

# **The Relationship of Pleural Manometry with Post-Thoracentesis Chest Radiographic Findings in Malignant Pleural Effusion**

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**Cover Letter:**

Dear Editors of *CHEST*:

We are submitting our manuscript titled, “The correlation of pleural manometry with post-thoracentesis chest radiographic findings in malignant pleural effusions” for your consideration of publication in *Chest*. Currently, the placement of an indwelling pleural catheter and chemical pleurodesis are both acceptable strategies for the management of malignant pleural effusions (MPE). Abnormal lung expansion and elevated pleural elastance are both considered contraindications for pleurodesis. However, the frequency of elevated pleural elastance in MPE has not been previously determined. In addition, the presence of increased pleural space elastance may suggest the presence of a significant number of patients with unexpandable lung, which may overall limit pleurodesis success.

Our investigation documents that an elevated pleural elastance is present in roughly 50% of MPE patients. In addition, we found a discordance between the post-thoracentesis radiograph findings and the pleural manometry findings in terms of identifying contraindications to pleurodesis based on current guidelines. Our observations may suggest that pleural manometry, in addition to the post-thoracentesis chest radiograph, may have a complementary role in selecting patients with MPE for accelerated pleurodesis strategy. The data presented may help further facilitate well-designed studies to evaluate pleurodesis outcomes when both pleural manometric findings and post-chest radiography are incorporated into the clinical design. We believe our findings have a scientific and clinical relevance for consideration of publication. We await your thoughtful review.

Sincerely for all the authors,

Amit Chopra, MD

**Abstract:**

**Introduction:** Both elevated pleural elastance ( $E-P_{EL}$ ) and radiographic evidence of incomplete lung expansion following thoracentesis have been used to exclude patients with a malignant pleural effusion (MPE) from undergoing pleurodesis. We report a cohort of MPE patients in which complete drainage was attempted with pleural manometry to determine the frequency of  $E-P_{EL}$  and its relationship with the post-thoracentesis radiographic findings.

**Methods:** We identified 70 consecutive MPE patients who underwent therapeutic pleural drainage with pleural manometry. The pressure/volume curves were constructed and analyzed to determine the frequency of  $E-P_{EL}$  and the relationship of  $P_{EL}$  to the post-thoracentesis chest radiographic findings.

**Results:**  $E-P_{EL}$  and incomplete lung expansion was identified in 36 of 70 (51.4%) and 38 of 70 (54%) patients respectively. Patients with normal  $P_{EL}$  had an odds ratio of 6.3 of having complete lung expansion compared to those with an  $E-P_{EL}$  ( $P=0.0006$ ). However, 20 of 70 (29%) of patients demonstrated a discordance between post-procedural chest radiographic findings and the pleural manometry results. Among patients who achieved complete lung expansion on the post-drainage chest radiograph, 9 of 32 (28%) had an  $E-P_{EL}$ . In addition,  $P_{EL}$  was normal in 11 of 38 (34%) patients who had incomplete lung expansion as detected by post-thoracentesis chest radiograph.

**Conclusions:** An  $E-P_{EL}$  and incomplete lung expansion post- thoracentesis are frequently observed in MPE patients. Nearly one third of the cohort demonstrated a discordance between the post-procedural chest radiographic findings and pleural manometry results. Our findings suggest that a prospective randomized trial should be done to compare both modalities (chest radiograph and pleural manometry) in predicting pleurodesis outcome.

## Introduction

Pleurodesis and indwelling pleural catheter (IPC) placement are the acceptable treatment options for the management of malignant pleural effusion (MPE).<sup>1</sup> In patients with expandable lung, both IPC and chemical pleurodesis are recommended as first line therapy as per current American Thoracic Society guidelines.<sup>1</sup> Adequate pleural apposition is a prerequisite in order to achieve successful pleurodesis in MPE. The current British Thoracic Society guidelines recommend demonstration of pleural apposition on a chest radiograph following pleural fluid removal as a criterion for pleurodesis in MPE.<sup>2</sup> A prior study by Lan and colleagues showed that pleurodesis was uniformly unsuccessful in those who had an E-P<sub>EL</sub> in MPE patients.<sup>3</sup> While both failure of complete drainage and an E-P<sub>EL</sub> approaches are contraindications for pleurodesis, there are currently no data examining the prevalence of E-P<sub>EL</sub> in patients with MPE who undergo an attempt at complete pleural drainage; in addition, the relationship of the pressure/volume (P/V) curve and the post thoracentesis chest radiograph findings have not previously been explored.

We performed a prospective observational study to compare post-drainage chest radiograph findings with pleural manometric findings in MPE undergoing attempted complete pleural drainage. The goals of this study were: 1) to determine the prevalence of E-P<sub>EL</sub> in patients with MPE; and 2) to compare pleural manometry findings with post-thoracentesis chest radiographic findings.

## Materials and Methods

We retrospectively reviewed consecutive patients with a diagnosis of MPE based on the positive pleural cytology who underwent an attempt at complete pleural drainage and had concomitant pleural manometry. A post-thoracentesis anteroposterior view chest radiograph was obtained immediately following thoracentesis. Each post-procedural chest radiograph was reviewed independently by a dedicated thoracic radiologist.

Post-procedural chest radiographs were evaluated for: a) complete lung expansion (CLE-CXR), which was defined as >90% pleural apposition on the frontal view; and b) incomplete lung expansion (ILE-CXR), defined as  $\leq 90\%$  pleural apposition; or drainage related pneumothorax (pneumothorax ex vacuo) on a frontal view chest radiograph<sup>4</sup>.

Pleural manometry was performed with an electronic acquisition system and damped water manometer as published previously.<sup>5</sup> In order to measure pleural pressures and pleural space elastance  $P_{EL}$  at the time of thoracentesis, the patient was placed in an upright sitting position with the arms resting on a level surface. The manometer was attached to a 3-way stopcock on the pleural catheter to allow repeated measures of pleural pressure during fluid removal. When using a water manometer, the zero-pressure level was set where the catheter entered the chest wall. The initial mean pleural pressure was measured after approximately 20 ml of pleural fluid was removed. Mean pleural pressure was measured during periods of tidal breathing and assessed over four to five respiratory cycles representing quiet breathing. During subsequent fluid removal, the pleural pressure was measured after each aliquot of 100 to 250 mL of pleural fluid. Pleural fluid drainage was discontinued if the following conditions occurred: a) the mean pleural pressure declined below  $-20$  cm  $H_2O$ ; b) the patient reported significant chest pain; or c) no further pleural fluid could be drained. The pressure/volume (P/V) curves were constructed for analysis and  $P_{EL}$  was calculated. The last pleural pressure measurement was considered valid by documenting the presence of fluid on thoracic ultrasound, or at least 50 ml of pleural fluid was removed. E-Pel was defined as the presence of either a monophasic P/V curve with a  $P_{EL} > 14.5$  cm  $H_2O/L$ , or a biphasic P/V curve in which the terminal portion of the biphasic P/V curve had a  $P_{EL}$  of  $> 14.5$  cm  $H_2O/L$  <sup>4</sup>. A monophasic P/V curve with a  $P_{EL} \leq 14.5$  cm  $H_2O / L$  represented normal  $P_{EL}$ .<sup>4</sup> Validation of the last mean pleural pressure is necessary since the pleural pressure may be artifactual low because of the local deformation forces around the catheter tip.<sup>5-7</sup>

Statistical analysis was performed using SigmaPlot (Systat Software, Inc.; San Jose, Ca) version 11.0. Continuous variables were presented as mean, median with standard deviation, and 5<sup>th</sup> - 95<sup>th</sup> percentile range. Categorical variables were expressed as percentages and interquartile ranges. The differences between the two groups were evaluated with either an unpaired t-test or Mann-Whitney rank sum test, depending on the characteristics of the distribution of the variable tested. For categorical data, 2 x 2 contingency tables were constructed, and the data was analyzed using a two-tailed Chi-square test. A p value of < 0.05 was considered statistically significant.

## Results

We identified 70 consecutive patients who had undergone therapeutic thoracentesis and concomitant pleural manometry. The demographics and tumor characteristics of our cohort are shown in **Table 1**. Fifty-seven of 70 (81.4%) patients had an adenocarcinoma. A non-lung primary was detected in 51 of 70 (72.8%) of the patients. The 70 patients who had undergone therapeutic thoracentesis and concomitant pleural manometry constituted the cohort that we analyzed. Selection of patients undergoing pleural manometry was determined by the capability of the clinician to perform the procedure and not by clinical or radiographic data.

The post-thoracentesis chest radiographs were available in all 70 patients and showed complete expansion in 32 of 70 (46%) while 38 of 70 (54%) had either incomplete drainage in 25 of 70 (36%) or a drainage related pneumothorax in 13 of 70 (18%).

Normal  $P_{EL}$  was observed in 34 of 70 (49%) patients. (**Table 2**) Of these 34 patients, 32 (94%) had a monophasic P/V curve with  $P_{EL} \leq 14.5$  cm H<sub>2</sub>O/L (**Figure 2a**). Two patients with normal lung expansion had an unusual “inverted” biphasic P/V curve with an initial high  $P_{EL}$  and a normal terminal  $P_{EL}$ . This may occur in

situations where  $P_{EL}$  is initially transiently elevated because of lobar atelectasis that resolves with pleural fluid removal. For the purposes of our analyses, we interpreted the two patients with the inverted biphasic P/V curves as representing normal  $P_{EL}$ .

Elevated  $P_{EL}$  was detected in 36 of 70 (51%) (**Table 2**); Nine of 36 (25%) had a monophasic P/V curve with a  $P_{EL} > 14.5$  cm H<sub>2</sub>O/L (mean 21.8, SD 4.1; median 20.8, range 18.2-31.6). (**Figure 2b**) Twenty-seven of 36 (75%) patients had a biphasic P/V curve with a  $P_{EL}$  for the initial portion of the curve ( $E1$ )  $\leq 14.5$  cm H<sub>2</sub>O/L (mean 8.8, SD 3.1; median 8.6, range 3.3-8.6) and a  $P_{EL}$  for the terminal portion of the curve ( $E2$ )  $> 14.5$  cm H<sub>2</sub>O/L (mean 41.4, SD 27.9; median 33.3, range 15.3-129.0). (**Figure 2c**).

There was no statistically significant difference in age, race, gender, tumor origin, or tumor cell type between the normal and the E- $P_{EL}$  group (**Table 3**); or CLE-CXR and ILE-CXR (**Table 4**). The mean pleural fluid volume drained was statistically significantly greater ( $p=0.04$ ) in the normal  $P_{EL}$  group (1589 mL) compared to the E- $P_{EL}$  group (1180 mL).

**Figure 1** and **Table 5** outline the relationship between the post-thoracentesis chest radiograph findings and pleural manometry results. Patients with normal  $P_{EL}$  had a significantly statistically higher rate of complete lung expansion on chest radiograph 23/34(68%) compared to those with E- $P_{EL}$  9/36(25%)( $P<0.005$ ) (**Figure 1**). Patients with E- $P_{EL}$  had a statistically significantly higher rate ( $P=0.002$ ,) of ILE-CXR 27/70(38.5%), than those with normal  $P_{EL}$  11/70 (15.7%). (**Figure 1**) Patients with normal  $P_{EL}$  had an odds ratio of 6.3 of having CLE-CXR compared to those with an E- $P_{EL}$  ( $P=0.0006$ ). Concordance between the  $P_{EL}$  and post-thoracentesis chest radiograph criteria for pleurodesis was found in 50 of 70 (71%) of cases; whereas, 20 of 70(29%) patients had a discordance between these two criteria (**Table 5**). Eleven of 38 (34%) patients with ILE-CXR had normal  $P_{EL}$  while 9 of 32 (28%) patients with complete lung expansion had an elevated  $P_{EL}$ .



## Discussion

In this analysis of 70 patients with MPE who underwent pleural drainage with pleural manometry, the post-thoracentesis chest radiographic findings and pleural manometry each identified a contraindication to pleurodesis in approximately 50% of the cohort.

The prevalence of ILE-CXR was 54% in our cohort and was higher than previously reported from prior studies, ranging 2% to 30%.<sup>8-10</sup> The degree of variability in ILE-CXR across various series may be due to heterogeneity in the accepted degree of pleural apposition (50%- 90%) on the post-drainage chest radiograph to determine chemical pleurodesis eligibility<sup>8-15</sup>. Interestingly, the studies which required higher degree of pleural apposition (>90%) to define lung expansion had higher prevalence rates of ILE-CXR than studies less rigorous degrees of apposition on chest radiograph. Our higher rate of ILE-CXR compared to previous studies may be explained by our requirement of at least 90% apposition of visceral and parietal pleura apposition to define adequate pleural fluid drainage.

We found the prevalence of E-P<sub>EL</sub> in MPE was approximately 50%. If the prevalence of E-P<sub>EL</sub> with MPE is closer to 50% as seen in our cohort, the manometry and post-pleural drainage chest radiograph findings reported could explain the low pleurodesis success rates (<50%) and suggest a plausible explanation for the lower pleurodesis success rates in the published literature.<sup>8 9 14-17</sup> To our knowledge, there are no published data available describing the prevalence of E-P<sub>EL</sub> in MPE patients during an attempt to completely drain a MPE. One prior study demonstrated that pleural manometry findings accurately predict the success of pleurodesis in MPE<sup>3</sup>. In that study, 14 of 57(25%) subjects had E-P<sub>EL</sub>. A P<sub>EL</sub> <19 cmH<sub>2</sub>O/L had a 98% (42/43) pleurodesis success rate, whereas those with P<sub>EL</sub> >19 cmH<sub>2</sub>O/L had 100% (14/14) pleurodesis failure.<sup>3</sup> However this study was never replicated in a larger study. A major limitation of that study was that P<sub>EL</sub> was calculated over first 500 ml of pleural fluid drainage and there was lack of evaluation of the entire P/V curve.

This may represent a cohort of patients with monophasic P/V curve and might have missed patients who have biphasic P/V curve with high terminal  $P_{EL}$  and thereby underestimating the frequency of E- $P_{EL}$ . In addition, the follow-up period for pleurodesis success was short and measured only at 1 month by CXR.

Nearly one-third of patients had discordance between post-drainage chest radiograph and pleural manometry findings.. These results suggest that the post-pleural drainage findings on chest radiograph alone are inadequately sensitive and inadequately specific to detect E-  $P_{EL}$ . Our analysis supports the premise that performing pleural manometry during thoracentesis may provide additional information in terms predicting the outcome of pleurodesis procedures. We believe that comparison of these two criteria with pleurodesis outcomes will need to be addressed.

The explanation for the discordance between these two criteria for pleurodesis of MPE patients remains unclear. The post-thoracentesis chest radiograph may show incomplete lung expansion while the  $P_{EL}$  is normal because either: a) drainage was prematurely stopped due to a mechanism other than unexpandable lung, such as presence of pleural adhesions not allowing complete drainage or chest pain due to catheter irritating diaphragm; or b) the  $P_{EL}$  may be falsely normal in cases of drainage related pneumothorax. In our study, drainage related pneumothorax was present roughly in one fifth of the cases, but approximately one third of patients had drainage related pneumothorax had a normal  $P_{EL}$ . Proposed mechanism for drainage related pneumothorax may result of air entry from the lung into the pleural space from the development of a pressure dependent alveolar-pleural fistula.<sup>4</sup> Air-leaks through these fistulas may elevate the pleural pressure into normal physiologic ranges, resulting in “pseudo-normalization” of  $P_{EL}$  and pressure/volume curves. Additionally, the presence of an air entry into the drainage system may interfere with an accurate reading of pleural pressures.

Our study has several limitations. First, the study cohort consisted of patients from a single center and may not be generalizable to all MPE patients. Second, we did not explore the mechanisms responsible for the discordance between the ILE-CXR and E-P<sub>EL</sub> results in our cohort. Although this may be a useful exercise in determining the eligibility for pleurodesis in MPE who demonstrate a discordance, this could not be performed in our retrospective analysis. We hypothesize that in future prospective studies that incorporate the success rate of pleurodesis, distinguishing the cause for the discordance may be impactful in establishing more reliable eligibility criteria for pleurodesis. Lastly, our assessment of lung expansion after pleural drainage was rudimentary as we relied on the post-thoracentesis chest radiographs alone; however, such an assessment is similar to prior studies.

## **Conclusion**

The present investigation suggests that 50% of patients with MPE have an abnormality in lung expansion as detected by pleural manometry and chest radiography. Incomplete lung expansion on post- thoracentesis chest radiograph and E-P<sub>EL</sub> are both considered as a contraindication to pleurodesis. However, we found a significant discordance between these two criteria. These results suggest that pleural manometry may have role in addition to the post-thoracentesis chest radiograph in selecting patients for pleurodesis; however, confirmation of this conjecture would require a similar study to ours plus an analysis of pleurodesis outcomes.

**Table 1:** Demographics and tumor type of patients with malignant pleural effusion undergoing thoracentesis with pleural manometry (N=70)

<b>Age -mean, median(range) years</b>	<b>59, 61 (37-78)</b>
Ethnicity	
White	42 (60%)
Black	28 (40%)
Gender	
Male	19 (27%)
Female	51 (73%)
Tumor origin	
Lung	19 (27%)
Non-lung	51 (73%)

Tumor cell type	
Adenocarcinoma	57 (81%)
Non-adenocarcinoma	13 (19%)

**Table 3:** Comparison of the demographic data, pleural fluid effusion size, tumor origin, and tumor cell type between the normal and elevated  $P_{EL}$  group

	Normal $P_{EL}$	Elevated $P_{EL}$	P value
<b>Age -mean, median(range) years</b>	59,61 (37-78)	64,64(44-84)	0.14
Ethnicity			
% white	65	56	0.46
%Black	35	44	
Gender			
%male	29	25	0.79
%female	71	75	
Tumor origin			
%lung	21	33	0.29
%non-lung	79	67	
Tumor cell type			
% adenocarcinoma	85	78	0.54
%non-adenocarcinoma	15	22	
Pleural fluid removed (ml)	1589,1510(733-2509)	1180,1088(500-2280)	<b>0.04</b>

\*  $P_{EL}$  = Pleural elastance

**Table 4:** Comparison of the demographic data, pleural fluid effusion size, tumor origin, and tumor cell type between the complete lung expansion and incomplete lung expansion

	CLE*	ILE**	P value
<b>Age -mean, median(range) years</b>	62,64 (38-79)	61,62(36-90)	0.80
Ethnicity			
% white	53	66	0.27
%Black	47	34	
Gender			
%male	31	24	0.51
%female	69	76	
Tumor origin			
%lung	34	29	0.65
%non-lung	66	71	
Tumor cell type			
% adenocarcinoma	84	81	0.74
%non-adenocarcinoma	16	19	

Pleural fluid removed (ml)	1589,1510(733-2509)	1262,1192(305-2300)	0.06
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\* CLE = Complete lung expansion

\*\* ILE= Incomplete lung expansion

**Table 5** Post-drainage chest radiograph with respect to pleural manometry findings (N=70)

Chest radiograph findings	Normal P <sub>EL</sub> (N=34)	Elevated P <sub>EL</sub> (N=36)
Complete lung expansion	23	9
Incomplete lung expansion	11	27

\* P<sub>EL</sub> = Pleural elastance

### Figure Legends:

**Figure 1:** Distribution of Post-drainage chest radiograph with respect to pleural manometry findings

**Figure 2a:** Monophasic pressure/volume curves with P<sub>EL</sub> <14.5 cm H<sub>2</sub>O/L

**Figure 2b:** Monophasic pressure/volume curves with a P<sub>EL</sub> >14.5 cm H<sub>2</sub>O/L

**Figure 2c:** Biphasic pressure/volume curves with an initial P<sub>EL</sub> ≤14.5 cm H<sub>2</sub>O/L and a terminal P<sub>EL</sub> >14.5 cm H<sub>2</sub>O/L

**Conflicts of Interest:** MAJ: consultant for Biogen; Institution grant support from Novartis, Mallinckrodt pharmaceuticals. JH: Consultant/Advisory Boards: IBIOS [IPF]; Roche/Genentech [IPF (Nintedanib)]; Boehringer Ingelheim [IPF (Pirfenidone)]. FM: unrestricted research grant from Centurion. AC: none

## Contribution of authors individually.

JHT is the guarantor of the paper and takes responsibility for the integrity of the work as a whole, from inception to published article. All authors contributed to the writing of the manuscript.

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