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Association of Hyperoxia During Cardiopulmonary Bypass and Postoperative Delirium in the Pediatric Cardiac ICU

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OBJECTIVE: ICU delirium commonly complicates critical illness associated with factors such as cardiopulmonary bypass (CPB) time and the requirement of mechanical ventilation (MV). Recent reports associate hyperoxia with poorer outcomes in critically ill children. This study sought to determine whether hyperoxia on CPB in pediatric patients was associated with a higher prevalence of postoperative delirium.

DESIGN: Secondary analysis of data obtained from a prospective cohort study.

SETTING: Twenty-two-bed pediatric cardiac ICU in a tertiary children's hospital.

PATIENTS: All patients (18 yr old or older) admitted post-CPB, with documented delirium assessment scores using the Preschool/Pediatric Confusion Assessment Method for the ICU and who were enrolled in the Precision Medicine in Pediatric Cardiology Cohort from February 2021 to November 2021.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Of 148 patients, who underwent cardiac surgery, 35 had delirium within the first 72 hours (24%). There was no association between hyperoxia on CPB and postoperative delirium for all definitions of hyperoxia, including hyperoxic area under the curve above 5 predetermined Pao_2 levels: 150 mm Hg (odds ratio [95% CI]: 1.176 [0.605–2.286], $p = 0.633$); 175 mm Hg (OR 1.177 [95% CI, 0.668–2.075], $p = 0.572$); 200 mm Hg (OR 1.235 [95% CI, 0.752–2.026], $p = 0.405$); 250 mm Hg (OR 1.204 [95% CI, 0.859–1.688], $p = 0.281$), 300 mm Hg (OR 1.178 [95% CI, 0.918–1.511], $p = 0.199$). In an additional exploratory analysis, comparing patients with delirium within 72 hours versus those without, only the *z* score for weight differed (mean [SD]: 0.09 [1.41] vs. −0.48 [1.82], $p < 0.05$). When comparing patients who developed delirium at any point during their ICU stay ($n = 45$, 30%), MV days, severity of illness (Pediatric Index of Mortality 3 Score) score, CPB time, and *z* score for weight were associated with delirium ($p < 0.05$).

CONCLUSIONS: Postoperative delirium (72 hr from CPB) occurred in 24% of pediatric patients. Hyperoxia, defined in multiple ways, was not associated with delirium. On exploratory analysis, nutritional status (*z* score for weight) may be a significant factor in delirium risk. Further delineation of risk factors for postoperative delirium versus ICU delirium warrants additional study.

KEYWORDS: cardiopulmonary bypass; delirium; hyperoxia; intensive care units; malnutrition; pediatrics

Nearly half of children who undergo cardiopulmonary bypass (CPB) develop delirium during their ICU stay (1–6). Delirium is a syndrome of acute disturbance of consciousness with a waxing and waning course that has been linked to increased risk of mortality, increased hospital length of stay (LOS), increased time on mechanical ventilation (MV), and decreased

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KEY POINTS

Question: Does hyperoxia on cardiopulmonary bypass increase the risk of postoperative delirium, and what risk factors exist for postoperative delirium in the pediatric cardiac population?

Findings: In this single-center retrospective cohort study, there was no association between hyperoxia (defined in multiple ways) and the development of postoperative delirium.

Meaning: Hyperoxia was not associated with delirium but warrants further study given the high levels of oxygen exposure that patients experience on cardiopulmonary bypass, and this study provides a novel approach and reference for future investigations into hyperoxia.

patient quality of life, independent of disease severity (1, 2, 6). Risk factors for delirium include young age, increased time on CPB, deep sedation and comatose states, cumulative exposure to sedatives (particularly benzodiazepines), immobility, developmental delay, high severity of illness, and the requirement of MV (1, 2, 5–9). The pathophysiology of delirium is complex and is likely the result of an underlying predisposition to cerebral dysfunction compounded by a variety of factors within the ICU environment. Our current understanding of delirium involves impaired cholinergic function, increased dopaminergic transition, oxidative stress, and inflammatory degradation of the blood-brain barrier resulting in local ischemia and neuronal apoptosis, among other contributors (8, 10). However, despite widespread acceptance of the deleterious effects of delirium in children and a growing understanding of the disease process, treatment options remain limited. Prevention of delirium is essential.

Much focus has surrounded preventable strategies for delirium, such as modifying iatrogenic factors such as depth and choice of sedation and the ICU environment. This has been realized through the clinical implementation of the A-F bundle, an interdisciplinary approach to key domains of patient care to include the assessment and management of pain, sedation, and delirium, early mobility and exercise, and family engagement (11). Given the ongoing need to create preventative strategies for decreasing the risk of delirium, recent literature has demonstrated that, in adults, periods of hyperoxia during CPB are associated with postoperative delirium (12). This association has not yet been studied in pediatrics. However, an association between hyperoxia on CPB and poorer outcomes, including higher mortality, has been elucidated among pediatric patients (13, 14). Additionally, several other studies have explored a link between hyperoxia during critical illness and mortality (15, 16). Therefore, this study sought to investigate the association between hyperoxia during CPB in pediatric patients and the development of delirium within the first 72 hours after CPB (postoperative delirium).

MATERIALS AND METHODS

This study was a retrospective analysis of a prospectively collected cohort of patients, who had been enrolled in the Precision Medicine in Pediatric Cardiology (PMPC) Cohort (17). This study was approved under the institutional review board number 70106, titled Genetic Basis of Arrhythmias in Pediatrics and Congenital Heart Disease, approved originally on September 22, 2006, and most recently updated and approved on February 19, 2021. Informed consent was obtained from patient guardians for use in the prospectively collected database. All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975.

All patients aged 0 days to 18 years, who underwent CPB, were admitted to the pediatric cardiac ICU, and whose families consented to enrollment in the PMPC database (approximately 80% of surgical patients) from February 2021 to November 2021 were screened for inclusion. Within this group, patients who had documented delirium screening with the Preschool (younger than 5 y) or Pediatric Confusion Assessment Method (age 5–18 y old) (ps/pCAM-ICU), a validated delirium screening method, within the first 72 hours of CPB were included. Patients were excluded if they were noted to be delirious pre-operatively, if they were mechanically ventilated and on continuous sedation infusions in the 24 hours before surgery, if this was their second time on CPB within the same hospitalization, or if their Richmond Agitation and Sedation Scale was less than –3, precluding delirium assessment.

Hyperoxia was defined in multiple ways for this analysis, given the variability of prior definitions used

in published studies (15, 16, 18). This exploratory analysis used multiple definitions of hyperoxia with a logistic regression framework to predict the primary outcome of the presence or absence of delirium within 72 hours of admission. Pao_2 values were collected every 5 minutes from the bypass record across the entire time on CPB for hyperoxia analysis. The general strategy on CPB, common across institutions, was to avoid hypoxia and to achieve oxygen saturations greater than 95% for all patients, including those with mixed lesions. Delirium assessments were conducted using the ps/pCAM-ICU, a highly valid and reliable scoring system for use in all pediatric ages, including newborns (19–21). Nursing staff had received continuing education as part of a quality improvement cycle for the implementation of delirium scoring before February 2021. Secondary exploratory analysis evaluated the association between clinical variables and postoperative delirium, including age, race, Pediatric Index of Mortality 3 Score (PIM3) (a validated ICU risk of mortality score) (22), STAT score (the Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery score, designed to predict risk of mortality based on congenital heart surgery procedure and which has been recently updated and validated) (23), *z* score for weight, CPB time, aortic cross-clamp time, the requirement of MV in the first 72 hours, and use of dexmedetomidine, opioid, or benzodiazepine infusions in the first 72 hours, ICU LOS, hospital LOS, and mortality. These same clinical variables were also analyzed for association with delirium across the entire ICU LOS.

Statistical Methods

Tables detailing primary and secondary variables of interest include the mean and SD for continuous normal variables, median and IQR values for continuous non-normal variables, and frequency and proportions for categorical variables. Differences between groups were then assessed for statistical significance; continuous variables following a normal distribution used a *t* test for differences in means, while non-normal continuous variables used the Wilcoxon rank-sum test to evaluate differences between the groups. Differences in categorical variables used the chi-square test unless cell counts were lower than 5; in this instance, the Fisher exact test was performed. An alpha of 0.05 was used for all tests for statistical significance.

The association between hyperoxia experienced during CPB and the presence of delirium within 72 hours of CPB was estimated using multivariable logistic regression. Logistic regression models were adjusted for CPB time, the requirement of postoperative MV, and *z* score for patient weight. The same logistic regression model was used to assess the association between opioid and benzodiazepine use in the first 72 hours and the development of postoperative delirium.

Hyperoxic AUC was estimated with the trapezoidal method. As there is no widely agreed upon Pao_2 value at which hyperoxia is diagnosed, the distribution of hyperoxic AUC measurements was assessed at five prespecified Pao_2 levels (150, 175, 200, 250, and 300). The area between the prespecified Pao_2 level and a patient's measured Pao_2 values was calculated for each patient at each prespecified level, providing an estimated hyperoxic AUC for each patient at each a priori Pao_2 level. Quartiles of hyperoxic AUC values were then calculated for the sample, and patients were assigned to an AUC group based on their own AUC value. The relationship between a patient's hyperoxic AUC quartile or continuous AUC measurement throughout their surgery and the presence of delirium was then assessed using logistic regression.

RESULTS

One hundred forty-eight patients were included in this study after screening 208 patients (**eFig. 1**, http://links.lww.com/CCX/B367). Of these, 35 (24%) patients screened positive for delirium within the first 72 hours following CPB. A total of 45 (30.4%) patients screened positive for delirium at any point during their ICU stay. Only two patients experienced mortality during the hospitalization, of which one was delirious during their hospitalization. Demographic data for the cohort is listed in **Table 1**.

The mean Pao_2 for this cohort while on CPB was 232 mm Hg (SD 61.2). Only one-quarter of patients experienced a median Pao_2 less than 200 mm Hg. No patients included in this study maintained a physiologic Pao_2 (Pao_2 of 80–100 mm Hg) while on CPB (**Fig. 1**).

Maximum Pao_2 value ever experienced, median Pao_2, and SD of Pao_2 while on CPB were not associated with postoperative delirium. A logistic regression model was created to analyze the relationship between

TABLE 1.
Demographics and Exploratory Analysis of Risk Factors in Patients With Postoperative Delirium (Within 72 hr of Cardiopulmonary Bypass)

Demographic Characteristics	Overall (n = 148)	Delirium Absent (n = 113)	Delirium Present (n = 35)	*p*
Sex, female (%)	63 (42.6)	51 (45.1)	12 (34.3)	0.348
Age (mo) (median [IQR])	7.0 (4.0, 50.3)	9.0 (3.0, 63.0)	7.0 (5.0, 22.0)	0.560
Race (%)				
Asian	3 (2.0)	3 (2.7)	0 (0.0)	1.0
Asian Indian	1 (0.7)	1(0.9)	0 (0.0)	
Black	11 (7.4)	9 (8.0)	2 (5.7)	
Hispanic	4 (2.7)	3(2.7)	1 (2.9)	
White	129 (87.2)	97 (85.8)	32 (91.4)	
Pediatric Index of Mortality 3 Score (median [IQR])	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)	0.260
STAT Score 1 (%)	38 (25.7)	29 (25.7)	9 (25.7)	0.782
STAT Score 2 (%)	48 (32.4)	34 (30.1)	14 (40.0)	
STAT Score 3 (%)	39 (26.4)	31 (27.4)	8 (22.9)	
STAT Score 4 (%)	13 (8.8)	10 (8.8)	3 (8.6)	
STAT Score 5 (%)	10 (6.8)	9 (8.0)	1 (2.9)	
z score for weight (mean [SD])	−0.04 (1.53)	0.09 (1.41)	−0.48 (1.82)	**0.050**
Mortality (%)	2 (1.4)	1(0.9)	1 (2.9)	0.418
Cardiopulmonary bypass time (median [IQR])	132.5 (90.0, 198.25)	129.0 (90.0, 188.0)	152 (105.0, 221.0)	0.166
Cross-clamp time (median [IQR])	54.0 (25.0, 89.8)	50 (24.0, 92.0)	66.0 (38.5, 81.0)	0.51
Mechanical ventilation use in first 72 hr (%)	115 (77.7)	84 (84.3)	31 (88.6)	0.103
Dexmedetomidine use in first 72 hr (%)	146 (98.6)	111(98.2)	35 (100)	1.0
Opioid use in first 72 hr (%)	66 (44.6)	48 (42.5)	18 (51.4)	0.462
Benzodiazepine use in first 72 hr (%)	7 (4.7)	4 (3.5)	3 (8.6)	0.357
ICU LOS (median [IQR])	4.0 (2.0, 7.0)	3.0 (1.0, 5.0)	5.0 (2.0, 9.0)	0.067
Hospital LOS (median [IQR])	8.0 (5.0, 15.0)	8.0 (4.0, 15.0)	10.0 (6.0, 15.0)	0.383

IQR = interquartile range, LOS = length of stay, STAT Score = the Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery score, designed to predict the risk of mortality based on congenital heart surgery procedure.
Comparison of demographic data and variables of interest between those who had no delirium versus those who developed delirium within 72 hours of cardiopulmonary bypass. Bold indicates $p < 0.05$, considered statistically significant.

postoperative delirium and hyperoxia using multiple previously published definitions of hyperoxia and controlling for CPB time, *z* score for patient weight, and requirement of postoperative MV (**Fig. 2**). These factors were controlled for based on the established literature and our findings from our demographic data, establishing an association with delirium. Hyperoxia was also defined as the area under the curve (AUC) and divided into quartiles above prespecified thresholds of hyperoxia at 150, 175, 200, 250, and 300 mm Hg. AUC, as a continuous measure above the same prespecified thresholds, was also included. There was no association between postoperative delirium and PaO_2 levels within any of the definitions that used AUC (Fig. 2).

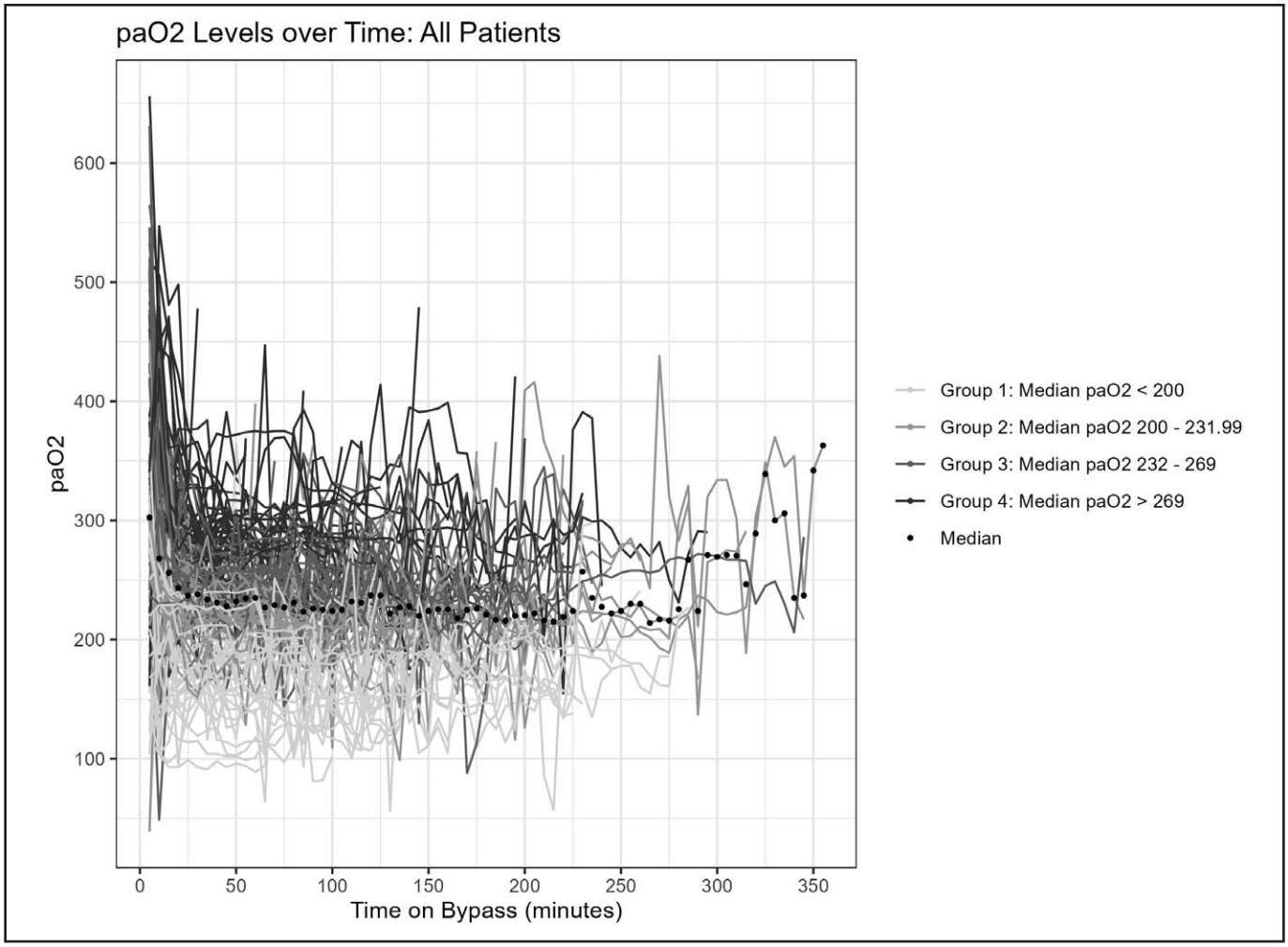

Figure 1. Pao_2 levels (mm Hg) over time for all patients, each represented individually.

An exploratory analysis assessed other risk factors for association with postoperative delirium (delirium within 72 hr of CPB) and determined that lower weight (*z* score for weight) was significantly associated with delirium within 72 hours of CPB (mean [SD]: 0.09 [1.41] vs. –0.48 [1.82], $p < 0.05$) (Table 1). Given that, there were multiple risk factors that had previously been associated with ICU delirium but were not associated with postoperative delirium, this same demographic data was further analyzed for association with delirium across the entire ICU stay. Ten additional patients experienced delirium in this group. *z* score for weight, CPB time, need for MV use in the first 72 hours, opioid use in the first 72 hours, ICU LOS, and hospital LOS were all significantly associated with delirium assessed at any point during the ICU stay (**Table 2**).

Further exploratory analysis, evaluating the association between the use of opioids and benzodiazepines as categorical variables and delirium within the first post-operative 72 hours was evaluated when controlling for the presence or absence of MV, CPB time, and *z* score for weight. No significant association was identified (**Fig. 3**). Dexmedetomidine use was not included in the final analysis, as all patients were exposed to dexmedetomidine.

DISCUSSION

Hyperoxia was not associated with postoperative delirium (occurring within 72 hr of CPB). In our exploratory analysis, lower weight was the only variable associated with postoperative delirium. Whereas the need for MV, opioid exposure, ICU LOS, and hospital LOS were all associated with delirium at any point during the ICU stay. In further exploratory analyses, when controlling for weight, CPB time, and exposure to MV, there was no significant association between the need for sedation or opioid use and the development of postoperative delirium.

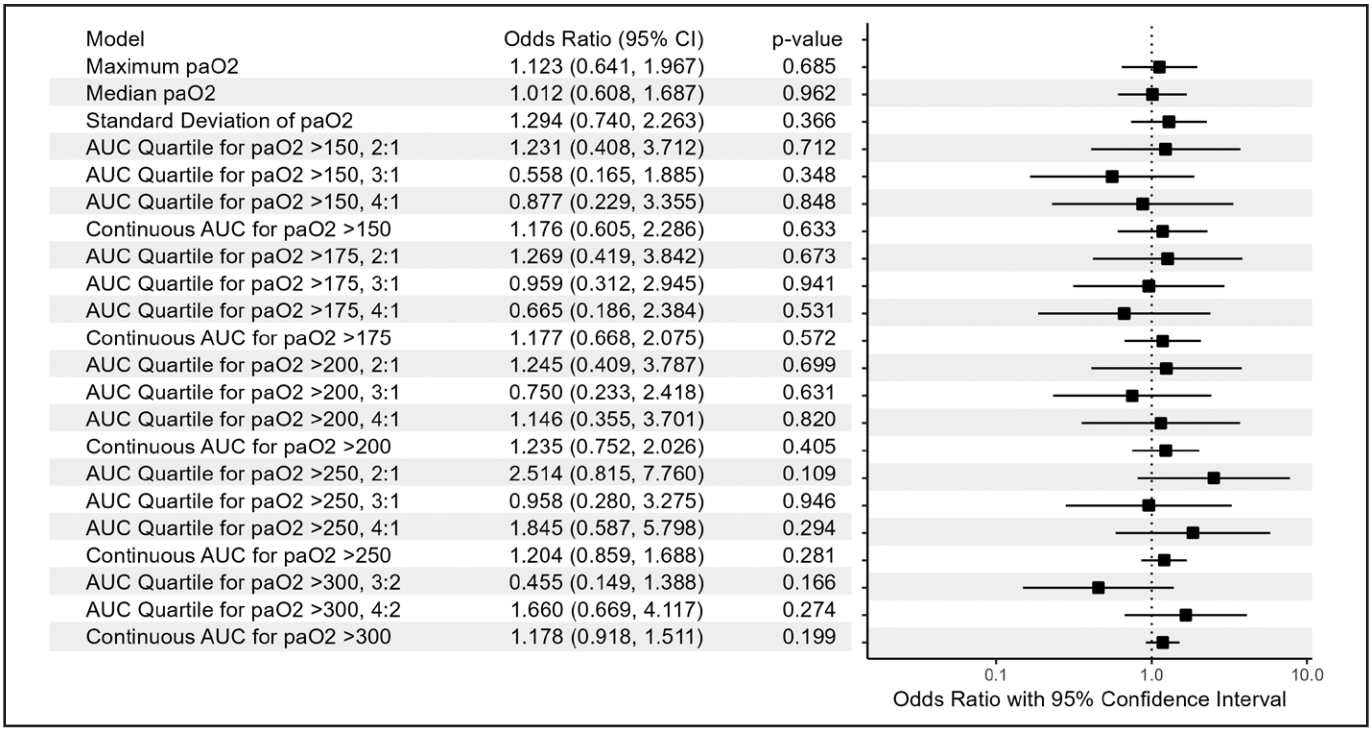

Figure 2. Logistic regression analysis for association of exploratory definitions of hyperoxia and association with delirium within 72 hours of cardiopulmonary bypass (CPB), controlling for time on CPB, *z* score for weight, and need for mechanical ventilation (MV), in the initial postoperative 72 hours. AUC = area under the curve.

Our data did not support the hypothesis that hyperoxia on CPB would lead to postoperative delirium due to free radical species and disruption of the blood-brain barrier based on current published literature on adult patients and animal model studies (12, 24–26). However, nearly every patient in the cohort experienced some amount of hyperoxia during their time on CPB, with a median Pao_2 on CPB of 232 mm Hg. The lack of association in the cohort may have been due to the absence of patients who experienced normoxia on CPB, but may also be due to differences in response to free radical species in the pediatric brain or differences in the blood-brain barrier between children and adults. Recent literature has looked specifically at aged mice to find mechanistic pathways for the development of delirium in response to reactive oxygen species, to which younger mice may be more resilient (27).

Notably, in this cohort of patients, there was an association between the *z* score for weight and the development of postoperative delirium, with a smaller age-adjusted weight being associated with an increased risk of delirium. Although a prior study has shown albumin levels less than 3 mg/dL to be associated with the development of delirium (1), this is the first pediatric study to find an association between nutritional status as determined by World Health Organization accepted weight standards and delirium. Weight is a metric that is already tracked in cardiac patients and is easier to follow than serial albumin levels. There are multiple reports of the association between poor nutritional status and mortality in the pediatric cardiac population, and this further underscores the importance of optimizing nutrition before congenital cardiac surgery (28, 29). Importantly, the group that experienced postoperative delirium differed from the cohort that included patients who experienced delirium at any point in their ICU stay. In this cohort, demographic variables associated with delirium were largely consistent with the currently published literature (1–6). ICU LOS, hospital LOS, opioid exposure, MV, and time on CPB were all associated with the development of delirium during the ICU stay. These were not associated with postoperative delirium. The difference in risk factors for early postoperative delirium versus later ICU delirium warrants further study as the pathophysiology between these groups may differ.

Interestingly, in a multivariable logistic regression model that controlled for MV, CPB time, and *z* score for weight, there was no association between opioid exposure and the development of delirium. We suspect

TABLE 2.
Exploratory Analysis of Risk Factors in Patients With ICU Delirium

Demographic Characteristics	Overall ($n = 148$)	Delirium Absent ($n = 103$)	Delirium Present ($n = 45$)	p
Sex, female (%)	63(42.6)	46 (44.7)	17 (37.8)	0.550
Age (mo) (median [IQR])	7.0 (4.0, 50.3)	10.0 (4.0, 64.0)	6.0 (4.0, 20.0)	0.087
Race (%)				
Asian	3 (2.0)	2 (1.9)	1 (2.2)	0.936
Asian Indian	1 (0.7)	1 (1.0)	0 (0)	
Black	11 (7.4)	9 (8.7)	2 (4.4)	
Hispanic	4 (2.7)	3 (2.9)	1 (2.2)	
White	129 (87.2)	88 (85.4)	41 (91.1)	
Pediatric Index of Mortality 3 Score (median [IQR])	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)	0.01 (0.01, 0.02)	**0.008**
STAT Score 1 (%)	38 (25.7)	28 (27.2)	10 (22.2)	0.780
STAT Score 2 (%)	48 (32.4)	30 (29.1)	18 (40.0)	
STAT Score 3 (%)	39 (26.4)	29 (28.2)	10 (22.2)	
STAT Score 4 (%)	13 (8.8)	9 (8.7)	4 (8.9)	
STAT Score 5 (%)	10 (6.8)	7 (6.8)	3 (6.7)	
z score for Weight (mean [SD])	−0.04 (1.53)	0.14 (1.37)	−0.47 (1.80)	**0.024**
Cardiopulmonary bypass time (median [IQR])	132.5 (90.0,198.25)	126.0 (89.5, 180.5)	154.0 (111.0, 225.0)	**0.022**
Cross-clamp time (median [IQR])	54.0 (25.0, 89.8)	50.0 (24.0, 90.5)	68.0 (35.0, 84.0)	0.275
Mechanical ventilation use in first 72 hr (%)	115 (77.7)	74 (71.8)	41 (91.1)	**0.010**
Dexmedetomidine use in first 72 hr (%)	146 (98.6)	101 (98.1)	45 (100)	1.0
Opioid use in first 72 hr (%)	66 (44.6)	38 (36.9)	28 (62.2)	**0.008**
Benzodiazepine use in first 72 hr (%)	7 (4.7)	3 (2.9)	4 (8.9)	0.200
ICU LOS (median [IQR])	4.0 (2.0, 7.0)	3.0 (1.0, 5.0)	6.0 (2.0, 13.0)	**< 0.001**
Hospital LOS (median [IQR])	8.0 (5.0, 15.0)	7.0 (4.0, 12.0)	11.0 (6.0, 28.0)	**0.002**

IQR = interquartile range, LOS = length of stay, STAT Score = the Society of Thoracic Surgeons-European Association for Cario-Thoracic Surgery score, designed to predict the risk of mortality based on congenital heart surgery procedure.
Comparison of demographic data and variables of interest between those who were never delirious versus those who experienced delirium at any point during their ICU stay. Bold indicates $p < 0.05$, considered statistically significant.

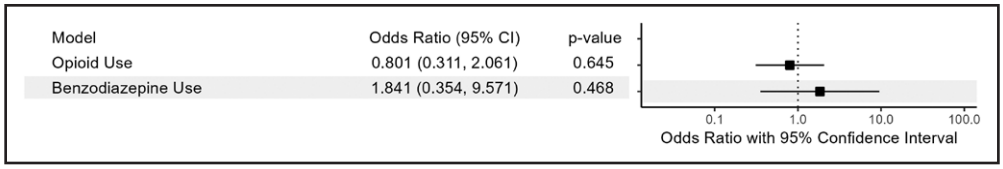

Figure 3. Exploratory analysis evaluating above variables and association with postoperative delirium within 72 hours of admission. Multivariable logistic regression model controls for *z* score for weight, cardiopulmonary bypass time, and presence or absence of postoperative mechanical ventilation.

that this is largely because MV is so intimately linked with more complex surgeries and subsequent opioid exposure. There was no association between benzodiazepine exposure and delirium, but only seven

patients were exposed to benzodiazepine infusions in this cohort, limiting the ability to truly assess an association.

Given the retrospective nature of the study, the findings are limited. Specifically, the incidence of delirium in this cohort was lower than what is reported in the literature for the pediatric cardiac ICU and often in the general PICU (1, 6). This reduction could be related to recent efforts to implement the A-F bundle as routine care and reduce benzodiazepine exposure in our cardiac ICU. However, the outcome was also based on nursing assessments recorded in the EHR rather than from specialized delirium screeners; for more than 30 patients, there was no consistent documentation of delirium screening in the EHR. While nurses underwent multiple training sessions before widespread use of the pCAM/psCAM, this may have contributed to our lower incidence of delirium.

In this cohort, few patients experienced normal Pao_2 levels while on CPB. Although there is some data on the relationship between toxic oxygen and mortality on CPB (13), the threshold for hyperoxia, which may contribute to delirium, may be significantly lower than what these patients experienced. Therefore, all patients may have been exposed to toxic oxygen, precluding significant results given the absence of a group without exposure. Additionally, it could be that hyperoxia has a more profound effect on certain subsets of patients, such as those with cyanotic heart disease or those admitted to the ICU immediately before surgery. However, the STAT score, which is a rough surrogate for these markers, did not suggest this in the dataset. Despite this limitation, this dataset provides a high level of oxygen data and is arguably one of the most thorough evaluations of hyperoxia reported in the literature for pediatrics. The statistical approach to hyperoxia was also novel. Current literature has no consensus on how to define hyperoxia for research purposes (17). Through an exploratory analysis, we evaluated multiple means of defining hyperoxia, both by absolute numbers and also based on cumulative exposure to supra-physiologic oxygen levels. This can serve as a future reference for studies to evaluate hyperoxia.

Finally, this study supports what is currently found in the literature with regard to both modifiable and nonmodifiable risk factors for delirium (1–3, 6). However, the association between a low *z* score for weight and the development of postoperative delirium is a new association that has been speculated based on low serum albumin but has not been fully reported in the literature. Future studies should prospectively evaluate patients with exposure to physiologic oxygen versus hyperoxia on CPB and the development of delirium. Additionally, if no association is found between hyperoxia and delirium in pediatrics, further studies could evaluate the difference between the blood-brain barrier and free radical scavengers in the brains of children versus adults as another means of elucidating the pathway of the development of delirium and targeting treatment interventions.

CONCLUSIONS

We found no association between hyperoxia on CPB and the development of postoperative delirium in a cohort of pediatric cardiac ICU patients; however, future study is warranted given the high levels of oxygen exposure that all patients experienced on CPB. An exploratory analysis revealed an association between nutritional status (*z* score for weight) preoperatively and the development of postoperative delirium, which is a potentially modifiable risk factor and target for study in the mechanistic pathways of the development of delirium. Furthermore, this study suggests different risk factors in the development of postoperative versus ICU delirium, and additional delineation of differences in risk factors warrants further study.

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