Limited predictability of maximal muscular pressure using the difference between peak airway pressure and positive end-expiratory pressure during proportional assist ventilation (PAV)

Po-Lan Su1, Pei-Shan Kao1,2, Wei-Chieh Lin3, Pei-Fang Su4 and Chang-Wen Chen3,5*

Abstract

Background: If the proportional assist ventilation (PAV) level is known, muscular effort can be estimated from the difference between peak airway pressure and positive end-expiratory pressure (PEEP) (ΔP) during PAV. We conjectured that deducing muscle pressure from ΔP may be an interesting method to set PAV, and tested this hypothesis using the oesophageal pressure time product calculation.

Methods: Eleven mechanically ventilated patients with oesophageal pressure monitoring under PAV were enrolled. Patients were randomly assigned to seven assist levels (20–80%; PAV20 means 20% PAV gain) for 15 min. Maximal muscular pressure calculated from oesophageal pressure (Pmus, oes) and from ΔP (Pmus, aw) and inspiratory pressure time product derived from oesophageal pressure (PTPoes) and from ΔP (PTPaw) were determined from the last minute of each level. Pmus, oes and PTPoes, with consideration of PEEPi were expressed as Pmus, oes, PEEPi and PTPoes, PEEPi, respectively. Pressure time product was expressed as per minute (PTPoes, PTPaw, PEEPi) and per breath (PTPoes, br, PTPaw, br).

Results: PAV significantly reduced the breathing effort of patients with increasing PAV gain (PTPoes 214.3 ± 80.0 at PAV20 vs. 83.7 ± 49.3 cmH2O s/min at PAV80, PTPoes, PEEPi 277.3 ± 96.4 at PAV20 vs. 121.4 ± 71.6 cmH2O s/min at PAV80, p < 0.0001). Pmus, aw overestimates Pmus, oes for low-gain PAV and underestimates Pmus, oes for moderate-gain to high-gain PAV. An optimal Pmus, aw could be achieved in 91% of cases with PAV60. When the PAV gain was adjusted to Pmus, aw of 5–10 cmH2O, there was a 93% probability of PTPoes <224 cmH2O s/min and 88% probability of PTPoes, PEEPi <255 cmH2O s/min.

Conclusion: Deducing maximal muscular pressure from ΔP during PAV has limited accuracy. The extrapolated pressure time product from ΔP is usually less than the pressure time product calculated from oesophageal pressure tracing. However, when the PAV gain was adjusted to Pmus, aw of 5–10 cmH2O, there was a 90% probability of PTPoes and PTPoes, PEEPi within acceptable ranges. This information should be considered when applying ΔP to set PAV under various gains.

Keywords: Pressure time product, Proportional assist ventilation, Airway pressure

* Correspondence: cwchen@mail.ncku.edu.tw
1Medical Intensive Care Unit, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
2Medical Device Innovation Center, National Cheng Kung University, Tainan, Taiwan
Full list of author information is available at the end of the article

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Background

Although mechanical ventilation is a crucial tool in decreasing the respiratory effort required by ventilated patients, diaphragmatic weakness can rapidly develop with complete diaphragmatic inactivity and mechanical ventilation [1]. This type of diaphragmatic powerlessness has been termed ventilator-induced diaphragmatic dysfunction (VIDD) [2]. Controlled mechanical ventilation is a major factor in VIDD, which may be attenuated with assisted ventilation [3, 4]. This suggests that maintaining appropriate respiratory effort may be essential to preserving diaphragm function, and the ability to monitor respiratory effort during mechanical ventilation should be an important clinical issue [5].

Pressure applied to the respiratory system is usually assumed to dissipate against resistant and elastic elements. In a mechanically ventilated patient, the applied pressure is shared between the patient and ventilator [6]. This equation is difficult to solve under conventional ventilation because it is challenging to obtain reliable values for respiratory system resistance and elastance. However, in proportional assist ventilation (PAV), obtaining reliable elastance is possible during spontaneous breathing because the end of inspiration can be determined [7–9].

PAV with load-adjustable gain factors (PAV+) is a ventilatory mode that delivers assistance in proportion to the instantaneous flow and volume by calculating the instantaneous pressure needed to overcome the elastic and resistive pressures; these are updated several times per minute during PAV ventilation [10]. The proportion assistance is expressed as a percentage of the total pressure assisted (i.e. gain). By using this algorithm, Carteaux et al. [11] proposed a look-up table for estimating peak muscular pressure from peak airway pressure (P_{aw, peak}) and positive end-expiratory pressure (PEEP) difference (ΔP), thus offering a way to keep the patient in a predefined comfort zone by adjusting the PAV gain. However, this algorithm has not yet been validated [12].

The oesophageal pressure time product (PTP_{oes}) is a standard reference to assess respiratory muscle pressure. In patients with successful weaning, inspiratory PTP_{oes} is usually <224–255 cmH2O·s/min throughout the weaning trial [13]. In addition to possible variability in respiratory elastance and resistance measured during PAV+, respiratory muscular PTP as estimated by Carteaux’s method requires several assumptions that may limit its accuracy (e.g. a triangular muscular pressure waveform and a defined inspiratory time based on P_{aw, peak}) [11]. Thus, the derived muscular PTP may not be equal to the PTP_{oes}. The present study aimed to verify the applicability of Carteaux’s method with measured P_{mus, oes}, P_{mus, oes}, P_{EEPi}, P_{TPoes} and P_{TPoes, PEEPi} under different PAV gain settings.

Methods

From June 2014 to October 2014, all mechanically ventilated patients in our respiratory intensive care unit (10 beds) were screened daily for appropriateness for study inclusion. Patients had to be haemodynamically stable without inotropic agents and had to be ventilated with an inspiratory oxygen fraction <0.5 and PEEP ≤8 cmH2O. They also had to agree to oesophageal balloon placement. Exclusion criteria were pregnancy, acute coronary syndrome, aortic dissection as a cause of admission, and nasal or oropharyngeal lesions that prohibited oesophageal balloon placement. We used a single type of ventilator, the Puritan-Bennett 840 with PAV+ mode (Tyco International, Princeton, NJ, USA). The National Cheng Kung University Hospital Ethics Committee (A-BR-102-090) approved this study. The patient’s next of kin gave informed consent.

The oesophageal balloon was placed in the lower third of the oesophagus and inflated with 0.5–1 mL of air. Airflow was measured via a pneumotachograph (PN 155362, Hamilton Medical, Bonaduz, Switzerland), while the airway and oesophageal pressures were individually measured using two differential pressure transducers (P/N 113252, Model 1110A, Hans Rudolph, Shawnee, KS, USA). The flow sensor was placed between the endotracheal tube and ventilator Y-piece. Tidal volume was obtained by integration of the flow signal. All signals were sampled and digitalized at 100 Hz, and data were stored in a data-acquisition system (AcqKnowledge, Biopac MP150, Goleta, CA, USA). All patients were assessed in a 30° supine position with endotracheal suction performed before measurement if clinically required.

For individual patients, seven PAV gain levels (percentage of assistance), namely PAV20 (20% gain), PAV30, PAV40, PAV50, PAV60, PAV70, and PAV80, were randomly applied for 15 min at each level unless the patients showed discomfort. Respiratory mechanics measured by the ventilator during PAV were recorded throughout the course. Passive respiratory mechanics were measured under constant flow at the end of this protocol by increasing the back-up mandatory ventilator rate until all the breathing efforts were suppressed [13, 14].

Physiological measurement

Validation of oesophageal pressure measurement

Appropriate oesophageal balloon placement was verified by the occlusion test [15]. The ratios of change in oesophageal pressure to the change in airway opening pressure (ΔP_{oes}/ΔP_{aw}) during three to five spontaneous respiratory efforts against a closed airway were determined to ensure oesophageal pressure measurement reliability.
Respiratory mechanics during PAV and passive mechanical ventilation

The respiratory mechanics (E_pav and R_pav) during different PAV levels were recorded as a display on the ventilator screen. The last five E_pav and five R_pav at each PAV level were used for comparison. The respiratory system mechanics under constant flow and volume-cycled passive mechanical ventilation were determined at the end of the protocol using constant flow and a rapid airway occlusion technique [16, 17].

Maximum inspiratory muscular pressure with P_oes tracing (P_mus, oes) and inspiratory oesophageal pressure time product per breath (PTP_oes, br)

Muscular pressure was calculated by taking into account dynamic E cw, which was obtained as the passive volume-oesophageal pressure slope [13]. P_mus, oes was defined as the maximum difference between the passive and active P_oes. The inspiratory PTP_oes was calculated as the area between the P cw and P_oes tracing, starting from the onset of inspiratory effort to the end of inspiratory flow. P cw was obtained by multiplying the tidal volume by dynamic E cw. The onset of inspiratory effort was determined by the rapid descent point from P_oes. We calculated PTP_oes with and without consideration of the intrinsic PEEP (PEEPi) [13]. Because gastric pressure was not measured, exact amounts of dynamic hyperinflation and expiratory muscle activity were unknown. The PTP_oes was thus presented in two forms, the upper bound PTP_oes which attributes the rapid descent of P_oes before the onset of inspiratory flow solely to inspiratory muscle activity, and the lower bound PTP_oes which attributes the rapid descent of P_oes solely to cessation of expiratory effort [13, 14]. PTP_oes, PEEP i and PTP_oes thus represent the upper and lower bounds of PTP, respectively (Fig. 1).

Maximum inspiratory pressure from ΔP and PAV gain (P_mus, aw) and inspiratory pressure time product from airway per breath (PTP_aw, br)

P_mus, aw during PAV was obtained by using the formula adopted by Carteaux [11]:

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

PTP_aw, br was calculated under the assumption of a triangular inspiratory path with the end of inspiratory effort at P_{aw, peak}.

Statistical analysis

The results are given as mean ± SD, unless otherwise specified. The Kruskal-Wallis test was used to compare means from different groups. Dunn’s multiple comparison test was performed over pairs of groups. Repeated measured analysis of variance (ANOVA) was used to compare the means of E_pav and R_pav measured by the ventilator during various PAV gain levels. Correlations between PTP_oes, br and P_mus, oes, PTP_oes, PEEP i, br and P_mus, oes, PEEP i, and PTP_aw, br and P_mus, aw were analysed using the two-tailed Spearman correlation test. Linear regression between PTP_oes, br and P_mus, oes, PTP_oes, PEEP i, br and P_mus, oes, PEEP i, PTP_aw, br and P_mus, aw was analysed with a forced regression line through the origin. Limits of agreement between P_mus, aw and P_mus, oes were examined using Bland-Altman analysis. All tests were two-sided, and a p value less than .05 was considered statistically significant.
All analyses were performed using Prism version 5 (GraphPad Software, San Diego, CA, USA).

**Results**

The results of 18 consecutive patients who fulfilled the inclusion criteria were recorded. Two patients were excluded from further analysis because of a low ΔPoes/ΔPaw ratio. One patient was excluded because of a poor oesophageal pressure signal, and four patients were excluded because of an inadequate duration of Poes tracing secondary to the pressure signal, and four patients were excluded because of a poor oesophageal contrac-
tion noted. FiO2 inspired oxygen fraction, ET T endotracheal tube, CHF congestive heart failure, COPD chronic obstructive pulmonary disease, Ers passive respiratory system elastance, Emax passive chest wall elastance, F female; M male, MV mechanical ventilation, MRSA methicillin-resistant Staphylococcus aureus, PEEP positive end-expiratory pressure, Rmax passive maximum end-inspiratory resistance, Rmin passive minimum (airway) end-inspiratory resistance, UTI urinary tract infection, ΔPoes/ΔPaw ratio of oesophageal pressure drop to airway pressure drop during airway occlusion, ΔPETT pressure loss through endotracheal or tracheostomy tube.

**PTPoes** and **PTPoes, PEEPi** during various PAV gain factors are shown in Fig. 3. Progressive reductions in **PTPoes** and **PTPoes, PEEPi** were noted with increasing PAV gain levels. Significant differences were found among those with low-gain and high-gain PAV (p < 0.0001). However, no significant difference in **PTPoes** or **PTPoes, PEEPi** was found between PAV20 vs. PAV30, PAV30 vs. PAV40, PAV40 vs. PAV50, or PAV50 vs. PAV60. Pmus, aw tended to underestimate Pmus, oes or Pmus, oes, PEEPi with all levels of PAV gain except PAV20 (Fig. 4a). The minimal difference between Pmus, aw and Pmus, oes was at the level of PAV30 (Fig. 4a). The Ti, aw estimated from the onset of inspiratory effort to Paw, peak was not different from that estimated from flow tracing from PAV20 to PAV50. However, the Ti, aw was significantly shortened compared to the Ti estimated from flow tracing within PAV60 to PAV80 (data not shown, p < 0.0001). Spearman correlation analysis revealed significant correlation between Pmus, aw and PT aw, br (r^2 = 0.9341), Pmus, oes and PTPoes, br (r^2 = 0.8751), and Pmus, oes, PEEPi and PTPoes, PEEPi, br (r^2 = 0.8862). Linear regression analysis disclosed the best-fit slope between PTPaw, br and Pmus, aw to be 0.56, between PTPoes, br and Pmus, oes to be 0.73, and between PTPoes, PEEPi, br and Pmus, oes, PEEPi to be 0.83.

**Table 1** Patient demographics and respiratory mechanics

| Case | Age (years)/ Sex | Diagnosis | Days on MV/ETT size (mm)/ΔPETT (cmH2O) | Baseline FiO2/PEEP Ers (cmH2O/L) | Emax (cmH2O/L) | Rmax (cmH2O/L/S) | Rmin (cmH2O/L/S) | ΔPoes/ΔPaw |
|------|------------------|-----------|--------------------------------------|---------------------------------|----------------|-----------------|-----------------|-----------|
| 1    | 61/M             | Emphysema, dementia | 13/7.5/3.73 | 0.35/0 | 21.71 | 9.96 | 22.38 | 10.37 | 0.94 |
| 2    | 88/M             | Pneumonia, COPD | 7/7.0/4.92 | 0.40/8 | 15.28 | 5.57 | 27.11 | 21.55 | 1.03 |
| 3    | 80/F             | UTI | 9/7.5/3.61 | 0.25/8 | 18.24 | 3.93 | 10.05 | 7.99 | 1.00 |
| 4    | 67/F             | MRSA bacteremia | 8/7.5/4.05 | 0.30/6 | 32.62 | 9.52 | 11.08 | 7.21 | 1.11 |
| 5    | 80/F             | UTI, old stroke | 4/7.5/5.36 | 0.40/6 | 21.18 | 6.06 | 22.29 | 17.93 | 0.91 |
| 6†   | 88/F             | UTI, CHF | 4/7.5/5.99 | 0.40/6 | 30.51 | 12.54 | 21.26 | 16.73 | 0.92 |
| 7    | 54/F             | Pneumonia, old stroke | 18/7.07/1.97 | 0.30/6 | 23.04 | 5.13 | 17.25 | 13.69 | 1.03 |
| 8    | 67/M             | Pneumonia | 4/7.5/3.93 | 0.40/6 | 16.74 | 3.00 | 12.46 | 9.31 | 0.92 |
| 9    | 79/F             | Pneumonia, CHF | 8/7.5/6.07 | 0.30/6 | 23.98 | 6.28 | 22.02 | 16.95 | 0.81 |
| 10   | 74/M             | COPD | 3/7.5/3.71 | 0.35/6 | 7.73 | 4.24 | 23.52 | 13.35 | 1.11 |
| 11c  | 84/F             | UTI, parkinsonism, asthma | 4/7.5/3.86 | 0.35/6 | 21.61 | 6.72 | 20.88 | 13.34 | 0.77 |

†Tracheostomy tube and ΔPETT only an approximation as equation only available for an 8.0-mm tracheostomy. †Cheyne-Stokes breathing noted. †Evident abdominal muscle contraction noted. FiO2 inspired oxygen fraction, ET T endotracheal tube, CHF congestive heart failure, COPD chronic obstructive pulmonary disease, Ers passive respiratory system elastance, Emax passive chest wall elastance, F female; M male, MV mechanical ventilation, MRSA methicillin-resistant Staphylococcus aureus, PEEP positive end-expiratory pressure, Rmax passive maximum end-inspiratory resistance, Rmin passive minimum (airway) end-inspiratory resistance, UTI urinary tract infection, ΔPoes/ΔPaw ratio of oesophageal pressure drop to airway pressure drop during airway occlusion, ΔPETT pressure loss through endotracheal or tracheostomy tube.
between $P_{\text{mus, aw}}$ and $P_{\text{mus, oes}}$ was from -11.2 to 8.8 cmH$_2$O. The maximal muscular pressures estimated from three different approaches under different PAV gain levels are shown in Table 2. PAV60 was associated with the highest probability (91%) of optimal $P_{\text{mus, aw}}$ (5–10 cmH$_2$O). However, the best PAV gain for optimal PAV assessed from $P_{\text{mus, oes}}$ or $P_{\text{mus, oes}, \text{PEEPi}}$ was quite diverse and was absent in two patients. The concordance rate for selection of optimal PAV gain was <50% between $P_{\text{mus, aw}}$ and $P_{\text{mus, oes}}$ and $P_{\text{mus, aw}}$ and $P_{\text{mus, oes}, \text{PEEPi}}$.

$P_{\text{mus, aw}}$ within 5–10 cmH$_2$O was not present in PAV20 but was present in 11–82% of breaths in other PAV gains. Around 80% of breaths in PAV50 or PAV60 were associated with $P_{\text{mus, aw}}$ within 5–10 cmH$_2$O. PTP$_{\text{oes}}$ <224 cmH$_2$O·s/min and PTP$_{\text{oes}, \text{PEEPi}}$ <255 cmH$_2$O·s/min are considered admissible according to Jubran et al. [13]. Despite the limited predictability of $P_{\text{mus, oes}}$ or $P_{\text{mus, oes}, \text{PEEPi}}$ from airway pressure tracing had limited accuracy. Third, the deduction of PTP$_{\text{aw}}$ from $\Delta P$ may underestimate PTP$_{\text{oes}}$ or PTP$_{\text{oes}, \text{PEEPi}}$. Fourth, an optimal $P_{\text{mus, aw}}$ (5–10 cmH$_2$O) could be achieved in 91% of patients with PAV60, and despite the lack of accuracy for predicting $P_{\text{mus, oes}}$ or $P_{\text{mus, oes}, \text{PEEPi}}$ from airway pressure tracing, maintaining $P_{\text{mus, aw}}$ within 5–10 cmH$_2$O was associated with >90% probability of admissible PTP$_{\text{oes}}$ and PTP$_{\text{oes}, \text{PEEPi}}$.

**Discussion**

Our analyses revealed several interesting findings. First, PTP$_{\text{oes}}$ and PTP$_{\text{oes}, \text{PEEPi}}$ significantly decreased with increasing PAV gain in patients with PAV. Second, the prediction of $P_{\text{mus, oes}}$ or $P_{\text{mus, oes}, \text{PEEPi}}$ from airway pressure tracing had limited accuracy. Third, the significant increase in PAV gain levels (PAV40, PAV50 and PAV60) were associated with >90% probability of admissible PTP$_{\text{oes}}$ and PTP$_{\text{oes}, \text{PEEPi}}$.

The significant increase in $P_{\text{aw, peak}}$ but minimal difference in tidal volume with increasing gain level indicates substantial adaptation of muscular pressure during PAV [18]. The lower elastance during low assist could be explained by high respiratory drive (i.e. inspiratory muscle activity does not return to zero during the 300 ms occlusion time), which underestimates the elastic recoil pressure at end-inspiration. PEEPi is unlikely to be a cause
because it did not increase with greater PAV assist in the current study [9].

The algorithm proposed by Carteaux et al. [11] is a simple bedside approach to estimate inspiratory muscular pressure ($P_{\text{mus, bw}}$) in mechanically ventilated patients under PAV. We found it to be of limited value in predicting $P_{\text{mus, oes}}$. $P_{\text{mus, bw}}$ tends to overestimate $P_{\text{mus, oes}}$ in PAV20 but more commonly underestimates $P_{\text{mus, oes}}$ from PAV40 to PAV80. Therefore, the proportion of alleviation of respiratory muscle output was usually incompletely attained as the PAV gain intended it to be. Besides, the wide 95% confidence interval from the Bland-Altman analysis of $P_{\text{mus, oes}}$ and $P_{\text{mus, bw}}$ implicated that $P_{\text{mus, oes}}$ could not be accurately predicted by $P_{\text{mus, bw}}$.

There are several possible explanations for these findings. First, for the unique condition where $P_{\text{mus, oes}}$ is usually overestimated in PAV20, a reasonable cause could be the ventilator flow control algorithm. Because respiratory effort is maximal in PAV20, the proportional-integral-derivative algorithm of the flow control system is prone to an airway pressure overshoot by the end of inspiration, which is further exaggerated fourfold in PAV20 for the calculation of $P_{\text{mus, bw}}$ [19, 20]. Second is a possible discrepancy between PAV+ and CMV measured respiratory mechanics [10]. Although the PAV+ mode was continuously updated, measured respiratory system resistance and elastance may be different from those obtained under CMV [10]. Moreover, the respiratory system resistance measured by PAV+ is not reliable in cases with severe expiratory flow limitations. Third is the presence of PEEPi. In a recently published PAV+ mode bench study [21], the assistance provided by
Table 2 Maximal muscular pressures determined through airway or oesophageal pressure with and without PEEPi

| Case | P_{max}, aw | aw | aw aw | aw aw | aw aw | aw aw | aw aw | aw aw | aw aw | aw aw |
|------|-------------|----|-------|-------|-------|-------|-------|-------|-------|-------|
| 1    | 25          | 18 | 15    | 11    | 9     | 7     | 4     |       |       |       |
|      | 20          | 19 | 18    | 13    | 15    | 13    | 7     |       |       |       |
|      | 21          | 22 | 19    | 14    | 16    | 14    | 8     |       |       |       |
|      | 1.5 ± 0.8   | 2.6 ± 0.8 | 1.4 ± 0.5 | 0.7 ± 0.5 | 1.1 ± 0.7 | 1.4 ± 0.8 | 0.3 ± 0.3 |       |       |       |
| 2    | 19          | 13 | 10    | 8     | 6     | 5     | 3     |       |       |       |
|      | 16          | 15 | 16    | 13    | 13    | 14    | 11    |       |       |       |
|      | 17          | 17 | 17    | 14    | 15    | 15    | 12    |       |       |       |
|      | 1.6 ± 0.7   | 1.1 ± 0.6 | 1.0 ± 0.6 | 1.4 ± 0.6 | 1.3 ± 0.8 | 1.3 ± 0.6 | 1.8 ± 0.6 |       |       |       |
| 3    | 17          | 10 | 8     | 6     | 5     | 4     | 3     |       |       |       |
|      | 14          | 13 | 14    | 14    | 11    | 11    | 8     |       |       |       |
|      | 18          | 16 | 14    | 15    | 12    | 14    | 9     |       |       |       |
|      | 1.6 ± 0.9   | 1.9 ± 1.0 | 1.0 ± 0.8 | 0.7 ± 0.8 | 1.0 ± 0.8 | 1.4 ± 1.1 | 0.3 ± 0.6 |       |       |       |
| 4    | 17          | 13 | 10    | 8     | 6     | 5     | 3     |       |       |       |
|      | 14          | 16 | 11    | 11    | 10    | 8     | 5     |       |       |       |
|      | 15          | 17 | 13    | 12    | 11    | 9     | 6     |       |       |       |
|      | 1.3 ± 0.9   | 1.2 ± 1.0 | 1.3 ± 0.9 | 1.7 ± 1.2 | 0.8 ± 0.4 | 1.2 ± 1.3 | 0.6 ± 0.5 |       |       |       |
| 5    | 13          | 9  | 7     | 5     | 5     | 4     | 3     |       |       |       |
|      | 9           | 9  | 8     | 7     | 8     | 6     | 4     |       |       |       |
|      | 10          | 10 | 9     | 8     | 8     | 6     | 4     |       |       |       |
|      | 0.3 ± 0.2   | 0.4 ± 0.4 | 0.0 ± 0.1 | 0.1 ± 0.1 | 0.3 ± 0.4 | 0.0 ± 0.1 | 0.1 ± 0.1 |       |       |       |
| 6    | 23          | 18 | 13    | 11    | 9     | 7     | 6     |       |       |       |
|      | 21          | 21 | 17    | 20    | 17    | 14    | 13    |       |       |       |
|      | 27          | 28 | 19    | 27    | 23    | 18    | 18    |       |       |       |
|      | 6.3 ± 4.0   | 7.4 ± 3.9 | 2.7 ± 1.4 | 6.8 ± 4.5 | 6.3 ± 4.8 | 4.2 ± 2.8 | 4.4 ± 3.2 |       |       |       |
| 7    | 14          | 9  | 7     | 5     | 4     | 3     | 2     |       |       |       |
|      | 4           | 5  | 4     | 4     | 3     | 2     | 2     |       |       |       |
|      | 7           | 7  | 7     | 6     | 4     | 4     | 3     |       |       |       |
|      | 3.0 ± 0.9   | 2.9 ± 0.8 | 3.0 ± 1.5 | 2.1 ± 0.7 | 1.6 ± 0.8 | 1.5 ± 0.5 | 1.3 ± 0.8 |       |       |       |
| 8    | 20          | 14 | 10    | 8     | 6     | 5     | 3     |       |       |       |
|      | 14          | 13 | 10    | 10    | 8     | 7     | 7     |       |       |       |
|      | 16          | 15 | 12    | 10    | 9     | 8     | 8     |       |       |       |
|      | 2.8 ± 0.7   | 2.2 ± 0.6 | 1.9 ± 0.8 | 0.8 ± 0.5 | 0.9 ± 0.3 | 1.0 ± 0.4 | 0.8 ± 0.4 |       |       |       |
| 9    | 26          | 18 | 13    | 9     | 8     | 5     | 3     |       |       |       |
|      | 12          | 11 | 10    | 8     | 8     | 6     | 4     |       |       |       |
|      | 14          | 13 | 12    | 10    | 10    | 8     | 8     |       |       |       |
|      | 2.1 ± 0.7   | 2.0 ± 0.7 | 2.0 ± 0.7 | 1.8 ± 0.6 | 2.1 ± 0.5 | 1.6 ± 0.5 | 1.7 ± 0.4 |       |       |       |
| 10   | 26          | 14 | 9     | 8     | 6     | 5     | 4     |       |       |       |
|      | 16          | 15 | 15    | 13    | 11    | 11    | 9     |       |       |       |
|      | 17          | 16 | 16    | 14    | 12    | 12    | 11    |       |       |       |
|      | 1.2 ± 1.0   | 1.2 ± 1.1 | 1.0 ± 1.0 | 0.4 ± 0.6 | 0.8 ± 0.8 | 0.1 ± 0.3 | 0.2 ± 0.5 |       |       |       |
| 11   | 28          | 19 | 14    | 12    | 10    | 7     | 4     |       |       |       |
|      | 16          | 14 | 13    | 12    | 8     | 12    | 5     |       |       |       |
|      | 28          | 32 | 29    | 28    | 17    | 18    | 10    |       |       |       |
|      | 12.0 ± 1.3  | 17.9 ± 3.5 | 16.2 ± 1.7 | 15.9 ± 2.9 | 8.6 ± 1.7 | 6.0 ± 1.9 | 5.0 ± 1.4 |       |       |       |

Maximum muscular pressure and intrinsic positive end-expiratory pressure (PEEPi) were calculated as average of 1-minute breaths in each proportional assist ventilation (PAV) gain. Muscular pressures between 5 and 10 cmH\(_2\)O are highlighted. \(P_{\text{max}}, \text{aw}\) maximal muscular pressure calculated from \(\Delta P\) and PAV gain, \(P_{\text{max}}, \text{oes}\) maximal muscular pressure calculated from maximum difference between passive and active \(P_{\text{oes}}\) without consideration of PEEPi, \(P_{\text{max}, \text{oes}, \text{PEEPi}}\) maximal muscular pressure calculated from maximum difference between passive and active \(P_{\text{oes}}\) with consideration of PEEPi.
PAV+ was approximately 25% lower than expected. PEEPi with the associated trigger delay was considered a major factor affecting PAV+ accuracy due to the lack of assist during the initial part of respiratory breath, ultimately resulting in global under-assistance.

PTPoes is a better surrogate of respiratory effort in ventilated patients. In this study, the analyses of correlation between Pmus,aw and PTPaw, Pmus,oes and PTPoes, Pmus,oes, PEEPi and PTPoes, PEEPi yielded highly significant results. However, predicting PTP from Pmus,aw and Pmus,oes differed in the best-fit slope value. The slope value was 0.56 when the linear regression was performed between Pmus,aw and PTPaw. The slope increased to 0.73 between PTPoes,br and Pmus,oes and to 0.83 between PTPoes, br and Pmus, oes, PEEPi. This implicates that the PTPaw should be corrected when projecting into PTPoes. We offer the following explanation for the discrepancy between PTPaw and PTPoes. First, the assumption of a triangular pressure-time product is flawed as respiratory muscle pressure generation is usually exponential [22–24]. The integration area above an exponential decay curve is usually larger than the integration area above a triangular line. Second, the inspiratory time is significantly shortened in high-gain PAV. The shortened inspiratory time should result in a smaller PTPaw from the triangular algorithm. A third possible cause is the influence of PEEPi. The algorithm proposed by Cardeaux et al. is also flawed as it does not consider PEEPi. The inclusion of PEEPi led to increases in Pmus, oes, PEEPi and PTPoes, PEEPi.

The predefined range of respiratory effort by Carteaux and colleagues [11] needs critical appraisal. Target limits of Pmus,aw, within 5–10 cmH2O or PTPaw between 50 and 150 cmH2O/s were derived mainly from a desirable inspiratory effort of PTPoes, PEEPi <125 cmH2O/s/min [14]. This recommended threshold is arbitrary, not supported by quantitative diaphragm electromyogram, and possibly well below the threshold of threatening diaphragm fatigue [14]. A wider range of PTPoes, PEEPi should be allowable with minimal risk of diaphragm fatigue [13, 25, 26]. As Pmus,aw frequently underestimates Pmus, oes in the usual levels of PAV, actual PTPoes, PEEPi values are usually higher than PTPaw. Interestingly, PTPoes, PEEPi measurements were usually <255 cmH2O/s/min when Pmus, aw were within 5–10 cmH2O. This implicates that the recommended grid table for PAV remains a helpful reference for selecting the PAV level, although the newly advocated threshold requires further study for verification.

There are several limitations to the current study. The first is the limited number of patients studied and the fact that all of the patients had started to have weaning trials as reflected by the oxygen fraction and external PEEPi level. Thus, our results may not be applicable to acutely ill patients under mechanical ventilation. The second is the lack of gastric pressure measurement, which meant that we could not clarify the contribution of expiratory muscle activity during PAV. However, we did not notice evident abdominal muscle contraction during PAV except in one patient with high PEEPi. Thus, the measured Pmus, oes, PEEPi should represent the inspiratory muscle motor outputs for most of our patients.

Conclusions

In summary, our results demonstrate limited accuracy of estimating respiratory effort from airway pressure tracing during PAV. Although Pmus, oes decreases with increasing PAV gain, Pmus, oes could not be precisely predicted from ΔP under various gain factors. In addition, PTPaw also underestimated PTPoes and PTPoes, PEEPi. However, when the PAV gain was adjusted to a Pmus, aw of 5–10 cmH2O, there was approximately 90% probability of maintaining the patient within an acceptable PTP range.

Abbreviations
CMV: continuous mandatory ventilation; Ecw: passive chest wall elastance during CMV; Epa: PAV-based patient elastance; Epav: passive respiratory system elastance during CMV; PAV: proportional assist ventilation; PAV20 to PAV80: 20 to 80% PAV gain; Ppeak, pneum: peak airway pressure during PAV; Pcw: chest wall elastic pressure; PEEP: positive end-expiratory pressure; PEET: intrinsic PEEP; Pmus,aw: maximal muscular pressure calculated from ΔP and PAV gain; Pmus,oes: maximal muscular pressure calculated from maximum difference between passive and active Poes without consideration of PEEPi; Pmus, oes, PEEPi: maximal muscular pressure calculated from maximum difference between passive and active Poes with consideration of PEEPi; Pmus,aw, Pmus, oes, PEEPi: respiratory muscle pressure product; PTPaw: inspiratory pressure time product calculated from ΔP and assuming a triangular inspiratory pressure time course per breath; PTPaw, br: inspiratory pressure time product calculated from the difference between the oesophageal pressure and the relaxed chest wall elastance curve per breath; PTPaw, br, PTPaw, br: inspiratory pressure time product calculated from the difference between the oesophageal pressure and the relaxed chest wall elastance curves with consideration of PEEPi; PTPoes, PEEPi: PTPoes, PEEPi with consideration of PEEPi; Rmax: passive maximum inspiratory resistance during CMV; Rmin: passive minimum (airway) inspiratory resistance during CMV; Rmin, PAV: PAV-based patient resistance; Tinsp: duration of the inspiratory time determined from flow tracing during various PAV gains without consideration of PEEPi; Tinsp, br: duration of the inspiratory time determined from the peak airway pressure during various PAV gains; VIDD: ventilator-induced diaphragmatic dysfunction; ΔP: peak airway pressure and PEEPi difference

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Authors’ contributions
PLS participated in the study design, collected and analysed data, and drafted the revised manuscript; FSK participated in the study, analysed data, and participated in draft revision; WCL participated in the study design and help revise the manuscript; PFS carried out statistical analysis and participated in the revised manuscript. CWC conceived of the study, participated in its design and coordination, and was involved in producing the final manuscript. All authors read and approved the final manuscript.
Competing interests
The authors declare that they have no competing interests.

Consent to publication
Written informed consent was obtained from the patients/families for publication of their individual details and accompanying measurements in this manuscript. The consent forms are held by the authors and are available for review by the Editor-in-Chief.

Ethical approval and consent to participate
This study was approved by The National Cheng Kung University Hospital Ethics Committee (A-IR-102-090). Consent to participate was obtained from the patients/families.

Author details
1Section of Chest Medicine and Respiratory Care, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan. 2Graduate Institute of Clinical Medical Sciences; Department of Respiratory Care, College of Medicine, Chang Gung University, Taoyuan, Taiwan. 3Medical Intensive Care Unit, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan. 4Department of Statistics, National Cheng Kung University, Tainan, Taiwan. 5Medical Device Innovation Center, National Cheng Kung University, Tainan, Taiwan.

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