Journal of Clinical Monitoring and Computing
https://doi.org/10.1007/s10877-024-01164-z

ORIGINAL RESEARCH

A non-invasive method to monitor respiratory muscle effort during mechanical ventilation

Guillermo Gutierrez[1]

Received: 5 January 2024 / Accepted: 8 April 2024

Abstract

Purpose This study introduces a method to non-invasively and automatically quantify respiratory muscle effort (P_{mus}) during mechanical ventilation (MV). The methodology hinges on numerically solving the respiratory system's equation of motion, utilizing measurements of airway pressure (P_{aw}) and airflow (F_{aw}). To evaluate the technique's effectiveness, P_{mus} was correlated with expected physiological responses. In volume-control (VC) mode, where tidal volume (V_T) is pre-determined, P_{mus} is expected to be linked to P_{aw} fluctuations. In contrast, during pressure-control (PC) mode, where P_{aw} is held constant, P_{mus} should correlate with V_T variations.

Methods The study utilized data from 250 patients on invasive MV. The data included detailed recordings of P_{aw} and F_{aw}, sampled at 31.25 Hz and saved in 131.1-second epochs, each covering 34 to 41 breaths. The algorithm identified 51,268 epochs containing breaths on either VC or PC mode exclusively. In these epochs, P_{mus} and its pressure-time product (P_{mus}PTP) were computed and correlated with P_{aw}'s pressure-time product (P_{aw}PTP) and V_T, respectively.

Results There was a strong correlation of P_{mus}PTP with P_{aw}PTP in VC mode ($R^2 = 0.91$ [0.76, 0.96]; $n = 17{,}648$ epochs) and with V_T in PC mode ($R^2 = 0.88$ [0.74, 0.94]; $n = 33{,}620$ epochs), confirming the hypothesis. As expected, negligible correlations were observed between P_{mus}PTP and V_T in VC mode ($R^2 = 0.03$) and between P_{mus}PTP and P_{aw}PTP in PC mode ($R^2 = 0.06$).

Conclusion The study supports the feasibility of assessing respiratory effort during MV non-invasively through airway signal analysis. Further research is warranted to validate this method and investigate its clinical applications.

Keywords Mechanical ventilation · Respiratory efforts · Acute respiratory failure · Static compliance · Dyspnea · Airway resistance · Numerical analysis

1 Introduction

The process of mechanically ventilating the respiratory system, that includes the lungs and thoracic cage, is often influenced by a patient's level of consciousness. For heavily sedated or paralyzed patients, insufflation is entirely passive. Yet, conscious patients may exhibit an active response, such as trying to exhale during insufflation risking injurious lung strain [1, 2], or developing forceful inhalations if experiencing air hunger [3], a stressful emotional state that may lead to long term psychologic sequela [4].

Quantification of patient effort during ventilatory support could help clinicians optimize ventilator settings and calibrate sedative administration. With that goal in mind, the current research proposes a non-invasive method to estimate the portion of airway pressure (P_{aw}) attributed to muscular effort (P_{mus}) during insufflation automatically.

1.1 Model development

The single compartment model of the respiratory system [5, 6] during positive pressure ventilation with negligible P_{mus}, may be expressed as [7]:

$$P_{passive}(t) = \frac{\Delta V(t)}{C_{rs}} + R_{rs}F_{aw}(t) + PEEP_a \tag{1}$$

✉ Guillermo Gutierrez
gutier@gwu.edu

1 Professor Emeritus Medicine, Anesthesiology and Engineering, The George Washington University, 700 New Hampshire Ave, NW Suite 510, Washington, DC 20037, USA

Published online: 11 May 2024

where $P_{passive}(t)$ is the airway pressure required to inflate the respiratory system devoid of patient assistance; $\Delta V(t)$ represents increases in lung volume from functional residual capacity; $F_{aw}(t)$ is airway flow; and $PEEP_a$ is the applied positive end-expiratory pressure. C_{rs} and R_{rs} denote the respiratory system's compliance and inspiratory resistance, respectively.

In the presence of respiratory muscle activity, Eq. 1 becomes,

$$P_{aw}(t) = \left[\frac{\Delta V(t)}{C_{rs}} + R_{rs}F_{aw}(t) + PEEP_a\right] + P_{mus}(t) \tag{2}$$

Substituting from Eq. 1 and rearranging,

$$P_{mus}(t) = P_{aw}(t) - P_{passive}(t) \tag{3}$$

The $P_{mus}(t)$ function, describing changes in P_{mus} during insufflation, is calculated using Eq. 3 with sequential $P_{aw}(t)$ measurements and $P_{passive}(t)$ values calculated from Eq. 1. According to Eq. 3, $P_{mus}(t)$ is negative for $P_{aw}(t) < P_{passive}(t)$, indicating inspiratory muscle effort, and positive for $P_{aw}(t) > P_{passive}(t)$, signifying expiratory muscle effort.

The calculation of $P_{passive}(t)$ requires prior knowledge of C_{rs} and R_{rs}, whose values are also derived from Eq. 1 using data from breaths with no muscle effort ($P_{mus}(t) = 0$). Although Eq. 1 by itself is indeterminate, a numerical solution has been developed [8]. This involves repeatedly solving Eq. 1 by applying a broad spectrum of plausible C_{rs} and R_{rs} values to each set of measurements ($\Delta V(k)$, $F_{aw}(k)$ and $PEEP_a$) made during passive insufflation. The outcome is a C_{rs} x R_{rs} matrix that encompasses all possible solutions of Eq. 1 for the given measurements, within the selected range of C_{rs} and R_{rs} values. A $(C_{rs}\text{-}R_{rs})_k$ function is next generated by identifying the matrix elements matching the measured $P_{aw}(k)$.

Replicating the above process for all n measurements made during insufflation generates a family of $(C_{rs}\text{-}R_{rs})_n$ functions on the C_{rs}-R_{rs} plane. Since the model assumes C_{rs} and R_{rs} to be constant during insufflation, these $(C_{rs}\text{-}R_{rs})_n$ functions intersect at their true values, This methodology has been rigorously tested for stability and validated with clinical data [8].

Although assumed constant during the insufflation, the algorithm also recognizes that C_{rs} and R_{rs} may change longitudinally due to treatment or clinical factors. This is addressed by treating C_{rs} and R_{rs} as the mean of fixed-length vectors, operating like quasi-circular buffers. In other words, as monitoring begins, C_{rs} and R_{rs} values from passive insufflations are added sequentially to respective vectors. Once the vectors accumulate 180 elements, their averages are taken as initial C_{rs} and R_{rs} for that patient. C_{rs} and R_{rs} values derived from subsequent breaths meeting $P_{mus}(t) = 0$ criteria are used to dynamically update these vectors with a First-In-First-Out (FIFO) method, ensuring their sizes remain constant. The choice of 180 elements, equivalent to 10 to 15 minutes of monitoring time, aims to strike a balance between gathering enough passive breath data for accurate calculation and the time required to produce initial Crs and Rrs values.

1.2 Model validation

It is possible to assess the validity of predicted $P_{mus}(t)$ by its consistency with anticipated physiological responses. Specifically, in patients ventilated with volume-control (VC) mode, where the tidal volume (V_T) is preset, $P_{mus}(t)$ is expected to associate with fluctuations in $P_{aw}(t)$. Conversely, for pressure-control (PC) mode, that provides a constant $P_{aw}(t)$ during the entire insufflation, $P_{mus}(t)$ should more closely correlate with alterations in V_T. The soundness of the $P_{mus}(t)$ estimate is intrinsically linked to the robustness of its separate correlations with $P_{aw}(t)$ and V_T, with a strong coefficient of determination R^2 signifying an accurate computation.

2 Methods

The algorithm was tested using F_{aw} and P_{aw} signals stored in a database of 250 patients treated with invasive ventilation at the Intensive Care Unit of The George Washington University Hospital. These patients had been enrolled in multiple studies approved by the Institutional Review Board (Nos. 101228, 110910, 111235) conducted between 2011 and 2015 in accordance with the 1964 Helsinki Declaration. The patients, or their appointed surrogates, gave informed consent for these studies, and the IRB allowed use of the anonymized data for subsequent research.

Table 1 shows demographic and enrollment data for the patients in the database. There was a preponderance of medical diagnoses (67%), 58% were male, with the largest percentage of patients being of Black ethnicity (54.4%).

All patients were intubated via the nasotracheal or orotracheal route and received ventilatory support using Servo_i or Servo_s ventilators (Getinge, Solna, Sweden) with various modes of ventilation. Treatment decisions were independent of the study. Enrollment occurred within 24 h of intubation, with patients monitored for 3 [2, 5] (median [IQR]) days.

F_{aw} and P_{aw} signals were acquired from the ventilator data port (Computer Interface Emulator CIE, Getinge, Solna, Sweden) at 31.25 Hz and stored as sequential time-windows, termed epochs, spanning 131.1 s and containing

Table 1 Demographics and enrollment data for the 250 patient database

Age (Years)	60 (18)
ICU Admission type:	
Medical	67%
Post-surgical	25%
Trauma	8%
Gender	
Male	58%
Female	42%
Ethnicity (% of total):	
Asian	2.4%
Black	54.4%
Latino	4.8%
Multiracial	1.6%
White	36.8%
Enrollment data – mean (SD):	
SOFA	6 (3)
SAPS II	42 (14)
BMI ($kg \cdot m^{-2}$)	28 (8)
PEEP (mmH_2O)	4.8 (3.7)
F_IO_2 (%)	51 (18)
pH	7.37 (0.10)
PO_2 (mmHg)	149 (73)
PCO_2 (mmHg)	39 (10)

SOFA = Sequential Organ Failure Assessment; SAPS II = Simplified Acute Physiological Score II; BMI = Body Mass Index; PEEP = Positive End Expiratory Pressure; F_IO_2 = Fractional Inspired O_2

4096 samples of each P_{aw} and F_{aw} signal. Commencing with records starting from 2011, data from each patient were analyzed sequentially from the time of enrollment to the cessation of monitoring, with software developed according to the algorithm of Fig. 1 written in Python 3.11 programming language. The algorithm simulates the real-time patient monitoring process used in clinical settings. Excluded from analysis were epochs on bi-level ventilation and Airway Pressure Release Ventilation (APRV).

Step 1: Data analysis begins by identifying epochs with a respiratory rate variability index [9] (RRVI) < 50%, a threshold observed during the N2 and N3 sleep stages [10]. Given their low RRVI, these epochs are considered to occur during times of minimal respiratory muscle activity and chosen for subsequent analysis.

Step 2: For each selected epoch, calculate C_{rs} and R_{rs} for every breath that meets the criteria for passive insufflation: (1) Ventilator triggered: ($PEEP_a$ – minimal P_{aw}) < 0.3 cmH_2O; (2) Full volume breaths: $V_T \geq 250$ mL with insufflation time (Ti) > 0.8 s; (3) Absence of $PEEP_i$: end exhalation (EE) $F_{aw} < 3\ L \cdot min^{-1}$ and breath's initial $P_{aw}(t_0)$ - prior breath's EE $P_{aw} < 2\ cmH_2O$ [11, 12], (4) No leaks in the circuit: inspired – expired $V_T < |30\ mL|$; and (5) Avoidance of lung overdistention: inspired $V_T < 740$ mL [13]. Store calculated C_{rs} and R_{rs} values sequentially in respective vectors. Once the vectors are filled with 180 elements, use their averages as initial C_{rs} and R_{rs} for the patient.

Step 3: Determine $P_{mus}(t)$ for each breath in subsequent epochs. Use the calculated C_{rs} and R_{rs} to compute $P_{passive}(k)$ from Eq. 1 and $P_{mus}(k)$ from Eq. 3 for all $P_{aw}(k)$, $F_{aw}(k)$, $\Delta V(k)$, and $PEEP_a$ measurements obtained at sequential times k during the insufflation. To insure calculations take place in the region of constant C_{rs}, defined as the analysis time, P_{mus} pressure-time product (P_{mus}PTP) is calculated by numerical integration of the $P_{mus}(t)$ function (trapezoidal method) from the time $\Delta V(t) \geq 150$ mL through 90% of the insufflation's duration. In addition to the primary calculations, other derived metrics are: the maximum and minimum P_{mus}, corresponding to the peak positive and negative values of P_{mus} (P_{mus}peak), the pressure-time product of airway pressure (P_{aw}PTP) over the analysis period, the peak value of airway pressure (P_{aw}peak), and tidal volume (V_T), defined as the largest volume change ($\Delta V(t)$) achieved during insufflation.

Initial C_{rs} and R_{rs} values are dynamically adjusted by the algorithm to reflect changes from disease progression or treatment. Epochs with RRVI < 50% are examined for breaths fulfilling the $P_{mus} = 0$ criteria from Step 2. C_{rs} and R_{rs} determined from these breaths are added to the initial vectors (FIFO), keeping a steady tally of 180 breaths. This method allows C_{rs} and R_{rs} to adapt to evolving clinical conditions, while minimizing the effects of short-term variations.

2.1 Correlation analysis

Upon analyzing the data from all 250 patients using the Fig. 1 algorithm, epochs were selected for correlation analysis based on specific criteria: (1) epochs ventilated on either PC or VC mode; (2) there was no indication of $PEEP_i$, as determined by the established criteria in Step 2, and assessed as an average across all breaths within the epoch; and (3) the epoch's data had the capacity for robust linear regression calculation, P_{aw} (maximum - minimum) < 4 cmH_2O for VC mode or a V_T range < 100 mL for PC mode.

2.2 Statistics

Occasional anomalies in data acquisition giving rise to one or two univariate outliers per epoch were corrected by the z-score method [14] with z = 3. The coefficient of determination R^2 was calculated using Pearson's linear regression for correlations of P_{mus} PTP with P_{aw} PTP, and P_{mus} PTP with V_T. Normality of the R^2 distributions was evaluated with the Kolmogorov-Smirnov test. Depending on the normality of the data, independent sample differences were assessed using Mann–Whitney test or Student's t-test, both

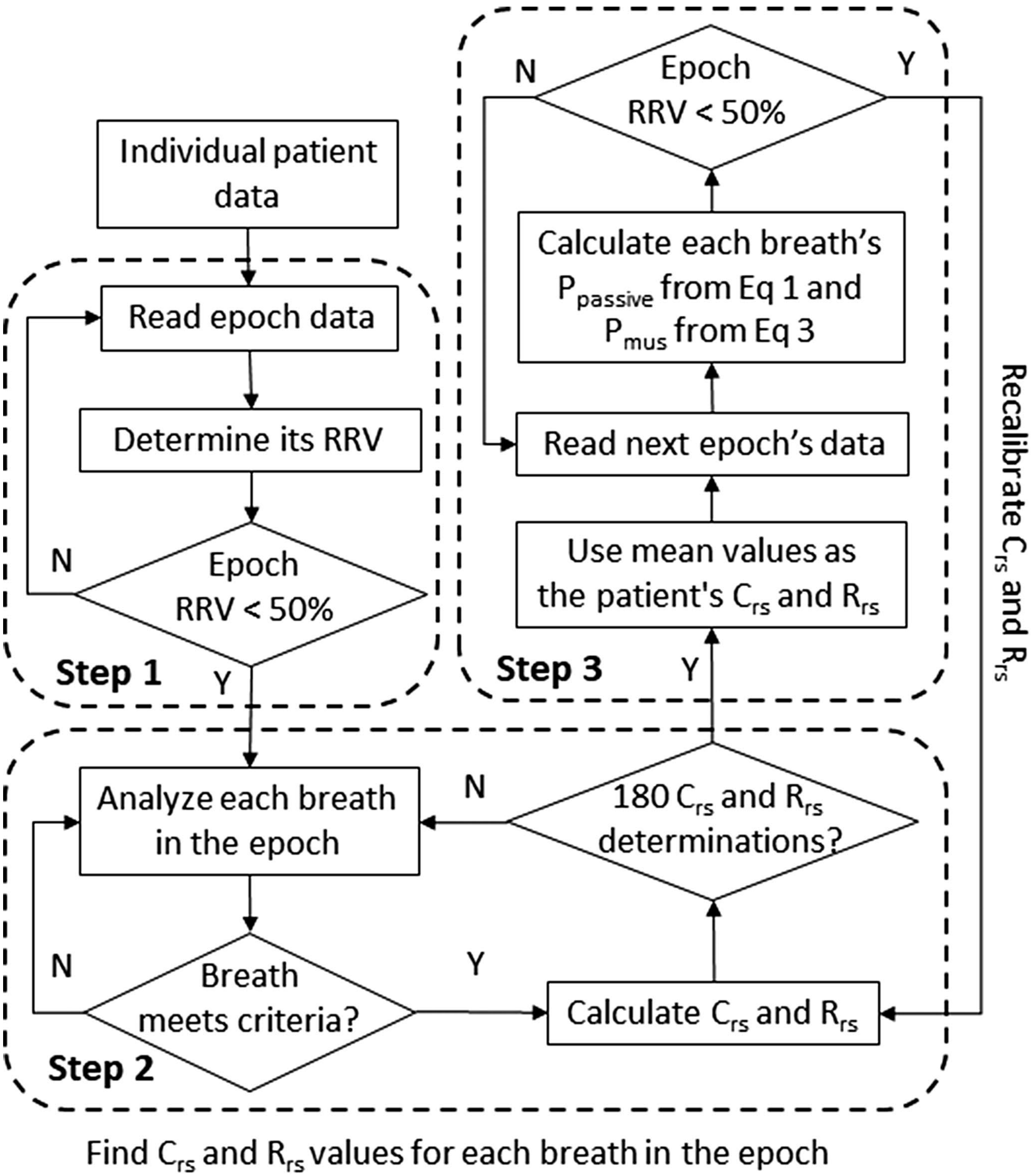

Fig. 1 Algorithm used to analyze data from 250 patients in chronologic order from 2011 to 2015. Stage 1: Search the database for epochs with respiratory rate variability (RRVI) < 50%, considered to occur when $P_{mus} = 0$. Stage 2: Identify all breaths in the selected epochs meeting a strict criteria for absent P_{mus} and $PEEP_i$. Apply the numerical solution of the equation of motion to calculate breath specific C_{rs} and R_{rs} and fill respective vectors sequentially to a length of 180 elements. Stage 3: Use the mean of these vectors as estimates for C_{rs} and R_{rs} to calculate $P_{passive}$ from Eq. 1 and P_{mus} from Eq. 3. Account for longitudinal variations in C_{rs} and R_{rs} by calculating their values in subsequent epochs with RRVI < 50% and incorporate them in the respective vectors FIFO

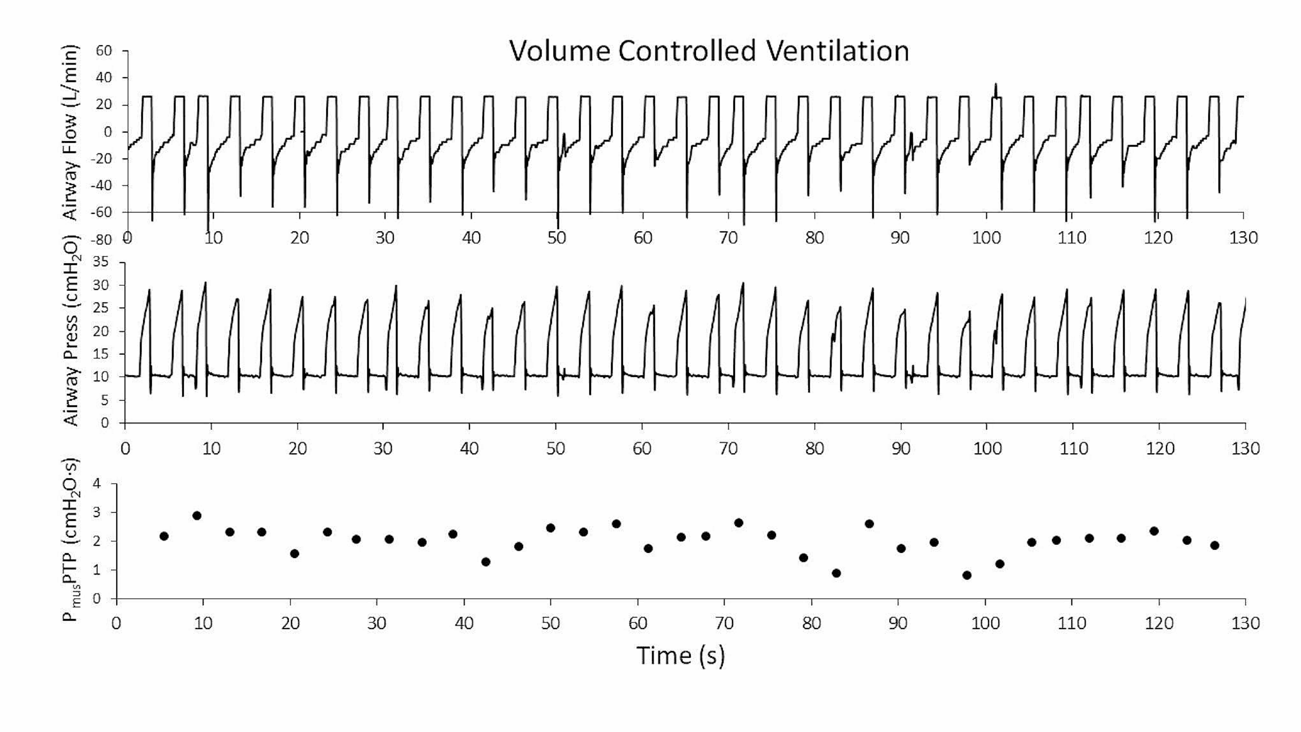

Fig. 2 Epoch lasting 131.1 s acquired from a patient on VC ventilation. The upper and middle panels show F_{aw} and P_{aw} signals, respectively. The bottom panel depicts calculated P_{mus}PTP as discrete points, each datum corresponding to the breath above

corrected for multiple testing by Bonferroni's method. Data are presented as mean (SD), unless noted otherwise. Two-sided p values are reported, with significance set at $p<0.05$.

2.3 Hypothesis testing

Method validation relied on establishing a strong correlation ($R^2>0.80$) between P_{mus}PTP and P_{aw}PTP in VC mode, and between P_{mus}PTP and V_T in PC mode. Conversely, the hypothesis predicts a weak or non-existent correlation in the opposite scenarios.

3 Results

3.1 Individual epochs examples

The following examples highlight the performance of the algorithm when applied to patient data under two different modes of ventilation, PC and VC:

The epoch shown in Fig. 2 was obtained from a 70-year-old woman with acute heart failure. The patient was on constant flow, VC ventilation with fractional inspired O_2 (F_IO_2) of 80%, mean V_T of 450 mL, respiratory rate (RR) of 16 bpm, and $PEEP_a$ of 10 cmH_2O.

F_{aw} and P_{aw} signals (upper and middle panels, respectively) are uniform in timing (RRVI = 30%) and configuration, showing minor fluctuations in P_{aw}peak. The epoch is typical of a sedated individual, with most breaths triggered by the ventilator. The lower panel shows calculated P_{mus}PTP as discrete points corresponding to the breaths above. P_{mus}PTP values are positive for all insufflations, indicating the occurrence of mild expiratory efforts not readily apparent from airway signal examination.

Figure 3 shows a subsequent epoch from the same patient, now on PC mode with $F_IO_2=60\%$, RR = 12 bpm, P_{aw}peak = 22 cmH_2O, and $PEEP_a=5$ cmH_2O. All breaths are ventilator triggered with low RRVI (24%) and V_T values ranging from 620 to 740 mL. Visual examination of the airway signals provides little insight into respiratory muscle activity, but the lower panel shows negative P_{mus}PTP values ranging from -1.8 to 0.3 $cmH_2O{\cdot}s$. The source of these inspiratory efforts is not apparent from the data, but could indicate air hunger or the presence of reverse triggering [15].

Figure 4 depicts the relationship between P_{mus}PTP with P_{aw}PTP and V_T for the data of Figs. 2 and 3. With the patient on VC ventilation, there is a strong proportional relationship between P_{mus}PTP and P_{aw}PTP (R^2 = 0.85) and none with V_T (R^2 = 0.00). Conversely, on PC mode there is negligible correlation between P_{mus}PTP and P_{aw}PTP (R^2 = 0.10) and a strong inverse correlation between P_{mus}PTP and V_T (R^2 = 0.95)

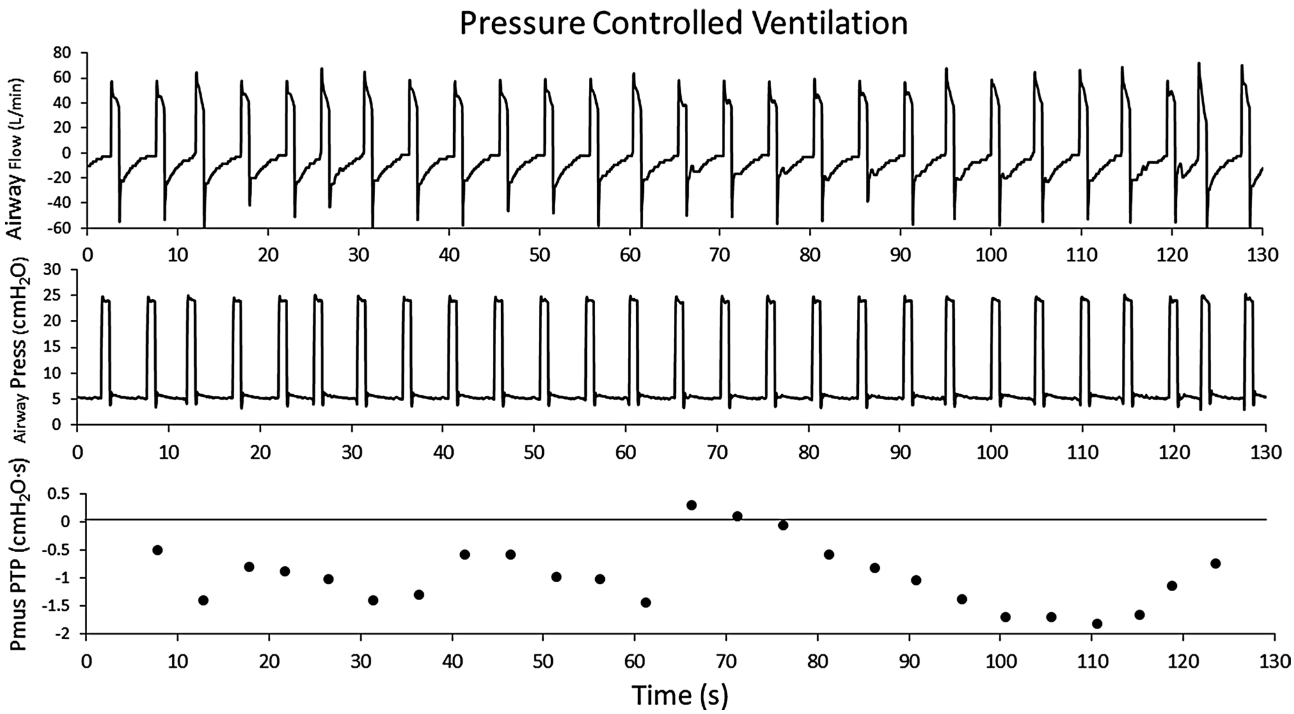

Fig. 3 Epoch lasting 131.1 s acquired from a patient on PC ventilation. The upper and middle panels show F_{aw} and P_{aw} signals, respectively. The bottom panel depicts calculated P_{mus}PTP as discrete points, each datum corresponding to the breath above

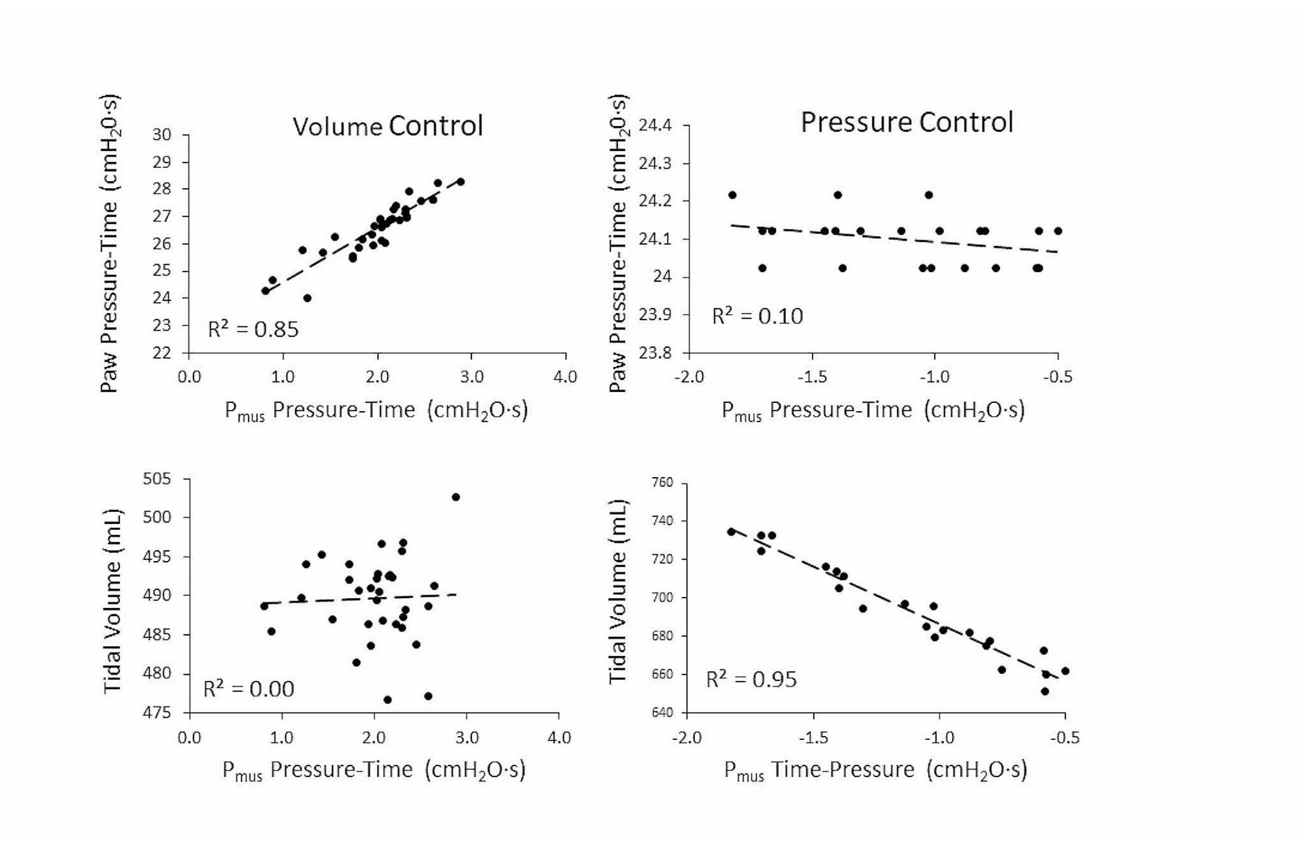

Fig. 4 Relationships of P_{mus}PTP vs. P_{aw}PTP and P_{mus}PTP vs. V_T for the examples shown in Figs. 2 and 3. With VC ventilation there is a strong correlation for P_{mus}PTP vs. P_{aw}PTP ($R^2=0.85$) while being absent for P_{mus}PTP vs. V_T ($R^2=0.00$). Conversely, PC ventilation is characterized by minimal correlation between P_{mus}PTP and P_{aw}PTP ($R^2=0.10$) and a robust inverse correlation between P_{mus}PTP and V_T ($R^2=0.95$).

Table 2 Number of Analyzed Epochs and Breaths Across Ventilation Modes

Mode	VC	PC	Total
Patients	57	67	
Analyzed epochs	17,648	33,620	51,268
% of Total	34%	66%	
Analyzed breaths	623,538	1,453,886	2,077,424
% of Total	30%	70%	
Outliers per epoch	1.6	2.1	
Analyzed breaths per epoch	34	41	

VC = Volume Control; PC = Pressure Control; Patients = Number of patients in the database having at least one analyzed epoch in the designated ventilation mode

Table 3 Measured Ventilation Parameters for the Analyzed Epochs

Mode		VC	PC
F_IO_2	(%)	41 (10)	48 (16) *
PEEP	(cmH_2O)	5.5 (0.9)	6.6 (1.9) *
Peak P_{aw}	(cmH_2O)	29 (7)	32 (6) *
RR	(bpm)	17 (4.3)	21 (6.1) *
V_T	(mL)	512 (84)	566 (148) *
V_T/PBW	($ml \cdot kg^{-1}$)	8.2 (1.2)	9.2 (2.6) *
Static C_{rs}	$mL \cdot cmH_2O^{-1}$	46 (15)	45 (26)
Inspired R_{rs}	$cmH_2O \cdot s \cdot L^{-1}$	15 (7)	8 (7) *

VC = Volume Control; PC = Pressure Control; F_IO_2 = Fraction Inspired O_2 concentration (%); PEEP = Positive end expiratory pressure; P_{aw} = Airway pressure; RR = Respiratory rate; V_T = Tidal volume; PBW = Predicted body weight. Compliance (C_{rs}) and resistance (R_{rs}) refer to the respiratory system, including the lungs and chest wall

Figures are shown as mean (SD). * $p < 0.001$ two-sided t test with Bonferroni's correction

Table 4 P_{mus} Related Variables Across Ventilation Modes

	Directionality	VC	PC
% of Total Efforts	Inspiratory	36 (32)	31 (33)
	Expiratory	64 (32)	69 (33)
P_{mus} per breath (cmH_2O)	Inspiratory	1.2 (1.7)	0.7 (2.3)
	Expiratory	5.0 (4.6)	6.4 (4.4) *
P_{mus}PTP per breath ($cmH_2O \cdot s$)	Inspiratory	1.0 (1.7)	1.1 (2.0)
	Expiratory	1.4 (1.4)	2.3 (2.4) *
P_{mus}PTP per minute ($cmH_2O \cdot s \cdot min^{-1}$) §	Inspiratory	17 (26)	26 (62) *
	Expiratory	39 (54)	89 (112) *

VC = Volume Control; PC = Pressure Control

P_{mus} = Peak inspiratory or expiratory pressure attributed to respiratory muscle effort

Inspiratory and expiratory refer to the direction of P_{mus}

P_{mus}PTP = P_{mus} pressure time product

per breath = Average value of all inspiratory or all expiratory values in an epoch

§ Calculated as the sum of P_{mus}PTP (either expiratory or inspiratory) in an epoch divided by the length an epoch in minutes (2.184 min)

Figures shown as mean (SD); * $p < 0.001$ comparing PC to VC; two-sided t test with Bonferroni's correction

3.2 Overall data analysis

In the analysis of the entire 250 patient dataset, the algorithm failed to determine initial C_{rs} and R_{rs} in 25 patients, as they lacked sufficient breaths meeting criteria for P_{mus} = 0. This was due to agitation following enrollment in the study in some patients and short monitoring time in others, either the result of technical difficulties or early ventilator weaning.

Application of the algorithm to the remaining 225 patients identified 551,642 epochs in which the algorithm could determine $P_{mus}(t)$ for individual breaths. From this cohort, 51,268 epochs were chosen for correlation analysis since they occurred exclusively on VC or PC ventilation modes. Table 2 displays the number of patients who were included based on having at least one epoch in the analyzed ventilation mode. Since most patients received treatment with more than one ventilation modality, it is possible for the same patient to have been included in both groups of Table 2. There were twice as many epochs on PC mode as compared to VC mode. Outliers were < 5% of the epoch's breaths, ensuring enough breaths remained for robust correlation analyses.

Table 3 shows ventilation parameters stratified by ventilation mode across the analyzed epochs. The greater ventilatory assistance noted with PC mode, in terms of F_IO_2, P_{aw}, $PEEP_a$, V_T and RR, hint at greater respiratory compromise when compared to epochs on VC mode.

Table 4 presents the percentage of inspiratory and expiratory efforts per epoch, the average P_{mus} and P_{mus}PTP per breath, and the sum of P_{mus}PTP values per epoch, stratified by ventilation modality and P_{mus} directionality (inspiratory or expiratory) within an epoch. Both modes displayed a mix of inspiratory and expiratory efforts, although expiratory efforts were more vigorous, both in magnitude and frequency, in PC mode ($p < 0.001$).

Table 5 lists R^2 values for the correlation of P_{mus}PTP with P_{aw}PTP and V_T across the analyzed epochs. In VC mode, P_{mus}PTP demonstrates a strong positive correlation with P_{aw}PTP ($P_{aw}PTP = 1.7\ P_{mus}PTP + 19.4$; $R^2 = 0.91$; $n = 17{,}648$ epochs), while such relationship is absent for V_T ($R^2 = 0.03$). Conversely, this pattern reverses in PC mode, resulting in a robust inverse association between P_{mus}PTP and V_T ($V_T = -43.6\ P_{mus}PTP + 615$; $R^2 = 0.88$; 33,620 epochs) and a negligible one with P_{aw}PTP ($R^2 = 0.06$).

Table 5 R^2 for the Correlation of $P_{mus}PTP$ with $P_{aw}PTP$ and V_T

Mode	VC	PC
Number of Epochs	17,648	33,620
$P_{mus}PTP$ vs. $P_{aw}PTP$	0.91 [0.76, 0.96] *	0.06 [0.01, 0.18] *
$P_{mus}PTP$ vs. V_T	0.03 [0.01, 0.09]	0.88 [0.74, 0.94]

VC = Volume Control; PC = Pressure Control; P_{mus} = Share of airway pressure attributed to respiratory muscle effort; $P_{mus}PTP$ = P_{mus} pressure time product; P_{aw} = Airway pressure; $P_{aw}PTP$ = P_{aw} pressure-time product; V_T = Tidal volume. Figures shown as median [IQR];

* $p < 0.001$ comparing R^2 for $P_{mus}PTP$ vs. $P_{aw}PTP$ to $P_{mus}PTP$ vs. V_T by Mann-Whitney with Bonferroni's correction

4 Discussion

A method is proposed to estimate $P_{mus}(t)$, a function describing respiratory muscle effort during individual insufflations, based on the numerical solution of a single-compartment model of the respiratory system. The method is non-invasive and may be used to continuously monitor patients on ventilatory support automatically by connecting a microprocessor to the data port of a mechanical ventilator.

A significant strength of the study is the extensive dataset used, comprising thousands of epochs collected continuously over several days from 250 patients mechanically ventilated using diverse ventilation modes. Specialized software assessed over two million individual breaths, consequently, the influence of sample size bias, random measurement variations, or the inclusion in the analysis of epochs with significant $PEEP_i$ levels is considered minimal.

Quantifying $P_{mus}(t)$ is inherently difficult due to the absence of a direct method of measurement method. The present "gold standard" [16] involves the difference between esophageal pressure, measured with a fluid-filled catheter, and chest wall recoil pressure under passive conditions. However, this method is complex, as it relies on uncertain factors like chest wall elastance and a specific chest wall recoil pressure point [17]. Additionally, the variability in chest wall mechanics and the challenge in accurately distinguishing respiratory phases add to the difficulties in obtaining precise measurements of $P_{mus}(t)$.

Given the challenges in directly measuring $P_{mus}(t)$, it is not unreasonable to assess the validity of its estimate indirectly by evaluating its consistency with expected physiological responses. The high R^2 values obtained from the correlations $P_{mus}PTP$ vs. $P_{aw}PTP$ in VC mode, and $P_{mus}PTP$ vs. V_T in PC mode, across more than 50,000 epochs, indicate a strong predictability between these variables and provides robust evidence supporting the accuracy of the predicted $P_{mus}(t)$.

The results of the study highlight the bidirectionality of P_{mus} during insufflation. Expiratory P_{mus} values were predicted in more than two-thirds of insufflations in either VC or PC modes. This finding, previously noted by others [18], may be significant considering the potential for lung injury due to elevated alveolar pressure during expiratory efforts. On the other hand, inspiratory efforts are often indicative of air hunger, a distressing condition with long-term psychological sequelae.

4.1 Confounders and limitations

A potential confounder is the possibility that epochs with significant $PEEP_i$ may have been unintentionally incorporated into the analysis. Failing to address intrinsic PEEPi can lead to an overestimation of expiratory P_{mus} and a corresponding underestimation of inspiratory P_{mus}. Although the automated data analysis precluded visual identification of epochs with substantial $PEEP_i$, efforts were made to prevent this occurrence by excluding epochs meeting established criteria for this condition. Further, the database contained a limited subset of patients with the diagnosis of asthma or chronic obstructive pulmonary disease (COPD) (8.3%) that were predisposed to the development of $PEEP_i$.

Another possible confounder is the presence of outliers related to anomalies in data acquisition or to double-triggered breaths. Outliers were systematically excluded by applying the z-score method to all $P_{aw}PTP$, V_T and $P_{mus}PTP$ datasets This approach resulted in the omission of one or two outliers per epoch, while ensuring > 30 breaths remained for regression analysis (Table 2).

Since $P_{mus}(t)$ was derived directly from $P_{aw}(t)$ (Eq. 3) and indirectly from V_T (Eq. 1), the possibility must be considered that mathematic coupling of shared variables [19] might have resulted in the robust correlations noted between P_{mus} PTP and P_{aw} PTP or with V_T. However, mathematic coupling is unlikely, given the complete lack of association between these variables when tested in the opposite modes.

Clinical application of the method is limited by the need for specialized data acquisition equipment. This concern is mitigated by the incorporation in modern ventilators of signal sampling algorithms whose output is readily accessed through a data port. Nonetheless, the sheer number of calculations needed to produce even a single breath's $P_{mus}(t)$ function, makes the use of a digital computer mandatory in the clinical application of the method.

Until additional studies are conducted, the performance of the method using airway signals generated by specialized ventilatory support techniques, such as bi-level ventilation and Airway Pressure Release Ventilation (APRV), remains uncertain.

5 Conclusions

The proposed method provides a non-invasive, real-time estimate of respiratory muscle activity during insufflation, one capable of distinguishing between expiratory and inspiratory efforts. This could help clinicians identify harmful respiratory patterns associated with expiratory efforts [20] that may result in injurious lung strain [12], or detect severe inspiratory exertions that indicate distressing dyspnea [3]. Efforts directed at validation, as well as establishing the range of applications for this method, warrant further investigation in future studies.

Glossary

C_{rs}	Respiratory system static compliance
$\Delta V(t)$	Lung volume change during insufflation
F_{aw}	Airway flow
$PEEP_a$	Applied positive end expiratory pressure
$PEEP_i$	Intrinsic PEEP present at end expiration
PC	Pressure control ventilation mode
PS	Pressure support ventilation mode
P_{aw}	airway pressure
$P_{aw}Peak$	Peak inspiratory pressure
$P_{aw}PTP$	P_{aw} pressure time product
P_{mus}	Respiratory muscles pressure
$Peak\_P_{mus}$	Peak respiratory muscles pressure
$P_{mus}PTP$	P_{mus} pressure time product
$P_{passive}$	P_{aw} required for passively inflation of the respiratory system
rs	Respiratory system
R_{rs}	Respiratory system inspiratory airway resistance
RRVI	respiratory rate variability index
VC	Volume control ventilation mode
V_T	Tidal volume

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10877-024-01164-z.

Acknowledgements The author thanks the Commission for Educational Exchange between the United States, Belgium and Luxembourg and the Fulbright Scholarship Board. Their generous support as a Fulbright Research Scholar granted the author the time and resources necessary to develop the ideas that formed the basis of this research.

Author contributions Single author manuscript. I take responsibility for all aspects of the research.

Data availability The datasets used and analyzed during the current study can be found in the Electronic Data Repository. The database storing the raw data is available from the author upon reasonable request.

Statements and declarations

Competing interests The author has applied for a U.S. patent based on the information presented in the manuscript.

Ethical approval and consent to participate The database used in the present study was collected during the conduct of several IRB approved studies (Nos. 101228, 110910, 111235) at The George Washington University Hospital, with the IRB allowing the use of deidentified data in further studies.

Consent for publication Not applicable.

References

1. Slutsky AS, Ranieri VM. (2013) Ventilator-induced lung injury. N Engl J Med. 369:2126–2136,. doi: 10.1056/NEJMra1208707. Erratum in: N Engl J Med. 370:1668–1669, 2014. PMID: 24283226.
2. Marini JJ, Rocco PRM, Gattinoni L. Static and dynamic contributors to ventilator-induced Lung Injury in Clinical Practice. Pressure, Energy, and Power. Am J Respir Crit Care Med. 2020;201:767–74. https://doi.org/10.1164/rccm.201908-1545CI. PMID: 31665612; PMCID: PMC7124710.
3. Demoule A, Hajage D, Messika J, Jaber S, Diallo H, Coutrot M, Kouatchet A, Azoulay E, Fartoukh M, Hraiech S, Beuret P, Darmon M, Decavèle M, Ricard JD, Chanques G, Mercat A, Schmidt M, Similowski T, REVA Network (Research Network in Mechanical Ventilation). (2022) Prevalence, Intensity, and Clinical Impact of Dyspnea in Critically Ill Patients Receiving Invasive Ventilation. Am J Respir Crit Care Med. 205:917–926. https://doi.org/10.1164/rccm.202108-1857OC. PMID: 35061577.
4. Worsham CM, Banzett RB, Schwartzstein RM. Dyspnea, Acute Respiratory failure, psychological trauma, and Post-ICU Mental Health: a caution and a call for Research. Chest. 2021;159:749–56. https://doi.org/10.1016/j.chest.2020.09.251. Epub 2020 Oct 1. PMID: 33011205; PMCID: PMC7528739.
5. Rohrer F. Der Zusammenhang Der Atemkräfte und ihre Abhängigkeit Vom Dehnungszustand Der Atmungsorgane. Pflüger's Arch. 1916;165:419–44. https://doi.org/10.1007/BF01681079.
6. Otis A, Fenn W, Rahn H. (1950) Mechanics of breathing in man. J Appl Physiol. 2:592–607. doi: 10.1152/jappl.1950.2.11.592. PMID: 15436363.
7. Rossi A, Gottfried SB, Higgs BD, Zocchi L, Grassino A, Milic-Emili J. (1985) Respiratory mechanics in mechanically ventilated patients with respiratory failure. J Appl Physiol 58:1849–1858. https://doi.org/10.1152/jappl.1985.58.6.1849. PMID: 4008405.
8. Gutierrez G. A novel method to calculate compliance and airway resistance in ventilated patients. Intensive Care Med Exp. 2022;10:55. https://doi.org/10.1186/s40635-022-00483-2. PMID: 36581716; PMCID: PMC9800666.
9. Gutierrez G, Ballarino GJ, Turkan H, Abril J, De La Cruz L, Edsall C, George B, Gutierrez S, Jha V, Ahari J. Automatic detection of patient-ventilator asynchrony by spectral analysis of airway flow. Crit Care. 2011;15:R167. https://doi.org/10.1186/cc10309. PMID: 21749683; PMCID: PMC3387605.
10. Gutierrez G, Williams J, Alrehaili GA, McLean A, Pirouz R, Amdur R, Jain V, Ahari J, Bawa A, Kimbro S. Respiratory rate variability in sleeping adults without obstructive sleep apnea. Physiol Rep. 2016;4:e12949. https://doi.org/10.14814/phy2.12949. PMID: 27597768; PMCID: PMC5027356.
11. Rossi A, Gottfried SB, Zocchi L, Higgs BD, Lennox S, Calverley PM, Begin P, Grassino A, Milic-Emili J. (1985) Measurement of

static compliance of the total respiratory system in patients with acute respiratory failure during mechanical ventilation. The effect of intrinsic positive end-expiratory pressure. Am Rev Respir Dis 131:672–677. https://doi.org/10.1164/arrd.1985.131.5.672. PMID: 4003913.

12. Brochard L. Intrinsic (or auto-) PEEP during controlled mechanical ventilation. Intensive Care Med. 2002;28:1376–8. https://doi.org/10.1007/s00134-002-1438-8.
13. Servillo G, Svantesson C, Beydon L, Roupie E, Brochard L, Lemaire F, Jonson B. Pressure–volume curves in acute respiratory failure: automated low flow inflation versus occlusion. Am J Respir Crit Care Med. 1997;155:1629–36. https://doi.org/10.1164/ajrccm.155.5.9154868.
14. Rousseeuw PJ, Hubert M. Anomaly detection by robust statistics WIREs. Data Min Knowl Discov. 2018;8:e1236. https://doi.org/10.1002/widm.1236.
15. Akoumianaki E, Lyazidi A, Rey N, Matamis D, Perez-Martinez N, Giraud R, Mancebo J, Brochard L, Richard JM. (2013) Mechanical ventilation-induced reverse-triggered breaths: a frequently unrecognized form of neuromechanical coupling. Chest. 143:927–938. https://doi.org/10.1378/chest.12-1817. PMID: 23187649.
16. Jonkman AH, Telias I, Spinelli E, Akoumianaki E, Piquilloud L. The oesophageal balloon for respiratory monitoring in ventilated patients: updated clinical review and practical aspects. Eur Respir Rev. 2023;32:220186. https://doi.org/10.1183/16000617.0186-2022. PMID: 37197768; PMCID: PMC10189643.
17. Mauri T, Yoshida T, Bellani G, Goligher EC, Carteaux G, Rittayamai N, Mojoli F, Chiumello D, Piquilloud L, Grasso S, Jubran A, Laghi F, Magder S, Pesenti A, Loring S, Gattinoni L, Talmor D, Blanch L, Amato M, Chen L, Brochard L, Mancebo J. PLeUral pressure working Group (PLUG—Acute Respiratory Failure section of the European Society of Intensive Care Medicine) (2016) Esophageal and transpulmonary pressure in the clinical setting: meaning, usefulness and perspectives. Intensive Care Med. 42:1360–1373. https://doi.org/10.1007/s00134-016-4400-x. PMID: 27334266.
18. Jubran A, Van de Graaff WB, Tobin MJ. (1995) Variability of patient-ventilator interaction with pressure support ventilation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 152:129–136. https://doi.org/10.1164/ajrccm.152.1.7599811. PMID: 7599811.
19. Archie JP Jr. Mathematic coupling of data: a common source of error. Ann Surg. 1981;193:296–303. https://doi.org/10.1097/00000658-198103000-00008. PMID: 7212790; PMCID: PMC1345065.
20. Carteaux G, Parfait M, Combet M, Haudebourg AF, Tuffet S, Mekontso Dessap A. Patient-self inflicted Lung Injury: a practical review. J Clin Med. 2021;10:2738. https://doi.org/10.3390/jcm10122738. PMID: 34205783; PMCID: PMC8234933.
21. Yoshida T, Nakahashi S, Nakamura MAM, Koyama Y, Roldan R, Torsani V, De Santis RR, Gomes S, Uchiyama A, Amato MBP, Kavanagh BP, Fujino Y. (2017) Volume-controlled Ventilation Does Not Prevent Injurious Inflation during Spontaneous Effort. Am J Respir Crit Care Med. 196:590–601. https://doi.org/10.1164/rccm.201610-1972OC. PMID: 28212050.