Validation of a Proposed Algorithm for Assistance Titration During Proportional Assist Ventilation With Load-Adjustable Gain Factors

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BACKGROUND: The present study aimed to validate a recently proposed algorithm for assistance titration during proportional assist ventilation with load-adjustable gain factors, based on a noninvasive estimation of maximum inspiratory pressure (peak P_{mus}) and inspiratory effort (pressure-time product [PTP] peak P_{mus}). METHODS: Retrospective analysis of the recordings obtained from 26 subjects ventilated on proportional assist ventilation with load-adjustable gain factors under different conditions, each considered as an experimental case. The estimated inspiratory output (peak P_{mus}) and effort (PTP-peak P_{mus}) were compared with the actual-determined by the measurement of transdiaphragmatic pressure- and the derived PTP. Validation of the algorithm was performed by assessing the accuracy of peak P_{mus} in predicting the actual inspiratory muscle effort and indicating the appropriate level of assist. RESULTS: In the 63 experimental cases analyzed, a limited agreement was observed between the estimated and the actual inspiratory muscle pressure (−11 to 10 cm H_2O) and effort (−82 to 125 cm H_2O × s/min). The sensitivity and specificity of peak P_{mus} to predict the range of the actual inspiratory effort was 81.2% and 58.1%, respectively. In 49% of experimental cases, the level of assist indicated by the algorithm differed from that indicated by the transdiaphragmatic pressure and PTP. CONCLUSIONS: The proposed algorithm had limited accuracy in estimating inspiratory muscle effort and with indicating the appropriate level of assist. *Key words: assistance; titration; proportional assist ventilation; inspiratory muscles output.* [Respir Care 2020;65(1):36–44.

Introduction

Proportional assist ventilation (PAV) with load-adjustable gain factors (PAV+) is a patient effort-driven mode of assisted ventilation, in which the ventilator provides pressure proportional to the patient's instant flow and volume, and thus is proportional to the elastic and resistive work load.[1-3] Previous studies demonstrated the effectiveness of PAV+ relative to conventional assisted modes of mechanical ventilation.[4-8] However, clinical use of this mode is limited, likely due to the lack of established criteria for titrating the level of support. The conventional method of assistance titration, based on tidal volume (V_T) and breathing frequency may be hindered during ventilation on PAV+; with this mode, significant variability in V_T has been observed, and patients retain their desired breathing pattern.[4,9]

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A clinical algorithm has been introduced to titrate the level of assistance during ventilation on PAV+, which uses a noninvasive estimation of respiratory muscle output (maximum inspiratory pressure [peak P_{mus}]) and effort (pressure-time product [PTP] of peak P_{mus}.[10] The level of support used peak P_{mus} to target a predefined range (5–10 cm H_2O), which is estimated to correspond to the generally accepted range of inspiratory muscle effort (PTP of 50–150 cm $H_2O \times$ s/min).

Clinical applicability of this algorithm was evaluated in a group of subjects on mechanical ventilation with various forms of acute respiratory failure.[10] By adjusting the gain in PAV+ by using this algorithm, the majority of the subjects were successfully weaned from the ventilator. The investigators concluded that peak P_{mus} and the derived pressure time product of peak P_{mus} might serve as accurate surrogates of pressure generated by the respiratory muscles and inspiratory muscle effort, respectively.[10] However, the calculation of peak P_{mus} and PTP-peak P_{mus} was based on assumptions that might result in significant discrepancies between estimated and actual inspiratory muscle output and effort, as measured by transdiaphragmatic pressure (P_{di}) and the derived PTP-P_{di}.

Su et al[11] previously investigated the accuracy of this method in subjects who were critically ill. Peak P_{mus} and PTP-peak P_{mus} were compared with peak muscle pressure and effort calculated from esophageal pressure (P_{es}) at different levels of ventilator assist. Weak correlations were observed between both peak P_{mus} and peak muscle P_{es}, and the derived PTPs. However, this study was limited by the small number of subjects, the lack of gastric pressure measurement, and the lack of P_{di} measurement. Furthermore, the investigators did not evaluate the accuracy of peak P_{mus} for predicting inspiratory effort and indicating the appropriate level of assist. The present study aimed to evaluate the association between estimated and the actual values of inspiratory muscle output and effort by comparing peak P_{mus} with P_{di}, and PTP-peak P_{mus} with PTP-P_{di}; identify confounding physiologic factors that contribute to discrepancies between compared variables; and validate the accuracy of the proposed algorithm for assistance titration.

QUICK LOOK

Current knowledge

During proportional assist ventilation with load-adjustable gain factors (PAV+), the conventional method of assistance titration, based on tidal volume and breathing frequency, may be hindered because significant variability in tidal volume has been observed in this mode and patients retain their desired breathing largely independent of mechanical load and assistance level.

What this paper contributes to our knowledge

The present study retrospectively evaluated an algorithm for assistance titration during ventilation on PAV+. The algorithm showed limited accuracy for indicating the appropriate assist level.

Methods

We retrospectively analyzed the recordings of 26 subjects who participated in 3 previous research protocols. The ethics committee of the hospital approved the study design, and informed consent was obtained from the subjects or their families. This study was performed at the Department of Intensive Care Medicine, University Hospital of Heraklion, Heraklion, Crete, Greece. All the subjects were ventilated on PAV+ (Puritan-Bennett 840 ventilator, Medtronic, PLC, Ireland) at different levels of assist, and instrumented with esophageal and gastric balloons. As part of the individual research protocols, 15 subjects were studied with and without an artificial increase in the elastic work of breathing, accomplished by applying sandbags to the entire surface of the chest and abdominal wall. Each subject at each experimental condition was regarded as an individual experimental case.

Measurements

Flow, volume, airway pressure (P_{aw}), P_{es}, gastric pressure, and P_{di} (P_{di} = gastric pressure $-$ P_{es}) pressures were measured on a breath-by-breath basis, as previously described.[4,12] The proper position of the esophageal and gastric balloons was initially verified by using standard tests and procedures.[13]

Data Analysis

In each experimental case, at least 10 breaths over a period of 3 min were randomly analyzed and averaged to obtain breath variables for the corresponding experimental case. Breaths with a low-quality P_{di} signal were excluded. P_{di} was defined as the highest value of P_{di} during inspiration, and the inspiratory effort per breath (PTP-P_{di}) and PTP-P_{di}/min were quantified.[4,12] As previously described, the following were measured in each selected breath: the neural and mechanical inspiratory times; the difference between neural and mechanical inspiratory times (Δt); the rate of the rise of P_{di} (dp/dt); the triggering delay; the intrinsic PEEP (PEEPi); and the presence of expiratory muscle activity and contribution of the diaphragm and inspiratory rib cage muscles to inspiratory output (see the supplementary materials at http://www.rcjournal.com).[4,12,14] The estimated peak P_{mus} and the estimated inspiratory effort (PTP-peak P_{mus}) were calculated by using the formulas proposed by Carteaux et al[10] as follow:

$$\text{peak } P_{mus} = (P_{aw}\text{Peak} - \text{PEEP}) \times \frac{100\text{-gain}}{\text{gain}}.$$

Where P_{aw}Peak = peak inspiratory P_{aw} and gain = the level of assist.

$$\text{PTP} - \text{peak } P_{mus} = \frac{\text{peak } P_{mus} \times T_I m}{2} \times f$$

where T_Im = mechanical inspiratory time and f = breathing frequency (see the supplementary materials at http://www.rcjournal.com).[10]

The differences were calculated between peak P_{mus} and P_{di} (dP), and between PTP-peak P_{mus}/min and PTP-P_{di}/min (ΔPTP); dP and ΔPTP/min were also expressed as the percentage of P_{di} (dP%P_{di}) and PTP-P_{di}/min (ΔPTP/min% PTP-P_{di}/min), respectively.

Correlations between peak P_{mus}, PTP-peak P_{mus}, dP, and ΔPTP with each of the following possible confounding physiologic factors were evaluated (as independent variables): dp/dt (an index of respiratory drive); PEEPi; presence of expiratory muscle activity (yes/no); ratio of gastric pressure to P_{es} changes during inspiration, an index of contribution of the diaphragm and inspiratory rib cage muscles to the inspiratory output); triggering delay; and difference between the mechanical inspiratory time and the neural inspiratory time (Δt).

Validation of the Proposed Algorithm

The validation of the proposed algorithm was performed by assessing the accuracy of peak P_{mus} to correctly classify the actual inspiratory muscle effort, determined by the PTP-P_{di}. Specifically, in each experimental case, we assessed whether the measured PTP-P_{di} was within the range of that predicted by the peak P_{mus} inspiratory muscle effort (ie, <50 cm H_2O × s/min to peak P_{mus} of <5 m H_2O 50–150 cm H_2O × s/min to peak P_{mus} of 5–10 cm H_2O and >150 cm H_2O × s/min, to peak P_{mus} of >10 cm H_2O, respectively). Analysis was performed in all experimental cases combined and in 3 subgroups, determined by the peak P_{mus} value: <5, 5–10, and >10 cm H_2O (see the supplementary materials at http://www.rcjournal.com).

Statistical Analysis

Continuous variables are reported as the mean ± SD for normally distributed data, and median and interquartile range (IQR) for non-normally distributed data. Continuous variables were compared (2-tailed) by using the Wilcoxon test (paired sample). Linear regression analysis was used, and the coefficient of determination was calculated to examine the relationship between continuous variables. Analysis of residuals confirmed the assumptions of linearity. The agreement (bias) between variables was expressed as the mean of the corresponding differences. The limits of agreements were expressed as the mean ±1.96 SD, and 95% CIs of the bias were calculated by using the Bland-Altman method. The correlation between continuous variables was assessed by using Spearman's rho, followed (when indicated) by multiple regression analysis. Validation of the algorithm was performed by using receiver operating characteristic curve analysis. All statistical tests were 2-tailed, and $P < .05$ was considered to be statistically significant. Statistical analysis was performed by using MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium). Statistical analysis was reviewed by an external statistician to confirm that no conflict existed between identified correlations and investigators' interpretations. The sample size required obtaining a size effect of 0.8 between compared variables for a 2-sided α of 0.05, and study power of 80% was calculated to be 25 cases.

Results

The recordings of 26 subjects with respiratory failure from different causes were included in the analysis. Subject demographic and clinical characteristics are presented in Supplementary Table 1 (see the supplementary materials at http://www.rcjournal.com). In 10 subjects, as part of the original study design, we retrieved recordings at different levels of ventilator assist (up to 4). Fifteen subjects were studied before and after the experimental increase in elastic respiratory work load, at either the same (10 subjects) or different (5 subjects) levels of assistance. Sixty-three different levels of assistance were identified, and a total of 725 sufficient breaths were available for analysis. The mean ± SD level of assistance was 50 ± 14.5%. Physiologic variables and breath characteristics (median values and IQR) are shown in Table 1.

The median (IQR) difference between PTP-peak P_{mus}/min and PTP-P_{di}/min was 14.65 (−13.52 to 45.615) cm H_2O × s/min; the median (IQR) difference between peak P_{mus} and P_{di} was 0.68 (−3.29 to 2.11) cm H_2O. The PTP-peak P_{mus}/min (median, 87.15 cm H_2O × s/min) was significantly higher than PTP-P_{di}/per min (median, 71.19 cm H_2O × s/min; P = .04). However, in 38 experimental cases (60.31%), the difference between the 2 variables was negative (PTP-peak P_{mus} was lower than PTP-P_{di}/min). No significant difference was found between peak P_{mus} (median, 8.77) cm H_2O and P_{di} (median, 8.50; P = .45) (Fig. 1).

A significant linear relationship was present between peak P_{mus} and P_{di} (coefficient of determination, $R^2 = 0.346$, slope = 0.5253, $P < .001$), and between PTP-peak P_{mus} and PTP-P_{di} (R^2 = 0.33, slope = 0.729, $P < .001$); however, there was significant scatter in the measurements. Scatter plots and corresponding regression equations are

Table 1. Inspiratory Effort Indices and Breath Characteristics

Characteristic	Median	IQR
Inspiratory effort indices		
peak P_{mus}, cm H_2O	8.770	5.9–11.99
PTP-peak P_{mus}, cm $H_2O \times$ s/min	87.150	59–127.4
P_{di}, cm H_2O	8.5	5.42–11.68
PTP-P_{di}, cm $H_2O \times$ s/min	71.190	42.9–113.6
dP, cm H_2O	−0.68	−3.29 to 2.11
dP% Pdi	10.11	−31.4 to 33.1
ΔPTP, cm H_2O	14.65	−13.5 to 45.6
ΔPTP% PTP-P_{di}, %	20.8	−20.6 to 90.8
Breath characteristics		
V_T, L	0.39	0.33–0.50
$T_I$neural, s	0.65	0.49–0.91
$T_I$mec, s	0.97	0.81–1.17
T_E, s	1.89	1.55–2.55
Δt, s	0.33	0.22–0.46
T_{tot}	2.79	2.16–3.21
Delay trigger, s	0.17	0.13–0.2
dp/dt, cm H_2O/s	13.8	8.4–23.5
f, breaths/min	21.6	18.8–27.8
PEEPi, cm H_2O	1.17	0.47–1.8
PEEP external, cm H_2O	9.4	6–7.8
$\Delta P_{gas}/\Delta P_{eos}$	0.19	0.11–0.33

IQR = 25th-75th interquartile range
peak P_{mus} = calculated (from the formula) peak inspiratory pressure
PTP = pressure-time product
P_{di} = transdiaphragmatic pressure
dP = difference between peak P_{mus} and Pdi
V_T = tidal volume
$T_I$neural = neural inspiratory time
$T_I$mec = mechanical inspiratory time
T_E = expiratory time
Δt = difference between mechanical and neural inspiratory time
T_{tot} = the total breath duration
dp/dt = rate of rise of P_{di}
ΔPTP = the difference between peak P_{mus}-PTP and P_{di}-PTP
f = breathing frequency
PEEPi = intrinsic PEEP
$\Delta P_{gas}/\Delta P_{eos}$ = change in gastric pressure to changes in esophageal pressure during inspiration

shown in Supplementary Figure 1 (see the supplementary materials at http://www.rcjournal.com).

Bland-Altman analysis revealed limited agreement between peak P_{mus} and P_{di}, and between PTP-peak P_{mus} and PTP-P_{di} (Fig. 2). The mean difference (bias), limits of agreement, and corresponding 95% CIs of bias are shown in Table 2. Correlations between peak P_{mus}, PTP-peak P_{mus}, the difference between peak P_{mus} and P_{di}, and the difference between PTP peak P_{mus} and PTP_{Pdi} with each of the possible confounding physiologic factors are shown in Supplementary Table 3 (see the supplementary materials at http://www.rcjournal.com). Significant positive correlations were found between the rate of increase in dp/dt and both peak P_{mus} ($r_s = 0.49$, $P < .001$) and PTP-peak P_{mus} ($r_s = 0.24$, $P = .03$). The difference between peak P_{mus} and P_{di} (dP) was inversely correlated with dp/dt ([Spearman's rank correlation coefficient] $r_s = -0.39$, $P = .001$), which indicated an increase in dP with a decrease in dp/dt. A significant positive correlation was found between ΔPTP and the difference between mechanical and neural inspiratory time ($r_s = 0.28$, $P = .04$).

Validation of the Proposed Algorithm

Based on the proposed algorithm at peak P_{mus} of <5, 5–10, and >10 cm H_2O, inspiratory muscle effort was estimated to be <50, 50–150, and >150 cm $H_2O \times$ s/min, respectively; accordingly, the level of assistance was proposed as excessive (overassist), adequate, or insufficient (underassist).

Overall, in 31 of 63 experimental cases (49.21%), the inspiratory effort determined by the PTP-P_{di} was classified in a different range than that predicted by the calculated peak P_{mus}. The sensitivity and specificity of peak P_{mus} to predict the actual inspiratory effort and thus to correctly characterize the level of assist were 81.2% and 58.1%, respectively. The area under the receiver operating characteristic curve was 0.70 (95% CI 0.57–0.83; $P = .012$) (Fig. 3).

Subgroup 1: peak P_{mus} <5 cm H_2O

Peak P_{mus} was <5 cm H_2O in 11 of 63 experimental cases, which suggests low inspiratory effort and an excessive level of assist. Inspiratory effort measured by PTP-P_{di}/min was within the range predicted by peak P_{mus} in 7 of 11 experimental cases (63.64%). In the remaining experimental cases (4/11 [36.36%]), PTP-P_{di}/min was within acceptable limits (50–150 cm $H_2O \times$ s/min), which suggested an adequate level of assist.

Subgroup 2: peak P_{mus} of 5–10 cm H_2O

Peak P_{mus} ranged between 5 and 10 cm H_2O in 29 of 63 experimental cases, which indicated an adequate level of assist. Inspiratory effort measured by the PTP-P_{di}/min was within the range of inspiratory effort predicted by peak P_{mus} in 18 of 29 experimental cases (62.07%). In 11 of 29 experimental cases (37.93%), PTP-P_{di}/min was either <50 (31.03%) or >150 $H_2O \times$ s/min (6.89%), which indicated excessive or insufficient ventilator assist, respectively.

Subgroup 3: peak P_{mus} >10 cm H_2O

Peak P_{mus} was >10 cm H_2O in 23 of 63 experimental cases, which indicated high inspiratory effort and insufficient ventilator assist. PTP-P_{di}/min was within the range predicted by peak P_{mus} in 4 of 23 experimental cases (17.39%). PTP-P_{di}/min ranged from 50 to 150 cm $H_2O \times$ s/min in 15 of 22 experimental cases (65.21%), and was <50 cm $H_2O \times$ s/min in 4 of 22 experimental cases (17.39%), which indicated adequate or excessive ventilator assist, respectively (Fig. 4).

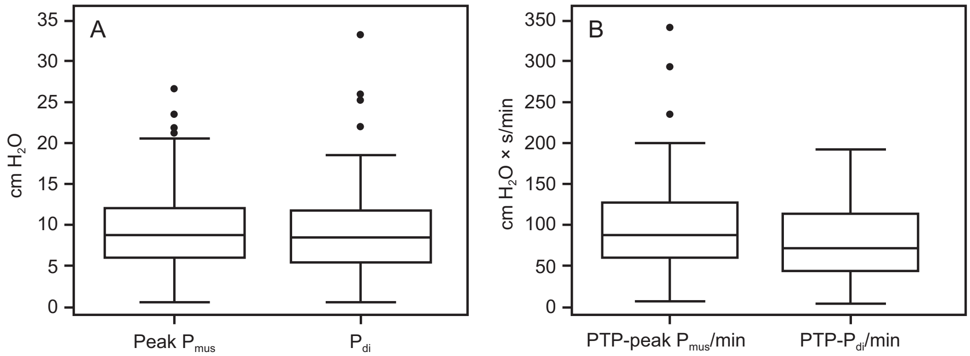

Fig. 1. Box and whiskers plots, representing a comparison of Peak P_{mus} and P_{di} (A), and PTP-Peak P_{mus} and PTP-P_{di} (B).The lower and upper edges of each box represent the 25th and 75th percentiles, respectively. Median values are shown by the lines within each box. Whiskers represent adjacent values. Points denote outliers. Peak P_{mus} = calculated peak inspiratory pressure; P_{di} = transdiaphragmatic pressure, PTP-peak P_{mus} = calculated pressure-time product of peak P_{mus}; PTP-P_{di} = pressure-time product of P_{di}.

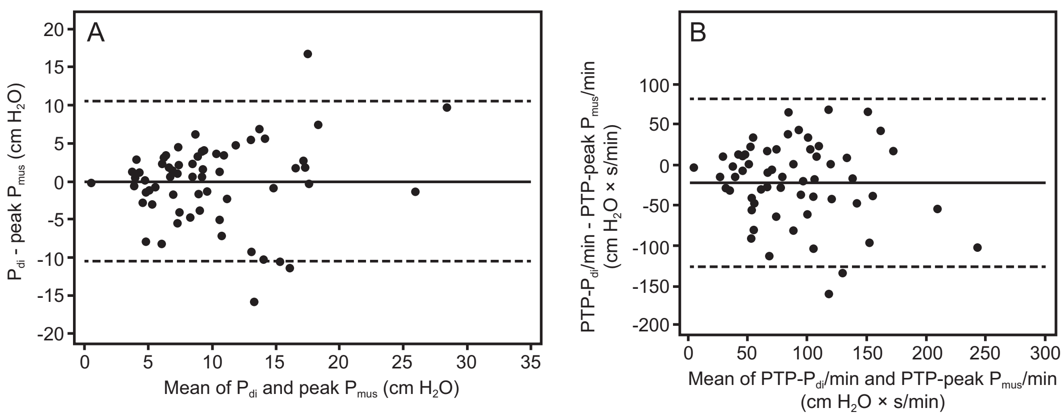

Fig. 2. Bland-Altman analysis presenting the mean difference (solid middle line) and 95% CI of the differences (±1.96 SD of the mean; dotted lines) between P_{di} and peak P_{mus} (A) and between PTP-P_{di} and PTP peak P_{mus} (B). Peak P_{mus} = calculated peak inspiratory pressure; P_{di} = transdiaphragmatic pressure; PTPP$_{di}$/min =pressure-time product of P_{di} per minute; PTP-peak P_{mus}/min = calculated pressure time product of peak P_{mus} per minute.

Table 2. Mean Difference (bias) of peak P_{mus}-P_{di} and PTP-peak P_{mus}-PTP-P_{di}, Limits of Agreement (±1.96 SD of the mean), and 95% CIs for the Mean and for the Upper and Lower Limits of Agreement

Factor	Mean Difference	Limits of Agreements	95% CI for the Bias	95% CI for the Upper Limit	95% CI for the Lower Limit
peak P_{mus}-P_{di}, cm H_2O	−0.059	−10.54 to 10.42	−1.40 to 1.28	8.10–12.73	−12.85 to −8.22
PTP peak P_{mus}-PTP_{Pdi}, cm H_2O × s/min	21.72	−81.80 to 125.25	8.42–35.03	102.39–148.10	−104.65 to −58.94

peak P_{mus} = calculated (from the proposed formula) peak inspiratory pressure
P_{di} = transdiaphragmatic pressure
PTP = pressure-time product

Discussion

The most significant findings of the present study were the following: (1) there was limited agreement between formula-derived estimates of peak P_{mus} and effort PTP-peak P_{mus}, and actual inspiratory pressure and effort measured by P_{di} and PTP-P_{di}, respectively, and (2) setting the ventilator assistance by using the proposed algorithm could result in either under- or overassistance in approximately half of the study cases.

With conventional modes of assisted ventilation, the assistance level is primarily determined based on the patient's breathing pattern; this frequently results in considerable dissociation between patient demands and ventila-

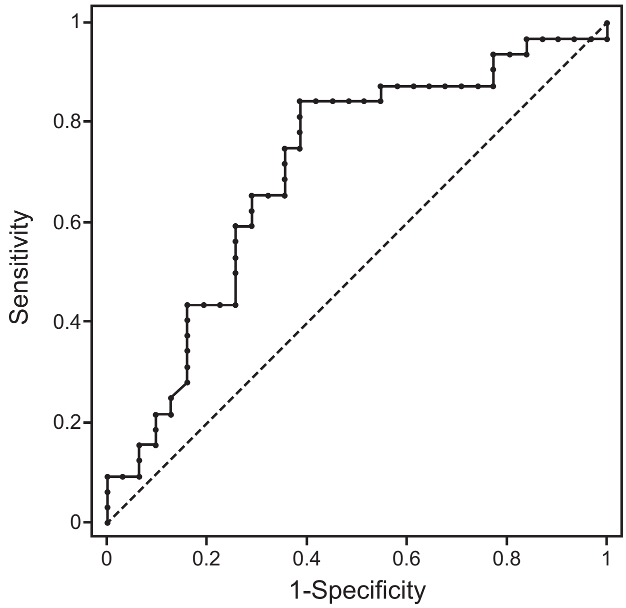

Fig. 3. Receiver operating curve for the prediction of the actual range of inspiratory effort by the calculated peak inspiratory pressure (peak P_{mus}), showing an optimal criterion of <9.85 cm H_2O.

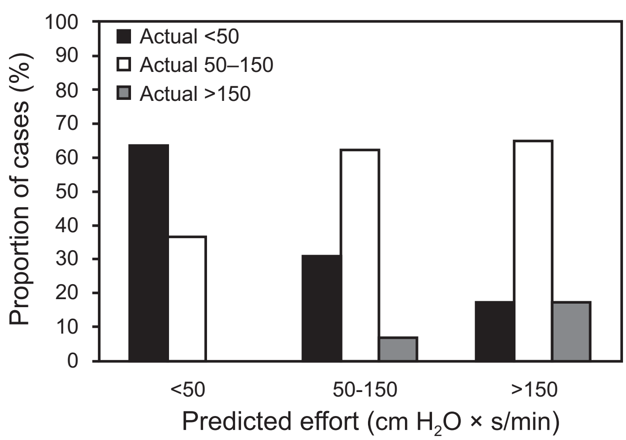

Fig. 4. Percentage of experimental cases with actual inspiratory effort (PTP-P_{di}) of <50, 50–150, or >150 cm H_2O × s/min, at each different range of predicted by peak P_{mus} inspiratory effort: <50, 50–150, and >150 cm H_2O × s/min. Peak P_{mus} = calculated peak inspiratory pressure, PTP-P_{di}: pressure-time product of transdiaphragmatic pressure per minute.

tor output.[15-19] Conversely, V_T and breathing frequency may be considerably modified by ventilator settings.[20] During ventilation on PAV+, titrating the assistance level by V_T and breathing frequency may be of limited effectiveness. Significant variability in V_T has been observed, and patients retain their desired breathing largely independent of mechanical load and assistance level.[1,4,12]

To simplify and unify titration of assistance level during ventilation on PAV+, Carteaux et al[10] introduced a simple algorithm, as described earlier in this article. However, that study did not validate the estimated variables or the proposed algorithm for assistance titration. In the present study, we validated the proposed algorithm by evaluating the accuracy of peak P_{mus} to predict the actual inspiratory effort, as determined by the accepted standard method of PTP-P_{di}. In up to 49% of cases, PTP-P_{di} was in a different range from that predicted by peak P_{mus}. Consequently, in nearly half of the experimental cases, gain adjustment by using the proposed algorithm could result in either over– or under–ventilation assistance. The lowest accuracy of peak P_{mus} was present in the subgroup of experimental cases characterized by peak P_{mus} of > 10 cm H_2O; in that subgroup, peak P_{mus} failed to predict the actual inspiratory effort in up to 83% of experimental cases.

Numerous studies have shown the deleterious effects of inappropriate assistance level (either excessive or insufficient) on the respiratory muscles. An excessive level of assistance results in diaphragmatic atrophy and contractile dysfunction.[21-25] Mechanical ventilation–induced diaphragm atrophy is associated with diaphragmatic dysfunction, which has been related to unfavorable clinical outcomes.[26-28] Excessive assistance may induce respiratory alkalosis, which, in patients with a preexisting low respiratory drive (ie, metabolic alkalosis and/or sedation) may promote periodic apnea.[29,30] Furthermore, in patients with obstructive lung diseases ventilated in assisted modes, excessive assistance may lead to high V_T and dynamic hyperinflation, which leads to triggering delay and ineffective efforts, thus adversely affecting patient outcomes.[15,16] Conversely, when ventilator support is insufficient for patient demands, vigorous inspiratory efforts may result in self-inflicted lung injury.[31-34] Furthermore, mismatch between ventilation demands and ventilator assistance may be associated with patient discomfort, increased work of breathing, and prolonged mechanical ventilation and ICU stay. The current study showed that the limited prediction value of peak P_{mus} was attributed to the disagreement between the estimated and actual inspiratory muscle output and effort.

Comparison Between peak P_{mus} and P_{di}

Although the difference was not statistically significant, we found low agreement between the 2 variables, indicated by the broad limit of agreement in the Bland-Altman analysis, significant scatter of the measurements, and low coefficient of correlation in the regression analysis. The discrepancy between these variables could arise from either a misleading calculation of peak P_{mus} and/or different physiologic factors related to both ventilator and subject characteristics.

The proposed equation for peak P_{mus} does not include PEEPi; therefore, peak P_{mus} is expected to be underestimated in patients who exhibit PEEPi. The extent of pressure underestimation depends on the levels of assistance and PEEPi; at low assistance and high levels of PEEPi, underestimation increases. In addition, because pressure delivery in PAV is driven by patient effort, the presence of PEEPi reduces the fraction of the patient's effort that is being assisted, which leads to underestimation of the proportion of assistance being provided. However, the presence of PEEPi may contribute minimally to disagreement between these compared variables; although we included a relatively high proportion of subjects with COPD, we found a low level of PEEPi (median value of 1.5 cm H_2O). At this level of PEEPi, underestimation is minimal, even at low levels of assist. Both ventilator and patient characteristics, including triggering delay, inspiratory muscle output, dynamic hyperinflation, expiratory and accessory muscle activity, and patient respiratory drive may also contribute (either separately or collectively) to the dissociation between peak P_{mus} and P_{di}.

Collectively, for all experimental cases, respiratory drive was the sole factor that significantly correlated with the difference between the estimated and the actual peak muscle pressure; as respiratory drive increased, the difference in peak muscle pressure decreased. This association is likely attributed to associated changes in peak P_{mus} because we found a significant positive correlation between peak P_{mus} and the respiratory drive. Changes in respiratory drive may alter ventilator output, mainly through changes in triggering delay.[18,35,36] Because the P_{aw} value is the primary determinant in the peak P_{mus} calculation, any increase or decrease of P_{aw} results in changes in the calculated peak pressure. Nevertheless, our data indicated that, for individual experimental cases, the difference between peak P_{mus} and P_{di} should be attributed to multiple factors rather than strictly to changes in respiratory drive. For example, we found that peak P_{mus} was significantly higher than P_{di} in experimental cases with relatively low respiratory muscle output and respiratory drive, and relatively high triggering delay. The inverse relationship was also observed.

Comparison Between PTP-peak P_{mus} and PTP-P_{di}

We found a significant difference between the inspiratory effort estimated by the proposed formula and actual inspiratory effort measured by P_{di} (PTP-P_{di}). This finding was demonstrated by both the low agreement between compared variables in Bland-Altman analysis as well as regression analysis. Disagreement between PTP-peak P_{mus} and PTP-P_{di} can mainly be attributed to the assumptions on which the calculations were based. First, PTP-peak P_{mus} was calculated as the area under the corresponding waveform during the inspiratory time when assuming that the rate of increase of inspiratory muscle pressure is constant (linear during neural inspiration); this resulted in a triangular area under the waveform. Nevertheless, results of physiologic studies indicate that the rate of increase in inspiratory muscle pressure (P_{mus}) or P_{di} typically exhibits a concave or convex shape.[37] Consequently, the area under the P_{di} waveform or pressure generated by respiratory muscles, or is expected to either be lower (in a concave shape) or higher (in a convex shape) compared with the area in the linear waveform (Supplementary Fig. 2 [see the supplementary materials at http://www.rcjournal.com]).

Second, PTP-peak P_{mus} was calculated based on the assumption that mechanical and neural inspiratory times were equal. Ideally, during assisted modes, the neural time may coincide with mechanical time. However, mechanical inspiration typically ends either before or after the end of neural inspiration,[17,18,35,38] even in modes in which inspiratory effort drives ventilation, as in PAV/PAV+.[4,12] Because PTP-peak P_{mus} is calculated by using the mechanical inspiratory time for a specific peak P_{mus} value, the derived PTP is expected to vary with the mechanical time (relative to neural time). In nearly all experimental cases in the present study, the mechanical time was higher than neural time, largely due to triggering delay.

The contribution of the difference between the neural and mechanical inspiratory time to the difference between PTP-peak P_{mus} and PTP-P_{di} was supported by a significant positive correlation between ΔPTP and the difference between neural and mechanical inspiratory times; increased time difference was associated with an increased difference between PTP-peak P_{mus} and PTP-P_{di}. Evidently, in individual experimental cases, the difference between PTP-peak P_{mus} and PTP-P_{di} can be attributed to by a combination of the above, at variable degrees of participation. Our findings were in agreement with those of a study by Su et al.[11] peak P_{mus} and the derived PTP were compared with Pmus, as calculated from P_{es}. Although the design and study population varied between the 2 studies, both revealed a weak correlation between estimated and actual inspiratory muscle output and effort.

Limitations and Clinical Implications

This study was a retrospective validation of proposed formulas to estimate peak muscle pressure and effort during ventilation with PAV+ and not clinically evaluate the proposed algorithm. The number of patients included here was lower than that in the study that proposed the algorithm. Analysis of our data showed high variability in the causes of error in the estimated values, which suggested that other sources of error may be identified by using a larger patient sample. The aim of setting the level of assist based on patient effort to avoid over- or underassist remains undisputed. However, this study highlighted the complexities of accurately estimating patient effort without invasive measurements and emphasized the need for further research in this direction. When adjusting the level of assist in PAV+, the caregiver may use the proposed algorithm as a starting point and may then adjust the assist level according to patient comfort and gas exchange.

Conclusions

This study showed that, in subjects on mechanical ventilation and with the PAV+ mode, there was significant disagreement between the actual and estimated respiratory muscle pressure and effort due to factors related to both subject and ventilator characteristics. Estimated peak inspiratory pressure showed limited accuracy in predicting actual inspiratory muscle effort; therefore, in nearly half of the analyzed experimental cases, adjusting the assistance level with the proposed algorithm could have led to over– or under–ventilator assist.

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