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RESEARCH ARTICLE

*Novel Insights into Preterm Respiratory Physiology: Celebrating the 100th Birthday of Dr. Mildred T. Stahlman*

# Respiratory and chest wall mechanics in very preterm infants

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## Abstract

Data on static compliance of the chest wall ($C_{cw}$) in preterm infants are scarce. We characterized the static compliance of the lung ($C_L$) and $C_{cw}$ to determine their relative contribution to static compliance of the respiratory system ($C_{rs}$) in very preterm infants at 36 wk postmenstrual age (PMA). We also aimed to investigate how these compliances were influenced by the presence of bronchopulmonary dysplasia (BPD) and impacted breathing variables. Airway opening pressure, esophageal pressure, and tidal volume ($V_T$) were measured simultaneously during a short apnea evoked by the Hering–Breuer reflex. We computed tidal breathing variables, airway resistance ($R$), and dynamic lung compliance ($C_{L,dyn}$), inspiratory capacity (IC), and $C_{rs}$, $C_L$, and $C_{cw}$. Functional residual capacity was assessed by the multiple breath washout technique ($FRC_{mbw}$). Breathing variables, compliances, and lung volumes were adjusted for body weight. Twenty-three preterm infants born at 27.2 ± 2.0 wk gestational age (GA) were studied at 36.6 ± 0.6 wk PMA. Median and interquartile range (IQR) $C_{rs}$/kg is 0.69 (0.6), $C_L$/kg 0.95 (1.0), and $C_{cw}$/kg 3.0 (2.4). Infants with BPD ($n = 11$) had lower $C_{rs}$/kg ($P = 0.013$), $C_L$/kg ($P = 0.019$), and $C_{cw}$/kg ($P = 0.027$) compared with infants without BPD. $C_{cw}/C_L$ ratio was equal between groups. $FRC_{mbw}$/kg ($P = 0.044$) and IC/kg ($P = 0.005$) were decreased in infants with BPD. Infants with BPD have reduced static compliance of the respiratory system, the lungs, and chest wall. Decreased $C_{rs}$, $C_L$, and $C_{cw}$ in infants with BPD explain the lower FRC and IC seen in these infants.

**NEW & NOTEWORTHY** Data on chest wall compliance in very preterm infants in the postsurfactant era are scarce. To our knowledge, we are the first group to report data on static respiratory system compliance ($C_{rs}$), lung compliance ($C_L$), and chest wall compliance ($C_{cw}$) in preterm infants with and without bronchopulmonary dysplasia (BPD) in the postsurfactant era.

*bronchopulmonary dysplasia; chest wall mechanics; prematurity*

## INTRODUCTION

Bronchopulmonary dysplasia (BPD) is one of the most common complications following preterm birth and leads to long-term negative respiratory sequelae (1, 2). Preterm birth interrupts normal lung development in utero, which is one of the key risk factors for the development of BPD (3). The characteristics of BPD have changed since surfactant was introduced in the early 1990s (4). The so-called "old" BPD affected less premature infants and was characterized by the damage of the airways, whereas the "new" BPD is a consequence of interrupted lung development and is characterized by fewer and simplified alveoli (5, 6).

The structural changes in the lung tissue affect the mechanical properties of the respiratory system. Changes in the mechanical properties are reflected by lower compliance of the lung ($C_L$) and the overall respiratory system ($C_{rs}$) in infants with BPD compared with infants without BPD (7). The lower $C_{rs}$ in infants with BPD persists at least up until 12 mo of age (8). Thus, the link between abnormal lung development and changes in the elastic properties of the lung is well-established. However, whether BPD also leads to structural changes in the chest wall and if these changes further decrease $C_{rs}$ remains unknown.

Although several studies report data for $C_{rs}$ and $C_L$ in preterm infants (7–10), published data on chest wall compliance ($C_{cw}$) are relatively scarce and refer to infants born before the routine administration of surfactant to preterm infants with respiratory distress (11–14). Stiffening of the chest wall with increasing postmenstrual age (PMA) suggested by two studies (12, 14) is attributed to developmental changes, including

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the ossification of the ribs and altered configuration of the thorax (14).

Factors suggesting an altered $C_{cw}$ in preterm infants with BPD compared with infants without BPD include a higher incidence of metabolic bone disease (15), increased chest wall distortion (16–18), and differences in the configuration of the chest after 8 mo of life. These differences are likely due to different operating lung volumes (19, 20). Survivors of BPD have a flatter chest compared with infants without BPD at 12 mo corrected age (19, 21).

We hypothesized that infants with BPD have a stiffer chest wall compared with infants without BPD, and that this stiffer chest wall contributes to the decreased $C_{rs}$ seen in infants with BPD. We aimed to characterize static $C_L$ and $C_{cw}$ and to determine their relative contribution to $C_{rs}$ in very preterm infants at 36 wk PMA. We further aimed to investigate how the presence of BPD influenced these compliances. Moreover, we aimed to understand the relationship between changes in compliance with breathing variables and lung volumes in infants with and without BPD.

## MATERIALS AND METHODS

### Study Design

We designed a prospective observational study to assess the relative contributions of the lung and the chest wall to the compliance of the respiratory system in very preterm infants. The study was approved by the Women and Newborn Health Service Human Research Ethics Committee (HREC:1883EW and 20130193EW) and the University of Western Australia (RA/4/1/5942 and RA/4/1/426).

### Study Population and Data Management

Infants were recruited from the Neonatal Intensive Care Unit at King Edward Memorial Hospital for Women (KEMH). All included infants were part of the Preterm Infant Functional and Clinical Outcomes (PIFCO) study (ACTRN12613001062718). Infants eligible for the study were born between July 23, 2017 and May 12, 2018, <32 wk gestation. The sample size was not predefined; we aimed to study a sufficient number of infants to provide an indication of the magnitude of effect size relating to lung disease. Infants with congenital malformations were excluded from the study. Written informed consent was obtained from the parents before enrolment into the study. Study data were collected and managed using Research Electronic Data Capture (REDCap) software hosted at the University of Western Australia (22).

### Assessment of Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia was assessed according to the National Institutes of Health/National Institute of Child Health and Human Development (NIH/NICHD) definition published in 2001 (23). Infants dependent on oxygen for more than 28 days were classified as having BPD. The severity of BPD was assessed based on oxygen requirements or the need for positive pressure ventilation at 36 wk PMA.

### Experimental Protocol and Measurements

The assessment was performed at 36 wk PMA. Infants were fed at least 30 min before the test and studied during unsedated quiet sleep in a supine position. Infants requiring continuous positive pressure ventilation or humidified high flow were taken off respiratory support during the assessment. The respiratory assessment included the measurement of functional residual capacity (FRC), breathing pattern variables, the dynamic compliance of the lung ($C_{L,dyn}$) and airways resistance ($R$) during quiet breathing, thoracoabdominal asynchrony during quiet breathing, and static $C_{rs}$, $C_L$, and $C_{cw}$ during short apneas.

#### *Functional residual capacity.*

We measured $FRC_{mbw}$ using the multiple-breath washout (MBW) technique with 4% sulfur hexafluoride ($SF_6$) as a tracer gas using an ultrasonic flowmeter (Exhalyzer D, EcoMedics AG, Switzerland) and analyzed using Wbreath version 3.28. The technique was described in detail by Schibler et al. in 2002 (24). Each infant had at least three $FRC_{mbw}$ measurements performed, and the technical acceptability was ascertained using published guidelines (25, 26).

#### *Breathing pattern.*

Breathing parameters and paradoxical breathing, defined as the fraction of the inspiratory ($T_I$ paradoxical breathing) and expiratory ($T_E$ paradoxical breathing) time during which the abdomen (AB) and the ribcage (RC) move in opposite directions, were measured by respiratory inductance plethysmography (RIP) (Bicore II, CareFusion, CA; QDC Pro-Disposable Belt, Nox Medical). Changes in lung volume during quiet breathing were computed from the AB and RC displacements measured by RIP. We identified local maxima and minima on the volume signal during at least 10 breaths of quiet breathing and computed respiratory rate (RR), tidal volume ($V_T$), minute ventilation ($\dot{V}E$), maximal expiratory flow, the percentage contribution of the abdomen to $V_T$ (% AB), and paradoxical breathing. RIP was calibrated with a pneumotachograph before the assessment. Twenty stable continuous breaths were recorded using a custom-made metal screen pneumotachograph connected to a differential pressure transducer (Honeywell 26PCAFA6D) attached to a silicone face mask (size 00, Laerdal, Medical AS, Norway). Moreover, the pneumotachograph was calibrated to the flow generated during 20 mL volume excursions at a rate of 60/min using a calibration syringe (5510 Series, Hans Rudolph Inc.) before the assessment.

#### *Lung mechanics during quiet breathing.*

Lung resistance ($R$) and dynamic lung compliance ($C_{L,dyn}$) were estimated by fitting the transpulmonary pressure ($P_{tp} = P_{ao} - P_{es}$) and flow signals to the equation of motion of the respiratory system by the least-squares method. $C_{L,dyn}$ is influenced by FRC and breathing pattern. Infants may modify FRC and their breathing pattern to increase $C_{L,dyn}$.

#### *Static compliances.*

$C_{rs}$, $C_L$, and $C_{cw}$ were measured during short apneas provoked via the Hering–Breuer reflex. The Hering–Breuer reflex was triggered by two to four rapid manual inflations at an inspiratory pressure of 20 $cmH_2O$ using a Neopuff Infant Resuscitator (Fisher & Paykel Healthcare, New Zealand). The positive inspiratory pressure of 20 $cmH_2O$ was released to a defined positive end-expiratory pressure of 5 $cmH_2O$ after the Hering–Breuer reflex was triggered. Technically,

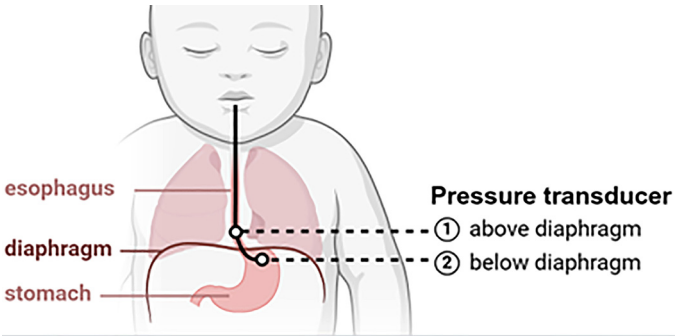


**Figure 1.** Position of the pressure catheter with one pressure transducer above the diaphragm and the other one below the diaphragm. Of note: the traces of the esophagus and the stomach are in the opposite phase (created with BioRender.com).

acceptable apneas for the assessment of static compliances were selected manually. Pleural pressure changes were estimated to be equal to esophageal pressure changes. Compliances were calculated as:

$$C_{rs} = \Delta V / \Delta P_{ao}, \quad (1)$$

$$C_L = \Delta V / \Delta (P_{ao} \pm P_{pl}) \quad (2)$$

$$C_{cw} = \Delta V / \Delta P_{pl} \quad (3)$$

where $\Delta V$ is the change in volume between 20 $cmH_2O$ and a positive end-expiratory pressure of 5 $cmH_2O$, and $\Delta P_{ao}$ and $\Delta P_{pl}$ are the corresponding changes in airway opening and pleural pressures, respectively (27).

Inspiratory capacity (IC) was estimated by the change in volume between the end-expiratory lung volume (estimated as the mean volume of three end-expiratory points during quiet breathing at zero end-expiratory pressure) to the volume reached when a positive inspiratory pressure of 20 $cmH_2O$ was applied.

Volume and compliance values were adjusted for body weight at the time of the test. Data analysis was performed in MATLAB (2019b, The MathWorks, Natick, MA).

Airway opening flow was measured by a metal screen pneumotachograph connected to a differential pressure transducer (Honeywell 26PCAFA6D) attached to a silicone face mask (size 00, Laerdal, Medical AS, Norway). Airway opening pressure ($P_{ao}$) was measured by a pressure transducer (Honeywell 26PCAFA6D) via a side port in the filter attached to the facemask. The proximal and the distal pressure transducer of a dual-tipped pressure transducer (Mikro-Tip Transducer, Millar Instrumental Inc., Houston, TX) were placed in the esophagus and in the stomach, respectively (Fig. 1). The correct positioning of the pressure transducer was verified by the operator monitoring the tracings. The correct position was confirmed, when the traces recorded from the transducers in the esophagus and the stomach were opposite in phase. All measurements were recorded by PowerLab data acquisition system with LabChart Pro (ADInstruments, Sydney, Australia) software and stored for later analysis.

### Statistical Analyses

Data were tested for normality using the Kolmogorov–Smirnov test and reported as means ± standard deviation (SD) or as median and interquartile range (IQR) according to their distribution. Differences in demographics, breathing patterns, and compliances between infants with and without BPD were compared using Student's $t$ test or Mann–Whitney test as appropriate for data distribution (28). Postnatal factors collinear with gestational age were identified using the variance inflation factor. These factors were regressed against gestational age and the unstandardized residuals were used as independent factors in the univariate and multivariable regression analyses. We used univariate regression analyses to identify which antenatal and postnatal factors are associated with compliance. Statistically significant factors were entered into the stepwise multivariable regression analysis to identify independent variables associated with compliance at 36 wk PMA. A $P$ value $<0.05$ was considered statistically significant. Data were analyzed within SPSS (v.25·0·0·0; IBM Corp.).

## RESULTS

A total of 23 patients were studied. The characteristics of the studied infants are shown in Table 1. The cohort included 12 infants without BPD and 11 infants with BPD. Of the infants with BPD, four infants had mild BPD, and seven infants had moderate ($n = 3$) or severe BPD ($n = 4$). Infants with BPD had a lower gestational age (GA) and birthweight and required mechanical ventilation for longer compared with infants without BPD.

### Breathing Parameters and Lung Volumes between Infants with and without BPD

Tidal breathing variables and lung volumes for infants with and without BPD are shown in Table 2. FRC/kg and IC/kg were lower in infants with BPD compared with infants without BPD. $FRC_{mbw}$/kg and IC/kg were lower in infants with BPD compared with infants without BPD.

**Table 1.** *Demographics of enrolled infants and comparison between infants with and without BPD*

| | No BPD ($n = 12$) | BPD ($n = 11$) | $P$ |
|---|---|---|---|
| Male, $n$ (%) | 7 (53.8) | 6 (46.2) | 0.85 |
| GA, wk | 28.4 (5.7) | 25.7 (4.3) | **<0.001** |
| Weight at birth, kg | 1.1 ± 0.2 | 0.7 ± 0.1 | **0.001** |
| Weight $z$-score at birth | −0.2 ± 0.7 | −0.2 ± 1.2 | 0.83 |
| Chorioamnionitis, $n$ (%) | 6 (50.0) | 4 (36.3) | 0.51 |
| Antenatal steroids, $n$ (%) | 11 (91.6) | 11 (100) | 0.33 |
| CRIB II | 8.1 ± 3.2 | 12.4 ± 1.8 | **<0.001** |
| Postnatal steroids, $n$ (%) | 0 (0.0) | 3 (27.2) | 0.052 |
| Any surfactant, $n$ (%) | 7 (58.3) | 11 (100) | **0.016** |
| Mechanical ventilation, days | 0.8 (4.7) | 11.8 (42.1) | **<0.001** |
| Noninvasive ventilation, days | 34.4 (49) | 64.3 (19.0) | 0.06 |
| Supplemental oxygen, days | 10.2 (15.3) | 84.7 (81.3) | **<0.001** |
| Weight at test, kg | 2.5 (1.2) | 2.7 (1.5) | 1.00 |
| Weight $z$-score at test | −0.6 ± 1.1 | −0.9 ± 1.2 | 0.72 |
| Length at test, cm | 45.2 (2.8) | 44.8 (2.6) | 0.70 |
| Length $z$-score at test | −0.8 (1.2) | −1.3 (1.0) | 0.37 |
| Chest circumference, cm | 30.9 ± 1.7 | 31.2 ± 1.9 | 0.71 |

Parametric data are reported as means ± SD, nonparametric data as median (IQR); $n$ represents number of infants. Bold font indicates statistical significance. BPD, bronchopulmonary dysplasia; GA, gestational age.

**Table 2.** *Tidal breathing and lung volume variables*

| | No BPD ($n$ = 12 infants) | BPD ($n$ = 11 infants) | $P$ Value |
|---|---|---|---|
| $V_T$/weight, mL/kg | 5.4 ± 1.7 | 4.2 ± 1.5 | 0.076 |
| $T_I/T_{tot}$, % | 45.0 ± 3.64 | 45.3 ± 4.0 | 0.819 |
| RR/min | 71 ± 15 | 77 ± 14 | 0.352 |
| $\dot{V}_E$, mL/min/kg | 357 (109) | 329 (132) | 0.190 |
| $FRC_{mbw}$/weight, mL/kg | 22.6 ± 2.5 | 20 ± 3.3 | **0.044** |
| IC, mL/kg | 8.8 ± 2.4[b] | 6.1 ± 1.7 | **0.005** |
| Abd. compartment, % | 77.2 ± 23.6 | 77.4 ± 35.8 | 0.989 |
| $T_I$ paradox. breathing, % | 36.4 ± 22.2 | 43.9 ± 22.3 | 0.426 |
| $T_E$ paradox. breathing, % | 30.2 ± 17.8[a] | 38.8 ± 20.8 | 0.298 |
| $R$, ($cmH_2O$·s/L)/kg | 30.9 ± 15.5[b] | 46.6 ± 29.7 | 0.101 |
| $C_{L,dyn}$, mL/$cmH_2O$/kg | 0.9 ± 0.3[b] | 0.7 ± 0.4 | 0.259 |
| Peak expiratory flow, mL/s | 28.7 (9.8) | 22.6 (14.0) | 0.260 |
| $T_{PTEF}/T_E$ | 0.42 ± 0.08 | 0.39 ± 0.06 | 0.303 |

Comparison between infants with and without BPD. Bold font indicates statistical significance. Abd, abdominal; BPD, bronchopulmonary dysplasia; $C_{L,dyn}$, dynamic lung compliance; $FRC_{mbw}$, functional residual capacity measured by multiple breath washout; IC, inspiratory capacity; $R$, airway resistance; RR, respiratory rate; $T_E$, expiratory time per breath; $T_I$, inspiratory time per breath; $T_{tot}$, total time per breath; $\dot{V}_E$, minute ventilation; $V_T$, tidal volume.

### Compliance in Infants with and without BPD

Measurements were well tolerated by all infants. Median (IQR) overall $C_{rs}$, $C_L$, and $C_{cw}$ normalized to body weight were 0.69 (0.6), 0.95 (1.0), and 3.0 (2.4) mL/$cmH_2O$/kg, respectively. $C_{cw}$/weight was approximately three times higher than $C_L$/weight.

$C_{rs}$, $C_L$, and $C_{cw}$ were significantly lower in infants with BPD compared with infants without BPD (Fig. 2). $C_{cw}/C_L$ ratio was equal between infants with and without BPD (2.95 ± 0.9 vs. 2.93 ± 1.3, $P = 0.484$).

### Relationship between Compliances and Antenatal and Postnatal Factors

The univariate regression analysis of $C_{rs}$ and antenatal and postnatal factors together are shown in Table 3. BPD explained 28.4% of the variability in $C_{rs}$. One infant received postnatal steroids until the day before the measurements and in two other infants, postnatal steroids were discontinued more than 3 wk before the measurements. None of the infants received bronchodilators or pulmonary vasodilators.

**Table 3.** *Outcome variable: normalized respiratory system compliance ($C_{rs}$/weight)*

| | Univariate Regression | | |
|---|---|---|---|
| | $R^2$ | $B$ | $P$ |
| GA, wk | 0.145 | 0.088 (0.047) | 0.073 |
| Weight $Z$ score at birth | 0.021 | 0.072 (0.108) | 0.514 |
| PMA at test, wk | 0.076 | −0.209 (0.159) | 0.203 |
| Chorioamnionitis | 0.017 | −0.119 (0.197) | 0.552 |
| Any surfactant | 0.009 | 0.101 (0.238) | 0.675 |
| Mechanical vent., days[a] | 0.002 | −0.005 (0.002) | 0.850 |
| Noninvasive vent., days[a] | 0.043 | −0.006 (0.006) | 0.341 |
| Respiratory support, days[a] | 0.026 | −0.004 (0.005) | 0.467 |
| Oxygen therapy, days[a] | 0.108 | −0.004 (0.002) | 0.125 |
| Any BPD | 0.284 | −0.482 (0.167) | **0.009** |

Bold font indicates statistical significance. BPD, bronchopulmonary dysplasia; $FRC_{mbw}$, functional residual capacity measured by multiple breath washout; GA, gestational age; IC, inspiratory capacity; PMA, postmenstrual age; vent, ventilation; $V_T$, tidal volume. [a]Unstandardized residual vs. gestation.

The univariate regression analyses of $C_L$ and $C_{cw}$ and antenatal and postnatal predictive factors are shown in Table 4. In the univariate regression analysis, BPD explained 27.1% and 26.1% of the variability in $C_L$ and $C_{cw}$, respectively. We then performed a multivariable regression analysis for $C_L$: the sole predictive factor was BPD [$B$ (95% CI): −0.52 (−1.215 to (−0.178)); adjusted $R^2 = 0.236$; $P = 0.011$].

## DISCUSSION

We measured the static mechanical properties of the respiratory system and its components $C_{cw}$ and $C_L$ together with the breathing pattern and lung volumes in preterm infants at 36 wk PMA. Data on chest wall compliance in preterm infants are scarce with available data dating back to the pre-surfactant era (11–13), limiting their relevance to infants born today. The main findings of our study include: *1*) $C_{rs}$ in

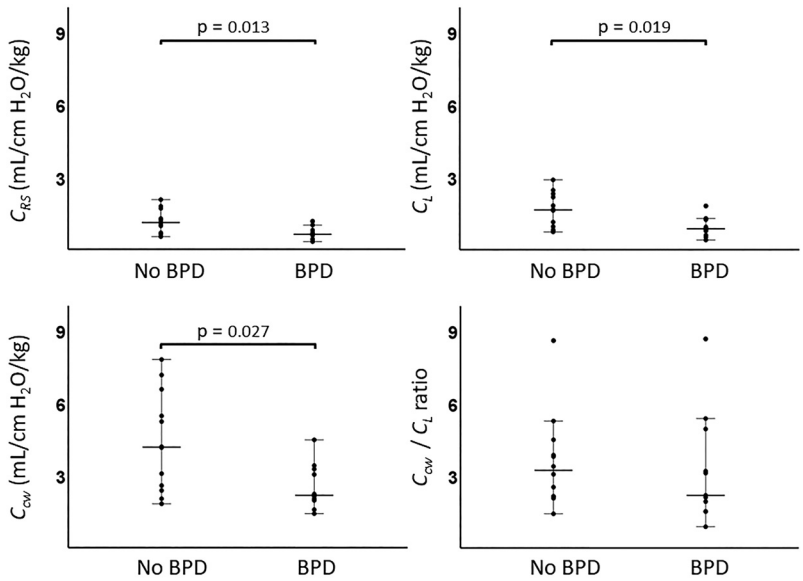


**Figure 2.** Static compliance of the respiratory system ($C_{rs}$), compliance of the lung ($C_L$), and compliance of the chest wall ($C_{cw}$) were statistically significantly lower in infants with bronchopulmonary dysplasia (BPD) compared with infants without BPD (Mann–Whitney $U$). No difference in the $C_{cw}/C_L$ ratio.

**Table 4.** *Univariate associations of normalized lung and chest wall compliance ($C_L$/kg), ($C_{cw}$/kg) with antenatal and postnatal exposures and breathing variables*

| | ($C_L$/kg) | | | ($C_{cw}$/kg) | | |
|---|---|---|---|---|---|---|
| | $R^2$ | *B* | *P* | $R^2$ | *B* | *P* |
| GA, wk | 0.200 | 0.153 (0.067) | **0.033** | 0.058 | 0.223 (0.195) | 0.267 |
| Weight *Z* score at birth | 0.009 | 0.071 (0.160) | 0.662 | 0.030 | 0.344 (0.429) | 0.431 |
| PMA at test, wk | 0.103 | −0.360 (0.231) | 0.135 | 0.016 | −0.377 (0.655) | 0.571 |
| Chorioamnionitis | 0.024 | −0.210 (0.291) | 0.478 | 0.016 | −0.458 (0.788) | 0.567 |
| Any surfactant | 0.000 | −0.024 (0.354) | 0.947 | 0.053 | 1.012 (0.929) | 0.289 |
| Mechanical vent., days[a] | 0.000 | −0.000 (0.013) | 0.985 | 0.012 | −0.017 (0.035) | 0.623 |
| Noninvasive vent., days[a] | 0.048 | −0.009 (0.009) | 0.316 | 0.007 | −0.009 (0.025) | 0.712 |
| Respiratory support, days[a] | 0.037 | −0.007 (0.008) | 0.377 | 0.000 | 0.000 (0.022) | 0.982 |
| Oxygen therapy, days[a] | 0.083 | −0.005 (0.003) | 0.183 | 0.129 | −0.016 (0.009) | 0.092 |
| Any BPD* | 0.271 | −0.696 (0.249) | **0.011** | 0.261 | −1.847 (0.678) | **0.013** |

Bold font indicates statistical significance. BPD, bronchopulmonary dysplasia; GA, gestational age; PMA, postmenstrual age; vent, ventilation. [a]Unstandardized residual vs. gestation; *was the only predictor in the multivariate regression analysis with the outcome variable $C_L$/kg.

infants with BPD is decreased as a consequence not only of a decreased $C_L$ but also of a decreased $C_{cw}$ despite $C_{rs}$ being mainly determined by $C_L$; *2*) the ratio of $C_{cw}/C_L$ is equal between infants with and infants without BPD; and *3*) infants with BPD have a reduced weight adjusted inspiratory capacity (IC/kg) and lung volume ($FRC_{mbw}$/kg) compared with preterm infants without BPD.

Our finding that $C_{cw}$ is three times $C_L$ is in line with the current literature from the presurfactant era (12, 14). We report similar values for $C_{cw}$ as in the studies by Davis et al. (11) in preterm infants and Papastamelos et al. (14) in term infants (2.8 ± 0.9 mL/cm$H_2O$/kg). However, we found lower $C_{cw}$ compared with the observations made by Gerhardt and Bancalari (12) in preterm infants at 36 wk PMA (5.3 mL/cm$H_2O$/kg vs. 3.0 mL/cm$H_2O$/kg). Infants measured in the study by Gerhardt and Bancalari were on average 5 wk more mature at birth (mean gestational age 32.0 wk vs. 27.2 wk gestation). Furthermore, they were measured within 2 wk after birth compared with a mean postnatal age of 9.4 ± 2.3 wk of infants' measurements obtained in our study. These differences are relevant as $C_{cw}$ decreases with increasing PMA (12). Postmenstrual age was not associated with $C_{cw}$ in our cohort, most likely because our infants were measured within a tight range of 2 wk PMA. The difference in gestation is unlikely to explain the lower $C_{cw}$, as the range in gestation in our infants was >8 wk and there was no association between gestation and $C_{cw}$ in our data. In addition, all infants measured in the study by Gerhardt et al. (18) were intubated at the time of the test and none of them received surfactant. Hence, the lower $C_{cw}$ seen in our infants may be the result of several factors including the differences in postnatal age at test, differences in the methodology of the measurements (intubated vs. self-ventilating infants), and differences in the use of surfactant. Moreover, the lower $C_{cw}$ in our infants compared with the infants reported from the pre-surfactant era could be explained by the steadily decreasing incidence of metabolic bone disease in premature infants over the past decades due to advances in enteral nutrition (29).

Chest wall compliance was lower in infants with BPD compared with infants without BPD. However, the $C_{cw}/C_L$ ratio was constant between infants with and without BPD. Previous studies reported a flatter chest seen in infants with BPD compared with infants without BPD at 12 mo corrected age (19, 21). The authors of these studies suggested the flatter chest might be related to a decreased $C_L$ resulting in an indrawing of the rib cage caused by the contraction of the diaphragm (19, 21). We measured the chest circumference in $n =$ 18 infants of our cohort and found no difference between infants with and without BPD that would explain the reduced compliance in infants with BPD. Differences in chest wall structure are also attributed to metabolic bone disease in infants with BPD (19). We did not compare laboratory indices of metabolic bone disease between infants with and without BPD. However, all of the included infants in our study were fed with a milk fortifier to increase cholecalciferol, calcium, and phosphorus intake to prevent metabolic bone disease. Furthermore, the ossification process of the chest wall is not complete at 36 wk PMA and it is unlikely that permanent changes in the chest wall structure are already present (14).

Other possible explanations for a decreased $C_{cw}$ at this young age include altered lung volumes: either a reduction in total lung capacity (TLC) consequent to restrictive lung pathology, or increased FRC as a result of gas trapping. Margraf et al. (30) reported reduced lung internal surface area in infants with BPD in the presurfactant era but did not measure TLC. Apart from this study, we could not find any data on reduced TLC in infants with BPD. Robin et al. (31) found that TLC is comparable between infants with BPD and without BPD older than 8 mo of age. In contrast, several studies suggest the presence of gas trapping in infants with BPD: increases in FRC and residual volume as a percentage of TLC were reported after 8 mo of life (31, 32). A decrease in $FRC_{mbw}$ and higher thoracic area on chest X-rays assessed simultaneously were reported in the first days of life in infants who subsequently developed BPD. The paradoxical finding of a lower $FRC_{mbw}$ and a higher thoracic area on chest X-rays could indicate gas trapping (33). $FRC_{mbw}$ cannot measure trapped gas as the washout techniques only allow measurements of the ventilated lung volume at FRC. One study reported that FRC measured by body plethysmography ($FRC_{pleth}$) was significantly increased in infants with BPD at 36 wk PMA ($P < 0.001$), whereas $FRC_{mbw}$ was decreased in infants with BPD at 36 wk PMA (34). Furthermore, FRC measured by imaging was higher in infants with BPD compared with infants without BPD at 39 wk PMA (35).

We report lower $FRC_{mbw}$/kg in infants with BPD compared with infants without BPD, which is consistent with previous reports (36, 37). However, we also found a lower IC/kg in infants with BPD compared with infants without BPD. A decreased IC/kg indicates increased FRC in infants with BPD, if the hypothesis that TLC is similar between infants with BPD and without BPD holds true. Although the presence of decreased FRC and IC might suggest a lower TLC and smaller chest size in infants with BPD, this explanation is less likely given the chest wall circumference was the same between the two groups. Instead, these findings further support the presence of trapped gas considering that FRC = TLC − IC and that we found a decreased IC/kg in infants with BPD: a reduced communicating lung volume (i.e., the gas that is accessible from the airway opening and measured by gas washout techniques, in our study $FRC_{mbw}$) compared with FRC indicates the presence of noncommunicating (trapped) gas into the lung (38). Similar or slightly decreased $V_T$/kg in infants with BPD are in line with the current literature (36, 37, 39).

$C_{rs}$ and $C_L$ were studied extensively in preterm infants with and without BPD in the pre- and postsurfactant era (3, 9, 19). Our $C_{rs}$ and $C_L$ values are in line with data reported in the literature (40). Moreover, our findings of decreased $C_{rs}$ and $C_L$ in infants with BPD agree with the current literature (8, 40, 41).

Infants with BPD had lower $C_{rs}$, $C_L$, and $C_{cw}$ compared with infants without BPD. However, we could not find any difference in $\dot{V}_E$/kg or $V_T$/kg between the two groups. Following the equation $V_T = \Delta P_{es} \times C$, infants with a lower compliance must generate more pressure than infants with higher compliance to achieve the same $V_T$/kg. We, therefore, conclude that infants with BPD generate greater pressure with their respiratory muscles compared with infants without BPD. These findings are consistent with the increased contractile function of the diaphragm we measured in very preterm infants with BPD compared with very preterm infants without BPD at 36 wk PMA (unpublished data).

Limitations of our study include the small sample size. We were limited to the measurement of 23 infants in this study due to time limitations and recruitment difficulties. We experienced technical difficulties with the measurements of three infants and were unable to analyze their data. We did not have access to body plethysmography to confirm our speculations on trapped gas leading to reduced $FRC_{mbw}$ in infants with BPD. The subdivision of $C_{rs}$ in the lung and chest wall compliance relies on properly estimating pleural pressure by measuring the esophageal pressure. Given the technical challenges of this measure, we cannot exclude measurement errors in some patients despite careful evaluation of the position of the esophageal probe. Moreover, infants with BPD are a heterogeneous group of infants and might have different underlying pathophysiology leading to the same diagnosis. A BPD diagnosis might not be the best criterion to assess differences in compliance in preterm infants. Eventually, we assessed $C_{cw}$ together with the lung function at 36 wk PMA. We have deliberately chosen 36 wk PMA, as it is the time point when infants are assessed for the severity of BPD. However, our results indicate that $C_{cw}$ was high in all infants independent of a BPD diagnosis. Therefore, the assessment of $C_{cw}$ might be best at a later time point, when the ossification process is more advanced.

To our knowledge, we are the first group to report data on static $C_{rs}$, $C_L$, and $C_{cw}$ in preterm infants with and without BPD in the postsurfactant era. Our comprehensive assessment of compliances in relation to tidal breathing parameters and lung volumes enables a thorough understanding of the compliances in very preterm infants with and without BPD.

### Conclusions

We found that the reduced $C_{rs}$ seen in infants with BPD born in the postsurfactant era results not only from structural alterations of the lung but also from a decrease of both $C_L$ and $C_{cw}$. $C_{cw}$ is approximately three times $C_L$: $C_{rs}$ is mainly determined by $C_L$. The lower $C_{cw}$ in infants with BPD could be explained by an increased FRC due to gas trapping rather than by changes in the mechanical properties of chest wall tissues. Nevertheless, the lower $C_{cw}$ adds to the detrimental effects of gas trapping in infants with BPD by increasing the work of breathing. The prolonged dependency on respiratory support in infants with BPD compared with infants without BPD might be a reflection of the increased work of breathing in these infants.

## DATA AVAILABILITY

Data will be made available upon reasonable request.


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Figure 1 and graphical abstract created with BioRender and published with permission.

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## DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

## AUTHOR CONTRIBUTIONS

B.S., J.J.P., and R.L.D. conceived and designed research; B.S. and Y.J.C. performed experiments; B.S. and C.V. analyzed data; B.S., C.V., Y.J.C., J.J.P., and R.L.D. interpreted results of experiments; B.S. and C.V. prepared figures; B.S. and C.V. drafted manuscript; B.S., C.V., Y.J.C., J.J.P., and R.L.D. edited and revised manuscript; B.S., C.V., Y.J.C., J.J.P., and R.L.D. approved final version of manuscript.

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