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ORIGINAL RESEARCH

Non-invasive assessment of respiratory muscle activity during pressure support ventilation: accuracy of end-inspiration occlusion and least square fitting methods

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Abstract

Pressure support ventilation (PSV) should be titrated considering the pressure developed by the respiratory muscles (P_{musc}) to prevent under- and over-assistance. The esophageal pressure (P_{es}) is the clinical gold standard for P_{musc} assessment, but its use is limited by alleged invasiveness and complexity. The *least square fitting* method and the *end-inspiratory occlusion* method have been proposed as non-invasive alternatives for P_{musc} assessment. The aims of this study were: (1) to compare the accuracy of P_{musc} estimation using the *end-inspiration occlusion* ($P_{musc,index}$) and the *least square fitting* ($P_{musc,lsf}$) against the reference method based on P_{es}; (2) to test the accuracy of $P_{musc,lsf}$ and of $P_{musc,index}$ to detect overassistance, defined as $P_{musc} \leq 1$ cmH$_2$O. We studied 18 patients at three different PSV levels. At each PSV level, P_{musc}, $P_{musc,lsf}$, $P_{musc,index}$ were calculated on the same breaths. Differences among P_{musc}, $P_{musc,lsf}$, $P_{musc,index}$ were analyzed with linear mixed effects models. Bias and agreement were assessed by Bland–Altman analysis for repeated measures. The ability of $P_{musc,lsf}$ and $P_{musc,index}$ to detect overassistance was assessed by the area under the receiver operating characteristics curve. Positive and negative predictive values were calculated using cutoff values that maximized the sum of sensitivity and specificity. At each PSV level, $P_{musc,lsf}$ was not different from P_{musc} ($p = 0.96$), whereas $P_{musc,index}$ was significantly lower than P_{musc}. The bias between P_{musc} and $P_{musc,lsf}$ was zero, whereas $P_{musc,index}$ systematically underestimated P_{musc} of 6 cmH$_2$O. The limits of agreement between P_{musc} and $P_{musc,lsf}$ and between P_{musc} and $P_{musc,index}$ were ± 12 cmH$_2$O across bias. Both $P_{musc,lsf} \leq 4$ cmH$_2$O and $P_{musc,index} \leq 1$ cmH$_2$O had excellent negative predictive value [0.98 (95% CI 0.94–1) and 0.96 (95% CI 0.91–0.99), respectively)] to identify over-assistance. The inspiratory effort during PSV could not be accurately estimated by the *least square fitting* or *end-inspiratory occlusion* method because the limits of agreement were far above the signal size. These non-invasive approaches, however, could be used to screen patients at risk for absent or minimal respiratory muscles activation to prevent the ventilator-induced diaphragmatic dysfunction.

Keywords Mechanical ventilation · Inspiratory effort · Respiratory muscles · Esophageal pressure · Least square fitting · End-inspiratory occlusion

Abbreviations

CI	Confidence interval
E_{cw}	Chest wall elastance
E_{rs}	Elastance of the respiratory system
P_0	Basal pressure
$P_{0.1}$	Airway occlusion pressure at 100 ms
P_{appl}	Pressure applied to the respiratory system
P_{aw}	Airway pressure
P_{cw}	Relaxation pressure of the chest wall
P_{el}	Elastic pressure
$P_{exp,es}$	End-expiratory plateau esophageal pressure
P_{musc}	Pressure developed by respiratory muscles during inspiration
$P_{musc,index}$	P_{musc} estimated by the *end-inspiration occlusion* method
$P_{musc,lsf}$	P_{musc} estimated by the *least square fitting* method
$P_{plat,aw}$	End-inspiratory plateau airway pressure

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$P_{plat,es}$	End-inspiratory plateau esophageal pressure
P_{res}	Resistive pressure
PEEP	Positive end-expiratory pressure
$PEEP_{tot}$	Total PEEP
PS	Pressure support
PS_{base}	Baseline PS
PS_{max}	Maximal PS
PS_{min}	Minimal PS
PSV	Pressure support ventilation
PTP	Pressure–time product
R_{rs}	Resistance of the respiratory system
ROC	Receiver operating characteristics
V	Volume
V′	Flow

1 Background

Pressure support ventilation (PSV) is a ventilatory mode that supports the pressure developed by respiratory muscles during inspiration (P_{musc}) with an external positive pressure applied at the airway opening, synchronized with the inspiratory effort. Since PSV supports the spontaneous breathing effort it should be titrated on patient's instantaneous P_{musc} to prevent under- and over-assistance, i.e. PSV-induced respiratory muscle fatigue and atrophy, respectively [1]. Unfortunately, since P_{musc} is not easily measured in clinical practice, the degree of support is in fact titrated taking into account the overall clinical appearance of the patient, few breathing pattern parameters as respiratory rate and tidal volume, and, finally the airway pressure (P_{aw}) and airflow waveforms on the ventilator screen.

The esophageal pressure method is the clinical gold standard for P_{musc} assessment [2], but it is seldom used in daily practice due its alleged invasiveness and complexity. The *least square fitting* [3] and the *end-inspiratory occlusion* methods [4] have been proposed as non-invasive alternatives. The *least square fitting* is the instantaneous computation of P_{musc} derived by solving the equation of motion [5] by P_{aw}, airflow, inspired volume, respiratory system elastance and resistance (E_{rs} and R_{rs}, respectively) [3]. The *end-inspiration occlusion* method estimates the end-inspiratory P_{musc} as the difference between the P_{aw} applied by the ventilator during the inspiratory phase P_{aw} and the plateau reached by P_{aw} during an end-inspiratory airway occlusion maneuver [4]. Both these methods have been evaluated in physiological studies, conducted on relatively few patients [3, 4] but to our knowledge their validation against the "reference" P_{es} method is lacking. Thus, it is not clear whether they are sufficiently accurate to guide PSV titration in clinical practice.

The primary aim of this study was to compare P_{musc} calculated from P_{es} with its estimation by the *end-inspiration occlusion* method ($P_{musc,index}$) and by the *least square fitting* method ($P_{musc,lsf}$) in critically ill patients ventilated with the PSV mode. The secondary aim was to test the accuracy of $P_{musc,lsf}$ and $P_{musc,index}$ to detect overassistance during PSV, defined as a near-passive patients ($P_{musc} \leq 1$ cmH_2O).

2 Methods

2.1 Patients

Consecutive patients were recruited in the Intensive Care Unit of Poliambulanza Foundation Hospital (Brescia, Italy) between January 2016 and June 2016. Inclusion criteria were: age > 18 years; dependence on invasive mechanical ventilation (i.e. not ready to be weaned or having failed a spontaneous breathing trial on the day of the study [6]); PSV used as ventilatory mode; absence of flow limitation as assessed by maneuver of compression of the abdomen [7–9]. Patients were excluded in case of: hemodynamic instability (defined as mean arterial pressure < 60 mmHg, systolic arterial pressure > 180 mmHg, heart rate < 40/min or > 150/min); $PaO_2/FIO_2 < 150$ mmHg; pH < 7.35 with $PaCO_2 > 45$ mmHg; contraindication to perform the maneuver of compression of the abdomen [7]; diagnosis of head injury, intracranial hemorrhage or cerebral ischemia. The protocol was approved by the local ethical committee (Comitato Etico Provinciale di Brescia, approval number NP2245). Written informed consent was obtained from the patient. In case of altered consciousness, the Ethics Committees waived the requirement for consent, as in Italy relatives are not regarded as legal representatives of the patient in the absence of a formal designation. Written informed consent was requested from all surviving patients as soon as they regained their mental competency. All investigations were conducted according to the principles expressed in the Declaration of Helsinki.

Esophageal pressure was measured by an esophageal balloon catheter (Marquat Gbm, Boissy-St-Léger Cedex, France) connected to a pressure transducer (AS3/CS3; Datex-Engstrom Division, Instrumentarium Corp., Helsinki, Finland). The esophageal balloon was introduced 40 cm from the nostril and inflated with 1 ml of air. The occlusion test was used to assess if the esophageal pressure was appropriately transduced [10]. The position of the balloon in the esophagus and its filling volume were optimized to obtain a ratio between esophageal and airway pressure swings during occlusion ranging between 0.8 and 1.2 [11, 12].

2.2 Study protocol

The clinical PSV level at the patient's enrollment was defined as *baseline PSV* (PS_{base}). Successively, in order to explore a wide clinical range of PS assistance, maximal and minimal PS (PS_{max} and PS_{min}, respectively) were titrated as follows: PS_{max} was sought by progressively increasing the PS until disappearance of any sign of inspiratory muscle activity after inspiratory triggering. This was assessed by visual inspection of the P_{es}, airway pressure and airflow waveforms. For safety reasons, the peak airway pressure was limited to a maximum of 35 cmH_2O, regardless of achieving complete absence of inspiratory muscles during inspiratory flow. The PS_{min} was identified by the lowest PS without dyspnea or rapid shallow breathing (respiratory rate/tidal volume $< 100\ min^{-1}\ l^{-1}$). Apart from the PS, all the other ventilatory variables remained constant throughout the study, as previously set by the attending physician.

The three PSV levels (PS_{base}, PS_{min} and PS_{max}) were delivered in random order to each patient for 20 min. At the end of each PS level period, five end-expiratory and end-inspiratory airway occlusion maneuvers were performed. These were performed at the end of each PS period in order to avoid carry over effects originating from the previous PS level. Each occlusion maneuver lasted 3 s and was separated by the previous and next maneuver by at least ten non-interrupted breaths.

2.3 Measurements and calculations

Immediately before the beginning of the occlusion maneuvers, P_{es}, P_{aw}, airflow and volume curves were recorded for 5 min at the sampling rate of 100 Hz (Datex-Ohmeda S/5 Collect; Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland) and reconstructed from the sampled data through the R software (R Core Team, 2018, R Foundation for Statistical Computing, Vienna, Austria). The following parameters were measured on the occluded breaths: total positive end-expiratory pressure ($PEEP_{tot}$), i.e. the airway pressure recorded during end-expiratory plateau, end-expiratory plateau esophageal pressure ($P_{exp,es}$), end-inspiratory plateau airway pressure ($P_{plat,aw}$), end-inspiratory plateau esophageal pressure ($P_{plat,es}$). The minimum acceptable length for a plateau was 0.25 s and its adequacy was judged by visual inspection [4]. Any occlusion pressure without a clearly identifiable plateau was discarded. Auto-PEEP was calculated as the difference between $PEEP_{tot}$ and the set PEEP. Airway occlusion pressure at 100 ms ($P_{0.1}$) was measured as the drop in airway pressure after 100 ms of an inspiratory attempt with occluded airway [13]. The onset of inspiration was identified by a fall in the esophageal pressure, the end of inspiration was identified by the last positive value of the inspiratory flow. P_{musc} was estimated as the maximal difference between the relaxation pressure of the chest wall (P_{cw}) and the esophageal pressure measured during inspiration. P_{cw} is the product of the inspired volume and the chest wall elastance (E_{cw}). E_{cw} was calculated as the ratio ($P_{plat,es} - P_{exp,es}$)/tidal volume. Patients were categorized as 'near-passive' if P_{musc} was equal or lower than 1 cmH_2O, all other patients being classified as 'active'. The Pressure–Time Product (PTP) was computed as the area between P_{cw} and P_{es} during inspiration multiplied by the respiratory rate (Fig. 1, left panel).

2.4 The least square fitting method

The pressure applied to the respiratory system during ventilation (P_{appl}) can be calculated at any time *t* by the equation of motion as the sum of elastic pressure (P_{el}) and resistive pressure (P_{res}) on the basal pressure (P_0) [5]:

$$P_{appl}(t) = P_{el}(t) + P_{res}(t) + P_0. \tag{1}$$

$P_{el}(t)$ is the product between $V(t)$, the volume at the time *t*, and E_{rs}. $P_{res}(t)$ is calculated as the flow, $V'(t)$, multiplied by R_{rs}. Finally, P_0 corresponds to $PEEP_{tot}$. Equation 1 can be rewritten as:

$$P_{aw}(t) = V(t) \cdot E_{rs} + V'(t) \cdot R_{rs} + PEEP_{tot}. \tag{2}$$

We calculated E_{rs} and R_{rs} as the coefficients of V and V', respectively, by fitting the equation of motion during PS_{max}. In this setting, based on previous report, we assumed that the inspiratory muscles were near totally relaxed, allowing a reliable calculation of passive respiratory mechanics [14, 15].

During assisted mechanical ventilation, P_{appl} is the sum of the airway pressure (P_{aw}), generated by the mechanical ventilator, and P_{musc}. Equation 2 can be rewritten as:

$$P_{aw}(t) + P_{musc}(t) = V(t) \cdot E_{rs} + V'(t) \cdot R_{rs} + PEEP_{tot}. \tag{3}$$

Equation 3 can be rearranged to estimate P_{musc} with the least square fitting [3] ($P_{musc,lsf}$):

$$P_{musc,lsf}(t) = V(t) \cdot E_{rs} + V'(t) \cdot R_{rs} + PEEP_{tot} - P_{aw}(t) \tag{4}$$

PTP_{lsf} was calculated as the area delimited by $P_{musc,lsf}(t)$ (Fig. 1, right panel).

2.5 The end-inspiratory occlusion method

P_{musc} estimation with this method is also known as $P_{musc,index}$ or PMI [4]. $P_{musc,index}$ was calculated as the difference between $P_{plat,aw}$ and the pressure applied by ventilator during the inspiratory phase:

$$P_{musc,index} = P_{plat,aw} - (PS + PEEP) \tag{5}$$

where $P_{plat,aw}$ is the sum of P_{el} and $PEEP_{tot}$ [16]:

$$P_{plat,aw} = P_{el} + PEEP_{tot}. \tag{6}$$

Therefore, Eq. 5 can be rewritten as

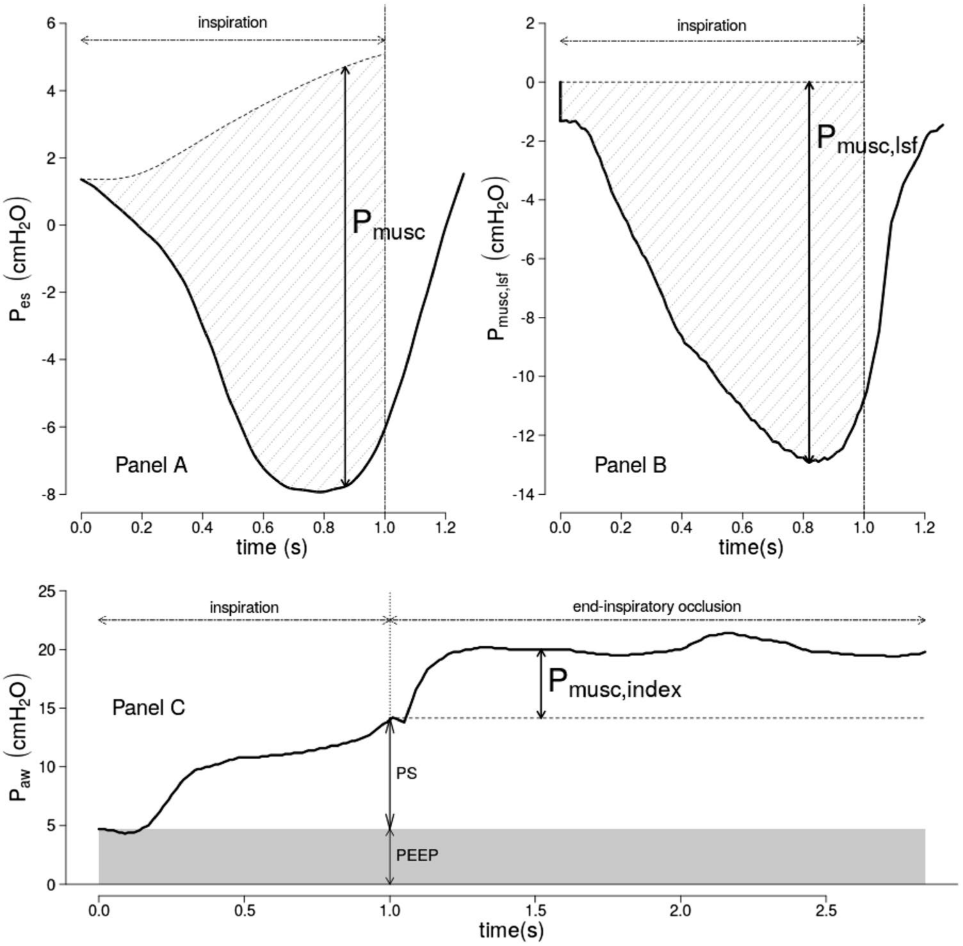

Fig. 1 Inspiratory effort assessed by esophageal pressure, least square fitting method and inspiratory occlusion method. P_{es} esophageal pressure, P_{musc} inspiratory swing measured between elastic recoil pressure of chest wall and esophageal pressure, $P_{musc,lsf}$ P_{musc} estimated with least square fitting method, P_{aw} airway pressure, $P_{musc,index}$ P_{musc} estimated with end-inspiratory occlusion method, *PS* pressure support level, *PEEP* positive end-expiratory pressure. **a** Esophageal pressure, continuous line: esophageal pressure; dashed line: elastic recoil pressure of the chest wall; dotted area: pressure–time product. **b** Least square fitting method, continuous line: $P_{musc,lsf}$; dashed line: baseline at 0 cmH$_2$O; dotted area: pressure–time product as calculated by *least square fitting* method. **c** End-inspiratory occlusion method, continuous line: airway pressure; dashed line: sum of PS and PEEP

$$P_{musc,index} = (P_{el} + PEEP_{tot}) - (PS + PEEP) \tag{7}$$

and by rearrangements

$$P_{musc,index} = P_{el} + (PEEP_{tot} - PEEP) - PS \tag{8}$$

Since autoPEEP is the difference between $PEEP_{tot}$ and PEEP,

$$P_{musc,index} = P_{el} + autoPEEP - PS. \tag{9}$$

Equation 9 makes evident that $P_{musc,index}$ includes both the pressure required to generate the tidal volume and the pressure necessary to overcome auto-PEEP while the P_{musc} needed to overcome the resistive load remains undetected.

P_{musc}, $P_{musc,lsf}$, $P_{musc,index}$, PTP and PTP_{lsf} were calculated on each breath in which the inspiratory occlusion maneuver was performed.

Each measurement was independently performed by at least 3 authors (among GN, BB, AG, EA, LP) and medians used for the analysis. "P_{musc}, $P_{musc,lsf}$, $P_{musc,index}$, PTP and PTP_{lsf} were calculated on all breaths in which the inspiratory occlusion maneuver was performed and that were of sufficient quality to be scored by all the 3 independent scorers".

2.6 Outcomes

The primary outcome was the agreement between P_{musc} calculated through the P_{es} method (deemed as the gold standard), $P_{musc,lsf}$ and $P_{musc,index}$. The secondary outcome was the accuracy of $P_{musc,lsf}$ and $P_{musc,index}$ to detect near-passive patients (defined as $P_{musc} \leq 1$ cmH$_2$O, see above).

2.7 Statistical analysis

Data are shown as mean ± standard deviation, median (1st-3rd quartile) or frequency (percentage).

In order to detect differences among P_{musc}, $P_{musc,lsf}$, and $P_{musc,index}$, we calculated a sample size of 18 patients obtained considering a size effect 0.4 on the primary endpoint, alpha error 0.05, power 0.8, T tests family and fixed model single regression coefficient as statistical test (G*Power 3.1.9.2, Heinrich-Heine-Universität, Düsseldorf, Germany [17].

Linear mixed effects models were used to compare variables (PS level as fixed effect, patients as random effect). The methods of P_{musc} measurement (esophageal pressure, least square fitting, end-inspiratory pause) and their relationships were similarly analyzed with linear mixed effects models (method and PS levels as fixed effects, patients as random effect). Comparison among groups were analyzed with the Tukey test.

Bias and agreement were assessed by Bland–Altman analysis for repeated measures [18]. The accuracy of $P_{musc,lsf}$ and $P_{musc,index}$ to detect near-passive patients was assessed by the area under the receiver operating characteristics (ROC) curve. The areas under ROC curves were compared with the DeLong test. We also calculated the positive and negative predictive values and the confidence intervals at 95% level (95% CI), using the values that maximized the sum of sensitivity and specificity as cut-offs.

A p value lower than 0.05 was considered significant. Statistical analyses were performed with R (R Core Team, 2018. R Foundation for Statistical Computing, Vienna, Austria) with packages "lme4" (version 1.1–17) and "multcomp" (version 1.4–8).

3 Results

We studied 18 consecutive patients whose baseline characteristics are shown in Table 1. Breathing pattern, respiratory drive and inspiratory effort data are shown in Table 2. By increasing the PS level, P_{musc} and respiratory rate decreased and tidal volume increased.

At all the three PSV levels, $P_{musc,lsf}$ was not different from P_{musc} ($p = 0.96$), whereas $P_{musc,index}$ was significantly lower than P_{musc} ($p < 0.001$) (Fig. 2, top panel). PTP_{lsf} was not different from PTP ($p = 0.92$, Fig. 2, bottom panel). The relationship between P_{musc} and $P_{musc,lsf}$ and between P_{musc} and $P_{musc,index}$ were weak although statistically significant ($r^2 = 0.34$, $p < 0.001$ and $r^2 = 0.19$, $p < 0.001$ respectively).

Figure 3 shows the Bland–Altman plots assessing the agreement between P_{musc} and $P_{musc,lsf}$ (left side) and P_{musc} and $P_{musc,index}$ (right side). The bias between P_{musc} and $P_{musc,lsf}$ was zero, whereas the bias between P_{musc} and $P_{musc,index}$ was 6 cmH_2O. Both plots show similar limits of agreement of ± 12 cmH_2O across bias.

There was a weak relationship between PTP and PTP_{lsf} ($r^2 = 0.27$, $p < 0.001$), with a bias of -7 cmH2O·s·min^{-1} (95% limits of agreement: from—192 to 178 cmH_2O·s·min^{-1}).

$P_{musc,lsf}$ and $P_{musc,index}$ were moderately accurate to identify a near-passive patients, with areas under ROC curve of 0.73 (95% CI 0.65–0.81) and 0.87 (95% CI 0.8–0.94), respectively ($p = 0.01$). Both $P_{musc,lsf} \leq 4 cmH_2O$ and $P_{musc,index} \leq 1 cmH_2O$ had very low positive predictive value [0.33 (95% CI 0.23–0.45) and 0.22 (95% CI 0.15–0.31), respectively)] but excellent negative predictive value [0.98 (95% CI 0.94–1) and 0.96 (95% CI 0.91–0.99), respectively)]. The sensitivity and specificity were as follow [0.89 (95% CI 0.72–0.98) and 0.73 (95% CI 0.66–0.79)] for $P_{musc,lsf}$, respectively, and [0.86 (95% CI 0.67–0.96) and 0.55 (95% CI 0.47–0.62)] for $P_{musc,index}$, respectively. In practical terms, one can very likely exclude that a patient is near-passive during PSV when $P_{musc,lsf} > 4 cmH_2O$ or $P_{musc,index} > 1$ cmH_2O.

Table 1 Patients characteristics

Age (years)	71 ± 13
Female, n (%)	6 (33%)
Body mass index (kg•m^{-2})	26 ± 6
Days on mechanical ventilation at enrollment	9 (3–20)
Patients with tracheostomy on study day, n (%)	7 (39%)
Length of stay in intensive care unit (days)	21 (14–32)
Hospital mortality, n (%)	3 (17%)
Pressure support level at enrollment (cmH_2O)	10 ± 3
Positive end-expiratory pressure (cmH_2O)	6 ± 1
FIO_2	0.37 ± 0.08
pH	7.48 ± 0.04
$PaCO_2$ (mmHg)	36 ± 7
PaO_2 (mmHg)	92 ± 21
$P_{0.1}$ at PS_{max} (cmH_2O)	1 ± 1
Elastance of the respiratory system (cmH_2O l^{-1})	19 ± 12
Resistance of the respiratory system (cmH_2O l^{-1} s)	10 ± 5

$P_{0.1}$ airway occlusion pressure at 100 ms, PS_{max} maximal pressure support (see "Methods" section for details)

Table 2 Inspiratory effort and breathing pattern at the three pressure support levels

	PS_{min}	PS_{base}	PS_{max}	*p*
Pressure support (cmH_2O)	4 ± 1	10 ± 3	18 ± 5	< 0.001
Tidal volume (ml)	453 ± 121	544 ± 163	703 ± 211	< 0.001
Respiratory rate (min^{-1})	27 ± 9	23 ± 8	18 ± 6	< 0.001
P_{musc} (cmH_2O)	12 ± 7	10 ± 8	5 ± 5	< 0.001
$P_{musc,lsf}$ (cmH_2O)	13 ± 7	9 ± 7	5 ± 6	< 0.001
$P_{musc,index}$ (cmH_2O)	7 ± 4	3 ± 5	− 2 ± 3	< 0.001
PTP (cmH_2O s min^{-1})	206 ± 164	135 ± 128	59 ± 103	< 0.001
PTP_{lsf} (cmH_2O s min^{-1})	277 ± 201	167 ± 192	54 ± 102	< 0.001
$P_{0.1}$ (cmH_2O)	3 ± 2	3 ± 2	1 ± 1	< 0.001

PS_{min} minimal pressure support, PS_{base} baseline pressure support, PS_{max} maximal pressure support (see "Methods" section for explanation)

P_{musc} inspiratory swing measured between elastic recoil pressure of the chest wall and esophageal pressure, $P_{musc,lsf}$ P_{musc} estimated with least square fitting, $P_{musc,index}$ P_{musc} estimated with end-inspiratory occlusion, *PTP* pressure–time product measured between elastic recoil pressure of the chest wall and esophageal pressure, PTP_{lsf} PTP calculated with least square fitting, $P_{0.1}$ airway occlusion pressure at 100 ms

All pairwise comparisons between the three PS levels were significant ($p < 0.05$)

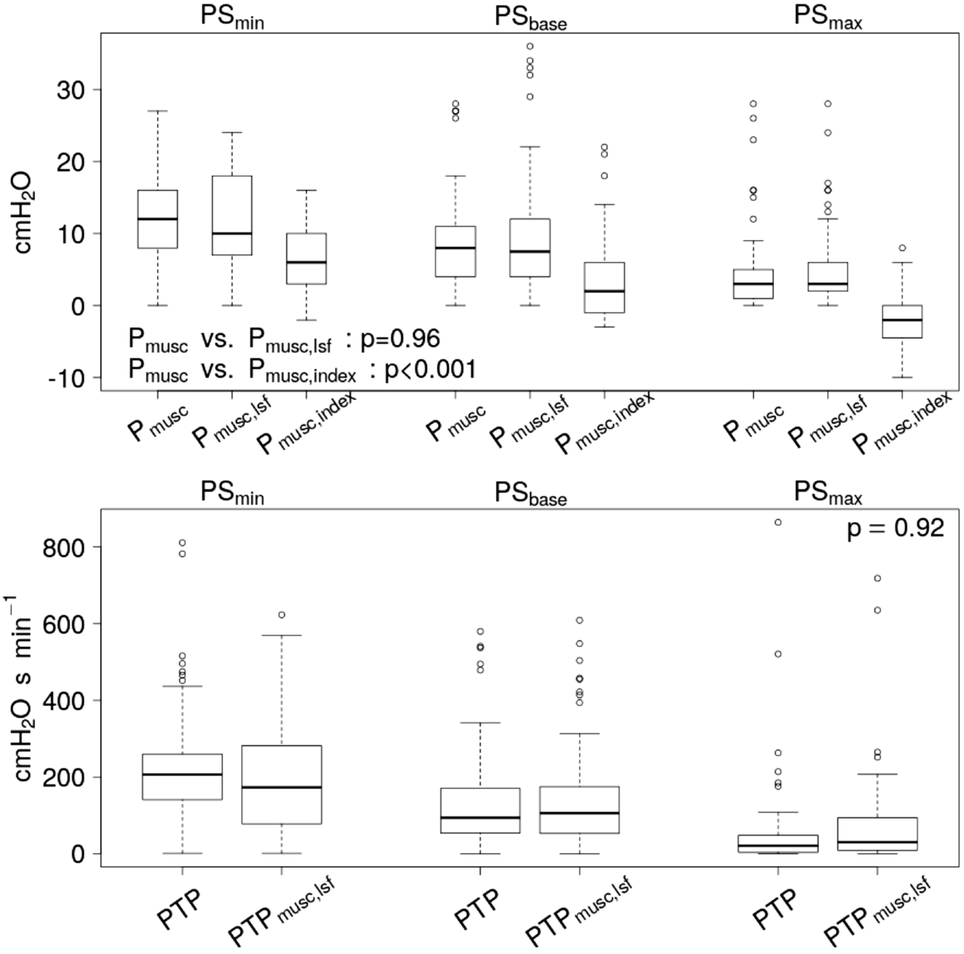

Fig. 2 Measured and estimated inspiratory effort at PSmin, PSbase and Psmax. PS_{min}: minimal pressure support; PS_{base}: baseline pressure support; PS_{max}: maximal pressure support (see "Methods" section for explanation). *Top*: P_{musc}: inspiratory swing measured between elastic recoil pressure of chest wall and esophageal pressure; $P_{musc,lsf}$: P_{musc} estimated with *least square fitting* method; $P_{musc,index}$: P_{musc} estimated with *end-inspiratory occlusion* method. *Bottom:* PTP: Pressure–time product; PTP_{lsf}: PTP estimated with the *least square fitting* method

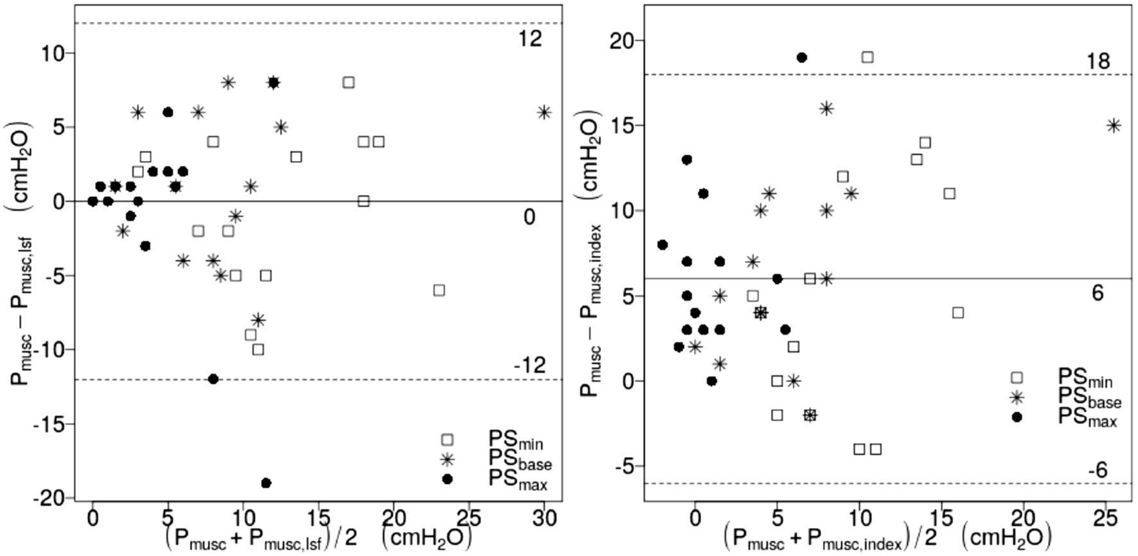

Fig. 3 Title: Bland–Altman plot for measured and calculated inspiratory effort. *PS_{min}* minimal pressure support, *PS_{base}* baseline pressure support, *PS_{max}* maximal pressure support, *P_{musc}* inspiratory swing of the pressure generated by respiratory muscles measured on esophageal pressure, *$P_{musc,lsf}$* inspiratory swing of the pressure generated by respiratory muscles calculated with *least square fitting* method, *$P_{musc,index}$* inspiratory pressure generated by respiratory muscles estimated with *end-inspiratory occlusion* method. Continuous line: bias; dashed line: 95% limits of agreement

4 Discussion

Our investigation showed that the pressure developed by inspiratory muscles cannot be accurately estimated by the *least square fitting* or *end-inspiratory occlusion* as the limits of agreement between measured and estimated inspiratory effort were far above the signal size. However, both non-invasive methods of P_{musc} estimation tested in the present study were able to exclude that a patient was near-passive during PSV.

The least square fitting method has been proposed to estimate respiratory mechanics [14] and inspiratory effort during PSV more than 20 years ago [3] and is still in use in some mechanical ventilators. Despite average values of P_{musc} and $P_{musc,lsf}$ were similar at different PSV levels, we found that the individual estimation of the inspiratory effort by $P_{musc,lsf}$ was largely inaccurate. Theoretically there are two main factors that could impair the accuracy of the *least square fitting* method: flow limitation [19, 20] and high respiratory drive [14]. We excluded flow-limited patients from the study using the manual compression of the abdomen method, that has been shown to detect flow limitation in resting supine and seated subjects, during exercise and mechanical ventilation [7–9]. Regarding the respiratory drive, we must point out that $P_{0.1}$ averaged 1 cmH_2O during PS_{max} (the level at which respiratory system elastance and resistance were calculated with the least square fitting method), a respiratory drive that ensures an effective near-relaxation during PSV [14]. Additionally, by re-assessing the agreement between P_{musc} and $P_{musc,lsf}$ using only the data of the 11 patients with $P_{0.1}$ equal or lower than 1 cmH_2O, the results shown in Fig. 3 were substantially confirmed (bias 0 cmH_2O, 95% limits of agreement from − 10 to 10 cmH_2O). For these reasons, we believe that the failure of *least square fitting* to estimate P_{musc} cannot be explained by high respiratory drive. Iotti and coworkers previously showed that the relationship between P_{musc} and $P_{musc,lsf}$ decreases by increasing the PS [3]. We performed a supplemental analysis by testing the relationship between P_{musc} and $P_{musc,lsf}$ at PS_{max} and, confirming the Iotti data, it was not significant ($r^2 = 0.002$, $p = 0.59$). In summary, despite its solid theoretical basis, our data suggest that P_{musc} estimation with the *least square fitting* is not accurate during PSV.

The *end-inspiratory occlusion* is a “static” method, that assumes that all the applied pressure (i.e. $P_{aw} + P_{musc}$) is spent to generate the volume and overcome $PEEP_{tot}$, and that the applied pressure spent to generate the inspiratory airflow is negligible [4]. Accordingly, the P_{musc} assessed with the *end-inspiratory occlusion* method does not include the resistive component of work of breathing and P_{musc} at end inspiration is usually lower than the maximum inspiratory deflection of P_{musc} during inspiration, as shown in Fig. 1 [4]. Our data confirm the systematic underestimation of P_{musc} by $P_{musc,index}$, with an average bias of 6 cmH_2O (Fig. 3). The *end-inspiratory occlusion* method can be performed with multiple occlusions, each at a different inspiratory volume in the tidal volume range [21, 22]. This alternative approach, requiring an external software to control the mechanical ventilator and the assessment of residual P_{res} at end inspiration, was able to overcome the P_{musc} underestimation and to reduce the 95% CI of agreement between P_{musc} and $P_{musc,index}$ to − 5 to 5 cmH_2O [22]. Therefore, we cannot exclude that a more complex application of *end-inspiratory occlusion* method could yield better results.

$P_{musc,index}$ and $P_{musc,lsf}$ may prove to maintain a sound clinical usefulness despite their poor agreement with P_{musc}. Diaphragm weakness is present in a high percentage of critically ill patients and is associated with increased morbidity and mortality. Indeed, a well recognized cause of diaphragm dysfunction is disuse secondary to ventilator-induced diaphragm inactivity [1] and preserving diaphragmatic contractions during mechanical ventilation attenuates the force loss induced by inactivity [23–25]. We found that both the $P_{musc,index}$ and $P_{musc,lsf}$ were able to exclude a near-passive state during ventilation. Thus, $P_{musc,index}$ and $P_{musc,lsf}$ may prove clinically useful if they are used to screen for patient’s passivity during PSV. Since we found that the near-passive condition is very unlikely whenever $P_{musc,lsf} > 4$ cmH_2O or $P_{musc,index} > 1$ cmH_2O, patients with $P_{musc,lsf}$ below 4 cmH_2O or $P_{musc,index}$ below 1 cmH_2O should be carefully assessed to exclude absent or minimal activation of inspiratory muscles, a condition often associated with auto-cycling. *End-inspiratory occlusion* is simpler and easier to perform at the bedside compared with the *least square fitting* method. Unfortunately some mechanical ventilators do not allow to perform end-inspiratory occlusions during PSV, precluding the assessment of $P_{plat,aw}$ and hence to infer relevant information about patient’s inspiratory effort and driving pressure [26].

One potential limitation of our study is the choice to explore the entire clinical range of the inspiratory support. This could have negatively affected the agreement between P_{musc} and its non-invasive estimates; however, we considered this pragmatic design a strength rather than a limitation, as it sought to validate the least square fitting and the end-inspiratory occlusion methods in a wide range of clinical circumstances. We cannot exclude, however, that different PSV levels than the ones tested in our study would have improved the performance of the non-invasive P_{musc} estimation method.

5 Conclusions

In conclusion, our investigation showed that the inspiratory effort during PSV could not be accurately estimated by the *least square fitting* or *end-inspiratory occlusion* method. These non-invasive approaches, however, proved valid to screen patients at risk for absent or minimal respiratory muscles activation to prevent the ventilator-induced diaphragmatic dysfunction.

Author contributions GN, AR and AB contributed to the conception and design of the study; GN, BB, AG, EA, LP, GC, VL contributed to the acquisition of data; GN and LP contributed to the analysis of the data; GN, LP and Salvatore Grasso drafted the manuscript; Nicola Latronico and Massimo Antonelli revised the manuscript; all authors contributed to the interpretation of the data, critically revised the manuscript and approved the final version to be submitted.

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Data availability The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval The protocol was approved by the local ethical committee (Comitato Etico Provinciale di Brescia, approval number NP2245).

Informed consent Written informed consent was obtained from the patient. In case of altered consciousness, the Ethics Committees waived the requirement for consent, as in Italy relatives are not regarded as legal representatives of the patient in the absence of a formal designation. Written informed consent was requested from all surviving patients as soon as they regained their mental competency.

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