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How to personalise ventilation of infants with congenital diaphragmatic hernia? A simulation study

Barbara Stankiewicz[1*], Magdalena Mierzewska-Schmidt[2], Krzysztof J. Pałko[1], Marek Darowski[1] and Maciej Kozarski[1]

Abstract

Background We aim to develop a non-invasive, bed-side method for supporting personalised ventilation of neonates with congenital diaphragmatic hernia (CDH). Currently, there are no CDH severity measures to do it. As ventilation inhomogeneity (VI) resulting from lung hypoplasia is highly variable in CDH patients, mechanical ventilation is a real challenge and the risk of lung injury is high.

Methods We conducted 250 simulations of conventional ventilation of CDH cases using the infant hybrid (numerical-physical) respiratory simulator and a ventilator. Utilising simulation results, we searched for a regression model describing patient ventilation parameters as a function of the respiratory system parameters, ventilator settings and two new CDH severity measures: VI-degree defined as a ratio of time constants ratio of the contralateral and ipsilateral lung (T_1/T_2) and chest-wall-to-lung compliance ratio (C_W/C_L). The regression model aimed to find the T_1/T_2 and C_W/C_L values for real CDH cases and estimate optimal, matched to VI-degree, peak inspiratory and mean airway pressure (PIP, MAP).

Results The developed regression models ($R^2 = 0.78 \div 0.98$; $P < 0.001$) enabled to find clinically hard-to-measure values of T_1/T_2 and C_W/C_L ratios for three patients, respectively: 9 and 6.52 (P_1), 3.5 and 4.96 (P_2), and 4 and 5.02 (P_3). The T_1/T_2 and C_W/C_L correlated with defect size (gamma coefficient: 1; $P < 0.05$), duration of mechanical ventilation and hospitalization (Spearmen's coefficient: 0.99; $P < 0.01$). The clinical and estimated PIP and MAP didn't differ statistically.

Conclusion The T_1/T_2 and C_W/C_L indices can help to personalize CDH infants' ventilation and might be used for prognostication.

Keywords Hernia, Diaphragmatic, Congenital, Ventilation inhomogeneity, Ventilator-Induced lung injury

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Background

Congenital diaphragmatic hernia (CDH) is a rare (26/10,000 births), severe disease with long-term morbidities and high mortality rate (~38%,), especially in the first week of life [1].

There are many potential predictors of CDH severity, but none is perfect [2]. Those predictors include hernia side (left/right) [3], defect size (A-D) [3, 4], liver position (abdomen/ thorax), the necessity for patch-repair, LHR (lung-to-head ratio) and o/e LHR (observed-to-expected LHR) [5, 6]. They are considered good indicators of the probability of survival, short- and long-term morbidities [6–8] or worse lung function in the future [8–11]. However, the efficacy of all these CDH severity measures is limited and more importantly, does not translate into individualised ventilator therapy guidelines [12–14], whereas mechanical ventilation is a crucial part of therapy of CDH newborns. Lung hypoplasia and ventilation inhomogeneity (VI) make these neonates especially prone to ventilator-induced lung injury (VILI) [12, 15, 16]. The first-line therapy recommended by the American Pediatric Surgical Association (APSA), CDH Euro Consortium and Canadian CDH Collaborative [13, 14] is conventional mechanical ventilation (CMV). There are only general recommendations concerning protective, gentle CMV, with limited peak inspiratory pressure (PIP = 25±2 cmH_2O), but not considering the severity of CDH and resulting problems in an individual patient. Because ventilation inhomogeneity is highly variable in different CDH cases and bed-side methods of VI assessment are scarce we would like to fill the gap by introducing a novel, non-invasive method of VI measurement in the hope to be able to adjust ventilation parameters to the needs of an individual baby.

In one-sided CDH, VI is mainly due to the fact that the ipsilateral lung is usually smaller and more hypoplastic than the contralateral one. Therefore, both lungs have different resistive-compliant properties as well as time constants. Based on that, we proposed a new VI index that is a ratio of time constants (T_1/T_2) of the contralateral (T_1) and ipsilateral lung (T_2). The time constant of a lung is a product of multiplying peripheral airway resistance by lung compliance.

The purpose of this study was to present the idea of personalised (optimal) conventional mechanical ventilation in one-sided CDH infants. We hope that an application of this method, when it is fully developed, might result in shortening of the mechanical ventilation, possibly also length of hospitalization stay and reduce the need for extracorporeal membrane oxygenation (ECMO) therapy.

Firstly, we hypothesised, that a mathematical regression model, describing patient ventilation parameters as a function of the respiratory system parameters, ventilator settings and two new CDH severity measures, enable:

- to find VI degree - time constant ratio of the contralateral to ipsilateral lung and the chest-wall-to-lung compliance ratio (C_w/C_L) for real ventilated patients;
- to estimate optimal, i.e. matched to the VI degree, pressure levels in the patient-ventilator system (PIP - peak inspiratory pressure, MAP - mean airway pressure) and the work done by a ventilator (WOB_{vt});

Secondly, we hypothesised that the new CDH measures (VI degree and C_W/C_L) correlate with the defect size, duration of mechanical ventilation and hospital stay, liver position (down/up) and o/e LHR (observed-to-expected lung-to-head ratio).

The regression models were intended to find some hidden mechanical parameters of the respiratory system in one-sided CDH infants, e.g. VI degree and C_W/C_L. These parameters may play crucial roles in terms of successful personalised CMV.

We also wanted to check if there is any association between driving pressure as a recognised factor of VILI risk in CDH infants and the new VI-degree index and C_W/C_L ratio. Finding such a relationships, even considering that this is just the first preliminary approach to this issue, might confirm the importance of the new CDH severity measures and indicate future study directions.

Methods

Respiratory system model

The structure of the respiratory system model used for the study purposes was presented in Fig. 1.

Study design

To test the study hypotheses and assess the values of the T_1/T_2 and C_W/C_L indices in three CDH cases (taken from [17]), a regression model of ventilation parameters as a function of patient respiratory system and ventilator settings had to be found. It required creation of a large enough database of all these parameters. It was realised by collecting data from laboratory simulations.

To verify study results and analyse the usefulness of the T_1/T_2 index as a VI measure, we compared the ventilation parameters (PIP, MAP, Z, WOB_{vt}) of three CDH cases with the estimated parameters based on multiple and non-linear regression models. We also searched for the correlation between the T_1/T_2 index and other well-known CDH severity indices: the defect size, o/e LHR, liver position, duration of mechanical ventilation and length of hospital stay.

The flow-chart of study design (Fig. 2) shows how clinical data were used to set conditions of laboratory

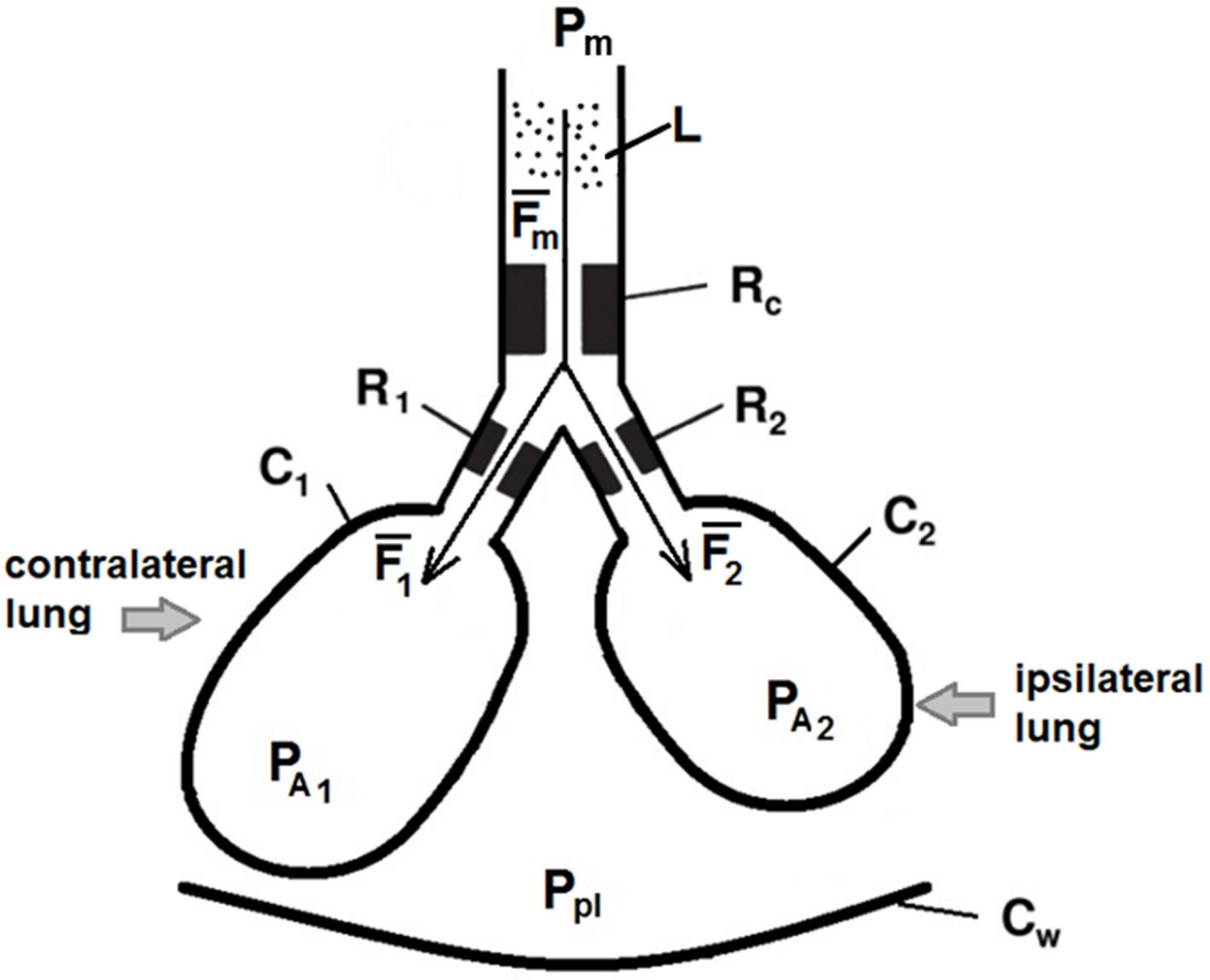

Fig. 1 Respiratory system model – numerical part of the Infant Hybrid Respiratory Simulator (IHRS). R_c - central airway resistance L - gas inertance, R_1, R_2 - peripheral airway resistance of the contralateral and ipsilateral lung, C_1, C_2 - compliance of the contralateral and the ipsilateral lung, C_W – chest wall compliance. F_m, F_1, F_2 – gas flow in central airway, contralateral and ipsilateral lung. P_m – airway pressure at the respiratory system inlet. P_{A1}, P_{A2}, P_{pl} – alveolar pressure in the contralateral and ipsilateral lung and pleural pressure, respectively. T_1 - time constant of the contralateral lung, T_2 – time constant of the ipsilateral lung; $T_1 = R_1 \cdot C_1$, $T_2 = R_2 \cdot C_2$. The T_1/T_2 index of ventilation inhomogeneity degree calculated as a ratio of T_1 and T_2

simulation, and how simulation data were utilised in regression models. The role of independent variables in the searched regression models was assigned to the mechanical parameters of the respiratory system and ventilator settings. Among the respiratory system parameters we chose:

- total dynamic resistance (R_{rs}) and total dynamic compliance (C_{rs}), as key mechanical parameters of the respiratory system, measured by the ventilator under clinical conditions;
- the chest-wall-to-lung compliance ratio (C_W/C_L) and the T_1/T_2 index of lung inhomogeneity; their different values were hypothetically assumed during laboratory simulations to realize study purposes.

We chose some of the ventilator settings, namely: the respiratory rate (RR) and positive end-expiratory pressure (PEEP) as input parameters. We omitted I: E (inspiratory-to-expiratory-time ratio) and minute ventilation (MV) because they were approximately constant in the clinic and during laboratory simulations.

Patients' demographic data was taken from [17]. They are presented in detail in an additional file [see Additional file 1, Table A1_1].

Simulations

These data were collected by simulations of conventional mechanical ventilation of CDH infants, realised by use of the set-up consisted of the Infant Hybrid Respiratory Simulator (IHRS; IBBE, PAS, Warsaw,

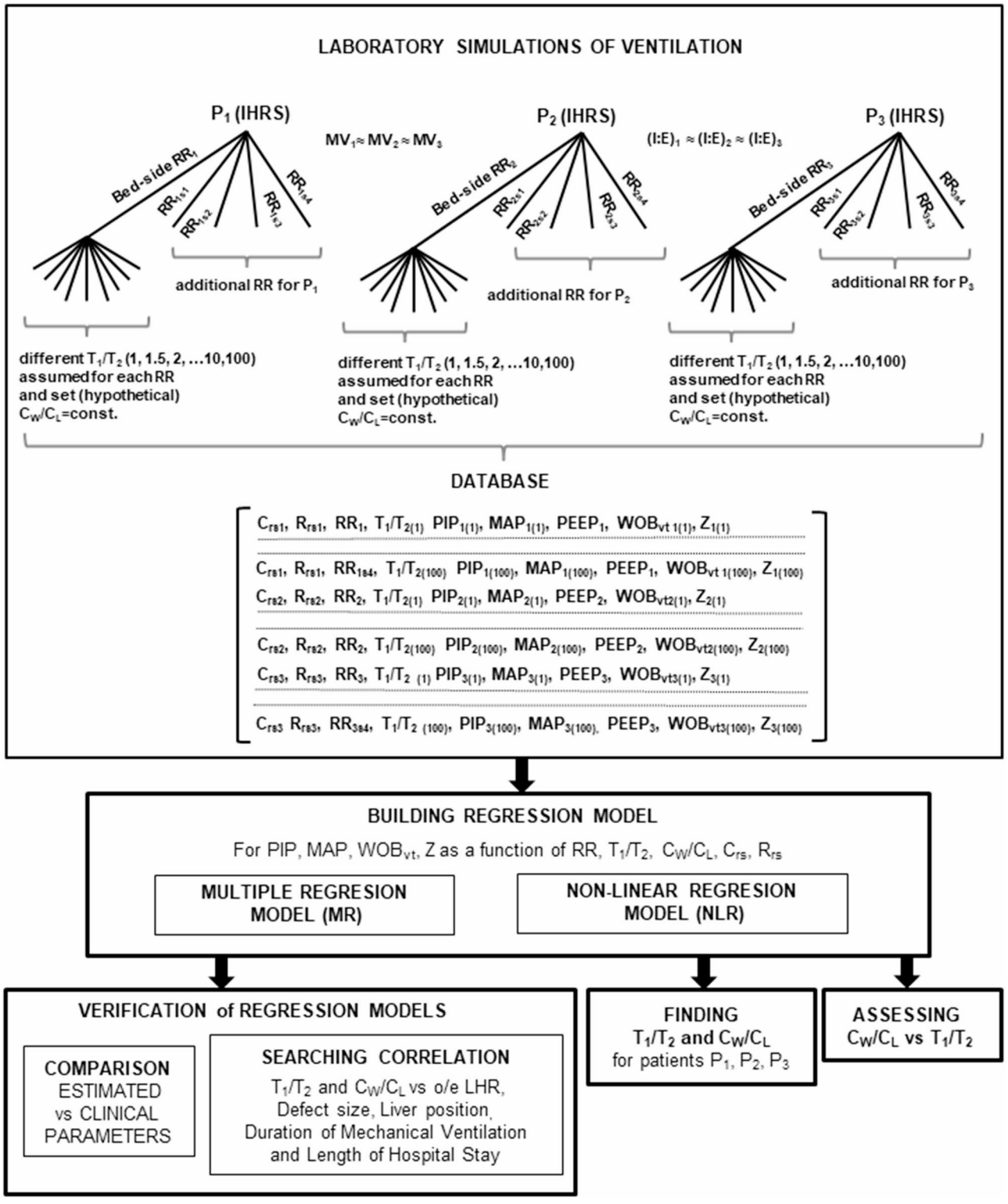

Fig. 2 Flowchart of the study design. P_1 (IHRS), P_2 (IHRS), P_3 (IHRS) – patients from [17] simulated using Infant Hybrid Respiratory Simulator (IHRS), of the same total airway resistance (R_{rs}) and respiratory system compliance (C_{rs}) as real patients. RR – respiratory rate, MV - minute ventilation, I:E – inspiration to expiration time ratio, PEEP – positive end-expiratory pressure, PIP – peak inspiratory pressure, MAP – mean airway pressure, Z – respiratory system impedance, WOB_{vt} – work of breathing done by ventilator, T_1/T_2 – time constants ratio of contralateral and ipsilateral lung, C_W/C_L – chest-wall-to-lung compliance ratio

Poland) [18], the Puritan Bennett 840 Ventilator (Medtronic, Fridley, MI, USA) and NICO 7300 monitor (Novametrix Medical Systems Inc., Wallingford, USA) connected to tablet computer (Fig. 3). IHRS was designed based on LabVIEW Real-Time Professional Development System 2013 (National Instruments Co., Austin, TX, USA).

We performed the simulated pressure-controlled ventilation of CDH infants (2, 2.6, 3.6 kg) taken from [17]. The ventilator settings were as follows: minute ventilation of 0.8 ± 0.1 L, inspiration-to-expiration-time ratio (I: E) of 1:2, respiratory rate (RR) of $40 \div 55$ bpm, and positive end-expiratory pressure (PEEP) equal to 4, 6 and 5 cmH_2O, for different T_1/T_2 index values ($1 \div 10$, 100). Peak inspiratory pressure (PIP), mean airway pressure (MAP), respiratory system impedance (Z) and work of breathing done by the ventilator (WOB_{vt}) were the measured dependent variables In total, about 5,000 samples (observations) were collected in 250 experiments.

Statistical methods

Within the study, we applied several statistical tests utilizing STATISTICA (data analysis software system), version 10; 32 www.statsoft.com). We performed the Shapiro-Wilk normality test and Leven's variance homogeneity test to choose the appropriate test. In effect, we picked the following non-parametric tests for the comparative analysis: Friedman's ANOVA, ANOVA Kruskal-Wallis, Wilcoxson's and signed rank test. In further paragraphs we indicated which test we used in a given case. Then, we calculated a determination coefficient (R^2) of the equations fitted to found dependencies, and also Spearman's (R_s) and gamma (γ) correlation coefficients with corresponding *P-value* of significance. In all performed tests, a $P < 0.05$ was considered statistically significant.

To create a regression model, we used the "Multiple Regression" (the linear model for many parameters) and the "Non-linear Estimation (Levenberg-Marquardt method) with the "User Regression Function with the least squares method as the loss function". Within the regression model assessment, the R^2 determination coefficient was calculated; it indicates the percentage of variability of the dependent variable (Y) explained by the model (e.g. if $R^2 = 0.9$, the model explains this variability in 90%). Additionally, the standard error of the mean (SEM) and 95% CI (confidence intervals) for each model coefficient was calculated with the corresponding P-level. We also tested the redundancy of independent variables and interrelationships.

Regression models

Parameters of multiple regression (MR) and non-linear Regression (NLR) model describing PIP, MAP, Z and WOB_{vt} as a function of the T_1/T_2 index, RR, C_{rs}, R_{rs} and the C_W/C_L ratio, were found using STATISTICA.

The equation of the multiple regression model (Eq. 1) and the non-linear regression model (Eq. 2) are as follows:

$$Y = b_0 + b_1 \cdot \left(\frac{T_1}{T_2}\right) + b_2 \cdot \left(\frac{C_W}{C_L}\right) + b_3 \cdot RR + b_4 \cdot C_{rs} + b_5 \cdot R_{rs} \pm SE_{Est} \quad (1)$$

$$Y = b_0 + b_1 \cdot \left(\frac{T_1}{T_2}\right)^2 + b_2 \cdot \left(\frac{T_1}{T_2}\right) + b_3 \cdot \left(\frac{C_W}{C_L}\right) + b_4 \cdot (RR)^2 + b_5 \cdot RR + b_6 \cdot {C_{rs}}^2 + b_7 \cdot C_{rs} + b_8 \cdot R_{rs} \quad (2)$$

where: Y is PIP, MAP, Z or WOB_{vt}, b_0,...b_n are coefficients of regression model, T_1/T_2 is an index of lung inhomogeneity, C_W/C_L is the ratio of the chest wall compliance to lung compliance, RR is respiratory rate, R_{rs} is total airway resistance of respiratory system, C_{rs} stands for the total compliance of the respiratory system and SE_{Est} stands for the standard error of estimation.

The values of the C_W/C_L ratio were obtained analytically based on the non-linear regression model equation (Eq. 2), by solving the set of equations of PIP, MAP,

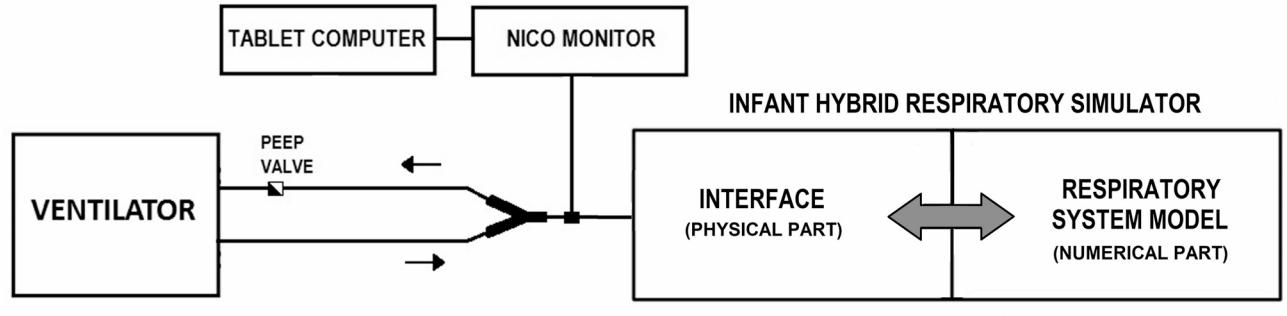

Fig. 3 The study set-up. The numerical part of the simulator interacts with the physical interface enabling the cooperation with a ventilator. NICO monitor with the Tablet Computer to collect respiratory data

Z and WOB_{vt}, at constant values of C_{rs}, R_{rs} and T_1/T_2, separately for each respiratory rate (RR); see supplement (Additional file 1).

Subsequently, the functional dependencies between the C_W/C_L ratios and the T_1/T_2 index of VI-degree were searched for each RR (40, 45, 50 and 55 bpm). Then, determination coefficient (R^2) and Spearman's correlation coefficient (R_s) were found for these dependencies.

Inhomogeneity extent versus C_W/C_L

Based on the data taken from the study by Cressoni et al. [19], we search for the dependency between lung inhomogeneity extent (IE) and the ratio of chest wall (C_W) and lung compliance (C_L). In the mentioned study, the changes in chest wall elastance (E_w=1/C_w) and lung elastance (E_L=1/C_L) were examined before and after VILI in 12 piglets. IE (% of lung volume) was assessed from CT scans conducted before and within 20 h after VILI. The obtained relationship of IE vs. C_W/C_L was approximated by a curve equation with the R^2 determination coefficient.

This part of the study was aimed to evaluate the obtained results and to show the similarity of dependencies: T_1/T_2 vs. C_W/C_L in CDH and IE vs. C_W/C_L in ARDS [19].

Assessment of VI-degree and C_W/C_L in clinical cases

Based on the equation Eq. 2 of the non-linear regression (NLR) model and found model coefficients (b_0,..., b_n), we searched for the pairs of T_1/T_2 (VI degree) and C_W/C_L ratio for three CDH patients (P_1, P_2, P_3) from [17] by solving the set of two equations for two output variables (PIP and MAP) with two unknowns (T_1/T_2 and C_W/C_L). The PIP or MAP played the role of Y in Eq. 2. The values of PIP, MAP, R_{rs}, C_{RS} and RR were the bed-side measured parameters values [17]. A separate set of equations was solved for each patient.

Comparison of estimated and clinical parameters

The estimated and clinical parameters of ventilation: PIP-PEEP, MAP and Z were compared using Friedman's ANOVA test, whereas WOB_{vt} received from NLR and MR models using signed rank test and Wilcoxson's test; WOB_{vt} was measured only under laboratory conditions [17].

Driving pressure

The value of PIP-PEEP served as an approximation of driving pressure ($\Delta P = P_{plat}$-PEEP). The plateau pressure (P_{plat}) is rarely observed in newborns due to high RR. It was not determined at the bed-side; the data were collected retrospectively [17]. We compare the ΔP in patients P_1, P_2 and P_3, using the ANOVA Kruskal-Wallis test.

Correlations of T_1/T_2 and C_W/C_L with other CDH severity indices

Finally, we searched for the correlation between T_1/T_2 and C_W/C_L vs. different recognised measures of CDH severity: the size of the defect (A-D) [8], the duration of mechanical ventilation (days), hospital stay (days), and two prenatal predictors: liver position (down/up) and o/e LHR (observed-to-expected lung-to-head ratio, in %). These CDH severity measures are considered the most reliable and predictive regarding to mortality, morbidities, need of FETO (fetoscopic endotracheal occlusion procedure) or ECMO use. The obtained dependencies were fitted with linear or polynomial functions, described by the determination coefficient (R^2). Moreover, Spearman's (R_s) and gamma (γ) correlation coefficients were assessed.

Searching for the correlations of T_1/T_2 and C_W/C_L with known CDH severity measures served as a test evaluating the research hypothesis. High and significant correlation coefficients (R_s>0.5, $P<0.05$) would mean the hypothesis is true and would indicate successful verification of the T_1/T_2 and C_W/C_L values obtained for the patients and preliminary confirmation of their clinical relevance.

Results

The proposed non-linear regression model explains the PIP and MAP variability in 92%, the WOB_{vt} - in 88% and the Z - in 98% ($R^2 = 0.88 \div 0.98$, $P<0.001$), while the multiple regression model - respectively in 92, 79, 78 and 92% ($R^2 = 0.78 \div 92$, $P<0.001$). The b_0,..., b_n coefficients of the MR model (Eq. 1) and NLR model (Eq. 2) with P-levels of significance, standard errors and confidence intervals (NLR model) are presented in detail in an additional file [see Additional file 2, Table A2_1 and Table A2_2].

The relationships of the C_W/C_L ratio vs. the T_1/T_2 index for different RR received based on our simulations are shown as coloured solid curves in Fig. 4. This figure also presents a dependency between the C_W/C_L ratio and IE (inhomogeneity extent as a % of lung volume) we found based on clinical data taken from the animal study of Cressoni et al. [19]. The dependencies: C_W/C_L vs. T_1/T_2 and C_W/C_L vs. IE have been approximated with the natural logarithm curves; $C_W/C_L = A \ln(T_1/T_2) + B$ ($R^2 = 0.84 \div 98$, $P<0.001$); $C_W/C_L = A \ln(IE) + B$ ($R^2 = 0.95$, $P<0.01$). The equations coefficients (A, B) and Spearmen's correlation coefficients (R_s) are shown in detail in an additional file [see Additional file 2, Table A2_3].

The developed regression model, the C_W/C_L vs. T_1/T_2 dependency and the values of ventilation parameters (PIP, MAP) collected from three CDH infants (P_1, P_2, P_3) [17] enabled us to find the pairs of T_1/T_2 and C_W/C_L for three patients: 9 and 6.52 (P_1), 3.5 and 4.96 (P_2), and 4 and 5.02 (P_3).

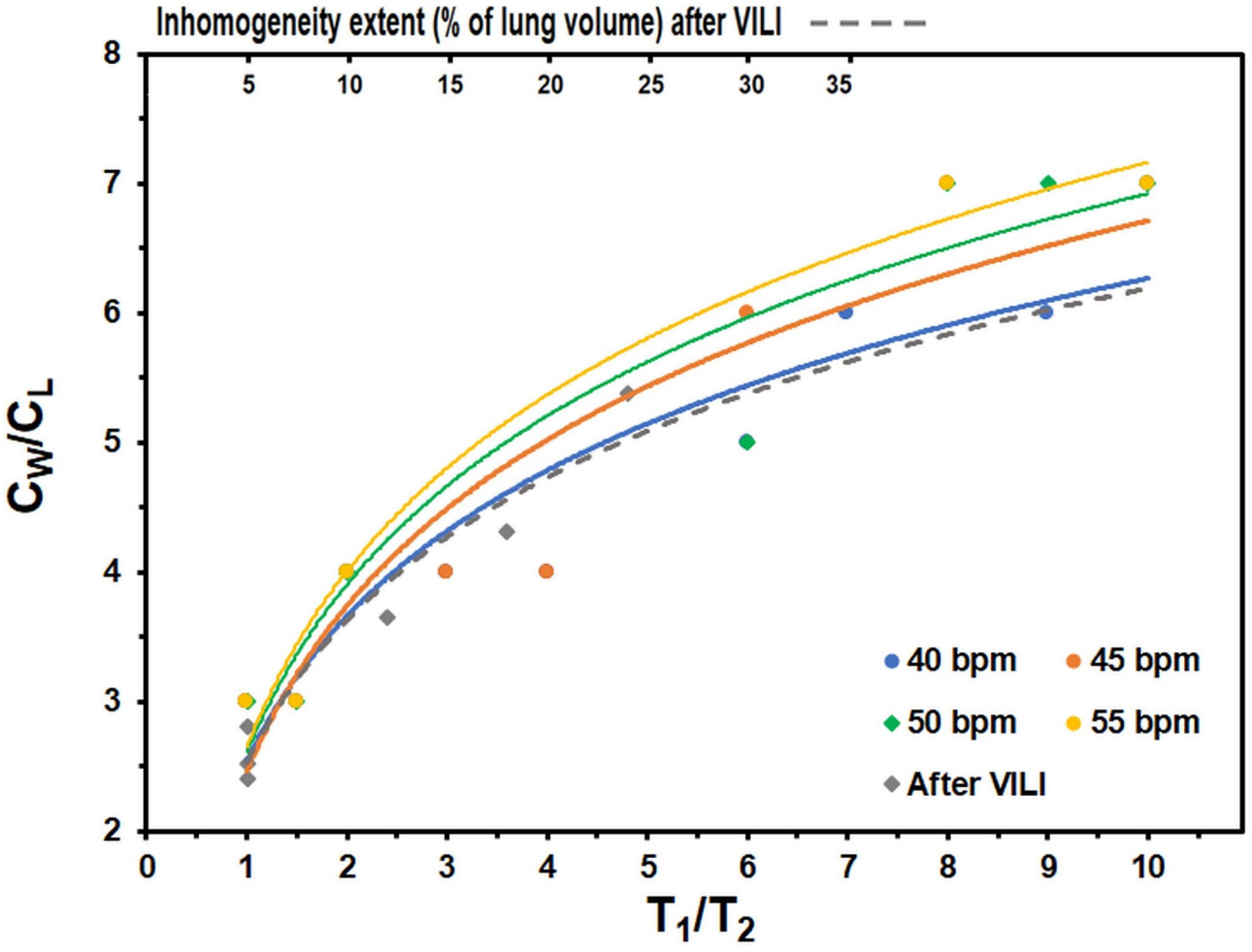

Fig. 4 Chest-wall-to-lung compliance ratio (C_W/C_L) vs. ventilation inhomogeneity. Coloured lines - simulation results, dashed grey line (After VILI) – animal study results found based on [19]. VILI – ventilator-induced lung injury. T_1/T_2 – time constants ratio. IE - inhomogeneity extent assessed based on CT scans. 40, 45, 50 and 55 bpm - respiratory rates

The Friedman ANOVA and Wilcoxon's tests indicated that the estimated (MR) and (NLR) and bed-side ventilation parameters (BSVP) didn't differ statistically (for PIP-PEEP: $p = 0.264$, MAP: $p = 0.717$, Z: $p = 0.097$ and WOB_{vt}: $p = 0.285$; Fig. 5).

Then, the ANOVA Kruskal-Wallis test showed significant difference in PIP-PEEP between patients ($P < 0.05$). Similarly, significant differences between patients were found for the T_1/T_2 and C_W/C_L indices ($P < 0.05$). Then, the Spearman's correlation coefficients for dependencies PIP-PEEP vs. T_1/T_2 and PIP-PEEP vs. C_W/C_L amounted R_s=0.949 ($P < 0.001$).

Finally, we checked the existence of any correlations between the T_1/T_2 index, C_W/C_L ratio and other known severity indices of CDH. These measures were: the defect size, duration of mechanical ventilation, length of hospital stay, and two indices assessed prenatally: o/e LHR and liver position. As a result we found correlations between the T_1/T_2 index, the C_W/C_L ratio and all mentioned CDH severity indices, but not all of them were significant. Significant and high correlations were obtained for the T_1/T_2 and C_W/C_L vs. the defect size ($\gamma = 1$, $P < 0.05$) (Fig. 6a-b), duration of mechanical ventilation (R_s=0.995, $P < 0.01$) and length of hospital stay (R_s=0.998 ÷ 0.999, $P < 0.005$); Fig. 6c-d.

High but non-significant correlations were received for dependencies between the T_1/T_2 index, the C_W/C_L ratio vs. o/e LHR (R_s=-0.833, $p = 0.373$; R_s=-0.937, $p = 0.228$; γ=-1, $p = 0.117$) and liver position (R_s=0.894, $p = 0.106$; $\gamma = 1$, $p = 0.096$).

Discussion

The proposed regression models enabled to estimate ventilation parameters of real CDH infants. The estimated and clinical parameters did not differ statistically. Based on the non-linear regression model (NRL) we assessed the values of T_1/T_2 and C_W/C_L for the mentioned real patients. The pairs of T_1/T_2 and C_W/C_L found for three

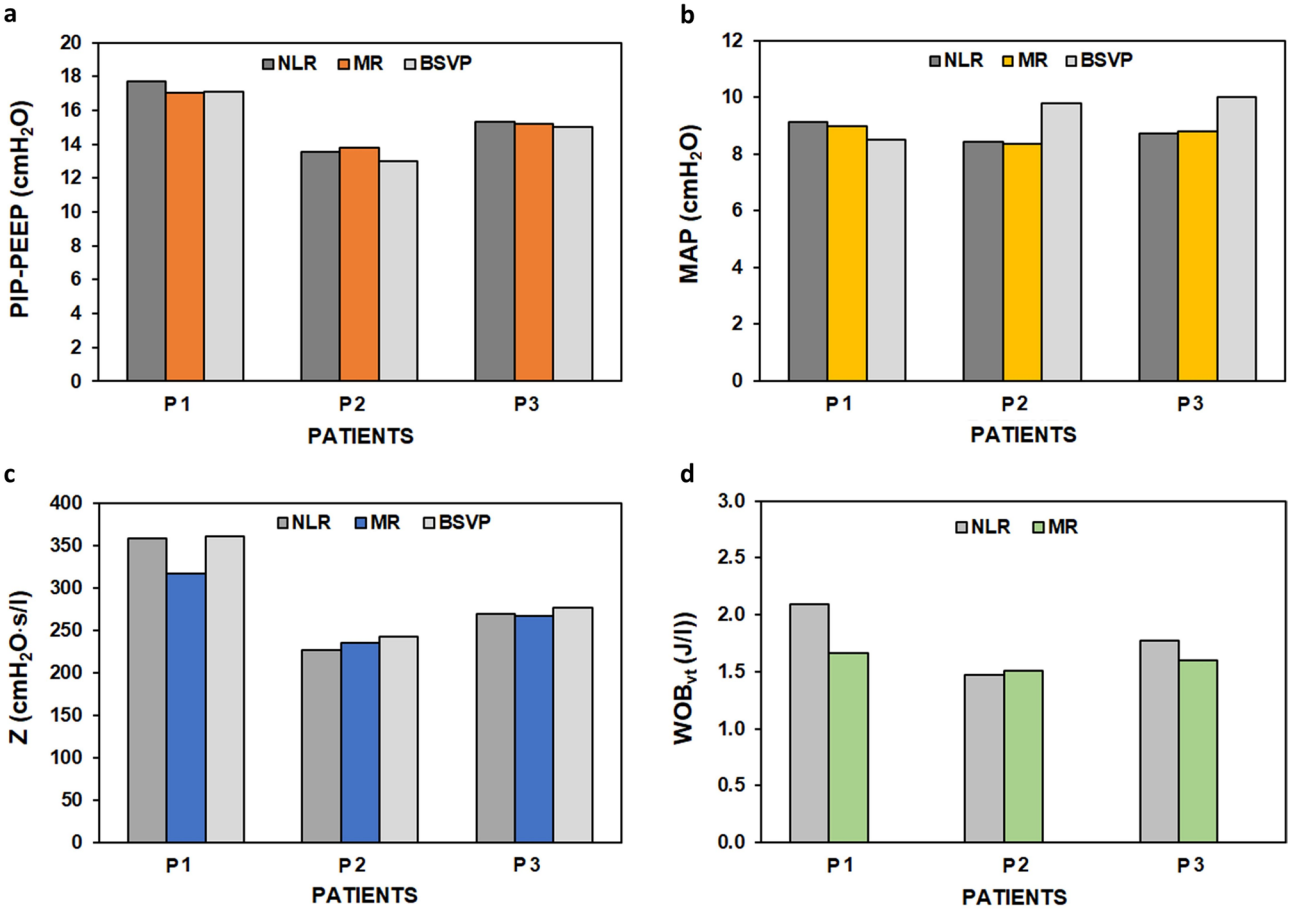

Fig. 5 Comparison of the estimated and clinical ventilation parameters. NLR - non-linear regression model, MR – multiple regression model, BSVP – bedside ventilation parameters form [17]. PIP-PEEP - the difference between peak inspiratory pressure and positive end-expiratory pressure (≈ driving pressure) (**a**), MAP - mean airway pressure (**b**), Z - respiratory system impedance (**c**), WOB_{vt} – work of breathing (**d**); clinically not measured. The differences in PIP-PEEP, MAP, Z and WOB_{vt} between the MR, NLR and BSVP were insignificant ($p = 0.264$, 0.717, 0.097 and 0.285, respectively). The difference in PIP-PEEP and Z between patients was significant ($P < 0.05$); whereas in MAP and WOB_{vt} it was insignificant ($p = 0.561$ and $p = 0.156$, respectively)

CDH infants taken from [17] were as follows: 9 and 6.52 (P_1), 3.5 and 4.96 (P_2), and 4 and 5.02 (P_3) respectively. We found that the high and significant correlations between T_1/T_2 and C_W/C_L vs. defect size, mechanical ventilation and hospital stay indicate that the research hypothesis is true and mean successful verification of the T_1/T_2 and C_W/C_L values found for clinical cases.

On the other hand, the correlations between the T_1/T_2 index and C_W/C_L ratio vs. o/e LHR and liver position were found insignificant. It would mean the hypothesis was not true. However, high values of correlation coefficients may indicate that it was rather due to the small sample of clinical cases.

The C_{rs} in CDH infants can be several times lower compared to the healthy ones [20, 21], and it usually decreases after surgery [6, 20, 22]. The relationship between the elastic properties of the lungs, the chest-wall and the respiratory system ($1/C_L$, $1/C_W$, $1/C_{rs}$) and the ongoing lung structure deterioration after VILI was shown in the animal study [19]. The lung deterioration was associated with an increase in the inhomogeneity extent (IE, in % of lung volume) visible in CT scans, and the decrease of C_{rs} and C_L, whereas the C_W increased. In effect, the C_W/C_L ratio raised from 2.5 at the baseline to 5.37 when symptomatic pulmonary oedema developed. Then, the increase in inhomogeneity extent (IE) was connected with the elevation of the C_W/C_L ratio (Fig. 4). The relationship of the C_W/C_L vs. IE can be described by the equation of $A \cdot \ln(x) + B$ analogous to the dependencies of C_W/C_L vs. T_1/T_2 obtained for different RR (40 ÷ 55 bpm). The coherence of Cressoni et al. [19] and ours studies' results indicates that the T_1/T_2 index seems to be appropriate measure of lung inhomogeneity degree, when the difference in time constants between lungs is significant, like in one-sided CDH.

Cressoni et al. [23] noticed that the inhomogeneity extent (IE) increased with ARDS severity; from 14±5% (mild ARDS) to 23±10% (severe ARDS). In healthy subjects, the IE attained 5±2% of lung volume. Similarly, as IE was positively correlated with ARDS severity [23], $T_1/$

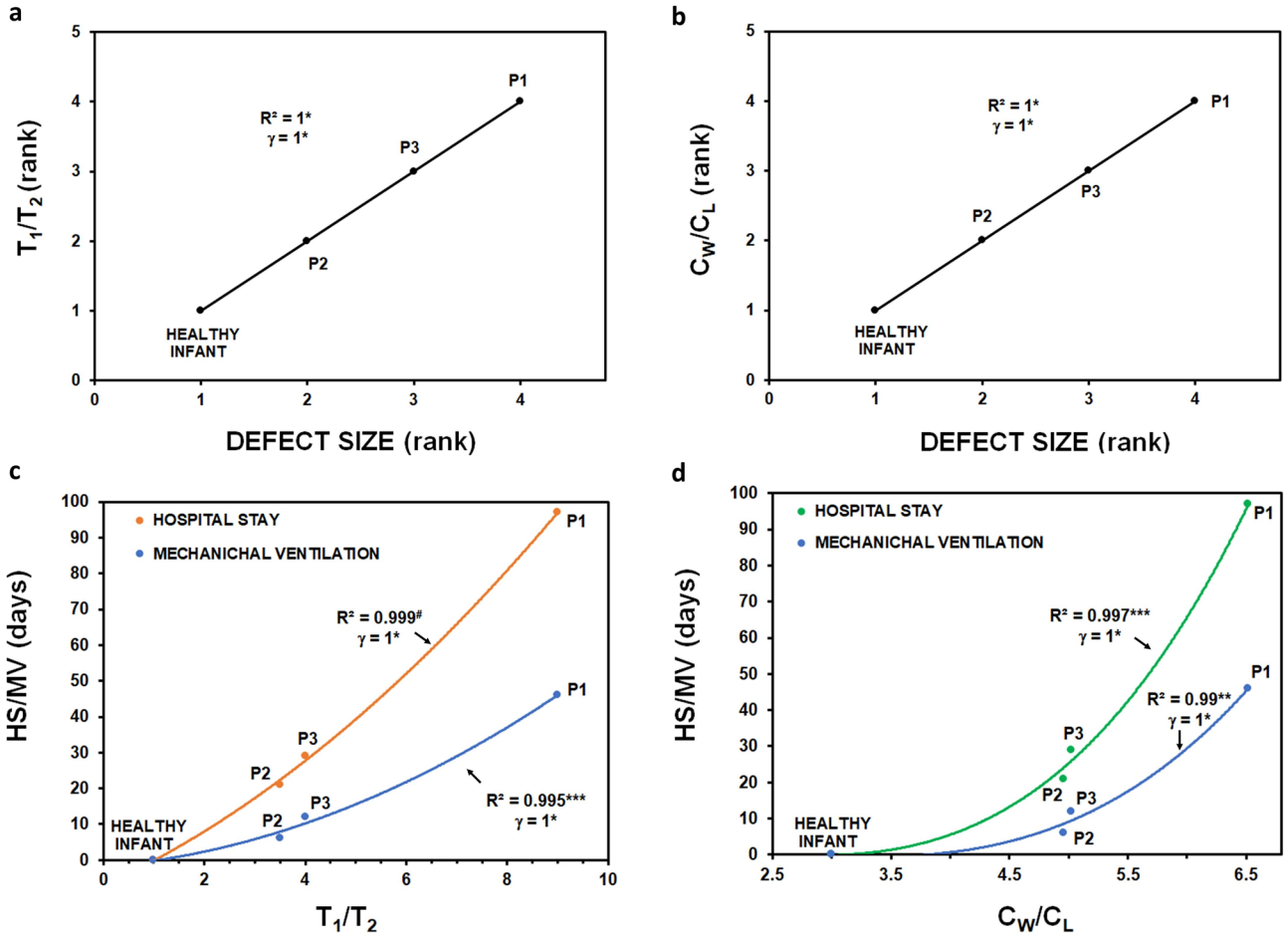

Fig. 6 Relationships between new and currently used CDH severity indices. The T_1/T_2 - ventilation inhomogeneity degree. C_W/C_L – chest-wall-to-lung compliance ratio. The T_1/T_2 and C_W/C_L vs. defect size (**a, b**), duration of mechanical ventilation (MV) and hospital stay (HS) (**c, d**). P_1, P_2, P_3 – patients. R^2, γ – determination and gamma correlation coefficient, respectively.*$P < 0.05$, **$P < 0.01$, ***$P < 0.005$, #$P < 0.001$

T_2 was positively correlated with CDH severity (defect size, duration of mechanical ventilation and hospitalization). The IE raise correlated with physiological dead space (V_D) increase ($R^2 = 0.34$, $P < 0.001$) [20], which is an effect of the elevated $\dot{V}/Q$ mismatch [24]. In CDH patients, perfusion may decrease and deteriorate over time, leading to a raise in the $\dot{V}/Q$ ratio of the ipsilateral lung [17, 25]. The raised V_D/V_T ratio was observed in the most severe CDH cases [26].

As far as CDH severity measures are concerned, according to the study by Partridge et al. [27] on 226 CDH patients (154 long-term survivors), intrathoracic liver position and requirement for patch repair were significantly increased in non-survivors ($P < 0.001$). Similarly, Takayasu et al. [6], analysing 20-years of experience of a single centre (49 CDH children) found that 50% of the patients with liver-up and 36% with patch repair had long-term complications. Also, Brandt et al. [11], who summed up 16 years of CDH infants' treatment (66 cases), stated that a liver was up in 51% of survivors and 80% of non-survivors.

Our three patients [17] were diagnosed with left-sided CDH of various severity (defect size B, C and C/D, Table A1_1). Based on o/e LHR values, the patients might have been classified as moderate (26–35%) and severe (15–25%) [8, 10]. Two of them, P_1 and P_3, had the liver in the thorax, and were qualified to patch repair. Patient P_1 was the most severe case of the three, with o/e LHR = 21% and defect size C/D. It is evaluated that for CDH infants with o/e LHR < 25% or liver-up, survival is less than 25% [10].

The assessed T_1/T_2 index of VI for P_1 was 9, whereas the C_W/C_L ratio was 6.52. We found correlations between these two indices and the duration of mechanical ventilation and hospital stay (R_s=0.995, $P < 0.01$ and R_s=0.998 ÷ 0.999, $P < 0.005$, respectively; Fig. 6c-d). Patient P_1 was mechanically ventilated for 46 days and hospitalised for 97 days. It was three times longer than P_3 which did not correspond with his o/e LHR = 28%, that was similar to P_1. However, the $T_1/T_2 = 4$ and $C_W/C_L = 5$ found for P_3 well correlated with the duration of mechanical ventilation (12 days) and hospital stay (29 days). We

also observed high correlation of the defect size with the T_1/T_2 and C_W/C_L (Fig. 6a-b); $\gamma = 1$, $P < 0.05$.

As shown in the cohort multicentre study [8], the median duration of mechanical ventilation and length of hospital stay in CDH infants with defect size "D" were 30 (IQR: 22–50) days and 89 (IQR: 64–132) days whereas with defect size "C": 22 (IQR: 14–34) days and 62 (IQR: 39–96) days, respectively. In the study [17], patient P_1 with the defect size "C/D" was ventilated for 46 days and discharged home at the age of 97 days, so he fitted in the ranges indicated in the above-mentioned cohort study [8]. The infant P_3 was ventilated for 12 days and discharged home at 29 days. It means that defect size should be assessed rather as "B/C" than as "C" because the duration of mechanical ventilation is within the IQR determined for "C" defect size [8], whereas the length of hospital stay fits the range for "B" defect size. It would be in concordance with the observation that CDH infants with the largest defects (C, D) require mechanical ventilation two or three times longer than those with A and B defects, respectively [8].

Finally, the baby P_2 with defect size "B" was ventilated for 6 days and discharged home at the age of 21 days, whereas, in the study [8], the IQR reference range is 7–16 days and 22–47 days, respectively. It indicates that defect size in patent P_2 should be rather assessed as "A/B" or "A".

The significant impact of the defect size and patch repair on the length of hospital stay ($P < 0.05$) was observed, e.g. by Pagliara et al. [28]; liver-up and o/e LHR correlated only with the mortality rate. The prolonged hospitalization may result from postoperative respiratory complications (pneumothorax, pneumonia, pleural effusion) [29].

The primary causes of VILI are non-physiological strain and stress applied to the extracellular lung matrix [10]. Additionally, in inhomogeneous lungs, the strain and stress are unevenly distributed and can locally reach harmful levels that cause lung injury [19]. In CDH infants, inhomogeneity of the lungs is common, but its degree is variable. In the case of substantial inhomogeneity, the stress and strain can be locally multiplied and lead to VILI, resulting in long-term morbidity and even mortality [19, 23]. The pressures and volumes needed to induce VILI in pathologic lungs are much smaller than in healthy lungs. The key to understanding this problem might be the concept of driving pressure that has been recently suggested as the main factor responsible for mortality in ARDS [22, 23]. Since ventilation inhomogeneity (VI) is observed both in ARDS and CDH, it could be hypothesised that driving pressure is also important in CDH, although it has not been studied yet. Driving pressure (ΔP) may be defined as the plateau pressure (P_{plat}) and PEEP difference. It can also be expressed as the ratio of tidal volume (V_T) to static respiratory system compliance (C_{stat}), indicating the decreased functional size of the lung ("baby lung concept") that was mainly observed in patients with ARDS but it is also the case in CDH neonates. The more severe CDH form, the more likely baby's lung is not only to be functionally but also anatomically small. Since the P_{plat} was not assessed clinically [17], we used PIP-PEEP as an approximation of the driving pressure. In our study, the driving pressure ($\Delta P \approx$ PIP-PEEP) evaluated in patients P_1, P_2 and P_3 differed significantly ($P < 0.05$). The ΔP positively correlated with VI degree (T_1/T_2) and C_W/C_L ratio (R_s=0.949, $P < 0.001$). However, it should be pointed out that much more clinical data is needed to prove the importance of these dependencies. This study showed that the more severe VI, the higher the ΔP was required to obtain the assumed minute ventilation. The higher the ΔP, the higher the risk of VILI [19, 22, 23]. This is in contradiction to the goals of "gentle ventilation", which assumes that the more severe CDH form (higher lung hypoplasia and VI degree), the more carefully high levels of PIP and driving pressure should be applied during ventilation. The challenge is to find the best solution to receive appropriate minute ventilation and to minimise VILI risk. Recently, the impact of both - driving pressure and mechanical energy as VILI risk factors has been extensively studied [30–32]. However, till now, there are no remedies how to improve the ventilation management of patients with VI, including CDH infants. The safe values of ΔP have not been established in CDH infants.

Regarding to the C_W/C_L vs. ΔP relationship under ventilation inhomogeneity, we noticed a correspondence between our results and the Chiumello et al. study [33] on respiratory system mechanics in ARDS children. They found that lung stress (P_{tp}) was significantly higher in ARDS children as compared to controls. As we found based on [33], the C_W/C_L ratio correlated with lung stress (P_{tp}); R_s=0.669, $P < 0.05$; we approximated this relationship with function: P_{tp}=9.748·ln (C_W/C_L) + 1.235 ($R^2 = 0.463$, $P < 0.05$). This, together with the dependency between lung stress and driving pressure (P_{tp}=3.135*ΔP + 1.058, $R^2 = 0.689$, $P < 0.001$), found by Chiumello et al. [33], indicates that the C_W/C_L raise was associated with the increase in ΔP.

The C_W/C_L ratio ranges between 3 and 5 [34, 40] in healthy babies but there is a lack of data on the C_W/C_L ratio in CDH neonates. Chiumello et al. [33] observed that the ARDS patients had significantly lower values of C_{rs} and C_L as compared to control subjects. However, C_w was similar in both groups. Analysing the study [33], we noticed that the C_W/C_L in ARDS children was higher and of wider range than in controls (4.56 ÷ 12 vs. 3.6 ÷ 4.53). In our study, the C_W/C_L ranged from 2.68±0.28 (2.53 ÷ 3) to 7±1 (5.94 ÷ 8.15). The causes and VI patterns of ARDS and CDH are different but lung inhomogeneity is also a

distinctive feature of this clinical entity and, as in CDH patients, makes ventilation therapy difficult is associated with high risk of VILI.

Another group of patients with VI who are exclusively susceptible to VILI are preterm infants, especially extremally low birth weight (ELBW) [16]. In this population, VI mainly results from lung immaturity and surfactant deficit, whereas VILI is associated with a high risk of developing bronchopulmonary dysplasia (BPD). BPD is the most common chronic lung disease of preterm infants who require mechanical ventilation and/or oxygen supplementation [35, 36].

Taken together, because mortality of BPD babies (particularly with severe BPD) is still high and there is significant variability in ventilator modes and settings (PIP, PEEP, V_T, RR) applied in several US and Sweden hospitals participating in the multicentre study [37, 38], it seems to be necessary to personalise ventilation therapy of these infants [37, 39]. Ventilator settings should take into account BPD severity and the actual lung mechanics [37, 40], including variable C_{rs} [41–43], elevated R_{rs} [38, 39, 41, 43, 44] and regional differences in time constants resulting from small airways obstruction and/or increased regional compliance [37, 44]. The differences of time constants can be significant, especially in severe BPD cases [37].

Importantly, as Miller et al. [37] indicated, severe BPD is an inhomogeneous lung disease that can be described by the lung model consisting of two functionally distinct compartments [37]. The first compartment, representing healthy lung regions, has normal resistance and compliance, whereas the second, predominant in severe BPD, representing damaged lung regions, has high resistance and relatively normal or increased compliance. In effect, there is a "quick" compartment of a relatively normal time constant (or relatively short in comparison to other lung regions) and a "slow" compartment of a long-time constant. Due to that, choosing ventilator settings is a challenge.

Miller et al. [37] lung inhomogeneity model for severe BPD infants is very close to ours' for one-sided CDH infants (Fig. 1). The damaged lung compartment, which is the sum of dysfunctional regions of the lungs, is the equivalent of the ipsilateral lung compartment in our model.

Ventilatory care of severe BPD infants is highly variable across medical centres, and there is no consensus about the optimal ventilator mode and settings [37–39]. In fact lung-protective ventilation may fail in some babies may fail. Miller et al. [37], based on respiratory pathophysiology and available studies' reports, proposed their approach to the ventilation of these infants. To enable patient full exhalation, one should minimise hyperinflation and air trapping and improve ventilation distribution (so $\dot{V}/Q$, too). The ventilator settings suggested by the authors for severe BPD include the very slow RR of 10–16 bpm, and very high V_T=10–15 ml/kg, PEEP = 8–12 cmH_2O, and PIP = 40–45 cmH_2O [38], however this approach is controversial.

The proposed recommendations seem hazardous due to the exceptionally high (as for CMV) values of V_T and PIP increasing the of volutrauma and barotrauma. They differ significantly from the lung-protective ventilation guidelines commonly used in preterm [16, 36] and CDH infants [12–14], including V_T=4–6 ml/kg, RR = 40–60 bpm and PIP = 25 ± 2 cmH_2O. However, it should be noted that the problem in acute BPD concerns a "slow" compartment (due to increased small airway resistance), whereas, in one-sided CDH, the problem is the "quick" compartment, which is due to reduced compliance of the ipsilateral lung. It might seem that during the ventilation of inhomogeneous lungs, only the effect of the difference in time constants is relevant; the higher the difference, the greater problem with establishing effective and safe ventilation. Additionally, whether we have a problem with "too fast" or "too slow" compartments (compared to healthy or less functionally disturbed lung regions) may also be significant, especially when it comes to V_T and RR settings. In the first case, a relatively high V_T and low RR may be preferred, whereas, in the second case - a relatively low V_T and high RR, which seems to be consistent with the assumptions of minimizing work of breathing, in the first case, lowering its resistive component, and in the second - elastic one [34, 40]. Surprisingly, the ventilator settings suggested by Miller et al. [37] are within the ranges found in the multicentre study mentioned above [38].

Coming back to our main subject, there is still a great need to improve ventilation management of CDH infants, especially at the early stage of therapy. That is hard to realize without a reliable assessment of VI degree, which is highly variable in CDH. There are no CDH severity measures that could be directly used to personalise the mechanical ventilation of these infants. The T_1/T_2 and C_W/C_L indices could fulfil the role. They enable the assessment of the mechanical properties of the respiratory system in a one-sided CDH neonate on CMV, giving a chance to individualise this therapy and make it more effective and safer, with less VILI.

Limitations

One of the study limitations is that the simulation plan and verification of the results were based on a small clinical sample. Verification of the results was also supported by the animal study [19] and clinical studies with ARDS patients [23, 33] in the context of pathological lung changes accompanied by VI. The VI pattern in the animal lung models affected by VILI and ARDS patients differs

from that in CDH patients. However, their common feature is the impact of VI-degree on the mechanical properties of the lungs. Techniques used for VI assessment in the mentioned studies and our study differed, too. However, due to that, we could relate our T_1/T_2 index to the inhomogeneity extent (IE), determined by lung CT scans.

The second study limitation is that I: E was not included as an independent variable. It was directed by the fact that during CDH infant ventilation, the most frequently set I: E values range between 1:1.5 and 1:2. Adding it to the study protocol would require performing a minimum of twice as many experiments (i.e. 500 or more). In the first stage of building the regression model, we decided to limit the number of experiments. We know that the regression model requires development, and the impact of I: E on the model must be evaluated in our future studies.

Pulmonary hypertension (PH) is considered an important contributor to CDH-associated morbidity and mortality. The problem is that the occurrence of pulmonary hypertension is difficult to predict, and there are many factors contributing to it. It is a complex phenomenon and a good topic for separate extensive research. Our study focused on the mechanical aspects of the respiratory system of a one-sided CDH infant and patient respiratory system interaction with a ventilator.

Conclusions

The developed regression models describe patient ventilation parameters as a function of the respiratory system parameters, ventilator settings and two new CDH severity measures. They enabled to find the values of some hidden mechanical parameters of the respiratory system of one-sided CDH infants that are hardly available (C_W/C_L, T_1/T_2) in clinical conditions. It seems that the T_1/T_2 and C_W/C_L indices can have practical clinical value. As they may correlate with the defect size, duration of mechanical ventilation and the length of hospital stay, they probably could be utilised as prognostic factors of CDH patient outcome.

The T_1/T_2 index of VI can play an analogue role as inhomogeneity extent (IE, % of lung volume) assessed from CT scans to evaluate regional lung inhomogeneity, e.g. in ARDS. The T_1/T_2 and IE similarly correlated with the C_W/C_L ratio. Therefore, the T_1/T_2 and C_W/C_L should help personalise respiratory therapy.

Although the study results seem to be promising, it should be remembered that the simulations were based on a small clinical sample and a limited number of clinical scenarios. Due to that, the study conclusions should be treated with great caution - without any generalisation to the CDH infant population. To confirm the clinical relevance of these findings and the reliability and usefulness of the new CDH severity indices, we plan to conduct a simulation study without the current limitations, based on a larger cohort of CDH patients and with a broader range of different clinical scenarios translated into laboratory simulations. A higher number of simulation experiments is needed to cover all possible combinations of independent variables. This way, the influence of additional variables (e.g. I: E, V_T, V_T/kg) on the regression model will be assessed in future studies. Only variables with a significant impact on the variability of a given output variable will be included in the regression model.

Abbreviations

APSA	American Pediatric Surgical Association
ARDS	Acute respiratory distress syndrome
BPD	Bronchopulmonary dysplasia
BSVP	Bed-side ventilation parameters
CDH	Congenital diaphragmatic hernia
CMV	Conventional mechanical ventilation
C_L	Lung compliance
C_{rs}	Total dynamic respiratory system compliance
C_W	Chest-wall compliance
CT	Computer tomography
ELBW	Extremally low-birth weight (preterm infants)
ECMO	Extracorporeal membrane oxygenation
E_L	Lung elastance; $E_L=1/C_L$
E_W	Chest wall elastance; $E_W=1/C_W$
FETO	Fetoscopic endotracheal occlusion procedure
FRC	Functional residual capacity
γ	Gamma correlation coefficient
IE	Inhomogeneity extent
I:E	Inspiration to expiration time ratio
ICU	Intensive Care Unit
IHRS	Infant hybrid respiratory simulator
IQR	Interquartile range
MAP	Mean airway pressure
MR	Multiple regression
MV	Minute ventilation
NLR	Non-linear regression
o/e LHR	Observed to expected lung to head ratio
P	Level of statistical significance
PH	Pulmonary hypertension
PIP	Peak inspiratory pressure
PEEP	Positive end-expiratory pressure
P_{plat}	Plateau pressure
P_{tp}	Transpulmonary pressure
ΔP	Driving pressure
R^2	Determination coefficient
RR	Respiratory rate
R_{rs}	Total dynamic airway resistance
R_s	Spearman's correlation coefficient
V_D	Dead space
V_T	Tidal volume
V̇/Q	Ventilation to perfusion ratio
VI	Ventilation inhomogeneity
VILI	Ventilator-induced lung injury
WOB_{vt}	Work of breathing done by ventilator

Supplementary Information

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Additional file 1: Methods - supplementary information

Additional file 2: Results – supplementary information

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Author contributions
BS and MMS contributed to the study conception and design. Material preparation and data collection were performed by BS, KP and MK. Data analysis was completed by BS and MD. The first draft of the manuscript was written by BS and MMS. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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