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Improved Cardiac Performance with Dexamethasone Therapy in Premature Neonates: Novel Insights Using Serial Echocardiographic Assessments

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Abstract: (1) Background: dexamethasone is used for the prevention and treatment of chronic lung disease (CLD) in premature neonates, and its impact on cardiac performance and pulmonary vascular resistance has not been well studied. (2) Methods: eligible neonates of <30 weeks gestational age (GA) had echocardiograms performed on them at three time points—before the initiation of dexamethasone (Echo-1), 24–48 h post the completion of dexamethasone therapy (Echo-2), and 7–14 days after course completion (Echo-3). (3) Results: 28 neonates with a 25.2 week mean GA and 652.9 g birthweight were included. The mean cumulative dose of dexamethasone was 0.98 mg/kg, given over 8–10 days. Echo-1 and Echo-2 showed a significant improvement in the right ventricular fractional area change (RV FAC 44.88 vs. 49.71, $p = 0.025$), tricuspid annular plane systolic excursion (TAPSE 0.65 cm vs. 0.70 cm, $p = 0.013$), and RV S′ (7.18 vs. 8.56, $p = 0.05$). The left ventricular (LV) ejection fraction was similar but with a significant increase in the LV S′ (4.77 vs. 6.01, $p = 0.006$). A longitudinal analysis at three time points showed a significant increase in RV FAC (0.02 units 95% CI (0.00–0.04), $p = 0.037$), TAPSE (0.09 units 95% CI (0.06–0.13), $p < 0.001$), RV S′ (0.97 units (95% CI = 0.11–1.84), $p = 0.028$), a reduction in the eccentricity index (0.07 units 95% CI (−0.14–−0.01), $p = 0.030$), and an increase in the LV S′ (0.56 units (95% CI = 0.18–0.94)). (4) Conclusion: The use of postnatal dexamethasone for the prevention/treatment of CLD in premature neonates resulted in an expected improvement in respiratory status along with a significant improvement in the echocardiographic measures of biventricular heart performance.

Keywords: preterm neonates; dexamethasone; echocardiograms; chronic lung disease; cardiac performance; pulmonary vascular resistance

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1. Introduction

Chronic lung disease (CLD) is a major morbidity in preterm neonates that is largely driven by the imbalance between pro- and anti-inflammatory mediators and is influenced by several factors, including sepsis, ventilation-induced trauma, free radical production, and pulmonary edema in an immature lung [1]. The use of the steroid dexamethasone in the prevention and treatment of CLD has been extensively explored [2–6]. Dexamethasone

induces lung maturational changes, promotes antioxidant activities, and helps with surfactant synthesis in the neonatal population [7]. Steroids were liberally used in the past in preterm neonates to treat and prevent CLD. However, due to concerns about adverse effects mainly on neuro-developmental outcomes, its use is now restricted for newborns at high risk for developing CLD or those who are ventilator dependent for prolonged periods in order to facilitate extubation. The current recommendation by the Canadian Pediatric Society (CPS) is that clinicians can consider a short course of low-dose dexamethasone in neonates at high risk for CLD or those with severe CLD [8].

Dexamethasone is known to have a broad range of effects on multiple organ systems, in addition to the lungs. The heart, in particular, is one such organ that has been postulated to be both directly impacted by steroid use as well as indirectly through possible changes in lung compliance. The effects of dexamethasone on left heart function are well documented and include myocardial thickening, hypertrophic cardiomyopathy involving the inter-ventricular septum and the left ventricle, and left ventricular outflow tract obstruction [9–12]. Some authors have described these effects as transient [10,13,14]. An increase in blood pressure has also been reported after dexamethasone use, with speculation on its ability to increase systemic vascular resistance and enhance responsiveness to catecholamines [15]. However, not much is known about its effects on the right ventricle and pulmonary vascular resistance (PVR). Pulmonary vascular remodeling with a resultant increase in PVR is an integral factor in the pathogenesis of CLD. Pulmonary hypertension (with resultant right ventricular dilatation and dysfunction) is now increasingly being recognized as a complication of CLD, significantly contributing to the morbidity and mortality in children with CLD [16–18].

As our understanding of CLD evolves, the interplay between lungs, PVR, right heart function, and steroids warrants careful attention. Echocardiography provides a safe and easy method to investigate cardiac function in preterm neonates. With the evolution of advanced echocardiographic techniques, such as tissue Doppler imaging, cardiac performance can be assessed in greater detail, which allows us to gain novel insights into the cardiopulmonary physiology of the preterm population. Hence, we designed this study to determine the longitudinal effects of low-dose dexamethasone therapy on echocardiographic parameters that measure PVR and cardiac performance in preterm neonates at risk of CLD.

2. Materials and Methods

This prospective cohort study was conducted at a level-three neonatal intensive care unit between April 2019 and July 2022. This center is a high-risk fetal–maternal center and is one of the largest tertiary perinatal centers in Canada, with around 5700 newborn deliveries per year and admitting an average of 1000 neonates per year. Ethical approval was obtained from our local Institutional Research Ethics Board (The Western University Health Science Research Ethics Board; REB 113654). Neonates with gestational age (GA) below 30 weeks who were being started on low-dose dexamethasone therapy for the prevention and treatment of CLD by the clinical care team were eligible for inclusion. Neonates with known structural congenital heart defects (except for atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA)), lung malformations, genetic or chromosomal anomalies, and those who received steroids for any other indication (e.g., post-extubation stridor, adrenal insufficiency, capillary leak syndrome) were excluded.

2.1. Dexamethasone Protocol

Preterm neonates at high risk of CLD received dexamethasone treatment orally or through intravenous (IV) injection over 8 to 10 days. Patient selection for this therapy was as per physician discretion until December 2021, after which patients were treated based on a standardized unit policy that specified dosage, postnatal days of use, and provided high-level guidance surrounding patient selection. Prior to the development of the policy, the cumulative dose of dexamethasone used was 0.35 mg/kg, which was then subsequently

changed to 1.05 mg/kg (postnatal days 7–14) or 1.925 mg/kg (postnatal day 14 onwards), administered over 8–10 days.

2.2. Data Collection

We conducted echocardiograms at three time points on all neonates recruited into the study: the first was completed immediately prior to initiation of dexamethasone (Echo 1), the second was completed within 24–48 h of completing the dexamethasone course (Echo 2), and the third was completed 7–14 days after completion of the dexamethasone course (Echo 3). Relevant clinical information, including GA, weight at time of echocardiogram, mode of ventilation, pressure parameters on the ventilator (mean airway pressure (MAP), positive end-expiratory pressure (PEEP), peak inspiratory pressure (PIP), fractional inspired oxygen (FiO_2), use of inotropic/vasoactive medications and diuretics, oxygen requirement, and blood gas, were obtained and recorded. Other data retrieved from an infant's chart included maternal age and obstetric history, namely use of antenatal steroids, mode of delivery, maternal infection, chorioamnionitis, Apgar scores at the 5th and 10th minutes of life, resuscitative needs at birth, and surfactant therapy. Data regarding neonatal course and outcomes such as survival, duration of invasive and non-invasive respiratory support, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), PDA requiring treatment, pulmonary hemorrhage, necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), and culture-positive sepsis were also collected.

2.3. Echocardiographic Measurements

Echocardiographic images were obtained using the Philips ultrasound machine with a 12 MHz/8 MHz cardiology probe, as appropriate. This was carried out by four experienced sonographers according to standard protocol using 2D, color, and Doppler imaging in parasternal, suprasternal, apical, and subcostal views. All measurements were conducted by experienced sonographers.

PVR was measured by the ratio of pulmonary artery acceleration time (PAAT) to right ventricular ejection time (PAAT: RVET), and right heart performance was measured using tricuspid annular plane systolic excursion (TAPSE), RV S' (Right Ventricle Lateral Wall Systolic Myocardial Velocity) by tissue Doppler imaging (TDI), right ventricular fractional area change (RV FAC), and right ventricular output (RVO) in mL/kg/min. The RVET and PAAT were measured via pulse wave (PW) Doppler imaging of the main pulmonary artery from the parasternal long-axis or short-axis view of the right ventricular (RV) outflow tract. We calculated PAAT as the time interval between the onset of systolic pulmonary arterial flow (onset of ejection) and peak flow velocity. To obtain the RVO, pulsed Doppler recordings of the flow at the level of the pulmonary valve were made from the parasternal long-axis or short-axis view, with care taken to minimize the angle of insonation. An average velocity time integral was derived by tracing the doppler waveform of three consecutive cardiac cycles using the incorporated cardiac software. The heart rate was measured from the peak-to-peak intervals of the Doppler velocity time signals. The diameter of the pulmonary valve insertion was measured at end-systole from a frame-by-frame videotape analysis of the 2D parasternal long-axis image and was averaged over three cardiac cycles.

Interventricular septal motion at end-systole (IVSs) was assessed by visual inspection of the interventricular septum from a 2D short-axis view acquired at the level of the papillary muscle. IVSs were considered 'flat' if there was complete absence of concavity towards the left ventricle. The eccentricity index (EI) was measured at end-systole, with EI defined as the ratio of D2/D1, where D1 is the left ventricle short-axis diameter perpendicular to the septum and D2 is the left ventricle short-axis diameter parallel to the septum. The TAPSE is the downward vertical distance the tricuspid annulus moves during systole, and we measured this using M-mode echocardiography in an apical 4-chamber view. From the apical window, an RV-focused apical 3-chamber (RV3C) view was acquired by rotating the transducer counterclockwise from the standard RV-4C view while maintaining a slight

rightward tilt to keep the right ventricle in view. The probe was rotated until the left side of the heart was completely out of view, the aortic valve was in the center of the image, and simultaneous visualization of RV inflow, outflow, and the inferior wall was achieved. Precaution was taken to avoid visualizing the anterior wall of the right ventricle. Our aim was to capture the maximum RV cavity while keeping these anatomic landmarks in view. Using this view, we measured the three-chamber RV FAC by manually tracing the endocardial borders at end-diastole and end-systole. The RV FAC (%) was calculated using the formula RV FAC (%) = (2-chamber RV area at end-diastole − 3-chamber RV area at end-systole)/3-chamber RV area at end-diastole) × 100%.

The presence or absence of PDA and patent foramen ovale (PFO) was also recorded. Left ventricular (LV) chamber dimensions, ejection fraction (EF), left ventricular output (LVO), LV S′ (Left Ventricular Lateral Wall Systolic Myocardial Velocity) with TDI, septal thickness, and LV posterior wall thickness in M mode were measured as per ASE recommendations [19]. Relative wall thickness (RWT) was calculated based on the formula RWT = (LV Posterior wall + Septal thickness)/LVIDd. All measurements were averaged over three consecutive cardiac cycles.

2.4. Outcome Measures

Our primary outcome was defined as a change in PVR and right heart performance. PVR was measured via the PAAT: RVET ratio. Right heart performance was measured via RV FAC, RVO, TAPSE and TDI RV S′. Our secondary outcome was the change in LV size (measured by septal thickness, posterior wall thickness, RWT) and function (measured by EF, LVO, TDI LV S′).

2.5. Sample Size

A sample size of N = 30 was based on a PVR mean (SD) of 0.35 (0.14) for Echo 1 and to detect a 25% change at Echo 2, using a dependent t-test with 5% alpha, 80% power, and an attrition rate of 10–20%.

2.6. Statistical Analysis

Continuous variables were summarized with means and standard deviations (or medians and interquartile ranges for non-normal distributions); paired and unpaired group differences were examined with dependent and independent *t*-tests, respectively. A repeated measures analysis of variance was used to examine the relationship between drug dosing groups and echo parameters between patients' first and second echo events. Relationships between continuous variables were examined with Pearson correlations. Categorical variables were summarized with frequencies and percentages, and paired group differences were examined with McNemar tests (or McNemar–Bowker tests, as appropriate). Logistic regression models were used to examine predictors of successful extubation. Trends over time were examined with linear, mixed models with maximum likelihood estimation, including echo events as fixed effects and patients as random effects using a scaled identity covariance structure with a random intercept. SPSS v.29 (IBM Corp., Armonk, NY, USA) was used for all analyses, and p-values < 0.05 were considered statistically significant.

3. Results

Thirty neonates were recruited for the study. Two withdrew consent, three patients were transferred out prior to study completion, two patients died during the study period, and one patient was clinically unstable (study flow diagram, Figure 1). The mean (SD) gestational age in the cohort was 25.2 (1.2) weeks, with a mean (SD) birthweight of 652.9 (156.3) grams. Dexamethasone administration was started at a mean (SD) age of 19.6 (9.2) days, with a mean (SD) cumulative dose of 0.98 (0.6) mg/kg given over 8–10 days. The baseline demographic and clinical characteristics are summarized in Table 1.

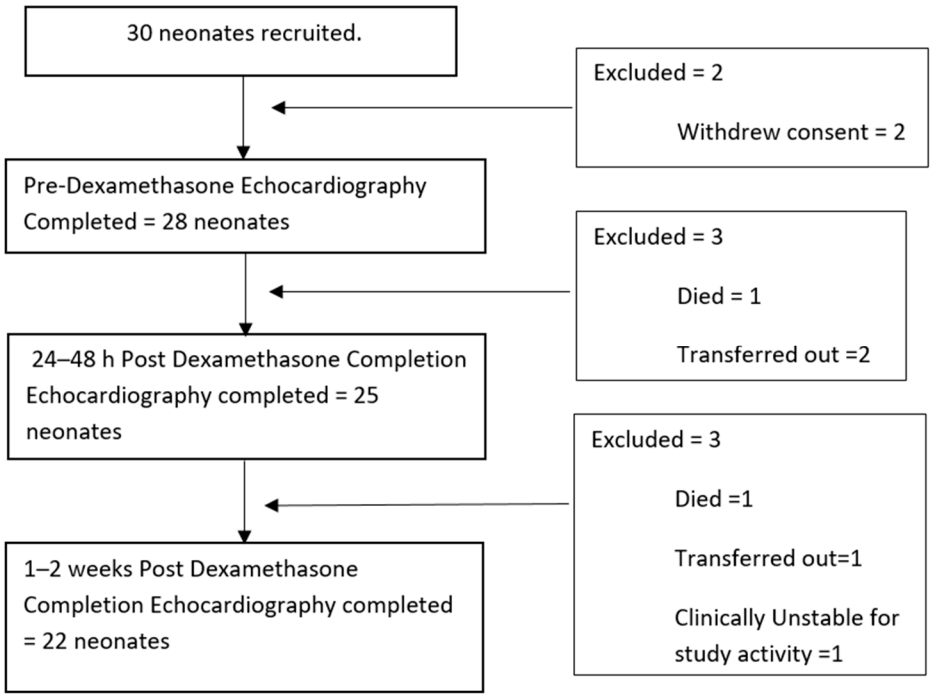

Figure 1. Study flow diagram.

Table 1. Baseline clinical and demographic characteristics (n = 28).

Variables		
Gestation age in weeks, mean (SD)		25.2 (1.2)
Birth weight in grams, mean (SD)		652.9 (156.3)
Male sex, *n* (%)		15 (53.6)
Antenatal steroids, *n* (%)	• Complete	18 (64.3)
	• Incomplete	8 (28.6)
	• None	2 (7.1)
C/section delivery, *n* (%)		15 (53.6)
Apgar score, median (IQR)	5 min	6 (3.25–8)
	10 min	7 (6–9)
Maternal chorioamnionitis, *n* (%)		3 (10.7)
Postnatal surfactant, *n* (%)		25 (89.3)
Cumulative dexamethasone in mg/kg, mean (SD)		0.98(0.6)
Cumulative dexamethasone dosage, *n* (%)	<1 mg/kg	16 (57.1)
	>1 mg/kg	12 (42.9)
Duration of dexamethasone course (days), mean (SD)		8.7 (1.5)
Postnatal age in days at dexamethasone course, mean (SD)		19.6 (9.2)

Abbreviations: C/section—cesarean section; SD—standard deviation; IQR—Interquartile range.

We compared the respiratory and echocardiographic parameters prior to the start of dexamethasone treatment and at the completion of the course (see Table 2). At the time of initiation of dexamethasone (Echo 1), 96.4% of the study neonates were intubated and ventilated. Immediately post dexamethasone course completion (Echo 2), the need for invasive ventilation had decreased to 52%. However, due to small cell sizes, we could not adequately test the differences in respiratory support between these two time points. In all

infants, the respiratory parameters showed significant improvement during the treatment course. The results showed that the MAP, PIP, and FiO_2 all significantly decreased post dexamethasone course (all $p < 0.05$).

Table 2. Echocardiographic parameters prior to dexamethasone (Echo1) and immediately after completion of dexamethasone course (Echo 2).

Parameter Type	Parameters		Prior to Dexamethasone, N = 28	Immediately after Completion of Dexamethasone, N = 25	*p* Value
Respiratory Parameters	Type of ventilatory support (%)	CMV	7 (25)	10 (40)	^
		HFOV	4 (14.3)	2 (8)	
		HFJV	16 (57.1)	1 (4)	
		Non-Invasive	1 (3.6)	12 (48)	
	Mean airway pressure in cm H_2O, mean (SD)		12.8 (2.46)	11.38 (2.51)	0.017
	FiO_2 in %, mean (SD)		48.52 (16.71)	37.52 (14.88)	0.003
	PIP in cm H_2O, mean (SD)		28.93 (6.38)	21.33 (4.71)	<0.001
	PEEP, cm H_2O, mean (SD)		10.17 (2.18)	9.15 (1.40)	0.065
Echocardiographic Parameters, Mean (SD)	LV FS (%)		41.36 (6.96)	47.8 (14.72)	0.062
	LV EF (%)		69.54 (9.82)	70.33 (11.58)	0.779
	LVO (mL/kg/min)		271.45 (87.45)	303.01 (135.11)	0.137
	LV VTI (cm)		10.5 (2.5)	11.32 (4.12)	0.196
	LVIDd (cm)		1.28 (0.28)	1.31 (0.33)	0.395
	LVIDs (cm)		0.76 (0.16)	0.73 (0.19)	0.381
	LV posterior wall (cm)		0.24 (0.05)	0.26 (0.04)	0.166
	Septal thickness (cm)		0.26 (0.07)	0.27 (0.07)	0.695
	Relative wall thickness		0.41 (0.72)	0.43 (0.11)	0.667
	LV S′ (cm/s)		4.77 (0.97)	6.013 (1.41)	0.006 *
	RV S′ (cm/s)		7.18 (2.10)	8.56 (2.24)	0.05
	Septum S′ (cm/s)		4.74 (1.01)	5.57 (0.75)	0.032 *
	RVET (s)		0.18 (0.04)	0.17 (0.03)	0.672
	PAAT (s)		0.06 (0.02)	0.07 (0.02)	0.152
	PAAT: RVET ratio		0.36 (0.11)	0.41 (0.13)	0.106
	RV VTI (cm)		9.81 (2.53)	10.60 (3.58)	0.358
	RV FAC in %, mean (SD)		44.88 (5.85)	49.71 (8.90)	0.025 *
	TAPSE (cm)		0.65 (0.12)	0.73 (0.17)	0.013 *
	PDA, n (%)		17 (60.7)	11 (39.3)	0.453
	Eccentricity index in %, mean (SD)		1.24 (0.31)	1.09 (0.16)	0.067

* $p < 0.05$; ^ Due to small cell sizes, we could not adequately test differences between respiratory support at Echo 1 vs. Echo 2 (i.e., chi-square test would not run); Abbreviations: CMV—Conventional Mechanical Ventilation; HFOV—High-Frequency Oscillatory ventilation; HFJV—High-Frequency Jet Ventilation; FiO_2—Fractional inspired oxygen; H_2O—water; PEEP—Peak End-Expiratory Pressure; LV FS—Left Ventricular Fractional Shortening; LV EF—left ventricular ejection fraction; LVO—left ventricular output; LV VTI—left ventricular velocity time integral; LVIDd—left ventricle internal diameter in diastole; LVIDs—left ventricle internal diameter in systole; LV S′—left ventricle systole prime; RV S′—right ventricle systolic prime; RVET—right ventricular ejection time; PAAT—pulmonary artery acceleration time; RV VTI—right ventricle velocity time integral; TAPSE—tricuspid annular plane systolic excursion; PDA—patent ductus arteriosus; SD—standard deviation.

3.1. Longitudinal Analysis of Respiratory and Echocardiographic Changes

Upon examining the change in respiratory parameters and echocardiographic parameters at all three echocardiogram time points—prior to course, immediately at steroid completion, and 7–14 days post steroid course completion—we found that, for each additional echocardiogram, the MAP significantly decreased, on average by 0.78 units ((95% CI = −1.39–−0.16), $p = 0.015$); the FiO_2 significantly decreased, on average by 4.54 units ((95% CI = −8.36–−0.71), $p = 0.021$); and the PIP significantly decreased, on average by 2.50 units ((95% CI = −4.77–−0.22), $p = 0.032$). The PEEP did not show a significant change over time ($p = 0.496$). Figure 2.

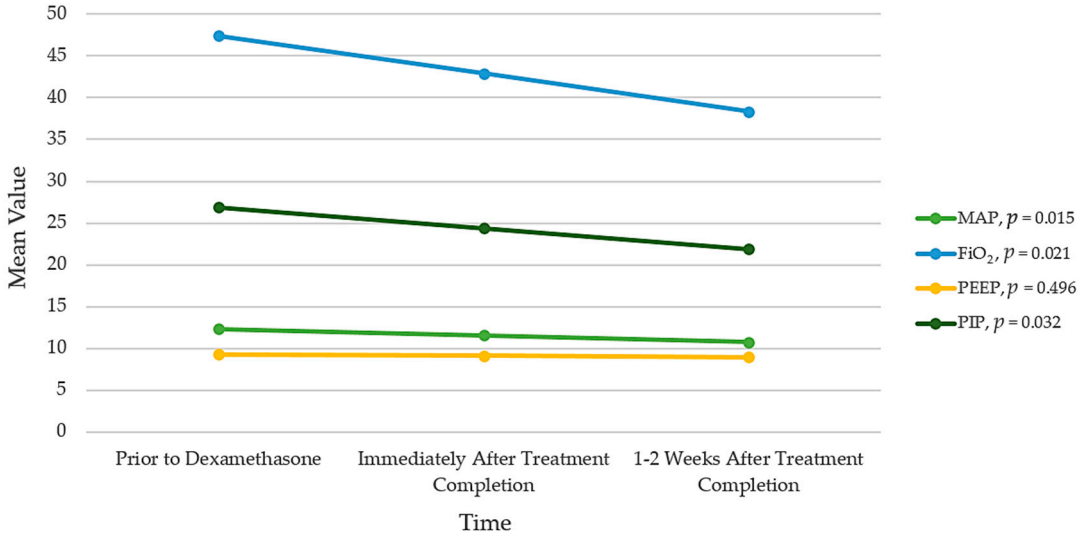

Figure 2. Changes in respiratory parameters at three time points: prior to dexamethasone, immediately after dexamethasone completion and 7–14 days after dexamethasone completion.

The echocardiographic parameters for each additional echocardiograph RV FAC significantly increased, on average by 0.02 units ((95% CI = 0.00–0.04), $p = 0.037$). In addition, the TAPSE significantly increased, on average by 0.09 cm ((95% CI = 0.06–0.13), $p < 0.001$); The eccentricity index significantly decreased, on average by 0.07 units (95% CI = −0.14–−0.01), $p = 0.030$. These findings are represented in Figure 3. The PAAT and PAAT:RVET ratio did not show significant change over time. From the LV perspective, the LV S′ significantly increased on average for each additional echocardiography by 0.56 units ((95% CI = 0.18–0.94), $p = 0.005$). The septal S′ increased by an average of 0.61 units per additional echocardiography ((95% CI = 0.23–1.00), $p = 0.003$). The RVS′ significantly increased on average per echocardiography by 0.97 units (95% CI = 0.11–1.84), $p = 0.028$. No significant changes were noted in the posterior wall thickness, relative wall thickness, LV chamber dimensions, or LV EF, or in the presence or absence of PDA.

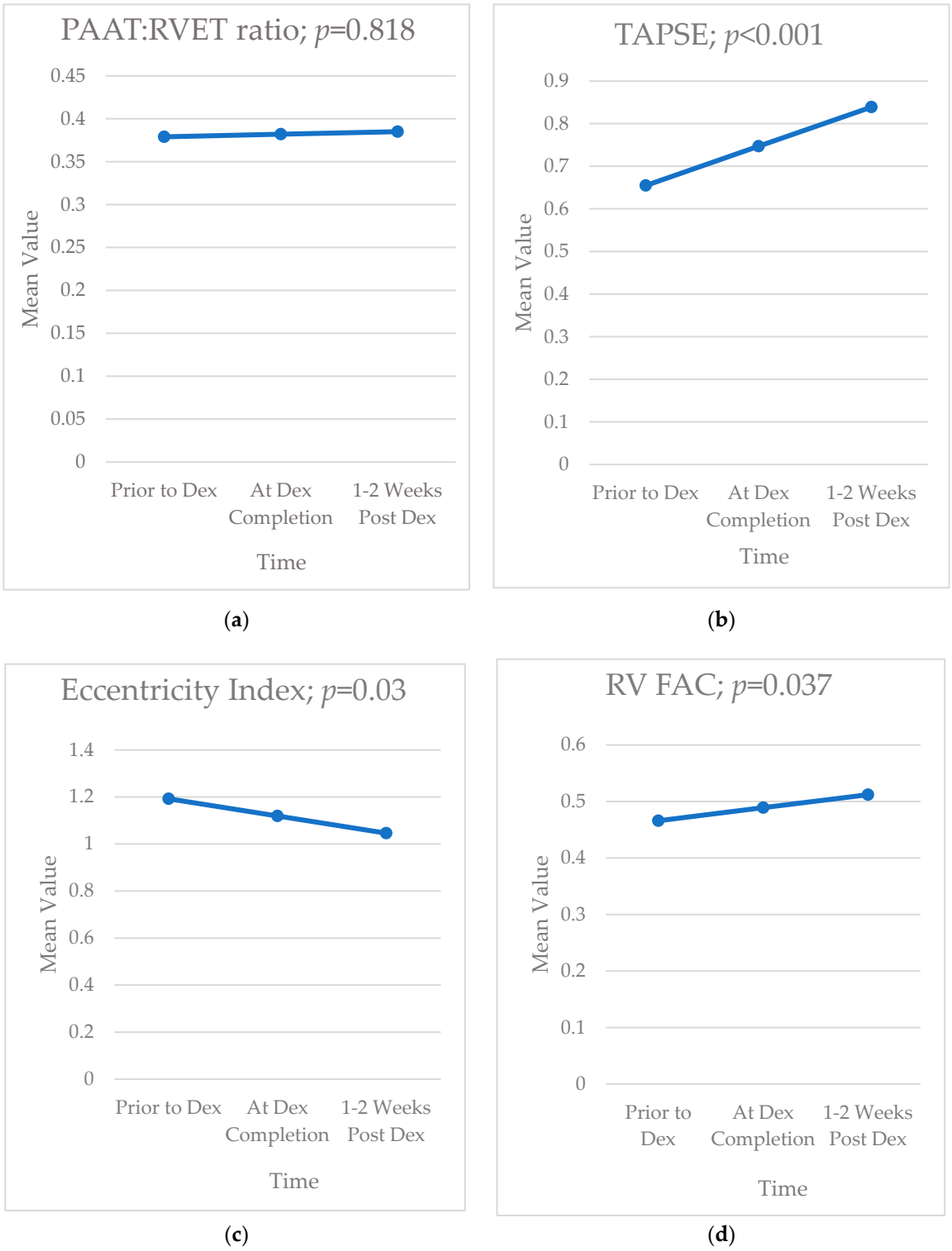

Figure 3. Changes in echocardiographic parameters at three time points; prior to dexamethasone (referred to as the "Prior to Dex" timepoint), immediately after dexamethasone completion (referred to as the "At Dex Completion" timepoint), and 7–14 days after dexamethasone completion (referred to as the "1–2 Weeks Post Dex" timepoint. Parameters include (**a**) PAAT:RVET (ratio, mean), (**b**) TAPSE (cm, mean), (**c**) eccentricity index (%, mean), and (**d**) RV FAC (%, mean).

3.2. Exploratory Analysis

We explored the extubation success (defined as successful extubation after dexamethasone initiation without need of re-intubation within the next 72 h) in this cohort. The rate of extubation success was 44.4% (12 out of 27). We ran a regression analysis to assess the clinical and echocardiographic variables that may predict the chances of a successful extubation. The baseline echo parameters showed no significant association with the outcome variable. The only significant predictor was a cumulative dexamethasone dose >1 mg/kg, with the odds of success increasing by 5.5 (95% CI = 1.05–28.88) when the cumulative dose was higher >1 mg/kg ($p = 0.044$). The change in RV function parameters (FAC and TAPSE) before and after the dexamethasone course did not have a significant correlation with cardiorespiratory outcomes such as days on mechanical ventilation, days on oxygen, and the development of chronic pulmonary hypertension. Using the oxygen saturation index (OSI) as a surrogate of the respiratory parameters, we examined the correlation between echocardiographic parameters and respiratory changes. We found no significant correlation between the OSI change and an RV FAC change ($r = -0.04$, $p = 0.887$) or TAPSE change ($r = 0.19$, $p = 0.399$). We examined whether there was a relationship between the dose of dexamethasone and the change in right ventricular function (TAPSE and RV FAC) and did not find a significant interaction.

3.3. Neonatal Outcomes

In this cohort, of the 25 patients who completed their follow-up, 23 (82.1%) were diagnosed to have BPD at 36 weeks corrected gestational age. Fourteen (50%) were discharged home on oxygen, 24 (85.7%) of the original cohort survived to discharge, and 4 (14.3%) received a diagnosis of chronic pulmonary hypertension.

4. Discussion

Our present study evaluated the effects of low-dose dexamethasone therapy in premature neonates on cardiorespiratory function and physiology. Using standard and advanced echocardiographic techniques, we investigated the effects of steroids on cardiac performance and pulmonary vascular resistance. Our results show that there was a significant improvement in respiratory parameters with dexamethasone therapy, along with an improvement in right heart systolic performance. The longitudinal systolic function of the LV also improved, as indicated by increases in the LV S′ and Septal S′. There was no significant reduction seen in the echocardiographic measures of PVR, and no change was seen in the LV wall thickness with the range of dexamethasone doses used in this cohort. Using echocardiography, we demonstrate the positive longitudinal changes to the markers of biventricular systolic heart function in extreme preterm neonates with dexamethasone therapy. Unlike previous studies, this is the first study to show an improvement in LV systolic function with dexamethasone therapy using load-independent technology such as TDI.

The use of dexamethasone therapy in the management of CLD is based on the beneficial effects of steroids on the lungs. Steroids have been shown to improve lung function, reduce inflammation, increase antioxidant activity, and increase surfactant synthesis. In this study, we saw an improvement in the respiratory parameters of infants with the initiation of dexamethasone. This improvement was sustained 1–2 weeks post dexamethasone completion and was mainly seen in the form of reduced inflation pressure and oxygen requirements, subsequently suggesting an overall improvement in compliance and gas exchange. These findings are in keeping with other studies [2–6,20]. Around 44% of the cohort was successfully extubated; however, the majority received a diagnosis of BPD. During the study period, two different dose regimes were used: a very-low-dose regime of a 0.35 mg/kg cumulative dose and a comparatively higher regimen of a 1.02 mg/kg cumulative dose. The latter dose was associated with a higher chance of extubation success. The latter dose is in keeping with the current recommendation by the CPS [8] and in line with the recently published network meta-analysis [5].

On examination of the RV indices, we found that dexamethasone therapy had a significant positive effect on right heart systolic performance, as measured by the RV FAC, TAPSE, and RV S′ through TDI. There was a longitudinal reduction in the eccentricity index, suggesting a favorable transition from a pulmonary to systemic pressure relationship. Interestingly, we did not see any significant changes in the PAAT and PAAT: RVET ratio—a surrogate measure of PVR. With the improvement in PVR, we expect the PAAT: RVET ratio to increase. In our study, the PAAT: RVET ratio increased from 0.30 to 0.41 post dexamethasone therapy but was not statistically significant. Evan et al. in 1994 [21] and more recently Sehgal et al. in 2022 [22] demonstrated a reduction in PVR with the use of steroids. In the Evan et al. study, 20 neonates who received dexamethasone therapy were observed to undergo an increase in the PAAT: RVET ratio after the initiation of dexamethasone, suggesting a decrease in pulmonary artery pressure; however, this change was not sustained and did not show a correlation with the improvement noted in the respiratory status. On the contrary, we did see a significant unit decrease in the eccentric index over time, which reflects a longitudinal reduction in pulmonary artery pressure. The lack of significant change in the PAAT: RVET ratio in our study could be due to the small sample size, two different dosing regimens making the assessment difficult, the inherent limitations of the measure to accurately reflect the actual state of PVR, technical limitations in the extreme preterm population, and/or shortcomings of the measurement, especially in the presence of a PDA.

Interestingly, an improvement in RV performance was consistently demonstrated at all study time periods. Sehgal et al. also reported an improvement in RV systolic performance [22]. Such improvement could be due to a concurrent improvement in pulmonary compliance and a reduction in inflation pressures. To explore this further, we looked at the correlation of OSI and RV performance and did not find a significant relation. As such, our findings suggest that the improvement in RV performance could be independent of respiratory changes and intrinsically related to dexamethasone. Such improvement may be linked to improved ventriculo–arterial coupling and reduced RV afterload, as suggested by the longitudinal decrease in the eccentricity index.

The parameters reflective of LV longitudinal systolic function in TDI were found to increase over time without changes in the LV EF or LVO. Such improvement in LV function could be driven by the RV itself based on the principles of biventricular interdependence and shared myocardial fibers, especially in the septal wall, as well as by the application of advanced imaging techniques such as TDI, which is load-independent. Both the LV EF and LVO are influenced by the loading conditions of the LV. Dexamethasone is known to increase systemic vascular resistance, thereby increasing the afterload on the LV, which could possibly explain the lack of a significant increase in the LV EF and LVO within our cohort. Alternatively, it could be a reflection of physiological maturation or a direct effect of steroids on both right and left ventricular myocytes. Animal model studies have demonstrated that dexamethasone can stimulate angiotensin-converting enzyme (ACE) activity in cardiac myocytes, potentially influencing cardiac remodeling [23]. Low-dose dexamethasone in hypertensive rat models has shown improved LV systolic and diastolic function, which may be due to LV angiogenesis and a reduction of wall collagen deposition area [24].

Several researchers have described changes such as increased LV posterior wall thickness and ventricular septal hypertrophy in response to dexamethasone administration to premature neonates [9–11]. Our results do not show any significant change in the septal and LV dimensions, possibly because our cumulative dose of dexamethasone was substantially lower than the doses used in these studies. Similar results were reported by Sehgal et al., who used a cumulative dexamethasone dose of 0.89 mg/kg [22], which is a very similar dose range to that in our study.

From the PDA perspective, 60% of the cohort had PDA prior to their dexamethasone course. This then dropped to 39% after the completion of the course, but was not statistically significant ($p = 0.453$). Specific PDA-related echocardiographic parameters were not further

investigated in our present study. Sehgal et al. showed significant ductal constriction post dexamethasone use, along with improvements in metrics of pulmonary over circulation [22]. There have been some other studies that have reported ductal closure with steroids [25,26]. However, a future prospective study to analyze the effects of steroid on ductal parameters would be interesting.

Given that our study period witnessed two different dose regimes, we had the opportunity to explore a dose response relationship between steroids and right heart performance. We did not see a significant interaction between the dose and the RV systolic function parameters. Furthermore, our study explored the role of these changes in predicting respiratory outcomes. Our exploratory analysis showed that the changes in echocardiographic parameters could not predict successful extubation, days on oxygen, days on mechanical ventilation, or the development of CPHTN.

Our study's limitations include a small sample size and a single institution's experience, which may limit the generalizability of the findings. In addition, we did not include a long-term follow-up later in infancy to evaluate the patient's outcomes beyond discharge. The two different dosing regimens may have reduced the significance of some of the cardiac markers. A larger multi-center prospective study that includes advanced echocardiographic assessment up to 24–26 months of corrected age would be valuable. We acknowledge that there are technical limitations to echocardiographic measures of PVR, which may not have allowed us to capture the intricate and subtle physiological changes in this unique population. We did not examine the effect on diastolic cardiac function. Future studies utilizing novel echocardiographic techniques such as speckle tracking and strain analysis are warranted. However, this is the first study to longitudinally examine the effect of steroids on cardiorespiratory physiology, RV hemodynamics, and LV systolic function using advanced imaging techniques, as well as explore the dose–response relationship between steroids and cardiac systolic performance. Our findings reflect that low-dose dexamethasone (mean cumulative dose 0.98 mg/kg) used in premature neonates at risk of BPD has a positive cardio-pulmonary effect.

5. Conclusions

In conclusion, the use of postnatal dexamethasone for the prevention/treatment of CLD in premature neonates resulted in the expected improvements in respiratory status along with significant improvements in the echocardiographic measures of right heart systolic performance. This change appeared to be independent of respiratory improvement. There was also improvement in LV systolic function performance, as measured by TDI, without any adverse effect on LV wall thickness. There was a longitudinal reduction in the eccentricity index, but no statistically significant reduction in PVR was demonstrated in this cohort. While the >1 mg/kg dose allowed a higher chance of extubation, different dose ranges did not have a significant relationship with changes in the echocardiographic parameters.

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