Weaning from mechanical ventilation (MV) is a key process in the recovery from critical illness. It is rapidly achieved in most patients when the original cause of respiratory failure has resolved, but more than 20% of patients require a more gradual method of withdrawing ventilation support. A combination of abnormalities affecting the thoracic (lung parenchyma and pleural space), cardiovascular, abdominal and neuromuscular systems may lead to delays in the process of weaning from MV. Despite varying improvement in lung volumes or lung mechanics, most human studies that have investigated the role of pleural effusion drainage on respiratory function reported significant relief of dyspnoea, a symptomatic improvement that has generally been attributed to enhanced diaphragmatic function. However, the impact of effusion drainage on diaphragmatic function has never formally been investigated in critically ill patients.

Pleural effusion is commonly associated with a restrictive syndrome that modifies chest wall and lung volumes in direct proportion to the effusion volume and the relative compliance of each compartment. Thus, it adversely affects the pressure-generating capacity of the diaphragm, through mechanical uncoupling of the lung and chest wall and caudal displacement of the diaphragm. The geometrically flattened diaphragm has a reduced functional capacity to develop tension, potentially leading to diaphragmatic dysfunction. Such dysfunction can lead to dyspnoea, sleep-disordered breathing, constitutional symptoms, atelectasis and respiratory failure, eventually prolonging the duration of MV. Given the importance of diaphragmatic function in weaning from MV, patients whose diaphragmatic function is impaired by pleural effusion may be a specific population for whom pleural drainage is associated with clinically significant benefits.

Several methods have been used in the clinical setting to assess diaphragmatic function. Among these, bedside ultrasonography has recently been proposed as a simple, non-invasive tool for quantifying diaphragm contractile activity. Ultrasound can be used to determine diaphragm displacement and thickening, measures which correlate well with traditional parameters of respiratory effort and work of breathing.

Our primary aim in this proof-of-concept study was to evaluate the impact of unilateral pleural effusion drainage on diaphragmatic function during the weaning period in mechanically ventilated patients in the intensive care unit.

Drainage of pleural effusion improves diaphragmatic function in mechanically ventilated patients

Michele Umbrello, Giovanni Mistrailletti, Andrea Galimberti, Ilaria R Piva, Ottavia Cozzi and Paolo Formenti

ABSTRACT

Background: Pleural effusion adversely affects the pressure-generating capacity of the diaphragm. It uncouples the lung and chest wall, which may result in diaphragmatic dysfunction. Information on the effects of effusion drainage on diaphragmatic function is limited, but several studies report relief of dyspnoea after drainage, which was attributed to improved diaphragmatic mechanics, even if this issue was never formally addressed.

Objective: To investigate the effect of drainage of unilateral pleural effusion on diaphragmatic function.

Design, setting and patients: In a prospective two-step protocol (at baseline and after drainage of effusion), we conducted a spontaneous breathing trial in fourteen critically ill, mechanically ventilated patients undergoing pressure support ventilation.

Main outcome measures: We used ultrasonography of the ipsilateral hemidiaphragm to evaluate and record respiratory displacement and thickening during tidal and maximal breathing efforts. We recorded and analysed airway pressures, respiratory system compliance, vital capacity, indices of respiratory effort and arterial blood gases.

Results: After drainage of the effusion, the respiratory rate decreased and tidal volume increased, but haemodynamic parameters were unaffected and oxygenation levels showed a non-significant increase. Drainage was associated with significant decreases in indices of respiratory drive and the maximal pressure generated by the respiratory muscles, as well as an increased compliance of the respiratory system. Diaphragmatic displacement and thickening significantly increased after drainage. We found there was a significant correlation between the volume of the effusion drained and the increase in tidal diaphragmatic thickening.

Conclusions: Drainage of a unilateral pleural effusion during weaning from mechanical ventilation improves diaphragmatic contractile activity and respiratory system performance.

Methods

We followed patients admitted consecutively to the ICU of a university hospital requiring invasive ventilation, observing them for the development of pleural effusion. We enrolled patients in our study when an ultrasonographic diagnosis...
of unilateral pleural effusion with an estimated volume > 400 mL was detected during the weaning phase from MV.\textsuperscript{21} We estimated the pleural effusion volume using the method proposed by Balik and colleagues,\textsuperscript{22} in which the maximal distance between the parietal and visceral pleura at end-expiration is recorded. This value (in millimetres) was multiplied by 20 to obtain the estimated effusion volume.

We conducted our study in accordance with the amended Declaration of Helsinki. The institutional review board (San Paolo Hospital Ethics Committee) approved our protocol, and we obtained written informed consent from each patient or their surrogate. Each endotracheally intubated patient was mechanically ventilated, according to clinical needs, using an Evita XL ventilator (Dräger).

Inclusion criteria were:

- evidence of reversal of the underlying cause of respiratory failure
- adequate oxygenation on low positive end-expiratory pressure (PEEP)
- stable cardiovascular condition
- afebrile status
- ability to initiate an inspiratory effort
- no significant respiratory acidosis
- adequate haemoglobin level
- alert mental status
- stable metabolic condition.\textsuperscript{23}

Exclusion criteria were:

- haemodynamic instability requiring vasopressors
- gas exchange impairment requiring PEEP > 10 cmH\textsubscript{2}O and/or Fi\textsubscript{O\textsubscript{2}} > 60%, to obtain Pa\textsubscript{O\textsubscript{2}} ≥ 10.6 kPa
- pressure support (PS) level ≥ 20 cmH\textsubscript{2}O
- core body temperature > 38°C or < 35°C
- impaired consciousness (as defined by a Richmond Agitation–Sedation score < -1)
- clinical suspicion or evidence of chronic obstructive pulmonary disease.

We performed MV weaning as a spontaneous breathing trial with pressure-support ventilation (PSV).

As a non-invasive index of respiratory drive, we measured P0.1\textsuperscript{24} (the airway pressure drop in the first 100 ms after an end-expiratory occlusion manoeuvre). We calculated the Pmusc index (PMI), an estimate of pressure developed by the inspiratory muscles at the end of an inspiratory effort,\textsuperscript{25} as follows:

\[ \text{PMI} = \text{Pplat} - (\text{PEEP} + \text{PS}) \]

in which Pplat is plateau pressure (airway pressure plateau reached after an inspiratory occlusion). This equation indicates the difference between the elastic recoil pressure of the respiratory system and the total pressure applied to the airways by the ventilator (PEEP + PS).

We recorded the maximal inspiratory pressure (MIP), the maximum pressure that can be generated against an occluded airway beginning at end-expiratory lung volume.\textsuperscript{26} We computed the total respiratory system compliance using the ratio of tidal volume to the difference between Pplat and total PEEP (pressure obtained after end-expiratory occlusion).

When the inspiratory occlusion manoeuvre is performed in spontaneously breathing patients who are undergoing PSV, the airway pressure tracing initially drops to a value which reflects the alveolar pressure at the time of occlusion. After a variable duration (usually < 0.5 s), the patient ceases their inspiratory effort and relaxes their inspiratory muscles. Before the next inspiratory effort, the airway pressure then reaches a new value, corresponding to Pplat, which was shown to adequately approximate the relaxed elastic recoil pressure of the respiratory system.\textsuperscript{25,27}

We assessed the vital capacity during an inspiratory manoeuvre, starting from end-tidal volume, with patients first expiring maximally and subsequently making a full inspiration.

**Ultrasonographic measurements**

The same trained operator (I P) performed the ultrasonography using a Logiq 7 ultrasound machine (GE Healthcare) equipped with a high-resolution 10 MHz linear phased-array probe and a 3.5 MHz convex phased-array probe. We marked the probe placement site because this has been shown to improve measurement reproducibility.\textsuperscript{28} We recorded the probe placement site. They were coded in such a way that the analyst had no knowledge of the patient or of the extent of the pleural effusion drained.

To evaluate diaphragm excursion, we performed ultrasonography as previously described.\textsuperscript{20} We scanned patients along the long axis of their intercostal spaces, with the liver serving as an acoustic window if the effusion was located on the right side, and the splenic window used for left-sided effusions. In the M mode, the diaphragm excursion was recorded as the mean of three sequential measurements.

We also used ultrasound to evaluate diaphragm thickness in the zone of apposition of the diaphragm to the rib cage, as previously described.\textsuperscript{20} To obtain adequate images of diaphragm thickness in 2D mode, we used the linear high-frequency probe (10 MHz). We measured the diaphragmatic thickness at end-inspiration (thickness EI) and at end-expiration (thickness EE) and used mean values of three measurements in analysis.

We calculated the thickening fraction (TF) (an index of diaphragmatic thickening) as follows:

\[ \text{TF} = \left( \frac{\text{thickness EI} - \text{thickness EE}}{\text{thickness EE}} \right) \times 100 \]
We considered TF during tidal breathing to reflect inspiratory effort, and used the TF during maximal breathing to assess maximal diaphragmatic function, as suggested by Goligher and colleagues.29

We assessed the intrarater and interrater reliability of our technique by randomly selecting 10 recordings (from 10 patients) and assessing the reproducibility of the analysis. One ultrasonographer (I P) analysed the same sets of recordings twice, and a different ultrasonographer (O C) also analysed the same sets of recordings twice. The repeat measurements obtained from each patient by the same ultrasonographer were used to assess the intrarater reproducibility, and for the interrater reproducibility, the measurements obtained by the two ultrasonographers from the same patient were used. The reproducibility is expressed as the intraclass correlation coefficient30 and the coefficient of repeatability.31 We calculated the coefficient of repeatability as twice the standard deviation of the differences in repeated measurements. For every measurement, the intraclass correlation coefficient was > 0.85, and the coefficient of repeatability was < 10%.

Study protocol

After enrolment of a patient, we determined the values of their respiratory mechanics (PEEP, mean airway pressure, compliance, P0.1, PMI, MIP, tidal volume, respiratory rate and vital capacity), arterial blood pressure, heart rate and arterial blood gas levels. We recorded an ultrasound scan of the diaphragm during quiet tidal breathing and after a maximal breathing effort reaching vital capacity.

We then drained the patient’s pleural effusion by inserting a small chest drainage catheter (Pleuracan, B Braun) under ultrasound guidance into the posterior or lateral portion of the 4th or 5th intercostal space. Drainage was performed under local anaesthesia, and no sedation was provided during the procedure. All baseline measurements were repeated after 2 hours with the patient in the same semi-recumbent position and the ventilator set as it was during the initial measurements. The PEEP, pressure support level and FiO2 were set before beginning the study and were not modified throughout the study period.

Statistical analysis

We analysed the data using Stata, version 11 (StataCorp), and assessed normality with the Shapiro–Francia test. We report results as means with SDs if they were normally distributed, or as medians with interquartile ranges (IQRs) otherwise. We performed a comparison between related variables with the paired Student t test or Wilcoxon signed-rank test, as needed. We assessed correlation using the Pearson or Spearman method, according to the distribution of the variable, and considered a two-tailed P < 0.05 as significant.

Results

Patient characteristics

Fourteen patients were enrolled consecutively in our study after we checked that they met the inclusion criteria and did not meet any exclusion criteria. We found an adequate ultrasonographic window for every patient, so all 14 were enrolled in the study. The demographic and clinical data of the patients at enrolment are shown in Table 1. All patients tolerated the study protocol well, and none developed signs of respiratory distress. Ten patients were successfully weaned from MV and discharged alive from the ICU, but four patients subsequently developed complications (unrelated to our weaning trial) that led to their deaths.

At the time of enrolment, the patients were ventilated with PEEP at a mean pressure of 8 cmH2O (SD, 2 cmH2O), a mean PS of 6 cmH2O (SD, 3 cmH2O) and a mean FiO2 of 54% (SD, 7%). We did not modify these settings during the protocol. The mean volume of effusion drained was 780 mL (SD, 240 mL).

Effect of drainage on ventilation and haemodynamics

Table 2 shows respiratory, haemodynamic and blood gas parameters during both steps of our study. Tidal volume increased after drainage, but minute ventilation was unchanged. The overall haemodynamic state remained

<table>
<thead>
<tr>
<th>Table 1. Patient clinical characteristics at enrolment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical characteristic</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
</tr>
<tr>
<td>Men, n (%)</td>
</tr>
<tr>
<td>Mean body weight, kg (SD)</td>
</tr>
<tr>
<td>Mean height, cm (SD)</td>
</tr>
<tr>
<td>Mean body mass index, kg/m² (SD)</td>
</tr>
<tr>
<td>Mean duration of ICU stay, days (SD)</td>
</tr>
<tr>
<td>Mean duration of mechanical ventilation, days (SD)</td>
</tr>
<tr>
<td>ICU mortality, n (%)</td>
</tr>
<tr>
<td>Admission type, n (%)</td>
</tr>
<tr>
<td>Medical</td>
</tr>
<tr>
<td>Surgical unscheduled</td>
</tr>
<tr>
<td>Right-sided pleural effusion, n (%)</td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Acute liver failure</td>
</tr>
<tr>
<td>Bowel perforation</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
</tr>
<tr>
<td>Bowel ischaemia</td>
</tr>
<tr>
<td>Urosepsis</td>
</tr>
<tr>
<td>Chest trauma</td>
</tr>
</tbody>
</table>

ICU = intensive care unit.
stable after drainage and oxygenation efficiency showed a non-significant improvement.

Ultrasonographic indices of diaphragmatic efficiency and measures of inspiratory effort

Measurements of inspiratory effort and ultrasound parameters are shown in Table 3. Effusion drainage was associated with significant decreases in P0.1 and PMI, as well as an increased respiratory system compliance. MIP also improved after evacuation of the effusion, and vital capacity showed a non-significant increase. Diaphragmatic displacement significantly increased after drainage.

Table 2. Respiratory and haemodynamic data before and after drainage of pleural effusion

<table>
<thead>
<tr>
<th>Variable (mean [SD])</th>
<th>Before drainage</th>
<th>After drainage</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal volume (mL)</td>
<td>350 (88)</td>
<td>420 (87)</td>
<td>0.045</td>
</tr>
<tr>
<td>Respiratory rate (L/min)</td>
<td>20 (5)</td>
<td>17 (4)</td>
<td>0.062</td>
</tr>
<tr>
<td>Minute ventilation (L/min)</td>
<td>7.0 (1.6)</td>
<td>7.2 (2.0)</td>
<td>0.760</td>
</tr>
<tr>
<td>Heart rate (L/min)</td>
<td>88 (17)</td>
<td>81 (10)</td>
<td>0.184</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>75 (10)</td>
<td>73 (10)</td>
<td>0.469</td>
</tr>
<tr>
<td>pH</td>
<td>7.39 (0.06)</td>
<td>7.41 (0.04)</td>
<td>0.340</td>
</tr>
<tr>
<td>PaCO2 (kPa)</td>
<td>6.7 (1.5)</td>
<td>7.1 (2.9)</td>
<td>0.706</td>
</tr>
<tr>
<td>PaO2 (kPa)</td>
<td>12.4 (5.5)</td>
<td>17.5 (11.2)</td>
<td>0.142</td>
</tr>
<tr>
<td>Base excess (mmol/L)</td>
<td>5.6 (4.5)</td>
<td>6.5 (3.7)</td>
<td>0.552</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>1.3 (1.6)</td>
<td>1.2 (1.3)</td>
<td>0.836</td>
</tr>
</tbody>
</table>

Table 3. Ultrasonographic and pressure measurements before and after drainage of pleural effusion

<table>
<thead>
<tr>
<th>Variable (mean [SD])</th>
<th>Before drainage</th>
<th>After drainage</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>P0.1* (cmH2O)</td>
<td>2.5 (0.9)</td>
<td>1.0 (0.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pmusc index† (cmH2O)</td>
<td>3.9 (0.7)</td>
<td>1.0 (0.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Maximal inspiratory pressure (cmH2O)</td>
<td>14 (4)</td>
<td>26 (7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Vital capacity (mL)</td>
<td>1085 (162)</td>
<td>1210 (202)</td>
<td>0.085</td>
</tr>
<tr>
<td>Respiratory system compliance (mL/cmH2O)</td>
<td>52 (12)</td>
<td>64 (16)</td>
<td>0.032</td>
</tr>
<tr>
<td>End-expiratory diaphragm thickness (cm)</td>
<td>0.22 (0.10)</td>
<td>0.23 (0.09)</td>
<td>0.819</td>
</tr>
<tr>
<td>End-inspiratory diaphragm thickness (cm)</td>
<td>0.26 (0.12)</td>
<td>0.35 (0.13)</td>
<td>0.103</td>
</tr>
<tr>
<td>Diaphragm displacement (cm)</td>
<td>0.71 (0.27)</td>
<td>1.12 (0.26)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Maximal end-inspiratory diaphragm thickness‡ (cm)</td>
<td>0.29 (0.12)</td>
<td>0.42 (0.17)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

* Non-invasive index of respiratory drive; denotes airway pressure drop in the first 100 ms after an end-expiratory occlusion manoeuvre.
† Estimate of pressure developed by inspiratory muscles at end of an inspiratory effort.
‡ Inspiratory value of diaphragm thickness while breathing at vital capacity.

Inspiratory thickness increased non-significantly during tidal breathing and significantly increased when measured at the end of a maximal inspiration during a vital capacity manoeuvre. The ultrasonographic TF of the diaphragm significantly increased after drainage, during tidal breathing and after a maximal vital capacity manoeuvre (Figure 1).

We found a significant correlation between the volume of the effusion drained and the improvement in diaphragm TF (Figure 2), but only a weak association (not reaching statistical significance) between the volume of the effusion and the improvement in vital capacity.

Discussion

Drainage of a unilateral pleural effusion during spontaneous assisted breathing, with low levels of PEEP and PS during the period of weaning from MV, was associated with:

- reduced inspiratory effort during tidal breathing and increased maximal force developed by the respiratory muscles
- ameliorated diaphragmatic function as detected by diaphragmatic ultrasound evaluation of TF and displacement
- improved compliance and tidal volume
- no significant changes in gas exchange.
Consequences of pleural effusion on respiratory mechanics

Despite a considerable volume of literature on the physiological effects of pleural drainage, evidence relating to its impact on clinical outcomes is limited. In bench-to-bedside studies, our group and other researchers have shown that increases in mean airway pressure usually overcome the negative effects from the effusion on the mechanical properties of the respiratory system only when the chest wall exhibits normal elastic behaviour. Such data suggest that the effusion should be evacuated only for patients with altered chest wall properties or those who do not tolerate raised airway pressure. However, those studies focused on lung behaviour and were all performed in deeply sedated, paralysed and mechanically ventilated patients. No studies have focused directly on the implications of evacuation of pleural effusion on diaphragmatic function during the weaning phase from MV. Consequently, clear guidance on the wisdom of evacuating the effusion in such circumstances remains unavailable.

Consequences of pleural effusion on the diaphragm

Mechanical abnormalities of the diaphragm, including diaphragm inversion and paradoxical motion, have been reported to develop as a consequence of pleural effusion. In some cases, significant reduction of dyspnoea associated with drainage has logically been attributed to improved diaphragmatic mechanics. Our results show how drainage of pleural effusion enhances diaphragmatic function as indicated by increasing TF, with a consequent reduction of inspiratory effort during tidal breathing. The potential mechanism by which drainage might improve respiratory function could be the relief of mechanical compromise of the diaphragm, as hypothesised 30 years ago.

When fluid accumulates in the pleural compartment, the thoracic or abdominal contents change configuration. For patients in whom this occurs, displacement or reversible deformation of normally juxtaposed structures routinely occurs. As a consequence, the diaphragm flattens, and this change in configuration may impair its pressure-generating capacity by alteration of its length–tension relationship. The functional significance of this impairment was first documented by Estenne and colleagues, who measured pulmonary and respiratory muscle function in non-ventilated patients before and after drainage. They found that chest wall expansion reduces respiratory muscle efficiency independently of the impairment in gas exchange. Their findings suggested that effusion drainage could help by reducing total thoracic volume and consequently repositioning the diaphragm onto a more advantageous portion of its length–tension curve. More recently, De Troyer and colleagues confirmed the findings of Estenne and colleagues by finding that experimentally induced pleural effusion caused caudal displacement of the diaphragm, and that the capacity of the muscle to generate pressure decreased as the effusion increased, as a consequence of its altered contour. However, the negative impact of pleural effusion on diaphragmatic function in critically ill patients undergoing assisted MV was never formally assessed.

Effects of drainage of pleural effusion during the weaning phase

During the weaning phase of MV, PS is a commonly used ventilation mode. Our results show that drainage of a large volume of pleural effusion in this phase of ventilation support could ease the transition to fully spontaneous breathing by improving diaphragmatic function. The finding that compliance increases after drainage is most
likely because of the relief of the stiffening effect exerted by the effusion on the respiratory system. Although other authors have reported a lesser effect of effusion drainage on compliance, this disparity is likely to be explained by the different volumes of effusion removed, or by different experimental conditions. By uncoupling the lung from the chest wall, pleural effusion can exert variable compressive effects, depending on the ratio of chest wall to lung compliance and the level of applied airway pressure. The fact that the MIP tends to increase after drainage suggests that restoration of a dome shape to the diaphragm could increase the tension of that muscle. It is expected that drainage unburdens the geometric disadvantage that the respiratory pump experiences due to the presence of an effusion, and this effect leads to greater efficiency of respiratory efforts.

Previous studies in animals have shown a “dose” relationship between pleural effusion and lung collapse and the consequent reduction in aerated volume. In the initial phase of thoracentesis, lung volume increases less than chest wall volume declines. Consequently, we found only a weakly positive correlation between the volume of effusion drained and the increase in vital capacity.

Importantly, however, we found a positive relationship between the volume of the effusion drained and the improvement in the diaphragm TF. It was not our aim to analyse any potential improved outcome related to drainage of pleural effusion, but previous studies have shown how increased values of diaphragmatic TF may augment the chances of successful extubation for patients.

Limitations
We acknowledge that there are some limitations to our study. We studied a relatively small patient population, which is, however, comparable to the numbers included in similar physiological studies. One obvious limitation of diaphragmatic ultrasonography, especially in ICU patients, is the poor acoustic window (resulting in poor quality images). However, as with other studies, we found it possible to complete the ultrasonographic evaluation in all our patients.

Because we selected only patients with unilateral effusion, extrapolating these results directly to patients with bilateral effusions may not be warranted. We did not record data for ultrasonographic characteristics of the contralateral hemidiaphragm, so did not take into account the fully integrated effects of MV and pleural effusion on bilateral diaphragmatic function.

We limited our focus to the effects of evacuation of pleural effusion, and the effects of PEEP on thoracic volume could themselves have affected diaphragm performance, as PEEP-induced volume expansion could have amplified the effusion-induced caudal displacement of the diaphragm, potentially biasing the results. However, similar values for PEEP are not uncommon during the weaning phase of MV.

We cannot rule out a possible contribution to our results of ventricular dysfunction, as it has been shown that decreased cardiac function may modify the position and function of the diaphragm. Our results might also be underestimated by chest drainage equipment causing hindrance to breathing. Finally, we did not measure gold standard indices of respiratory effort, such as those measured with oesophageal and gastric balloons, but we had previously shown that diaphragmatic thickening is a reliable indicator of respiratory effort compared with those more direct, semi-invasive indices.

Conclusion
When a patient is weaned from MV, their diaphragmatic function is impaired by the presence of a large volume of effusion, and pleural drainage appears to significantly improve diaphragmatic contractile force. Further research is necessary to replicate our findings in larger cohorts of mechanically ventilated patients and to measure the potential benefits of drainage on the duration of ventilation and other relevant clinical outcomes.

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Competing interests
None declared.

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