



Pleural Space Elastance and Its Relation to Success Rates of Pleurodesis in Malignant Pleural Effusion

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Background: Pleurodesis fails in 10%–40% of patients with recurrent malignant pleural effusions malignant pleural effusion and dyspnea. This study aimed to assess the values of pleural elastance (P_{EL}) after the aspiration of 500 mL of pleural fluid and their relation to the pleurodesis outcome, and to compare the pleurodesis outcome with the chemical characteristics of pleural fluid.

Methods: A prospective study was conducted in Kasr El-Aini Hospital, Cairo University, during the period from March 2019 to January 2020. The study population consisted of 40 patients with malignant pleural effusion. The measurement of P_{EL} after the aspiration of 500 mL of fluid was done with “ P_{EL} 0.5” (cm H_2O/L), and the characteristics of the pleural fluid were chemically and cytologically analyzed. Pleurodesis was done and the patients were evaluated one month later. The P_{EL} values were compared with pleurodesis outcomes.

Results: After 4-week of follow-up, the success rate of pleurodesis was 65%. The P_{EL} 0.5 was significantly higher in failed pleurodesis than it was in successful pleurodesis. A cutoff point of P_{EL} 0.5 >14.5 cm H_2O/L was associated with pleurodesis failure with a sensitivity and specificity of 93% and 100%, respectively. The patients with failed pleurodesis had significantly lower pH levels in fluid than those in the successful group ($p < 0.001$).

Conclusion: P_{EL} measurement was a significant predictor in differentiating between failed and successful pleurodesis. The increase in acidity of the malignant pleural fluid can be used as a predictor for pleurodesis failure in patients with malignant pleural effusion.

Keywords: Pleural Elastance; Malignant Pleural Effusion; Pleurodesis

Introduction

Malignant pleural effusion (MPE) presents a severe medical condition that can result in breathlessness, pain, cachexia, and reduced physical activity. Epidemiological information is limited, but an estimated 50,000 new diagnoses of MPE are made in the UK each year¹. The incidence of MPE is likely to rise as global cancer incidence increases and overall survival improves².

Pleurodesis or achievement of pleural symphysis preventing the need for repeated pleural fluid drainage is the cornerstone of palliative treatment in this population³. Successful pleurodesis requires the visceral and parietal pleural to maintain physical contact while sclerosant agent is infused³.

Non-expandable lung (NEL) that is usually assessed by chest radiography points out the predicted outcome of failed

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pleurodesis due to inability of the visceral and parietal pleura to contact. Therefore, NEL is considered to be an absolute contraindication for pleurodesis. The pleural manometry (PM) which is the direct measurement of pressure in the pleural space through a catheter appears to be a promising modality for predicting lung expansion post pleural fluid drainage³.

Pleural elastance (P_{EL}) which is the change in pleural liquid pressure in cm H₂O per liter of fluid removed, reflects the ability of the underlying lung to freely expand as the pleural fluid being removed. In other words, higher values of P_{EL} (more pressure change per a given volume of fluid removed) indicates an underlying stiff lung and vice versa³.

Pleural manometry was proven to be the method of choice for detecting an un-expandable lung⁴.

This highlights the need for PM data to understand pleural pathophysiology better to optimize care for MPE patients.

The current study aimed to assess the values of P_{EL} after aspiration of 500 mL of pleural fluid (P_{EL} 0.5) and its relation to pleurodesis outcome, also to compare the pleurodesis outcome with chemical characteristics of pleural fluid.

Materials and Methods

A prospective cross-sectional study was conducted in Kasr El-Aini hospital, Cairo University, from March 2019 to January 2020.

1. Population

It was carried on 40 patients, 22 male patients and 18 female patients. The study was approved by the institutional review board at Kasr Al-Aini Hospital, Cairo University (IRB #D-3-2019) and informed consent was obtained from all enrolled patients. Patients with MPE who agreed to participate were included in the study. Exclusion criteria were as follows: 1, very small amount of pleural effusion; 2, multi-loculated malignant pleural effusion; 3, patients with type II respiratory failure; 4, patients presenting with major organ failure; and 5, patients who have bleeding disorders that interfere with thoracocente-

sis and pleural biopsy.

Patients were examined by B-mode transthoracic ultrasound with curvilinear transducer (3.5 MHz) to assess the pleura before thoracoscopy regarding the presence of pleural thickening, nodulations, adhesions, septations, or encystations (Hitachi 5500, Tokyo, Japan).

2. Measurement of pleural pressure

The patient was sitting with his arms on the back of the chair, causing the intercostal spaces to be extended and to facilitate access. The skin was cleaned with betadine antiseptic solution. Lidocaine 2% (5–10 mL) was given as local anesthetic in the site of puncture. One milligram of atropine was injected intramuscularly. The needle was inserted under sonographic guidance.

Thoracocentesis was performed for all patients with the use of wide-bore catheter and IV sets. As shown in Figure 1A, the measurement of pleural pressure was done by a simple water column manometer that designed for measuring central venous pressure. The water manometer consists of two lengths of intravenous tubing connected through a three-way valve to a wide-bore catheter inserted in the pleural space. The tubing from the thoracocentesis catheter to the measuring scale extends 40 to 50 cm below the level of the catheter insertion into the chest similar to a U-shaped water manometer. The system (IV tubing) is purged of air with normal saline. Zero value was set at the thoracic puncture level. After pressure recording, the water manometer described above was removed. As shown in Figure 1B, the catheter was connected to a fluid drainage bag through IV tubing for drainage. Initial pleural pressure was measured before removing any fluid and after the removal of 500 mL. P_{EL} was calculated (P_{EL} =change in pleural liquid pressure in cm H₂O per liter of fluid removed). P_{EL} 0.5 is referred to the P_{EL} while the first 0.5 L of fluid is aspirated. After measuring P_{EL} medical thoracoscopy was done for tissue biopsy and intercostal tube was inserted. When the amount of drained fluid decrease to 100 mL or less per day, lung radiologically re-expanded against the chest wall by chest X-ray (CXR) and biopsies proved to be malignant, chemical pleurodesis was done.

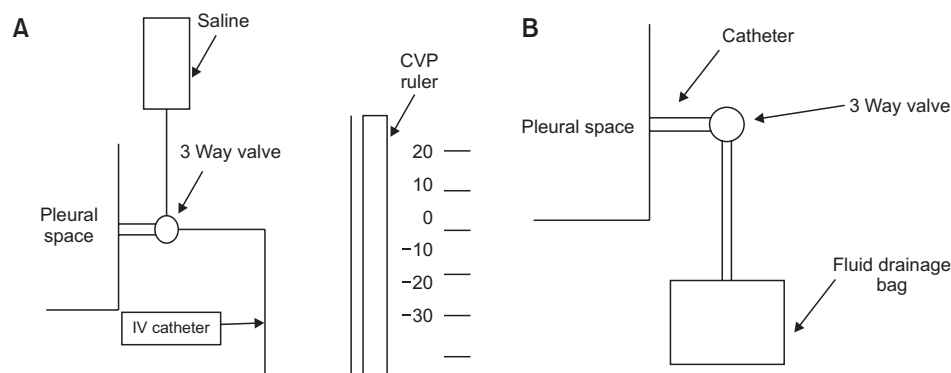


Figure 1. A schematic diagram representing the setup of pleural manometry. CVP: central venous pressure.

3. Method of chemical pleurodesis

One milligram of atropine was injected intramuscularly to control vasovagal tone. Injection of 20 mL of 2% lidocaine into the pleural space through the intercostal tube. Injection of the sclerosing agent doxycycline (vibramycin), 15–20 mg/kg dissolved into 50 mL of normal saline injected into the pleural space through the tube followed by 20 mL of normal saline to flush the chest tube. Clamping the chest tube for 2 hours, after that the tube was opened. The chest tube was removed when the drainage was less than 150 mL/24 hours and a chest X-ray was obtained.

4. Assessment of success

At the end of the 4-week follow-up period, the radiographic response (CXR) was classified as follows: A, successful: if no radiographic evidence of fluid re-accumulation was noted at 4 weeks; B, partial successful: indicated re-accumulation of fluid that did not produce symptoms and did not require repeat pleural drainage of any sort. A or B considered to be in the successful group; C, all other outcomes were scored as failed.

5. Statistical methods

The data collected tabulated and statistically analyzed using Minitab 17.1.0.0 for windows (Minitab Inc., State College, PA, USA), by the following methods: (1) descriptive statistics: continuous data were represented as mean and standard deviation (SD), while non-numerical data as number and percentage (%); (2) analytic statistics: independent t test: used to compare mean of two independent groups; person chi-square test: used to test the association between categorical variables.

All statistical tests were two-sided, p-value considered significant if <0.05.

Results

The mean age of the studied patients was 60.98±10.32 years old. They were 22 males (55%) and 18 females (45%). Eighteen patients (45%) were smokers. All patients presented by dyspnea either alone (70%) or with chest pain (30%). Twelve patients (30%) were diabetics.

Pleural fluid biochemical analysis as regarding mean and SD was as follows: albumin 2.45±0.61 g/dL, protein 4.46±1.01 g/dL, lactate dehydrogenase (LDH) 603.4±517 IU/L, pH 7.33±0.11, glucose 100.2±66.3 mg/dL.

Radiological examination revealed that most of the patients (52.5%) had right-side pleural effusion. The mean value of P_{EL} 0.5 (cm H₂O/L) was 11.85 and 5.88 (SD) with range (4–24).

Macroscopic findings that were encountered during thoracoscopy were as follows: pleural masses in five patients

(12.5%), thickened pleura in four patients (10%). Pleural nodules were the commonest feature either alone in 20 patients (50%) or associated with thick pleura in 11 patients (27.5%). Regarding pleural fluid cytological exam: malignant cells were found in 10 patients (25%), 10 patients (25%) had predominant lymphocytes, four patients (10%) had predominant mesothelial cells, while no obvious predominant cell in cytological examination where found in 16 patients (40%).

Finally, the histopathological diagnosis revealed malignant mesothelioma in 26 patients (65%) while 14 patients (35%) had metastatic tumors, nine patients (22.5%) had metastatic adenocarcinoma of breast origin, two patients (5%) had poorly differentiated adenocarcinoma. Three patients (7.5%) had metastatic adenocarcinoma from the lung, one patient (2.5%) had metastatic non-small cell lung cancer, one patient (2.5%) had metastatic small cell lung cancer, and one patient (2.5%) had metastatic high-grade squamous cell carcinoma.

More than half of the patients had no complications after pleurodesis. There was pain in 12 patients (30%), infection in four patients (10%) in whom antibiotics were received according to culture and sensitivity and surgical emphysema in one patient (2.5%).

The patients were then classified into two groups regarding the pleurodesis outcome 1 month later, depending on CXR finding, to find the associated factors that precipitated the failure of pleurodesis.

Fourteen out of 40 patients were failed to pleurodesis (35%) and 26 out of 40 (65%) had successful pleurodesis based on radiological assessment after 1 month as described above.

No impact of age, sex, and smoking habits on pleurodesis

Table 1. Impact of patient's demography and pleural fluid characteristics on pleurodesis outcome

Variable	Failed pleurodesis	Successful pleurodesis	p-value
Age, yr	63.6±10.1	59.6±10.3	0.24*
Sex			0.84 [†]
Female	6 (42.9)	12 (46.2)	
Male	8 (57.1)	14 (53.9)	
Smoking			0.64 [†]
No	7 (50)	15 (57.7)	
Yes	7 (50)	11 (42.3)	
Complain duration, mo	2.14±1.74	2.5±1.95	0.55*
Effusion location			0.66 [†]
Left	6 (42.9)	13 (50)	
Right	8 (57.1)	13 (50)	

Values are presented as mean±standard deviation or number (%).

*Independent t test. [†]Chi-square test, p-value considered significant if <0.05.

outcome ($p=0.24$, $p=0.84$, and $p=0.64$) respectively (Table 1). There was no impact of complain duration nor location of pleural effusion on pleurodesis outcome ($p=0.55$, $p=0.66$, and $p=0.53$), respectively (Table 1). There was no significant statistical difference between the two groups except in pleural fluid pH, which was significantly lower in the failed pleurodesis group (Table 2). P_{EL} 0.5 (cm H₂O/L) was significantly higher in group with failed pleurodesis (mean±SD, 18.29±4.65) than the successful group (mean±SD, 8.38±2.65) ($p<0.001$) (Figure 2).

The receiver operating characteristic curve showed that the P_{EL} was a significant predictor measure in differentiating between failed and successful pleurodesis (area under the curve [AUC] 94%, $p<0.001$). At cutoff point >14.5, the sensitivity and specificity were 93% and 100%, respectively (Figure 3).

The patients with successful pleurodesis consumed significantly shorter duration of intercostal tube insertion with 6.08±1.6 days (mean±SD) than the failed one 10.64±2.92 days (mean±SD) ($p<0.001$).

Discussion

An unexpandable lung in MPE causes pleurodesis failure but is difficult to detect pre-drainage. Measurement of P_{EL} has

been shown as an attractive tool to predict unexpandable lung in malignant pleural effusion. However, due to technical limitations it has been underutilized in the clinical practice. In the past years, little attention has been paid to the measurement of P_{EL} before pleurodesis. Most of the trials use radiographic lung expansion as a surrogate for normal pleural physiology.

In our study, we measured P_{EL} in 40 patients with MPE during aspiration of 500 mL of fluid and compared it with the pleurodesis outcome after 1 month. Fourteen out of 40 patients were failed to pleurodesis (35%). Twenty-six out of 40 (65%) had successful pleurodesis. This was based on radiological assessment after 1 month as described above.

In a recent study by Chopra et al.⁵, 70 patients with MPE in whom complete drainage was done with PM were evaluated. The aim was to determine the frequency of elevated P_{EL} and its relation to post-thoracentesis radiographic findings. Post-thoracentesis CXRs showed incomplete expansion in 54% of patients. This higher prevalence of unexpandable lung was explained by the investigators due to the rigorous requirement in their study that necessitated at least 90% apposition of visceral and parietal pleura to define lung expansion⁵.

In our study, P_{EL} was significantly higher in the failed pleurodesis group ($p<0.001$) (Figure 2). The P_{EL} was a significant predictor variable in differentiating between failed and

Table 2. Pleural effusion characteristics in both groups

Variable	Failed pleurodesis	Successful pleurodesis	p-value
Albumin, g/dL	2.42±0.70	2.47±0.58	0.81*
Protein, g/dL	4.56±1.21	4.41±0.91	0.68*
LDH, IU/L	694±487	555±535	0.41*
pH	7.24±0.08	7.39±0.10	<0.001*
Glucose, mg/dL	108.50±85.20	95.80±54.90	0.62*
Predominant cell in cytology			0.61 [†]
Mesothelial cell	1 (7.1)	3 (11.5)	
Malignant cell	4 (28.6)	6 (23)	
Lymphocytes	2 (14.3)	8 (30.8)	
No predominant cell	7 (50)	9 (34.6)	
Thoracoscopic findings			0.86 [†]
Masses	2 (14.3)	3 (11.5)	
Nodules	7 (50)	13 (50)	
Thick pleura	2 (14.3)	2 (7.7)	
Nodules and thick pleura	3 (21.4)	8 (30.8)	
Pathology			0.14 [†]
Mesothelioma	7 (50)	19 (73.1)	
Metastatic	7 (50)	7 (26.9)	

Values are represented as mean±standard deviation or number (%).

*Independent t test. [†]Chi-square test, p-value considered significant if <0.05.

LDH: lactate dehydrogenase.

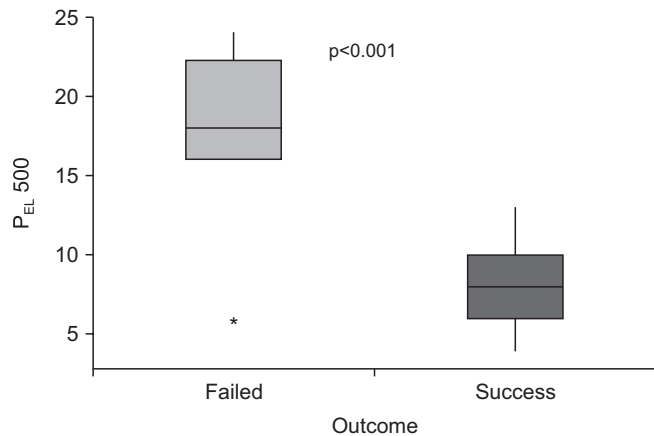


Figure 2. Pleural elastance in both groups. P_{EL}: pleural elastance.

successful pleurodesis (AUC 94%, $p < 0.001$). At cutoff point >14.5 , the sensitivity and specificity were 93% and 100%, respectively (Table 3).

In an early study, Lan et al.⁶ reported that elevated P_{EL} ≥ 19 cm H₂O/L during removal of 500 mL of fluid was associated with 79% sensitivity and 94% specificity for NEL.

In the study done by Chopra et al.⁵, patients with normal P_{EL} (≤ 14.5 H₂O/L) had significantly higher rate of complete lung expansion in CXR. On the other hand, patients with elevated P_{EL} (>14.5 H₂O/L) had significantly higher rate of incomplete lung expansion in CXR than those with normal elastance⁵.

However, one-third of patients in that cohort had discordance between post-drainage CXR and PM findings. Therefore, they postulated that CXR alone is inadequately sensitive and inadequately specific to detect high P_{EL}. Additionally, PM was found to be an important adjunctive measurement in term of prediction of pleurodesis outcome⁵.

A recent EDIT (Elastance-Directed Intrapleural Catheter or Talc Pleurodesis in Malignant Pleural Effusion) trial that is currently undergoing was based on importance of PM in personalizing the management of malignant pleural effusion⁷.

A pilot study of the EDIT involved P_{EL} assessment during large-volume thoracentesis. Patients with P_{EL} >14.5 cm H₂O/L were allocated to immediately receive an indwelling pleural catheter, the remainder underwent standard care that involved immediate drain placement for talc pleurodesis. In the published pilot study, high P_{EL} was detected in seven of 13 patients (54%) with 100% sensitivity and 67% specificity for NEL⁷.

All of the above-mentioned data paves a new pathway of an elastance-directed MPE management. And put forth the concept of personalized treatment protocols into clinical practice.

In concordance with Ferreiro et al.⁸, we did not find significant statistical difference between succeeded and failed cases in relation to the value of pleural fluid total proteins nor the value of pleural fluid albumin.

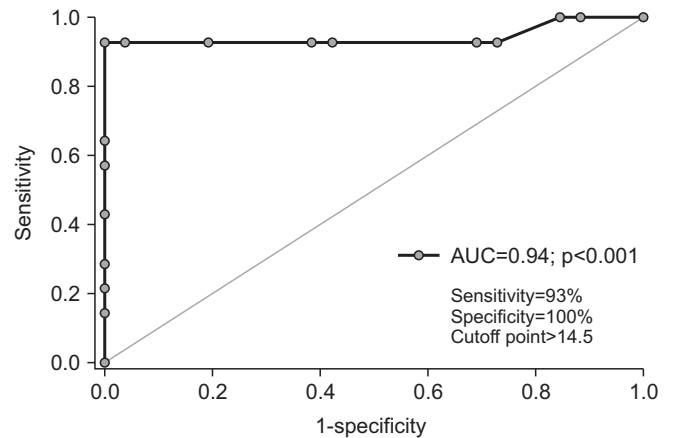


Figure 3. Receiver operating characteristic curve of pleural elastance. AUC: area under curve.

Different investigators addressed the implication of pleural fluid glucose to predict successful pleurodesis. Pantazopoulos et al.⁹, reported that lower level of pleural fluid glucose was associated with pleurodesis failure, with a cutoff point of 65 mg/dL had a high sensitivity (90.7%) with an acceptable specificity (76.8%) ($p < 0.001$). Heffner et al.¹⁰, had similar results and reported a cutoff points that discriminated failure from success 72 mg/dL. However, in the present study, we were not able to find a significant difference between the two groups in relation to the value of pleural fluid glucose. This may be attributed to the high prevalence of diabetes in the studied patients; thus, they had elevated levels of glucose in serum and their pleural fluid.

In the present study, the mean value of pleural fluid LDH in the patients with succeeded pleurodesis was 555 IU/L, while in failed cases, the mean value was 694 IU/L. Although LDH mean value in failed cases was higher than succeeded cases, the difference between them did not reach statistical significance ($p = 0.41$). These results were in concordance with the results obtained in the study performed by Ferreiro et al.⁸, Yildirim et al.¹¹, and Rafei et al.¹², who found no correlation between the values of pleural fluid LDH and the success or failure of pleurodesis.

In the studied patients, pleural fluid pH was significantly lower in the failed group. This was in agreement with Yildirim et al.¹¹, who found a cutoff point 7.34 below which pleurodesis is most likely to fail. Pleural fluid pH is determined by the acids generated from glucose metabolism of cells within the pleural space, as well as the efflux of those acids and the influx of glucose across the pleural membranes. Diffusion across the pleura can be affected in acute inflammatory states (e.g., infection), chronic fibrotic conditions (e.g., rheumatoid pleurisy) and tumor infiltration in pleural malignancies. Due to abnormal pleura in patients with low pH effusions, the rate of transport of CO₂ and lactic acid out of pleural space is slowed

Table 3. A brief comparison of the most commonly used sclerosing agents

Sclerosant agent	Chemical nature	Remarks
Talc	Hydrated magnesium silicate	Most effective Most commonly used High success rate ¹³
Doxycycline	Antibiotic of tetracycline group	Lower success rate than talc ¹⁴
Silver nitrate	Topical antibiotic	Good safety profile Equal in efficacy when compared with talc and doxycycline ¹⁵
Bleomycin	Cytotoxic, chemotherapeutic drug	Less commonly used due to systemic toxicity and high cost ¹³

and accumulation occurs resulting in decreased pleural fluid pH.

This study revealed malignant mesothelioma in 26 patients (65%) while 14 patients (35%) had metastatic tumors. This was in agreement with Yildirim et al.¹¹, who found that pleural mesothelioma was the most common malignancy producing MPE.

In the current study, doxycycline was used as a sclerosant agent due to its availability and low cost. However, several chemical irritants have been used to induce pleurodesis. The most commonly used are talc, doxycycline, silver nitrate, and bleomycin (Table 3).

A limitation of the current study is that P_{EL} was calculated over the first 500 mL of pleural drainage and there was a lack of evaluation of the entire pressure volume curve. This may have missed patients with biphasic P/V curve with high terminal P_{EL} .

In summary, our study highlights the importance of P_{EL} measurement in patients with MPE to anticipate pleurodesis outcome. Elastance of less than 14.5 cm H₂O predicts an expandable lung and hence could be treated by intercostal tube insertion and injection of pleurodesis agents. On the other side, elastance of more than 14.5 cm H₂O indicates an unexpandable lung and hence these patients should be managed differently, as indwelling pleural catheter would be the best treatment option.

Further studies are needed to confirm these findings. In addition, finding simpler ways for measuring P_{EL} are warranted to facilitate its implication in the current medical practice.

Authors' Contributions

Conceptualization: Assal HH, Masoud HH. Methodology: Ahmed AA. Formal analysis: Assal HH, Ahmed AA. Data curation: El-Zorkany MM. Software: El-Zorkany MM. Validation: Masoud HH. Investigation: Ahmed AA. Writing - original draft preparation: Ahmed AA. Writing - review and editing: Assal HH, Masoud HH, El-Zorkany MM. Approval of final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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