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

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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 ($P_{mus,\ oes}$) and from ΔP ($P_{mus,\ aw}$) and inspiratory pressure time product derived from oesophageal pressure (PTP_{oes}) and from ΔP (PTP_{aw}) were determined from the last minute of each level. $P_{mus,\ oes}$ and PTP_{oes} with consideration of PEEPi were expressed as $P_{mus,\ oes,\ PEEPi}$ and $PTP_{oes,\ PEEPi}$, respectively. Pressure time product was expressed as per minute (PTP_{oes}, $PTP_{oes,\ PEEPi}$, PTP_{aw}) and per breath ($PTP_{oes,\ br}$, $PTP_{oes,\ PEEPi,\ br}$, $PTP_{aw,\ br}$).

Results: PAV significantly reduced the breathing effort of patients with increasing PAV gain (PTP_{oes} 214.3 ± 80.0 at PAV20 vs. 83.7 ± 49.3 cmH_2O•s/min at PAV80, $PTP_{oes,\ PEEPi}$ 277.3 ± 96.4 at PAV20 vs. 121.4 ± 71.6 cmH_2O•s/min at PAV80, $p < 0.0001$). $P_{mus,\ aw}$ overestimates $P_{mus,\ oes}$ for low-gain PAV and underestimates $P_{mus,\ oes}$ for moderate-gain to high-gain PAV. An optimal $P_{mus,\ aw}$ could be achieved in 91% of cases with PAV60. When the PAV gain was adjusted to $P_{mus,\ aw}$ of 5–10 cmH_2O, there was a 93% probability of PTP_{oes} <224 cmH_2O•s/min and 88% probability of $PTP_{oes,\ PEEPi}$ < 255 cmH_2O•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 $P_{mus,\ aw}$ of 5–10 cmH_2O, there was a 90% probability of PTP_{oes} and $PTP_{oes,\ PEEPi}$ 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

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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 $cmH_2O \cdot s/min$ 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 $P_{mus,\ oes}$, $P_{mus,\ oes,\ PEEPi}$, PTP_{oes}, and $PTP_{oes,\ PEEPi}$ 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 cmH_2O. 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 (AcqKnowledgement, 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 ($\Delta P_{oes}/\Delta P_{aw}$) 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]. $PTP_{oes,\ PEEPi}$ 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]:

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

$PTP_{aw,\ br}$ 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. Correlatios between $PTP_{oes,\ br}$ and $P_{mus,\ oes}$, $PTP_{oes,\ PEEPi,\ br}$ and $P_{mus,\ oes,\ PEEPi}$, and $PTP_{aw,\ br}$ and $P_{mus,\ aw}$ were analysed using the two-tailed Spearman correlation test. Linear regression between $PTP_{oes,\ br}$ and $P_{mus,\ oes}$, $PTP_{oes,\ PEEP,\ br}$ and $P_{mus,\ oes,\ PEEPi}$, and $PTP_{aw,\ br}$ 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.

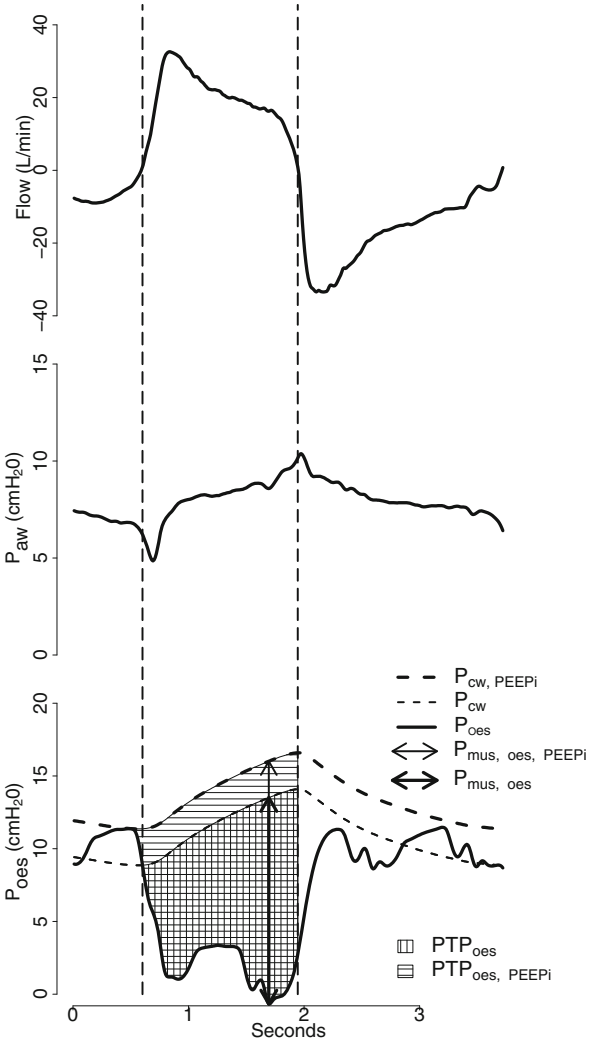

Fig. 1 Graphic illustration of flow, airway pressure (P_{aw}), and oesophageal pressure tracing (P_{oes}) during proportional assist ventilation. Chest wall recoil pressure (P_{cw}) was calculated from the product of tidal volume and dynamic chest wall elastance. Upper bound oesophageal pressure time product ($PTP_{oes,\ PEEPi}$) was calculated as the integration of the difference between $P_{cw,\ PEEPi}$ and P_{oes}. Lower bound oesophageal pressure time product (PTP_{oes}) was calculated as the integration of the difference between P_{cw} and P_{oes}. $P_{mus,\ oes}$ and $P_{mus,\ oes,\ PEEPi}$ represent the maximal difference between passive and active P_{oes}

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 $\Delta P_{oes}/\Delta P_{aw}$ ratio. One patient was excluded because of a poor oesophageal pressure signal, and four patients were excluded because of an inadequate duration of P_{oes} tracing secondary to the intolerance of the patients to low-gain PAV. Ultimately, 11 patients with an adequate duration of PAV recording at all stages of PAV support were analysed. The clinical demographics and respiratory mechanics of these patients are shown in Table 1. The tidal volume, $P_{aw,\ peak}$, E_{pav}, and R_{pav} under various PAV gain levels are shown in Fig. 2. Significantly higher tidal volumes were found with high PAV gains. As predicted, P_{peak} increased with PAV gain. There were no significant changes in R_{pav}, but E_{pav} was significantly higher with a high PAV gain ($p < 0.0001$).

PTP_{oes}, $PTP_{oes,\ PEEPi}$, peak muscular pressure and duration of inspiration (Ti) with different PAV gains and their correlation analysis

PTP_{oes} and $PTP_{oes,\ PEEPi}$ during various PAV gain factors are shown in Fig. 3. Progressive reductions in PTP_{oes} and $PTP_{oes,\ PEEPi}$ 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 PTP_{oes} or $PTP_{oes,\ PEEPi}$ was found between PAV20 vs. PAV30, PAV30 vs. PAV40, PAV40 vs. PAV50, or PAV50 vs. PAV60. $P_{mus,\ aw}$ tended to underestimate $P_{mus,\ oes}$ or $P_{mus,\ oes,\ PEEPi}$ with all levels of PAV gain except PAV20 (Fig. 4a). The minimal difference between $P_{mus,\ aw}$ and $P_{mus,\ oes}$ was at the level of PAV30 (Fig. 4a). The $T_{i,\ aw}$ estimated from the onset of inspiratory effort to $P_{aw,\ peak}$ was not different from that estimated from flow tracing from PAV20 to PAV50. However, the $T_{i,\ aw}$ 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 $P_{mus,\ aw}$ and $PTP_{aw,\ br}$ ($r^2 = 0.9341$), $P_{mus,\ oes}$ and $PTP_{oes,\ br}$($r^2 = 0.8751$), and $P_{mus,\ oes,\ PEEPi}$ and $PTP_{oes,\ PEEPi,\ br}$ ($r^2 = 0.8862$). Linear regression analysis disclosed the best-fit slope between $PTP_{aw,\ br}$ and $P_{mus,\ aw}$ to be 0.56, between $PTP_{oes,\ br}$ and $P_{mus,\ oes}$ to be 0.73, and between $PTP_{oes,\ PEEPi,\ br}$ and $P_{mus,\ oes,\ PEEPi}$ to be 0.83.

Bland-Altman analysis of P_{mus} between $P_{mus,\ aw}$ and $P_{mus,\ oes}$ and selection of optimal P_{mus}

There was limited agreement between $P_{mus,\ aw}$ and $P_{mus,\ oes}$ as determined by Bland-Altman analysis (Fig. 4b). The bias was -1.2 cmH_2O. The 95% confidence interval

Table 1 Patient demographics and respiratory mechanics

Case	Age (years)/ Sex	Diagnosis	Days on MV/ETT size (mm)/ ΔP_{ETT} (cmH_2O)	Baseline FiO_2/PEEP (cmH_2O)	E_{rs} (cmH_2O/L)	E_{cw} (cmH_2O/L)	R_{max} (cmH_2O/L/S)	R_{min} (cmH_2O/L/S)	$\Delta P_{oes}/\Delta P_{aw}$
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 bacteraemia	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[b]	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	18/7.0[a]/1.97[a]	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	0.30/6	7.73	4.24	23.52	13.35	1.11
11[c]	84/F	UTI, parkinsonism, asthma	4/7.5/3.86	0.35/6	21.61	6.72	20.88	13.34	0.77

[a]Tracheostomy tube and ΔP_{ETT} only an approximation as equation only available for an 8.0-mm tracheostomy. [b]Cheyne-Stokes breathing noted. [c]Evident abdominal muscle contraction noted. *FiO_2* inspired oxygen fraction, *ETT* endotracheal tube, *CHF* congestive heart failure, *COPD* chronic obstructive pulmonary disease, *E_{rs}* passive respiratory system elastance, *E_{cw}* 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, *$\Delta P_{oes}/\Delta P_{aw}$* ratio of oesophageal pressure drop to airway pressure drop during airway occlusion, *ΔP_{ETT}* pressure loss through endotracheal or tracheostomy tube

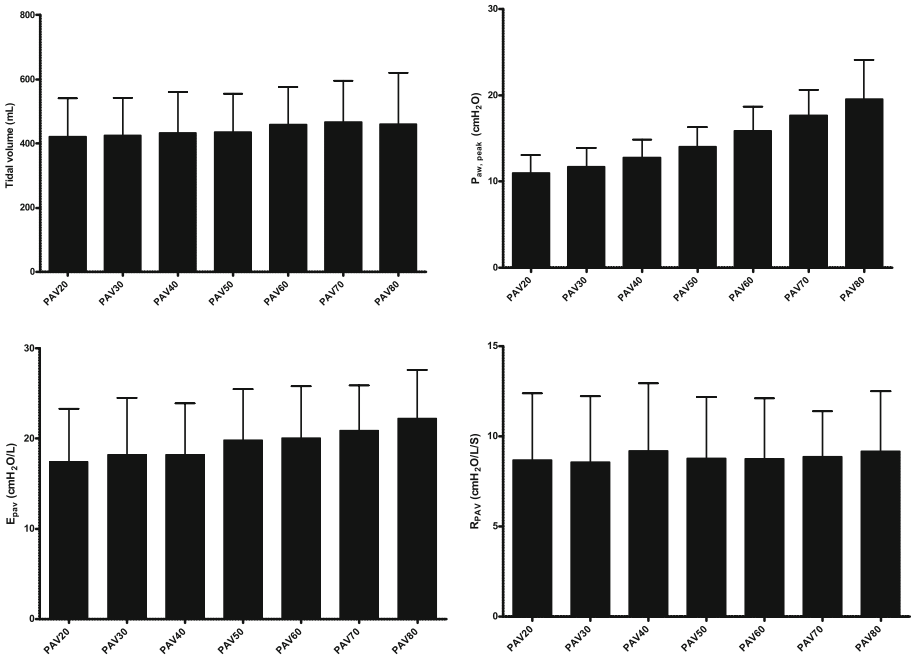

Fig. 2 Tidal volume, peak airway pressure ($P_{aw, peak}$) and respiratory mechanics during proportional assist ventilation (*PAV*) under different gains. *PAV20* indicates a mean gain level of 20%. Significant differences in tidal volume were found between PAV60 vs. PAV20, PAV70 vs. PAV20, PAV70 vs. PAV30, and PAV70 vs. PAV40. Significant differences in $P_{aw, peak}$ were found among individual $P_{aw, peak}$ levels under different gains, except the $P_{aw, peak}$ of PAV20 vs. $P_{aw, peak}$ of PAV30 and $P_{aw, peak}$ of PAV70 vs. $P_{aw, peak}$ of PAV80. For PAV-based patient elastance (E_{pav}), significant differences were found between PAV20 vs. PAV50, PAV60, PAV70, and PAV80; PAV30 vs. PAV50, PAV60, PAV70, and PAV80; PAV40 vs. PAV50, PAV60, PAV70, and PAV80; PAV50 vs. PAV70 and PAV80; PAV60 vs. PAV80; and PAV70 vs. PAV80. No significant difference was found in PAV-based patient resistance (R_{pav}) among various gains. For the E_{pav} and R_{pav} comparison, one patient was not included because of insufficient numbers of E_{pav} and R_{pav} in PAV20 and PAV30

between $P_{mus,\ aw}$ and $P_{mus,\ oes}$ was from -11.2 to 8.8 cmH_2O. 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_{mus} according to $P_{mus,\ aw}$ (5–10 cmH_2O). However, the best PAV gain for optimal PAV assessed from $P_{mus,\ oes}$ or $P_{mus,\ oes,\ PEEPi}$ was quite diverse and was absent in two patients. The concordance rate for selection of optimal PAV gain was <50% between $P_{mus,\ aw}$ and $P_{mus,\ oes}$ and $P_{mus,\ aw}$ and $P_{mus,\ oes,\ PEEPi}$.

$P_{mus,aw}$ within 5–10 cmH_2O 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 $P_{mus,aw}$ within 5–10 cmH_2O. PTP_{oes} <224 cmH_2O·s/min and $PTP_{oes,\ PEEPi}$ <255 cmH_2O·s/min are considered admissible according to Jubran et al. [13]. Despite the limited predictability of $P_{mus,\ oes}$ or $P_{mus,\ oes,\ PEEPi}$ from $P_{mus,\ aw}$, patients with $P_{mus,\ aw}$ between 5 and 10 cmH_2O are had 93% probability of PTP_{oes} <220 cmH_2O·s/min and 88% probability of $PTP_{oes,\ PEEPi}$ <255 cmH_2O·s/min, regardless of the PAV gain. Only two breaths were associated with PTP_{oes} values <40 cmH_2O·s/min. When $P_{mus,aw}$ was achieved within 5–10 cmH_2O, three PAV gain levels (PAV40, PAV50 and PAV60) were associated with >90% probability of admissible PTP_{oes} and $PTP_{oes,\ PEEPi}$.

Discussion

Our analyses revealed several interesting findings. First, PTP_{oes} and $PTP_{oes,\ PEEPi}$ significantly decreased with increasing PAV gain in patients with PAV. Second, the prediction of $P_{mus,\ oes}$ or $P_{mus,\ oes,\ PEEPi}$ from airway pressure tracing had limited accuracy. Third, the deduction of PTP_{aw} from ΔP may underestimate PTP_{oes} or $PTP_{oes,\ PEEPi}$. Fourth, an optimal $P_{mus,\ aw}$ (5–10 cmH_2O) could be achieved in 91% of patients with PAV60, and despite the lack of accuracy for predicting $P_{mus,\ oes}$ or $P_{mus,\ oes,\ PEEPi}$ from airway pressure tracing, maintaining $P_{mus,\ aw}$ within 5–10 cmH_2O was associated with PTP_{oes} <224 cmH_2O·s/min or $PTP_{oes,\ PEEPi}$ <255 cmH_2O·s/min in approximately 90% of breaths.

The significant increase in $P_{aw,\ peak}$ 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

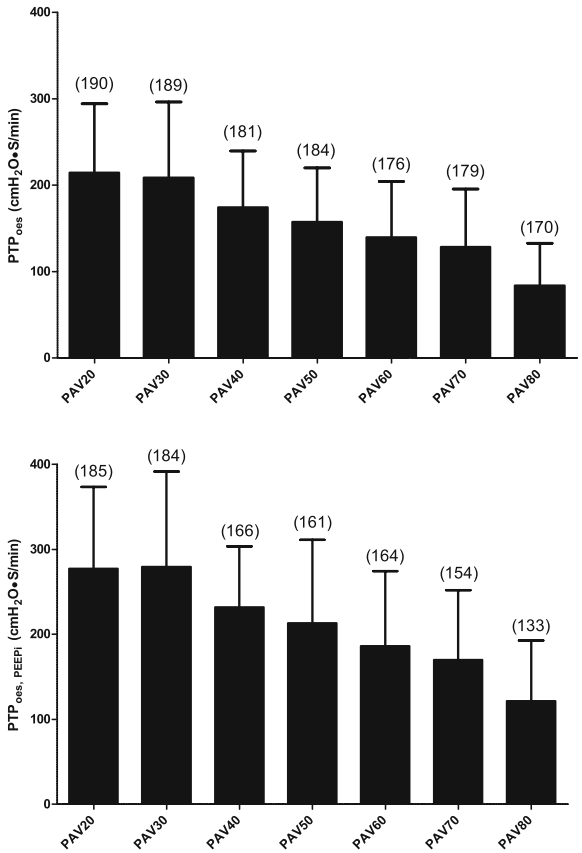

Fig. 3 Inspiratory pressure time product (*PTP*) under different gain levels. PTP calculated from the difference between the oesophageal pressure and the relaxed chest wall elastance curve (PTP_{oes}) decreased progressively with increasing gain with or without intrinsic positive end-expiratory pressure (*PEEPi*). For PTP_{oes}, a significant difference was found between proportional assist ventilation 20% gain (*PAV20*) vs. PAV40, PAV50, PAV60, PAV70, and PAV80; PAV30 vs. PAV50, PAV60, PAV70, and PAV80; PAV40 vs. PAV60, PAV70, and PAV80; PAV50 vs. PAV70 and PAV80; PAV60 vs. PAV80; and PAV70 vs. PAV80. Similar patterns were found with $PTP_{oes, PEEPi}$. Values in *parentheses* are the number of breaths analysed in each gain level

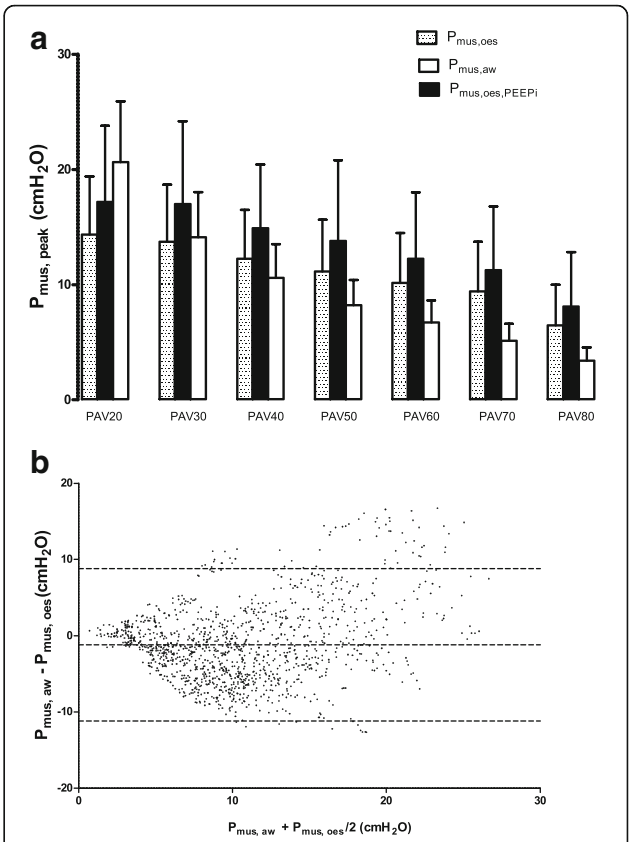

Fig. 4 a Maximum muscular pressure (P_{mus}) determined using either oesophageal pressure tracing or airway pressure under different proportional assist ventilation (PAV) gains. Significant differences ($p < 0.05$) were observed for all gain levels. **b** Bland-Altman analysis plot showing bias and agreement between maximal muscular pressure calculated from ΔP and PAV gain ($P_{mus, aw}$) and maximal muscular pressure calculated from maximum difference between passive and active P_{oes} without consideration of PEEPi ($P_{mus, oes}$). The *middle dashed line* is the mean difference (bias). The *outer dashed line* is the 95% confidence interval of the difference between $P_{mus, aw}$ and $P_{mus, oes}$ (±1.96 SD)

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 ($P_{mus, aw}$) in mechanically ventilated patients under PAV. We found it to be of limited value in predicting $P_{mus, oes}$. $P_{mus, aw}$ tends to overestimate $P_{mus, oes}$ in PAV20 but more commonly underestimates $P_{mus, oes}$ 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 $P_{mus, oes}$ and $P_{mus, aw}$ implicated that $P_{mus, oes}$ could not be accurately predicted by $P_{mus, aw}$.

There are several possible explanations for these findings. First, for the unique condition where $P_{mus, oes}$ 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 $P_{mus, aw}$ [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_{mus} and PEEPi (cmH_2O)	PAV20	PAV30	PAV40	PAV50	PAV60	PAV70	PAV80
1	$P_{mus,\ aw}$	25	18	15	11	9	7	4
	$P_{mus,\ oes}$	20	19	18	13	15	13	7
	$P_{mus,\ oes,\ PEEPi}$	21	22	19	14	16	14	8
	PEEPi level	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	$P_{mus,\ aw}$	19	13	10	8	6	5	3
	$P_{mus,\ oes}$	16	15	16	13	13	14	11
	$P_{mus,\ oes,\ PEEPi}$	17	17	17	14	15	15	12
	PEEPi level	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	$P_{mus,\ aw}$	17	10	8	6	5	4	3
	$P_{mus,\ oes}$	17	14	13	14	11	11	8
	$P_{mus,\ oes,\ PEEPi}$	18	16	14	15	12	14	9
	PEEPi level	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	$P_{mus,\ aw}$	17	13	10	8	6	5	3
	$P_{mus,\ oes}$	14	16	11	11	10	8	5
	$P_{mus,\ oes,\ PEEPi}$	15	17	13	12	11	9	6
	PEEPi level	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	$P_{mus,\ aw}$	13	9	7	5	5	4	3
	$P_{mus,\ oes}$	9	9	8	7	8	6	4
	$P_{mus,\ oes,\ PEEPi}$	10	10	9	8	8	6	4
	PEEPi level	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	$P_{mus,\ aw}$	23	18	13	11	9	7	6
	$P_{mus,\ oes}$	21	21	17	20	17	14	13
	$P_{mus,\ oes,\ PEEPi}$	27	28	19	27	23	18	18
	PEEPi level	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	$P_{mus,\ aw}$	14	9	7	5	4	3	2
	$P_{mus,\ oes}$	4	5	4	4	3	2	2
	$P_{mus,\ oes,\ PEEPi}$	7	7	7	6	4	4	3
	PEEPi level	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	$P_{mus,\ aw}$	20	14	10	8	6	5	3
	$P_{mus,\ oes}$	14	13	10	10	8	7	7
	$P_{mus,\ oes,\ PEEPi}$	16	15	12	10	9	8	8
	PEEPi level	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	$P_{mus,\ aw}$	26	18	13	9	8	5	3
	$P_{mus,\ oes}$	12	11	10	8	8	6	4
	$P_{mus,\ oes,\ PEEPi}$	14	13	12	10	10	8	6
	PEEPi level	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	$P_{mus,\ aw}$	26	14	9	8	6	5	4
	$P_{mus,\ oes}$	16	15	15	13	11	11	9
	$P_{mus,\ oes,\ PEEPi}$	17	16	16	14	12	12	11
	PEEPi level	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	$P_{mus,\ aw}$	28	19	14	12	10	7	4
	$P_{mus,\ oes}$	16	14	13	12	8	12	5
	$P_{mus,\ oes,\ PEEPi}$	28	32	29	28	17	18	10
	PEEPi level	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_2O are highlighted. $P_{mus,\ aw}$ maximal muscular pressure calculated from ΔP and PAV gain, $P_{mus,\ oes}$ maximal muscular pressure calculated from maximum difference between passive and active P_{oes} without consideration of PEEPi, $P_{mus,\ oes,\ PEEPi}$ maximal muscular pressure calculated from maximum difference between passive and active P_{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.

PTP_{oes} is a better surrogate of respiratory effort in ventilated patients. In this study, the analyses of correlation between $P_{mus,\ aw}$ and PTP_{aw}, $P_{mus,\ oes}$ and PTP_{oes}, $P_{mus,\ oes,\ PEEPi}$ and $PTP_{oes,\ PEEPi}$ yielded highly significant results. However, predicting PTP from $P_{mus,\ aw}$ and $P_{mus,\ oes}$ differed in the best-fit slope value. The slope value was 0.56 when the linear regression was performed between $P_{mus,\ aw}$ and PTP_{aw}. The slope increased to 0.73 between $PTP_{oes,\ br}$ and $P_{mus,\ oes}$ and to 0.83 between $PTP_{oes,\ PEEPi,\ br}$ and $P_{mus,\ oes,\ PEEPi}$. This implicates that the PTP_{aw} should be corrected when projecting into PTP_{oes}. We offer the following explanation for the discrepancy between PTP_{aw} and PTP_{oes}. First, the assumption of a triangular pressure-time product is flawed because 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 PTP_{aw} 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 $P_{mus,\ oes,\ PEEPi}$ and $PTP_{oes,\ PEEPi}$.

The predefined range of respiratory effort by Carteaux and colleagues [11] needs critical appraisal. Target limits of $P_{mus,\ aw}$ within 5–10 cmH_2O or PTP_{aw} between 50 and 150 $cmH_2O{\cdot}s/min$ were derived mainly from a desirable inspiratory effort of $PTP_{oes,\ PEEPi}$ <125 $cmH_2O{\cdot}s/min$ [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 $PTP_{oes,\ PEEPi}$ should be allowable with minimal risk of diaphragm fatigue [13, 25, 26]. As $P_{mus,\ aw}$ frequently underestimates $P_{mus,\ oes}$ in the usual levels of PAV, actual $PTP_{oes,\ PEEPi}$ values are usually higher than PTP_{aw}. Interestingly, $PTP_{oes,\ PEEPi}$ measurements were usually <255 $cmH_2O{\cdot}s/min$ when $P_{mus,\ aw}$ were within 5–10 cmH_2O. 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 PEEP 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 $P_{mus,\ oes,\ PEEPi}$ 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 $P_{mus,\ oes}$ decreases with increasing PAV gain, $P_{mus,\ oes}$ could not be precisely predicted from ΔP under various gain factors. In addition, PTP_{aw} also underestimated PTP_{oes} and $PTP_{oes,\ PEEPi}$. However, when the PAV gain was adjusted to a $P_{mus,\ aw}$ of 5–10 cmH_2O, there was approximately 90% probability of maintaining the patient within an acceptable PTP range.

Abbreviations

CMV: continuous mandatory ventilation; E_{cw}: passive chest wall elastance during CMV; E_{pav}: PAV-based patient elastance; E_{rs}: passive respiratory system elastance during CMV; PAV: proportional assist ventilation; PAV20 to PAV80: 20 to 80% PAV gain; $P_{aw,\ peak}$: peak airway pressure during PAV; P_{cw}: chest wall elastic pressure; PEEP: positive end-expiratory pressure; PEEPi: intrinsic PEEP; $P_{mus,\ aw}$: maximal muscular pressure calculated from ΔP and PAV gain; $P_{mus,\ oes}$: maximal muscular pressure calculated from maximum difference between passive and active P_{oes} without consideration of PEEPi; $P_{mus,\ oes,\ PEEPi}$: maximal muscular pressure calculated from maximum difference between passive and active P_{oes} with consideration of PEEPi; P_{mus}: respiratory muscular pressure; PTP: inspiratory pressure time product; $PTP_{aw,\ br}$: inspiratory pressure time product calculated from ΔP and assuming a triangular inspiratory pressure time course per breath; PTP_{aw}: inspiratory pressure time product calculated from ΔP and assuming a triangular inspiratory pressure time course; $PTP_{oes,\ br}$: inspiratory pressure time product calculated from the difference between the oesophageal pressure and the relaxed chest wall elastance curve per breath; PTP_{oes}: inspiratory pressure time product calculated from the difference between the oesophageal pressure and the relaxed chest wall elastance curve; $PTP_{oes,\ PEEPi,\ br}$: inspiratory pressure time product calculated from the difference between the oesophageal pressure and the relaxed chest wall elastance curve per breath with consideration of PEEPi; $PTP_{oes,\ PEEPi}$: PTP_{oes} with consideration of PEEPi; R_{max}: passive maximum inspiratory resistance during CMV; R_{min}: passive minimum (airway) inspiratory resistance during CMV; R_{pav}: PAV-based patient resistance; T_i: duration of the inspiratory time determined from flow tracing during various PAV gains without consideration of PEEPi; $T_{i,\ aw}$: 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 PEEP difference

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Availability of data and materials

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Authors' contributions

PLS participated in the study design, collected and analysed data, and drafted the revised manuscript. PSK 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-BR-102-090). Consent to participate was obtained from the patients/families.

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