Management of malignant pleural effusion

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Pleural Pressure Swing and Lung Expansion After Malignant Pleural Effusion Drainage

The benefits of high temporal resolution pleural manometry
Abstract

Background
Malignant pleural effusion is a common complication in end stage cancer patients and can cause severe dyspnea. Therapeutic thoracentesis is often limited to 1-1.5 L. Pleural manometry can be used to recognize a not-expanded lung.

Methods
Interval pleural pressure measurements with a high temporal resolution were performed after each removal of 200 ml of fluid in order to observe pleural pressure swings. Pleural elastance was defined as the difference in pleural pressure divided by the change in volume. Chest X-rays were performed to evaluate lung expansion, re-expansion pulmonary edema, and fluid residue.

Results
Thirty-four procedures in 30 patients were eligible for analysis. Four patients had incomplete lung expansion following drainage. No re-expansion pulmonary edema was observed. Pleural pressure swing after 200 mL drainage was higher when lung did not expand. Pleural elastance after removal of 500 mL was higher in the not-expanded subgroup.

Conclusions
We demonstrated that a high pleural pressure swing after removal of only 200 ml was related to incomplete lung expansion. We confirmed the association between pleural elastance and lung expansion.
Introduction

Approximately 50% of patients with metastatic disease develop malignant pleural effusion (MPE). Depending on primary pathology, median life expectancy is only a few months. Most patients suffer from dyspnea, chest discomfort or cough. Pleurodesis is the standard of care in case of fluid recurrence but intention-to-treat analysis shows that it is only effective in 46% of patients. A common reason for pleurodesis failure is the presence of a non-expanded lung.

Therapeutic thoracentesis is a frequently performed medical intervention and aims to improve quality of life. Pleural pressure ($P_{pl}$) is related to lung expansion and pleural pressure drops below -20 cm H$_2$O are used as cut-off to avoid re-expansion pulmonary edema (RPE). Development of chest discomfort during drainage is associated with a drop in pleural pressure and a reason to terminate drainage, in contrast to cough. However, pleural pressures below -20 cm H$_2$O also occur in patients without any complaints. Despite the benefits of large volume removal, these concerns have let to limit fluid drainage to 1-1.5 liters in the absence of pleural manometry.

Pleural pressure changes during respiration and is usually read at end-expiration. Since changing pleural pressure during respiration might be affected by stiffness of the lung, we hypothesized that these changes during respiration would be increased in not-expanded lungs. This might be used to select patients at risk for pleurodesis failure who would preferentially benefit from indwelling catheters. We therefore developed high temporal resolution pleural manometry to observe pleural pressure changes during respiration.

Materials and Methods

Consecutive patients presented for therapeutic thoracentesis were asked to participate in the study. The study was approved by the Medical Ethical Board. Since pleural manometry is optional in standard treatment, no special written informed consent procedure was deemed necessary. There was no predefined maximum volume of drained fluid, since large volume thoracenteses are deemed to be safe even without pleural manometry. MPE diagnosis was defined by the presence of malignant cells or histologically proven pleural involvement. Massive pleural exudative effusion in patients with progressive malignant disease was also considered to be MPE following exclusion of alternative diagnoses.
Therapeutic Thoracentesis and pleural manometry

Patients were placed in an upright position. The presence of pleural fluid was confirmed by ultrasound. After local anaesthesia with Lidocain (1%), an 8 Ch (2.7 mm) pleural catheter (Rucomed) was inserted, and connected to a three-way stopcock. One arm of the stopcock was attached to a fluid tube connected to a modified Thopaz vacuum pump, which was set at -40 cm H$_2$O during the procedure. The other arm of the stopcock was connected to an electronic pressure transducer (BD DTXplusTM disposable pressure transducer sets), positioned in alignment with the catheter insertion point. A measurement unit was developed in order to be able to measure negative pressures. This unit consisted of a Wheatstone bridge and an analog-to-digital converter (USB 6009 from National Instruments). Signals were recorded using in-house developed software (Labview National Instruments). The system was designed to measure pressure signals with a temporal resolution of less than 100 milliseconds. This was calibrated against a water manometer and enabled us to observe pressure change during respiration. Drainage was terminated when flow ceased or the patient experienced chest discomfort or persistent cough despite pausing drainage. In particular, no predefined maximum for drained volume or pleural pressure was set.

Interval pleural pressure was measured before drainage (baseline pressure) and after each 200 mL of drained fluid. The closing pressure was defined as the last interval measurement after drainage was terminated and was repeated when disturbed by cough. During interval measurements, pleural pressure was recorded 40 times per second for approximately 13 seconds, which was arbitrarily chosen.

Analyses

In the test phase for this analysis we found that pleural pressure during interval measurements fluctuated during inspiration and expiration (Figure1). During each interval, inspiratory and expiratory pleural pressures were determined per breath. The average of these values was used to calculate the pleural pressures representative of each interval ($P_{pl\text{-insp}}$ and $P_{pl\text{-exp}}$). Subsequently for each interval the mean pleural pressure was calculated as ($P_{pl\text{-insp}} + P_{pl\text{-exp}}$)/2. Total pleural pressure drop was defined as the difference between mean baseline and mean closing pleural pressure. Pleural elastance ($E_p$) was calculated at intervals of 200 mL and defined by the change in mean pleural pressure divided by the change in volume ($\Delta P_p/\Delta V$). $E_p$ after removal of 500 mL, as used in previous studies, was defined as the mean of elastances after 400 mL and 600 mL. Pleural pressure swing during respiration ($P_{pl\text{-swing}}$) was defined as the difference between the $P_{pl\text{-insp}}$ and $P_{pl\text{-exp}}$. 
Evaluation

Chest X-rays (CXRs) were performed within 24 hours post thoracentesis and were evaluated by two experienced chest physicians blinded to thoracentesis details such as volume and complaints. The amount of remaining pleural fluid was estimated, and both lung expansion and radiographically RPE were reported. Patients were grouped based on lung expansion and presence of pleural fluid after thoracentesis.

Statistical analysis

The association between pleural pressure values (baseline, closing, total drop, swing after 200 mL, and elastance at 500 mL) and lung status (expanded vs. not-expanded, and expanded empty vs. expanded not empty vs. not-expanded) were tested using ANOVA.

FIGURE 1- Interval measurement. Illustrative explanation of the calculations

(In this particular example, lung did not expand.)

- **Ppl-exp** Average of pleural pressures measured at end-expiration
- **Ppl-insp** Average of pleural pressures measured at end-inspiration
- **Ppl-mean** Mean of Ppl-exp and Ppl-insp
- **Ppl-swing** Difference in Ppl between Ppl-exp and Ppl-insp
- **Ppl** Pleural pressure
Results

Patient and Effusion characteristics

Forty-five serial measurement series were performed during therapeutic thoracenteses in 40 patients. Ten patients were not evaluable since no CXR was performed within 24 hours and were therefore excluded from analysis. Thirty-four drainages in 30 patients were eligible for this analysis. Mean age was 59 years (range 35-88 years). Twenty-two out of 34 patients were female. Both two male and two female patients were analyzed twice because of recurrent effusion. Most common malignancy was breast cancer (n=14), 8 patients suffered from lung cancer, and as much patients suffered from ovarian cancer as mesothelioma (n=3). The remaining patients suffered from other malignancies, such as renal cell carcinoma (n=2), melanoma, lymphoma, sarcoma and ACUP (all n=1).

Therapeutic thoracentesis

The mean amount of fluid removed was 1300 mL (range 190-3190 mL). Half of the aspirations were performed in the left pleural space (50%). No patient developed either clinical or radiological signs of RPE. Half of the patients (n=17) were considered to have expanded lungs without (residual) pleural fluid after the intervention. No significant difference was found in the amount of fluid removed between patients with expanded or not-expanded lungs. In 13 patients the lung was expanded following incomplete drainage (no hydropneumothorax). Four Chest X-rays were reported to show incomplete drainage and a not expanded lung. The combination of a not-expanded lung with complete fluid evacuation was not reported. Sixteen patients experienced pain during drainage and 20 patients started coughing during the procedure.

Pleural pressure

Mean baseline pleural pressure was 7.10 cm H$_2$O (SD 5.45 cm H$_2$O) and mean closing pressure was -3.51 cm H$_2$O (SD 8.89 cm H$_2$O). The mean drop in pleural pressure was 10.62 cm H$_2$O (SD 10.06 cm H$_2$O). The mean pleural pressure swing after the first 200 mL drained was 3.54 cm H$_2$O (range 0.73 to 8.36 cm H$_2$O). A difference was observed between the volume/pressure curves of the expanded group and the not-expanded group (Figure 2). Two out of four patients in the not-expanded group showed a pressure drop of more than 25 cm H$_2$O whereas this did not occur in the expanded group.
Pleural Pressure Swing and Lung Expansion After Malignant Pleural Effusion Drainage

2.2

FIGURE 2 - Relation between pleural pressure and lung expansion

Thirty patients were considered to have expanded lungs (A) and in four patients lungs did not expand (B). In contrast to the data from the expanded lungs (A), a significant drop in pleural pressure is observed in the not-expanded lungs (B). The observed data are presented (grey circles) along with the estimated mean (black solid line) pressure and 95% confidence bands (black dashed lines).

Analysis

The not-expanded subgroup showed an insignificant higher opening pressure, a lower closing pressure (not significant), and a larger total drop in pressure. Pleural pressure swing (after removal of 200 mL) was significantly higher in patients with not-expanded lungs. Also elastance (after removal of 500 mL) was significantly higher when the lung was reported to be incompletely expanded (Table 1). No associations between pleural pressure and complaints were found.

<table>
<thead>
<tr>
<th></th>
<th>Expanded n=30† (95% CI)</th>
<th>Not-Expanded n=4 (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline ( P_{pl} ) (cm H(_2)O)</td>
<td>6.52 (4.84 – 8.20)</td>
<td>11.45 (-4.66 – 27.56)</td>
<td>0.09</td>
</tr>
<tr>
<td>Mean closing ( P_{pl} ) (cm H(_2)O)</td>
<td>-2.50 (-5.38 – 0.38)</td>
<td>-11.15 (-34.10 – 11.79)</td>
<td>0.067</td>
</tr>
<tr>
<td>Total ( P_{pl} ) drop (cm H(_2)O)</td>
<td>9.02 (6.13 – 11.91)</td>
<td>22.61 (-5.70 – 50.91)</td>
<td>0.009</td>
</tr>
<tr>
<td>( P_{pl\text{-swing}} ) after 200 mL (cm H(_2)O)</td>
<td>3.23 (2.64 – 3.84)</td>
<td>5.90 (1.27 – 10.53)</td>
<td>0.007</td>
</tr>
<tr>
<td>( E_{pl} ) after 500 mL (cm H(_2)O/L)</td>
<td>9.79 (7.48 – 12.11)</td>
<td>24.89 (-5.75 – 55.53)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

TABLE 1 - Pleural pressure and lung expansion

<table>
<thead>
<tr>
<th>( P_{pl\text{-drop}} )</th>
<th>Difference between mean baseline ( P_{pl} ) and mean closing ( P_{pl} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P_{pl\text{-swing}} )</td>
<td>Difference between inspiratory ( P_{pl} ) and expiratory ( P_{pl} ) (as explained in Figure 1)</td>
</tr>
<tr>
<td>( E_{pl} )</td>
<td>Pleural elastance</td>
</tr>
<tr>
<td>( P_{pl} )</td>
<td>Pleural pressure</td>
</tr>
</tbody>
</table>

† Four patients had two therapeutic thoracenteses. These patients had expanded lungs.

‡ In two patients (both had expanded lungs) drainage was less than 500 mL. These patients have been excluded for analysis of \( E_{pl} \) after 500 mL drainage

p-value less than 0.05 was considered to be significant.
Conclusion

To our knowledge, this is the first report where pleural pressures were measured with high temporal resolution. This enabled us to calculate pleural pressure swings. We have shown that changes in pleural pressure during respiration are higher when the lung fails to expand. One single (high resolution) pleural pressure measurement provides sufficient information about expected lung expansion. This might increase pulmonologist’s interest in performing pleural manometry.

In physiological state, pleural pressure is a result of in- and outward forces changing during respiration. Inspiration will cause increased intra-thoracic volume. This increased intra-thoracic volume is accompanied by an increased negative pleural pressure. The expansion of the lung during inspiration is primarily the result of an increase in negative pleural pressure in the thoracic cavity as result of the expansion of the rib cage. Impairment of complete lung expansion will therefore cause greater differences between pleural pressures measured during inspiration and expiration. Ideally, lung function tests would have been performed during drainage to observe changes in tidal volume as well.

There were two changes introduced in the procedure that increase the accuracy of the intermittent pleural pressure measurements. Firstly, in previous reports of pleural pressure measurements, water manometer measurements were performed after removal of a fixed amount of fluid. Use of water manometers is prone to errors since they have to be read at a certain point (most often at end-expiration) of the respiratory cycle. This is considered to be a real issue because pleural pressure differences can be observed during respiration that range up to 20 cm H₂O. It is even more challenging in dyspneic patients. Calculating the mean pleural pressure using high frequency recordings is therefore considered to be more reliable. Secondly, in contrast to those previous studies, a pump was used that creates a constant negative pressure of 40 cm H₂O. In laboratory setting, with manual suction using the same catheter and a 50 mL syringe, negative pressures over 100 cm H₂O can easily be reached (data not shown). Therefore, we believe that a pump regulates the pressure in the patient’s chest more accurately, preventing patients from dramatic pleural pressure falls. This might also impact on the intermittent pleural pressure measurements as the tissue recoil after suction and removal of the fluid is not an instantaneous process but takes time.

Removal of large volumes was without complications such as RPE. As Feller-Kopman et al have previously reported, RPE might be rare and independent of the volume of drained effusion. In our study, only three patients had pleural pressures below -20 cm H₂O, and all were without any pain or discomfort during drainage. In a large
series Feller-Kopman concluded that development of chest discomfort was, in contrast to cough, associated with a potentially unsafe fall in pleural pressure. Chest discomfort should be a reason to terminate drainage. However, like in our cohort, pleural pressures below -20 cm H$_2$O were also shown to occur in patients without causing any symptoms.  

Elastance was associated with lung status and the extent of drainage. As previously demonstrated by Lan et al, elastance higher than 19 cm H$_2$O / L was associated with both a not-expanded lung and pleurodesis failure. As proof of concept, we reproduced relationship between pleural elastance (after 500 mL) and lung expansion. Although we identified only four patients with not expanded lungs, its incidence (12%) seems in line with earlier observations. Only a few patients underwent pleurodesis later on and association between pleural pressure swing and pleurodesis success could thus not be studied.

A few weaknesses of this study need to be addressed. Firstly, we have chosen for a Chest X-ray within 24 hours after drainage as the endpoint, since it can be reviewed independently. The use of ultrasound would be incorporated in further studies as well since it informs instantly about lung expansion and is sensitive too. In most patients (n=32) CXR was performed immediately following drainage. CXR was obtained one day afterwards in only two patients, and was reported to show one expanded lung after complete drainage and one not expanded lung after incomplete drainage. The latter might have been drained completely initially, and the fluid might have re-accumulated in the time between drainage and CXR. Secondly, besides an expanded lung and a trapped lung, a third entity has been described: lung entrapment.

Pleural pressure curves of those patients are biphasic. Initial parts of these curves are similar to expanded lungs. The second phase of those curves show a steep decline in pleural pressure. These patients can therefore not be identified at the earliest phase of drainage. Serial pleural pressure swing measurements would help to identify lung entrapment as well, but this contrasts the purpose of this study (i.e. early recognition of the not-expanded lung)

Further studies are required before a validated cut-off level of pleural pressure swing can be used to predict lung expansion. In contrast to previous studies in which series of interval measurements were performed, only one single measurement can be associated with a not-expanding lung. Whether high temporal pressure measurements are predictive for pleurodesis success and RPE identification should also be tested in a larger cohort. Reducing the number of required interval measurements makes pleural manometry a more attractive procedure.