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Declining Incidence of Postoperative Neonatal Brain Injury in Congenital Heart Disease

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Abstract

BACKGROUND—Brain injury is common in neonates with complex neonatal congenital heart disease (CHD) and affects neurodevelopmental outcomes.

OBJECTIVES—Given advancements in perioperative care, we sought to determine if the rate of preoperative and postoperative brain injury detected by using brain magnetic resonance imaging (MRI) and associated clinical risk factors have changed over time in complex CHD.

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APPENDIX For supplemental Methods, a figure, and a table, please see the online version of this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

METHODS—A total of 270 term newborns with complex CHD were prospectively enrolled for preoperative and postoperative brain MRIs between 2001 and 2021 with a total of 466 MRI scans. Brain injuries in the form of white matter injury (WMI) or focal stroke and clinical factors were compared across 4 epochs of 5-year intervals with logistic regression.

RESULTS—Rates of preoperative WMI and stroke did not change over time. After adjusting for timing of the postoperative MRI, site, and cardiac group, the odds of newly acquired postoperative WMI were significantly lower in Epoch 4 compared with Epoch 1 (OR: 0.29; 95% CI: 0.09-1.00; $P = 0.05$). The adjusted probability of postoperative WMI declined significantly by 18.7% from Epoch 1 (24%) to Epoch 4 (6%). Among clinical risk factors, lowest systolic, mean, and diastolic blood pressures in the first 24 hours after surgery were significantly higher in the most recent epoch.

CONCLUSIONS—The prevalence of postoperative WMI has declined, whereas preoperative WMI rates remain constant. More robust postoperative blood pressures may explain these findings by minimizing periods of ischemia and supporting cerebral perfusion. These results suggest potential modifiable clinical targets in the postoperative time period to minimize the burden of WMI.

Keywords

brain injury; congenital heart disease; neurodevelopmental outcomes

Neurodevelopmental (ND) impairments are the most common morbidity that children with congenital heart disease (CHD) face, with a significant impact on academic achievement, quality of life, and transition to independence.[1,2] Although overall survival rates have improved considerably for the most complex forms of CHD with a growing adult congenital population,[3] we have not seen similar improvements in ND outcomes.[4] Neonatal brain injury is common in the patient with complex forms of CHD, requiring a neonatal operation.[5] Specifically, the risk of acquired preoperative brain injury ranges between 10% and 35%,[6-8] and the risk of newly acquired postoperative brain injury ranges between 33% and 75%.[9-11] White matter injury (WMI) remains the most common form of brain injury followed by small focal stroke.[9] Importantly, moderate to severe forms of neonatal WMI are associated with worse motor outcomes in late infancy,[12-14] making WMI a clinically relevant outcome to target to optimize ND outcomes. Over the last 2 decades, several clinical and patient-specific risk factors have been identified for both preoperative and new postoperative neonatal brain injury in the CHD population.[6-11]

During this same time period, the field of congenital cardiology has witnessed significant progress in outcomes among newborns with complex CHD, leading to lower mortality and morbidity.[15,16] Other similar patient populations such as premature infants have seen declines in rates of neonatal brain injury.[17] Thus, we hypothesized that these improvements in clinical care may also extend to other important outcomes such as neonatal brain injury in the CHD population.

The primary aim of the present study was to describe temporal trends of neonatal brain injury and associated clinical risk factors in an unselected group of neonates with complex

CHD who participated in an ongoing prospective cohort study over the last 20 years with preoperative and postoperative brain magnetic resonance imaging (MRI).

METHODS

Between 2001 and 2021, full-term newborns with complex CHD who were expected to require a neonatal operation (ie, within the first 30 days of life) at 2 sites (University of California San Francisco [UCSF] and British Columbia Children's Hospital [BCCH]) were consecutively invited to participate in a prospective cohort study obtaining preoperative and postoperative brain MRI and subsequent ND follow-up in infancy and childhood. Patients from BCCH were enrolled between 2006 and 2014 (coinciding when our collaborators were employed at BCCH). Brain imaging and ND findings from earlier versions of this cohort were previously reported.[6,9,12] Patients who were born before 36 weeks' gestation, had a suspected congenital infection, had clinical evidence of a congenital malformation or syndrome, and/or had a suspected or confirmed genetic or chromosomal anomaly were excluded. Enrollment criteria remained constant over the study period although various factors may have influenced our ability to approach every single eligible patient (ie, study staff availability, MRI staff availability, patient instability). The institutional committee on human research approved the study protocol at each site, and parents of each participant provided informed consent.

The study cohort mainly included patients diagnosed with either dextro-transposition of the great arteries (d-TGA) or single-ventricle physiology (SVP). d-TGA was defined as great vessel malposition with the aorta arising from the right ventricle and pulmonary artery arising from the left ventricle with or without a ventricular septal defect. SVP was defined as the absence of 1 of 2 functioning ventricles requiring a palliative surgical intervention for survival in the newborn period. The vast majority of participants included in this analysis had hypoplastic left heart syndrome (66 of 90 [73.3%]) and the minority with hypoplastic right heart syndrome (24 of 90 [26.7%]). Among the patients with hypoplastic left heart syndrome, the vast majority underwent a Norwood procedure with a Sano/right ventricular-to-pulmonary artery shunt while a small number (n = 5) had a modified Blalock-Taussig-Thomas shunt placed. A small number of participants included in this analysis had other diagnoses resulting in biventricular physiology after neonatal repair. Specifically, these diagnoses included tetralogy of Fallot or double outlet right ventricle with pulmonary outflow obstruction (n = 16), pulmonary atresia with intact ventricular septum (n = 3), coarctation of the aorta (n = 8), interrupted aortic arch with ventricular septal defect (n = 9), and truncus arteriosus (n = 5).

MRI STUDY

Preoperative MRI studies were performed as soon as the infant could be safely transported to the MRI scanner as determined by the clinical team. Postoperative studies were performed after completion of perioperative care and before discharge from the hospital. Imaging time points were separated by an average of 15 days in the entire cohort. Detailed MRI methods are listed in the Supplemental Methods. A neuroradiologist at each site reviewed each MRI for focal, multifocal, or global changes, blinded to clinical variables. Brain injury was

characterized as stroke, WMI, intraventricular hemorrhage, and/or global hypoxic-ischemic injury as previously described.[9] We have previously described high inter-rater reliability of the neuroradiology scores applied to grade the severity of brain injury.[18] The description of postoperative brain injuries was limited to newly acquired lesions not evident on the preoperative scan. Intraventricular hemorrhage was characterized as grade I, II, III, or periventricular hemorrhagic infarct using the system of Papile et al.[19] No subjects were found to have intraventricular hemorrhage higher than grade II, and thus this form of brain injury was not analyzed in the present study. The quantitative assessment of WMI was performed by a trained rater (T.G. and T.S.) and reviewed by an experienced neonatal neurologist (S.P.M.). Punctate WMI was characterized by areas of T1 hyperintensity and was manually delineated on all available preoperative and postoperative scans. The total WMI volume was determined by manual segmentation, as previously described.[20]

CLINICAL VARIABLES

Clinical data were prospectively collected from the medical records or at the bedside by a team of trained neonatal research nurses and reviewed by a pediatric cardiac intensivist and cardiologist (P.M. and S.P.). This included data from the intraoperative course collected from perfusion records. We summarized inotropic use in the first 24 hours after surgery using the vasoactive infusion score (VIS) as previously described.[21]

STATISTICAL ANALYSIS

The entire cohort was categorized into 4 equal epochs of time based on date of birth (2001-2005; 2006-2010; 2011-2015; and 2016-2021). Baseline demographic characteristics were compared across epoch categories by using standard descriptive statistics.

Our primary outcome was the presence of WMI. Given that different risk factors are associated with preoperative vs postoperative WMI, the primary outcome was assessed separately for either preoperative or postoperative WMI. Our primary exposure was epoch of time as described earlier. We tested the primary hypothesis by evaluating the association between epoch of time and presence of WMI. Secondary outcomes included other forms of brain injury, namely presence of stroke on MRI and a quantitative assessment of WMI using WMI volumes. To assess the relationship between epoch of time and our primary outcome of WMI, logistic regression was used with epoch as the independent variable and WMI as the dependent variable at each time point (preoperative or postoperative MRI). We included variables in the model a priori based on previous literature and biological plausibility to account for potential unmeasured confounding (site and cardiac lesion). A univariable analysis was also performed for both continuous and categorical clinical and demographic factors assessing previously reported or biologically plausible predictors of WMI (only predictors that occurred temporally before the MRI were considered for inclusion in the model).

Variables with an association of $P < 0.1$ were included in the final multivariable logistic regression model. Collinearity was tested among variables that were significant in the univariable analysis. Post-estimation commands were used to assess probabilities as well as comparisons between the 4 categories of the primary predictor epoch. A separate analysis

was then performed focusing on clinical risk factors stratified according to cardiac group (d-TGA or SVP) given variable clinical management strategies for both lesions. This was not performed for the “other” CHD category given the small sample size in that group. A chi-square test for categorical variables or a one-way analysis of variance test was used for continuous variables, including the blood pressure data analyzed. All analyses were performed by using Stata 16.0 software (StataCorp).

RESULTS

A total of 270 participants were enrolled over the study period; 246 participants had a preoperative brain MRI, and 220 had a postoperative brain MRI for a total of 466 MRI scans. Twenty-four participants did not have a preoperative MRI due to scheduling complications (n = 15), death (n = 1), or hemodynamic instability (n = 7) or had a motion-degraded MRI that could not be evaluated (n = 1). Fifty participants did not have a postoperative MRI due to death (n = 13), placement of a permanent pacemaker (n = 5), or scheduling complications or parental decline to perform a postoperative MRI (n = 31) or had a motion-degraded MRI that could not be evaluated (n = 1). A total of 258 participants had a preoperative and/or postoperative MRI (not all had both a preoperative and a postoperative MRI). The sample size in each of the 4 epochs of time is listed in Figure 1. Baseline demographic characteristics according to epoch of time are listed in Table 1. The univariable analysis of demographic characteristics and clinical factors according to presence of WMI is presented in Supplemental Table 1.

Brain injury rates and clinical risk factors are noted in Table 2 according to epoch of time for the entire cohort (participants who had a preoperative and/or postoperative MRI; N = 258). The absolute frequency of preoperative WMI did not change significantly over the study period. Compared with Epoch 1, the odds and probability of preoperative WMI were similar in Epoch 2 (OR: 1.46; 95% CI: 0.67-3.16; $P = 0.34$), Epoch 3 (OR: 0.9; 95% CI: 0.35-2.31; $P = 0.83$), and Epoch 4 (OR: 0.97; 95% CI: 0.38-2.51; $P = 0.95$) (Central Illustration). Similarly, the absolute frequency of preoperative stroke did not change over the study period. Of the preoperative clinical risk factors, only the frequency of balloon atrial septostomy decreased over the study period.

The absolute frequency of newly acquired postoperative WMI decreased over the study period (Central Illustration). In addition to site and cardiac lesion, of the demographic and clinical factors, only postmenstrual age at the time of postoperative MRI was associated with new postoperative WMI and thus included in the final multivariable analysis (Supplemental Table 1). After adjusting for these variables, the odds of newly acquired postoperative WMI were significantly lower in Epoch 4 (OR: 0.29; 95% CI: 0.09-1.00; $P = 0.05$) compared with Epoch 1 (Table 3). The probability of postoperative WMI decreased by 6.2% from Epoch 2 to Epoch 3 and by 15% from Epoch 3 to Epoch 4. Over the entire study period, the adjusted probability of postoperative WMI declined significantly by 18.7% from Epoch 1 to Epoch 4. The frequency of stroke seemed to change over the 4 time periods (Table 2), although in the univariable logistic regression, this was driven by an increase in stroke rates from Epoch 1 to Epoch 2 (OR: 2.67; 95% CI: 0.99-7.22; $P = 0.05$) rather than any consistent pattern of

increase or decrease over time. The odds of new postoperative stroke in Epoch 4 was not different from Epoch 1 (OR: 0.84; 95% CI: 0.22-3.17; $P = 0.79$).

Given the different management strategies for patients with SVP vs d-TGA, we stratified the intraoperative and postoperative clinical risk factors according to cardiac group. Table 4 (d-TGA) and Table 5 (SVP) list the relationship between individual clinical factors according to epoch of time in a univariable analysis. For both groups, there was no difference in timing of surgery over the study period. In the d-TGA group, there was some variability in cardiopulmonary bypass strategy, although no specific pattern was identified. Both groups exhibited longer cardiopulmonary bypass and cross-clamp times over the study period. For the SVP group, systolic, postoperative mean, and diastolic blood pressures were significantly higher in Epoch 4 compared with Epochs 1 to 3 (Figure 2A). For the d-TGA group, mean and diastolic blood pressures were significantly higher in Epoch 4 compared with Epochs 2 and 3, although similar to Epoch 1 (Figure 2B). Among the d-TGA group, inotropic support in the first 24 hours after surgery as measured by the VIS was not different over the study period. In the SVP group, VIS was significantly higher in Epochs 2 and 3 but similar in Epochs 1 and 4. However, in both cardiac groups, we noted a significant trend of greater use of epinephrine and dopamine and less use of milrinone in Epoch 4 compared with earlier epochs.

Finally, we assessed WMI volumes as a secondary outcome and noted similar trends. Mean preoperative WMI volumes were similar over time (Supplemental Figure 1A). In the univariable analysis, mean postoperative WMI volumes declined over time (Supplemental Figure 1B), with the largest decline noted between Epoch 3 and Epoch 4 (coefficient: −82.3; 95% CI: −154.4 to −10.2; $P = 0.02$). After adjustment for site, cardiac lesion, and postmenstrual age at MRI, we noted a similar trend toward a decline in postoperative WMI volume from Epoch 3 to Epoch 4 (coefficient: −69.8; 95% CI: −146.9 to 7.2; $P = 0.07$). The percent variance in the outcome of WMI volume as a measure of severity explained by epoch alone was 2.5%, whereas it was 6.9% for cardiac group alone and 3.3% for postmenstrual age at MRI alone. Thus, cardiac group seemed to have the strongest effect on postoperative WMI severity (as measured by WMI volume). SVP patients with WMI had volumes on average 61.4 mm^3 higher compared with patients with d-TGA (95% CI: 9.6 to 113.2; $P = 0.02$).

DISCUSSION

In this long-standing prospective cohort study of newborns with critical CHD over 20 years, we report diminished postoperative WMI over time, whereas preoperative WMI has remained relatively constant. Although a myriad of measured and unmeasured clinical factors may influence risks of preoperative and postoperative WMI, we identify higher postoperative blood pressures as a potential protective mechanism to prevent postoperative WMI. In our cohort, higher blood pressure may be explained by changes in the choice of postoperative inotropic infusions favoring epinephrine over milrinone. These results suggest potential modifiable clinical targets in the postoperative time period to minimize burden of WMI, while also recognizing that the perinatal and preoperative times continue to be high risk for newborns with complex CHD.

Over the last 2 decades, cross-sectional studies prospectively enrolling asymptomatic newborns with critical CHD to undergo brain MRI have shown that risk of new postoperative brain injury, including WMI, ranges between 33% and 75%.[9-11,22,23] More recent studies have reported lower rates among patients with d-TGA,[23] consistent with the present results. Risk factors for new postoperative brain injury have included both intraoperative and postoperative factors such as hypoxemia,[24] hypotension and low cardiac output syndrome,[9,24] longer time to surgery,[22] and brain immaturity.[7,25] In addition, those with single-ventricle anatomy are known to be at higher risk for new postoperative brain injury, particularly WMI.[9,10] During this same time period, significant progress has been made in optimizing outcomes among newborns with complex CHD, leading to lower mortality and morbidity.[15] A recent example of the changing landscape in this patient population includes the observation that collaborative quality improvement efforts across institutions through large and transparent clinical registries such as PC4 (Pediatric Cardiac Critical Care Consortium) have led to declines in mortality and severe morbidities.[16] Similar to these trends, we found a consistent decline in newly acquired postoperative WMI over the last 2 decades, with a probability of ~11% in the most recent epoch compared with 30% in the earliest epoch. We also noted a trend toward decline in new postoperative WMI severity with lower WMI volumes in the most recent time period. However, it should be noted that cardiac group, specifically SVP, had the greatest effect on severity of new postoperative WMI.

To further identify causes for this decline, we evaluated several clinical risk factors known to be associated with brain injury over the study period. Previous studies have identified low mean blood pressures as an independent risk factor for new postoperative WMI in neonates with critical CHD.[9,24] We noted higher systolic, mean, and diastolic blood pressures in the first 24 hours after surgery in the most recent epoch compared with earlier epochs, particularly for the SVP group, which may be explained by the shift in clinical practice in the most recent epochs with a much higher rate of epinephrine use compared with milrinone. The mechanism of WMI is believed to be secondary to hypoxic-ischemic or inflammatory injury to susceptible immature premyelinating oligodendrocytes.[26] It is well established that newborns with critical CHD have immature brains[27] and thus are particularly vulnerable to hemodynamic instability inciting WMI at various points during their neonatal course. Our data suggest that a more robust blood pressure can have a protective effect on risk of new WMI in the setting of relative brain immaturity by maintaining cerebral perfusion and preventing ischemic events.

This concept and the shift in clinical management to a greater use of epinephrine in this cohort are contrary to published work showing the deleterious effects of elevated systemic vascular resistance (SVR) and subsequent low cardiac output syndrome after stage I Norwood palliation.[28,29] Studies have shown a link between high SVR events with in-hospital cardiac arrest and mortality after the Norwood procedure. As a result, studies have shown a benefit to afterload reduction both in the operating room[30] as well as postoperatively.[31] A greater use of milrinone and higher hemoglobin concentration were both associated with successful transition out of a low cardiac output state[31] among infants who underwent a stage I Norwood palliation. Thus, it seems that avoiding a low cardiac

output state with measures to decrease afterload and SVR may be a competing risk for maintaining adequate cerebral perfusion.

Cerebral perfusion may be unique in its dependence on pressure autoregulation. Among pediatric patients undergoing cardiac surgery, hypotension is associated with impairments in autoregulation.[32] Impaired autoregulation in turn would increase susceptibility to cerebral ischemia during periods of hypotension associated with aggressive afterload reduction. Thus, maintaining arterial blood pressure above the lower limits of the cerebral autoregulation curve would be protective to prevent cerebral ischemia.[33] The tension between achieving optimal cerebral perfusion pressure and beneficial afterload reduction to avoid elevated SVR and low cardiac output requires new approaches to measure both cerebral autoregulation limits and cardiac output.

Interestingly, we noted this trend of declining postoperative WMI rates despite longer support times in the operating room. Previous studies have suggested that longer cardiopulmonary bypass and cross-clamp times are risk factors for new postoperative brain injury,[10] although other studies have suggested that intraoperative factors play a minimal role in risk of brain injury and ND outcomes.[4] It is possible that higher intraoperative support times may reflect improved technical performance and decreased prevalence of residual lesions, further contributing to an optimal hemodynamic state[34] and also protecting the brain.

In contrast to declining postoperative WMI rates, we observed that acquired preoperative WMI rates have not changed over the last 2 decades. The probability of WMI in the most recent epoch remains at ~20%. Various risk factors have been identified for preoperative WMI, including prematurity and younger gestational age at delivery,[20] hypoxemia,[8] hypotension,[7,18] and brain immaturity.[6] We have previously shown that prenatal detection of CHD is associated with less severe preoperative brain injury.[35] Interestingly, despite a significant increase in prenatal diagnosis over the course of the study period, we did not identify a decline in preoperative WMI rates. This may be secondary to a lack of an adequate sample of postnatally diagnosed patients as a comparison group in the more recent epochs of time influencing our effect size. However, this suggests the likely presence of other unmeasured risk factors in the perinatal and transitional time period that can contribute to risk of preoperative WMI. For example, circulatory physiology during perinatal transition, both immediately in the delivery room as well as continued effects in the subsequent preoperative days, have the potential to affect cerebral perfusion and oxygen delivery to the brain.[36]

We did not identify any significant temporal trends to risk of stroke either in the preoperative or postoperative time period, although there was a trend toward declining rates of preoperative stroke. Most patients in this cohort had small strokes that were believed to be embolic in origin either closely linked to procedures (eg, balloon atrial septostomy) or due to central venous catheters required as part of clinical care in the perioperative period. Importantly, we have shown that these small, focal strokes do not seem to affect developmental outcomes in infancy.[12]

STUDY STRENGTHS AND LIMITATIONS

The present study is strengthened by the prospective cohort design over a consecutive 20-year period enrolling an unselected group of newborns primarily based on their cardiac lesion, minimizing bias due to clinical presentation. Despite this strength, there are a number of limitations to our study, as noted in the following section.

Our findings are limited to 2 centers, potentially minimizing generalizability to other centers by not considering unmeasured confounders such as changes in personnel over the study period. In a sensitivity analysis only including participants from one site (UCSF), we observed similar patterns although we lost significance, likely due to a smaller sample size. Second, postoperative MRIs were performed on average 1 week later in the most recent epoch of time. Although the natural history of WMI lesions is to eventually disappear and become less visible on MRI, this process is believed to occur over a much longer time period.[37] Previous studies from our group analyzing preoperative and postoperative MRIs noted that although some lesions became smaller and more difficult to detect, none disappeared over the average time of 15 days between scans.[18] Despite this finding, we elected to include postmenstrual age at the time of postoperative MRI in the multivariable regression model. Other limitations include a switch in magnet field strength from 1.5-T to 3-T (for UCSF only) during the study period as well as an increased frequency of unsedated scans in the more recent time periods. In theory, this can lead to decreased visualization and detection of white matter lesions, although we would have expected to see a similar trend in preoperative WMI rates as well. Overall, imaging protocols did not change significantly over the study period for detection of brain injuries; however, there were scanner upgrades and other improvements in imaging technology over the 20-year period. We would have expected this to result in a greater detection of more subtle injuries over time; however, we noted the opposite for new postoperative brain injury. The postoperative hemodynamic data reported in the present study were not obtained continuously but rather specific data points were chosen based on evaluation of the vital signs over a 24-hour period by trained study staff. Specific criteria were used to obtain these data points that remained consistent over the study period. This is based on limitations of capturing and analyzing continuous vital sign data at the time of study initiation in 2001.

CONCLUSIONS

Newly acquired postoperative WMI has declined over time despite increased complexity of patients and longer intraoperative support times. More robust blood pressures in the postoperative period may be protective against WMI by minimizing periods of ischemia if blood pressure falls below the lower limits of cerebral autoregulation. The concept of higher blood pressures to support cerebral perfusion may be at the expense of maintaining an ideal SVR to promote cardiac output, which can lead to increased mortality, particularly in the single-ventricle group. Future efforts may include identifying patient-specific optimal blood pressure ranges to support both postoperative cardiovascular physiology as well as optimize oxygen delivery to the brain. The perinatal and preoperative time periods continue to be high risk for newborns with complex CHD, underscoring the importance of investigations to

identify risk factors and solutions to protect the vulnerable brain in the setting of complex CHD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS AND ACRONYMS

BCCH	British Columbia Children's Hospital
CHD	congenital heart disease
d-TGA	dextro-transposition of the great arteries
MRI	magnetic resonance imaging
ND	neurodevelopmental
SVP	single-ventricle physiology
SVR	systemic vascular resistance
UCSF	University of California San Francisco
VIS	vasoactive infusion score
WMI	white matter injury

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

Neonatal brain injury and subsequent ND impairment are common in patients undergoing surgery for complex CHD. Over the last 2 decades, the incidence of preoperative WMI has remained stable, while that of new postoperative injury has declined.

TRANSLATIONAL OUTLOOK:

Further studies are needed to establish whether high blood pressure and stable postoperative hemodynamics may protect against brain injury in neonates undergoing surgery for CHD.

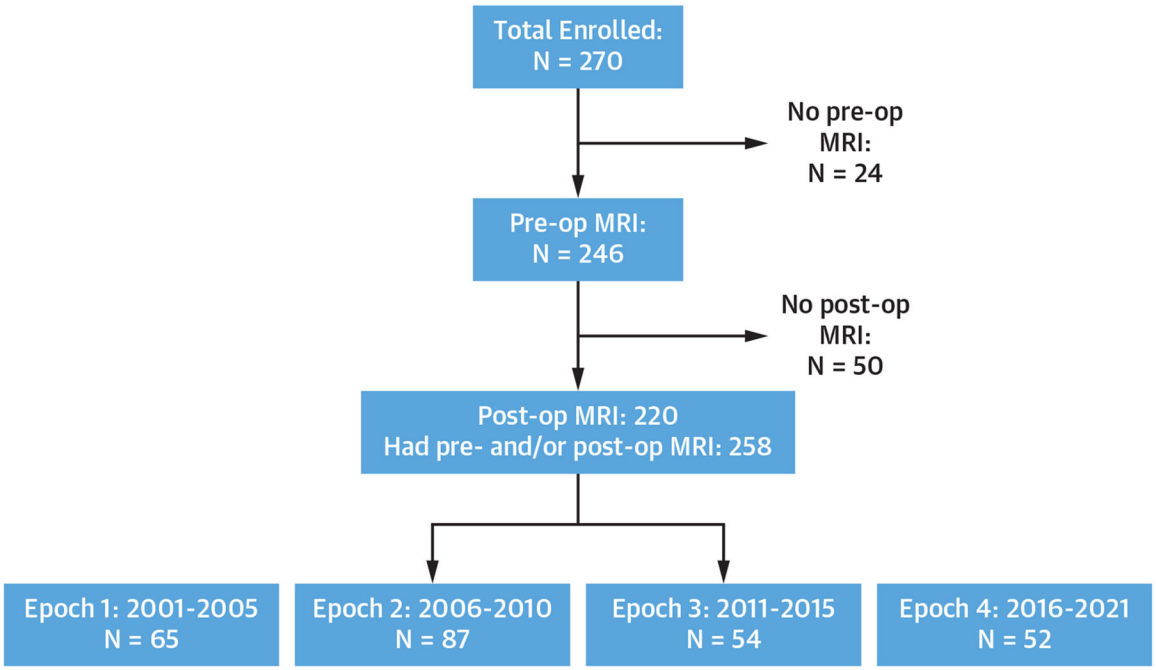
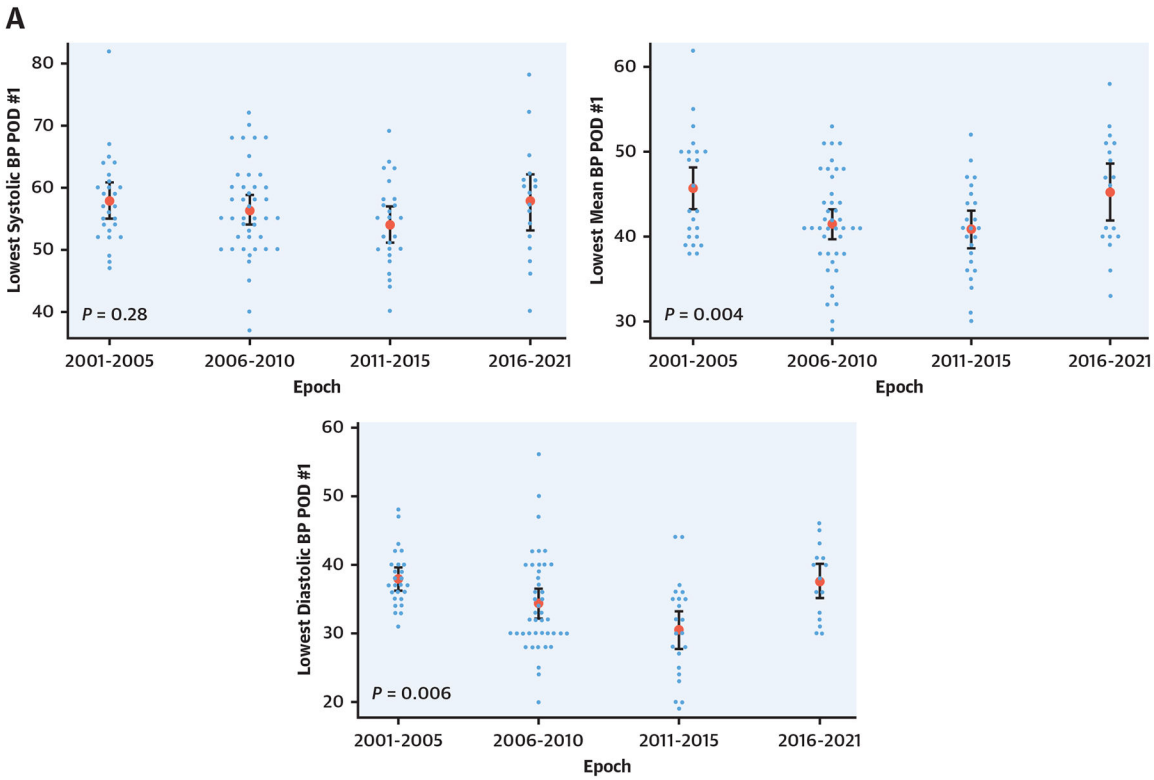


FIGURE 1. Study Participant Flowchart

Participants were categorized into 4 epochs of time based on year of birth. MRI = magnetic resonance imaging; post-op = postoperative; pre-op = preoperative.



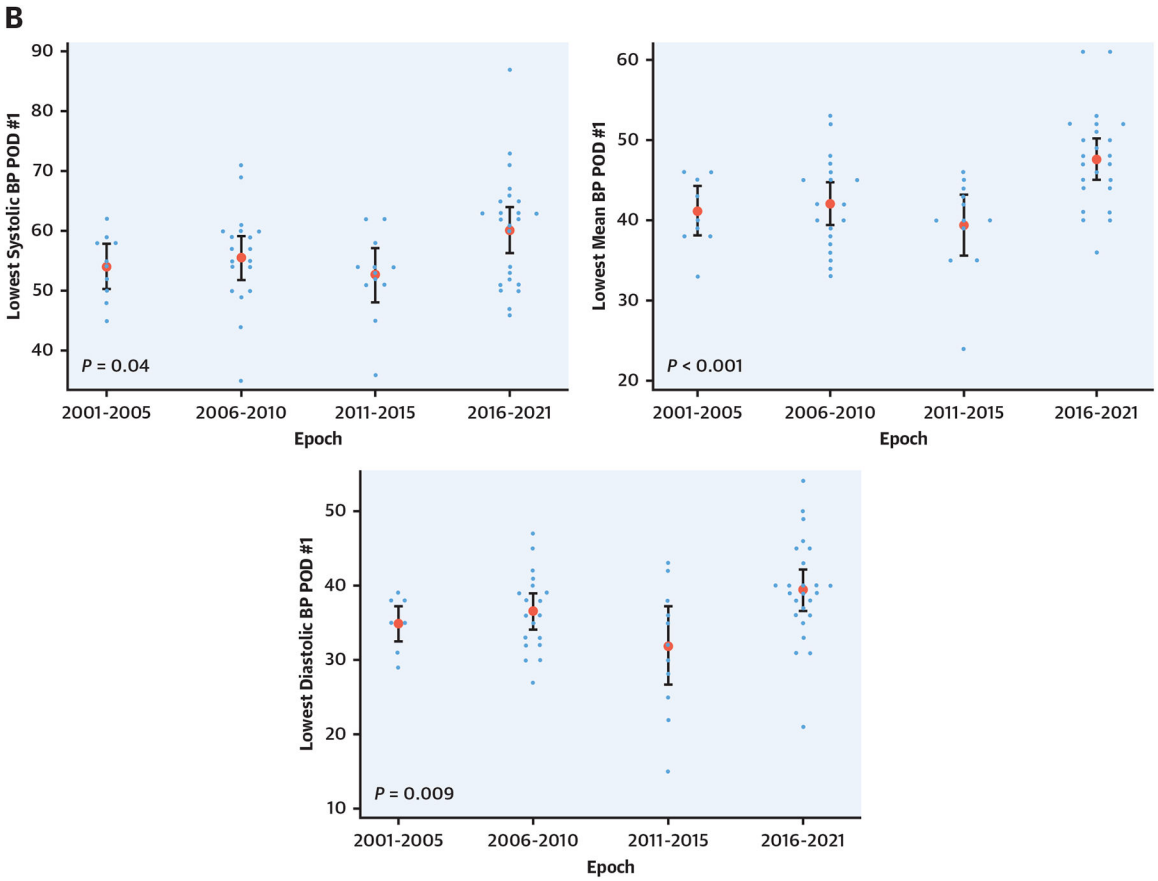
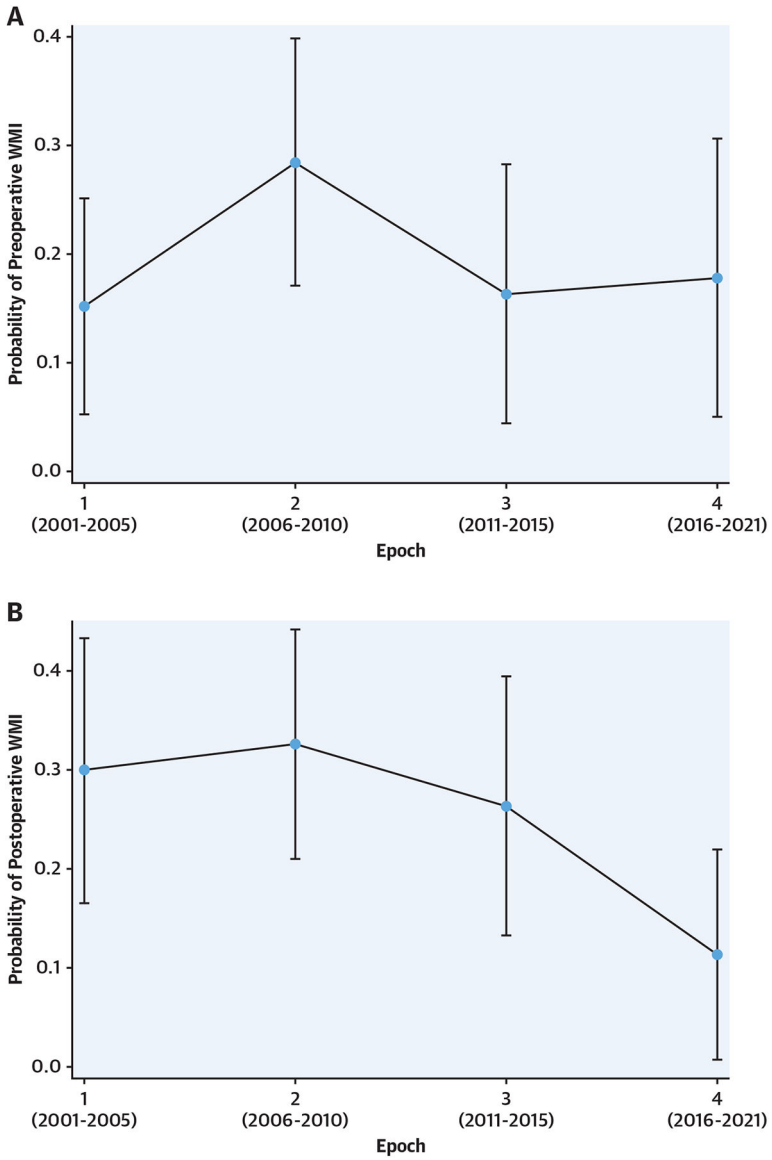


FIGURE 2. Blood Pressure Data From POD #1 Stratified According to Cardiac Group

Lowest systolic, mean, and diastolic blood pressures on postoperative day (POD) #1 are depicted with mean and 95% CIs for dextro-transposition of the great arteries **(A)** and single-ventricle physiology **(B).** In the dextro-transposition of the great arteries group, lowest mean and diastolic blood pressures are significantly higher in the most recent epoch compared with earlier epochs. In the single-ventricle physiology group, lowest systolic, mean, and diastolic blood pressures are significantly higher in the most recent epoch compared with earlier epochs.



CENTRAL ILLUSTRATION. Temporal Trends of White Matter Injury in Newborns With Congenital Heart Disease

(A) Unadjusted average predicted probability of preoperative white matter injury (WMI) according to epoch of time. There was no significant difference in the probability of preoperative WMI across the time periods. **(B)** Adjusted predicted probability of newly acquired postoperative WMI according to epoch of time. The adjusted odds of newly acquired postoperative WMI was significantly lower in Epoch 4 (OR: 0.29; 95% CI: 0.09-1.00; $P = 0.05$) compared with Epoch 1. Over the entire study period, the adjusted probability of postoperative WMI declined significantly by 18.7% from Epoch 1 to Epoch 4.

Table 1

Baseline Demographic Characteristics of Study Cohort According to Epoch of Time (N = 258)

	Year by Epoch				
	2001-2005 (n = 65)	**2006-2010 (n = 87)**	**2011-2015 (n = 54)**	**2016-2021 (n = 52)**	***P* Value[a]**
Male	45 (69.2)	56 (64.3)	37 (68.5)	33 (63.5)	0.87
Race/ethnicity					0.03
White	35 (53.9)	53 (60.9)	26 (48.1)	17 (33.3)	
Hispanic	21 (32.3)	13 (14.9)	16 (29.6)	20 (39.2)	
Black	2 (3.1)	2 (2.3)	1 (1.8)	4 (7.8)	
Asian	3 (4.6)	9 (10.3)	8 (14.8)	4 (7.8)	
Other	4 (6.1)	10 (11.5)	3 (5.6)	6 (11.8)	
Site UCSF	65 (100.0)	38 (43.7)	29 (53.7)	52 (100.0)	<0.001

[a]Chi-square test was used for categorical variables.

UCSF = University of California San Francisco.

Table 2

Clinical and Demographic Variables According to Epoch of Time for the Entire Cohort (N = 258)

	Year by Epoch				
	2001-2005 (n = 65)	**2006-2010 (n = 87)**	**2011-2015 (n = 54)**	**2016-2021 (n = 52)**	***P* Value[a]**
Preoperative variables					
Cardiac group					0.10
d-TGA	35 (53.9)	46 (52.9)	28 (51.8)	18 (34.6)	
SVP	20 (30.8)	26 (29.9)	16 (29.6)	28 (53.8)	
Other	10 (15.4)	15 (17.2)	10 (18.5)	6 (11.5)	
Prenatal diagnosis	17 (26.1)	40 (45.9)	41 (77.4)	46 (88.5)	<0.0001
Delivery mode, vaginal	47 (72.3)	63 (72.4)	34 (64.1)	36 (72.0)	0.72
GA birth, wk	39.1 ± 1.3	38.8 ± 1.6	38.9 ± 1.1	38.8 ± 0.96	0.45
Birth weight, kg	3.3 ± 0.5	3.3 ± 0.6	3.1 ± 0.5	3.3 ± 0.4	0.09
Birth HC, cm	34.4 ± 1.5	34.0 ± 2.0	33.2 ± 3.3	33.3 ± 3.3	0.05
SNAP-PE[b]	14.5 (11-19.5)	16 (11-22)	16 (13-19)	20 (15-26.5)	0.09
PMA at preoperative MRI, wk	40.1 ± 1.7	39.8 ± 1.7	39.7 ± 1.7	39.5 ± 0.9	0.15
Preoperative arrest	2 (3.3)	3 (3.5)	4 (7.5)	1 (2.0)	0.50
Preoperative WMI	13 (20.0)	23 (26.7)	9 (18.4)	9 (19.6)	0.61
Preoperative stroke	13 (20.0)	15 (17.4)	4 (8.2)	5 (10.9)	0.25
BAS	22 (33.8)	39 (44.8)	16 (30.2)	4 (7.8)	<0.0001
Operative and postoperative variables					
DOL operation, d	9 (7-13)	9 (6-13.5)	8 (6-12)	8 (7-12)	0.35
CPB used	60/65 (92.3)	75/87 (86.2)	46/54 (85.2)[c]	46/52 (88.5)	0.45
CPB strategy					<0.001
Full flow	40 (66.7)	27 (36.0)	13 (29.5)	12 (26.1)	
RCP	14 (23.3)	21 (28.0)	15 (34.1)	25 (54.3)	
DHCA	4 (6.7)	9 (12.0)	10 (22.7)	0 (0.0)	
Low flow	2 (3.3)	18 (24.0)	6 (13.6)	9 (19.6)	
CPB time, min	125.1 ± 56.8	151.7 ± 58.9	148.8 ± 55.7	180.3 ± 60.0	0.0001
Cross-clamp time, min	57.3 ± 24.5	65.8 ± 25.6	77.9 ± 31.9	88 ± 48.9	0.0001

	Year by Epoch				
	2001-2005 (n = 65)	**2006-2010 (n = 87)**	**2011-2015 (n = 54)**	**2016-2021 (n = 52)**	***P* Value[a]**
Lowest flow on CPB, cc/kg/min	109.0 ± 59.1	79.7 ± 47.5	73.2 ± 41.5	70.2 ± 41.0	0.001
Largest base deficit on CPB	−0.79 ± 3.9	−3.0 ± 3.9	−3.8 ± 3.1	−5.0 ± 3.1	<0.001
Lowest SBP POD #1	58.1 ± 7.6	56.6 ± 8.4	53.5 ± 6.7	59.2 ± 8.9	0.007
Lowest MBP POD #1	45.2 ± 6.1	41.6 ± 6.4	40.6 ± 5.4	46.6 ± 6.2	<0.001
Lowest DBP POD #1	37.4 ± 4.3	34.7 ± 7.1	31.6 ± 7.0	38.5 ± 5.9	<0.001
VIS POD #1	8.9 ± 5.6	12.6 ± 4.8	12.4 ± 3.7	8 ± 3.5	<0.001
Epinephrine use POD #1	20/65 (30.8)	16/38 (42.1)	20/30 (66.7)	49/52 (94.2)	<0.001
Milrinone use POD #1	34/65 (52.3)	25/38 (65.8)	21/30 (70.0)	16/52 (30.8)	0.001
Dopamine use POD #1	38/65 (58.5)	21/38 (55.3)	25/30 (83.3)	49/52 (94.2)	<0.0001
Postoperative arrest	3/54 (5.6)	10/68 (14.7%)	3/41 (7.3)	2/39 (5.1)	0.22
Postoperative ECLS	4/53 (7.5)	10/71 (14.1)	4/43 (9.3)	0 (0.0)	0.09
PMA postoperative scan, wk	42.4 ± 2.1	42.1 ± 2.1	41.9 ± 2.1	44.1 ± 2.5	<0.001
Postoperative WMI (n = 220)	16/55 (29.1)	27/77 (35.1)	13/45 (28.9)	4/43 (9.3)	0.02
Postoperative stroke	6 (10.9)	19 (24.7)	4 (8.9)	4 (9.3)	0.05
Hospital LOS, d	24 (17-35)	23 (15-35)	22 (20-47)	39.5 (22.5-60.5)	0.002

Values are n (%), mean ± SD, median (IQR), or n/N (%). [a]Chi-square test for categorical variables or one way analysis of variance for continuous variables. [b]The Score for Neonatal Acute Physiology with Perinatal Extension (SNAP-PE) is a marker of birth illness severity. A higher number reflects greater illness severity. [c]Data missing on 2 participants from UBC.

BAS = balloon atrial septostomy; CPB = cardiopulmonary bypass; d-TGA = dextro-transposition of the great arteries; DBP = diastolic blood pressure; DHCA = deep hypothermic circulatory arrest; DOL = day of life; ECLS = extracorporeal life support; GA = gestational age; HC = head circumference; LOS = length of stay; MBP = mean blood pressure; MRI = magnetic resonance imaging; PMA = postmenstrual age; POD = postoperative day; RCP = regional cerebral perfusion; SBP = systolic blood pressure; SVP = single-ventricle physiology; VIS = vasoactive infusion score; WMI = white matter injury.

TABLE 3

Multivariable Logistic Regression of Newly Acquired Postoperative WMI

	Adjusted OR (95% CI)	*P* Value
Epoch		
1 (2001-2005)	Ref	Ref
2 (2006-2010)	1.13 (0.47-2.73)	0.78
3 (2011-2015)	0.84 (0.32-2.17)	0.72
4 (2016-2021)	0.29 (0.09-1.00)	0.05
Cardiac group		
d-TGA	Ref	Ref
SVP	1.48 (0.71-3.12)	0.71
Other	1.42 (0.57-3.54)	0.57
PMA at MRI	0.86 (0.74-1.10)	0.06
Site		
UCSF	Ref	Ref
UBC	0.82 (0.36-1.90)	0.64

In the adjusted analysis, there is a significantly lower odds of new postoperative WMI in the most recent epoch compared with the first epoch. The effect of other variables is also listed (cardiac group, PMA at MRI, and site).

Abbreviations as in Tables 1 and 2.

TABLE 4

Clinical Factors According to Epoch of Time for Participants With d-TGA

	Year by Epoch				
	2001-2005 (n = 35)	**2006-2010 (n = 46)**	**2011-2015 (n = 28)**	**2016-2021 (n = 18)**	***P* Value[a]**
Preoperative variables					
Male	29 (82.8)	31 (67.4)	21 (75.0)	11 (61.1)	0.29
Race/ethnicity					0.05
White	20 (57.1)	32 (69.6)	16 (57.1)	7 (38.9)	
Hispanic	12 (34.3)	4 (8.7)	8 (28.6)	7 (38.9)	
Black	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	
Asian	0 (0.0)	5 (10.9)	3 (10.7)	1 (5.6)	
Other	0 (0.0)	5 (10.9)	1 (3.6)	2 (11.1)	
Prenatal diagnosis	2 (5.7)	16 (34.8)	16 (59.3)	15 (83.3)	<0.0001
Delivery mode, vaginal	24 (68.6)	36 (78.3)	17 (63.0)	18 (100.0)	0.03
GA birth, wk	39.3 ± 1.4	39.0 ± 1.4	38.8 ± 1.2	39.2 ± 0.75	0.47
Birth weight, kg	3.5 ± 0.6	3.4 ± 0.5	3.1 ± 0.5	3.4 ± 0.4	0.06
Birth HC, cm	34.4 ± 1.5	34.1 ± 1.3	33.4 ± 1.7	34.1 ± 1.	0.09
SNAP-PE[b]	16 (12-23)	18 (11-25)	16.5 (14-23)	17.5 (15-20)	0.86
PMA preoperative MRI, wk	40.4 ± 1.8	39.9 ± 1.5	39.8 ± 2.0	39.8 ± 0.7	0.44
Preoperative arrest	0 (0.0)	0 (0.0)	2 (7.4)	0 (0.0)	0.07
Preoperative WMI	7 (20.0)	12 (26.1)	2 (7.4)	4 (23.5)	0.27
Preoperative stroke	11 (31.4)	10 (21.7)	2 (7.4)	3 (17.6)	0.14
BAS	22 (62.3)	37 (80.4)	15 (55.6)	3 (16.7)	<0.0001
Operative and postoperative variables					
DOL operation	10 (7-13)	9 (6-13)	7.5 (6-10)	8.5 (7-11)	0.24
CPB strategy	34	42	26	18	<0.001
Full flow	31 (91.2)	23 (54.8)	9 (34.6)	8 (44.4)	
RCP	1 (2.9)	0 (0.0)	3 (11.5)	5 (27.8)	
DHCA	0 (0.0)	1 (2.4)	10 (38.5)	0 (0.0)	
Low flow	2 (5.9)	18 (42.9)	4 (15.4)	5 (27.8)	
CPB time, min	152.8 ± 48.8	162 ± 56.0	158.1 ± 36.4	198.8 ± 55.6	0.04

	Year by Epoch				
	2001-2005 (n = 35)	2006-2010 (n = 46)	2011-2015 (n = 28)	2016-2021 (n = 18)	*P* Value[a]
Cross-clamp time, min	69.9 ± 20.4	78.8 ± 22.5	87.5 ± 20.3	106.2 ± 53.0	0.0002
Lowest flow during CPB, cc/kg/min	134.4 ± 36.4	108.5 ± 34.8	87.7 ± 32.0	86.6 ± 34.7	<0.001
Largest base deficit	−0.1 ± 3.2	−2.1 ± 4.1	−3.2 ± 2.8	−4.4 ± 1.6	0.0001
Lowest SBP POD #1	57.8 ± 7.2	56.2 ± 7.6	53.9 ± 6.9	57.4 ± 9.1	0.28
Lowest MBP POD #1	45.7 ± 6.1	41.4 ± 5.8	40.8 ± 5.4	45.2 ± 6.7	0.006
Lowest DBP POD #1	37.9 ± 4.1	34.2 ± 7.0	30.5 ± 6.7	37.5 ± 5.0	0.004
VIS POD #1	11.0 ± 5.0	11.4 ± 5.2	11.8 ± 3.5	8.7 ± 2.3	0.75
Epinephrine use POD #1	13/35 (37.0)	5/10 (50.0)	11/13 (84.6)	18/18 (100.0)	<0.001
Milrinone use POD #1	22/35 (62.8)	7/10 (70.0)	10/13 (77.0)	4/18 (22.2)	0.07
Dopamine use POD #1	24/35 (68.6)	7/10 (70.0)	12/13 (92.3)	17/18 (94.4)	0.04
Postoperative arrest	0 (0.0)	3 (7.5)	0 (0.0)	0 (0.0)	0.15
Postoperative ECLS	1 (3.3)	5 (11.9)	1 (4.0)	0 (0.0)	0.26
PMA postoperative MRI, wk	42.3 ± 2.0	42.1 ± 2.0	41.9 ± 2.2	42.5 ± 1.2	0.69
Postoperative WMI, n = 220	8/33 (24.2)	14/40 (35.0)	7/26 (26.9)	1/16 (6.2)	0.17
Postoperative stroke	0 (0.0)	11/40 (27.5)	3/26 (11.5)	0 (0.0)	0.001
Hospital LOS, d	20 (17-30)	18 (15-32)	20 (20-34)	26 (18-37)	0.14
Site (UCSF)	35 (100.0)	10 (21.7)	12 (42.9)	18 (100.0)	<0.001

Values are n (%), mean ± SD, median (IQR), n, or n/N (%). [a]Chi-square test for categorical variables or one way analysis of variance for continuous variables. [b]SNAP-PE is a marker of birth illness severity. A higher number reflects greater illness severity.

Abbreviations as in Tables 1 and 2.

TABLE 5

Clinical and Demographic Factors According to Epoch of Time for Participants With SVP

	Year by Epoch				
	2001-2005 (n = 20)	2006-2010 (n = 26)	2011-2015 (n = 16)	2016-2021 (n = 28)	*P* Value[a]
Preoperative variables					
Male	10 (50.0)	16 (61.5)	12 (75)	19 (67.9)	0.43
Race/ethnicity					0.43
White	13 (65.0)	11 (42.3)	9 (56.2)	8 (29.6)	
Hispanic	3 (15.0)	7 (26.9)	4 (25.0)	10 (37.0)	
Black	0 (0.0)	2 (7.7)	0 (0.0)	3 (11.1)	
Asian	3 (15.0)	3 (11.5)	3 (18.7)	3 (11.1)	
Other	1 (5.0)	3 (11.5)	0 (0.0)	3 (11.1)	
Prenatal diagnosis	14 (70.0)	16 (61.5)	15 (93.7)	26 (92.9)	0.01
Delivery mode, vaginal	16 (80.0)	20 (76.9)	10 (62.5)	13 (48.1)	0.07
GA birth, wk	38.6 ± 1.1	39.0 ± 1.3	39.0 ± 1.3	38.6 ± 1.0	0.43
Birth weight, kg	3.1 ± 0.4	3.3 ± 0.5	3.1 ± 0.6)	3.2 ± 0.4	0.71
Birth HC, cm	34.6 ± 1.2	34.3 ± 1.9	32.9 ± 5.5	32.8 ± 4.2	0.28
SNAP-PE[b]	15 (11-18)	15 (11-22)	16 (12-18)	20 (15-31)	0.22
PMA preoperative MRI, wk	39.2 (1.3)	39.9 (1.7)	39.7 (1.5)	39.3 (1.1)	0.36
Preoperative arrest	0 (0.0)	3 (11.5)	1 (6.2)	0 (0.0)	0.16
Preoperative WMI	2 (10.0)	9 (34.6)	5 (35.7)	5 (21.7)	0.20
Preoperative stroke	2 (10.0)	4 (15.4)	2 (14.3)	2 (8.7)	0.88
BAS	0 (0.0)	1 (3.8)	1 (6.2)	1 (3.7)	0.77
Operative and postoperative variables					
DOL operation, d	7 (5-9)	8.5 (6-12)	6 (5-9)	8 (6-12)	
CPB strategy	18	25	13	23	0.13
Full flow	3 (16.7)	2 (8.0)	1 (7.7)	3 (13.0)	
RCP	12 (66.7)	18 (72.0)	11 (84.6)	17 (73.9)	
DHCA	3 (16.7)	5 (20.0)	0 (0.0)	0 (0.0)	
Low flow	0 (0.0)	0 (0.0)	1 (7.7)	3 (13.0)	
CPB time, min	104.3 ± 48.6	140.2 ± 64.5	133.8 ± 55.8	151.0 ± 40.2	0.04

	Year by Epoch				
	2001-2005 (n = 20)	2006-2010 (n = 26)	2011-2015 (n = 16)	2016-2021 (n = 28)	*P* Value[a]
Cross-clamp time, min	42.3 ± 18.6	47.9 ± 13.6	62.8 ± 31.7	59.8 ± 22.4	0.01
Lowest flow on CPB, cc/kg/min	62.5 ± 58.9	34.9 ± 18.3	53.4 ± 44.9	60.8 ± 44.0	0.11
Largest base deficit	−1.9 ± 5.2	−4.0 ± 3.4	−5.1 ± 3.	−5.1 ± 3.1	0.06
Lowest SBP POD #1	54.1 ± 5.4	55.5 ± 8.0	52.7 ± 7.1	60.1 ± 9.8	0.04
Lowest MBP POD #1	41.2 ± 4.3	42.0 ± 5.7	39.4 ± 6.0	47.6 ± 6.1	0.0003
Lowest DBP POD #1	34.9 ± 3.2	36.6 ± 5.2	31.9 ± 8.3	39.4 ± 6.8	0.009
VIS POD #1	6.5 ± 5.9	13.9 ± 4.4	13.7 ± 2.	8.6 ± 3.5	0.0001
Epinephrine use POD #1	5/20 (25.0)	11/21 (52.4)	7/8 (87.5)	26/28 (92.8)	0.025
Milrinone use POD #1	8/20 (40.0)	16/21 (76.2)	7/8 (87.5)	10/28 (35.7)	0.001
Dopamine use POD #1	8/20 (40.0)	11/21 (52.4)	8/8 (100.0)	26/28 (92.8)	<0.001
Postoperative arrest	1 (6.2)	4 (26.7)	3 (21.4)	2 (10.0)	0.34
Postoperative ECLS	3 (20.0)	4 (23.5)	3 (23.1)	0 (0.0)	0.15
PMA postoperative MRI, wk	42.2 ± 2.1	42.4 ± 1.7	41.9 ± 1.8	44.8 ± 2.5	0.0001
Postoperative WMI, n = 220	5/14 (35.7)	8/23 (34.8)	4/13 (30.8)	3/23 (13.0)	0.31
Postoperative stroke	6/14 (42.9)	4/23 (17.4)	1/13 (7.7)	4/23 (17.4)	0.16
Hospital LOS, d	34.5 (24-50)	31 (25-37)	36 (22-57)	55 (39-81)	0.02
Site (UCSF)	20 (100.0)	21 (80.8)	8 (50.0)	28 (100.0)	<0.001

Values are n (%), mean ± SD, median (IQR), n, or n/N (%). [a]Chi-square test for categorical variables or one way analysis of variance for continuous variables. [b]SNAP-PE is a marker of birth illness severity. A higher number reflects greater illness severity.

Abbreviations as in Tables 1 and 2.