BJA

British Journal of Anaesthesia, 125 (1): e148–e157 (2020)

doi: 10.1016/j.bja.2020.02.026
Advance Access Publication Date: 6 May 2020
Clinical Investigation

CLINICAL INVESTIGATION

Oesophageal pressure and respiratory muscle ultrasonographic measurements indicate inspiratory effort during pressure support ventilation

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Abstract

Background: Bedside measures of patient effort are essential to properly titrate the level of pressure support ventilation. We investigated whether the tidal swing in oesophageal (ΔPes) and transdiaphragmatic pressure (ΔPdi), and ultrasonographic changes in diaphragm (TFdi) and parasternal intercostal (TFic) thickening are reliable estimates of respiratory effort. The effect of diaphragm dysfunction was also considered.

Methods: Twenty-one critically ill patients were enrolled: age 73 (14) yr, BMI 27 (7) kg m^{-2}, and $Pa_{O_2}/F_{I_{O_2}}$ 33.3 (9.2) kPa. A three-level pressure support trial was performed: baseline, 25% (PS-medium), and 50% reduction (PS-low). We recorded the oesophageal and transdiaphragmatic pressure–time products (PTPs), work of breathing (WOB), and diaphragm and intercostal ultrasonography. Diaphragm dysfunction was defined by the Gilbert index.

Results: Pressure support was 9.0 (1.6) cm H_2O at baseline, 6.7 (1.3) (PS-medium), and 4.4 (1.0) (PS-low). ΔPes was significantly associated with the oesophageal PTP (R^2=0.868; P<0.001) and the WOB (R^2=0.683; P<0.001). ΔPdi was significantly associated with the transdiaphragmatic PTP (R^2=0.820; P<0.001). TFdi was only weakly correlated with the oesophageal PTP (R^2=0.326; P<0.001), and the correlation improved after excluding patients with diaphragm dysfunction (R^2=0.887; P<0.001). TFdi was higher and TFic lower in patients without diaphragm dysfunction: 33.6 (18.2)% *vs* 13.2 (9.2)% and 2.1 (1.7)% *vs* 12.7 (9.1)%; P<0.0001.

Conclusions: ΔPes and ΔPdi are adequate estimates of inspiratory effort. Diaphragm ultrasonography is a reliable indicator of inspiratory effort in the absence of diaphragm dysfunction. Additional measurement of parasternal intercostal thickening may discriminate a low inspiratory effort or a high effort in the presence of a dysfunctional diaphragm.

Keywords: critical care; diaphragm; intercostal muscle; oesophageal pressure; pressure support ventilation; ultrasonography; work of breathing

Editor's key points

- The authors investigated the utility of bedside tools in estimating inspiratory effort, including the tidal swing in oesophageal and transdiaphragmatic pressure and ultrasonography-observed thickening of the diaphragm and parasternal intercostal muscles.
- Tidal swings of oesophageal and transdiaphragmatic pressure were closely related to gold-standard indices of inspiratory effort.

Received: 10 October 2019; **Accepted:** 25 February 2020

- Inspiratory diaphragmatic thickening correlated weakly with inspiratory effort, although this improved when diaphragmatic dysfunction was excluded.
- Where diaphragmatic thickening is low, parasternal intercostal thickening may allow improved consideration of inspiratory effort.

Mechanical ventilation is the most used supportive therapy in the ICU.[1] Pressure support ventilation (PSV) is the mode of assisted ventilation generally used during the weaning phase.[2,3] Under PSV, the work necessary to generate the ventilation is shared between the ventilator and the patient.[4] In recent years, a U-shaped relationship between ventilator assistance and complications has emerged, as both under- and over-assistance can lead to deleterious consequences.[5] A safe compromise between the benefits and risks is to achieve acceptable levels of muscle unloading while preserving spontaneous breathing.[5]

As patient inspiratory effort cannot be adequately assessed from physical examination or ventilator waveforms,[6] direct measures are required to properly titrate the ventilatory support. Oesophageal pressure (Pes) and transdiaphragmatic pressure (Pdi) represent the reference methods for measuring the pressure generated by the respiratory muscles.[7,8] With this regard, the 'gold-standard' parameters for the assessment of respiratory effort are work of breathing (WOB) and pressure–time product (PTP).[9] However, their calculation is complex and requires offline analysis, confining this technique mainly to the research setting; easier, bedside-available tools for the assessment of patient effort are required for everyday clinical practice. The tidal swing of Pes (ΔPes) has recently been suggested as a target.[5] Such assessment is relatively straightforward and can be performed in real time at the bedside. As PTP is calculated as the integral over time of the Pes (or Pdi) tracing on a breath-by-breath basis, a close relationship with the tidal swings of Pes (or Pdi) is very likely. However, a formal validation of this parameter compared with gold standard is lacking in critically ill patients, with several issues potentially limiting its use to assess breathing effort. Indeed, if the strength of this association between ΔPes (or Pdi) and the gold-standard indices of inspiratory effort is high, then the former could be used at the bedside as a reasonable proxy for breathing effort, avoiding the need for specific software or other technology to perform the calculations.

Ultrasound has gained in popularity as a diagnostic tool in the ICU. In the last decades, diaphragm ultrasound has emerged as a potential tool for monitoring the respiratory effort of critically ill patients.[10,11] However, few studies have investigated the relationship between diaphragm and intercostal muscle ultrasound and gold-standard indices of respiratory effort in critically ill patients.

The aims of the present study were (i) to test whether the bedside assessment of ΔPes is a reliable indicator of gold-standard indices of respiratory effort, and (ii) to assess the change in diaphragm and parasternal intercostal inspiratory thickening with increasing patient effort. Secondary outcomes were the correlation between transdiaphragmatic tidal pressure swing and indices of respiratory effort and the impact of diaphragm dysfunction on the ultrasonographic assessment of respiratory effort.

Methods

Subjects

Consecutive patients were enrolled if they were intubated and undergoing PSV with a PEEP >5 cm H_2O. Exclusion criteria were haemodynamic instability requiring vasopressors, hypoxaemia requiring PEEP >10 cm H_2O or F_{IO_2} >60%, pressure support >10 cm H_2O, Richmond Agitation and Sedation Scale score <−1, and history of chronic obstructive pulmonary disease (COPD). The study was approved by the Institutional Review Board (Comitato Etico Interaziendale Milano Area 1, 11941/2017), and written informed consent was obtained according to Italian regulations.

Measurements

Detailed methods are reported in the Supplementary material, including calculation of inspiratory WOB and both oesophageal and transdiaphragmatic PTPs. Patients were studied in the semi-recumbent position. As per choice of the consultant intensivist, the lungs of the patients were ventilated with either a Mindray SV800 (Mindray Medical International, Shenzhen, China) or a Hamilton-G5 ventilator (Hamilton Medical AG, Bonaduz, Switzerland). In both cases, the ventilation mode was set as follows: flow triggering at 2 L min^{-1}, pressure ramp 200 ms, and cycling off at 25% of the peak inspiratory flow. Automatic tube compensation was not used.

Flow was measured with a heated pneumotachograph (Fleisch No. 1, Metabo SA, Epalinges, Switzerland). Airway pressure (Paw) was measured proximal to the tracheal tube with a dedicated pressure transducer (MPX 2010DP; Motorola, Solna, Sweden). Pes was measured using a standard balloon catheter (Smart Cath; Viasys, Palm Springs, CA, USA), and correct positioning was assessed by the occlusion test.[12] A similar catheter was advanced into the stomach to measure gastric pressure (Pga). Both balloons were inflated with 1.5 ml of air and connected to air-filled pressure transducers. Flow, Paw, Pes, and Pga were collected at a sampling rate of 100 Hz, and then stored for subsequent analysis (Colligo; Elekton, Milan, Italy). Transdiaphragmatic pressure was obtained by electronic subtraction as Pga–Pes.

Pattern of breathing and respiratory effort

In each step, tidal volume, ventilatory frequency, minute ventilation, inspiratory time, duty cycle (inspiratory/total time), peak inspiratory flow, dynamic intrinsic PEEP (PEEPi), WOB[13] (expressed per minute or per litre of ventilation), oesophageal and transdiaphragmatic PTP[14] (expressed per breath and per minute), and the tidal swing in oesophageal and transdiaphragmatic pressures (ΔPes and ΔPdi, respectively) were measured. Mean values were computed over five consecutive breaths. End-expiratory and end-inspiratory occlusions were performed to measure P0.1[15] and Pmusc, index.[16] Supplementary Figure S1 illustrates the parameters for the assessment of inspiratory breathing effort.

The inspiratory contribution of the diaphragm was assessed with the Gilbert index, defined as ΔPga/ΔPdi during the phase of lowest support.[17] Lower values indicate a lower contribution of the diaphragm to inspiratory effort. A negative index was used to define diaphragm dysfunction.[18]

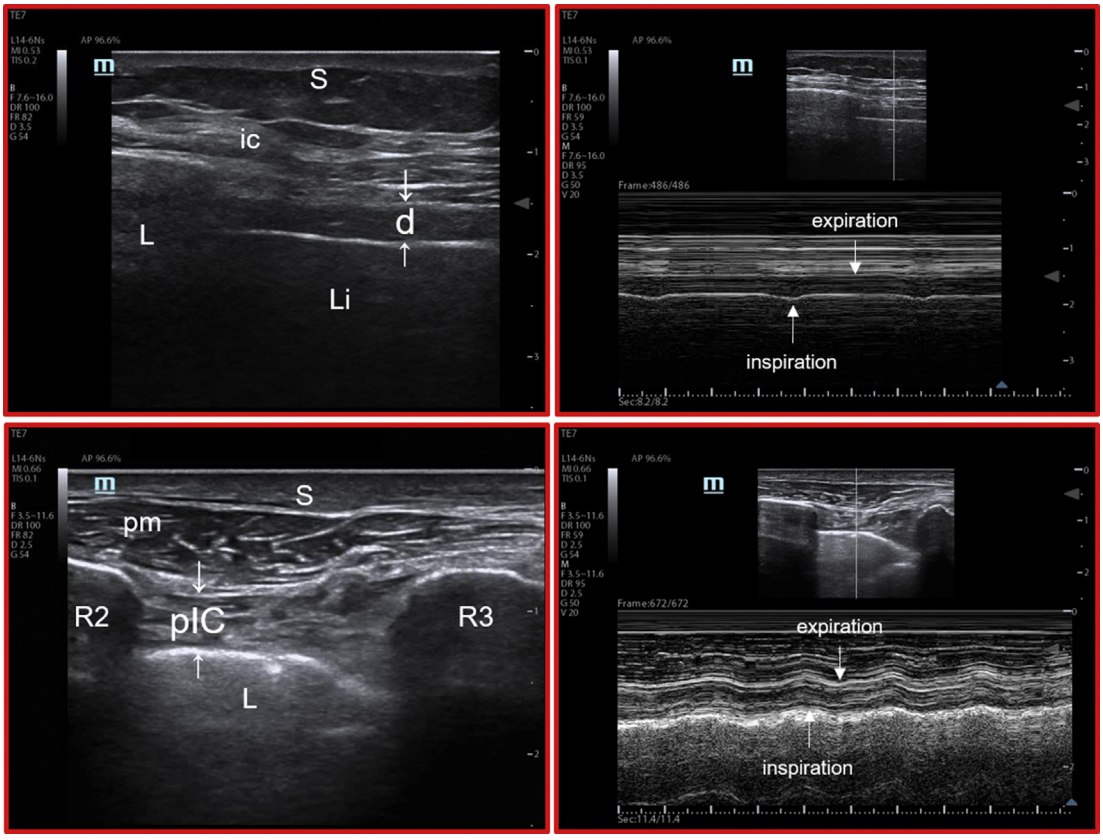

Fig 1. Ultrasonographic view of the diaphragm and parasternal intercostal muscles. Upper left panel: B-mode scan of the diaphragm in the zone of apposition. The diaphragm (d) is identified as a three-layer structure (non-echogenic central layer bordered by two echogenic layers, the peritoneum and the diaphragmatic pleurae, indicated by the white arrows). ic, intercostal muscles; L, lung; Li, liver; S, subcutaneous tissue. Upper right panel: M-mode image of diaphragm thickening during inspiration. Lower left panel: B-mode scan of the intercostal muscles. The parasternal intercostals (pIC) are identified above the pleural line and between the hyper-echogenic layers of the fascial borders, as indicated by the white arrows. L, lung; pm, *pectoralis* muscle; R2, second rib; R3, third rib; S, subcutaneous tissue. Lower right panel: M-mode image of parasternal intercostal thickening during inspiration.

Ultrasonographic measurements

Ultrasonography was performed by the same trained operator (PF), with 9 yr of experience and qualifications in respiratory ultrasound, using a Mindray TE7 Ultrasound System (Mindray Medical International) with a 12 MHz linear probe. Images were recorded for a subsequent computer-assisted quantitative analysis by a trained investigator (MU), unaware of the ventilatory condition.

Diaphragm thickness was assessed in the zone of apposition of the diaphragm to the ribcage. The linear probe was placed above the right 10th rib in the mid-axillary line, as described previously.[10] The inferior border of the costophrenic sinus was identified as the transition from the artifactual representation of the lung to the visualisation of the liver.

The inspiratory thickening of the parasternal intercostal muscles was assessed with a linear probe placed 3 cm laterally from the sternum and oriented along the sagittal plane, between the second and third ribs, as described.[19] Muscle thickness was measured above the pleural line between the two hyper-echogenic layers of the fascial borders. For both the diaphragm and the parasternal intercostal muscles, three subsequent measures were averaged. The thickening fraction of each muscle (TF) was calculated as

$$TF = \frac{(\text{end} - \text{inspiratory thickness} - \text{end} - \text{expiratory thickness})}{\text{end} - \text{expiratory thickness}} * 100$$

Table 1 Patient characteristics at baseline. Data are expressed as mean (standard deviation) or number (percentage), as appropriate. Age is expressed as mean (range). F_{IO_2}, fraction of inspired oxygen; *n*, sample size; SAPS II, Simplified Acute Physiology Score, second version. Septic shock was caused by meningitis, pancreatitis, neck fasciitis, or urinary tract infection.

Variable	Study population (*n*=21)
Age	73 (25–88) yr
Male sex	17 (81%)
Actual body weight	79.3 (18.7) kg
Ideal body weight	64.5 (4.8) kg
Body height	1.70 (0.06) m
BMI	27.0 (6.7) kg m^{-2}
SAPS II	37.6 (13.3)
Diagnosis	
Pneumonia	10 (47.7%)
Septic shock	5 (23.8%)
Acute decompensated heart failure	4 (19.0%)
Aspiration	2 (9.5%)
PEEP	7.0 (2.0) cm H_2O
F_{IO_2}	0.36 (0.06)

Figure 1 shows the ultrasonographic view of the diaphragm and parasternal intercostal muscles.

Protocol

The study consisted of two consecutive phases. Initially, the patients underwent a trial of three levels of PSV, lasting 30 min each. The first level was set by the attending physician (PS-baseline). Pressure support was reduced by 25% (PS-medium), and then by 50% (PS-low), in this order. PEEP and F_{IO_2} were unchanged, as was the sedation level. During the last 5 min of each step, the pattern of breathing and indices of respiratory effort were assessed, arterial blood was sampled for gas determinations, and haemodynamic parameters were recorded. To avoid any possible development of fatigue at low levels of assistance, which might have then influenced the following steps, we decided to perform a decremental pressure support test and we did not randomise the sequence of pressure support levels.

In the second phase, the patients were deeply sedated and switched to square flow, controlled mechanical ventilation with tidal volume 750 ml and PEEP 0 cm H_2O. This step was necessary to obtain quasi-static measurements of partitioned respiratory mechanics, which are in turn needed for the exact calculation of WOB and PTP. Chest-wall compliance was measured with end-expiratory and end-inspiratory occlusions. The absence of spontaneous breathing was verified by observing the Pes waveform.

Statistics

As, to our knowledge, no previous publications have addressed a similar topic, a formal sample size calculation was not performed, and we enrolled a convenience sample with a similar size to other physiological investigations. Data were analysed using Stata 13.0 (StataCorp, College Station, TX, USA) for Windows. Normality was assessed by the Shapiro–Francia test. Descriptive results are reported as mean (standard deviation) if normally distributed, or median [25th–75th percentiles] otherwise. The analysis on the variables recorded over the three steps (PS-baseline, PS-medium, and PS-low) was performed by analysis of variance for repeated measurements, with step as a within-subject factor. The comparison between

Table 2 Respiratory pattern, drive, and effort in the different study steps. Data are expressed as mean (standard deviation). PS, pressure support; PTP, pressure–time product. The analysis on the variables recorded over the three different steps (PS-baseline, PS-medium, and PS-low) was performed on all the patients by analysis of variance for repeated measurements, with step as a within-subject factor. The significance of the within-subject factors was corrected with the Greenhouse–Geisser method. Pairwise *post hoc* multiple comparisons were carried out according to Tukey honestly significant difference method when appropriate. *P<0.01 *vs* PS-baseline; †P<0.01 *vs* PS-medium.

Variable	Pressure support level			P-value
	PS-baseline	PS-medium	PS-low	
Ventilatory frequency (bpm)	19.8 (7.3)	21.2 (6.2)	22.8 (6.6)*†	0.0080
Tidal volume (ml)	516 (112)	516 (124)	512 (121)	0.8650
Minute ventilation (L min^{-1})	9.9 (3.2)	10.6 (2.8)	11.4 (3.3)*	0.0098
Inspiratory time (s)	1.11 (0.27)	1.02 (0.20)*	1.00 (0.22)*	0.0082
Duty cycle	0.34 (0.09)	0.36 (0.10)*	0.36 (0.08)*	0.0003
Peak inspiratory flow (ml s^{-1})	771 (169)	750 (168)	734 (164)*	0.0489
Intrinsic PEEP (cm H_2O)	0.6 (0.5)	0.6 (0.5)	0.7 (0.5)	0.1450
Mean airway pressure (cm H_2O)	9.1 (2.2)	8.4 (2.0)*	7.7 (1.9)*†	<0.0001
Oesophageal pressure swing (cm H_2O)	−2.6 (1.8)	−4.5 (2.6)*	−7.2 (3.4)*†	<0.0001
Transdiaphragmatic pressure swing (cm H_2O)	3.5 (2.2)	5.2 (2.5)*	7.4 (3.1)*†	<0.0001
Oesophageal PTP/breath (cm H_2O s)	2.73 (1.17)	4.07 (2.28)*	5.92 (2.78)*†	<0.0001
Oesophageal PTP (cm H_2O s min^{-1})	55.4 (35.1)	84.2 (55.2)*	130.9 (69.7)*†	<0.0001
Transdiaphragmatic PTP/breath (cm H_2O s)	3.12 (1.37)	4.48 (2.14)*	5.89 (2.54)*	0.0419
Transdiaphragmatic PTP (cm H_2O s min^{-1})	64.1 (39.4)	94.9 (56.8)*	132.3 (70.9)*†	<0.0001
Work of breathing per litre (J L^{-1})	0.19 (0.17)	0.34 (0.23)*	0.57 (0.36)*†	<0.0001
Work of breathing per minute (J min^{-1})	2.0 (2.3)	3.8 (3.2)*	6.9 (5.7)*†	<0.0001
P0.1 (cm H_2O)	1.0 (0.6)	1.5 (0.6)*	2.0 (0.9)*†	<0.0001
Pmusc, index (cm H_2O)	2.4 (1.9)	4.6 (1.7)*	6.8 (1.9)*†	<0.0001

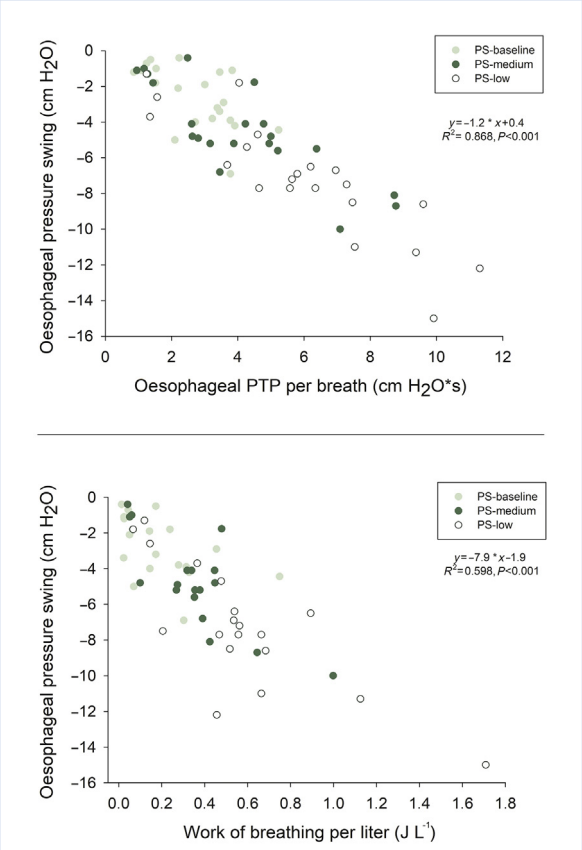

Fig 2. Correlation of oesophageal tidal pressure swing with oesophageal pressure–time product (PTP) (upper panel) or work of breathing (lower panel) during the different phases of the study. The analysis was conducted on all patients by a linear fixed-effects model for repeated measures to deal with the longitudinal structure of our data set (patients with repeated measurements over time). The extent of the association between variables was expressed as the coefficient of determination (R^2).

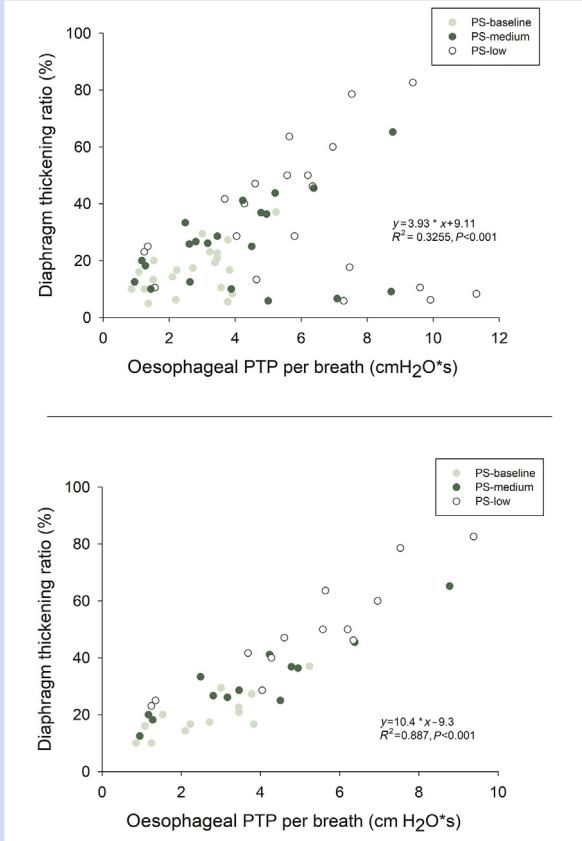

Fig 3. Diaphragm inspiratory thickening and oesophageal pressure–time product (PTP) during the different phases of the study in all patients (upper) and only in patients without diaphragm dysfunction (lower panel). The analysis was conducted by a linear fixed-effects model for repeated measures to deal with the longitudinal structure of our data set (patients with repeated measurements over time). The extent of the association between variables was expressed as the coefficient of determination (R^2). The analysis was conducted on all patients (upper panel; n=21) and only in patients without diaphragm dysfunction (lower panel; n=13). Diaphragm dysfunction was defined as a negative Gilbert index.

patients with and without diaphragm dysfunction was performed by analysis of variance for repeated measurements, with step as a within-subject factor and diaphragm dysfunction as a fixed between-subject factor. The model included the interaction effect of step on diaphragm dysfunction. The statistical significance of the within-subject factors was corrected with the Greenhouse–Geisser method. Pairwise *post hoc* multiple comparisons were carried out according to Tukey method. Regression was conducted by a linear fixed-effects model for repeated measures to deal with the longitudinal structure of our data set (patients with repeated measurements over time). The association between variables was expressed as the coefficient of determination (R^2). Two-tailed P-values <0.05 were considered for statistical significance.

Results

Patient characteristics

Twenty-one consecutive patients were enrolled. The patient characteristics at baseline are reported in Table 1. The patients were studied after an average ICU stay of 5 [3; 8] days. Both diaphragm and parasternal intercostal ultrasound examinations could be performed in all patients. Pressure support was on average 9.0 (1.6) cm H_2O at baseline, and it was reduced to 6.7 (1.3) (PS-medium) and 4.4 (1.0) (PS-low) during the study (P<0.0001).

Effects of PSV changes

Table 2 reports the respiratory pattern during the three steps. Reduction of pressure support was associated with a significant increase of ventilatory frequency, whereas tidal volume was not modified. As a result, minute ventilation significantly increased. Inspiratory time shortened and the duty cycle was longer with lower levels of support. On the other hand, the reduction of pressure support was not associated with

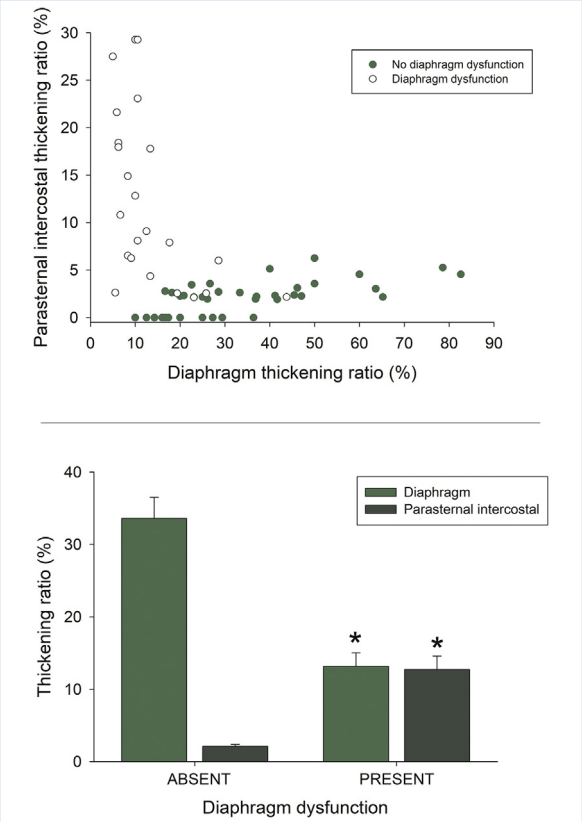

Fig 4. Relationship between diaphragm and intercostal inspiratory thickening (upper panel), and comparison of diaphragm and intercostal inspiratory thickening in patients with or without diaphragm dysfunction (lower panel). The analysis was conducted on all patients. *P<0.01 *vs* patients without diaphragm dysfunction.

changes in PEEPi, whereas mean airway pressure significantly decreased.

Respiratory drive and effort

The indices of respiratory drive and effort during the different steps are reported in Table 2. As expected, the progressive reduction of support led to a significant increase in both ΔPes and ΔPdi, and in the oesophageal and transdiaphragmatic PTP (per breath and per minute). Similarly, WOB—both per litre of ventilation and per minute—significantly increased. ΔPes was significantly associated with both the oesophageal PTP per breath (R^2=0.868; P<0.001) and per minute (R^2=0.666; P<0.001), and with the WOB per litre of ventilation (R^2=0.683; P<0.001) and per minute (R^2=0.549; P<0.001) (Fig. 2, upper and lower panels). Similarly, ΔPdi was significantly associated with the transdiaphragmatic PTP per breath (R^2=0.820; P<0.001) and per minute (R^2=0.599; P<0.001) (Supplementary Fig. S2).

Ultrasonographic indices of respiratory effort

Diaphragm and parasternal intercostal thicknesses are reported in Supplementary Table S1. The expiratory thickness of both muscles was unchanged in the different steps, whereas the inspiratory thickness, and hence the thickening fraction, significantly increased with lowering levels of support (Supplementary Fig. S3). Diaphragm thickening fraction significantly correlated with the oesophageal PTP per breath or per minute, albeit with a low coefficient of determination (R^2=0.326; P<0.001 and R^2=0.279; P<0.001, respectively) (Fig. 3, upper panel). Diaphragm thickening fraction was significantly associated with the transdiaphragmatic PTP per breath and per minute (R^2=0.482; P<0.001 and R^2=0.510; P<0.001, respectively).

Gas exchange and haemodynamic parameters

The reduction of pressure support was not associated with any modification in gas exchange or haemodynamic parameters (Supplementary Table S2).

Effect of diaphragm dysfunction

Eight patients (38.1%) had diaphragm dysfunction, as defined by a negative value of the ΔPga/ΔPdi ratio (i.e. the Gilbert index) during the phase of lowest support. Supplementary Table S3 shows the characteristics of patients with and without diaphragm dysfunction. After excluding these patients from the analysis, diaphragm thickening fraction had a stronger correlation with the oesophageal PTP per breath or per minute (R^2=0.887; P<0.001 and R^2=0.653; P<0.001, respectively) (Fig. 3, lower panel). The relationship of diaphragm and intercostal thickening in patients with and without diaphragm dysfunction is reported in Figure 4 (upper panel). The average value of diaphragm thickening fraction was higher and that of parasternal intercostal was lower in patients without as compared with patients with diaphragm dysfunction: 33.6 (18.2)% *vs* 13.2 (9.2)%; P<0.001 and 2.1 (1.7)% *vs* 12.7 (9.1)%; P<0.001, respectively (Fig. 4, lower panel).

Discussion

The main findings of this study are (i) the bedside-available ΔPes and ΔPdi were related to the gold-standard indices of inspiratory effort, such as the PTP or WOB; (ii) the ultrasonographic assessment of diaphragm thickening yielded an only acceptable estimate of respiratory effort, which was significantly improved when patients with diaphragm dysfunction were excluded from the analysis; and (iii) the ultrasonographic assessment of parasternal intercostal thickening could help in the bedside assessment of respiratory effort in the presence of a low thickening fraction of the diaphragm.

The balance between the beneficial and detrimental effects of spontaneous breathing effort is one of the contemporary challenges in critical care.[5] Preserving spontaneous activity might protect against the development of diaphragm contractile dysfunction.[20,21] However, an excessive respiratory drive can generate pressures incompatible with lung protection.[22] As a consequence, spontaneous breathing during mechanical ventilation has been considered a 'double-edged sword',[23] requiring an appropriate bedside monitoring of inspiratory effort. Despite being suggestive of an increased workload, specific breathing patterns, the use of accessory muscles, an increased ventilatory frequency or a reduced tidal volume, and the inspection of ventilator waveforms do not allow any quantitative assessment of breathing effort.[6,24]

Bedside estimation of patient inspiratory effort

The contraction of inspiratory muscles increases the size of the ribcage, reducing pleural pressure. When the diaphragm contracts, a pressure gradient is generated between the abdomen and the thorax (i.e. Pdi).[25] Pes, the most accurate clinically available estimate of pleural pressure, provides a global assessment of all inspiratory muscles,[26] whereas Pdi is specific to the diaphragm.[18]

The standard method to assess breathing effort is calculation of the WOB.[9] However, as work is performed when a volume is displaced, WOB is insensitive to isometric contractions. Moreover, duration and frequency of contractions are not taken into account. To overcome this limitation, the concept of PTP was developed.[14] When calculated from Pes tracings, it represents a global assessment of respiratory muscle activity (PTPes). As a specific measurement of diaphragm effort, diaphragm PTP (PTPdi) can be constructed from Pdi tracings. Pressure–time product is sensitive to the frequency and duration of contractions (including isometric efforts), and it correlates with oxygen consumption over a broad range of inspiratory loads.[27]

All these measurements are difficult to obtain and interpret at the bedside, as they generally need an offline calculation. As such, both are rarely used in clinical care and are mostly considered a research tool.[4,9]

On the other side, the assessment of ΔPes or ΔPdi is relatively straightforward and can be performed at the bedside, making it the ideal candidate for monitoring patient effort. However, several theoretical limitations must be considered. First, the duration and frequency of contractions are not taken into account.[28] Moreover, ΔPes is not corrected for the chest-wall recoil pressure or PEEPi, potentially leading to under- or overestimation of the real effort. Several investigations used ΔPes or ΔPdi during PSV as an estimate of the respiratory muscle effort.[29–32] However, to the best of our knowledge, no previous formal validation of the relationship of such tidal swings has been performed in critically ill patients.

That increasing levels of pressure support progressively unload the respiratory muscles is not a new finding.[33–36] The novelty of our study is that both ΔPes and ΔPdi are strongly correlated with gold-standard indices of respiratory effort, such as WOB and PTP, over a relatively wide range of loading conditions. Of note, we found a higher correlation between ΔPes and PTP per breath *vs* that per minute, likely suggesting that the role of ventilatory frequency has to be considered. Moreover, ΔPes had a higher correlation with PTP than with WOB, possibly because it can be sensitive to the presence of isometric contractions.

Respiratory muscle ultrasound

Several recent studies demonstrated the utility of diaphragm ultrasonography to monitor respiratory workload.[10,11] Although the duration of the ultrasound examination was not formally measured in this investigation, in our clinical experience, a thorough (diaphragm and intercostal) respiratory muscle ultrasonographic assessment can generally be performed in less than 5 min. The inspiratory thickening fraction of the diaphragm (TFdi) has shown fair correlation to ΔPdi, PTPdi, and PTPes.[36–38] The noninvasive nature, low costs, steep learning curve, and straightforward calculations are its main advantages. However, TFdi is insensitive to duration and frequency of contractions, and does not account for recruitment of accessory muscles.[10] Moreover, those studies included highly selected patient groups, namely, patients undergoing noninvasive ventilation or postoperative patients. Notably, these are populations, in which diaphragm dysfunction is uncommon. On the other side, in critically ill patients with acute respiratory failure, a prevalence up to 60% has been reported.[39,40]

Several risk factors are known to be associated with the occurrence of diaphragm dysfunction in the ICU; some may be present before ICU admission, such as inadequate nutrition, sepsis, and the severity of the disease,[41] whereas others develop during the stay, likely as a consequence of treatment and supportive therapies, such as corticosteroids, neuromuscular blocking agents, or mechanical ventilation itself.[42] In our study, eight out of 21 patients (38.1%) showed signs of diaphragm dysfunction. No prior phrenic nerve dysfunctions were described in our case mix, so we assume that the dysfunction of the diaphragm has likely been acquired in the ICU. Although investigation of the causes leading to diaphragm dysfunction was not the primary aim of our study, we found that those patients had a higher duration of mechanical ventilation before enrolment in the study and a more severe disease, as described by a higher Simplified Acute Physiology Score, second version.

As expected, we found that TFdi increased with decreasing levels of support. However, at variance with previous reports,[36,38] TFdi correlated poorly with PTPes. The relationship of the two variables disclosed the presence of two groups of patients: one with a linear increase between TFdi and PTPes, and one, in which, despite the increase in the global inspiratory effort, diaphragm thickening did not increase. We reasoned that the presence of diaphragm dysfunction might affect the relationship between diaphragm thickening and inspiratory effort. Interestingly, when patients with diaphragm dysfunction were removed from the analysis, a much stronger relationship between TFdi and PTPes was found, suggesting that the presence of diaphragm dysfunction limits the use of TFdi as an index of patient effort.

Intercostal muscle ultrasound

Diaphragm dysfunction is associated with a compensatory increase in the activation of the (inspiratory) parasternal intercostal muscles,[43,44] and a greater recruitment of ribcage muscles was demonstrated in weaning failure as compared with weaning success patients.[30,45] We speculated that the assessment of extra-diaphragmatic respiratory muscle activity could help to identify conditions of increased inspiratory effort in the presence of diaphragm dysfunction.

We found a complex relationship between TFic and TFdi: a low TFdi could be associated with low or elevated levels of TFic. On the other hand, high levels of TFic were only present in the case of a low diaphragm thickening, suggesting that intercostal muscles may be recruited in case of an increased respiratory workload in the presence of diaphragm dysfunction. In other words, a low TFdi may reflect a low inspiratory effort, or an elevated effort with inspiratory work performed by accessory muscles, possibly because of the concomitant presence of diaphragm dysfunction. The assessment of TFic might help to distinguish these two situations. As a further analysis, we found that patients without diaphragm dysfunction had a higher diaphragm and a lower intercostal thickening than those with diaphragm dysfunction.

To the best of our knowledge, no prior studies investigated TFic in critically ill patients. Recent studies in healthy volunteers or COPD patients showed how the ultrasonographic assessment of parasternal intercostal muscle thickness is both reliable and reproducible,[19,46] and that these muscles thicken during inspiration.[47]

Our study has some limitations: first, we studied a relatively small population, which is, however, comparable with that of similar physiological studies.[35,36] Moreover, the patients were observed over a limited time frame: we are unaware if and how much the results would change over time and their clinical relevance. Patients with COPD were excluded, and the average PEEPi was relatively low, so the results cannot be directly extrapolated in case of severe flow limitation. The reliability of oesophageal pressure measurements was assessed with an occlusion test after placement of the catheter. Although the calibration procedure was not repeated after every reduction in pressure support, it is unlikely that the different conditions might have affected the Paw–Pes relationship, as both studies in healthy volunteers and in patients with respiratory failure demonstrated how neither changes in mean airway pressure nor in lung volumes affected this ratio.[12,48] Moreover, we measured flow with an in-line Fleisch pneumotachograph, which might have slightly increased resistance and dead space, and airway pressure was measured with a dedicated pressure transducer. However, as two possible mechanical ventilators could be used, we preferred to use the same data acquisition system rather than capturing the data directly from the two different ventilators.

Eventually, our study lacked a direct assessment of diaphragm weakness, and diaphragm dysfunction was defined as a negative Gilbert index. The gold-standard method for the quantification of diaphragm strength involves magnetic or electrical phrenic nerve stimulation; however, these techniques require specific apparatuses not always available. Moreover, several investigations defined diaphragm dysfunction similarly.[45,49,50]

In conclusion, the present study provides new physiological guidance for the bedside monitoring of inspiratory effort during PSV. We found that ΔPes and ΔPdi are adequate indicators of gold-standard indices of inspiratory effort. Moreover, diaphragm ultrasound is a reliable indicator of inspiratory effort, provided that no diaphragm dysfunction is present, whereas the presence of diaphragm dysfunction negatively affects the relationship between diaphragm thickening and inspiratory effort. The additional measurement of parasternal intercostal thickening may help to discriminate if a low diaphragm thickening depends on a low inspiratory effort or a high effort in the presence of diaphragm dysfunction.

Declaration of interest

The authors declare that they have no conflicts of interest.

Authors' contributions

Study design: MU
Literature search: PF, ACL, MG, AC, SC
Patient enrolment: PF, ACL, MG, AC, SC
Recording of clinical data: ACL, MG, AC, SC
Data analysis/interpretation: MU, PF
Writing of article: MU
DC had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. All authors read and approved the final version of the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.02.026.

References

1. Mehta AB, Syeda SN, Wiener RS, Walkey AJ. Epidemiological trends in invasive mechanical ventilation in the United States: a population-based study. *J Crit Care* 2015; **30**: 1217–21
2. Jabaley CS, Groff RF, Sharifpour M, Raikhelkar JK, Blum JM. Modes of mechanical ventilation vary between hospitals and intensive care units within a university healthcare system: a retrospective observational study. *BMC Res Notes* 2018; **11**: 425
3. Ouellette DR, Patel S, Girard TD, et al. Liberation from mechanical ventilation in critically ill adults: an official American College of Chest Physicians/American Thoracic Society clinical practice guideline: inspiratory pressure augmentation during spontaneous breathing trials, protocols minimizing sedation, and noninvasive ventilation immediately after extubation. *Chest* 2017; **151**: 166–80
4. Bellani G, Pesenti A. Assessing effort and work of breathing. *Curr Opin Crit Care* 2014; **20**: 352–8
5. Goligher EC, Ferguson ND, Brochard LJ. Clinical challenges in mechanical ventilation. *Lancet* 2016; **387**: 1856–66
6. Banner MJ, Kirby RR, Kirton OC, DeHaven CB, Blanch PB. Breathing frequency and pattern are poor predictors of work of breathing in patients receiving pressure support ventilation. *Chest* 1995; **108**: 1338–44
7. Hedenstierna G. Oesophageal pressure: benefit and limitations. *Minerva Anestesiol* 2012; **78**: 959–66
8. Mauri T, Yoshida T, Bellani G, et al. Oesophageal and transpulmonary pressure in the clinical setting: meaning, usefulness and perspectives. *Intensive Care Med* 2016; **42**: 1360–73
9. American Thoracic Society/European Respiratory Society. ATS/ERS statement on respiratory muscle testing. *Am J Respir Crit Care Med* 2002; **166**: 518–624
10. Umbrello M, Formenti P. Ultrasonographic assessment of diaphragm function in critically ill subjects. *Respir Care* 2016; **61**: 542–55
11. Zambon M, Greco M, Bocchino S, Cabrini L, Beccaria PF, Zangrillo A. Assessment of diaphragmatic dysfunction in the critically ill patient with ultrasound: a systematic review. *Intensive Care Med* 2017; **43**: 29–38
12. Chiumello D, Consonni D, Coppola S, Froio S, Crimella F, Colombo A. The occlusion tests and end-expiratory oesophageal pressure: measurements and comparison in controlled and assisted ventilation. *Ann Intensive Care* 2016; **6**: 13
13. Diehl JL, El Atrous S, Touchard D, Lemaire F, Brochard L. Changes in the work of breathing induced by tracheotomy in ventilator-dependent patients. *Am J Respir Crit Care Med* 1999; **159**: 383–8
14. Sassoon CS, Light RW, Lodia R, Sieck GC, Mahutte CK. Pressure-time product during continuous positive airway

pressure, pressure support ventilation, and T-piece during weaning from mechanical ventilation. *Am Rev Respir Dis* 1991; **143**: 469–75
15. Whitelaw WA, Derenne JP. Airway occlusion pressure. *J Appl Physiol* 1985; **74**: 1475–83. 1993
16. Foti G, Cereda M, Banfi G, Pelosi P, Fumagalli R, Pesenti A. End-inspiratory airway occlusion: a method to assess the pressure developed by inspiratory muscles in patients with acute lung injury undergoing pressure support. *Am J Respir Crit Care Med* 1997; **156**: 1210–6
17. Gilbert R, Auchincloss Jr JH, Peppi D. Relationship of rib cage and abdomen motion to diaphragm function during quiet breathing. *Chest* 1981; **80**: 607–12
18. Doorduin J, van Hees HW, van der Hoeven JG, Heunks LM. Monitoring of the respiratory muscles in the critically ill. *Am J Respir Crit Care Med* 2013; **187**: 20–7
19. Wallbridge P, Parry SM, Das S, et al. Parasternal intercostal muscle ultrasound in chronic obstructive pulmonary disease correlates with spirometric severity. *Sci Rep* 2018; **8**: 15274
20. Goligher EC, Fan E, Herridge MS, et al. Evolution of diaphragm thickness during mechanical ventilation. Impact of inspiratory effort. *Am J Respir Crit Care Med* 2015; **192**: 1080–8
21. Futier E, Constantin JM, Combaret L, et al. Pressure support ventilation attenuates ventilator-induced protein modifications in the diaphragm. *Crit Care* 2008; **12**: R116
22. Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med* 2017; **195**: 438–42
23. Mauri T, Cambiaghi B, Spinelli E, Langer T, Grasselli G. Spontaneous breathing: a double-edged sword to handle with care. *Ann Transl Med* 2017; **5**: 292
24. Colombo D, Cammarota G, Alemani M, et al. Efficacy of ventilator waveforms observation in detecting patient-ventilator asynchrony. *Crit Care Med* 2011; **39**: 2452–7
25. Laporta D, Grassino A. Assessment of transdiaphragmatic pressure in humans. *J Appl Physiol* 1985; **58**: 1469–76. 1985
26. Umbrello M, Chiumello D. Interpretation of the transpulmonary pressure in the critically ill patient. *Ann Transl Med* 2018; **6**: 383
27. Collett PW, Perry C, Engel LA. Pressure-time product, flow, and oxygen cost of resistive breathing in humans. *J Appl Physiol* 1985; **58**: 1263–72. 1985
28. de Vries H, Jonkman A, Shi ZH, Spoelstra-de Man A, Heunks L. Assessing breathing effort in mechanical ventilation: physiology and clinical implications. *Ann Transl Med* 2018; **6**: 387
29. Jubran A, Tobin MJ. Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. *Am J Respir Crit Care Med* 1997; **155**: 906–15
30. Parthasarathy S, Jubran A, Laghi F, Tobin MJ. Sternomastoid, rib cage, and expiratory muscle activity during weaning failure. *J Appl Physiol* 1985; **103**: 140–7. 2007
31. Beck J, Gottfried SB, Navalesi P, et al. Electrical activity of the diaphragm during pressure support ventilation in acute respiratory failure. *Am J Respir Crit Care Med* 2001; **164**: 419–24
32. Kallet RH, Hemphill 3rd JC, Dicker RA, et al. The spontaneous breathing pattern and work of breathing of patients with acute respiratory distress syndrome and acute lung injury. *Respir Care* 2007; **52**: 989–95
33. Brochard L, Pluskwa F, Lemaire F. Improved efficacy of spontaneous breathing with inspiratory pressure support. *Am Rev Respir Dis* 1987; **136**: 411–5
34. L'Her E, Deye N, Lellouche F, et al. Physiologic effects of noninvasive ventilation during acute lung injury. *Am J Respir Crit Care Med* 2005; **172**: 1112–8
35. Bellani G, Mauri T, Coppadoro A, et al. Estimation of patient's inspiratory effort from the electrical activity of the diaphragm. *Crit Care Med* 2013; **41**: 1483–91
36. Umbrello M, Formenti P, Longhi D, et al. Diaphragm ultrasound as indicator of respiratory effort in critically ill patients undergoing assisted mechanical ventilation: a pilot clinical study. *Crit Care* 2015; **19**: 161
37. Goligher EC, Laghi F, Detsky ME, et al. Measuring diaphragm thickness with ultrasound in mechanically ventilated patients: feasibility, reproducibility and validity. *Intensive Care Med* 2015; **41**: 642–9
38. Vivier E, Mekontso Dessap A, Dimassi S, et al. Diaphragm ultrasonography to estimate the work of breathing during non-invasive ventilation. *Intensive Care Med* 2012; **38**: 796–803
39. Dres M, Dube BP, Mayaux J, et al. Coexistence and impact of limb muscle and diaphragm weakness at time of liberation from mechanical ventilation in medical intensive care unit patients. *Am J Respir Crit Care Med* 2017; **195**: 57–66
40. Jung B, Moury PH, Mahul M, et al. Diaphragmatic dysfunction in patients with ICU-acquired weakness and its impact on extubation failure. *Intensive Care Med* 2016; **42**: 853–61
41. Demoule A, Jung B, Prodanovic H, et al. Diaphragm dysfunction on admission to the intensive care unit. Prevalence, risk factors, and prognostic impact—a prospective study. *Am J Respir Crit Care Med* 2013; **188**: 213–9
42. Dres M, Demoule A. Diaphragm dysfunction during weaning from mechanical ventilation: an underestimated phenomenon with clinical implications. *Crit Care* 2018; **22**: 73
43. De Troyer A, Kelly S. Chest wall mechanics in dogs with acute diaphragm paralysis. *J Appl Physiol Respir Environ Exerc Physiol* 1982; **53**: 373–9
44. Ward ME, Eidelman D, Stubbing DG, Bellemare F, Macklem PT. Respiratory sensation and pattern of respiratory muscle activation during diaphragm fatigue. *J Appl Physiol* 1985; **65**: 2181–9. 1988
45. Laghi F, Cattapan SE, Jubran A, et al. Is weaning failure caused by low-frequency fatigue of the diaphragm? *Am J Respir Crit Care Med* 2003; **167**: 120–7
46. Cala SJ, Kenyon CM, Lee A, Watkin K, Macklem PT, Rochester DF. Respiratory ultrasonography of human parasternal intercostal muscle in vivo. *Ultrasound Med Biol* 1998; **24**: 313–26
47. Yoshida R, Tomita K, Kawamura K, et al. Measurement of intercostal muscle thickness with ultrasound imaging during maximal breathing. *J Phys Ther Sci* 2019; **31**: 340–3

48. Baydur A, Cha EJ, Sassoon CS. Validation of oesophageal balloon technique at different lung volumes and postures. *J Appl Physiol* 1985; **62**: 315–21. 1987
49. Diehl JL, Lofaso F, Deleuze P, Similowski T, Lemaire F, Brochard L. Clinically relevant diaphragmatic dysfunction after cardiac operations. *J Thorac Cardiovasc Surg* 1994; **107**: 487–98
50. Lerolle N, Guerot E, Dimassi S, et al. Ultrasonographic diagnostic criterion for severe diaphragmatic dysfunction after cardiac surgery. *Chest* 2009; **135**: 401–7

Handling editor: Jonathan Hardman