RESPIRATORY MUSCLES

Can diaphragmatic contractility be assessed by airway twitch pressure in mechanically ventilated patients?

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Background: In critically ill patients inspiratory muscle function may be assessed by measurements of maximal inspiratory airway pressure and the response of twitch transdiaphragmatic pressure (Pdi tw) to bilateral phrenic nerve stimulation. The first is limited by its total dependence on patient cooperation. Although the second approach is independent of patient volition, it is impractical because it requires oesophageal and gastric balloons. Because airway pressure is easily and non-invasively recorded in patients with artificial airways, we hypothesised that twitch airway pressure (Paw tw) reliably predicts Pdi tw and twitch oesophageal pressure (Poes tw) in mechanically ventilated patients.
Methods: Thirteen mechanically ventilated patients recovering from an episode of acute respiratory failure received phrenic nerve stimulation at end exhalation. The rapid occlusion technique was used to record respiratory system mechanics.
Results: Stimulations were well tolerated. Mean (SE) Paw tw at end exhalation was –8.2 (1.2) cm H_2O and Poes tw and Pdi tw were –7.3 (1.1) and 10.4 (1.8) cm H_2O, respectively. Stimulations produced a good correlation between Paw tw and Pdi tw ($p<0.001$), although the limits of agreement were wide. The results were similar for Poes tw. No relationship was found between the Paw tw/Poes tw ratio and respiratory system compliance or airway resistance. Paw tw reproducibility was excellent (mean coefficient of variation 6%, range 3–9%).
Conclusions: Despite a good correlation between Paw tw and Poes tw, Paw tw did not reliably predict Poes tw or Pdi tw in mechanically ventilated patients. Nevertheless, the excellent reproducibility of Paw tw suggests that it may be a useful means of monitoring inspiratory muscle contractility in the routine care of mechanically ventilated patients.

I n critically ill patients the assessment of inspiratory muscle function is limited to measurement of maximal inspiratory airway pressure.[1] Maximal inspiratory pressure is a voluntary manoeuvre and is thus highly dependent on patient motivation and cooperation. Not surprisingly, maximal inspiratory pressure values are not helpful in clinical decision making such as predicting weaning outcome.[2] In contrast, twitch transdiaphragmatic pressure (Pdi tw) in response to bilateral stimulation of the phrenic nerves can measure diaphragmatic contractility independent of patient cooperation.[3–6] Recordings of Pdi tw, however, require the placement of oesophageal and gastric balloons which has impeded the clinical application of this approach.

In search of a non-invasive surrogate for Pdi tw, we[7 8] and other investigators[5 6 9] have assessed the ability of twitch airway pressure (Paw tw) to predict Pdi tw and twitch oesophageal pressure (Poes tw) in healthy subjects and in ambulatory patients with and without underlying lung disease. These investigations have shown that, while resting at functional residual capacity, glottic closure and probably upper airway collapse interfere with the accurate transmission of pressure changes from the thorax to the upper airway. In healthy subjects and in patients without chronic obstructive pulmonary disease, however, adequate transmission of changes in pressure from the thorax to the upper airway can be maintained by instructing subjects to perform gentle inspiratory[7] or expiratory[5] manoeuvres during the stimulation.

The glottis is bypassed by the artificial airway in intubated, mechanically ventilated patients. Whether the presence of an artificial airway could ensure the accurate transmission of the changes in intrathoracic pressure elicited by phrenic nerve stimulation to the upper airway remains unclear.[10] The current investigation was therefore devised to test the hypothesis that

Paw tw reliably predicts Pdi tw and Poes tw in critically ill, mechanically ventilated patients with an artificial airway.

To record accurate values of Pdi tw and Poes tw at a desired lung volume, it is necessary to monitor the extent of muscle recruitment elicited by the stimulation and the lung volume at which the stimulation is delivered.[1] These goals can be achieved by monitoring the amplitude of the compound motor action potential elicited by phrenic nerve stimulation—for example, surface electrodes—and by monitoring the value of oesophageal pressure just before stimulation.[1] For Paw tw to be an accurate and completely non-invasive tool for assessing respiratory muscle function, we therefore sought to devise a stimulation protocol and a set of Paw tw inclusion criteria that are independent of the oesophageal pressure signal. Finally, we also sought to determine the reproducibility and tolerability of Paw tw measurements.

METHODS

Thirteen clinically stable patients who required mechanical ventilation for at least 48 hours because of an episode of respiratory failure were studied (table 1). No patient with a cardiac pacemaker was enrolled, and no patient had received neuromuscular blocking agents in the 2 days before the study. Patients were ventilated in the assist control mode using a Puritan-Bennett 7200a ventilator through a cuffed endotracheal (n=9) or tracheostomy tube (n=4). The study was approved by the local ethics committee and informed consent was obtained from all patients or next of kin.
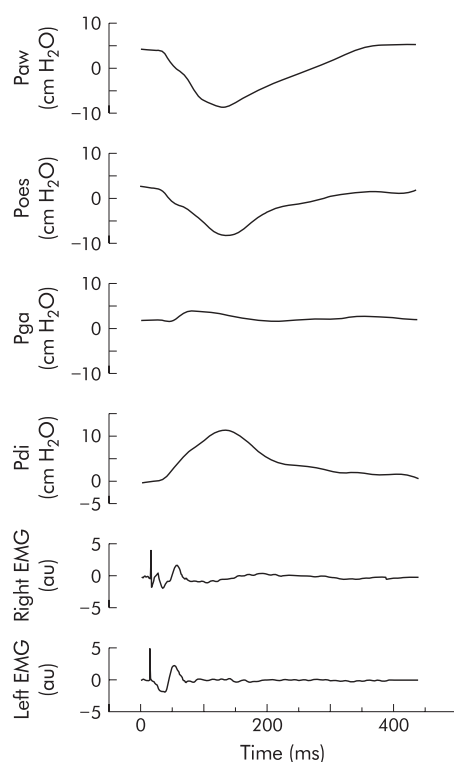
Oesophageal pressure (Poes) and gastric pressure (Pga) were separately measured with two thin walled, balloon tipped catheters coupled to pressure transducers. Proper positioning of the oesophageal balloon was ensured by the occlusion technique.[11] Transdiaphragmatic pressure was obtained

Table 1 Characteristics of study patients

Patient no	Age (years)	Diagnosis	ETT (ID mm)	Tracheostomy (ID mm)	Days on ventilator
1	28	C7 incomplete quadriplegia, idiopathic cardiomyopathy	7.0		6
2	54	Postoperative sepsis, COPD	8.0		11
3*	48	Postoperative sepsis, renal failure		8.0	30
4*	81	Subdural haematoma, COPD	7.5		5
5	84	Heart failure, pneumonia		6.0	22
6	65	Myocardial infarction, cardiogenic shock	8.0		17
7*	64	C5–C6 quadriplegia, pneumonia, alveolar haemorrhage, COPD		8.0	8
8*	70	Gastrointestinal bleed, pneumonia	8.0		13
9	61	Myocardial infarction, pneumonia, COPD		6.0	25
10	43	Cocaine induced bronchospasm	7.5		2
11	45	Demyelinating polyneuropathy	8.0		16
12*	75	Heart failure, cardiac arrest, COPD	7.5		5
13*	78	Pancreatitis, myocardial infarction	8.0		5

*Pulmonary function tests were available.
COPD=chronic obstructive pulmonary disease; ETT=endotracheal tube; ID=internal diameter.

Figure 1 Airway (Paw), oesophageal (Poes), gastric (Pga), and transdiaphragmatic (Pdi) pressures and electromyographic (EMG) signals of the right and left hemidiaphragm in a representative patient (patient #9). Following phrenic nerve stimulation, muscle depolarisation produces compound motor action potentials which are followed by a rise in transdiaphragmatic pressure and similar falls in airway and oesophageal pressure.

Box 1 Acceptance criteria of twitch responses for analysis

(1) Consistent end expiratory lung volume immediately before each stimulation as reflected by constancy of oesophageal pressure.
(2) Absence of oesophageal peristalsis at time of twitch stimulation.
(3) Absence of cardiac artifact on the oesophageal pressure tracing at the time of diaphragmatic contraction.
(4) Absence of airflow immediately before stimulation.
(5) Stable airway pressure before stimulation.
(6) Less than 20% variability in amplitude of compound diaphragmatic action potential (CDAP) of either hemidiaphragm.
(7) Absence of electrocardiographic artifact on CDAP.
(8) Relaxation of the diaphragm as signalled by silence on the diaphragmatic EMG.

ing the optimal locations of the electrodes on either side of the anterior axillary line. To optimise the skin to electrode conduction of the diaphragmatic EMG signal, the skin was carefully prepared with an abrasive paste, alcohol, and an antiperspirant solution. Single bilateral phrenic nerve stimulation was performed using two magnetic stimulators (Magstim 200; Jali Medical Inc, Newton, MA, USA) with two sets of double 40 mm coils (D40-1183.00) that generated a magnetic field of 3.2 Tesla at maximal output. The area of stimulation associated with the CDAP of greatest amplitude was located by moving the stimulating probe around the posterior border of the sternomastoid muscle at the level of the cricoid cartilage.[8] Thereafter, all stimulations were delivered with maximal output.

Protocol
Patients were studied with the head of the bed raised 30° from the horizontal position. Endotracheal suctioning was performed before the start of the study. Passive ventilation was effected by gradually increasing the back-up rate of the ventilator until the patient's inspiratory muscle activity was completely suppressed.[12] Tidal volume (638 (68) ml), inspiratory flow (61 (10) l/min), fractional concentration of inspired oxygen (0.40 in all instances), and the set level of positive end expiratory pressure (5 cm H_2O in all instances) were kept constant. The mechanics of the respiratory system were quantified using the constant flow, rapid occlusion technique.[13]

To prevent twitch potentiation[14] the patients were maintained on passive ventilation for 20 minutes; 8–10 bilateral phrenic nerve stimulations were then delivered with the magnetic stimulators at intervals of approximately 15 seconds.

by subtracting Poes from Pga. Airway pressure (Paw) was measured at the external end of the endotracheal or tracheostomy tube with a side port connected to a pressure transducer. Just distal to this side port, a pneumotachograph continuously measured flow. Between the pneumotachograph and the Y-piece of the ventilator, an in-line valve allowed for intermittent airway occlusion.

Compound diaphragmatic action potentials (CDAPs) were recorded bilaterally with two sets of surface electrodes at the level of the 7th and 8th intercostal space and the anterior axillary line. The noise to signal ratio was decreased by tying any excess in electromyography (EMG) cable in a coil and by test-

Table 2 Twitch pressures and respiratory system mechanics in 13 critically ill mechanically ventilated patients

Patient no	Paw tw (cm H_2O)	Poes tw (cm H_2O)	Pdi tw (cm H_2O)	Total PEEP (cm H_2O)	Resistance (cm H_2O/l/s)	Compliance (ml/cm H_2O)	Time constant (s)
1	−17.3	−15.9	28.2	7.3	16	64	1.00
2	−6.2	−5.7	7.4	4.7	16	68	1.07
3	−14.6	−12.2	16.5	5.2	10	62	0.59
4	−4.7	−4.4	10.4	6.1	21	72	1.55
5	−7.6	−7.3	11.6	6.3	22	40	0.86
6	−2.8	−3.6	4.3	6.1	15	65	0.98
7	−5.4	−2.9	4.4	6.1	15	64	0.98
8	−8.9	−5.3	7.0	8.0	10	55	0.57
9	−10.6	−11.3	12.8	7.9	16	65	1.04
10	−11.8	−10.7	12.1	6.4	15	58	0.87
11	−4.7	−5.0	6.8	5.4	11	48	0.53
12	−5.0	−4.6	4.6	7.2	16	62	0.97
13	−6.6	−6.0	9.3	6.9	12	57	0.70
Mean	−8.2	−7.3	10.4	6.4	15	60	0.90
SE	1.2	1.1	1.8	0.1	1	2	0.08

Paw tw=airway twitch pressure; Poes tw=oesophageal twitch pressure; Pdi tw=transdiaphragmatic twitch pressure; PEEP=positive end expiratory pressure.
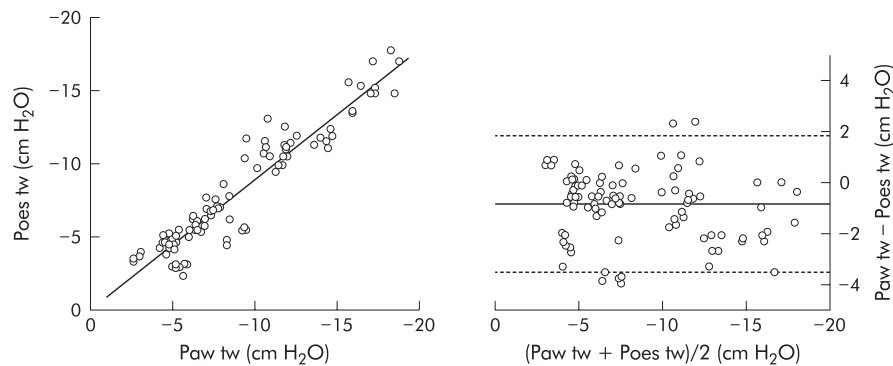
Figure 2 Left panel: Twitch airway pressure (Paw tw) versus twitch oesophageal pressure (Poes tw) in response to phrenic nerve stimulation. The correlation between Paw tw and Poes tw was 0.95 (p<0.0001). Right panel: Bland-Altman plot of the difference between Paw tw and Poes tw versus the mean of Paw tw and Poes tw. The bias (mean of the difference between Paw tw and Poes tw (solid line)) was −0.9 cm H_2O and the limits of agreement (bias ±2SD) ranged from −3.6 to 1.8 cm H_2O.

Rapid airway occlusion during phrenic nerve stimulation was effected by closing the in-line valve at end exhalation.

Data analysis

Data were recorded and digitised using a 12-bit analogue to digital converter connected to a computer. Twitch pressures were measured as the difference between the value of each pressure signal immediately after stimulus delivery and the maximal pressure displacement. Individual twitch responses were rejected from analysis according to the criteria shown in box 1.

All data are reported as mean (SE) values. Linear regression analysis and Bland-Altman plots[15] were performed when appropriate. Variability of twitch pressure measurements over time was determined by calculating the coefficient of variation.

RESULTS

In all patients magnetic stimulation elicited airway, oesophageal, and transdiaphragmatic twitch pressures (fig 1, table 2). All patients tolerated the stimulations well and none asked to be withdrawn from the protocol. Of the 133 twitches recorded in our patients, 37 were discarded for the following reasons: decreased CDAP amplitude (n=13); persistent airflow at time of twitch (n=10); oesophageal peristalsis (n=6); cardiogenic changes in oesophageal pressure (n=4); ECG tracing superimposed on CDAP (n=3); active exhalation during stimulation (n=1). No twitch was discarded because the diaphragm was

not relaxed. End expiratory lung volume, as determined by the end exhalation Poes value, was stable during all remaining stimulations except for one stimulation in patient #8.

In absolute terms (ignoring the minus sign), the mean Paw tw (−8.2 (1.2) cm H_2O) was greater than the mean Poes tw (−7.3 (1.1) cm H_2O, p<0.03) and smaller than the mean Pdi tw (10.4 (1.8) cm H_2O, p<0.03). The relationship between Paw tw and Poes tw is shown in fig 2 (left panel). The correlation coefficient for the relationship between Paw tw and Poes tw was 0.95 (p<0.0001). The bias (mean of the difference between Paw tw and Poes tw) was −0.9 cm H_2O, and the limits of agreement (bias ±2SD) ranged from −3.6 to 1.8 cm H_2O (fig 2, right panel).

The relationship between Paw tw and Pdi tw is shown in fig 3. The correlation coefficient is −0.89 (p<0.001), the bias was 2.5 cm H_2O, and the limits of agreement were −4.4 to 9.4 cm H_2O.

The total level of positive end expiratory pressure ranged from 5.2 to 8.0 cm H_2O (table 2). The resistance and compliance of the patients' respiratory systems ranged from 10 to 22 cm H_2O/l/s and from 40 to 72 ml/cm H_2O, respectively (table 2). The relationships between the ratio of Paw tw to Poes tw and the resistance, compliance, and time constant of the respiratory system were weak (correlation coefficients of −0.25, 0.02, and −0.19, respectively).

Among five patients with a clinical history of obstructive lung disease (three of whom had pulmonary function tests), the correlation coefficient of Paw tw to Poes tw was 0.94 (p<0.001) with a bias of −0.5 cm H_2O and limits of agreement
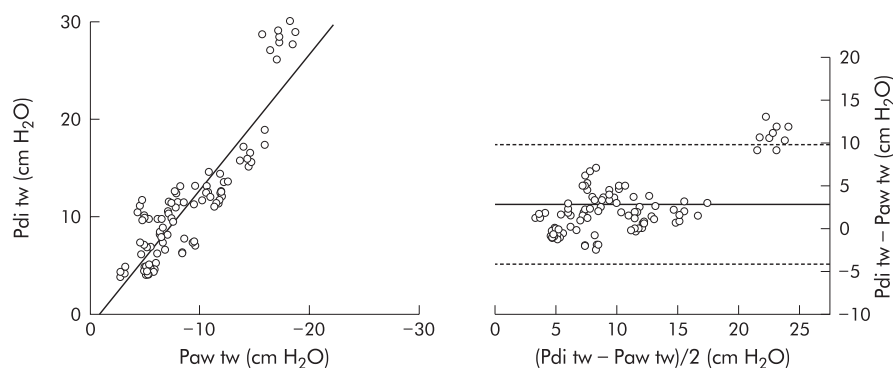
Figure 3 Left panel: Twitch airway pressure (Paw tw) versus twitch diaphragmatic pressure (Pdi tw) in response to phrenic nerve stimulation. The correlation between Paw tw and Pdi tw was −0.89 (p<0.001). Right panel: Bland-Altman plot of the difference between Paw tw and Pdi tw versus the mean of Paw tw and Pdi tw. The bias (mean of the difference between Paw tw and Pdi tw (solid line)) was 2.5 cm H_2O and the limits of agreement (bias ±2SD) ranged from −4.4 to 9.4 cm H_2O.

of −2.0 to 3.0 cm H_2O. Among eight patients without a clinical history of obstructive lung disease (three of whom had pulmonary function tests), the correlation coefficient of Paw tw to Poes tw was 0.96 (p<0.0001) with a bias of −1.2 cm H_2O and limits of agreement of −1.5 to 3.8 cm H_2O.

The mean coefficients of variation for Paw tw, Poes tw, and Pdi tw for each patient were 6 (1)% (range 3–9), 8 (1)% (range 5–12), and 8 (1)% (range 4–11), respectively.

DISCUSSION
We have shown in critically ill mechanically ventilated patients that (1) Paw tw is closely related to Poes tw and Pdi tw, (2) the limits of agreement are too wide for Paw tw to reliably predict either Poes tw or Pdi tw in all patients, (3) the reproducibility of Paw tw is excellent, and (4) criteria can be developed to identify reliable Paw tw recordings independent of the availability of an oesophageal pressure signal.

Changes in pressure at the pleural surface, such as those effected by respiratory muscle contraction, will generate swings in Poes and Paw. Following cervical magnetic twitch stimulation the amplitudes of Poes tw and Paw tw are therefore a function of how well the change in pleural pressure is transmitted to the oesophageal and airway pressure transducers, respectively. If the changes in pleural pressure are not efficiently transmitted to the external end of the endotracheal tube, then Paw tw might be less negative than Poes tw. Inefficient transmission becomes likely when the time constant of the patient's respiratory system is prolonged. In our patients the time constant of the airway and tracheal tube (0.90 (0.08) s) was much longer than the time constant of the respiratory system reported in healthy subjects (~0.2 s).[16] Surprisingly, however, Paw tw was more negative than Poes tw in 10 of 13 patients (table 2). Moreover, the ratio of Paw tw to Poes tw was not affected by the patients' respiratory mechanics. At least two non-mutually exclusive mechanisms could explain why Paw tw was more negative than Poes tw.

Firstly, our patients were studied in the supine position. When supine, a variable portion of the oesophageal balloon rests beneath the heart. The compression of the oesophagus and balloon by the heart could, from a functional stand point, increase the elastance of the anatomical structures surrounding the balloon. The increased elastance of these structures would dampen the transmission of intrathoracic pressure to the lumen of the oesophagus. Indeed, in studies by Baydur et al[11] structures surrounding the oesophagus appeared to change their elastance on moving from the upright to the supine position. These investigators measured the tidal changes in Poes and Paw during gentle inspiratory efforts against an occluded airway in different body positions. The mean ratio of tidal swing in Paw to tidal swing in Poes was

close to unity (1.04, range 0.99–1.10) when the subjects were sitting, but the ratio decreased to 0.90 (range 0.61–1.10) when the subjects became supine. If the elastance of structures surrounding the oesophageal balloon was independent of posture, the Paw to Poes ratio should have remained constant when posture changed.

Secondly, respiratory muscle contractions do not necessarily produce uniform swings in Poes throughout the length of the oesophagus. Isolated contraction of the diaphragm, such as elicited by electrical stimulation of the phrenic nerves,[9][14] produces an outward motion of the lower rib cage and an inward motion of the upper rib cage. The deformation of the upper rib cage dissipates the pressure swing and, thus, swings in Poes are greater in the region of the diaphragm than in the upper thorax.[9] In contrast, cervical magnetic stimulation causes contraction of both the diaphragm and upper rib cage muscles.[14][18] Contraction of the latter contributes to the generation of intrathoracic pressure[17] and to outward motion of the upper rib cage.[14][17] These effects might create a cephalo-caudal gradient in pleural pressure whereby the swing in Poes would be greatest in the cephalad portion of the intrathoracic oesophagus. If contraction of the upper rib cage muscles produces a more pronounced cephalo-caudal pressure gradient than the caudal-cephalad pressure gradient achieved by contraction of the diaphragm, then a balloon located in the lower third of the oesophagus would underestimate the global intrathoracic pressure changes. While this potential mechanism remains untested, it could partly explain why Paw tw is greater than Poes tw in some patients, even when they are sitting with the back supported at a 90° angle.[8]

Despite the differences between Paw tw and Poes tw and between Paw tw and Pdi tw, a good correlation was noted between Paw tw and the other two variables (figs 2 and 3). Nonetheless, careful examination of the plots of Paw tw versus Poes tw (fig 2) and of Paw tw versus Pdi tw (fig 3) reveals some scatter of data points above and below the correlation line. The extent of this scatter around the correlation line is quantified by the limits of agreement in the Bland-Altman plots in figs 2 and 3 (right panels). For example, with a bias of −0.9 cm H_2O and limits of agreement of ±2.7 cm H_2O, a Poes tw value of −7 cm H_2O could be associated with values of Paw tw ranging from −5.2 to −10.6 cm H_2O. This range of possible Paw tw values constitutes 77% of the recorded Poes tw value. Thus, despite the good correlation between Paw tw and Poes tw, Paw tw is a poor predictor of Poes tw. The limits of agreement between Paw tw and Pdi tw are even greater, so Paw tw is also a poor predictor of Pdi tw. Watson et al[10] assessed the applicability of Pdi tw recordings in critically ill patients. Similar to our findings, they suggested that Paw tw did not reliably predict Pdi tw and Poes tw. Given the variety of causes of respiratory failure in our patients and

in those of Watson *et al*,[10] it is unlikely that studying additional patients would change these results.

Although Paw tw was a poor predictor of Poes tw and Pdi tw, its reproducibility was excellent. Indeed, the 6% reproducibility of Paw tw is similar to the 5% reproducibility requirement for an acceptable recording of forced expiratory volume in one second and forced vital capacity.[19] Given the excellent reproducibility of Paw tw, we propose that Paw tw values may be used to accurately follow contractility of the diaphragm[14] and, possibly, of the rib cage muscles[14 18] in mechanically ventilated patients (see section on practical implications).

Technical considerations

Lung volume is a critical determinant of the amplitude in twitch pressure elicited by stimulation of the phrenic nerves.[9 14] Monitoring the end expiratory value of Poes is conventionally used to ensure a consistent lung volume before each phrenic nerve stimulation.[3–7 10 14 18] One potential criticism of using Paw tw as a surrogate for Poes tw and Pdi tw is therefore the inability to monitor end expiratory lung volume.[10] Nevertheless, only one of 133 twitches in our investigation was discarded because the Poes tracing revealed poor control of end expiratory lung volume. The remarkable consistency of end expiratory lung volumes for each of our patients is probably explained by their lack of respiratory efforts. Both the configuration of Paw tracings and silence on the diaphragmatic EMG indicate that our patients were passively ventilated at the time of the stimulations. Of note, dynamic hyperinflation was not a confounding factor in Paw tw measurements in our patients because the airway was occluded at end exhalation for 2–3 seconds before delivering each stimulation.

The above observations underscore the fact that it is possible to devise a protocol and a set of inclusion criteria (see inclusion criteria 4–8 in box 1) that do not require the availability of an oesophageal pressure tracing to exclude technically flawed stimulations. This is a key distinction between our study and that of Watson *et al*[10] who used oesophageal pressure tracings to discriminate between acceptable and unacceptable Paw tw values.

Practical implications

Our findings have important implications for the assessment of respiratory muscle contractility in the critically ill patient. Firstly, Paw tw is independent of patient cooperation. Secondly, it is non-invasive, relatively easy to employ, and well tolerated by patients. Finally, and most importantly, the excellent reproducibility of Paw tw makes it a robust physiological measure.

These three characteristics make Paw tw a potentially powerful tool in the evaluation of respiratory muscle contractility in critically ill patients. In particular, repeated Paw tw measurements should make it possible to track changing inspiratory muscle function over days or weeks, such as in patients with Guillain-Barré syndrome, and better guide management of patients who repeatedly fail trials of weaning from mechanical ventilation.

Another feature of Paw tw that is attractive for monitoring respiratory muscle function over time is its dependence on lung volume.[7 9] Lung volume is an important determinant of respiratory muscle pressure output.[9 14] If the end expiratory lung volume were to increase over time, the amplitude of Paw tw would decrease independently of changes in the intrinsic contractile properties of the respiratory muscles such as recovery from respiratory muscle fatigue.[9] In other words, changes in operational lung volume over time do not necessarily mean that Paw tw will not give meaningful information on changes in respiratory muscle contractility. Indeed, it is the Paw tw value at a given operational lung volume that parallels the contractility of the respiratory muscles at a given moment.

Finally, another role of Paw tw in the intensive care unit may also be the possible identification of the minimum value of Paw tw necessary for sustaining spontaneous breathing and incorporation of this value into algorithms used in clinical decision making regarding the discontinuation of mechanical ventilation

In conclusion, despite a good correlation between Paw tw and Poes tw, Paw tw did not reliably predict Poes tw or Pdi tw in mechanically ventilated patients. Nevertheless, the excellent reproducibility of Paw tw suggests that it may be used to monitor inspiratory muscle contractility in mechanically ventilated patients.

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