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ARTICLE

Decreasing delivery room CPAP-associated pneumothorax at ≥35-week gestational age

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OBJECTIVE: We previously reported an increase in pneumothorax after implementing delivery room (DR) continuous positive airway pressure (CPAP) for labored breathing or persistent cyanosis in ≥35-week gestational age (GA) neonates unexposed to DR-positive pressure ventilation (DR-PPV). We hypothesized that pneumothorax would decrease after de-implementing DR-CPAP in those unexposed to DR-PPV or DR-O_2 supplementation (DR-PPV/O_2).
STUDY DESIGN: In a retrospective cohort excluding DR-PPV the primary outcome was DR-CPAP-related pneumothorax (1st chest radiogram, 1st day of life). In a subgroup treated by the resuscitation team and admitted to the NICU, the primary outcome was DR-CPAP-associated pneumothorax (1st radiogram, no prior PPV) without DR-PPV/O_2.
RESULTS: In the full cohort, occurrence of DR-CPAP-related pneumothorax decreased after the intervention (11.0% vs 6.0%, $P < 0.001$). In the subgroup, occurrence of DR-CPAP-associated pneumothorax decreased after the intervention (1.4% vs. 0.06%, $P < 0.001$).
CONCLUSION: The occurrence of CPAP-associated pneumothorax decreased after avoiding DR-CPAP in ≥35-week GA neonates without DR-PPV/O_2.

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INTRODUCTION

The International Liaison Committee on Resuscitation (ILCOR) remarked in 2010 that in contrast with preterm infants "there is no evidence to support or refute the use of delivery room (DR)-continuous positive airway pressure (CPAP) in the term baby" [1–6]. Despite the paucity of evidence, the neonatal resuscitation program (NRP), the ILCOR and the Japanese Resuscitation Council, but not the European Resuscitation Council, added consideration of CPAP for any gestational age (GA) neonate with "labored breathing" or "persistent cyanosis," but otherwise normal heart rate and spontaneous respiration without gasping [7–9]. The change in guidelines was followed by increased use of DR-CPAP and a 40-47% increase in pneumothorax (from 0.8% to 1.2% in Japan and from 0.38% to 0.56% at Parkland Hospital) in term and late preterm infants [10, 11]. Retrospective cohort studies suggested an association of DR-CPAP with pneumothorax in term and late preterm infants [10–17]. The frequency of pneumothorax among term or late preterm infants exposed to CPAP and admitted to the NICU ranges between 5% and 17% [11, 13, 15]. In one study of neonates who were admitted to the newborn nursery after DR-CPAP, the frequency of pneumothorax was 2% among those who received DR-CPAP without DR-positive pressure ventilation (PPV) and 0% among those who received both DR-PPV and DR-CPAP [18].

In a cohort at Parkland Hospital including term and late preterm infants without DR-PPV, the frequency of symptomatic pneumothorax and thoracentesis/thoracostomy increased by 47% after implementing new NRP guidelines [11, 12]. The association of pneumothorax with DR-CPAP was stronger in neonates receiving room air than in those receiving supplemental oxygen in the DR (DR-O_2) [11]. Concerns were raised about lack of information on neonates admitted to the newborn nursery, NICU admission rate, length of stay, and lack of a protocol for radiograms in that study [19].

Randomized controlled trials (RCTs) have demonstrated benefits of CPAP for respiratory distress in late-preterm infants and term neonates with O_2 requirement. In contrast, to our knowledge there is no evidence from RCTs supporting DR-CPAP for neonates receiving neither DR-PPV nor DR-O_2 (DR-PPV/O_2). In neonates with transient tachypnea of the newborn, CPAP versus free-flow O_2 reduced the duration and severity of respiratory distress but did not affect the need for mechanical ventilation [20, 21]. In neonates with meconium aspiration syndrome, CPAP reduced the need for mechanical ventilation [22]. In neonates born at ≥30 weeks GA with respiratory distress in nontertiary centers, CPAP versus O_2 alone reduced treatment failure or need for up-transfer [23]. In neonates born at ≥31 weeks GA with respiratory distress in special care nursery, high-flow nasal cannula resulted in more frequent respiratory failure than CPAP [24]. In neonates born at $34^{0/7}$–$38^{6/7}$ weeks GA by elective cesarean section, prophylactic DR-CPAP at 5 cm with 24–30% O_2 for 20 min starting at ≤10 min of life

reduced total NICU admissions; however, it did not reduce transient tachypnea or NICU admissions for respiratory distress compared with controls of which 31% received DR-O_2. No neonate in that latter study developed a pneumothorax [25].

We hypothesized (1) that the occurrence of pneumothorax on the first day of life in term and late-preterm neonates not requiring DR-PPV/O_2 could be reduced by 50% after avoiding DR-CPAP and (2) that pneumothorax was independently associated with DR-CPAP.

METHODS

Setting

Parkland Hospital is a large county hospital with ~12,000 total deliveries each year. Parkland's NICU serves around 1300 patients per year in a 96-bed unit. All low-risk deliveries are attended by an NRP-trained nurse and pediatric resident or pediatric nurse practitioner. Criteria for direct admission from the DR to the Mother-Baby-Unit include the following: stable neonates of GA ≥35 weeks and birth weight ≥2100 g; Apgar score ≥7 at five minutes; maximum 3 min of DR-PPV; lack of symptoms at the time of leaving the DR (maximum 30 min of age); lack of maternal diabetes mellitus class B or higher; and lack of congenital anomalies needing monitoring or surgery within 24 h.

A NICU resuscitation team is called to the DR for neonates at high risk for needing resuscitation (e.g., malformations), fetal compromise (i.e., non-reassuring fetal heart tones) or poor respiratory effort not resolving with short-term PPV with a self-inflating bag. The resuscitation team is comprised of a resuscitation nurse, respiratory therapist, and neonatal nurse practitioner or pediatric resident. Assisting as needed are an in-house NICU fellow and neonatology attending.

Skills and knowledge of the NRP guidelines are regularly assessed and reinforced using simulation and ongoing training. DR interventions are documented by the resident or nurse practitioner and by the resuscitation nurse in the electronic health record (EHR). During high-risk deliveries, an obstetric nurse records interventions on a paper chart in real time. This paper record is scanned into the EHR.

On July 1st 2011, Parkland Hospital implemented the 2010 NRP which allowed DR-CPAP for neonates with labored breathing or persistent cyanosis (Supplementary Fig. 1). CPAP was started at 5 cm H_2O and increased by 1 cm as needed (maximum 7 cm). DR-CPAP was provided with facemask and Neopuff T-piece resuscitator with 10 L/min flow rate. If the patient required CPAP for transport to the NICU, the patient was transitioned to bi-nasal prongs (Hudson Prongs; Teleflex, Wayne, PA) connected to a positive end expiratory pressure valve with 10 L/min flow.

In 2012, Parkland standardized criteria for chest radiogram for late preterm and term neonates admitted to the NICU due to respiratory distress or concerns for sepsis in order to prevent irradiation of neonates without rapidly resolving mild symptoms (Supplementary Fig. 2).

Design and inclusion and exclusion criteria

This retrospective cohort study included (1) a full birth cohort consisting of all neonates born at ≥35 weeks GA from 01/01/2012 to 12/31/2020, excluding those who received DR-PPV and (2) a NICU subgroup consisting of neonates who had a resuscitation team call and were subsequently admitted to the NICU.

Infants born 01/01/2012 to 03/31/2017 constituted the pre-intervention epoch or Epoch-1. Infants born in 2012–2015 were included in a previous study [11]; in the current study data on pneumothorax were limited to the first radiogram on the first day of life and individual patient-level data were extracted in the full cohort. Infants born 04/01/2017 to 12/31/2020 constituted the post-intervention epoch or Epoch-2.

Intervention (Supplementary Fig. 1)

The intervention was the adoption of guidelines directing the resuscitation team to avoid DR-CPAP from neonates ≥35-weeks GA exhibiting grunting, tachypnea, or retractions without preductal saturation lower than the range of NRP guidelines; these infants were observed without supplemental O_2 and without CPAP in the DR. Neonates with lower saturation were provided with supplemental O_2 and DR-CPAP was considered according to the most recent NRP guidelines (versions 6 and 7). All the other interventions were those of the NRP guidelines. The resuscitation team continued to observe neonates in the DR until they no longer had respiratory distress and were off CPAP and off O_2. If respiratory distress,

CPAP or supplemental O_2 persisted for >30 min, they were admitted to the NICU.

The team including faculty and fellows involved in this project initiated a series of presentations at divisional and resuscitation meetings directed at increasing buy-in from all stakeholders, including all members of the resuscitation team. The resuscitation neonatology attending ensured each cohort of residents adhered to the new protocol by directing training simulations.

Outcome variables

For the full cohort, data were collected by electronic capture from the EHR to create a database of all neonates born at 35–43 weeks GA. Electronic capture of pneumothorax used natural language processing (NLP) of free text in the radiologist's impression and narrative, i.e., text-processing technique combining computer programming with linguistics, allowing collection of unstructured data from notes (key words, abbreviations, acronyms) [26]. The algorithm was validated by comparing predicted pneumothorax by logistic regression analysis using the algorithm (Supplementary Table 1) with pneumothorax documented by chart review in neonates in several neonates the NICU subgroup. Cohen kappa was ≥0.9 for all variables [27].

The primary outcome for the full cohort was DR-CPAP-related pneumothorax, i.e., after DR-CPAP, noted on the radiologist's impression of the first radiogram during the first 24 hours of life. Secondary measures were NICU admissions and length of stay in NICU.

For the NICU subgroup, data were collected prospectively from two prospective databases: the DR resuscitation database and the NICU database and by additional data extraction from the EHR. Data included DR-CPAP, DR-O_2, GA, sex, weight, length, race/ethnicity and pneumothorax diagnosed by the radiologist on the first radiogram during the first 24 hours of life. GA was obtained from the best obstetrical estimate except for women with late prenatal care if the neonatal GA estimate by modified Ballard score differed from the obstetrical estimate by >2 weeks.

The primary outcome for the NICU subgroup was DR-CPAP-associated pneumothorax, defined as pneumothorax noted on the first radiogram during the first 24 h of life after exposure to DR-CPAP excluding CPAP initiated in the NICU and any prior PPV. Each diagnosis of pneumothorax was verified by individual chart review as positive chest radiogram reading (impression) from a pediatric radiologist or confirmation by a single pediatric radiologist (KM) in case the reading was equivocal. A secondary outcome was provision of thoracentesis or thoracostomy.

Secondary outcomes among neonates without DR-PPV/O_2 included occurrence of DR-CPAP usage for respiratory distress and occurrence of spontaneous pneumothorax. A spontaneous pneumothorax was defined as a pneumothorax diagnosed on the first chest radiogram on the first day of life in a neonate who had not received any positive pressure (CPAP or PPV) any time before diagnosis of the pneumothorax. Secondary outcomes among neonates with DR-O_2 but without DR-PPV included occurrence of CPAP usage, occurrence of CPAP-associated pneumothorax and occurrence of spontaneous pneumothorax.

Analysis

Continuous variables are presented as mean (SD) or median (interquartile range [IQR]). Statistical analyses were done using SPSS version 28 for Mac (IBM, Inc, Armonk, NY) or SAS 9.4 (SAS Institute, Inc, Cary, NC) for two-tailed tests, with $P < 0.05$ considered significant. Analyses included chi-square analysis, Student's t test, Mann–Whitney test, chi-square analysis, Fisher's exact test, Cohen kappa (exact test) and intraclass correlation coefficient. Changes over time were analyzed, depending on data distribution, by statistical process control (P chart, Montgomery rules) using QI Macros for Excel (KnoWare International, Denver, CO) (if baseline was stable), or by interrupted time series analysis to evaluate secular trends [28].

In the full cohort, the association of pneumothorax with DR-CPAP was assessed by generalized linear regression with Poisson distribution and robust estimate to calculate the adjusted relative risk (aRR), risk difference (aRD) and number needed to harm (aNNH), taking into account epoch, GA, sex, race/ethnicity and small for GA (birthweight <10th centile) [29]. Sensitivity analysis was done to adjust for possible overestimation by electronic capture.

In the NICU subgroup the aRR could not be assessed because data were unavailable in neonates admitted from the DR to the newborn nursery. Thus, the association of pneumothorax with DR-CPAP was assessed by logistic regression analysis to yield adjusted odds ratio (aOR), which was also adjusted for DR-O_2, one-minute Apgar score and respiratory distress.

Table 1. Demographics.

Variable	Epoch-1 01/2012–03/2017	Epoch-2 04/2017–12/2020	P value
Full cohort	$n = 51{,}818$	$n = 42{,}651$	
Gestational age, mean ± SD, weeks	39.0 ± 1.4	38.9 ± 1.4	<0.001
Birth weight, mean ± SD, g	3362 ± 493 ($n = 51{,}802$)	3346 ± 489 ($n = 42{,}639$)	<0.001
Birth length, mean ± SD, cm	49.4 ± 2.9 ($n = 51{,}747$)	50.4 ± 2.7 ($n = 42{,}583$)	<0.001
Intrauterine growth restriction, n/total (%)	1690/51,733 (3.3)	2563/42,571 (6.0)	<0.001
Small for gestational age, n (%)	104/51,802 (0.2)	106/42,639 (0.2)	0.12
Female, n (%)	25,391 (49.0)	21,268 (49.9)	0.008
Race and ethnicity, n (%)			<0.001
Hispanic	41,437 (80.0)[a]	32,519 (76.2)[b]	
Black, non-Hispanic	6414 (12.4)[a]	6792 (15.9)[b]	
White, non-Hispanic	2266 (4.4)[a]	2016 (4.7)[b]	
Asian	1271 (2.5)[a]	945 (2.2)[b]	
Other or unknown	430 (0.8)[a]	379 (0.9)[a]	
NICU subgroup	$n = 3986$	$n = 4101$	
Gestational age, mean ± SD, weeks	38.1 ± 1.7	38.1 ± 1.7	0.85
Birth weight, mean ± SD, g	3186 ± 697	3201 ± 672	0.34
Birth length, mean ± SD, cm	49.3 ± 3.1 ($n = 3966$)	49.7 ± 2.9 ($n = 4093$)	<0.001
Intrauterine growth restriction n/total (%)	447/3966 (11.3)	469/4091 (11.5)	0.79
Small for gestational age, n (%)	499 (12.5)	488 (11.9)	0.40
Maternal diabetes mellitus, n (%)	1012/3983 (25.4)	1070/4100 (26.1)	0.48
Female, n (%)	1795 (45.0)	1914 (46.7)	0.13
Race and ethnicity, n (%)			<0.001
Hispanic	2951 (74.2)[a]	2852 (69.6)[b]	
Black, non-Hispanic	649 (16.3)[a]	839 (20.5)[b]	
White, non-Hispanic	273 (6.9)	308 (7.5)	
Asian	103 (2.6)	99 (2.4)	
Cesarean section, n (%)	1934 (48.5)	1945 (47.4)	0.33
Apgar score 1 min, median (IQR)	8 (8, 8)	8 (8, 8)	0.95
Apgar score 5 min, median (IQR)	9 (8, 9)	9 (9, 9)	0.03

Student *t*-test or chi-square analysis; different alphanumeric superscripts indicate significant pair-wise differences between the two epochs using Bonferroni correction.
SD Standard deviation, *NICU* Neonatal intensive care unit, *IQR* Interquartile range.

Sample size

For the NICU subgroup a total sample size of 319 was estimated to detect an aOR of 2 for the association of pneumothorax with DR-CPAP, with 90% power and a two-tailed alpha of 0.05, assuming 14% DR-CPAP and 5.6% pneumothorax as previously [11]. For the full cohort, a sample size of 33,752 or 74,391 was estimated assuming (1) that either 1 of 2 or 1 of 10 of neonates, respectively, receiving DR-CPAP would be admitted to the NICU and (2) 0.4% pneumothorax [11].

A sample size of 2118 was estimated to detect a 50% decrease in pneumothorax in the NICU subgroup, and a sample size of 1366 or 7186 was needed to detect a 50% decrease in CPAP-related pneumothorax in the full cohort, assuming 17% pneumothorax and, respectively, 1:2 or 1:10 NICU admissions after DR-CPAP.

RESULTS
Full cohort (Supplementary Fig. 3)

The full cohort included 94,469 neonates with an average GA of 39 weeks (Table 1). The proportion of babies of Hispanic ethnicity decreased and those of other racial/ethnic groups and IUGR increased in Epoch-2. Comparison of electronic capture and chart review of pneumothorax yielded a Cohen kappa >0.9 (Supplementary Table 2). There was ≥90% agreement for all variables (Supplementary Table 2). Usage of DR-CPAP and occurrence of CPAP-related pneumothorax progressively increased during

Epoch-1 and decreased during Epoch-2 (both $P < 0.001$) (Supplementary Fig. 3). In contrast, the occurrence of pneumothorax without DR-CPAP did not change significantly.

The aRR of pneumothorax after DR-CPAP exposure was 66.44, CI 53.06–83.20 (Table 2a). The esimated aRD was 0.10, CI 0.09–0.12 and the aNNH 10, CI 8–11. Sensitivity analysis correcting for false positive pneumothorax (Supplementary Table 2) yielded a RD of 0.08 (CI 0.07–0.09) and NNH of 13 (CI 11–15).

The percent of NICU admissions with respiratory distress, including transient tachypnea, decreased in Epoch-2 ($P < 0.001$); median length of NICU stay also decreased ($P < 0.001$) (Table 3). The percent NICU admissions after DR-CPAP decreased from Epoch-1 to Epoch-2 ($P < 0.001$) (Table 3).

NICU subgroup

In the entire NICU subgroup, the aOR of pneumothorax with DR-CPAP among neonates without DR-O_2 exposure, 31.46 (CI 19.68–50.28), was almost four times that among neonates with DR-O_2 exposure, 8.33 (CI 5.39–12.88) ($P < 0.001$) (Table 2b). The aOR of pneumothorax with Epoch reached significance ($P < 0.001$) if CPAP was removed from the model (Fig. 1).

DR-CPAP was started at 5 cm H_2O in 99.7% and rarely increased to 6 cm ($n = 29$) or 7 cm ($n = 1$). Among 1005 neonates with DR-CPAP, 252 (25%) were taken off CPAP in the DR; the aOR of

Table 2. Association of baseline variables with pneumothorax on 1st day, 1st chest X-ray among neonates in the two cohorts (excluding DR-PPV). a. Full cohort. b. NICU subgroup, excluding PPV or CPAP initiated in the neonatal intensive care unit. c. Association of variables with pneumothorax on 1st day, 1st chest X-ray among neonates who were exposed to DR-CPAP in the NICU subgroup (excluding DR-PPV).

Factor	Adjusted relative risk (95% CI)	P Value
a. Full cohort*		
Epoch-2 vs Epoch-1	0.711 (0.568–0.890)	0.003
DR-CPAP vs no DR-CPAP	66.441 (53.057–83.201)	<0.001
Gestational age (per week)	1.317 (1.233–1.406)	<0.001
Male vs. female	1.664 (1.329–2.082	<0.001
Race/ethnicity		<0.001
Hispanic	Ref	
Black, non-Hispanic	0.411 (0.273–0.618)	<0.001
White, non-Hispanic	1.021 (0.666–1.565)	0.93
Asian	0.372 (0.119–1.170)	0.09
Other or unknown	0.960 (0.368–2.500)	0.93
Small for gestational age	2.058 (0.947–4.473)	0.07

Factor	Adjusted odds ratio (CI)	P Value
b. NICU subgroup, excluding PPV or CPAP initiated in the neonatal intensive care unit**		
Epoch-2 vs Epoch-1	0.78 (0.58–1.05)	0.10
DR-CPAP vs no DR-CPAP		<0.001
With DR-O_2	8.33 (5.39–12.88)	<0.001
Without DR-O_2	31.46 (19.68–50.28)	<0.001
Gestational age (per week)	1.47 (1.35–1.60)	<0.001
Male vs. female	1.67 (1.26–2.22)	<0.001
Race/ethnicity:		<0.001
Hispanic	Ref	
Black, not Hispanic	0.36 (0.22–0.56)	<0.001
White, not Hispanic	0.83 (0.50–1.39)	0.48
Other or unknown	0.54 (0.21–1.37)	0.19
Small for gestational age	0.90 (0.57–1.42)	0.65
Maternal diabetes mellitus	0.38 (0.24–0.61)	<0.001
Apgar score at 1 min	1.23 (1.09, 1.39)	0.001
Respiratory distress on first day	Ref	
None	a	0.996
Respiratory distress syndrome	0.12 (0.08–0.18)	<0.001
Transient tachypnea or retained lung fluid	0.25 (0.16–0.41)	<0.001
Pneumonia	0.20 (0.06–0.71)	0.01
Meconium aspiration syndrome	0.19 (0.08–0.47)	<0.001
Other		

Factor	Adjusted odds ratio (95% CI)	P Value
c. Association of variables with pneumothorax on 1st day, 1st chest X-ray among neonates who were exposed to DR-CPAP in the NICU subgroup (excluding DR-PPV)*		
Gestational age (per week)	1.58 (1.39–1.80)	<0.001
Race/ethnicity		0.009
Hispanic	Ref	
Black, non-Hispanic	0.32 (0.16–0.65)	0.002
White, non-Hispanic	1.36 (0.66–2.82)	0.41
Other or unknown	0.64 (0.18–2.29)	0.49

Table 2. continued

Factor	Adjusted odds ratio (95% CI)	P Value
Apgar score at 1 minute	1.27 (1.08–1.51)	0.005
CPAP level when leaving the DR and respiratory distress on 1st day of life		<0.001
<5 cm H_2O, no respiratory distress	Ref	
<5 cm H_2O, respiratory distress	0.38 (0.15–1.02)	0.054
≥5 cm H_2O, no respiratory distress	13.05 (6.53–26.08)	<0.001
≥5 cm H_2O, respiratory distress	0.58 (0.29–1.14)	0.12

*$n = 462$ Pneumothorax in 98,596 neonates, C statistic: 0.71.
**$n = 272$ Pneumothorax in 7963 neonates, C statistic: 0.86.
***Stepwise logistic regression, $n = 160$ pneumothoraces in 997 neonates.
CI 95% confidence interval, DR-CPAP Administration of continuous positive pressure in the delivery room, DR-PPV Positive pressure ventilation in the delivery room.
ᵃmargins too wide to be assessed.

pneumothorax was higher among those without respiratory distress who left the DR with CPAP level ≥5 cm (Table 2 c).

Among neonates not receiving DR-PPV/O_2, DR-CPAP usage decreased significantly from 6.9% in Epoch-1 to 1.2% in Epoch-2 ($P < 0.001$) (Table 3, Fig. 2A). This decrease of CPAP usage was reflected in a change in the primary outcome of DR-CPAP-associated pneumothorax from 1.4% to 0.06% ($P < 0.001$) and a decrease in any pneumothorax from 3.0 to 1.2 ($P < 0.001$) but not in spontaneous pneumothorax ($P = 0.22$) (Fig. 2B–D). The frequency of CPAP-associated pneumothorax among those exposed to DR-CPAP decreased from 20.2% to 5.3% from Epoch-1 to Epoch-2 ($P = 0.04$) (Table 3). There was no change in thoracentesis or thoracostomy or in time of admission for meconium aspiration syndrome. The percentage of transient tachypnea or retained lung fluid and the percentage of pneumonia decreased in Epoch-2 ($P < 0.05$).

Among neonates exposed to DR-O_2, DR-CPAP usage decreased from 54% in Epoch-1 to 27% in Epoch-2 ($P < 0.001$) (Table 3). Occurrence of any pneumothorax on the first day of life decreased from 9.4% to 6.2% ($P < 0.001$) and occurrence of CPAP-associated pneumothorax decreased from 7.8% to 3.8% ($P < 0.001$). Occurrence of spontaneous pneumothorax increased from 1.3% to 2.3% ($P = 0.049$). Among neonates with spontaneous pneumothorax, none of the variables found to be independently associated with pneumothorax in the entire NICU cohort (Table 2b) changed in Epoch-2 (data not shown). Among all neonates exposed to DR-O_2 the percentage of pneumonia and that of other respiratory distress decreased in Epoch-2 ($P < 0.05$).

DISCUSSION

This is to best of our knowledge the first study showing that de-implementing DR-CPAP at 5–7 cm H_2O in neonates delivered at 35–43 weeks' GA with labored breathing but not receiving DR-PPV/O_2 was followed by a decrease in DR-CPAP-associated pneumothorax and DR-related pneumothorax without worsening of other outcomes. There was also a decrease in DR-CPAP and in DR-CPAP-associated pneumothorax in neonates receiving DR-O_2 in Epoch-2. The aOR of pneumothorax with DR-CPAP was higher in neonates who did not receive DR-O_2 than those who did, as reported previously [11]. In the full cohort DR-CPAP was associated with an increased risk of pneumothorax on the first day of life in neonates not receiving DR-PPV. The high aRR of 66

Table 3. Outcome Variables During the two Epochs.

Group	Variable	Epoch-1 01/2012–03/2017	Epoch-2 04/2017–12/2020	P value
Full cohort (n = 94,469)	Number	n = 51,818	n = 42,651	
	DR-CPAP, n (%)*	1014 (2.0)	916 (2.1)	0.04
	NICU admissions among those with DR-CPAP, n (%)	754 (74)	298 (33)	<0.001
	Pneumothorax on first day, n (%)			
	after DR-CPAP*	112 (11.0)[a]	55 (6.0)[b]	0.003
	no DR-CPAP*	89 (0.2)[a]	58 (0.1)[a]	0.17
	All	201 (0.4)[a]	113 (0.3)[b]	<0.001
	NICU admission with respiratory distress, n (%)	1873 (3.6)	1373 (3.2)	<0.001
	NICU admission with transient tachypnea or retained lung fluid, n (%)	724 (1.4)	406 (1.0)	<0.001
	Length of stay of NICU admissions with respiratory distress, days, median (IQR)	5 (2,9)	4 (2,8)	<0.001
NICU subgroup No DR-PPV/O_2 (n = 6097)	Number	2975	3122	
	DR-CPAP, n (%)	204 (6.9)	38 (1.2)	<0.001
	Respiratory distress on first day, n (%)			
	None	2226 (74.8)[a]	2597 (83.2)[b]	<0.001
	Respiratory distress syndrome	11 (0.4)	7 (0.2)	
	Transient tachypnea or retained lung fluid	428 (14.4)[a]	239 (7.7)[b]	
	Pneumonia	199 (6.7)[a]	169 (5.4)[b]	
	Meconium aspiration syndrome	4 (0.1)	6 (0.2)	
	Other	107 (3.6)	104 (3.3)	
	Any pneumothorax on 1st day, n (%)	89 (3.0)	39 (1.2)	<0.001
	Thoracentesis or chest tube placement, n (%)	13 (0.4)	14 (0.4)	0.95
	CPAP-associated pneumothorax, n	41	2	
	(% among all in NICU subgroup)	(1.4)	(0.06)	<0.001
	(% among those with DR-CPAP)	(20.2)	(5.3)	0.04
	Spontaneous pneumothorax, n (%)	44 (1.5)	35 (1.1)	0.22
	Length of stay, days: median (IQR)	5 (2, 8)	4 (2,7)	<0.001
	Time of admission for meconium aspiration syndrome, minutes, median (IQR)	67 (52, 95) n = 4	30 (21, 102) n = 6	0.35
NICU subgroup DR-O_2, no DR-PPV (n = 1990)	Number	1011	979	
	DR-CPAP, n (%)	550 (54.4)	260 (26.6)	<0.001
	Respiratory distress on first day, n (%)			
	None	289 (28.6)[a]	397 (40.6)[b]	<0.001
	Respiratory distress syndrome	37 (3.7)	26 (2.7)	
	Transient tachypnea or retained lung fluid	421 (41.6)	374 (38.2)	
	Pneumonia	153 (15.1)[a]	103 (10.5)[b]	
	Meconium aspiration syndrome	16 (1.6)	26 (2.7)	
	Other	95 (9.4)[a]	53 (5.4)[b]	
	Any pneumothorax on 1st day, n (%)	95 (9.4)	61 (6.2)	0.009
	Thoracentesis or chest tube placement, n (%)	28 (2.8)	16 (1.6)	0.09
	CPAP-associated pneumothorax, n	79	37	
	(% among all in NICU subgroup)	(7.8)	(3.8)	<0.001
	(% among those with DR- CPAP)	(14.6)	(14.4)	0.95
	Spontaneous pneumothorax, n (%)	12 (1.2)	23 (2.3)	0.049

Data are number (%) or median (interquartile range).
Fisher's exact test, chi-square analysis or Mann–Whitney test.
Pneumothorax on first chest radiogram on first day of life.
CPAP-associated pneumothorax, confirmed pneumothorax on 1st radiogram and during the 1st 24 h after DR-CPAP, excluding positive pressure initiated in the NICU and prior PPV; spontaneous pneumothorax, confirmed pneumothorax on 1st radiogram and 1st day postnatal without any prior PPV or CPAP.
*predicted per NLP algorithm.
Different alphanumeric superscripts indicate significant pair-wise differences between the two epochs using Bonferroni correction.
NICU Neonatal intensive care unit, *DR* Delivery room, *IQR* Interquartile range, *DR-CPAP* Delivery room continuous positive airway pressure.

and low frequency of pneumothorax led to a aRD of 0.10 and aNNH of 10.

CPAP decreases morbidity and mortality in preterm infants with respiratory distress syndrome (RDS) [1, 2]. CPAP facilitates airway fluid clearance, improves lung compliance and oxygenation and decreases apnea [3]. Systematic review of RCTs using DR-CPAP instead of endotracheal intubation in extreme preterm infants at risk for RDS showed an increase in frequency of pneumothorax in
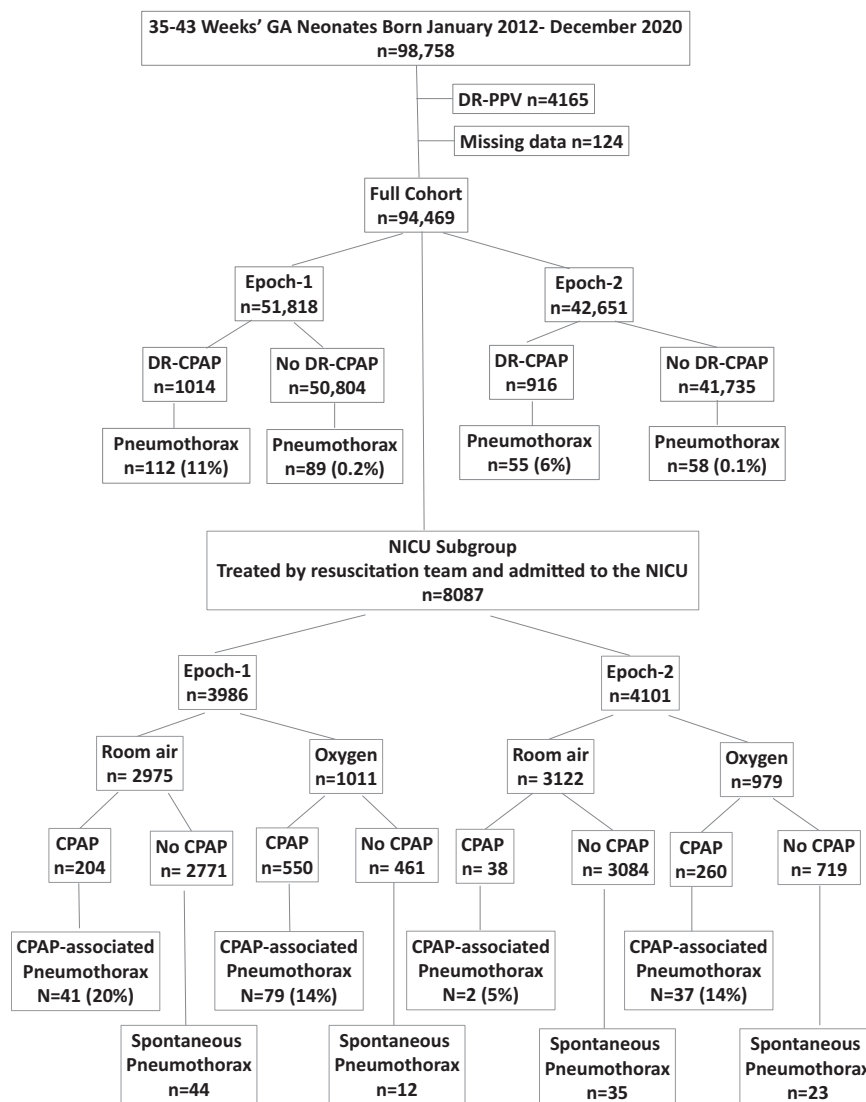
Fig. 1 Flow diagram: pneumothorax on first day of life vs. DR-CPAP and DR-O$_2$. CPAP-associated pneumothorax, confirmed pneumothorax on 1st chest radiogram & 1st day of life after exposure to DR-CPAP without DR-PPV, excluding positive pressure initiated in the NICU and prior PPV; spontaneous pneumothorax, confirmed pneumothorax on 1st chest radiogram & 1st day of life without prior exposure to PPV or CPAP. Abbreviations: GA gestational age, DR delivery room, NICU neonatal intensive care unit, DR-PPV delivery room positive pressure ventilation, CPAP continuous positive airway pressure, PTX pneumothorax on 1st chest radiogram & 1st day of life.

one trial using DR-CPAP at 8 cm H$_2$O, but not other trials using 5 cm [4, 5]. Higher risk of CPAP-associated pneumothorax in late preterm and term infants is likely due to higher surfactant load at delivery, lower surface tension, higher lung compliance and lower chest compliance than in preterm infants [10–17].

In this study, the decrease in NICU admissions for respiratory distress in Epoch-2 was mediated by less pneumothorax and less transient tachypnea. Successful perinatal transition without exposure to DR-CPAP among neonates not receiving DR-PPV/O$_2$ may have resulted from less exposure to dead space due to the internal space of the mask on CPAP [30, 31]. Implementation of the Update of the Japan Resuscitation Council Guidelines in 2010 resulted in increased prevalence of respiratory support within 24 h of life [30]. Reduction of DR-CPAP use in neonates receiving DR-O$_2$ (typically among those receiving <40% O$_2$) in Epoch-2 likely resulted from expansion of clinical practice beyond bounderies of the protocol, as reported in other studies [32, 33].

The increase in spontaneous pneumothorax in Epoch-2 among neonates exposed to DR-O$_2$ was unexpected. Since it occurred without any change in variables shown to be independently

associated with pneumothorax, it is possible that the increase in spontaneous pneumothorax in Epoch-2 could be due to other variables that were not available in this study. Alternatively, it is possible that the increase in spontaneous pneumothorax resulted from the fact that some DR-associated pneumothoraces might not have been caused by CPAP.

The higher frequency of pneumothorax in males compared with females observed in the current study was already observed in other studies in neonates including our previous study [11, 15]. Spontaneous pneumothorax is more frequent in males than females in children and adults [34]. We are not aware of mechanisms involved.

Strengths of this study include (1) availability of information on DR-PPV, DR-CPAP, pneumothorax on the first day and respiratory outcomes, NICU admission and length of stay in a large prospective full cohort, yielding values of aRR, aRD and aNNH; (2) electronic data capture using validated algorithms with almost near-perfect agreement (kappa ≥0.81) [26] and ≥90% observed agreement for all variables; (3) strict definition of CPAP-associated pneumothorax in a nested NICU subgroup; (4) change in practice
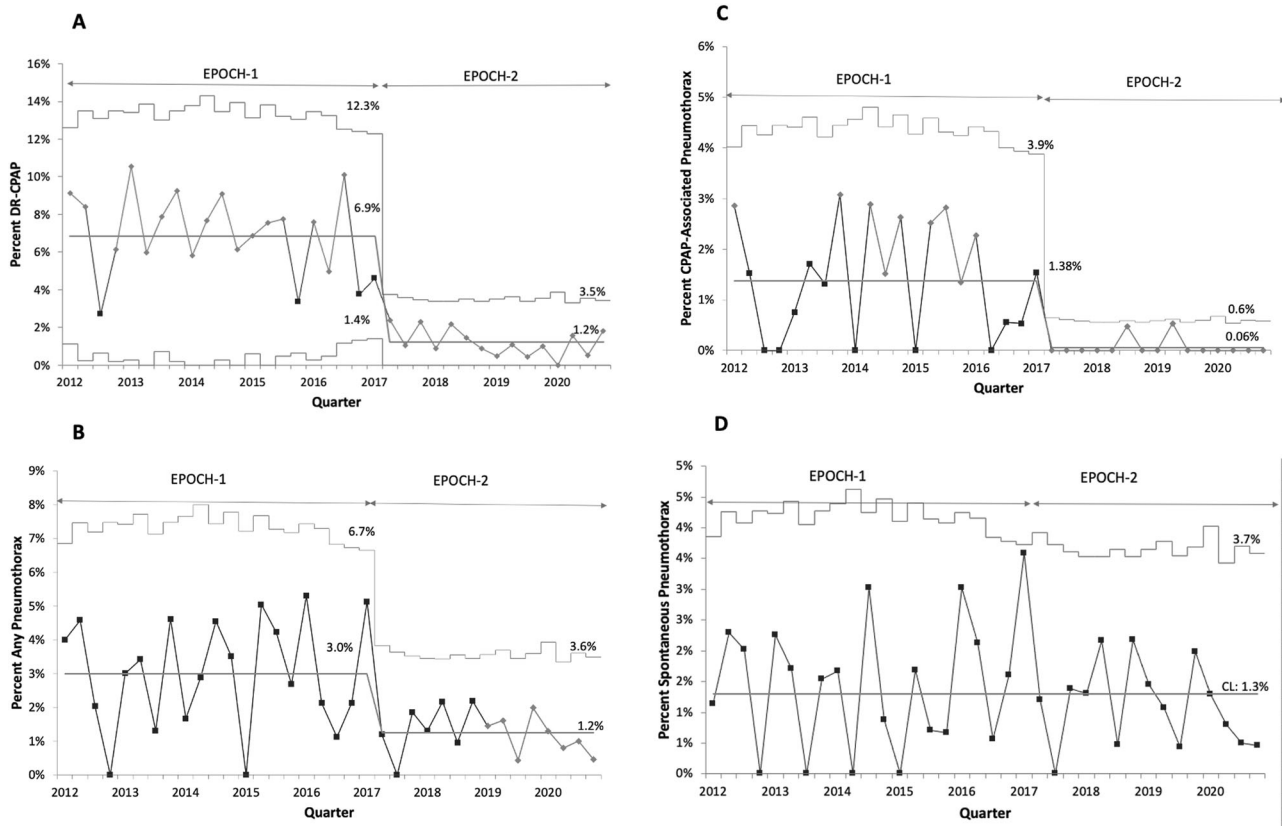
Fig. 2 Changes over time (Control P charts) in exposure to DR-CPAP (Panel A) and pneumothorax during the first day of life (Panels B-D) among 6097 neonates in NICU subgroup who did not receive O$_2$ in the delivery room during the two Epochs. Panel (**A**): DR-CPAP: The frequency of DR-CPAP decreased from 6.9% in Epoch-1 to 1.2% in Epoch-2. Panel (**B**). Any pneumothorax: The frequency of any pneumothorax decreased from 3.0% in Epoch-1 to 1.2% in Epoch-2. Panel (**C**). CPAP-associated pneumothorax: The frequency of CPAP-associated pneumothorax decreased from 1.38% in Epoch-1 to 0.06% in Epoch-2. Panel (**D**) Spontaneous pneumothorax: The frequency of spontaneous pneumothorax did not change significantly from Epoch-1 to Epoch-2. CPAP-associated pneumothorax, confirmed CPAP-associated pneumothorax (following DR-CPAP, pneumothorax visible on 1st radiogram and 1st day postnatal, excluding positive pressure initiated in the NICU and prior PPV); spontaneous pneumothorax, confirmed pneumothorax on 1st radiogram and 1st day postnatal without any prior PPV or CPAP. Abbreviations: DR-CPAP delivery room continuous positive airway pressure, NICU neonatal intensive care unit, O$_2$ oxygen, Epoch-1 baseline, Epoch-2 after de-implementation of DR-CPAP in neonates not needing oxygen or positive pressure ventilation in the delivery room, UCL upper control limit, CL central line, CPAP continuous positive airway pressure, DR delivery room, PPV positive pressure ventilation.

involving de-implementation of DR-CPAP in neonates not needing DR-PPV/O$_2$ with strict guidelines about indication for radiograms and high compliance with processes of care; (5) consistency of results by using standard statistics vs analysis of change with time. These factors eliminated several limitations in a previous manuscript [11, 12, 18].

Limitations of this study included (1) lack of randomization, (2) lack of availability of point of care ultrasonogram to diagnose pneumothorax leading to inability to assess the frequency of asymptomatic pneumothorax and to determine whether an symptomatic pneumothorax was present before CPAP or PPV, (3) lack of individual chart review in the full cohort, leading to only estimates of RR, RD and NNH (4) lack of exact data on the timing and duration of administration of each level of DR-CPAP and inability to differentiate the roles of face mask vs nasal prongs CPAP on pneumothorax development, (5) lack of standardization of the use of CPAP, which may have resulted in overuse of CPAP in some cases; (6) lack of data on CPAP < 5 cm H$_2$O and (7) lack of data on severity of respiratory distress. This study was not designed to assess benefits and risks of DR-CPAP at 5-7 cm H$_2$O in neonates delivered at 35–43 weeks' GA with labored breathing and persistent cyanosis, in whom RCTs and observational studies have shown that DR-CPAP may improve respiratory distress [20–25, 35].

De-implementing DR-CPAP ≥5 cm in neonates ≥35-week GA with labored breathing but not receiving DR-PPV/O$_2$ was followed by a decrease in DR-CPAP-associated pneumothorax without worsening of other outcomes. Studies including RCTs are needed to test whether using DR-CPAP at <5 cm may improve outcomes in neonates ≥35-week GA with mild respiratory distress without increasing the risk of pneumothorax.

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AUTHOR CONTRIBUTIONS

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This project was initially approved as quality improvement by the University of Texas Southwestern Medical Center Institutional Review Board and by Parkland Health and Hospital Systems. The entire project including the retrospective full cohort as described was later approved as a research project. The need for informed consent was waived for the entire project.

ADDITIONAL INFORMATION

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