subjects received general endotracheal anesthesia, traditionally consisting of fentanyl or etomidate and pancuronium and maintenance with fentanyl, isoflurane and pancuronium. Post-operative data collected upon admission to the PCICU included blood gas with lactate, hematocrit, electrolytes including ionized calcium, and the use of infusions such as calcium chloride, dopamine, dobutamine, epinephrine, milrinone, nipride and aminocaproic acid. Dexmedetomidine dose (mcg/kg/hr) and total duration (hours) were recorded for each subject receiving dexmedetomidine. Furthermore, the total dose (mcg/kg) received in the first 24 post-operative hours and the total dose (mcg/kg) received over the subject's entire post-operative course were calculated.

Post-operatively, all subjects were monitored with continuous full disclosure telemetry throughout the duration of their hospitalization. The study nurse performed complete daily assessments of the telemetry, including alarm review. Arrhythmias identified by the study nurse were confirmed and mechanisms determined by pediatric electrophysiologists. Each post-operative arrhythmia was coded with respect to timing of arrhythmia onset, arrhythmia type and any associated intervention.

The data collection period for each subject was from the time of the surgical procedure until discharge home, or until the next surgical procedure if performed prior to discharge from the hospital. If a subject experienced multiple arrhythmias after a single procedure, any additional arrhythmias were classified as a new arrhythmia only if it was distinctly different from the previous.

Outcome Measures

The primary outcome measure was the overall incidence of arrhythmias, which was further categorized into the incidence of tachyarrhythmias and bradyarrhythmias. Tachyarrhythmias were divided into subgroups, including accelerated junctional rhythm, junctional ectopic tachycardia, atrial tachycardia, ventricular tachycardia and accelerated ventricular rhythm. Bradyarrhythmias included sinus pauses and second-degree or third-degree atrioventricular block.

Arrhythmias were deemed clinically significant if they received some type of intervention. Interventions for arrhythmias included pharmacotherapy, vagal maneuvers, surface cooling, temporary or permanent pacing, direct current cardioversion, defibrillation or cardiopulmonary resuscitation.

Statistics

An initial comparison between the subjects receiving dexmedetomidine and all controls was performed. Of note, an a priori sample size analysis was not conducted prior to the study. The demographic and clinical data were compared using Pearson Chi-square test for categorical variables and Wilcoxon rank-sum test for continuous variables.

Because this study design is an observational study, and treatment assignment was not controlled, significant differences were observed in baseline characteristics between the two study groups. To correct for the potential bias these differences would introduce, propensity score matching analysis was performed. By definition, the propensity score is the conditional probability of receiving a treatment given observed covariates. The propensity score is then used to balance the covariates in the two groups and therefore reduce the effect of bias.[15]

The variables selected for inclusion in the propensity score as potential confounders were variables previously demonstrated to affect the development of post-operative arrhythmias, informed from previous literature (Supplemental Figure 1).[1–3, 6, 7] Variables that demonstrated high collinearity with chosen variables were excluded. Variables were also excluded from the analysis if there were a high number of missing values or too few subjects in one category. To avoid an effect on the overall analysis, missing values for the 24 included variables were imputed via multiple imputation methods, ultimately generating a complete dataset. Of these variables, only one had a relatively higher number of missing values (sodium level, 37% missing), while the majority of the remaining variables had no missing values, or <2% missing.

A propensity score was obtained by calculating the predicted value for each observation from a logistic regression model that regressed dexmedetomidine usage on the potential confounders. Optimal matching techniques were used to select subjects who received dexmedetomidine with controls by choosing subjects with the nearest propensity score by a 1:1 ratio.[16] All subjects in the dexmedetomidine group were successfully matched to subjects in the control group. The two matched groups were then compared on the outcomes of interest using McNemar’s test for categorical variables and Wilcoxon signed-rank test for continuous variables. Conditional logistic regression was fitted to the matched data to assess

the association of dexmedetomidine with the arrhythmia outcomes adjusting for propensity score, age and BSA, as age and BSA were not well balanced between the groups after propensity score matching.

To evaluate potential dose-dependent effects of dexmedetomidine among patients who received dexmedetomidine, multiple logistic regression analysis was performed to determine the odds ratio for each arrhythmia outcome per 10 unit increase in dexmedetomidine dose, adjusting for potential confounding variables. The variables chosen for inclusion in the logistic regression analysis were the same variables included in the propensity score matching analysis. Focusing only on the dexmedetomidine patients resulted in a more homogenous sample of patients, alleviating but not eliminating concern for confounding.

The primary objective of this study was to evaluate the association of dexmedetomidine use specifically at admission to the PCICU on subsequent arrhythmia outcomes. Although control subjects were not exposed to dexmedetomidine at admission to the PCICU, a proportion of controls were exposed to dexmedetomidine at a later point during the course of their hospitalization. Therefore, a subsequent sensitivity analysis was performed, repeating the propensity score matching after excluding those controls that were exposed to dexmedetomidine at a later time after PCICU admission. Similar propensity score matching techniques were used to match subjects in the dexmedetomidine group with the control subjects that were never exposed to dexmedetomidine. All dexmedetomidine subjects were successfully matched in a 1:1 ratio with controls. The two newly matched groups were again compared on the outcomes of interest using McNemar's test for categorical variables and Wilcoxon signed-rank test for continuous variables. Conditional logistic regression was re-fitted to the new matched data to assess the association of dexmedetomidine with the arrhythmia outcomes, adjusting for variables that were not as well balanced after propensity score matching; including age, BSA, CPB time and aminocaproic acid use at PCICU admission. A two-tailed p-value of <0.05 was used to determine statistical significance. The 95% confidence intervals (CI) for the difference in proportions for the arrhythmia outcomes were obtained to evaluate for clinically meaningful differences. Data were analyzed using R version 2.15.

Results

A total of 1,593 post-surgical cases were included. Of the 1,593 cases, 468 subjects received dexmedetomidine and 1,125 subjects comprised the initial control group. The baseline and peri-operative characteristics of the entire cohort and of the two groups are summarized in Table 1. The dexmedetomidine and control groups differed significantly with regards to several characteristics, many of which are known to affect the incidence of post-operative arrhythmias.[1–3, 6, 7] The subjects in the dexmedetomidine group were older, had a higher BSA, had shorter CPB and cross-clamp times and had lower lactate levels at admission to the PCICU. Although there was no gender mismatch, the dexmedetomidine group had a lower surgical complexity (RACHS-1) category and less use of calcium chloride, dopamine and epinephrine at PCICU admission.

The incidence rates of post-operative arrhythmias in the entire cohort and comparisons between the dexmedetomidine and control groups are presented in Table 2. The overall incidence of any post-operative arrhythmia was 49%, similar to previously reported values.[1–4] Compared to controls, subjects in the dexmedetomidine group had significantly fewer tachyarrhythmias (29% vs. 38%, $p<0.001$), tachyarrhythmias receiving intervention (14% vs. 23%, $p<0.001$), bradyarrhythmias (18% vs. 22%, $p=0.03$), and bradyarrhythmias receiving intervention (12% vs. 16%, $p=0.04$).

Due to significant differences in baseline characteristics, which could bias the dexmedetomidine group towards a decreased incidence of arrhythmias, subjects were matched in a 1:1 fashion via propensity score matching. After propensity score matching, the baseline and peri-operative characteristics between the groups became similar, with the exception of age and BSA (Table 3). Although this difference remained, the plot of standardized difference in means before and after matching (Supplemental Figure 1) demonstrates that the two groups were well matched overall.

Analysis of the arrhythmia outcomes between the two matched groups revealed no significant association between the administration of dexmedetomidine in the immediate post-operative period and the development of post-operative tachyarrhythmias or bradyarrhythmias (Table 4). The 95% confidence intervals for the difference in proportions for the corresponding arrhythmia outcomes demonstrated an estimated difference no greater than 0.10 between matched groups. Additionally, there were no statistically significant differences in specific arrhythmia subtypes detected in the matched analysis (Supplemental Table 1), although the precision of the 95% confidence intervals does not rule out the possibility of small differences between study populations.

A significant difference remained in age and BSA between the two groups after propensity score matching. The subjects in the dexmedetomidine group were of an older age and had a higher BSA. To better control for these observed differences, conditional logistic regression analysis was performed, adjusting for the propensity score, age and BSA while accounting for the correlation in the matched data. As shown in Table 5, after adjusting for these variables, dexmedetomidine exposure continued to show no significant association with subsequent arrhythmia development.

Further analysis was performed to evaluate for a potential dose-dependent effect among subjects receiving dexmedetomidine at PCICU admission. The median dose in the first 24 post-operative hours (mcg/kg/hr), the total dose (mcg/kg) in the first 24 post-operative hours, the total dose (mcg/kg) over the subject's entire post-operative course and the total duration (hours) were obtained for the 468 subjects receiving dexmedetomidine, and are presented in Table 6. Initial analyses suggested that subjects developing arrhythmias received higher doses of dexmedetomidine. Therefore, logistic regression analysis was performed (Table 7). The total dexmedetomidine dose (mcg/kg) received over the first 24 post-operative hours demonstrated no significant association with the odds of arrhythmia development. Similarly, the total dose (mcg/kg) received over the subject's entire post-operative course did not increase the odds of tachyarrhythmia development, however, it was associated with a dose-dependent increase in the odds of bradyarrhythmias (odds ratio [OR]

1.04, 95% CI 1.01 – 1.07) and bradyarrhythmias receiving intervention (OR 1.05, 95% CI 1.01 – 1.08) for every 10mcg/kg increase in dexmedetomidine dose over the entire post-operative course.

Next, we sought to determine if the timing of the arrhythmia was influenced by dexmedetomidine exposure. Of the subjects that developed arrhythmias, 83.7% occurred within the first four post-operative days, and of those with tachyarrhythmias in particular, 83.2% occurred within the first four post-operative days. After excluding subjects with arrhythmias that occurred more than four days post-operation, dexmedetomidine exposure at PCICU admission was not associated with the development of subsequent arrhythmias (p=0.39) or tachyarrhythmias (p=0.84) within the first four post-operative days.

Because the primary objective of this study was to evaluate for an association of arrhythmia outcomes related to exposure to dexmedetomidine specifically at the time of admission to the PCICU, subjects were considered controls if they were not receiving dexmedetomidine at the time of PCICU admission, regardless of whether or not they were exposed to dexmedetomidine at a later point in their hospitalization. To avoid potential confounding introduced by exposure to dexmedetomidine at a later time, a subsequent sensitivity analysis was performed repeating the propensity score analysis after excluding those controls exposed to dexmedetomidine at a later time. The plot of standardized difference in means before and after matching for the new matched cohort demonstrates that the two groups were again well matched overall (Supplemental Figure 2). As shown in Supplemental Table 2, dexmedetomidine exposure at PCICU admission was not associated with a significant change in the incidence of post-operative arrhythmias, compared to the control subjects that were never exposed to dexmedetomidine. Despite propensity score matching, a few variables were not as well balanced between the groups, including age, BSA, CPB time and the use of aminocaproic acid in the immediate post-operative period. Conditional logistic regression analysis was repeated adjusting for these factors. As shown in Table 8, after matching subjects exposed to dexmedetomidine at PCICU admission with controls that were never exposed to dexmedetomidine, and after accounting for potential confounding variables, dexmedetomidine use at PCICU admission was not associated with a clinically or statically significant decrease in overall tachyarrhythmia development. Dexmedetomidine exposed subjects did experience a non-significant trend toward an increased odds of post-operative bradyarrhythmias and a statistically significant, possibly clinically relevant increased odds of bradyarrhythmias receiving therapy (OR 2.18, 95% CI 1.02 to 4.65).

Discussion

The purpose of this study was to evaluate the association of dexmedetomidine use in the immediate post-operative period at admission to the PCICU and subsequent post-operative arrhythmia development in a large cohort of patients undergoing congenital heart surgery. To our knowledge, this is the largest cohort of subjects used to study for this association.

Although dexmedetomidine use was associated with a lower incidence of arrhythmias in the initial univariate analysis, after propensity score matching for variables that may affect the risk of arrhythmia development, dexmedetomidine exposure specifically at admission to the

PCICU was not associated with a decreased incidence of post-operative tachyarrhythmias or an increased incidence of post-operative bradyarrhythmias.

Previous studies have evaluated the association between peri-operative dexmedetomidine and post-operative arrhythmias in children. Chrysostomou et al. evaluated 32 subjects receiving dexmedetomidine in the immediate post-operative period after congenital heart surgery compared to 20 historical controls. They observed a dramatic decrease in the incidence of post-operative ventricular (0% vs. 25%, p=0.01) and supraventricular (6% vs. 25%, p=0.05) tachyarrhythmias associated with dexmedetomidine, without a significant increase in bradyarrhythmias.[13] In our unmatched, overall cohort, we likewise observed a lower incidence of tachyarrhythmias associated with dexmedetomidine (29% vs. 38%, p<0.001). However, after propensity score matching, the incidence of tachyarrhythmias became similar (29% vs. 31%, p=0.66). Thus, after adjusting for baseline differences using a matched cohort, we failed to demonstrate a clinically meaningful reduction in the incidence of tachyarrhythmias with dexmedetomidine administration at PCICU admission. As demonstrated by the 95% confidence interval for the difference in proportions after matching (Table 4), any difference in the incidence of arrhythmias associated with dexmedetomidine exposure is not clinically meaningful (<0.10).

At our institution, certain patients are more likely to receive dexmedetomidine than others, which is underscored by the significant differences observed in baseline characteristics between the dexmedetomidine and control groups (Table 1). Typically, patients receiving dexmedetomidine at the time of admission to the PCICU are older (>28 days) and are those in whom early extubation is anticipated. As such, these patients often have shorter surgical CPB times and cross clamp times, and have fewer abnormalities on their post-operative arterial blood gas. Our observational study began enrollment at a time when dexmedetomidine use was infrequent in our unit, thus we were able to identify reasonably well-matched controls in a 1:1 fashion using propensity score matching. Significant differences in age and BSA remained after propensity score matching, however, after adjusting for these variables using conditional logistic regression, we were unable to discern any appreciable difference in the odds of developing arrhythmias (Table 5).

Among subjects exposed to dexmedetomidine at PCICU admission, a dose-dependent decrease in tachyarrhythmia incidence was not observed. However, there was a statistically significant, but small and possibly clinically insignificant, increase in the odds of developing bradyarrhythmias and bradyarrhythmias receiving intervention with every 10 mcg/kg increase in dexmedetomidine dose over the entire post-operative course (Table 7). Hosokawa et al. reported a significantly higher cumulative adverse event rate of bradycardia or hypotension associated with dexmedetomidine in 21% of pediatric patients vs. 8% receiving standard sedation after cardiac surgery (p=0.04).[12] Although bradyarrhythmias associated with dexmedetomidine have generally been mild, there have been previous case reports of serious bradyarrhythmias, such as sudden pauses, sinus arrest and loss of pacemaker capture occurring after dexmedetomidine administration.[10, 17–19] These findings would suggest caution when administering dexmedetomidine in patients with predisposing conduction abnormalities and in those who are pacemaker dependent.

As this study primarily evaluated for an association with dexmedetomidine exposure at PCICU admission and arrhythmia outcomes, a proportion of subjects that were initially considered controls were exposed to dexmedetomidine at a later time in their hospitalization. After excluding these control subjects and repeating the propensity score matching analysis, subjects exposed to dexmedetomidine at admission to the PCICU did not experience fewer tachyarrhythmias or more bradyarrhythmias compared to control subjects that were never exposed to dexmedetomidine (Supplemental Table 2). After adjusting for certain possible confounding variables with conditional logistic regression, dexmedetomidine use continued to show no statistical or clinical meaningful decrease in odds of post-operative tachyarrhythmias, however, subjects exposed to dexmedetomidine had a statistically significant, but small and possibly clinically relevant increase in odds of post-operative bradyarrhythmias receiving intervention (Table 8).

There were several limitations of our study. Although propensity score matching was performed to address significant differences in baseline characteristics between the dexmedetomidine and initial control groups, our study was not randomized. A randomized clinical study would provide stronger evidence for a true effect of dexmedetomidine on post-operative arrhythmia development. Additionally, the decision to initiate dexmedetomidine was at the discretion of the clinical team. Although we used statistical methods to adjust for factors that may cause selection bias, the true effect of selection bias is not known. Our study did not account for any potential association between the year the surgery was performed and the outcomes of interest. Finally, although we have accounted for an extensive list of known confounders, there may have been additional peri-operative variables, such as intra-operative anesthetic doses and cardiopulmonary bypass conditions, not accounted for that could further contribute to the risk of arrhythmias. There have been prior studies demonstrating antiarrhythmic effects of dexmedetomidine for the acute treatment of tachyarrhythmias,[5, 11, 20] however our study served to evaluate dexmedetomidine as an agent to prevent tachyarrhythmias in the post-operative period, rather than as an acute treatment of tachyarrhythmias.

In this non-randomized prospectively assembled retrospective observational study, the use of dexmedetomidine in the immediate post-operative period after congenital heart surgery was not associated with a clinically meaningful reduction in the incidence of tachyarrhythmias. Given the precision of the reported confidence intervals, our study gives evidence to exclude a clinically meaningful association. Furthermore, there was not a clinically meaningful dose-dependent effect observed on tachyarrhythmia incidence.

While dexmedetomidine exposure at admission to the PCICU was not associated with a decreased incidence of post-operative tachyarrhythmias, the dexmedetomidine group demonstrated a statistically significant and possibly clinically relevant, increase in the odds of bradyarrhythmias receiving intervention, compared to control subjects that were never exposed to dexmedetomidine. Furthermore, among the subjects receiving dexmedetomidine at PCICU admission, there was a similar statistically significant, but potentially clinically insignificant dose-dependent increase in the odds of all bradyarrhythmias and bradyarrhythmias receiving intervention.

In conclusion, dexmedetomidine use in the immediate post-operative period is not associated with a decrease in subsequent tachyarrhythmia development, and may be associated with a significant, but small, increase in the odds of developing bradyarrhythmias receiving intervention. These findings are clinically important as they demonstrate that the use of dexmedetomidine in the immediate post-operative period solely for the prevention of subsequent tachyarrhythmia development may not be warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline and peri-operative characteristics of the entire cohort and the control and dexmedetomidine (DEX) groups

	All (n = 1,593)	Control (n = 1,125)	DEX (n = 468)	p-Value*
Age at surgery (days)	167 (41 – 908)	127 (13 – 379)	784 (175 – 1794)	<0.001‡
Gender				
Male	54% (864)	56% (625)	51% (239)	0.10†
Female	46% (729)	44% (500)	49% (229)	
Weight (kg)	6.2 (3.8 – 12.2)	5.2 (3.4 – 8.6)	11.4 (6.4 – 17)	<0.001‡
Height (cm)	64 (53.5 – 89)	60 (52 – 74.9)	84 (63 – 104.5)	<0.001‡
BSA	0.33 (0.24 – 0.55)	0.30 (0.23 – 0.43)	0.52(0.33 – 0.70)	<0.001‡
RACHS-1 Category	3 (2 – 3)	3 (2 – 4)	3 (2 – 3)	<0.001‡
Race§				
White	85% (1342)	85% (953)	84% (389)	0.56†
Other	15% (240)	15% (166)	16% (74)	
CPB Time (min)	103 (64 – 146)	106 (65 – 152)	94.5 (64 – 133)	0.01‡
Cross Clamp Time (min)	35 (4 – 59)	38 (5 – 61)	31 (0.5 – 55.8)	0.03‡
Labs upon PCICU admission				
pH	7.35 (7.29 – 7.40)	7.35 (7.28 – 7.40)	7.36 (7.31 – 7.41)	<0.001‡
pCO2	44 (39 – 51)	45 (40 – 52)	43 (38 – 49)	<0.001‡
pO2	81 (47 – 152)	74 (44 – 137)	99 (59 – 166)	<0.001‡
Base Excess	−1.3 (−4.0 – 1.6)	−1.3 (−4.0 – 1.8)	−1.3 (−3.9 – 1.2)	0.68‡
Lactate	1.8 (1.2 – 3.3)	2.1 (1.3 – 3.9)	1.4 (1.0 – 2.0)	<0.001‡
Hematocrit	39 (35 – 43)	39 (35 – 44)	38 (34 – 42)	<0.001‡
Potassium	3.6 (3.2 – 4.0)	3.6 (3.2 – 4.0)	3.6 (3.2 – 4.0)	0.53‡
Ionized Calcium	5.5 (4.9 – 6.1)	5.5 (4.9 – 6.1)	5.4 (4.9 – 6.0)	0.04‡
Infusions upon PCICU admission				
Calcium Chloride	11% (169)	13% (146)	5% (23)	<0.001†
Dopamine	23% (368)	26% (295)	16% (73)	<0.001†
Epinephrine	19% (304)	21% (237)	14% (67)	0.002†
Milrinone	67% (1063)	68% (766)	63% (297)	0.07†
Nipride	25% (394)	20% (228)	35% (166)	<0.001†
Aminocaproic Acid	21% (342)	16% (176)	35% (166)	<0.001†
Dexmedetomidine	29% (468)			

Values are represented as median (interquartile range) or % (n)

BSA: body surface area; RACHS-1: Risk Adjustment for Congenital Heart Surgery version 1; CPB: cardiopulmonary bypass; PCICU: pediatric cardiac intensive care unit

[*] p-Value represents the relationship between the control and DEX groups

[†] Pearson Chi-square test

[‡] Wilcoxon rank-sum test

[§] Due to missing data, n for the variable does not equal the total group n

Table 2

Arrhythmia incidence in the entire cohort and the control and dexmedetomidine (DEX) groups; 95% confidence interval (CI) for the difference in proportions between the control and DEX groups

	All (n = 1,593)	Control (n = 1,125)	DEX (n = 468)	p-Value*	Proportion Difference (95% CI)†
One or More Arrhythmia	49% (783)	51% (570)	46% (213)	0.06	−0.05 (−0.11 – 0.002)
Tachyarrhythmia (TA)	36% (568)	38% (431)	29% (137)	<0.001	−0.09 (−0.14 – −0.04)
TA Receiving Intervention	20% (326)	23% (261)	14% (65)	<0.001	−0.09 (−0.13 – −0.05)
Bradyarrhythmia (BA)	21% (335)	22% (253)	18% (82)	0.03	−0.04 (−0.09 – −0.008)
BA Receiving Intervention	15% (232)	16% (177)	12% (55)	0.04	−0.04 (−0.08 – −0.004)
JET	7% (116)	9% (99)	4% (17)	<0.001	−0.05 (−0.08 – −0.03)
JET Receiving Intervention	7% (105)	8% (89)	3% (16)	<0.001	−0.05 (−0.07 – −0.02)

Values are represented as % (n)

JET: Junctional Ectopic Tachycardia

*p-Value represents the relationship between the control and DEX groups, using Pearson Chi-square test

†Values are represented as point estimate of proportion difference (95% confidence interval for the difference in proportions); DEX minus control

Table 3

Baseline and peri-operative characteristics of the control and dexmedetomidine (DEX) groups after propensity score matching

	Control (n = 468)	DEX (n = 468)	p-Value*
Age at surgery (days)	180 (108 – 957)	782 (175 – 1793)	<0.001‡
Gender			
Male	52% (244)	51% (239)	0.79†
Female	48% (224)	49% (229)	
BSA	0.35 (0.28 – 0.55)	0.51(0.33 – 0.69)	<0.001‡
RACHS-1 Category	2 (2 – 3)	3 (2 – 3)	0.59‡
Race			
White	84% (394)	84% (393)	>0.99†
Other	16% (74)	16% (75)	
CPB Time (min)	95 (61 – 130)	94 (63 – 133)	0.32‡
Cross Clamp Time (min)	33 (0 – 57)	30.5 (2 – 56)	0.93‡
Labs upon PCICU admission			
pH	7.37 (7.32 – 7.41)	7.36 (7.31 – 7.41)	0.81‡
pCO2	43 (38 – 49)	43 (38 – 49)	0.26‡
pO2	97 (50 – 167)	99 (58 – 166)	0.90‡
Base Excess	−0.7 (−3.5 – 1.7)	−1.4 (−3.9 – 1.2)	0.16‡
Lactate	1.4 (1.1 – 2.1)	1.4 (1.0 – 2.0)	0.09‡
Hematocrit	38 (34 – 43)	38 (34 – 42)	0.33‡
Potassium	3.5 (3.1 – 3.9)	3.6 (3.2 – 3.9)	0.20‡
Ionized Calcium	5.4 (4.9 – 6.0)	5.4 (4.9 – 6.0)	0.89‡
Infusions upon PCICU admission			
Calcium Chloride	7% (31)	5% (23)	0.33†
Dopamine	14% (66)	16% (73)	0.58†
Epinephrine	15% (68)	14% (67)	>0.99†
Milrinone	66% (308)	63% (297)	0.50†
Nipride	35% (164)	35% (166)	0.95†
Aminocaproic Acid	27% (128)	35% (166)	0.005†

Values are represented as median (interquartile range) or % (n)

BSA: body surface area; RACHS-1: Risk Adjustment for Congenital Heart Surgery version 1; CPB: cardiopulmonary bypass; PCICU: pediatric cardiac intensive care unit

*p-Value represents the relationship between the control and DEX groups

†McNemar's test

‡Wilcoxon signed-rank test

Table 4

Arrhythmia incidence and 95% confidence interval (CI) for the difference in proportions between the control and dexmedetomidine (DEX) groups after propensity score matching

	Control (n = 468)	DEX (n = 468)	p-Value*	Proportion Difference (95% CI)†
One or More Arrhythmia	41% (194)	46% (213)	0.22	0.05 (−0.02 – 0.10)
Tachyarrhythmia (TA)	31% (144)	29% (137)	0.66	−0.02 (−0.07 – 0.04)
TA Receiving Intervention	17% (81)	14% (65)	0.16	−0.03 (−0.08 – 0.01)
Bradyarrhythmia (BA)	15% (72)	18% (82)	0.44	0.03 (−0.03 – 0.07)
BA Receiving Intervention	9% (41)	12% (55)	0.17	0.03 (−0.01 – 0.07)

Values are represented as % (n)

*McNemar's test

†Values are represented as point estimate of proportion difference (95% confidence interval for the difference in proportions); DEX minus control

Table 5

Conditional logistic regression on matched data to evaluate for the association of dexmedetomidine administration on arrhythmia outcomes, adjusting for propensity score, age and BSA

	Odds Ratio	95% CI		p-Value
		Lower	Upper	
One or More Arrhythmia	1.27	0.94	1.71	0.13
Tachyarrhythmia (TA)	0.94	0.67	1.32	0.72
TA Receiving Intervention	0.81	0.54	1.23	0.33
Bradyarrhythmia (BA)	1.39	0.91	2.13	0.13
BA Receiving Intervention	1.30	0.79	2.13	0.30

BSA: body surface area; CI: confidence interval

Table 6

Dexmedetomidine (DEX) duration and dose data among subjects receiving DEX

	DEX (n = 468)
Total DEX Duration (hr)	12.8 (3.8 – 39.0)
DEX Dose (mcg/kg/hr) Hour 0–24*	0.69 (0.50 – 0.84)
Total DEX Dose (mcg/kg) Hour 0–24†	6.82 (3.00 – 13.85)
Total DEX Dose (mcg/kg)‡	9.13 (3.88 – 20.28)

Values are represented as median (interquartile range)

*Median DEX dose (mcg/kg/hr) in the first 24 post-operative hours

†Total DEX dose (mcg/kg) in the first 24 post-operative hours

‡Total DEX dose (mcg/kg) over the entire post-operative course

Table 7

Logistic regression analysis of total dexmedetomidine (DEX) dose (mcg/kg) in the first 24 post-operative hours and total DEX dose (mcg/kg) over the entire post-operative course, adjusting for potential confounders

	Odds Ratio (95% CI) First 24 Post-Operative Hours*	Odds Ratio (95% CI) Entire Post-Operative Course*
One or More Arrhythmia	0.96 (0.74 – 1.24)	1.02 (1.00 – 1.05)
Tachyarrhythmia	0.77 (0.57 – 1.03)	1.01 (0.98 – 1.04)
Tachyarrhythmia Receiving Intervention	0.98 (0.68 – 1.41)	1.03 (1.00 – 1.06)
Bradyarrhythmia	1.00 (0.73 – 1.38)	1.04 (1.01 – 1.07)‡
Bradyarrhythmia Receiving Intervention†	1.15 (0.79 – 1.67)	1.05 (1.01 – 1.08)‡

*Expressed as the odds ratio (95% confidence interval of the odds ratio) per 10 unit increase in dexmedetomidine dose (mcg/kg)

†Due to number of events, nine variables were chosen for inclusion (age, cardiopulmonary bypass time, RACHS-1 category, pH, lactate, milrinone, epinephrine, calcium chloride, hematocrit)

‡Indicates a p-value <0.05

Table 8

Conditional logistic regression on matched data to evaluate for the association of dexmedetomidine (DEX) administration on arrhythmia outcomes compared to controls never exposed to DEX, adjusting for propensity score, age, BSA, CPB time, and aminocaproic acid.

	Odds Ratio	95% CI		p-Value
		Lower	Upper	
One or More Arrhythmia	1.22	0.79	1.89	0.37
Tachyarrhythmia (TA)	0.69	0.42	1.13	0.14
TA Receiving Intervention	0.65	0.36	1.16	0.15
Bradyarrhythmia (BA)	1.7	0.98	2.97	0.06
BA Receiving Intervention	2.18	1.02	4.65	0.04

BSA: body surface area; CPB: cardiopulmonary bypass; CI: confidence interval